Primary Tumor Resection in Patients With Metastatic Colorectal Cancer Is Associated With Reversal of Systemic Inflammation and Improved Survival

Natalie Turner,[1,2,3] Ben Tran,[1,2,3,4] Phillip V. Tran,[5] Mathuranthakan Sinnathamby,[2] Hui-Li Wong,[1,3] Ian Jones,[6] Matthew Croxford,[7] Jayesh Desai,[1,2,3] Jeanne Tie,[1,2,3,4] Kathryn Maree Field,[2] Suzanne Kosmider,[4] Susie Bae,[8] Peter Gibbs[1,2,3,4,8]

Abstract

The effect of primary tumor resection on systemic inflammation and survival in metastatic colorectal cancer was evaluated. Reversal of an elevated neutrophil/lymphocyte ratio was associated with significantly improved overall survival and was more frequent in patients with greater primary tumor bulk. With additional validation, systemic inflammation and primary tumor bulk can help to refine patient selection for elective primary resection.

Background: The true survival benefit of noncurative primary tumor resection in patients with de novo metastatic colorectal cancer (mCRC) remains uncertain. The present study examined the effect of primary tumor resection on systemic inflammation and survival in patients with mCRC. **Materials and Methods:** Consecutive patients with de novo mCRC who had undergone primary tumor resection were identified from a prospective database. Patients were excluded if they had undergone resection of metastases, had undergone delayed primary resection, or if blood samples were unavailable. The neutrophil/lymphocyte ratio (NLR) was used as a biomarker of systemic inflammation. Overall survival (OS) was compared between patient groups according to the pre- and postprimary resection NLR. The associations between the reversal of an elevated NLR and primary tumor bulk or performance status were explored. **Results:** A total of 145 eligible patients were identified from the database, with a median age of 70 years. The baseline NLR was elevated (>5) in 65 patients, 36 (55%) of whom had a low NLR after surgery. The reversal of an elevated NLR was associated with significantly improved OS (hazard ratio, 0.53; $P = .017$). A similar benefit was seen after excluding patients undergoing emergency primary resection. NLR reversal was more frequent in patients with larger primary tumors or good performance status. **Conclusion:** The present study is the first to demonstrate a relationship between the reversal of a systemic inflammatory response and the improved survival after primary resection in those with mCRC. A greater effect was seen in patients with large primary tumors. If validated, these observations could guide clinical decision-making in patients with mCRC at presentation.

Clinical Colorectal Cancer, Vol. 14, No. 3, 185-91 © 2015 Elsevier Inc. All rights reserved.

Keywords: Colorectal Cancer, Immune response, Neutrophil/lymphocyte ratio, Noncurative resection, Primary resection

N.T. and B.T. contributed equally and are considered co-first authors.

[1]Walter & Eliza Hall Institute of Medical Research, Melbourne, Australia
[2]Department of Medical Oncology, The Royal Melbourne Hospital, Parkville, Australia
[3]University of Melbourne, Melbourne, Australia
[4]Department of Oncology, Western Health, Footscray, Australia
[5]Department of Radiology, Western Health, Footscray, Australia
[6]Department of Colorectal Surgery, The Royal Melbourne Hospital, Parkville, Australia
[7]Department of Colorectal Surgery, Western Health, Footscray, Australia
[8]BioGrid Australia, Melbourne, Australia

Submitted: Dec 12, 2014; Revised: Feb 17, 2015; Accepted: Feb 26, 2015; Epub: Mar 7, 2015

Address for correspondence: Ben Tran, MBBS, Department of Medical Oncology, The Royal Melbourne Hospital, Grattan Street, Parkville 3050 Australia
E-mail contact: ben.tran@mh.org.au

1533-0028/$ - see frontmatter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.clcc.2015.02.004

Introduction

Colorectal cancer (CRC) is one of the most common malignancies worldwide, accounting for around 1,350,000 new cases and nearly 700,000 deaths annually.[1] Advances in the medical and surgical management of metastatic CRC (mCRC) cancer have led to significant improvements in survival. However, with the exception of a proportion of patients with surgically resectable isolated metastases, the treatment intent has remained palliative.[2-5] For patients with incurable de novo metastatic disease, the optimal management of the primary tumor remains an unanswered clinical question, in particular, in patients with a minimally symptomatic or asymptomatic primary lesion.

