Randomized clinical trial

Randomized clinical trial on enhanced recovery *versus* standard care following open liver resection

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Background: **Enhanced recovery programmes (ERPs) have been shown to reduce length of hospital stay (LOS) and complications in colorectal surgery. Whether ERPs have the same benefits in open liver resection surgery is unclear, and randomized clinical trials are lacking.**

Methods: **Consecutive patients scheduled for open liver resection were randomized to an ERP group or standard care. Primary endpoints were time until medically fit for discharge (MFD) and LOS. Secondary endpoints were postoperative morbidity, pain scores, readmission rate, mortality, quality of life (QoL) and patient satisfaction. ERP elements included greater preoperative education, preoperative oral carbohydrate loading, postoperative goal-directed fluid therapy, early mobilization and physiotherapy. Both groups received standardized anaesthesia with epidural analgesia.**

Results: **The analysis included 46 patients in the ERP group and 45 in the standard care group. Median MFD time was reduced in the ERP group (3 days *versus* 6 days with standard care; $P < 0{\cdot}001$), as was LOS (4 days *versus* 7 days; $P < 0{\cdot}001$). The ERP significantly reduced the rate of medical complications (7 *versus* 27 per cent; $P = 0{\cdot}020$), but not surgical complications (15 *versus* 11 per cent; $P = 0{\cdot}612$), readmissions (4 *versus* 0 per cent; $P = 0{\cdot}153$) or mortality (both 2 per cent; $P = 0{\cdot}987$). QoL over 28 days was significantly better in the ERP group ($P = 0{\cdot}002$). There was no difference in patient satisfaction.**

Conclusion: **ERPs for open liver resection surgery are safe and effective. Patients treated in the ERP recovered faster, were discharged sooner, and had fewer medical-related complications and improved QoL. Registration number: ISRCTN03274575 (http://www.controlled-trials.com).**

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Introduction

Liver resection is the preferred treatment for a variety of primary and secondary liver tumours. In the UK, 1600 liver resections are performed every year for colorectal cancer metastases alone[1]. Liver surgery is associated with a high rate of postoperative morbidity ranging from 15 to 48 per cent[2,3]. The most recent figures from the UK reflect this, with a mean length of hospital stay (LOS) after liver resection reported as 10 (median 8) days[4]. There is increasing evidence that major postoperative complications may affect long-term cancer survival[5].

Enhanced recovery programmes (ERPs) have been shown to reduce morbidity and LOS following colorectal surgery[6]. It has been suggested that they may have similar benefits for other surgical specialties, including liver surgery. Despite a large volume of research examining ERPs in colorectal surgery, a recent Cochrane review stated that, although such programmes are safe, many of the trials had variable compliance with the elements of enhanced recovery and lacked sufficient outcome parameters to justify implementation of ERPs as a standard of care for colorectal resection[7]; it concluded that more trials in ERPs were warranted.

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To date there is limited evidence for the use of ERPs in liver resection surgery. Three cohort studies using retrospective controls[8–10] and one pilot study with no control group[11] have shown that ERPs are feasible and safe in both open and laparoscopic liver resection surgery. Only one randomized clinical trial (RCT) has been conducted in this area; it examined the use of laxatives within an ERP, but did not compare ERP with standard care[12]. None of these liver ERP studies measured any markers of quality of life (QoL). Therefore, a comprehensive ERP was designed, based on Enhanced Recovery After Surgery (ERAS®) Society recommendations[13], to investigate its effect on short-term recovery and morbidity following open liver resection compared with standard perioperative care in a randomized trial at the Royal Surrey County Hospital.

Methods

This RCT was conducted between March 2011 and May 2012. The trial was ethically approved by the National Health Service Research Ethics Committee, and monitored by the Trust Research and Development Department. The trial was registered at controlled-trials.com (ISRCTN03274575).

Participants and recruitment

All adult patients presenting for open liver resection at the Royal Surrey County Hospital were eligible. Patients were excluded if they underwent an entirely laparoscopic operation, needed a second concomitant procedure (for example bile duct repair), were found to be inoperable at the time of surgery, or were unable to consent.

Patients were first approached in the outpatient clinic and given a trial information sheet. A second, more comprehensive, discussion took place in the preassessment unit before consent was obtained. Patients were then randomized either to treatment within the ERP or standard care. The randomization sequence of group allocation by means of brown opaque envelopes was generated by an independent statistician from the University of Surrey.

