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**Does enhanced recovery after surgery programs improve clinical outcomes in liver cancer surgery?**

Sánchez-Pérez B *et al*. ERAS® liver cancer surgery and outcomes

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**Abstract**

Enhanced recovery after surgery (ERAS) programs have been widely applied in liver surgery since the publication of the first ERAS guidelines in 2016 and the new recommendations in 2022. Liver surgery is usually performed in oncological patients (liver metastasis, hepatocellular carcinoma, cholangiocarcinoma, *etc.*), but the real impact of liver surgery ERAS programs in oncological outcomes is not clearly defined. Theoretical advantages of ERAS programs are: ERAS decreases postoperative complication rates and has been demonstrated a clear relationship between complications and oncological outcomes; a better and faster postoperative recovery should let oncologic teams begin chemotherapeutic regimens on time; prehabilitation and nutrition actions before surgery should also improve the performance status of the patients receiving chemotherapy. So, ERAS could be another way to improve our oncological results. We will discuss the literature about liver surgery ERAS focusing on its oncological implications and future investigations projects.

**Key Words:** Enhanced recovery after surgery programs; Liver surgery; Key components; Long-term oncological outcomes; Enhanced recovery after surgery compliance

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**Core Tip:** Improved adherence to enhanced recovery after surgery (ERAS®) protocols have reduced the occurrence of overall and major complications. The implementation of ERAS® allows early access to adjuvant therapies ERAS® protocols may reduce surgical stress and modulate immune response There is a lack of consensus regarding the cut-off point for compliance with the ERAS® components. More studies are needed to show us the real role of ERAS® in oncological results in the field of liver surgery.

**INTRODUCTION**

Enhanced recovery after surgery (ERAS®) pathways are frequently used in patients undergoing liver surgery (ERAS-LS) in high-volume hospitals. These pathways are claimed to reduce overall complications, optimize recovery, favor early discharge, and reduce medical costs[1-3].

ERAS® has also been suggested to improve long-term outcomes in cancer patients. Thus, there is evidence of improved outcomes after the implementation of ERAS® protocols in colorectal[4,5], gastric[6],urologic[7] and liver[8] surgery. However, a thorough analysis of the data available revealed some limitations, including group heterogeneity; missing information on the use of chemotherapy; differences in lines of treatment; and clinical benefits observed only in specific age groups and disease stages. These limitations raise uncertainty about the actual efficacy of ERAS® in cancer.

The purpose of ERAS® pathways is to improve patient's functional and nutritional status, reduce surgical stress, and minimize inflammatory response, thereby reducing the occurrence of complications.

Postoperative complications have a significant negative impact on cancer patients, being the most relevant that they delay access to adjuvant chemotherapy. In the case of metastatic colorectal or gastric cancer, adjuvant chemotherapy must be initiated within 6-8 postoperative weeks to optimize outcomes in terms of disease-free survival and overall survival[9,10]. Improved adherence to ERAS® protocols has been reported to reduce the occurrence of overall and major complications (Clavien-Dindo III-IV) in colorectal[2], gastric[3], and liver[1] surgery. Therefore, the implementation of ERAS® would decrease the frequency of postoperative events, thereby enabling early access to adjuvant therapies and improving long-term outcomes in cancer patients.

Another clinical benefit of ERAS® is that it minimizes inflammatory response and improves immune response. It is widely known that surgery activates a variety of mechanisms with an impact on clinical outcomes in cancer. One of these mechanisms is the reduction of cell-mediated immunity. Thus, surgery reduces the cytotoxic activity of natural killer cells and T-helper lymphocytes; moreover, surgical procedures cause a decrease in antiangiogenic factors and an increase in proangiogenic factors[11]. As a result, these effects on inflammatory and immune response have been suggested to enable the control of tumor dissemination and potentially improve long-term outcomes in cancer. However, this benefit did not translate into improved outcomes in reported series of patients undergoing liver surgery[8-12].

Although ERAS® protocols may reduce surgical stress and modulate immune response, disease-free survival and overall survival in liver surgery are known to depend on other factors. Some of these factors include tumor size, lymph node involvement, the presence of cirrhosis, biological markers, and genetic factors (KRAS, BRAF, *etc.*), to name a few[13,14].

