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## ENHANCED RECOVERY AFTER HEPATIC SURGERY

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### Study: Clarification, Narrative systematic review

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**Key words:** Liver surgery; Hepatectomy; Enhanced recovery after surgery; systematic review

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## **ABSTRACT**

### ***Introduction:***

In a majority of cases, enhanced recovery after surgery (ERAS) 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, ERAS would be particularly useful in hepatic 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 ERAS in hepatic surgery.

### ***Method:***

This is a systematic narrative review of the literature on the efficacy of EAS in hepatic 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 hepatic surgery, ERAS 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 ERAS programs in hepatic 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 ERAS as often as possible. Given a lack of robust evidence, pre-habilitation, which is a preoperative optimization process leading to improved functional reserve, has yet to be assigned a place in ERAS programs pertaining to hepatic surgery. Possible roadblocks to application of an ERAS program can be overcome through coordination by a team leader, a motivated multidisciplinary team, training courses and

dedicated teaching sessions.

**Conclusion :**

ERAS is a care improvement process that has a major play to play in organization of hepatic surgery, and its large-scale application is to be recommended.

**KEY POINTS**

- 1) The objective of ERAS is to decrease complication rates and to facilitate improved recovery. Its application in hepatic surgery is premised on a satisfactory level of evidence.
- 2) Implementation of an ERAS program in hepatic 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.
- 3) Duration of hospital stay can be reduced by a mean 2.3 days, and functional recovery time by a mean 2.5 days.
- 4) Laparoscopy must be carried out whenever possible.
- 5) The rare published medico-economic studies have shown that ERAS in hepatic surgery has no significant impact on costs.

## **1. INTRODUCTION**

The concept of *Fast Track* or *Enhanced Recovery After Surgery* (ERAS) 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, peri-operative 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 ERAS 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 [www.grace-asso.fr](http://www.grace-asso.fr), have published recommendations specific to hepatic surgery; the main outlines are summarized in Table 1.

Wishing to achieve an overall synthetic vision of the results of ERAS in hepato-biliary surgery, we have carried out a systematic review of the literature.

## **2. 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 key words: "liver surgery" AND "ERAS" OR "enhanced recovery after surgery". Research activities carried out during February 2018 were updated

in March 2018 (Flow chart, Figure I). 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 II) and 11 meta-analyses (results in Table III) were included.

### **3. WHY ERAS IN HEPATIC SURGERY?**

Notwithstanding improved surgical techniques, as well as laparoscopic approach and anesthetic care (37), hepatic 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 hepatic 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 ERAS program 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 ERAS program is to be expected, this does not hold true for the complications “specific” to hepatic surgery.

### **4. THE PARTICULARITIES OF ERAS IN HEPATIC 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);
- *Peri-operative* (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 ERAS in hepatic 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 hepatic surgery. At-risk patients (weight loss >10-15%, severe malnutrition BMI <18.5Kg/m<sup>2</sup>, 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 immuno-nutrition 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.
- *Peri-operative*
  - 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.
  - Laparotomy: 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).
  - Laparoscopy: The second international consensus conference on laparoscopic hepatic 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).
- Peri-operative 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 ERAS protocol likely to dynamically evolve as scientific knowledge advances.

## **5. THE RESULTS OF ERAS IN HEPATIC SURGERY**

Improved postoperative recovery is, by definition, central to ERAS programs. 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.

## 5.1 MORBIDITY

Sound data confirm that complications following hepatic surgery have a negative impact on short-term and long-term survival (39,41).

The objective of the ERAS programs is to decrease complications by reducing response to surgical stress (1-3).

In the different published studies on hepatic surgery (Table II), 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 ERAS group (1%-49%) versus control group (10%-64%) (17-25) (Table II).

A meta-analysis dealing with the impact of ERAS following non-colorectal (bariatric, hepatic, pancreatic, esophago-gastric, uro-gynecological) 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 ERAS in hepatic 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 III) 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 ERAS 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 ERAS protocol and; (c) varied appraisals of morbidity.