Preoperative care

Patients randomized to the ERP underwent extra and more detailed explanation of the usual perioperative course than those in the standard care group. They received a checklist and information booklet about the operation and postoperative rehabilitation, giving them daily mobilization and nutritional goals.

Patients in the ERP group received one 125-ml bottle of Fortisip Compact® (Nutricia Clinical Care, Trowbridge, UK) three times a day for 3 days before surgery in addition to their normal diet. Patients following the ERP were also instructed to drink 800 ml preOp® (4 cartons; Nutricia Clinical Care) at 21.00 hours on the evening before, and 400 ml at 06.00 hours on the morning of surgery.

Patients in the standard care group followed the normal preoperative starvation guidelines of nil by mouth from midnight. All patients in both groups were admitted on the morning of surgery. No preoperative bowel preparation or premedication was given.

Perioperative care and anaesthesia

Both groups had the same standardized anaesthetic. Anaesthesia was induced with 2–4 mg/kg propofol, 2–3 μg/kg fentanyl and 0·15–0·30 mg/kg cisatracurium. The trachea was intubated and the lungs ventilated mechanically. Anaesthesia was maintained with sevoflurane in oxygen-enriched air, together with intravenous remifentanil (0·05–0·10 μg per kg per min), phenylephrine (0·05–0·20 μg per kg per min to maintain mean arterial blood pressure above 55 mmHg) and glyceryl trinitrate (1–5 mg/h to maintain central venous pressure at 0–2 mmHg). Routine antibiotic prophylaxis was administered.

A thoracic epidural (between levels T10 and T6) was placed in all patients for postoperative analgesia. Patients received 10 ml of 0·125 per cent levobupivacaine via the epidural catheter as a bolus at the start of the operation, followed by an infusion of 0·1 per cent levobupivacaine and 2 μg/ml fentanyl that was continued into the postoperative period.

Normothermia was achieved during surgery with a forced-air warming blanket. Intermittent pneumatic leg compression devices were applied to all patients. Nausea and vomiting were treated initially with 25 mg intramuscular or intravenous cyclizine, or 4 mg intravenous ondansetron if this failed.

Surgical technique

All patients had open surgery performed by one of three consultant surgeons. A right subcostal incision with xiphisternal extension was used. All surgical procedures were performed in a similar way, with transection of the liver parenchyma by an ultrasonic dissection technique using the Cavitron Ultrasonic Surgical Aspirator (CUSA®; ValleyLab, Boulder, Colorado, USA). The exact procedure and the need for Pringle manoeuvre was decided by the

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individual operating surgeon. Routine abdominal drains were avoided and only placed if deemed necessary by the operating surgeon. No perioperative fluids were administered until hepatic resection had been completed and haemostasis obtained. Patients in both groups then received 1000 ml compound sodium lactate (Hartmann's solution; Baxter, Norfolk, UK) for initial intravenous fluid resuscitation; all patients then received a further 500 ml of 6 per cent Volulyte® (Fresenius Kabi, Runcorn, UK), a hydroxyethyl starch.

Postoperative care

Immediately after the operation all patients were extubated, and transferred to a level 2 high-dependency unit for further observation. Patients in the ERP group received fluid resuscitation and additional monitoring using the LiDCOrapid™ (LiDCO, Cambridge, UK) and goal-directed fluid therapy (GDFT) for 6 h after hepatic resection (*Fig. S1*, supporting information). This involved 250-ml intravenous boluses of colloid (6 per cent Volulyte®) to maximize stroke volume, in accordance with the protocol. The LiDCOrapid™ is an uncalibrated system that uses a specific algorithm from the pulse power analysis of the arterial waveform to calculate the stroke volume. This is based on the principle that fluctuations in blood pressure about the mean are directly proportional to the stroke volume[14]. After the 6 h of GDFT, a maintenance fluid infusion of compound sodium lactate was started, at a rate of 1–2 ml per kg per h. Oral intake was encouraged and maintenance fluid was stopped as soon as adequate intake was achieved.

Patients in the standard care group received fluid optimization by the admitting intensive care team, using traditional markers of hypovolaemia, such as pulse rate, central venous pressure, urine output, arterial lactate and mixed venous saturations from the central line. Maintenance fluids were then started at 1–2 ml per kg per h and continued until oral intake was satisfactory.

