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LETTER TO THE EDITOR

Personalized treatment selection in colorectal cancer with peritoneal metastasis: Do we need statistically validated indicators or cultural shift?

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Abstract

The study by Wu *et al* analyzed the correlation between nutritional and inflammatory markers and prognosis in patients with colorectal cancer peritoneal metastasis. The authors propose the neutrophil-to-lymphocyte ratio (NLR) as a predictor of overall survival (OS) and developed a nomogram incorporating NLR, hemoglobin (Hb), and peritoneal cancer index (PCI) to estimate 1- and 2-year survival. Although the nomogram shows high accuracy, the group of patients analyzed is heterogeneous with respect to the surgical treatment received, and no clear definitions are given for normal Hb and there is no reason for choosing a very high PCI (≥ 20). Patient selection for cytoreductive surgery with hyperthermic intraperitoneal chemotherapy requires a multidisciplinary approach. Over-simplification of the selection pathway may deny access to curative treatments to patients who could benefit. While methodologically sound, the study does not consider the effect of treatment received on OS, thus introducing a potential bias.

Key Words: Colorectal cancer; Peritoneal metastasis; Inflammation; Nutrition; Biomarkers; Prognosis; Overall survival; Cytoreductive surgery

Core Tip: In this study, Wu conducted a single-center retrospective analysis on patients with colorectal cancer and peritoneal metastasis. Findings indicate that a high neutrophil-to-lymphocyte ratio and low hemoglobin levels are independent risk factors for poor prognosis in this population. The developed nomogram accurately predicted overall survival for this patient group, demonstrating its potential as a valuable prognostic tool for this population. Over-simplification of the selection pathway may deny access to curative treatments to patients who could benefit.

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TO THE EDITOR

We are delighted to read the high-quality article by Wu *et al*[1], published in the *World Journal of Gastrointestinal Oncology*. The aims of this paper are to investigate the correlation between nutritional and inflammatory markers and the prognosis of patients with Colo-rectal cancer peritoneal metastasis (CRC-PM). The manuscript argues for the predictive role of neutrophil-to-lymphocyte ratio (NLR) with respect to patients' overall survival (OS), based on blood sampling performed one week before surgery regardless of the treatment the patient receives. It also constructs a nomogram, built on NLR, hemoglobin (Hb) and Peritoneal Cancer Index (PCI), to predict the probability of 1- and 2-year survival in operated patients.

High NLR and low Hb were identified as independent predictive risk factors for poor prognosis in patients with CRC-PM. The established nomogram demonstrated high accuracy in predicting OS for patients with CRC-PM, indicating its potential as a valuable prognostic tool for this patient population.

Key aspects of the study

As highlighted by the authors in the introduction, treatment impacts the OS of patients: The OS of chemo-treated-only patients is 13 months while for those who received a cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) it is up to 41.7 months[2,3].

CRS + HIPEC carries an increased risk of morbidity and mortality[4]. In addition, post-operative complications, particularly severe ones, are an independent risk factor in relation to OS[5]. The author's purpose is developing methods to identify patients who are most likely to benefit from CRS + HIPEC because of its high morbidity and mortality rates. The authors support their decision to use "prognostic nutritional indexes" (PNI) in CRC-PM metastases with studies by Tong *et al*[6] and Yang *et al*[7], and to use NLR and Hb's predictive value with studies by Song *et al*[8], Li *et al*[9], Nishijima *et al*[10] and Nakamura *et al*[11].

Additionally, they chose to use PCI, with a cutoff ≥ 20, and preoperative Hb level, with a threshold that is either normal or low, to create a nomogram.

Critical issues

Although CRS (+/-HIPEC) is a complex surgery with high morbidity and mortality, recent experiences have allowed us to reevaluate the real impact of these in the therapeutic course of patients[12]. When compared to similar-risk oncological procedures, comparative analysis shows that CRS + HIPEC is safe, frequently safer across the spectrum of NSQIP safety metrics[13].

Some crucial elements were identified by the studies presented to support the decision to use PNI. Tong's paper[6] refers to Endometrioid Endometrial Carcinoma that infiltrates the myometrium in patients with metabolic syndrome.