To conclude, an overall decrease in complication rates in the ERAS programs 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).

## **5.2 MORTALITY**

There were no significant differences between the ERAS 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 II and III). 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.

## **5.3 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, ERAS 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 ( $n=50$  ERAS,  $n=50$  control) who were matched with regard to extent of resection, tumor location and open/laparoscopic surgical approach. In the ERAS 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 hepatic 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 ERAS group (26-36) (Table III).

Using these data, we may summarize by concluding that application of an ERAS program in hepatic surgery brings about a mean reduction in length of hospital stay (duration) of 2.3 days (Table II). 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.

#### **5.4 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 ERAS strategy 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 ERAS program 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: 1) good tolerance of oral nutrition; 2) good pain control by oral analgesics; 3) independent mobilization; 4) normal or improving bilirubin levels; 5) 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 ERAS 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).

#### **5.5 ECONOMIC IMPACT**

ERAS programs 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 ERAS 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 ERAS implementation in hepatic 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 ERAS 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 ERAS 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 ERAS 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 ERAS have dealt with the relevant economic data, and they are marked by pronounced methodological biases (53).

## **6. THE ROLE OF LAPAROSCOPY IN ERAS PROGRAMS**

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 ERAS

program. 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 ERAS program 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 hepatic metastases in an ERAS program highlighted a 12% reduction in postoperative complications (95%IC : 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 ERAS program, which was applied in the two arms of the trial, but rather to the chosen surgical approach (laparoscopy versus laparotomy).

A meta-analysis comparing ERAS 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 ERAS 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 ERAS program 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).

## **7. PRE-HABILITATION**

Pre-habilitation 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 pre-habilitation measures include physical activity, nutritional support and/or immunonutrition, correction of anemia and psychological optimization. And as is the case

with ERAS, when each of these interventions was tested alone (unimodal treatment), results were mixed.

Up until now, only one single blind randomized controlled trial in hepatic 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 pre-habilitation 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 pre-habilitation in hepatic surgery. Moreover, the level of evidence derived from the studies in digestive surgery favorable to pre-habilitation remains at an early stage; sounder results are awaited before pre-habilitation measures are incorporated into ERAS programs.

## **8. OBSTACLES TO IMPLEMENTATION OF AN ERAS PROGRAM**

Notwithstanding the high level of evidence of the ERAS programs, 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 ERAS program 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 ERAS protocol, 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 ERAS protocol 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 ERAS protocol, 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 ERAS, and regularly planned audits (42, 58).

## **9. CONCLUSIONS**

ERAS program implementation in hepatic 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 pre-habilitation 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 ERAS in hepatic surgery, it will be necessary to carry out additional clinical studies.