All patients were allowed to eat and drink a normal diet. However, patients on the ERP were encouraged to take oral supplements (Fortisip Compact®) immediately on waking. A multidimensional approach to prevent ileus was adopted for those in the ERP group, by avoiding intravenous opioids and excess intravenous fluids, in accordance with the ERAS® Society guidelines[13].

After surgery patients in the ERP group received physiotherapy twice a day (compared with the standard treatment of once a day), until they were deemed independently mobile. They were encouraged to mobilize as soon as possible. Patients in the standard care group were mobilized by either the bedside nurse or physiotherapist. All patients received deep vein thromboembolism prophylaxis after operation.

In the ERP group oral paracetamol (1 g four times daily, reduced in patients with extended right-sided resections) and tramadol hydrochloride (50–100 mg four times daily) were started on the morning after surgery. Patients in the standard care group were given additional oral analgesics only if they requested them. On the morning of the second postoperative day (POD), patients in the ERP group received a bolus dose of 3 mg diamorphine via the epidural catheter before its removal by the bedside nurse. Central venous and urinary catheters were removed within 4 h of the epidural being removed. Abdominal drains were usually removed on day 1 or 2 depending on clinical need. Oral morphine was prescribed for breakthrough analgesia as required. The epidural catheter in the standard care group was managed by an acute pain team and was removed on POD 3 or 4, according to the usual protocol. All catheters and drains were removed as directed by the surgical team. The ERP and standard care are summarized in *Table 1*.

Primary outcome measures

LOS was measured from time of surgery to day of discharge. Patients were deemed to be medically fit for discharge when they met certain criteria, as judged daily by an independent assessor who was blinded to the patient group allocation and unaware of the ERP. These criteria were: good pain control with oral analgesia, tolerance of solid food, independently mobile, normal or decreasing serum bilirubin level, and willingness of the patient to be discharged.

Secondary outcome measures

Pain scores were measured daily using a visual analogue scale (VAS) ranging from 0 to 10. Morbidity was calculated as the percentage of patients with at least one complication after surgery. General complications were defined using the Postoperative Morbidity Survey[15]. Complications were graded according to the Dindo–Clavien classification[16]. Mortality was defined as death in hospital or within 30 days after surgery. Other measures included volume of intravenous fluid administered in the first 6 and 24 h after surgery, and time to return of bowel sounds, passage of flatus, tolerance of a full diet, bowel opening and mobilization.

Patients completed the validated EQ-5D™ (EuroQol Group, Rotterdam, The Netherlands)[17] QoL measure in the preassessment clinic after giving informed consent,

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Table 1 Summary of enhanced recovery programme and comparison with standard care

	ERP	Standard care
Before surgery	Information and education, including mobilization and dietary goals	NA
	Oral nutritional supplements	NA
	Carbohydrate drink	NA
During surgery	Standard anaesthetic protocol and surgical management	Standard anaesthetic protocol and surgical management
	Thoracic epidural for postop. analgesia	Thoracic epidural for postop. analgesia
	All patients extubated and taken to level 2 HDU	All patients extubated and taken to level 2 HDU
POD 0	Eat and drink normally	Eat and drink normally
	Oral nutritional supplements	NA
	Goal-directed fluid therapy for 6 h to optimize stroke volume	Fluid resuscitation to standard markers: CVP, urine output, lactate, mixed venous saturations
	LiDCOrapid™ — 250 ml colloid boluses	Fluid therapy at discretion of intensive care team
	Chest physiotherapy	NA
POD 1	Physiotherapy/mobilization twice daily	Physiotherapy once daily
	Stop i.v. maintenance fluid	Fluid therapy at discretion of intensive care team
	Oral nutritional supplements	NA
	Eat and drink normally	Eat and drink normally
POD 2	Diamorphine 3 mg via epidural	NA
	Epidural removed in the morning, or stopped and capped off if INR $\geq$ 1·5	Epidural managed by acute pain team
	Regular oral analgesics and oral morphine as needed	NA
	Physiotherapy/mobilization twice daily	Physiotherapy once daily
	Urinary catheter removed 4 h after epidural	NA
	Removal of surgical drains (if appropriate)	Removal of surgical drains (if appropriate)
	CVC removed	CVC removed at discretion of surgical team
	Blinded assessment of discharge criteria	Blinded assessment of discharge criteria
POD 3 (+4)	Physiotherapy/mobilization twice daily	Epidural managed by acute pain team; usually removed on POD 3 or 4
	Home if meets blinded assessment of discharge criteria	Urinary catheter removed 12 h after epidural in accordance with current guidelines
	Blinded assessment of discharge criteria	Blinded assessment of discharge criteria

