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REVIEW

Enhanced recovery after liver surgery

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Summary
Introduction: In a majority of cases, enhanced recovery after surgery program (ERP) leads to a reduced rate of postoperative complications and shortened hospital stays following digestive surgery. The program's preoperative, perioperative and postoperative measures are implemented by the members of a motivated multidisciplinary team. Having shown its merits in digestive surgery, ERP would be particularly useful in liver surgery due to the elevated rates of morbidity and mortality this type of operation continues to entail. The objective of this review was to evaluate the efficacy of ERP in liver surgery.
Method: This is a systematic narrative review of the literature on the efficacy of ERP in liver surgery by laparotomy or laparoscopy.
Results: Notwithstanding a number of studies ($n = 30$: 5 randomized trials, 14 cohort studies and 11 meta-analyses) less sizable than with regard to digestive surgery in general and colorectal surgery in particular, analysis of the literature confirms that in liver surgery, ERP is associated with an overall decrease in complications by 30 to 60%, but without improvement in the rates of hospital readmission and postoperative mortality. All of the studies report a reduction in average length of stay (ALOS) by 2.3 days and in functional recovery, a more objective indicator than ALOS, by 2.5 days. As of now, the economic impact of the ERP programs in liver surgery is neither positive nor negative, the above-mentioned savings being counterbalanced by heightened costs for material and equipment. Laparoscopic surgery is independently associated with better outcomes in terms of complications, functional recovery and ALOS; that is why it is important to incorporate this surgical approach in ERP as often as possible. Given a lack of robust evidence, Prehabilitation, which is a preoperative optimization process leading to improved functional reserve, has yet to be assigned a place in ERP programs pertaining to liver surgery. Possible roadblocks to application of an ERP program can be overcome through coordination by a team leader, a motivated multidisciplinary team, training courses and dedicated teaching sessions.
Conclusion: ERP is a care improvement process that has a major play to play in organization of liver surgery, and its large-scale application is to be recommended.

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Key points

- The objective of ERP is to decrease complication rates and to improve recovery. Its application in liver surgery is premised on a goodlevel of evidence.
- Implementation of an ERP program in liver surgery is associated with a decrease in morbidity ranging from 30 to 60%, and with a readmission rate similar to what has been observed in conventional management.
- Duration of hospital stay can be reduced by a mean 2.3 days, and functional recovery time by a mean 2.5 days.
- Laparoscopy should be preferred whenever possible.
- The rare published medico-economic studies have shown that ERP in liver surgery has no significant impact on costs.

Introduction

The concept of *Fast Track* or *Enhanced Recovery programme After Surgery* (ERP) was first introduced in the 1990s by H. Khelet and his colorectal surgery team, its objectives being to reduce the rate of postoperative complications and to shorten hospital stays [1]. Wishing to achieve decreased response to surgical stress and improved recovery, the program is built around a coherent sequence of preoperative, perioperative and postoperative measures based on scientific data in the literature. No single element is liable to improve surgical outcome; the key to success consists in synergy and in the sequencing of the phases of the program, one after another in the right order [1,2]. And if the program is to function effectively, with durably sound results, it behooves the multidisciplinary team working with a patient to possess complete and comprehensive vision of the care pathway and outcomes, with periodic readjustments brought on by regularly programmed audits [1,2].

For over 10 years and following publication of more than 580 studies, application of this type of program in digestive surgery has yielded a significant decrease in complication rates, more rapid functional recovery and less protracted hospital stays without heightened readmission rates [3]. Some of the reasons for improved quality of care are: the introduction of mini-invasive surgical approaches, deeper understanding of surgical stress, and optimized anesthetic care [1—3].

Since the publication of ERP recommendations for colorectal surgery, dedicated protocols for pancreatic (2012), urological (2013), gastric (2014), major gynecological (2015) and bariatric surgery (2016) have followed [1]. On the same token, several learned societies, including the French-speaking http://www.grace-asso.fr, have published recommendations specific to liver surgery; the main outlines are summarized in Table 1.

Wishing to achieve an overall synthetic vision of the results of ERP in hepatobiliary surgery, we have carried out a systematic review of the literature.

Method

In accordance with the PRISMA recommendations [6], the Pubmed and Pubmed Central data bases have been interrogated with regard to all the studies carried out over the past 10 years (2008—2018) with the following keywords: ''liver surgery'' and ''enhanced recovery after surgery''. Research activities carried out during February 2018 were updated in March 2018 (Flow chart; Fig. 1). Among the studies indexed ($n = 1009$) subsequent to elimination of duplicates and studies deemed not relevant on the basis of the title and the abstract; 5 randomized studies; 14 cohort studies (results in Table 2) and 11 meta-analyses (results in Table 3) were included.

