



Letters to the Editor



Will Enhanced Recovery After Surgery Lead to Better Immunotherapy Outcomes in Cancer Patients?

Tianhang Li*

Medical School of Nanjing University, Nanjing, Jiangsu, China

Received: November 29, 2022 | Revised: December 20, 2022 | Accepted: January 31, 2023 | Published online: February 27, 2023

Promising outcomes in cancer treatment have been achieved with the rapid development of cancer immunotherapy. The application of neoadjuvant therapy based on the immune-checkpoint blockade (ICB) and conventional chemotherapy has become a complement treatment strategy for tumor surgical resection.¹ In addition, immunotherapy has emerged an adjuvant therapy for a range of cancers.² However, many factors have been reported to influence the efficacy of cancer immunotherapy, such as complex genetic heterogeneity, tumor mutational load, innate or adaptive immune resistance, and the regulatory network of the tumor microenvironment (TME).³ Nevertheless, in the context of surgical oncology, the correlation between immunotherapy efficacy and peri-operative management remains unknown.

Enhanced Recovery After Surgery (ERAS), first conceptually introduced by Henrik Kehlet in 1997, is an optimal peri-operative management pathway centered on alleviating peri-operative stress caused by surgery, early mobilization and restoration of the gastrointestinal system, and strict pain control.⁴ The ERAS approach has been shown to significantly decrease hospital stay length after surgery as well as promote a quick recovery and reduce complication incidence and treatment-related costs.^{5,6} Overall, ERAS is an integrated approach of innovative peri-operative surgical treatment and technology. Intriguingly, a range of studies have verified that the application of ERAS could play a protective role in the immune system, including inhibiting inflammatory factors^{7,8} and regulating immune cells.⁹ Considering that the effect of cancer immunotherapy, especially ICB, is dependent on reinvigoration of the immune microenvironment in both the tumor and the whole system, we hypothesize that the strict use of ERAS as the peri-operative management strategy in combination with neoadjuvant or adjuvant immunotherapy would greatly enhance the outcomes of immunotherapy, thereby leading to a better prognosis for cancer patients.

The relationship between ERAS and ICB efficacy is based on the detailed intervention behaviors in the ERAS process. As men-

tioned above, ERAS management mainly aims to inhibit surgery-induced peri-operative stress and promote early mobilization and rapid restoration of the digestive system and pain control. First, surgery-related stress is alleviated by ERAS through minimally invasive surgery and early pre-operative and intra-operative intervention of surgical adverse events. Martínez *et al.* observed differences in the immune status of colorectal cancer patients and found a greater pro-inflammatory response in patients who underwent open surgery compared to those who had laparoscopic surgery, and the recovery to baseline immune levels occurred faster in the laparoscopic surgery group compared to the open surgery group.¹⁰ Moreover, Okholm *et al.* comprehensively analyzed inflammatory responses between laparoscopic and open surgery for gastric cancer patients and found that laparoscopy-assisted gastric surgery decreased the immune response compared to open surgery.¹¹ Thus, ERAS could help restore the normal function of the immune system faster and avoid unnecessary activation of immune cells caused by surgery-related stress, which is important for promoting more efficient activation of anti-cancer immunity during ICB therapy. Second, early mobilization and rapid restoration of the gastrointestinal system are critical for maintaining adequate nutritional status and exercise levels for cancer patients. In 2017, Schmidt *et al.* proposed that increased immunological anti-cancer activity could be caused by exercise and physical activity due to an increase in the number of anti-cancer immune cells and cytokines.¹² More recently, Santos *et al.* utilized a mouse model to verify that exercise could inhibit the tumor vasculature, reprogram the TME, and enhance the anti-cancer immunity mediated by CD8⁺ T cells via CXCR3, which subsequently boosts ICB responses.¹³ Therefore, promoting early mobilization and physical activity is an efficient approach to reinvigorating anti-cancer immunity and enhancing ICB efficacy. It is important to note that surgical pain not only increases physical stress, but also causes psychological abnormalities such as depression and anxiety.^{14,15} Thus, the psychological status is another crucial element that affects the immune status of cancer patients. Both stressors and depression can decrease activation of cytotoxic T-cells and natural-killer-cells, which interferes with immune surveillance in cancer patients.¹⁶ Therefore, strict pain control in the peri-operative phase could help improve the psychological status of cancer patients and maintain anti-cancer immunity, further enhancing the efficacy of ICB.

With the rapid advancement of robot-assisted surgical systems and minimally invasive endoscopic techniques, the positive effects of ERAS in surgical oncology could be greatly magnified. In the

Keywords: ERAS; Cancer immunotherapy; Peri-operative management; ICB.

Abbreviations: ERAS, Enhanced Recovery After Surgery; ICB, immune-checkpoint blockade; TME, tumor microenvironment.

*Correspondence to: Tianhang Li, Medical School of Nanjing University, Nanjing, Jiangsu 210000, China. ORCID: <https://orcid.org/0000-0001-8741-7121>. Tel: +86-83501038, E-mail: DG20350057@smail.nju.edu.cn

How to cite this article: Li T. Will Enhanced Recovery After Surgery Lead to Better Immunotherapy Outcomes in Cancer Patients? *Explor Res Hypothesis Med* 2023; 000(000):000–000. doi: 10.14218/ERHM.2022.00122.

era of immunotherapy, ERAS may add new vitality to the optimized application of ICB for cancer patients. We expect that in the future, basic science experiments and clinical trials can address this hypothesis.