ERP, enhanced recovery programme; NA, not applicable; HDU, high-dependency unit; POD, postoperative day; CVP, central venous pressure; i.v., intravenous; INR, international normalized ratio; CVC, central venous catheter.

and on POD 2, 3, 5, 7, 10, 14 and 28. The measure consists of a descriptive system and a VAS. The descriptive system contains the dimensions mobility, self-care, usual activities, pain/discomfort and anxiety/depression, from which an overall health value index can be calculated (range −0·59 to +1·00). With repeated EQ-5D™ measures taken in the postoperative period, differences between groups in health-related QoL were calculated using the area under the curve (AUC) method. The VAS records the patients self-rated health state, on a scale from 0 to 100. A satisfaction questionnaire was filled out by patients at home after discharge, and included questions on pain management, expectations regarding timing of discharge and mobilization.

Statistical analysis

The sample size calculation was based on the level of variation (mean(s.d.) 9·21(4·95) days) of postoperative LOS determined by retrospective audit of all patients undergoing liver resection at the Royal Surrey County Hospital in the previous 12 months. It was assumed that a clinically significant reduction in LOS would be 3 days. The sample size was calculated with a power of 80 per cent using a two-sided two-sample Student's *t* test. A minimum of 89 patients was calculated to be required (45 in each group).

Continuous data with a normal distribution were statistically tested for group differences using a two-sample Student's *t* test. Data without a normal distribution were analysed using the Mann–Whitney *U* test. Fisher's exact test or χ^2 test was used for analysis of dichotomous secondary outcome measures. Statistical analyses were performed with SPSS® for Windows® version 19 (IBM, Armonk, New York, USA).

Results

A total of 104 consecutive patients were enrolled in the trial. Thirteen patients were withdrawn after randomization because of changes to their original oncological

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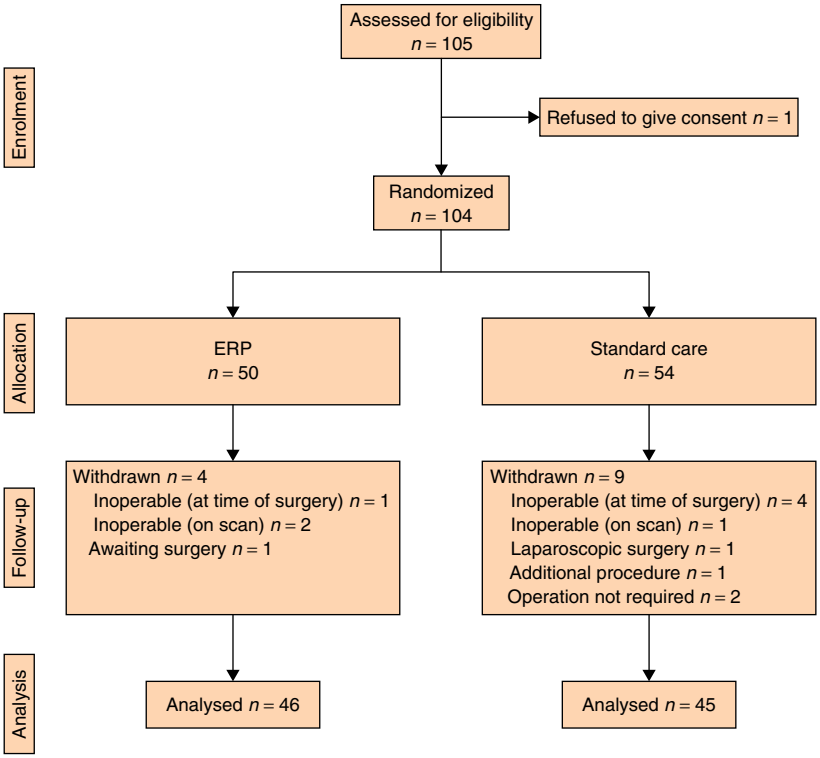

Fig. 1 CONSORT diagram for the trial. ERP, enhanced recovery programme

staging. They either underwent additional procedures, were inoperable at the time of surgery, or had a laparoscopic resection (*Fig. 1*). Ninety-one patients completed the study, 45 who received standard care and 46 treated within the ERP.