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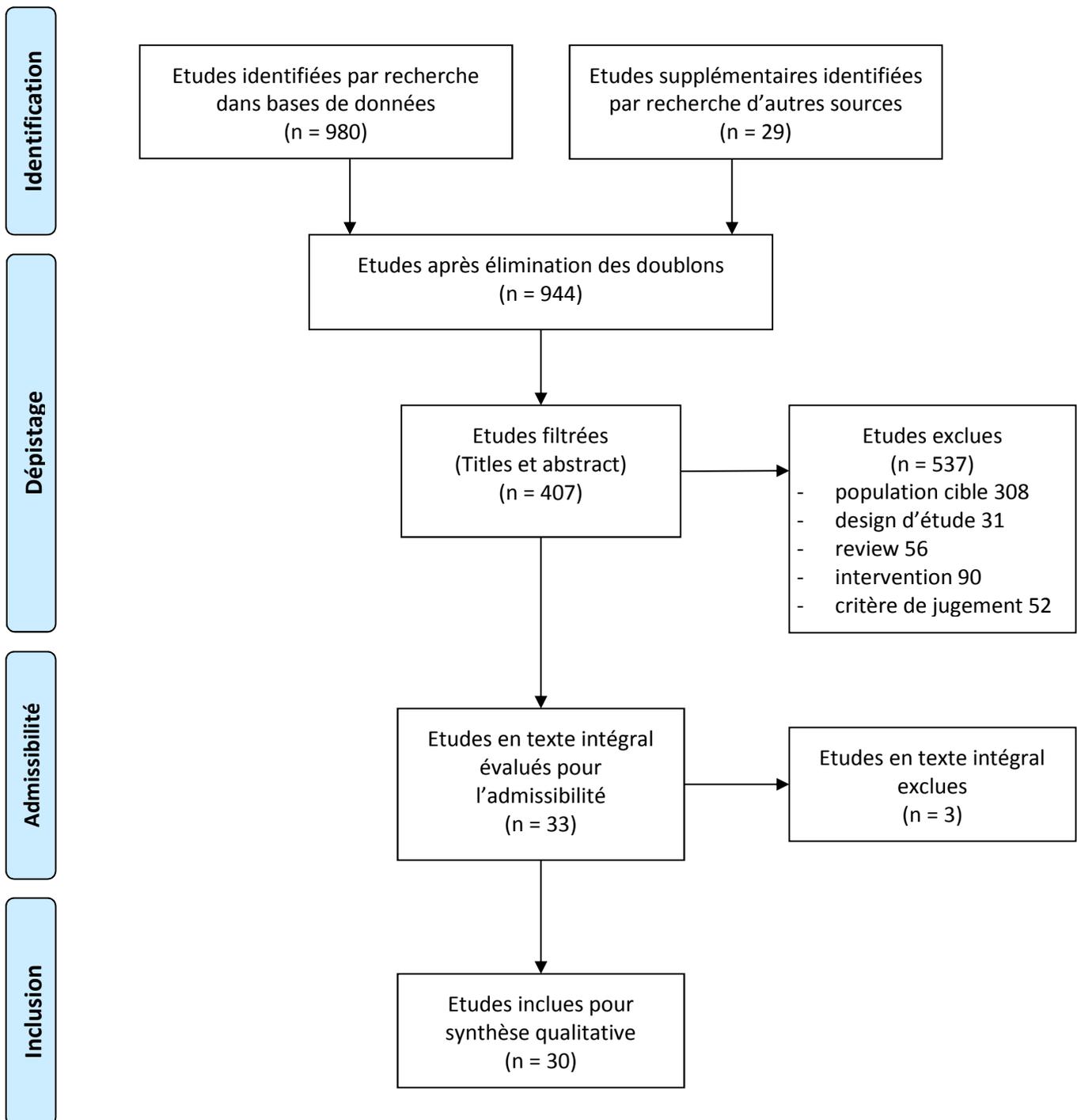
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