Why ERAS in liver surgery?

Notwithstanding improved surgical techniques, as well as laparoscopic approach and anesthetic care [37], liver surgery remains a major operation with mortality ranging from 3 to 5% and postoperative morbidity from 17 to 56%, particularly in patients suffering from sarcopenia and/or underlying hepatopathy [38].

Possible pulmonary, renal or septic complications [38,39], or hepatic insufficiency can lead to longer hospitalization, additional health care (medication, laboratory or imaging examinations, re-do surgery) and increased risk of mortality at 30 days (HR = 2.96, 95% CI 1.07—8.17) [40]. All of these consequences have a direct impact on health costs.

From an oncological standpoint, complications following liver surgery (metastases, hepatocellular carcinoma...) are associated with reduced overall and disease-free survival. The activation of pro-inflammatory mediators responsible for impairment of immune response to cancer is one explanation for this phenomenon, as is delayed access to adjuvant treatment [39,41].

And yet, it is possible to implement and develop an ERP after this type of major surgery. The development of a laparoscopic approach, comprehension of the surgical stress associated with hepatic resection and optimized anesthetic care could help to minimize postoperative complications [1].

As is the case in other surgical areas, while a decrease in general complications following application of an ERP is to be expected, this does not hold true for the complications ''specific'' to liver surgery.

The particularities of ERP in liver surgery

For each protocol — and the liver is no exception to the rule — there exists a common and constant base, represented by a number of generic elements throughout the care pathway [1,42]:

- preoperative (informative consultation, reduced preoperative fasting, antibiotic or antithrombotic prophylaxis, no anxiolytic premedication);
- perioperative (short-acting anesthetic agents, suitable vascular filling, prevention of hypothermia, laparoscopic approach when medical expertise is available);
- postoperative (no gastric tube, systematic prevention of nausea and vomiting, early mobilization and refeeding, regularly programmed audits).

That much said, other elements have been added to the protocols dedicated to each specialty. Indeed, recommendations for ERP in liver surgery have incorporated the following specific elements [4,5]:

- preoperative:
  - preoperative nutrition for undernourished patients. Malnutrition is a recognized reversible risk factor for complications in liver surgery. At-risk patients (weight

Table 1 Summary of the ERP recommendations in liver surgery.

n	Element	Summary	Level of evidence	Degree of recommendation
1	Preoperative consultation	The patient should have a systematic dedicated consultation and targeted education before hepatectomy	Moderate	High
2	Preoperative nutrition	At-risk patients (weight loss > 10—15%, severe malnutrition BMI < 18.5 Kg/m^2, Albuminemia < 30 g/L) should receive nutritional correction 7 days before surgery (which can be put off for 15 days)	High	High
3	Immunonutrition	Limited evidence	Low	Low
4	Reduced preoperative fast	Preoperative fast not exceeding 6 h for solids and 2 h for liquids	Moderate	High
		Dedicated carbohydrate solution 2 h before induction to be proposed	Low	Low
5	Oral bowel preparation	Bowel preparation is not indicated	Low	Low
6	No anxiolytic premedication	Long-acting anxiolytic premedication is to be avoided. Anxiolytics with short half-life are to be preferred to anesthetic induction	Moderate	High
7	Antithrombotic prophylaxis	Low-molecular-weight heparin, 2—12 h before surgery	Moderate	High
		Intermittent pneumatic compression of the lower limbs during hepatectomy	Low	Low
8	Preoperative steroids	Metilprednysolone can be used before hepatectomy on healthy parenchyma to reduce intraoperative stress, without increasing risk of complications. To be avoided in diabetics	Moderate	Low
9	Antibiotic prophylaxis and skin preparation	Intravenous antibiotic therapy 1 h before incision (one dose)	Moderate	High
		Prophylactic postoperative antibiotic therapy not recommended		
		Detersive skin cleaning with Chlorhexidine 2% superior to iodine solution	Moderate	High
10	Incision	No recommendations. Mercedes incision to be avoided (risk of eventration)	Moderate	High
11	Mini-invasive approach	Laparoscopic surgery can be carried out by trained teams, particularly left lobectomy or resections of anterior segments	Moderate	High
12	Feeding tube (FT)	Systematic FT use increases the risk of pulmonary complications after hepatectomy	High	High
13	Systematic abdominal drainage	There exists no scientific proof for or against systematic abdominal drainage after hepatectomy	Low	Low
14	Prevention of hypothermia	Normothermia must be maintained during the hepatectomy	Moderate	High
15	Nutrition	A light meal (drink, dessert) is authorized from D1. Parenteral nutrition only in case of malnutrition or prolonged ileus (> 5D)	Early refeeding = moderate	High
			Dietary supplements = moderate	Low
			No systematic postoperative parenteral nutrition = high	High

