Advanced Local Therapies for the Treatment of Limited Systemic mCRC

November 15, 2014 | Oncology Journal [1], Colorectal Cancer [2], Gastrointestinal Cancer [3]
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Due to advances in chemotherapy, biologic therapy, and the development of liver-oriented treatment options, the survival of patients with metastatic cancer has more than doubled, and increasing numbers of patients have been cured, even among those with advanced disease.

In the past 2 decades, the survival of patients with metastatic cancer has more than doubled, and increasing numbers of patients have been cured, even among those with advanced disease. This progress is due to multiple factors, including advances in systemic chemotherapy, biologic therapy, and the development of liver-oriented treatment options—as summarized by this comprehensive review.[1] The senior author, Dr. Fong, is one of the key pioneers in the field.

The basic anatomy of the involved organ systems and the characteristics of metastases in colorectal cancer make liver failure the cause of death in the majority of patients with advanced-stage disease; therefore, sterilizing liver lesions may potentially lead to cure. However, the heterogeneity of the disease makes clear that a much more complicated interplay of factors is required to predict outcomes and prognosis; the involved factors include but are not limited to: patient physical characteristics (age, comorbidities), clinical condition (size, location, and number of liver lesions; carcinoembryonic antigen level; disease-free interval; previous systemic therapy and responses), gross pathology factors (resection margin, tumor-infiltrating lymphocyte cells), and more importantly, the molecular biology (genetic and epigenetic) of the cancer.

As the authors have pointed out, “useful clinical staging criteria” as well as the Clinical Risk Score (CRS) are needed for a fair evaluation of all liver-oriented therapies: resection, tumor ablation, and radiation therapy (which includes external beam, proton beam, and regional brachytherapy/radioembolization). The need for clinical criteria/guidelines that can help ensure that these patients receive appropriate therapies at the most opportune time is becoming an urgent issue. Although current existing criteria and guidelines[2,3] have various limitations and restrictions because of the limited evidence for these therapies (eg, evidence limited by small sample size, or by the heterogeneity of patient populations that include patients with colorectal cancer and patients with hepatocellular carcinoma), it is crucial for practitioners to follow the existing guidelines while at the same time being aware of and becoming familiar with the evolving criteria and guidelines. More importantly, with the continuing advances in molecular and genetic technology, a genetic profile of the patient, the primary malignancy, and metastases will aid in the assessment of the prognosis of a patient with colorectal cancer with resectable hepatic metastases. In addition, genetic profiling will guide us in the selection of more effective systemic treatment (including but not limited to chemotherapy, biologic therapy, and/or immunotherapy) to improve the survival and the cure rate from surgical resection and/or other liver-directed therapies. For example, a very recent analysis demonstrated that RAS mutations predict radiologic and pathologic response from preoperative chemotherapy in colorectal cancer patients with resectable metastatic lesions; therefore, RAS mutational status can be used to complement the current prognostic indicators for patients undergoing curative resection of liver metastases after preoperative modern chemotherapy.[4] The other critical factor that needs to be pointed out is that the availability of technology and operator expertise play crucial roles with regard to the clinical outcomes of colorectal cancer patients with potentially curable liver metastases when liver resection or other liver-oriented procedures are employed.

Given that the authors are the experts in this field, it might have helped readers more if they had given more direction regarding when and how (choice and sequencing) to employ liver-directed nonsurgical approaches in the clinical setting. It might also have been helpful if the authors had shared some of their opinions (based on their experience) and data (even preliminary) regarding preoperative chemotherapy and clinical outcomes of surgical resection vs nonsurgical procedures, since there has been limited information on these issues available from randomized and/or
prospective studies. The European Organisation for Research and Treatment of Cancer (EORTC) 40983 trial initially showed that perioperative chemotherapy with FOLFOX4 (folinic acid, fluorouracil, and oxaliplatin) increases progression-free survival compared with surgery alone for patients with resectable liver metastases from colorectal cancer; however, there was no overall survival advantage demonstrated in the final assessment.[5] So far, there are no prospective trials comparing radiofrequency ablation (RFA) with liver resection for colorectal cancer patients with resectable liver metastases. An analysis that combined two separate EORTC trials suggested that there was no clear difference in the rate of local recurrence after RFA vs after liver resection. However, nonlocal hepatic recurrences were seen more frequently in patients treated with RFA than in those who had surgical resection, with more advanced disease occurring in patients who had RFA.[6]

Again, this review provides a comprehensive summary of the liver-directed treatment techniques and options for colorectal patients with hepatic metastases, which may help oncologists in their management of this patient population, and therefore improve patients’ overall outcomes.

**Financial Disclosure:** The author has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

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