

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Update on Surgical Resection of Liver Metastases From Colorectal Cancer

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H&O What are the medical interventions used in patients with resectable hepatic metastases from colorectal cancer?

NP First, it is important to provide specific definitions. Patients with hepatic metastases from colorectal cancer who are considered to be resectable upfront can receive either adjuvant or neoadjuvant chemotherapy. Adjuvant chemotherapy involves individuals with resectable disease who undergo surgical resection of their metastases, followed by chemotherapy postoperatively. Neoadjuvant chemotherapy involves individuals whose disease is also considered resectable and are given several cycles of chemotherapy prior to liver resection and consideration for several cycles of chemotherapy postoperatively. “Perioperative chemotherapy” is a term chiefly used in Europe to describe treatment of patients with resectable liver metastases who are given several cycles of chemotherapy prior to resection and postoperatively given several more. This term is similar to neoadjuvant chemotherapy. A third definition is “conversion chemotherapy,” which has evolved concomitantly with the development of new systemic agents. In this setting, patients with borderline resectable disease or unresectable liver metastases are given newer agents in the hope of converting their disease from unresectable to resectable status. In several series from around the world, approximately 16% of patients who presented with unresectable liver-only metastases were converted to resectable status with the newer agents now available. Overall, approximately 20% of individuals who present with liver metastases will become resectable. This figure is

increasing due to the ability of newer therapies to convert unresectable disease to resectable disease. Therefore, when compared to rates of several years ago, the number of patients undergoing resection is increasing. When I was training, it was classically considered that if a patient had more than four hepatic metastases from colorectal cancer, resection was not possible. Today, however, the number of lesions is not considered as important as the amount of functional liver left behind after surgery. Because of these new criteria more patients are able to undergo resection.

H&O Why else is the number of patients eligible for surgical resection of liver metastases from colorectal cancer increasing?

NP There are several reasons for the increase in the number of patients eligible for surgical resection of liver metastases from colorectal cancer. First, the techniques of hepatic resection have improved. Today, techniques such as portal vein embolization to induce hypertrophy in the remaining functional liver and staged hepatic resections are available to the experienced hepatic surgeon. In my own experience, it was not uncommon years ago for patients to receive several units of blood during hepatic resection; today, only in exceptional cases do patients require this type of transfusion during surgery. Moreover, as mentioned, a previous contraindication to hepatic resection—more than four lesions—has now been overcome. Furthermore, as discussed, the newer chemotherapeutic agents are converting tumors from unresectable to resectable status. The pool of resectable patients has therefore unquestionably increased. The only potentially curative approach to hepatic metastases from colorectal cancer is surgical resection. Despite all the medical progress in the last decade in the advanced disease setting—increasing the survival of patients with unresectable disease from approximately 6 months to over 20 months—nonsurgical approaches are only palliative in nature. As an adjunct to hepatic resec-

tion, in my view, the newer agents should be considered in patients with resectable or unresectable metastases because of their potential to prolong survival.

H&O What agents are responsible for the conversion of patients from unresectable to resectable status?

NP The two major agents used in conversion chemotherapy have been oxaliplatin (Eloxatin, Sanofi-Aventis) and irinotecan, which have been combined with the standard of care during the 1980s and 1990s, 5-fluorouracil (5-FU) and leucovorin (ie, FOLFOX and FOLFIRI). These agents have demonstrated the ability to convert unresectable disease to resectable disease. It is important to remember, however, that, as opposed to 5-FU/leucovorin, oxaliplatin can cause hepatic toxicity, injuring the normal liver parenchyma that is left behind during resection of liver metastases. Irinotecan can cause steatohepatitis, fatty infiltration with infiltrating lymphocytes; oxaliplatin can cause sinusoidal dilatation, what surgeons refer to as “blue liver,” leading to an enhanced risk of hemorrhage during surgery. Also, the monoclonal antibody bevacizumab (Avastin, Genentech) can affect normal liver tissue by hampering wound healing. These agents, therefore, are able to allow the surgeon to resect a larger number of patients, but at the same time they increase the risks to the normal liver tissue. It is important to consider these issues in the adjuvant and neoadjuvant/perioperative settings.

H&O What trials are investigating the use of chemotherapy in patients with hepatic metastases from colorectal cancer?