Table 1 (*Continued*)

n	Element	Summary	Level of evidence	Degree of recommendation
16	Postoperative glucose control	Insulin treatment to maintain normoglycemia	Moderate	High
17	Prevention of gastroparesia	Greater omentum flap on left hepatectomy surface	High	High
18	Stimulation of intestinal transit	No indication	High	High
19	Early mobilization	Must be encouraged the day after the operation	Low	Low
20	Analgesia	No systematic indication of epidural anesthesia for open hepatectomies. An intrathecal infusion and a cicatricial catheter are possible alternatives	Moderate	High
21	Systematic prevention of postoperative nausea and vomiting	Multimodal approach = intravenous administration of two anti-emetic molecules	Moderate	High
22	Vascular filling	Maintenance of central venous pressure < 5 cm H_2O is recommended, and balanced crystalloids are to be preferred to saline solutions or colloids	Moderate	High
23	Audit	Regularly programmed audits increase team adhesion and improve results	Moderate	High

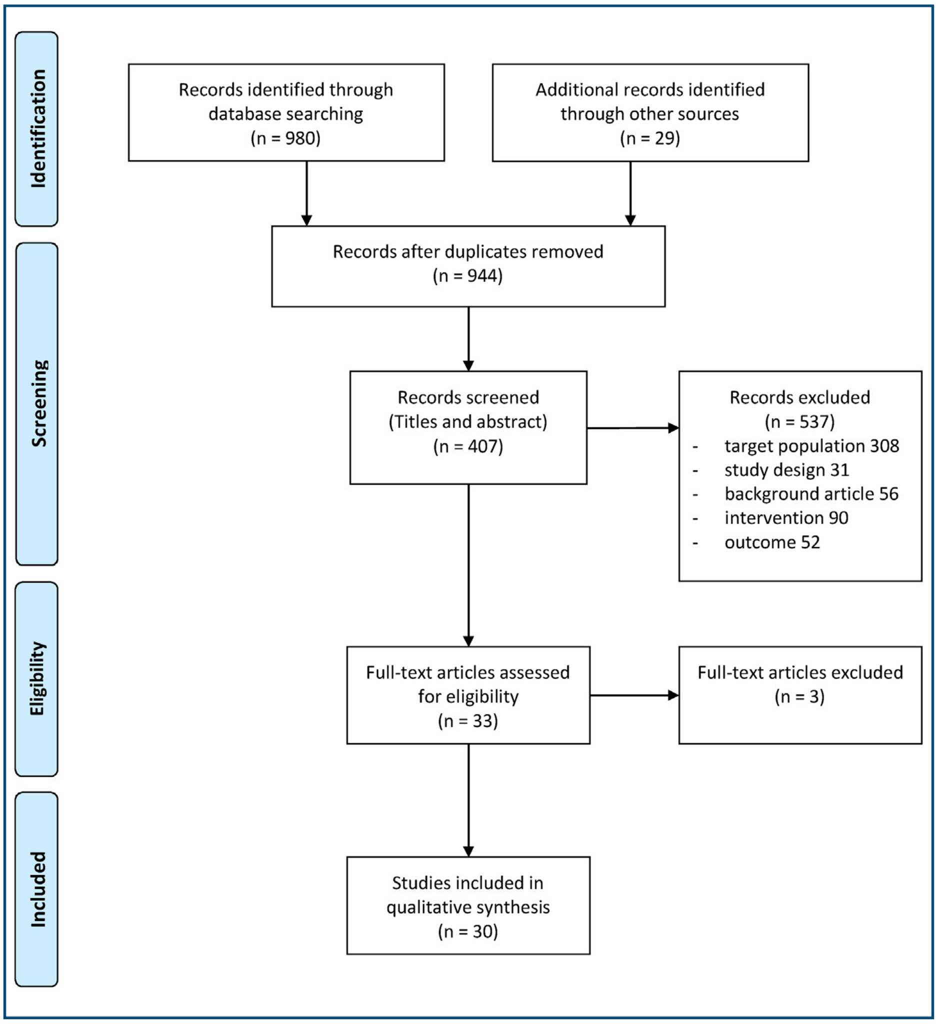

Fig. 1. Research strategy, selection of studies.

Table 2 Cohort studies and randomized trials.