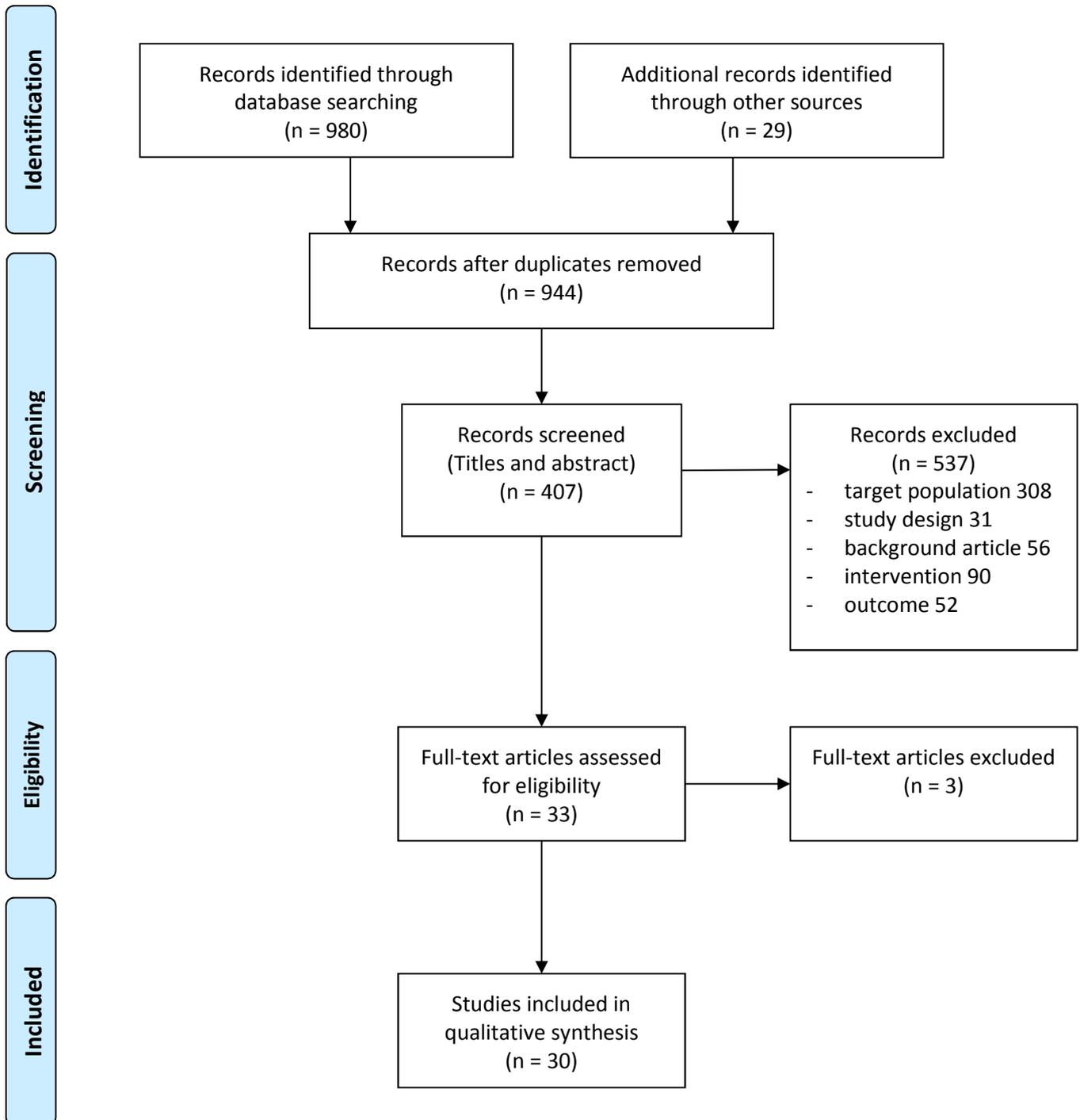
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**Fig.1 Stratégie de recherche, sélection des études**