In the light of the aforementioned, the following question arises: Does ERAS-LS actually improve clinical outcomes in cancer?

**THERE IS A RANGE OF LIMITATIONS THAT MITIGATE THE EFFECTIVENESS OF ERAS-LS IN IMPROVING OUTCOMES IN CANCER, NAMELY:**

(1) Despite ERAS guidelines published in 2016[15] and 2022[16], there is substantial variability in the number and definition[17-19] of the items used in the different ERAS-LS protocols, which hinders comparison of series.

(2) A set of key components has been established to reduce the occurrence of complications[6], including postoperative information and education; multimodal analgesia; targeted use of fluids; avoiding the use of probes and drains; and early food intake and mobilization. However, the specific impact of each of these components on clinical outcomes is still unknown. There is very scarce evidence available on the influence of these items on outcomes in cancer[20].

And (3) in addition, there is no evidence on the optimal level of adherence to the items studied (> 50%, > 70%, > 80%). These cut-off values may vary depending on the disease to be treated, with a > 70%-80% adherence having been established for liver resection in the management of hepatocarcinoma or metastatic colorectal cancer[18-21] *vs* < 50% for cholangiocarcinoma[19].

**CONCLUSION**

In conclusion, ERAS® pathways reduce the number and severity of postoperative complications[22], which enables a higher volume of patients to receive timely adjuvant therapy[23,24]. Additionally, ERAS® reduces inflammatory response and improves immune response during the immediate postoperative period. However, there is limited evidence available in the literature on its positive effects on long-term outcomes in cancer, in terms of relapse rates, disease-free survival or overall survival. Further studies are needed to shed light on the actual role of ERAS® in the clinical outcomes of cancer patients undergoing liver surgery.

**REFERENCES**

1 **Feng J**, Li K, Xu R, Feng H, Han Q, Ye H, Li F. Association between compliance with enhanced recovery after surgery (ERAS) protocols and postoperative outcome in patients with primary liver cancer undergoing hepatic resection. *J Cancer Res Clin Oncol* 2022; **148**: 3047-3059 [PMID: 35075571 DOI: 10.1007/s00432-021-03891-1]

2 **Ripollés-Melchor J**, Ramírez-Rodríguez JM, Casans-Francés R, Aldecoa C, Abad-Motos A, Logroño-Egea M, García-Erce JA, Camps-Cervantes Á, Ferrando-Ortolá C, Suarez de la Rica A, Cuellar-Martínez A, Marmaña-Mezquita S, Abad-Gurumeta A, Calvo-Vecino JM; POWER Study Investigators Group for the Spanish Perioperative Audit and Research Network (REDGERM). Association Between Use of Enhanced Recovery After Surgery Protocol and Postoperative Complications in Colorectal Surgery: The Postoperative Outcomes Within Enhanced Recovery After Surgery Protocol (POWER) Study. *JAMA Surg* 2019; **154**: 725-736 [PMID: 31066889 DOI: 10.1001/jamasurg.2019.0995]

3 **Gianotti L**, Fumagalli Romario U, De Pascale S, Weindelmayer J, Mengardo V, Sandini M, Cossu A, Parise P, Rosati R, Bencini L, Coratti A, Colombo G, Galli F, Rausei S, Casella F, Sansonetti A, Maggioni D, Costanzi A, Bernasconi DP, De Manzoni G. Association Between Compliance to an Enhanced Recovery Protocol and Outcome After Elective Surgery for Gastric Cancer. Results from a Western Population-Based Prospective Multicenter Study. *World J Surg* 2019; **43**: 2490-2498 [PMID: 31240434 DOI: 10.1007/s00268-019-05068-x]

4 **Gustafsson UO**, Oppelstrup H, Thorell A, Nygren J, Ljungqvist O. Adherence to the ERAS protocol is Associated with 5-Year Survival After Colorectal Cancer Surgery: A Retrospective Cohort Study. *World J Surg* 2016; **40**: 1741-1747 [PMID: 26913728 DOI: 10.1007/s00268-016-3460-y]