Author	Year	Study	Comparison	Patients	Lap/Open	Morbidity (%)	Mortality (%)	ALOS (days)	Functional recovery (days)	Cost effectiveness
van Dam [7]	2008	Cohort	ERP vs. control	161	O	31 vs. 41	0 vs. 2	[a] 6 vs. 8		
Stoot [8]	2009	Cohort	ERP vs. control (Lap.)	26	L	1 vs. 1	0	5 vs. 7	[a] 3 vs. 5	
Sanchez-Perez [9]	2012	Cohort	ERPvs. control	43	L	12 vs. 12	0	2 vs. 3		
Schultz [10]	2012	Cohort	ERP (descriptive)	100	L-O	25	0	2 lap—5 *ouverte*		
Jones [11]	2013	RCT	ERPvs. control	91	L	15 vs. 11	2 vs. 2	[a] 4 vs. 7	[a] 3 vs. 6	
Dunne [12]	2014	Cohort	Initial vs. delayed ERP	304	L	38 vs. 38		6 vs. 6		
Dasari [13]	2015	Cohort	ERP vs. control	184	L-O	34 vs. 33	1 vs. 1	6 vs. 6	5 vs. 5	
He [14]	2015	RCT	ERP vs. control	86	L	15 vs. 16	0 vs. 0	[a] 6 vs. 10		[a] 7742yen ERAS vs. 9470yen control
Savikko [15]	2015	Cohort	ERP vs. control	134	L-O	[a] 37 vs. 71	0	[a] 4 vs. 6		
Hughes [16]	2016	Cohort	ERP (descriptive)	603	L-O	34	1.5	7		
Joliat [17]	2016	Cohort	ERP vs. control	174	L-O	[a] 49 vs. 64	1 vs. 2	[a] 8 vs. 10		42,356€ ERAS vs. 38,726€ control
Liang [18]	2016	RCT	ERP vs. control (Lap.)	187	L	[a] 33 vs. 44	0	[a] 6 vs. 10	[a] 5 vs. 8	
Page [19]	2016	Cohort	ERP vs. control	117	O	[a] 1 vs. 10		[a] 5 vs. 6		Reduction of costs ERAS group
Ratti [20]	2016	Cohort	EERP open vs. ERP lap. vs. control (HCC)	207	L-O	[a] 12—16 vs. 26		[a] 4 vs. 6	[a] 3 vs. 5	
Kaibori [21]	2017	cohort	ERPvs. control (HCC)	71	O	19 vs. 21		[a] 13 vs. 16		
Wong-Lun-Hing [22]	2017	RCT	ERP open vs. Lap (LLS)	24	L-O	8 lap vs. 36 open	0 lap vs. 9 open	[a] 4 lap vs. 4.5 open	3 vs. 3	
Fretland [23]	2018	RCT	ERP open vs. Lap (CRLM)	280	L-O	[a] 19 lap vs. 31 open	0 lap vs. 0.7 open	[a] 3.6 lap vs. 4.2 open		Same costs for the groups
Ovaere [24]	2018	Cohort	ERP vs. control	229	L-O	[a] 11 vs. 32	0 vs. 0	[a] 4 vs. 6.5		[a] 1912.2€ RAC vs. 3666.7€ control
Tufo [25]	2018	Cohort	ERP 70y vs. 80y	127	L-O	[a] 20 vs. 25.5	1.5 vs. 2.8	6 vs. 6		

Pt: patients; RCT: randomized controlled trial; vs.: versus; Lap: laparoscopy; LLS: left lateral sectionectomy/left lobectomy; y: years; ALOS: average length of stay; CRLM: colorectal liver metastasis; HCC: hepatocellular carcinoma.

[a] Statistically significant difference.

Table 3 Meta-analyses.

