In Patients With Colorectal Liver Metastases, Can We Still Rely on Number to Define Treatment and Outcome?

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The surgical strategies of “classic, reversed, or combined” resection of colorectal cancer and colorectal liver metastases have to be tailored to a specific patient, and all three strategies have a role in the treatment of stage IV colorectal cancer today.

We congratulate Dr. Weiser and colleagues for an excellent and concise review of the approaches available for colorectal cancer patients with a limited number of metastases, defined as “oligometastatic disease.”[1] This commentary provides us with the opportunity to revisit the concept of “oligometastatic disease” that was developed in the era predating the use of effective chemotherapy, when surgery predominantly defined patient outcomes. At that time, a small number of metastases was considered a sign of favorable biology. Today up to 25 % of patients with metastatic colorectal cancer are candidates for resection of colorectal liver metastases (CLM). Patients with CLM encompass a broad spectrum of clinical presentations, and new concepts of prognostication are emerging.

To achieve optimal outcomes, patients with CLM should undergo a planned sequence of therapeutic interventions that include perioperative chemotherapy and surgery. The surgeon and the medical oncologist are pivotal in keeping the patient on a therapeutic track that will optimize the benefits derived from chemotherapy and surgery. In this commentary, we provide approaches and perspectives that represent alternatives to the important concepts discussed by Weiser et al. We have organized our remarks around five key questions raised by the authors.

1. Should the number of lesions still be included in the criteria used to select patients for surgical resection?

In 2003, Altendorf-Hofmann et al demonstrated no survival differences between patients who underwent R0 resection for 1 to 3, 4, 5 to 7, or 8 to 11 metastases (Figure 1).[2] In light of these data, we think that response to modern chemotherapy may help determine the biology of the disease better than the number of lesions. In recent studies, pathologic response to chemotherapy predicted outcome and outperformed the traditional predictors of outcome, including the number of metastases.[3]These findings may explain why the resection of multiple CLM was associated with more favorable long-term outcomes in previous studies. Because the number of lesions does not necessarily correlate with the biology of the disease, we use high-quality CT scans to assess the radiologic response to chemotherapy—which correlates with pathologic response.[4] The specific radiologic criteria we use go beyond the Response Evaluation Criteria In Solid Tumors and include morphologic changes in the CLM (eg, homogeneous loss of enhancement with well-defined margins) as a size-independent predictor of outcome.[5] In addition, we have shown that RAS mutations (KRAS and NRAS) predict poorer overall and disease-free survival, as well as a pattern of early lung recurrence in patients undergoing resection for CLM.[6,7] On multivariate analysis, RAS mutational status outperformed traditional predictors of outcome, such as the number and size of CLM. Because RAS mutational status is highly concordant (> 90%) between the primary tumor and the CLM, this prognostic information can be obtained early in the evaluation of the disease via pretreatment biopsy or from the resected primary tumor.

2. Does a small number of lesions define the extent of resection and the approach?

One or two lesions may call for limited liver surgery in some patients, but if unfavorably located (eg, involvement of two hepatic veins), these few lesions may necessitate extensive resection. This could have a direct impact on decisions regarding the type and sequence of surgical procedures or the use of perioperative therapy. In patients with unfavorably located lesions, preoperative portal vein embolization may be useful prior to surgery and should be integrated into the multidisciplinary
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3. Should CLM be resected at the time of primary colorectal cancer resection (“combined approach”), or should the resection of primary and metastatic lesions be staged?