The markers that were taken into account in the Yang *et al*[7] were albumin (discarded in the present study because it was not significant) and lymphocyte count. Furthermore, only 2.1% of the population was in TNM stage IV, and in this stage, the PNI did not significantly affect cancer-specific survival ($P = 0.841$) or OS ($P = 0.757$).

As for the predictive value of NLR, the studies used to support the choice have some limitations: In Song *et al*[8] manuscript, less than 5% of the patients were metastatic (without specifying the location of the secondary lesions). In Li *et al*[9] meta-analysis the conclusions are the following: "NLR gains a prognostic value for patients with CRC. NLR should be monitored in CRC patients for rational stratification of the patients and adjusting the treatment strategy. "The TNM stage of the patients is unknown in over half of the articles used; in three manuscripts where the stage is known, patients in stage IV are not included in the analysis; and in two additional articles patients in stage IV make up less than 5% of the total. Nishijima *et al*'s manuscript is off-target because it deals with the lymphocyte-monocyte ratio; in this meta-analysis, less than 5% of the population under study has metastatic colorectal cancer[10]. Nakamura *et al*'s study concerns the stomach, in 35 patients with carcinomatosis at staging laparoscopy and concludes that "The preoperative NLR was a significant independent predictor of the presence of peritoneal metastasis during staging laparoscopy"[11]. Regardless of tumor type, patients with a high NLR could be reasonable candidates for staging laparoscopy.

In the Wu *et al*[1] the study cohort is of 133 patients (38.3% with PCI ≥ 20): All underwent CRS, but 57.2% with a cytoreduction score of 2. Only 35/133 (26.4%) received HIPEC. The authors, while reporting the importance of treatment to improve OS decide to create a group in which both radically and palliatively treated patients are pooled. What was the

criterion for defining PCI ≥ 20 as one of the indicators to be used in the nomogram and is not explained. The value of Hb that is considered normal is never defined in the text. It is not known whether these patients received perioperative chemotherapy.

The following are listed as prognostic factors influencing OS in the literature: Extent of peritoneal disease in accordance with PCI (there are more than two subgroups, commonly: PCI < 7-11; PCI between 11 and 15, PCI > 15 also, some studies consider a PCI > 20 to be outside the chances of benefiting from any treatment), optimal surgical cytoreduction (CC0-CC1), type of peri-operative chemotherapy received by the patient, and tumor biology. The role played by HIPEC (and the various application protocols) is a matter of debate[3,14].

The population on which NRL is tested and then the nomogram constructed is heterogeneous in both PM burden and treatment received. Any chemotherapy treatments received by patients are not known. The value of one of the nomogram pillars (Hb) is not defined. The authors combine patients who received only palliative care and those who received radical treatment into one group.

CONCLUSION

Despite growing interest in treating peritoneal metastasis and an increasing number of centers performing peritoneal disease research, this therapeutic option remains very niche. Due to the concern evoked by the morbidity and mortality documented in the experiences published in the initial (pioneering) phase of this type of treatment, the majority of oncologists and even surgeons exclude patients with peritoneal metastasis from treatments with potentially curative intent. The selection of patients who are eligible for CRS +/- HIPEC is critical in order to provide the best possible therapy while not wasting healthcare resources[14]. If, in order to provide a tool for patient selection, a nomogram or a single laboratory marker is proposed that does not account for the burden of peritoneal disease, the patient's clinical history, and/or the biological characteristics of the neoplasm, there is a very high risk of excluding potentially curable patients from treatment. From a purely statistical standpoint, Wu *et al*[1] is methodologically sound, albeit based on a small study cohort and with very low significance. However, failing to assess the effect of the type of treatment received on OS introduces a bias that cannot be corrected. The complexity of disease burden assessment and surgical treatment requires evaluation within a multidisciplinary oncologic team for these patients. The excessive simplification of the patient selection pathway and the use of the proposed tools by oncologists or surgeons not skilled in peritoneal malignancy risk preclude possible curative treatment for patients with CRC-PM.

FOOTNOTES

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