5 **Pisarska M**, Torbicz G, Gajewska N, Rubinkiewicz M, Wierdak M, Major P, Budzyński A, Ljungqvist O, Pędziwiatr M. Compliance with the ERAS Protocol and 3-Year Survival After Laparoscopic Surgery for Non-metastatic Colorectal Cancer. *World J Surg* 2019; **43**: 2552-2560 [PMID: 31286185 DOI: 10.1007/s00268-019-05073-0]

6 **Tian YL**, Cao SG, Liu XD, Li ZQ, Liu G, Zhang XQ, Sun YQ, Zhou X, Wang DS, Zhou YB. Short- and long-term outcomes associated with enhanced recovery after surgery protocol *vs* conventional management in patients undergoing laparoscopic gastrectomy. *World J Gastroenterol* 2020; **26**: 5646-5660 [PMID: 33088158 DOI: 10.3748/wjg.v26.i37.5646]

7 **Crettenand F**, M'Baya O, Grilo N, Valerio M, Dartiguenave F, Cerantola Y, Roth B, Rouvé JD, Blanc C, Lucca I. ERAS® protocol improves survival after radical cystectomy: A single-center cohort study. *Medicine (Baltimore)* 2022; **101**: e30258 [PMID: 36107599 DOI: 10.1097/MD.0000000000030258]

8 **St-Amour P**, St-Amour P, Joliat GR, Eckert A, Labgaa I, Roulin D, Demartines N, Melloul E. Impact of ERAS compliance on the delay between surgery and adjuvant chemotherapy in hepatobiliary and pancreatic malignancies. *Langenbecks Arch Surg* 2020; **405**: 959-966 [PMID: 32918147 DOI: 10.1007/s00423-020-01981-1]

9 **Petrelli F**, Zaniboni A, Ghidini A, Ghidini M, Turati L, Pizzo C, Ratti M, Libertini M, Tomasello G. Timing of Adjuvant Chemotherapy and Survival in Colorectal, Gastric, and Pancreatic Cancer. A Systematic Review and Meta-Analysis. *Cancers (Basel)* 2019; **11** [PMID: 30999653 DOI: 10.3390/cancers11040550]

10 **Kang J**, Chong SW, Park EJ, Baik SH, Lee KY. Safety and feasibility of in-hospital early chemotherapy initiation after surgery in patients with stage II-IV colon cancer. *Medicine (Baltimore)* 2019; **98**: e15371 [PMID: 31045781 DOI: 10.1097/MD.0000000000015371]

11 **Bassani B**, Baci D, Gallazzi M, Poggi A, Bruno A, Mortara L. Natural Killer Cells as Key Players of Tumor Progression and Angiogenesis: Old and Novel Tools to Divert Their Pro-Tumor Activities into Potent Anti-Tumor Effects. *Cancers (Basel)* 2019; **11** [PMID: 30939820 DOI: 10.3390/cancers11040461]

12 **Lambert J**, Mair T, Arujunan K, Shugaba A, Uwadiae H, Livesey A, Ahmad R, Sgourakis G, Gaffney C, Subar D. The effect of the enhanced recovery programme on long-term survival following liver resection for colorectal liver metastases. *Langenbecks Arch Surg* 2023; **408**: 239 [PMID: 37337084 DOI: 10.1007/s00423-023-02968-4]

13 **Nevola R**, Ruocco R, Criscuolo L, Villani A, Alfano M, Beccia D, Imbriani S, Claar E, Cozzolino D, Sasso FC, Marrone A, Adinolfi LE, Rinaldi L. Predictors of early and late hepatocellular carcinoma recurrence. *World J Gastroenterol* 2023; **29**: 1243-1260 [PMID: 36925456 DOI: 10.3748/wjg.v29.i8.1243]

14 **Li J**, Ma X, Chakravarti D, Shalapour S, DePinho RA. Genetic and biological hallmarks of colorectal cancer. *Genes Dev* 2021; **35**: 787-820 [PMID: 34074695 DOI: 10.1101/gad.348226.120]

