

# ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: James L. Abbruzzese, MD

## Surgical Management of Liver Metastases From Colorectal Cancer

Nicholas Petrelli, MD  
Medical Director  
Helen F. Graham Cancer Center  
Professor of Surgery  
Thomas Jefferson University

**H&O** What is the role of surgery in the management of colorectal cancer patients with liver metastases?

**NP** Surgical resection is currently the only curative approach for patients with liver metastases from colorectal cancer, and is the gold standard treatment for patients who present with liver metastases from this disease site. However, the majority of patients with colorectal cancer-associated liver metastases are not candidates for surgical resection; only 10–20% have been eligible for surgery in the past.

**H&O** Is this percentage increasing?

**NP** Yes, for several reasons. The techniques that are now available for controlling hemorrhage have improved over the years. Newer surgical approaches such as staged hepatic resections and interventional radiology techniques such as portal vein embolization for liver hypertrophy are also reasons for the increase in resections. New systemic cytotoxic drugs and targeted agents have converted patients who initially present with unresectable metastases to resectable candidates. A large single-institution European report found that with current treatment approaches, unresectable disease can be converted to resectable disease in approximately 15% of patients. We are only now beginning to explore what the eventual outcome might be in terms of overall survival for these patients. Preoperative evaluation has improved with better patient selection, as has intraoperative management of patients with regards to

anesthesia. Finally, the postoperative care available today is better than it was 10 years ago. All these advancements have led to an increase in the number of individuals who are candidates for surgical resection.

**H&O** What are the prognostic factors that would indicate a surgical candidate?

**NP** One of the most important factors when considering whether a patient is eligible for surgery is that there be no evidence of intra-abdominal extrahepatic disease. That being said, recent data indicate that resecting extrahepatic disease at the time of hepatic metastases resection can result in excellent survival. However, this approach is still investigational. At the present time, extrahepatic disease is a contraindication for hepatic resection of metastases from colorectal cancer outside of a clinical trial setting.

Other factors include the length of time from the original resection of the primary colorectal cancer to the time of liver metastases presentation. The longer the time between initial resection and the development of metastases, the better the prognosis. However, I must emphasize that this time interval is not a contraindication to resection but a prognostic factor in terms of survival.

The number of lesions is also a prognostic factor, although advances in treatment have changed the profile of a good candidate for surgery. Until recently, it was thought that only patients with up to four lesions were candidates for resection. However, we now know that more important than the number of lesions is the amount of functioning liver that remains after surgery, within certain limitations. In an ongoing clinical trial being conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), Protocol C09, individuals presenting with up to six metastatic liver lesions from colorectal cancer are eligible for hepatic resection and/or ablation.

**H&O** What potential advances in surgical techniques are currently being investigated?

**NP** In actuality, the general principles/techniques of hepatic resection have not changed dramatically. What occurred has been the development of adjunctive procedures. For example, as stated above, embolization of the portal vein is a way of creating hypertrophy of the liver

that will remain in situations when a large portion of the liver is planned to be resected. This approach has reduced the incidence of deaths due to hepatic failure associated with major hepatic resections. Whether or not this approach were taken with a specific patient would depend on the amount of liver that was planned to be resected at the time of initial surgery. Also, staged hepatic resections with the removal of a portion of the liver, allowing the liver to recover and then a second resection has been a major advancement.

In addition, anesthesia techniques that help minimize blood loss during surgery are also being investigated. Other technical aspects of surgery include methods of managing blood loss and controlling bleeding with coagulants—a very useful tool in this setting because the liver is a very vascular organ.

Advances in all of these areas are expanding the indications for liver metastases resection so that this surgery can be performed in more patients safely with acceptable morbidity and mortality.

#### **H&O** Could you further describe how drug treatment is increasing the number of patients who are candidates for resection?