NP One trial with highly anticipated results, by the European Organization for the Research and Treatment of Cancer (EORTC 40983) that was presented at the annual meeting of the American Society of Clinical Oncology (ASCO) in 2007, selected patients with resectable hepatic metastases (1–4 lesions) and no evidence of extrahepatic disease. This phase III, multi-institution, prospective trial randomized 364 patients to undergo either surgery followed by observation or perioperative chemotherapy with FOLFOX prior to and after resection. This trial demonstrated that progression-free survival in patients who underwent resection was improved by 9.2% at 3 years for those who received the perioperative chemotherapy with FOLFOX (42.4%) versus those who received surgery alone (33.2%). When the complications of surgery in the trial were analyzed, an increase in postoperative complications was seen in those who received perioperative chemotherapy. Biliary fistulae, hepatic failure, and intra-

abdominal infections, as well as the need for re-operation, were increased in these patients. The ability to use these agents preoperatively has indeed affected the morbidity of patients undergoing resection, raising the important question, which needs to be answered in a prospective trial, of whether adjuvant or neoadjuvant chemotherapy is less toxic to the liver. Can the same efficacy outcomes be achieved with chemotherapy after hepatic resection rather than before? The American College of Surgeons Oncology Group (ACOSOG), National Surgical Adjuvant Breast and Bowel Project (NSABP), and North Central Cancer Treatment Group (NCCTG) are currently planning a phase III multicenter trial comparing neoadjuvant chemotherapy in patients with hepatic metastases from colorectal cancer to adjuvant, postoperative chemotherapy. I believe that, in view of the toxicities seen in the EORTC 40983 trial, the findings of this current trial will be quite important.

Following the results of EORTC 40983, EORTC is planning another trial, which will compare perioperative FOLFOX alone to FOLFOX plus cetuximab (Erbix, Bristol Myers-Squibb/ImClone). This trial will be the first evaluation of a targeted agent in the setting of resectable hepatic metastases. In the ACOSOG, NSABP, and NCCTG trial comparing neoadjuvant to adjuvant treatment, there is consideration as well for the use of a targeted agent. Presented at the 2008 ASCO annual meeting, the CRYSTAL trial demonstrated that the treatment effect of cetuximab in stage IV colorectal cancer patients with *K-Ras* wild type was significantly enhanced compared with standard chemotherapy alone, whereas patients with *K-Ras* mutant could not be shown to benefit from cetuximab treatment. In view of these data, future trials will use this gene marker to stratify patients into groups that will or will not receive an epidermal growth factor receptor–targeted agent. In the ensuing years, a combination of chemotherapy with targeted agents in resectable hepatic metastases will be investigated thoroughly. However, the community must be cautious because the CAIRO2 study, presented at ASCO 2008, demonstrated in stage IV colorectal cancer patients that the addition of cetuximab to bevacizumab, capecitabine (Xeloda, Roche), and oxaliplatin resulted in a significant decrease in progression-free survival compared to bevacizumab, capecitabine, and oxaliplatin without cetuximab.

Another important trial to mention in the setting of resectable hepatic metastases is NSABP C09, a phase III trial. This trial enrolled patients with 1–6 hepatic metastases (in comparison, EORTC 40983 included patients with 1–4) and no evidence of extrahepatic disease. All patients underwent surgery upfront and postoperatively received systemic capecitabine with oxaliplatin either with or without intra-arterial floxuridine (FUDR) on a

randomized basis. Intra-arterial FUDR was the variable, to assess its effect on disease-free and overall survival. This trial, in the adjuvant setting of advanced disease, was designed to answer an important question, in my view. Unfortunately, the NSABP was unable to meet its accrual requirements and the trial was closed early. Although the trial, which had a simple and straight-forward schema, met the criteria for fast accrual in NSABP, it was not on the forefront of the field because most medical oncologists are moving away from the use of intra-arterial FUDR after hepatic resection in favor of newer systemic and targeted agents.

H&O What research has been conducted into the use of a combination of chemotherapy and a targeted agent in the setting of unresectable disease?

NP First, the CRYSTAL and CAIRO2 studies, discussed earlier, enrolled patients with stage IV unresectable colorectal disease. However, a phase II trial organized by the NCCTG (N014A) enrolled patients with unresectable liver-only metastases. These patients received FOLFOX plus cetuximab and were expected either to progress and subsequently receive a different regimen, to remain stable but unresectable and continue to receive FOLFOX plus cetuximab, or to experience conversion from unresectable to resectable liver metastases and subsequently undergo hepatic resection. The researchers were attempting to discover whether this combination regimen would yield a conversion rate higher than the previously demonstrated 16%. The trial had a conversion rate of approximately 25% and a higher-than-expected rate of hematologic toxicity. The trial called for at least a 30% conversion rate to be called successful.

H&O What does the future hold in this setting?

NP I am optimistic about the future of the treatment of hepatic metastases from colorectal cancer. However, the community must also be aware of the potential liver toxicity of the newer agents. We have learned that hepatic metastases must be treated with a multidisciplinary approach, with cooperation between surgeons and medical oncologists, especially in the patient group designated for conversion chemotherapy. The surgeon must follow the patient with the medical oncologist because as soon as the patient is deemed resectable, the surgery should go forward and the team should not continue chemotherapy to get a “better response.” The use of biomarkers such as *K-Ras* is allowing clinicians to determine which patients will, or, more importantly perhaps, will not respond to a given targeted agent. Lastly, in the near future, I believe gene-expression profiling will be used to improve patients’ quality of life and overall survival.

Suggested Readings

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