Author	Year	Comparison	Pt	ERP (D)	Functional recovery (D)	Morbidity (%)	Mortality (%)	Cost effectiveness
Lei [26]	2014	ERP vs. control	372	WMD = −2.32, 95% CI−3.54−1.11; *P* < 0.001		RR = 0.66, 95% CI 0.47−0.93; *P* = 0.02		
Hughes [27]	2014	ERP vs. control	838	2.5−7 vs. 3−11	3−5 vs. 5−6.7	25 vs. 31	5 vs. 7.5	
Ni [28]	2015	ERP vs. control	723	WMD = −2.77, 95% CI−3.87−1.66; *P* < 0.00001		RR = 0.66, 95%CI 0.49−0.88; *P* = 0.005		
Wu [29]	2015	ERP vs. control	1400	WMD = −2.25, 95% CI −3.10 −1.40; *P* < 0.00001		RR = 0.65, 95% CI 0.52−0.81; *P* = 0.0001	RR = 0.98, 95% CI 0.06−15.17; *P* = 0.987	WMD = −0.45, 95% CI − 0.78 −0.12; *P* = 0.007
Yang [30]	2016	ERP vs. control	580	MD = −3.31, 95%CI: −3.95−2.67; *P* < 0.00001		OR = 0.34, 95% CI 0.15−0.75; *P* = 0.008		WMD = 1.0, 95% CI 1.49−0.51; *P* < 0.0001
Song [31]	2016	ERP vs. control	634	WMD = −2.71, 95% CI−3.43−1.99; *P* < 0.00001	WMD = −2.30, 95% CI−3.77−0.83; *P* = 0.002	RR = 0.67, 95 % CI 0.48−0.92; *P* = 0.01	RR = 0.98, 95% CI 0.06−15.17; *P* = 0.99	
Ahmed [32]	2016	ERP vs. control	810	MD = −2.74, 95% CI−3.60−1.87; *P* < 0.00001	MD = −2.09, 95% CI−3.32−0.86; *P* = 0.0008	OR = 0.90, 95% CI 0.66−1.21; *P* = 0.48	OR = 0.68, 95%CI 0.14−3.34; *P* = 0.64	
Li M [33]	2016	ERP vs. control	1027	WMD = −2.24, 95% CI−3.69−0.79; *P* < 0.005		RR = 0.94, 95% CI 0.79−1.12; *P* = 0.49	RR = 0.63, 95% CI 0.19−2.15; *P* = 0.46	
Li L [34]	2017	ERP vs. control	524	WMD =2.72, 95% CI 3.86−1.57; *P* < 0.00001	WMD = 2.67, 95% CI 3.68−1.66; *P* < 0.00001	OR = 0.45, 95% CI 0.30−0.67; *P* < 0.0001		
Zhao [35]	2017	ERP vs. control	996	MD = −3.17, 95% CI−3.99−2.35, *P* < 0.001		OR = 0.52, 95% CI 0.37−0.72; *P* < 0.0001		
Wang [36]	2017	ERP vs. control	2572	WMD = −2.07, 95% CI −2.76 −1.38; *P* < 0.00001		OR = 0.65, 95% CI 0.50−0.84; *P* = 0.001	OR = 0.81, 95% CI 0.31−2.12; *P* = 0.67	SMD = −0.31, 95% CI −0.47 −0.14; *P* = 0.0002

Pt: patients; ALOS: average length of stay; OR: odds ratio; RR: relative risk; MD: mean difference; WMD: weighted mean difference; CI: confidence interval; SMD: standardized mean difference.

loss > 10—15%, severe malnutrition BMI < 18.5 Kg/m^2, Albuminemia < 30 g/L) should be eligible for nutritional correction during the 7 days preceding surgery (which can be put-off for 15 days) [43];
  - proof of the efficacy of preoperative immunonutrition is presently weak. That said, a randomized controlled multicenter study on this topic — PROPILS [44] — was completed in June 2018, inclusions of 400 patients had been planned; the results are awaited with pronounced anticipation;
- perioperative:
  - preoperative steroids (30 mg/kg, 30 min — 2 h before surgery). Administration of methylprednisolone can be carried out prior to hepatectomy on a healthy liver so as to reduce intraoperative stress, without increasing the risk of complications [45]. This measure is nevertheless to be avoided in diabetics;
  - paparotomy: The choice of incision is left to the discretion of the surgeon. That said, it is preferable to avoid ''mercedes'' incision, which is associated with a higher rate of postoperative eventration than ''J'' (Makuuchi) incision and inverted ''L''-shaped incision [46];
  - paparoscopy: The second international consensus conference on laparoscopic liver surgery [47] concluded that for minor resections, laparoscopic approach is now standardized, and that it is associated with less blood loss, shorter hospital stay and fewer complications. Major resections by laparoscopy are not yet considered as standard, and remain limited to expert centers;
  - postoperative drainage. Absence of prophylactic drainage after hepatectomy is not associated with increased risk of complications [48]. However, given the low level of evidence, no learned society has put forward recommendations for or against drainage;
  - prevention of gastric emptying disorders. In cases of hepatectomy or left lobectomy, gastric emptying disorders, which result from contact of the sectioned edge with the stomach, could be minimized by interposing a greater omentum flap;
- postoperative:
  - epidural analgesia is not more advantageous, in terms of attenuated inflammatory response or lessened pain, than multimodal anesthesia including, among other anesthetics, analgesia by cicatricial catheter [49];
  - perioperative and postoperative blood glucose surveillance. Due to the transitory resistance to insulin induced by surgical stress, hyperglycemia is frequently noted. As a result, insulin treatment must be initiated at an early phase of the hepatectomy so as to maintain normoglycemia (80—120 mg/dL). Preoperative oral carbohydrate supplementation seems to reduce resistance to insulin following hepatectomy [4].