Acknowledgments

None.

Funding

None

Conflict of interest

The authors have no conflicts of interest related to this publication.

References

- [1] Forde PM, Chaft JE, Smith KN, Anagnostou V, Cottrell TR, Hellmann MD, *et al.* Neoadjuvant PD-1 blockade in resectable lung cancer. *N Engl J Med* 2018;378(21):1976–1986. doi:10.1056/NEJMoa1716078, PMID:29658848.
- [2] Rizzo A, Mollica V, Marchetti A, Nuvola G, Rosellini M, Tassinari E, *et al.* Adjuvant PD-1 and PD-L1 Inhibitors and Relapse-Free Survival in Cancer Patients: The MOUSEION-04 Study. *Cancers (Basel)* 2022; 14(17):4142. doi:10.3390/cancers14174142, PMID:36077679.
- [3] Vesely MD, Zhang T, Chen L. Resistance mechanisms to anti-PD cancer immunotherapy. *Annu Rev Immunol* 2022;40:45–74. doi:10.1146/annurev-immunol-070621-030155, PMID:35471840.
- [4] Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth* 1997;78(5):606–617. doi:10.1093/bja/78.5.606, PMID:9175983.
- [5] Ashok A, Niyogi D, Ranganathan P, Tandon S, Bhaskar M, Karimundackal G, *et al.* The enhanced recovery after surgery (ERAS) protocol to promote recovery following esophageal cancer resection. *Surg Today* 2020;50(4):323–334. doi:10.1007/s00595-020-01956-1, PMID:32048046.
- [6] Bogani G, Sarpietro G, Ferrandina G, Gallotta V, Di Donato V, Ditto A, *et al.* Enhanced recovery after surgery (ERAS) in gynecology oncology. *Eur J Surg Oncol* 2021;47(5):952–959. doi:10.1016/j.ejso.2020.10.030, PMID:33139130.
- [7] Wang G, Jiang Z, Zhao K, Li G, Liu F, Pan H, *et al.* Immunologic response after laparoscopic colon cancer operation within an enhanced recovery program. *J Gastrointest Surg* 2012;16(7):1379–1388. doi:10.1007/s11605-012-1880-z, PMID:22585532.
- [8] Liu X, Wang Y, Fu Z. Impact of enhanced recovery after surgery on postoperative neutrophil-lymphocyte ratio in patients with colorectal cancer. *J Int Med Res* 2020;48(6):300060520925941. doi:10.1177/0300060520925941, PMID:32495673.
- [9] Wang WK, Tu CY, Shao CX, Chen W, Zhou QY, Zhu JD, *et al.* Impact of enhanced recovery after surgery on postoperative rehabilitation, inflammation, and immunity in gastric carcinoma patients: a randomized clinical trial. *Braz J Med Biol Res* 2019;52(5):e8265. doi:10.1590/1414-431X20198265, PMID:31116313.
- [10] Martínez-Martínez AB, Arbonés-Mainar JM. Colorectal cancer: immune response in laparoscopic versus open colorectal surgery. *Cir Cir* 2022;90(3):295–302. doi:10.24875/CIRU.21000146, PMID:35636961.
- [11] Okholm C, Goetze JP, Svendsen LB, Achiam MP. Inflammatory response in laparoscopic vs. open surgery for gastric cancer. *Scand J Gastroenterol* 2014;49(9):1027–1034. doi:10.3109/00365521.2014.917698, PMID:24852697.
- [12] Schmidt T, van Mackelenbergh M, Wesch D, Mundhenke C. Physical activity influences the immune system of breast cancer patients. *J Cancer Res Ther* 2017;13(3):392–398. doi:10.4103/0973-1482.150356, PMID:28862198.
- [13] Gomes-Santos IL, Amoozgar Z, Kumar AS, Ho WW, Roh K, Talele NP, *et al.* Exercise training improves tumor control by increasing CD8+ T-cell infiltration via CXCR3 signaling and sensitizes breast cancer to immune checkpoint blockade. *Cancer Immunol Res* 2021;9(7):765–778. doi:10.1158/2326-6066.CIR-20-0499, PMID:33839688.
- [14] Lovich-Sapola J, Smith CE, Brandt CP. Postoperative pain control. *Surg Clin North Am* 2015;95(2):301–318. doi:10.1016/j.suc.2014.10.002, PMID:25814108.
- [15] Wang Y, Zhang Q, Dai X, Xiao G, Luo H. Effect of low-dose esketamine on pain control and postpartum depression after cesarean section: a retrospective cohort study. *Ann Palliat Med* 2022;11(1):45–57. doi:10.21037/apm-21-3343, PMID:35144397.
- [16] Reiche EM, Nunes SO, Morimoto HK. Stress, depression, the immune system, and cancer. *Lancet Oncol* 2004;5(10):617–625. doi:10.1016/S1470-2045(04)01597-9, PMID:15465465.