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**DOES <sup>1</sup> ENHANCED RECOVERY AFTER SURGERY (ERAS®) PROGRAMS  
IMPROVE CLINICAL OUTCOMES IN LIVER CANCER SURGERY?**

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 (ERAS®) programs; liver surgery; key components; long-term oncological outcomes; ERAS® compliance.

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**Core Tip:** 1. Improved adherence to ERAS® protocols has reduce the occurrence of overall and major complications. 2. The implementation of ERAS® allows early access to adjuvant therapies 3. ERAS® protocols may reduce surgical stress and modulate immune response 4. There is a lack of consensus regarding the cut-off point for compliance with the ERAS® components 5. 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<sup>1-3</sup>.

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<sup>4-5</sup>, gastric<sup>6</sup>, urologic<sup>7</sup> and liver<sup>8</sup> 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<sup>9-10</sup>. Improved adherence to ERAS® protocols has been reported to reduce the occurrence of overall and major complications (Clavien-Dindo III-IV) in colorectal<sup>2</sup>, gastric<sup>3</sup>, and liver<sup>1</sup> 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<sup>11</sup>. 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<sup>8-12</sup>.

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 (DFA), and genetic factors (KRAS, BRAF, etc), to name a few<sup>13-14</sup>.

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:

Despite ERAS guidelines published in 2016<sup>15</sup> and 2022<sup>16</sup>, there is substantial variability in the number and definition<sup>17-18-19</sup> of the items used in the different ERAS-LS protocols, which hinders comparison of series.

A set of key components has been established to reduce the occurrence of complications<sup>6</sup>, 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<sup>20</sup>.

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<sup>18-21</sup> versus <50% for cholangiocarcinoma<sup>19</sup>.

## **CONCLUSION**

In conclusion, ERAS® pathways reduce the number and severity of postoperative complications<sup>22</sup>, which enables a higher volume of patients to receive timely adjuvant therapy<sup>23-24</sup>. 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, <sup>2</sup> 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.

## **ACKNOWLEDGEMENTS**

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PRIMARY SOURCES

1	Tian-Gen Ni. "Enhanced recovery after surgery programs in patients undergoing hepatectomy: A meta-analysis", World Journal of Gastroenterology, 2015	20 words — 2%
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