Patient characteristics, preoperative risk scores and surgical data are shown in *Table 2*. Patients in the ERP group had higher Portsmouth modification of the Physiological and Operative Severity Score for the EnUmeration of Mortality and morbidity (P-POSSUM) operative severity scores, reflecting more major resections in this group ($P = 0{\cdot}012$). More patients in the ERP presented with colorectal metastases ($P = 0{\cdot}021$) and correspondingly more patients had received preoperative neoadjuvant chemotherapy ($P = 0{\cdot}021$).

Time to being medically fit for discharge was significantly reduced in the ERP group compared with the standard care group (median (interquartile range) 3 (3–4) *versus* 6 (6–7) days; $P < 0{\cdot}001$) (*Fig. 2*). Actual LOS (including readmissions) was also significantly reduced in this group (4 (3–5) *versus* 7 (6–8) days; $P < 0{\cdot}001$) (*Fig. 2*).

Overall morbidity and complication rates tended to be reduced in the ERP group (17 *versus* 31 per cent) but this did not reach statistical significance ($P = 0{\cdot}126$). Liver surgery-specific complication rates were similar in both groups (15 *versus* 11 per cent; $P = 0{\cdot}612$) (*Table S1*, supporting information). However, significantly fewer patients in the ERP group had any general complication (3 *versus* 12 patients; $P = 0{\cdot}020$) (*Table S2*, supporting information). The total numbers of general complications were also reduced from 20 in the standard care group to only four in the ERP group ($P = 0{\cdot}009$).

Two patients in the ERP group were readmitted (both for abdominal collections) compared with none who received standard care, but this was not significant ($P = 0{\cdot}153$). There was one death in each group ($P = 0{\cdot}987$). Both deaths resulted from postoperative small liver syndrome in patients who had undergone extensive preoperative neoadjuvant chemotherapy.

There was only one epidural failure; a patient in the standard care group required conversion to morphine patient-controlled analgesia. Forty-four of 46 patients in the ERP group followed the planned protocol of stopping the epidural infusion on POD 2. Two patients in this group with preoperative chronic pain syndromes kept the epidural in place for longer. Pain scores measured daily showed no difference between the two groups, except on POD 2 when mean(s.d.) pain scores were significantly

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Table 2 Patient demographics and operative details

	ERP ($n = 46$)	Standard care ($n = 45$)
Age (years)*	64 (27–83)	67 (27–84)
Sex ratio (M : F)	31 : 15	23 : 22
Body mass index (kg/m^2)†	25·6(5·0)	26·9(4·4)
ASA fitness grade		
I	0	2
II	43	38
III	3	5
Diagnosis		
Colorectal metastases	35	26
Other metastases	10	10
Benign disease	1	9
Neoadjuvant chemotherapy	36	25
P-POSSUM†		
Physiological score	16·4(3·4)	16·8(3·6)
Operative severity score	19·4(3·7)	17·1(4·8)
Operation		
Major resection (≥ 3 segments)	21	12
Minor resection	25	33
Specimen weight (g)*	373·3 (156·3–780·5)	179·5 (69·6–606·3)
Blood loss (ml)*	350 (174–900)	340 (150–645)
Need for blood transfusion	7	3
Death	1	1

*Values are median (interquartile range) and †mean(s.d.). ERP, enhanced recovery programme; ASA, American Society of Anesthesiologists; P-POSSUM, Portsmouth modification of the Physiological and Operative Severity Score for the EnUmeration of Mortality and morbidity.

lower in the ERP group (2·5(1·4) *versus* 3·3(2·0); $P = 0·044$) (*Fig. S2*, supporting information).

Total intravenous fluids given in the first 6 and 24 h were similar in the ERP and standard care groups (6 h: median 2750 *versus* 2550 ml, $P = 0·071$; 24 h: 4557 *versus* 4422 ml, $P = 0·535$). Significantly more colloid was used in the first 6 h after the operation in the ERP group as part of GDFT (median 1500 *versus* 1000 ml; $P < 0·001$). Patients in the ERP group resumed oral intake sooner after surgery (median 115 *versus* 330 min; $P < 0·001$) and drank more in the first 24 h (1375 *versus* 810 ml; $P < 0·001$). All patients were able to tolerate an oral diet by POD 1. However, one patient developed an incarcerated port-site hernia from a previous laparoscopic procedure on POD 5, and was temporarily unable to tolerate an oral diet.

