EDITORIAL

Primum non nocere: A Word of Caution Regarding Prophylactic Colectomy in the Setting of Incurable Metastatic Disease

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Most patients with metastatic colorectal cancer cannot be cured. The primary goal of treatment for these patients is symptom palliation, in hopes of prolonging survival while maintaining quality of life. Modern cytotoxic chemotherapeutic and biologic agents have extended survival, with the result that half of our stage IV patients now live with disease for more than 2 years. This has given rise to considerable controversy regarding the role of surgery for incurable stage IV patients. There is no debate regarding the need to resect symptomatic primary lesions such as those causing obstruction, bleeding, or pain; however, the benefits of removing asymptomatic primary lesions remain unknown. What is the optimal management of an asymptomatic primary lesion, and what is the role of colorectal cancer debulking?

Many additional questions are relevant in the debate over prophylactic colectomy for incurable colorectal cancer. When considering leaving the primary lesion in situ and proceeding directly to chemotherapy, we need answers to the following: How often do asymptomatic primary lesions become symptomatic and require palliative intervention? How do the associated complications impact patients' quality of life and survival? When considering resection of asymptomatic primary lesions, we need to know how often prophylactic surgery results in complication, and how the complication affects further treatment, survival, and quality of life.

In this issue of *Annals of Surgical Oncology*, Venderbosch et al. attempt to answer some of these questions by retrospectively analyzing two randomized trials, CAIRO and CAIRO2, which were originally designed to investigate the impact of chemotherapy on survival in patients

with metastatic disease.¹ Outcome, including time to disease progression (PFS) and overall survival, was analyzed on the basis of whether patients underwent resection of their primary lesion ($n = 547$) or not ($n = 300$) before chemotherapy. Patients who entered the CAIRO study after resection of a primary tumor had a marginally longer PFS (6.7 vs. 5.9 months) and longer survival (16.7 vs. 11.4 months) than those who did not undergo resection. Similarly, patients who underwent resection of a primary tumor before entering CAIRO2 had longer PFS (10.5 vs. 7.8) and longer survival (20.7 vs. 13.4 months) than those who did not undergo resection. The authors imply that resection of the primary lesion leads to improved survival, and they therefore argue for prophylactic colectomy in the setting of incurable metastatic disease.

Although the analysis appears straightforward, the observations can be accounted for by patient selection. We must ask why the results and conclusions are discordant with other published studies.^{2–4} To understand this, we need to examine the details of the CAIRO trials on which this retrospective analysis is based. The capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO) study of the Dutch Colorectal Cancer Group prospectively compared sequential with combined use of chemotherapy including a fluoropyrimidine (capecitabine), irinotecan, and oxaliplatin.⁵ This important trial demonstrated that up-front combination chemotherapy results in survival similar to that achieved by sequential use of the same drugs, starting with capecitabine monotherapy. Thus, sequential use of cytotoxics is a reasonable alternative to up-front combination therapy. In the CAIRO2 study, previously untreated patients with advanced colorectal cancer were randomized to capecitabine, oxaliplatin, and bevacizumab, as well as the same regimen with the addition of cetuximab.⁶ As in the CAIRO trial, CAIRO2 showed that the combined approach yielded no improvement in response rates or overall survival.

The subtle but critical point here is that patients were enrolled either at diagnosis or after recovery from resection of the primary lesion. Therefore, the indication for resection, and the morbidity and mortality associated with surgery, were not recorded. In fact, the denominator of the surgery cohort is patients who underwent surgery and recovered sufficiently to receive chemotherapy. We do not know how many patients underwent surgery and experienced complications that delayed chemotherapy, attenuated the course of chemotherapy, or rendered administration of chemotherapy impossible. Perhaps more importantly, we do not know how many patients died directly as a result of prophylactic surgery.