Use of generic elements as a ''hard core'' to be supplemented and enriched by specific elements allows for elaboration of a fully complete ERP likely to dynamically evolve as scientific knowledge advances.

The results of ERP in liver surgery

Improved postoperative recovery is, by definition, central to ERP. In order for its efficacy to be assessed, recovery must be measured as objectively as possible by means of one or more indicators. In this review we shall focus on different indicators or primary endpoints such as morbidity, mortality, average length of hospital stay (ALOS) and the economic repercussions of ERS programs.

Morbidity

Sound data confirm that complications following liver surgery have a negative impact on short-term and long-term survival [39,41].

The objective of the ERP is to decrease complications by reducing response to surgical stress [1—3].

In the different published studies on liver surgery (Table 2), given the low patient population, decrease in complications is not necessarily always significant [7—25].

However, when focusing on the nine most recent studies (2016—2018), including two randomized trials, we have observed a significant decrease in complications in the ERP group (1%—49%) versus control group (10%—64%) [17—25] (Table 2).

A meta-analysis dealing with the impact of ERP following non-colorectal (bariatric, hepatic, pancreatic, esophagogastric, urogynecological) surgery in 6511 patients (3456 ERAS vs. 3055 control) highlighted a 30% decrease in complications in the ERAS group (OR 0.70, 95% CI: 0.56—0.86, P = 0.001) [50].

These results are in agreement with those of 11 more selective meta-analyses (26—36) on the impact of ERP in liver surgery in a number of patients ranging from 372 to 2575; once again, a significant decrease in complications in the ERAS group (0.34 < OR < 0.94) (Table 3) appear.

However, when these different results are observed in detail, they are not homogeneous. While all of the meta-analyses under consideration [26—36] are in agreement as to a reduction in grade I complications (according to the Clavien—Dindo definition) in the ERP group, only two of them report a reduction in more severe (Clavien—Dindo grades II—IV or II—V) complications [30,34]. Moreover, the results of these two meta-analyses should be considered with caution given (a) variable definitions of severe complications and (b) the almost exclusively Asian authorship of the studies included, a possible source of bias.

The hypotheses possibly explaining this heterogeneity are based on (a) varied selection criteria (illness severity, resection indications, surgical approach, extension of resection); (b) varied compliance (within a center or between centers) with items in the ERP and; (c) varied appraisals of morbidity.

To conclude, an overall decrease in complication rates in the ERPs is accompanied by similar readmission rates [31,36], even when analyzing the sub-groups in randomized (OR = 2.10, 95% CI = 0.31—14.24, P = 0.45) and non-randomized (OR = 0.95, 95% CI = 0.66—1.36, P = 0.79) studies [36].

Mortality

There were no significant differences between the ERP group and the control group in either the studies [7—11,13—18,22—25] or the meta-analyses [27,29,31—33,36] (Tables 2 and 3). One of the explanatory hypotheses is that mortality subsequent to a hepatectomy remains a relatively rare event. What is more, in none of the studies was mortality considered as the primary endpoint; lastly, the size of a sample allowing a major difference in mortality to be underscored would be much greater than that of all the studies published up until now.

Length of hospital stay

Length of hospital stay has long since been considered as an indirect marker of recovery and of health care system performance [51].

Generally speaking, ERP in hepatobiliary surgery is associated with pronouncedly shortened hospital stay. A recent European case-control study compared ERAS versus standard care pathways in hepatobiliary surgery in 100 patients ($n = 50$ ERP, $n = 50$ control) who were matched with regard to extent of resection, tumor location and open/laparoscopic surgical approach. In the ERP group, a reduction of 38% (2.5 days) in length of hospital stay (4 days ERAS group vs. 6.5 days control group, $P < 0.001$) was observed, but there was no significant difference in terms of postoperative complication or hospital readmission rate [24].

The meta-analyses in liver surgery taking this type of indicator into consideration reported a mean reduction in length of hospital stay of 2.07 to 3.31 days in the ERP group [26—36] (Table 3).

Using these data, we may summarize by concluding that application of an ERP program in liver surgery brings about a mean reduction in length of hospital stay (duration) of 2.3 days (Table 2). However, non-medical logistics-related factors can also determine length of hospital stay and, in some cases, delay a patient's return home. Some of the most common factors are: absence of a family network or home help services, incompatibility between the theoretical date of discharge and its organizational feasibility (no discharge over the weekend, no medical products available at the town pharmacy, etc.) [42]. Moreover, in some cases a patient may fulfill the existing discharge criteria but experience ''cultural'' anxiety regarding a return home considered as premature [42,51]. The time interval between a patient's surgical intervention and that person's functional recovery seems to be a more objective parameter than length of hospital stay, especially insofar as logistical constraints may vary between one center or country and the next. From a medical standpoint, authorization for discharge (on medical indication) is justified when the listed consensual criteria for functional recovery [52,53] have been fulfilled.