**Fig.1 Research strategy, selection of studies**



**Table I. Summary of the ERAS recommendations in hepatic 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 <18.5Kg/m <sup>2</sup> , Albuminemia < 30 g/l) should receive nutritional correction 7 days before surgery (which can be put off for 15 days)	High	High
3	Immuno-nutrition	Limited evidence	Low	Low
4	Reduced preoperative fast	Preoperative fast not exceeding 6h for solids and 2h for liquids. .	Moderate	High
		Dedicated carbohydrate solution 2h before induction to be proposed.	Low	Low
5	Oral bowel preparation	Bowel preparation is not indicated	Low	Low
6	No anxiolytic pre-medication	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, 2-12h 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 1h before incision (one dose). Prophylactic postoperative antibiotic therapy not recommended.	Moderate	High
		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
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 <5cm H <sub>2</sub> O 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

**Table II – 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	ERAS vs control	161	0	31 vs 41	0 vs 2	* 6 vs 8		
toot [8]	2009	cohort	ERAS vs control (Lap.)	26	L	1 vs 1	0	5 vs 7	* 3 vs 5	
anchez-erez [9]	2012	cohort	ERAS vs control	43	L	12 vs 12	0	2 vs 3		
ultz [10]	2012	cohort	ERAS (descriptive)	100	L-O	25	0	2 lap - 5 ouverte		
nes [11]	2013	RCT	ERAS vs control	91	L	15 vs 11	2 vs 2	* 4 vs 7	* 3 vs 6	
inne [12]	2014	cohort	initial vs delayed ERAS	304	L	38 vs 38		6 vs 6		
sari [13]	2015	cohort	ERAS vs control	184	L-O	34 vs 33	1 vs 1	6 vs 6	5 vs 5	
He [14]	2015	RCT	ERAS vs control	86	L	15 vs 16	0 vs 0	* 6 vs 10		* 7742yen ERAS vs 9470yen control
rikko [15]	2015	cohort	ERS vs control	134	L-O	* 37 vs 71	0	* 4 vs 6		
ghes [16]	2016	cohort	ERAS (descriptive)	603	L-O	34	1.5	7		
liat [17]	2016	cohort	ERAS vs control	174	L-O	* 49 vs 64	1 vs 2	* 8 vs 10		42,356€ ERAS vs 38,726€ control
ang [18]	2016	RCT	ERAS vs control (Lap.)	187	L	* 33 vs 44	0	* 6 vs 10	* 5 vs 8	
age [19]	2016	cohort	ERAS vs control	117	0	* 1 vs 10		* 5 vs 6		Reduction of costs ERAS group
atti [20]	2016	cohort	ERAS open vs ERAS lap. vs control (HCC)	207	L-O	* 12-16 vs 26		* 4 vs 6	* 3 vs 5	
bori [21]	2017	cohort	ERAS vs control (HCC)	71	0	19 vs 21		* 13 vs 16		
ong-Lung-ing [22]	2017	RCT	ERAS open vs Lap (LLS)	24	L-O	8 lap vs 36 open	0 lap vs 9 open	* 4 lap vs 4.5 open	3 vs 3	
tland [23]	2018	RCT	ERAS open vs Lap (CRLM)	280	L-O	* 19 lap vs 31 open	0 lap vs 0.7 open	* 3.6 lap vs 4.2 open		Same costs for the groups
aere [24]	2018	cohort	ERAS vs control	229	L-O	* 11 vs 32	0 vs 0	* 4 vs 6.5		* 1912.2€ RAC vs

ufo [25]	2018	cohort	ERAS 70y vs 80y	control	127	L-0	* 20 vs 25.5	1.5 vs 2.8	6 vs 6	3666.7€ control
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patients, RCT=randomized controlled trial, vs=versus Lap= laparoscopy, LLS=Left Lateral Sectionectomy/left lobectomy, y=years, \*=statistically significant difference,  
 SS=Average length of stay, CRLM=colorectal liver metastasis, HCC=hepatocellular carcinoma

**Table III – Meta-analyses**

Author	Year	Comparison	Pt	ERAS (D)	Functional recovery (D)	Morbidity (%)	Mortality (%)	Cost effectiveness
Li [26]	2014	ERAS 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		
James [27]	2014	ERAS vs control	838	2.5-7 vs 3-11	3-5 vs 5-6.7	25 vs 31	5 vs 7.5	
Li [28]	2015	ERA 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		
Qu [29]	2015	ERAS 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
Ng [30]	2016	ERAS 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
Ng [31]	2016	ERAS 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	
Red [32]	2016	ERAS 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=.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	
M [33]	2016	ERAS 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	
L [34]	2017	ERAS 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<.00001	OR = 0.45, 95% CI 0.30-0.67; p <.00001		
Ho [35]	2017	ERAS 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< 0.00001	OR = 0.81, 95% CI 0.31-2.12; p = 0.67	SMD = -0.31, 95% CI -0.47 -0.14; p=0.0002
Ng [36]	2017	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 = 0.0001		

Patients, ALOS=average length of stay, OR=Odds Ratio, RR=Relative Risk, MD=Mean Difference, WMD= Weighted Mean Difference, CI=Confidence Interval, dms = standardized difference