The two options for staged surgery are the “classic approach,” which is resection of the primary tumor first, and the “reverse approach,” which is resection of the CLM first. Specific factors that have been shown to increase the rate of postoperative complications in combined procedures are the presence of a diverting stoma, rectal location of the primary tumor, duration of the surgery, intraoperative blood loss, and the need for transfusion.[9] The fact that the combined approach could increase the surgical risk for some patients is supported by a large multi-institutional analysis that demonstrated a more than threefold increase in morbidity and mortality for simultaneous colorectal and liver resection compared with hepatectomy alone.[10] Such complications will have a negative impact on the well-defined sequence of chemotherapy and surgery for patients with stage IV disease. The factor that has the greatest impact on long-term survival is the presence of CLM. This needs to be considered in the timing of chemotherapy and surgery for the primary tumor and for CLM. We plan surgery with the goal of removing all liver disease first. This sometimes requires two or three surgical procedures and may include portal vein embolization.[11] In our practice, contrary to the authors’ experience, resecting CLM first is not a “select circumstance” in patients undergoing liver surgery, even in the “era of laparoscopic surgery.”[12] In addition, we recently showed that the morbidity and mortality of proctectomies performed after this “reversed strategy” are similar to the morbidity and mortality of rectal resection performed at the initial surgery.[13]

4. What is the role of chemotherapy in patients who require resection for CLM?

When discussing the role of chemotherapy in the treatment of CLM today, it is important to include targeted agents. Although no randomized controlled trial to date has specifically looked at the role of VEGF receptor inhibition in the neoadjuvant setting, we recently showed that radiographic response to VEGF inhibition is associated with improved overall and disease-free survival.[5] Synthesizing the data from the European Organisation for Research and Treatment of Cancer (EORTC) 40983 study and our data, we recommend a limited course of preoperative modern chemotherapy (eg, 4 to 6 cycles) along with targeted therapy (eg, 3 to 5 cycles), except in patients who have already received modern adjuvant chemotherapy for the primary tumor within 1 year. This allows us to prevent some patients from undergoing unnecessary surgery or, conversely, to select surgery for patients with borderline resectable disease. In our experience with patients who have undergone resection for synchronous vs metachronous CLM, the number of patients with synchronous metastases compared with the number who have metachronous metastases has increased from a ratio of about 1:1 in 1996 to a ratio of 4:1 in 2011 (Figure 2). Synchronous disease portends a poorer prognosis, and because its incidence is increasing, we favor the use of the most effective preoperative chemotherapy.

5. What is the role of pelvic radiotherapy in the setting of locally advanced rectal cancer and metastatic disease?

Radiotherapy, especially when delivered preoperatively, has proven to be more effective than surgery alone at providing improved locoregional control for locally advanced rectal cancer.[14,15] However, the addition of radiotherapy might not provide significant gains in overall survival benefit in rectal cancer patients with systemic disease, including those with CLM. In a study of 141 patients with stage IV rectal cancer, more than half the patients with local recurrence in the pelvis also had recurrent systemic metastases.[16] Another study of patients with stage IV rectal cancer who were treated with postoperative concurrent chemotherapy and radiotherapy vs chemotherapy alone.
demonstrated no difference in overall survival (2 years), local recurrence-free survival, or disease-free survival. Thus, the overall oncologic outcomes in this patient cohort are largely determined by metastatic disease rather than by local recurrence. Additionally, the response of the primary rectal cancer to systemic chemotherapy alone is highly variable, with observed histologic response rates ranging from 30% to more than 90% and observed complete pathologic response rates of 6% to 35%, indicating that pelvic irradiation may indeed provide added local benefit in a select subset of patients. Therefore, we concur with the authors that the role of pelvic irradiation in patients with metastatic and locally advanced rectal cancer is not uniform, and patient selection must balance the potential benefit of optimal local control against the potential harm in the time away from effective systemic chemotherapy.

In conclusion, the surgical strategies of “classic, reversed, or combined” resection of colorectal cancer and CLM have to be tailored to a specific patient, and all three strategies have a role in the treatment of stage IV colorectal cancer today. The question of how to prognosticate patients with stage IV colorectal disease at diagnosis that is addressed by Weiser et al is a very timely one, given that the proportion of colorectal cancer patients with synchronous CLM is increasing. Since the number of metastases might not help the clinician to accurately prognosticate these patients or define the surgical strategy, we recommend focusing on surgical considerations such as lesion location and the response of the tumor to therapy as surrogate markers of tumor biology. We believe clinical surrogate parameters are a function of the mutational profile of the tumor, which actually determines its biology, and that these surrogate parameters should ultimately be replaced by mutational testing that is precisely correlated to outcomes and patterns of disease.

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