Functional recovery

Two studies that have considered functional recovery time as an evaluation criterion report different results. A first cohort study of 184 patients comparing the periods before and after initiation of an ERP failed to show differences in either functional recovery time (5 vs. 5 days, NS), or length of hospital stay (6 vs. 6 days, NS) [13]. By contrast, a second randomized controlled study of 91 patients comparing an ERP to a control group with a standard program showed a 50% reduction in functional recovery time (3 vs. 6 days, $P < 0.001$) [11].

While the first study [13] did not specify the list of criteria for authorized discharge, the second study [11] applied the following criteria:

- good tolerance of oral nutrition;
- good pain control by oral analgesics;
- independent mobilization;
- normal or improving bilirubin levels;
- the patient's wish for discharge from hospital.

The two meta-analyses employing this indicator reported a relative difference in mean functional recovery time of −2.30 days, (95% CI −3.77 −0.83; $P = 0.002$) [31] and − 2.67 days (95% CI −3.68—1.66; $P < 0.00001$) [34] in favor of the ERP group.

''Supplementary'' hospitalization time is defined as the difference between functional recovery time and actual length of hospital stay. In the Orange II trial (left lobectomy: laparoscopic vs. open surgery), it averaged 20 to 40%, and was attributed to logistical reasons in 38 to 46% of cases, and to medical reasons in 8 to 15% [22].

Economic impact

ERP often bring about health care savings in digestive surgery [53], which may be explained by less time spent in ICUs, reduced consumption during medical treatments (drainages, intravenous therapies, etc.) and a lessened need for biological and imagery-based examinations [17], which may be associated with a lower rate of complications and/or standardized care pathways [17].

In hepatobiliary surgery, on the other hand, up until now ERP has shown no significant impact on the aforementioned medico-economic aspects.

A study carried out in the United States focusing on reduction of unnecessary expenses and wasted resources demonstrated that ERP implementation in liver surgery was associated with a 41% decrease of the additional costs inherent to laboratory examinations and a 22% diminution of expenses related to medical treatment [19].

However, two recent European studies failed to observe any overall economic effect [17,24]. Detailed analysis paradoxically showed an increase in costs incurred during the intraoperative period, the augmentation being due to a heightened percentage of operations performed by laparoscopy [17,24] and to use of an ultrasound dissector (Cavitron Ultra Sound Aspirator: CUSA) [24] in the ERP group. Cost reduction during the postoperative period in the ERAS group may be attributed to shortened hospital stays and lessened complications; so it is that the balance sheet was at the ''break-even point'', notwithstanding the expenses necessarily entailed by ERP implementation.

One must not forget that whether in the operating theater or in intensive care, length of hospital stay is strongly contingent on the habits prevailing in different centers and countries. That is why the most relevant indicator is not absolute difference, but rather relative difference before vs. after implementation [17].

Even though three meta-analyses pertaining to 580, 1400 and 2572 patients respectively reported a significant reduction of hospitalization costs [29,30,36] in the ERP group, interpretation of these findings should take into account the geographical heterogeneity of the studies (Asia, Europe, the United States) and the inclusion of patients operated laparoscopically, a confounding factor for cost increase.

To sum up, only a small number of the randomized controlled studies on ERPs have dealt with the relevant economic data, and they are marked by pronounced methodological biases [53].

The role of laparoscopy in ERPs

Taken alone, when compared with open surgery, mini-invasive surgery is associated with more rapid recovery, which is largely explained by reduced inflammatory response [54].

In digestive surgery, several studies have focused on the role of laparoscopy in an ERP. In a review of the literature, it was found that laparoscopically operated patient groups in an ERAS program had less lengthy hospital stays and lower rates of readmission at 30 days [42].

In hepatobiliary surgery, a study of the Orange II trial [22] comparing mini-invasive vs. open surgical approaches in left lobectomy and postulating functional recovery as the primary endpoint in an ERP was discontinued due to insufficient inclusion; on the one hand, the investigators noted that ''keyhole'' surgery was preferred in 74% of cases; on the other hand, before the end of the study the surgical community was convinced of the advantages of laparoscopy and did not wish to keep on randomizing the two types of approach.

A second randomized controlled trial involving 280 patients (the OSLO-COMET Trial) and comparing laparoscopic to open surgery in management of liver metastases in an ERP highlighted a 12% reduction in postoperative complications (95% CI: 1.67—21.8, $P = 0.021$) in the mini-invasive group [23]. It should be noted that in this superiority trial, comparison pertained not to the ERP, which was applied in the two arms of the trial, but rather to the chosen surgical approach (laparoscopy versus laparotomy).