Bowel sounds returned sooner ($P < 0·001$), flatus passed earlier ($P = 0·008$) and bowels were opened sooner ($P = 0·001$) in the ERP group (although 19 patients in the ERP group had been discharged home before the bowels were opened, compared with 7 in the standard care group).

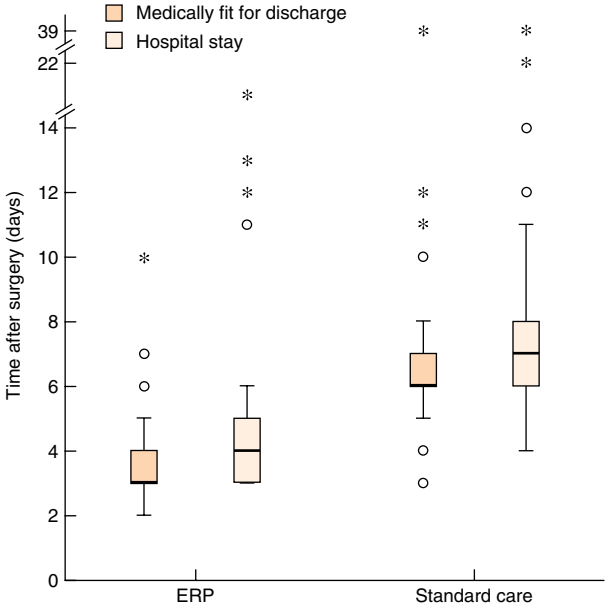

Fig. 2 Comparison of time after surgery until medically fit for discharge and length of hospital stay between patients who were treated according to an enhanced recovery programme (ERP) and those who received standard care. Median (bold line), interquartile range (box) and range not including outliers (error bars) are shown. Outliers (more than 1·5 box lengths) and extreme outliers (more than 3 box lengths) are represented by circles and asterisks respectively. Both, **b** $P < 0·001$ (Mann–Whitney U test)

Almost a third of patients in the ERP group (13 of 46) were independently mobile on the morning of POD 2 and more than three-quarters (37 of 46) by POD 3; in contrast, only four of 45 patients receiving standard care were independently mobile on POD 3 ($P < 0·001$).

There were 19 enhanced recovery elements used in this programme; however, 13 of these also comprised part of the previous standard care. For each of these elements there was a high compliance rate (*Table 3*).

In both groups the QoL measures showed an initial reduction from baseline, as expected after surgery (*Fig. 3*). There was a significant difference in QoL between the two groups during the 28 days after surgery, as measured by the multidimensional health value index. The median AUC was 37·2 for the ERP group compared with 35·6 for the standard care group ($P = 0·002$). There was no significant difference in the EQ-VAS scores, reflecting the patient's own health perception. In addition, there was no difference in satisfaction rates between groups. The questionnaire included questions about timing of discharge ($P = 0·318$), quality of pain control ($P = 0·729$) and whether patients started mobilizing at the correct time ($P = 0·627$).

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Table 3 Nineteen enhanced recovery elements based on recent Enhanced Recovery After Surgery Society recommendations[13]

	ERP		Standard care	
	Element present	No. in EFP group who followed element	Element present	No. in standard care group who followed element
Preop. information, education, counselling + daily goals	Yes	46	No	0
Preop. physiological optimization	Yes	46	Yes	45
Avoid preop. bowel preparation	Yes	46	Yes	45
Preop. fasting + carbohydrate drink up to 2 h before surgery	Yes	46	No	0
Avoid anaesthetic premedication	Yes	46	Yes	45
Prophylaxis against thromboembolism	Yes	46	Yes	45
Antimicrobial prophylaxis	Yes	46	Yes	45
Standard anaesthetic protocol	Yes	46	Yes	45
PONV — multimodal approach	Yes	46	Yes	45
Avoid nasogastric tube	Yes	46	Yes	45
Prevent intraop. hypothermia	Yes	46	Yes	45
Periop. fluid management — goal-directed fluid therapy	Yes	46	No	0
Avoid routine surgical drainage	Yes	46	Yes	45
Urinary drainage: 1–2 days only	Yes	30	No	0
Prevention of ileus — multimodal approach	Yes	46	Yes	44
Postop. analgesia — thoracic epidural (avoid i.v. opiates)	Yes	46	Yes	44
Periop. nutritional care (supplements)	Yes	46	No	0
Postop. glucose control	Yes	46	Yes	45
Early mobilization — intensive physiotherapy (twice daily)	Yes	46	No	0
Overall	19 of 19		13 of 19	

ERP, enhanced recovery programme; PONV, postoperative nausea and vomiting; i.v. intravenous.