Several retrospective studies and meta-analyses have demonstrated an association between primary tumor resection and improved survival outcomes in patients with metastatic disease at presentation, with a ~30% relative reduction in risk of death and a 3- to 6-month improvement in overall survival (OS).[6-11] However, the data have not been entirely consistent across the published studies.[12,13] In the absence of a persuasive biologic mechanism, a confounding effect of selecting patients for primary resection who already have superior survival has yet to be excluded as the explanation for the observed survival benefits. Countering the argument for routine primary tumor resection is the associated risk of surgical morbidity and mortality, the potential detrimental effects on survival of the consequent delay in the delivery of systemic therapy, and the results from multiple series suggesting that the large majority of intact primary tumors will ultimately never require intervention.[11,14-17]

Inflammation within the primary tumor, reflecting a robust local anticancer immune response, has been shown to positively affect the outcomes, such as recurrence and survival, in multiple tumor types.[18] In contrast, the presence of tumor-associated systemic inflammation in patients with both localized and metastatic cancer negatively affects survival.[18-20] The reversal of this systemic inflammatory response after effective systemic chemotherapy has been shown to be associated with improved OS in patients with mCRC.[21-24] One well-established biomarker of systemic inflammation is the peripheral blood neutrophil/lymphocyte ratio (NLR), which is calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. The NLR has demonstrated prognostic utility in early stage[25,26] and advanced colorectal cancer.[27-30] Moreover, it is easily calculated from the blood tests performed routinely in the pre- and postoperative setting.

In a previous study from our group, we demonstrated a significant survival advantage from primary tumor resection in a cohort of patients with mCRC compared with no resection.[27] Moreover, exploratory analyses have suggested that a small subgroup of patients with reversal of an elevated NLR after primary tumor resection had outcomes similar to those with a low NLR at baseline.[27]

The present study aimed to further evaluate the prognostic effect of reversal of systemic inflammation, as measured by the NLR, after primary tumor resection in a larger patient cohort. In addition, we planned to evaluate the primary tumor and patient characteristics that might predict for increased likelihood of a reversed NLR.

Materials and Methods

Patient Cohort

Patients presenting with de novo mCRC from January 1, 2000 to July 1, 2010, who had undergone primary tumor resection, were identified from the multisite CRC Australian Comprehensive Cancer Outcomes and Research Database (ACCORD), which prospectively records the point-of-care comprehensive clinicopathologic and follow-up data for consecutive patients with CRC treated at the participating centers. The patients were excluded from the present analyses if a delay had occurred of $\geq$7 weeks between diagnosis and primary tumor resection, if the primary tumor resection had occurred after any systemic therapy, or if they had, at any time, undergone resection of metastatic disease with curative intent. The other exclusion criteria were a lack of available pre- and/or postoperative blood samples. Preoperative (baseline) samples were required within 14 days of surgery, and postoperative samples were required to be $\geq$ 30 days after surgery and before any systemic therapy. The relevant ethics committees approved the present study.

Measurement of Systemic Inflammation

The NLR was calculated from the pre- and postoperative blood samples, with a prospectively defined threshold of 5 used to classify patients with systemic inflammation.[31] The reversal of NLR was defined as a change in NLR from $>$ 5 (high) to $\leq$ 5 (low).

Tumor Burden

The association between the primary tumor bulk and likelihood of NLR reversal was evaluated using the maximum tumor length in millimeters as a surrogate marker for the primary tumor bulk. These measurements were extracted from the pathology report of the primary tumor resection.

Statistical Analysis

Because this was a retrospective cohort study, all eligible patients identified in the ACCORD were included, with no formal statistical power calculations for sample size. The Kaplan-Meier method and the Mantel-Cox log-rank test were used for the survival analyses. The proportions were compared using the χ^2 method or Fisher's exact test. The association between the primary tumor burden and the reversal of NLR was evaluated using the Mann-Whitney *U* test. For all analyses, 2-sided *P* values of $<$ .05 were considered significant.

Results

From the ACCORD, 145 patients with de novo metastatic CRC who met the eligibility criteria were identified. The patient and tumor characteristics are listed in Table 1. No significant associations were found between the baseline NLR and gender, Eastern Cooperative Oncology Group (ECOG) performance status, chemotherapy use after surgery, or primary tumor site. However, significantly more patients with a high baseline NLR required emergency surgery (surgery within 24 hours of presentation) than those with a low baseline NLR (Table 1).

Changes in NLR

In a comparison of NLR values between the baseline and postoperative blood samples, a change in the NLR classification was seen

Download English Version:

https://daneshyari.com/en/article/2751346

Download Persian Version:

https://daneshyari.com/article/2751346

Daneshyari.com