15 **Melloul E**, Hübner M, Scott M, Snowden C, Prentis J, Dejong CH, Garden OJ, Farges O, Kokudo N, Vauthey JN, Clavien PA, Demartines N. Guidelines for Perioperative Care for Liver Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. *World J Surg* 2016; **40**: 2425-2440 [PMID: 27549599 DOI: 10.1007/s00268-016-3700-1]

16 **Joliat GR**, Kobayashi K, Hasegawa K, Thomson JE, Padbury R, Scott M, Brustia R, Scatton O, Tran Cao HS, Vauthey JN, Dincler S, Clavien PA, Wigmore SJ, Demartines N, Melloul E. Guidelines for Perioperative Care for Liver Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations 2022. *World J Surg* 2023; **47**: 11-34 [PMID: 36310325 DOI: 10.1007/s00268-022-06732-5]

17 **Burchard PR**, Dave YA, Loria AP, Parikh NB, Pineda-Solis K, Ruffolo LI, Strawderman M, Schoeniger LO, Galka E, Tomiyama K, Orloff MS, Carpizo DR, Linehan DC, Hernandez-Alejandro R. Early postoperative ERAS compliance predicts decreased length of stay and complications following liver resection. *HPB (Oxford)* 2022; **24**: 1425-1432 [PMID: 35135723 DOI: 10.1016/j.hpb.2022.01.008]

18 **Pérez Reyes M**, Sánchez Pérez B, León Díaz FJ, Pérez Daga JA, Mirón Fernández I, Santoyo Santoyo J. Implementation of an ERAS protocol on elderly patients in liver resection. *Cir Esp (Engl Ed)* 2023; **101**: 274-282 [PMID: 35918049 DOI: 10.1016/j.cireng.2022.07.019]

19 **Jongkatkorn C**, Luvira V, Suwanprinya C, Piampatipan K, Leeratanakachorn N, Tipwaratorn T, Titapun A, Srisuk T, Theeragul S, Jarearnrat A, Thanasukarn V, Pugkhem A, Khuntikeo N, Pairojkul C, Kamsa-Ard S, Bhudhisawasdi V. Compliance with enhanced recovery after surgery predicts long-term outcome after hepatectomy for cholangiocarcinoma. *World J Gastrointest Surg* 2023; **15**: 362-373 [PMID: 37032797 DOI: 10.4240/wjgs.v15.i3.362]

20 **Ripollés-Melchor J**, Abad-Motos A, Zorrilla-Vaca A. Enhanced Recovery After Surgery (ERAS) in Surgical Oncology. *Curr Oncol Rep* 2022; **24**: 1177-1187 [PMID: 35403970 DOI: 10.1007/s11912-022-01282-4]

21 **Wong-Lun-Hing EM**, van Dam RM, Heijnen LA, Busch OR, Terkivatan T, van Hillegersberg R, Slooter GD, Klaase J, de Wilt JH, Bosscha K, Neumann UP, Topal B, Aldrighetti LA, Dejong CH. Is current perioperative practice in hepatic surgery based on enhanced recovery after surgery (ERAS) principles? *World J Surg* 2014; **38**: 1127-1140 [PMID: 24322177 DOI: 10.1007/s00268-013-2398-6]

22 **Noba L**, Rodgers S, Chandler C, Balfour A, Hariharan D, Yip VS. Enhanced Recovery After Surgery (ERAS) Reduces Hospital Costs and Improve Clinical Outcomes in Liver Surgery: a Systematic Review and Meta-Analysis. *J Gastrointest Surg* 2020; **24**: 918-932 [PMID: 31900738 DOI: 10.1007/s11605-019-04499-0]

23 **Pang Q**, Duan L, Jiang Y, Liu H. Oncologic and long-term outcomes of enhanced recovery after surgery in cancer surgeries - a systematic review. *World J Surg Oncol* 2021; **19**: 191 [PMID: 34187485 DOI: 10.1186/s12957-021-02306-2]

24 **Biagi JJ**, Raphael MJ, Mackillop WJ, Kong W, King WD, Booth CM. Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. *JAMA* 2011; **305**: 2335-2342 [PMID: 21642686 DOI: 10.1001/jama.2011.749]

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