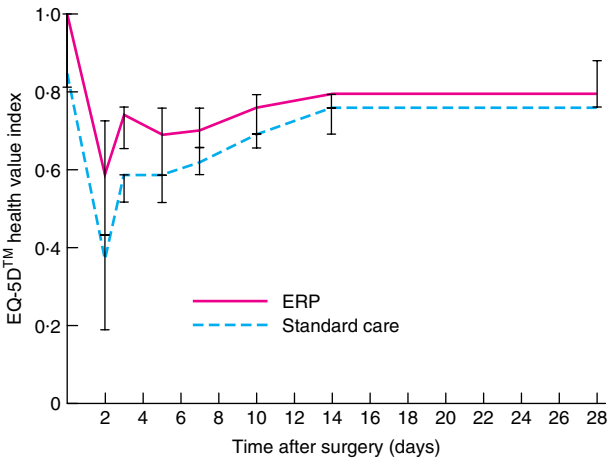

Fig. 3 Comparison of median EQ-5D™ health value index scores between patients who were treated according to an enhanced recovery programme (ERP) and those who received standard care. Error bars represent 95 per cent confidence intervals

Discussion

This RCT has demonstrated the efficacy of a specifically designed ERP in reducing both the time until being medically fit for discharge and LOS by 3 days in patients undergoing open liver resection. This is in keeping with previous studies on enhanced recovery in open or laparoscopic liver resection[8–10]. In the present study a third of patients in the ERP group left hospital on POD 3.

Interestingly, LOS in the standard care group was also decreased compared with historical data[3]. This could be due to changes in culture within the authors' unit, with healthcare professionals becoming more familiar with the principles of enhanced recovery resulting in alterations to standard care. Additionally, there may have been a 'Hawthorne effect'[18], whereby patients altered their behaviour because they were participating in a trial, accompanied by changes in behaviour of the care givers.

Although the total amount of intravenous fluids administered in the first 6 and 24 h was similar in both groups, the ratio of fluid given was different, with patients in the ERP group receiving larger volumes of colloid. Oral intake was encouraged in the ERP, facilitating earlier discontinuation of intravenous maintenance fluid. The subsequent reduction in postoperative crystalloid administered to the ERP group may have contributed to the reduction in postoperative ileus[19]. Gustafsson and colleagues[20] compared the impact of different enhanced recovery elements in 953 patients, and found that the risk of postoperative symptoms delaying discharge increased by 16 per cent and the risk of complications by 32 per cent for each additional litre of fluid given

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during the day of operation. Targeted fluid therapy or GDFT can be used to optimize intravascular volume and therefore tissue perfusion, and may reduce LOS and postoperative complications after abdominal surgery[21]. This may have been particularly important in the present trial as the patients were relatively hypoperfused during liver resection.

In this trial the LiDCOrapid™ was used to monitor cardiac output and guide intravenous fluid therapy. Other trials of ERP have used transoesophageal Doppler monitoring for this purpose[22], but this is often poorly tolerated by conscious patients. The LiDCOrapid™ was used because the patients in this study were awake during the period of fluid optimization. Although the LiDCOrapid™ is uncalibrated, stroke volume optimization may still be achieved by monitoring the response to individual fluid challenges[23].

A notable finding in this trial was that, although epidural catheters were removed earlier in the ERP group (on POD 2), there was no increase in pain scores. This was probably due to early instigation of regular oral analgesia. Early removal of epidural catheters after major surgery may, if tolerated, be useful as early mobilization is a key component of ERPs, and an epidural is an impediment to this. To facilitate early mobilization, patients in the ERP group received physiotherapy sessions twice a day, compared with once in the standard treatment group. In addition, invasive tubes and catheters were removed as early as possible. This resulted in patients in the ERP group becoming independently mobile sooner than those who received standard care.