**NP** Results from single-institution studies, the majority conducted in France, have evaluated what is known as “conversion therapy.” These studies have demonstrated that 15% to 16% of individuals who present with initially unresectable hepatic metastases from colorectal cancer can be converted to resectable disease using agents such as oxaliplatin and/or irinotecan in combination with 5-fluorouracil and leucovorin. These two agents have made a dramatic impact in terms of converting unresectable metastases to resectable disease. Which brings up the issue of definitions. It is important that physicians utilize the same definitions. For example, we have already defined “conversion therapy” as agents that are given to patients with unresectable liver metastases in an attempt to convert those metastases to resectable disease. Adjuvant therapy should be used in the context of agents that are given to patients postoperatively following initially resectable liver metastases. Lastly, neoadjuvant therapy should be defined in the context of patients who present with initially resectable disease but are given agents prior to hepatic resection.

In an ongoing phase II study by the North Central Cancer Treatment Group (NCCTG), patients who present with unresectable hepatic metastases are being treated with oxaliplatin plus 5-fluorouracil/leucovorin (FOLFOX-6) plus cetuximab (Erbix, Bristol-Myers Squibb/ImClone). The goal of this study is to convert 30% of patients from unresectable to resectable metastases.

The overall aim of these studies is to determine whether patients whose disease is converted from unresectable to resectable experience the same survival benefit as patients who initially present with resectable metastases. The single-institution data are encouraging, but this question needs to be evaluated in a prospective clinical trial, which is now ongoing.

#### **H&O** Do novel agents have promise as conversion therapy?

**NP** Yes, absolutely. Both bevacizumab (Avastin, Genentech) and cetuximab are being integrated into conversion therapy regimens.

Most likely, in the near future there will also be a clinical trial evaluating hepatic resection in patients with extrahepatic disease, both intra-abdominally and at single sites. This approach is very exciting because extrahepatic intra-abdominal disease has always been a contraindication for surgery, but new agents are changing that paradigm.

#### **H&O** Are there specific cautions regarding surgical resection of liver metastases?

**NP** It is important to remember that the data being referred to here are from clinical trials performed by high-volume liver surgeons with extensive experience in high-volume hospitals. Hepatic resection is major surgery and can be fraught with complications; it is essential that this procedure be done by an experienced hepatic surgeon, with an experienced anesthesia team and state of the art postoperative care.

Another issue that is important in regard to hepatic resection is related to the side effects of some of the targeted agents. For example, specific issues include the impact of bevacizumab on postsurgical wound healing, potentially causing delayed surgery after bevacizumab administration and the impact of this agent on hepatic regeneration following surgery, based on the role of vascular endothelial growth factor in this process. Considering the pharmacokinetics of bevacizumab it has been recommended waiting at least 8 weeks after the last dose of this agent before performing hepatic resection. In addition, the chemotherapeutic agents oxaliplatin and irinotecan have been associated with sinusoidal dilation and steatohepatitis, respectively. In one report patients who received irinotecan before hepatic resection and developed steatohepatitis had an increased 90 day surgical mortality compared with patients who did not have steatohepatitis. In view of these data the specific chemotherapy regimen given before hepatic resection should be carefully considered in view of the potential risk of hepatotoxicity.

Lastly, I would encourage physicians in the United States to consider a clinical trial for their patients with

liver metastases from colorectal cancer. Increased enrollment will enable us to conduct trials more rapidly so that the next generation of patients can experience an improved quality of life and longer survival.

### **H&O** What ongoing clinical trials might physicians want to consider for these patients?

**NP** NSABP C09, discussed above, is a randomized phase III trial of patients with one to six liver metastases from colorectal cancer. Patients are randomized to receive capecitabine plus oxaliplatin with or without intra-arterial floxuridine (FUDR) following surgery (randomization is done prior to surgery).

The phase II NCCTG trial N014A is evaluating FOLFOX-6 plus cetuximab in patients with unresectable liver metastases. As mentioned above, this study is aiming to increase the hepatectomy conversion rate to 30%.

The Southwest Oncology Group is conducting a phase II trial of neoadjuvant therapy with capecitabine, oxaliplatin, and bevacizumab. This trial is enrolling patients who present with resectable disease.