Should we expect greater rates of complication in these patients? Indeed, perioperative morbidity and mortality is unusually high after colectomy in stage IV colorectal cancer patients. A meta-analysis by Scheer et al., including 850 patients from seven high-quality and relevant studies, noted postoperative morbidity ranging from 19–47%.⁷ Major complications included obstruction, hemorrhage, and sepsis. Other studies have observed high mortality rates, ranging from 5–10% in this patient cohort.^{8–13} Such high rates of morbidity and mortality should make us vigorously question the rationale for prophylactic surgery.¹⁴

Another point relevant to the study by Venderbosch et al. is that patients were not stratified on the basis of resection of the primary tumor in either CAIRO or CAIRO2. Therefore, these groups may not be balanced in regard to other factors that affect outcome. Indeed, patients who underwent resection had a lighter burden of disease, with lower serum LDH, fewer metastatic lesions, and less extrahepatic disease. Thus, we should not be surprised that the no-surgery group had worse outcome; the patients in the no-surgery group had more extensive metastatic disease. The authors attempted to correct for the imbalance with a multivariable analysis, but this cannot account for all confounders, including less obvious factors that may also lead to bias. For instance, it is possible that physicians were more likely to send a patient for resection of a primary lesion if the patient was fit, had less advanced (metastatic) disease, and was perceived to have longer life expectancy than patients who were not sent for resection of primary disease. Patients in CAIRO2 who did undergo resection were younger than those who did not. Similar treatment-related biases have been noted in other studies, including an analysis reviewing over 9000 Medicare beneficiaries from the Surveillance, Epidemiology, and End Results (SEER) Medicare-linked database.¹⁰ The authors observed that patients who underwent resection of their primary tumor were most likely to receive chemotherapy, which indicates treatment bias: physicians sent patients to resection whom they deemed more salvageable. Similar

treatment-related bias was noted in the meta-analysis reported by Scheer et al.⁷ The authors compared 536 patients with unresectable metastatic disease who underwent colectomy for removal of an asymptomatic primary lesion with 314 patients who did not undergo colectomy. They found that the patients who did not undergo colectomy had more extensive liver and extrahepatic disease than those who did. The authors concluded that patients with more widespread disease were relatively overrepresented in the group treated nonsurgically—which might explain their poorer prognosis.

What happens if we leave the primary tumor in place and immediately treat with chemotherapy? How often do patients experience a complication, such as bleeding, obstruction, or perforation, requiring intervention? The National Surgical Adjuvant Breast and Bowel Project C-10 (NASBP C-10) addressed this issue in a study of patients with unresectable stage IV disease receiving chemotherapy.² The trial specifically asked whether the addition of bevacizumab to FOLFOX increased complications in patients with stage IV disease who had not undergone removal of their primary lesion. In this analysis of 86 eligible patients, the major complication rate was 14%, with 12% requiring surgical intervention. The authors concluded that leaving the primary lesion in place did not result in an unacceptably high rate of obstruction, perforation, bleeding, or death. Furthermore, they stated that survival was not compromised by leaving the primary tumor in situ. Another study of patients with stage IV disease randomized to receive chemotherapy showed no differences in gastrointestinal complications (fistulas, peritonitis, obstruction) between patients who had the primary lesion removed ($n = 280$) and those who did not ($n = 82$).³ Poultsides et al. retrospectively analyzed 233 consecutive patients, treated from 2000 to 2006, who presented with synchronous metastatic colorectal cancer and an unresected primary tumor and received chemotherapy as initial treatment.⁴ Ninety-three percent of these patients never required surgical palliation of a primary lesion. Considered altogether, these data lend support to the argument that asymptomatic patients with stage IV colorectal cancer can tolerate chemotherapy and have a low rate of tumor-related complication, and therefore do not necessarily require surgery for removal of the primary tumor.

Why does the primary lesion remain asymptomatic in most patients treated with systemic chemotherapy? The explanation is clear: Primary tumors are as, or more, responsive to chemotherapy than metastatic disease. For example, in a study of stage II and III rectal cancers, FOLFOX chemotherapy with bevacizumab was utilized without radiation, and all patients were observed to have downsizing of the primary lesion. In fact, 27% of the 31 patients in this study had a complete pathologic response,

with no viable tumor cells noted at the time of rectal resection.¹⁵ Similarly, in a series of 14 patients with stage IV colorectal cancer who received chemotherapy followed by surgical resection, five had a complete pathologic response of the primary tumor.¹⁶

These data should give us pause. In the setting of widespread and unresectable colorectal cancer, we must exercise caution when recommending colectomy for an asymptomatic primary lesion. As with any prophylactic surgery, complications are not well tolerated by patients... or physicians. Indeed, by rushing into resection of an asymptomatic primary lesion, we run a high risk of negatively affecting the patient's quality of life and even shortening survival.

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