In addition to the reduced LOS, there was a trend towards a reduction in overall morbidity in the ERP group. The overall complication rate of 17 per cent within the ERP compares favourably with rates of 37·7 and 41 per cent in previous studies of enhanced recovery for open liver resection[8,9]. Complications related to liver surgery (such as persistent bile leak or transient hepatic dysfunction) are unlikely to be affected by an ERP and, in keeping with this, no differences in such complications were noted between groups. However, there was a reduction in general medical morbidity in the ERP group. A recent meta-analysis of six colorectal RCTs found a similar reduction in morbidity in the ERP group[6], but this was not confirmed in a more recent RCT[24] or previous studies of enhanced recovery in liver surgery[8–10]. Here, the overall mortality rate for both groups was 2 per cent, similar to reported rates[3,25].

The relationship between the individual enhanced recovery elements is complex and it is still unclear which are most important. The exact definition of some of the elements is also open to interpretation. Comparison between different trials can be difficult because of the different number of enhanced recovery elements used, but there is also the question of compliance with these elements in the different studies. Even in a recent RCT on enhanced recovery in colonic surgery, compliance was only around 73 per cent in the ERP group compared with 40 per cent in controls[24]. Outcomes have been shown to improve with higher rates of compliance[20], and thus the high compliance in the present trial may have contributed to the improved outcome. Interestingly, as 13 of 19 elements were already included in the standard care pathway, it appears that the six other elements had an effect in reducing postoperative medical complications. Unfortunately the reduction in morbidity cannot be attributed clearly to any one element of the ERP, such as early mobilization, use of nutritional supplements or the use of GDFT. Potentially the benefit comes through combining the elements to produce a series of 'marginal gains', and all elements must be delivered for an ERP to be fully effective[20].

Of the six individual elements that differed between the ERP and standard treatment, carbohydrate loading is one of the more extensively researched. Gustafsson and colleagues[20] showed that carbohydrate loading reduced postoperative symptoms that could delay discharge (for example nausea and vomiting) by up to 44 per cent. Insulin resistance and consequent hyperglycaemia is an independent predictor of morbidity and mortality in major surgery[26]. Carbohydrate loading can reduce insulin resistance by up to 50 per cent[27] and so may confer a major advantage.

Reducing complications may also influence longer-term outcomes, as complications after major surgery have been shown to reduce survival[28,29]. A recent editorial has also suggested that enhanced recovery may have a role in improved cancer outcomes[5], owing to changes in cell-mediated immunity and because patients may be fit enough for postoperative neoadjuvant chemotherapy more quickly.

The present RCT was not double-blinded because of the nature of the intervention, a common difficulty with research in this area. In an attempt to minimize bias, an independent blinded clinician determined whether patients met the predefined fitness for discharge criteria; this has not been done in any other published trials of ERPs.

Despite randomization, there were baseline differences between the two groups. A significantly greater proportion of patients in the ERP group had received preoperative neoadjuvant chemotherapy. Chemotherapy has two potential effects on the patient; it can cause liver parenchymal damage, increasing the risk of postoperative liver dysfunction[30], and it can reduce cardiovascular fitness and therefore physiological reserve. Patients in the ERP group

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also had higher P-POSSUM operative severity scores. In spite of these differences, patients in this group were still discharged sooner.

This study demonstrated an improvement in short-term QoL in the ERP group. A recent systematic review found that, although there was no evidence that an ERP adversely affected QoL, there was no strong evidence for an improvement either[31]. There is limited research in this area. Only ten studies were included in this review and many of them used only single-dimensional tools to measure QoL (such as fatigue scores only).

This study has demonstrated that an ERP is a safe and effective intervention for patients undergoing open liver resection surgery. A comprehensive ERP with a high level of compliance with the different elements can result in a significant reduction in LOS and fewer postoperative medical complications, together with improved short-term QoL.

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Supporting information

Additional supporting information may be found in the online version of this article:

Fig. S1 Goal-directed fluid therapy protocol

Fig. S2 Comparison of mean pain scores on postoperative day 0 to 5 between patients who were treated according to an enhanced recovery programme and those who received standard care

Table S1 Liver surgery-specific complications with Dindo–Clavien grading

Table S2 General complications with Dindo–Clavien grade

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