The American College of Surgeons Cooperative Group is also preparing a clinical trial evaluating adjuvant versus neoadjuvant therapy for colorectal hepatic metastases.

### **Suggested Reading**

Khatri VP, Petrelli NJ, Belghiti J. Extending the frontiers of surgical therapy for hepatic colorectal metastases: is there a limit? *J Clin Oncol.* 2005;23:8490-8499.

Vauthey JN, Zorzi D, Pawlik TM. Making unresectable hepatic colorectal metastases resectable—does it work? *Semin Oncol.* 2005;32(6 suppl 9):S118-S122.

Petrelli N, Abruzzese J, Mansfield P, Minsky B. Hepatic resection: the last surgical frontier for colorectal cancer. *J Clin Oncol.* 2005;23:4475-4477.

Ellis L, Curley S, Grothey A. Surgical Resection after downstaging of colorectal liver metastasis in the era of bevacizumab. *J Clin Oncol.* 2005;23:4853-4855.

Fernandez F, Ritter J, Goodwin J, et al. Effect of steatohepatitis associated with irinotecan or oxaliplatin pretreatment on resectability of hepatic colorectal metastases. *J Am Coll Surg.* 2005;200:845-853

Vauthey J, Pawlik T, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90 day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol.* 2006;24:2065-2072.

---

(Continued from page 654)

### **H&O** Where do you see advances being made in the future in the treatment of Hodgkin lymphoma?

**PM** In children, there has been a large effort to eliminate radiation because it has many more disadvantages than it does in adults. There is more time for children to develop cardiac problems or secondary cancers. Also, children can develop growth deformities. Pediatric studies have begun to use response-adapted treatment, meaning that if a patient has a rapid response to chemotherapy, radiation might not be employed. If the response is sluggish or incomplete, the patient will receive radiation. Positron-emission tomography (PET) rather than CT has been used in this regard because CT scans are difficult to interpret due to the residue of the tumor that remains. It is difficult to assess whether that residue is malignant or not. Thus, physicians are examining rapid responses, meaning negative PET scans within the first or second month, as a way to figure out whether to reduce treatment, especially radiation. Some adult trials are ongoing using PET scanning to judge the extent of treatment. Thus, rapid-response to initial therapy is an area for future investigation, with the

potential to reduce initial treatment based on how quickly the PET scan appears to be normal.

### **Suggested Readings**

Adams MJ, Lipsitz SR, Colan SD, et al. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. *J Clin Oncol.* 2004;22:3139-3148.

Adams MJ, Ng AK, Mauch PM, Lipschultz SE. Cardiac status predicts quality of life in Hodgkin's disease survivors. *J Clin Oncol.* 2006;24(18S pt 1). Abstract 9029.

Das P, Ng AK, Stevenson MA, Mauch PM. Clinical course of thoracic cancers in Hodgkin's disease survivors. *Ann Oncol.* 2005;16:793-797.

Kim HK, Silver B, Li S, Neuberg D, Mauch P. Hodgkin's disease in elderly patients (> or =60): clinical outcome and treatment strategies. *Int J Radiat Oncol Biol Phys.* 2003;56:556-560.

Nakatsuka S, Aozasa K. Epidemiology and pathologic features of Hodgkin lymphoma. *Int J Hematol.* 2006;83:391-397.

Ng AK, Li S, Neuberg D, et al. Comparison of MOPP versus ABVD as salvage therapy in patients who relapse after radiation therapy alone for Hodgkin's disease. *Ann Oncol.* 2004;15:270-275.

Ng AK, Li S, Neuberg D, Silver B, Weeks J, Mauch P. Factors influencing treatment recommendations in early-stage Hodgkin's disease: a survey of physicians. *Ann Oncol.* 2004;15:261-269.

Ng AK, Mauch PM. Late complications of therapy of Hodgkin's disease: prevention and management. *Curr Hematol Rep.* 2004;3:27-33.