A meta-analysis comparing ERP versus standard management in hepatobiliary surgery showed a reduction in length of hospital stay in the sub-group of ERAS patients having undergone laparoscopy (WMD = −3.64, 95% CI = −4.63 to −2.64, $P < 0.00001$) as compared to an ERP sub-group having undergone laparotomy (WMD = −1.79, 95% CI = −2.52 to − 1 .06, $P < 0.00001$) [36].

Independently of the specific weight of the ERP or of care pathway standardization, the observed benefits finally remain the same: better outcomes and improved recovery. That is why it matters to incorporate laparoscopy into ERAS to the greatest possible extent [17].

Prehabilitation

Prehabilitation represents a proactive process of preoperative optimization, which begins with disease diagnosis and continues up until an operation, the objective being to ameliorate functional reserves in the perspective of surgery [55,56].

Known Prehabilitation measures include physical activity, nutritional support and/or immunonutrition, correction of anemia and psychological optimization. And as is the case with ERP, when each of these interventions was tested alone (unimodal treatment), results were mixed.

Up until now, only one single blind randomized controlled trial in liver surgery testing the effect of 4 weeks of physical activity versus control on 35 patients ($n = 16$ control group, $n = 19$ experimental group) has reported improved cardiopulmonary resistance to effort in the Prehabilitation arm. However, no difference was shown between the two groups in rate of postoperative complications or length of hospital stay [57].

To conclude, up until now no study has been published on multimodal Prehabilitation in liver surgery. Moreover, the level of evidence derived from the studies in digestive surgery favorable to Prehabilitation remains at an early stage; sounder results are awaited before Prehabilitation measures are incorporated into ERPs.

Obstacles to implementation of an ERP

Notwithstanding the high level of evidence of the ERPs, success of initiation, rate of compliance and speed of implementation can vary considerably from one center to the next. Some elements are simpler to put into practice than others, particularly when they are not far from daily routine; examples include prophylactic antibiotic treatment, thromboprophylaxis . . . and laparoscopic approach. Other elements are more difficult to put into practice, even when coaching has been carried out; examples include absence of intraoperative drainage, early removal of urinary catheter, absence of opioids and ''policy'' of restrictive intraoperative vascular filling [42].

Frequently cited obstacles to ERP implementation include lack of nursing staff or financial resources, difficulties in communication or collaboration between team members, and natural averseness to change. Moreover, elements of the ERAS protocol with a low level of evidence are perceived as the most difficult, and those with a high level of evidence as the least difficult to incorporate [58].

A meta-analysis of 11 studies in colorectal surgery has shown that out of 19 items in the ERP, only a mean number of 14 were actually used, and that they had little real impact on results [59]. In hepatobiliary surgery, there already exists a certain consensus with regard to elements such as a preoperative sweetened drink, absence of gastric catheter or systematic abdominal drainage, reduction of intraoperative infusions, refeeding and early mobilization, and early removal of urinary catheter [36].

The fact that compliance with the ERP has been one of the keys to its success is well-documented; for example, a French study on 1904 patients, 490 of whom had undergone colorectal surgery, showed that length of hospital stay was inversely proportional to the number of satisfactorily applied items of the ERAS program [60].

Given the obstacles to implementation and the difficulty of determining the relative importance of each component of an ERP, it has been suggested that some degree of flexibility allowing for a personalized rather than a rigorously applied protocol could be proposed as a reflection of the wide-ranging variety of patients and procedures for whom and to which an ERAS program could be applied [61]. Factors facilitating its implementation could include special coordination by a team leader, a motivated multidisciplinary team, training courses and teaching sessions dedicated to the advantages of ERP, and regularly planned audits [42,58].

Conclusions

ERP implementation in liver surgery has been shown to be associated with a significant reduction in terms of postoperative complications, functional recovery time and length of hospital stay; on the other hand, it has failed to modify readmission rates. And while the laparoscopic approach can appreciably improve the results of this type of program, the level of evidence in favor of multimodal Prehabilitation in hepatobiliary surgery has remained low.

However, these conclusions should be modulated by the facts that (a) the available meta-analyses are based on a low number of randomized and cohort studies and (b) they are geographically heterogeneous (Europe, United States, China). In other words, in order to obtain a more precise perspective on the efficacy of ERP in liver surgery, it will be necessary to carry out additional clinical studies.

Disclosure of interest

RB and OS declare that they have no competing interest.

KS declares ties of interest with the Sanofi, MSD and B-Braun laboratories.

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