

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: Clifford A. Hudis, MD

Colorectal Cancer In Focus

Liver-Directed Therapies in Colorectal Cancer

Michael Choti, MD, MBA
The Jacob C. Handelsman Professor of Surgery
Chief of the Handelsman Division of
Surgical Oncology
Johns Hopkins University
Baltimore, Maryland

H&O Can you provide some background on colorectal cancer and its spread to the liver?

MC Colorectal cancer (CRC) remains a major health problem. Despite the advances that have been made in screening and treatment, CRC is the second leading cause of cancer mortality in the United States involving both men and women. The mortality rate of CRC has dropped in the last decade. However, CRC is increasing in prevalence and incidence worldwide. Approximately 20% of patients have stage IV disease (metastatic) when diagnosed; most have locoregional disease at presentation, but many of these patients can go on to develop metastases at a later date. There are a variety of patterns of metastatic spread among patients with CRC, but the liver is one of the most common sites. Approximately 40% of patients with metastatic disease have liver only metastases, and in about 65% of patients, the liver is at least one of the components of metastatic disease.

H&O Can you discuss the so-called “curative-intent” therapy?

MC Even in patients with metastatic disease, we can offer options to cure the cancer in some cases. This typically involves resection or removal of all evident disease, including the metastatic sites. Most commonly, this is offered to patients with liver-only spread, but in selected cases the curative-intent paradigm can

be offered to those with extrahepatic disease. In this strategy, it is important to thoroughly and accurately stage the patient for the full extent of disease in order to address all sites when possible. In patients who have the primary tumor in place and have metastatic disease, a resection of the primary tumor and the metastases is necessary when offering a curative-intent therapy paradigm. It is also important to consider whether the disease is in fact resectable. The definition of whether cancer in the liver is resectable has evolved in recent years. In the past it was a restricted definition based on tumor number and sites, but at present, as long as all the metastatic disease can be safely removed, the patient may be considered resectable.

In some cases, more advanced techniques can sometimes be used to expand the opportunity to offer curative-intent approaches. When too much of the liver would need to be resected, preconditioning of the liver to expand the remnant or uninvolved liver or 2-staged liver resections can be done. In other cases, preoperative chemotherapy can be used to shrink the metastases, potentially converting a patient from unresectable to resectable. The percentage of patients with liver-only metastases who are candidates for surgical therapy have increased significantly, and thus our ability to offer curative therapy has also increased in the last decade.

H&O What are some other liver-directed therapies besides resection?

MC In patients who are not candidates for liver resection, there are other potential treatment strategies. One technique is tumor ablation; this should most commonly be used as a curative-intent strategy, much as resection is used, and generally only in cases where resection cannot be done. In some cases, ablation is used in combination with resection to treat all evident metastatic disease. With radiofrequency tumor ablation—the most common ablation technique—a probe is inserted in the tumor under image guidance, and electric energy is used to heat the tumor and surrounding margin to destroy the cancer cells. The role of palliative or partial ablative approaches is unproven, and generally they are not recommended.

Intra-arterial approaches have shown some benefit as well. With intra-arterial approaches, of which there is a variety, therapy is injected into the hepatic artery and directed to the tumor. Embolization techniques, either chemoembolization or radioembolization, deliver either chemotherapy or yttrium-90 beads, respectively, directly to the tumor-bearing liver while limiting the effects on the healthy parts of the liver or the rest of the body. These methods typically offer only partial destruction of the tumor but may in some cases improve survival. In addition, such regional approaches can be used in selected cases to shrink the tumors, with the goal of converting an unresectable situation to one in which surgical therapy can be done.

Radiation therapy is another liver-directed therapy. Historically, this approach has been difficult to perform, but now with computer-assisted stereotactic radiation therapy techniques, we can more accurately direct radiation therapy to specific areas in the liver.

H&O How does one make the decision of which therapy to utilize in a patient?

MC When planning a strategy for a patient with metastatic CRC, it is very helpful to evaluate the patient in a multidisciplinary setting in which high quality imaging is performed and an experienced team of medical oncologists, surgical oncologists, radiation oncologists, and interventional radiologists are able to strategize as to the best therapeutic approach. A multidisciplinary assessment allows us to review the case (both the biology of the patient and the distribution of the disease) to determine if the patient is a candidate for a curative-intent strategy. The assessment determines if the patient may be resectable, not resectable, or potentially convert-

ible with preoperative therapy. Based on the patient's status, it is then possible to determine the strategy and the sequence of therapies that may be offered.

Often, it is difficult to have a multidisciplinary team of experts in one center, particularly when expertise in all disciplines may not be available. In such cases, it is not uncommon to manage patients via a virtual multidisciplinary team. For example, the patient may be initially evaluated by a medical oncologist in the community. The scans can be reviewed by an experienced hepatobiliary surgeon at a higher volume center to determine resectability. In such cases, we aim to implement resources to develop remote multidisciplinary teams, where the medical oncologist in the community and a surgical oncologist at an expert cancer center work together and share communication as how to best treat the patient.

H&O What research efforts are under way?

MC One area we are interested in is defining the optimal sequencing of chemotherapy relative to liver surgery in patients who have resectable disease. While we know that both resection and chemotherapy may be recommended, we do not know if it is preferable to resect the cancer first and then give chemotherapy postoperatively, or to first administer some chemotherapy prior to performing the liver surgery. Currently, a large national cooperative trial (National Surgical Adjuvant Breast and Bowel Project C-11), which is sponsored by the National Cancer Institute, is studying this question. In this trial, patients are randomized to receive either liver resection followed by postoperative chemotherapy or preoperative chemotherapy followed by surgery and then more chemotherapy. This is an exciting trial, which is currently active and enrolling patients.

There are other ongoing studies also looking at new methods for performing ablation and image-guided therapies. New chemotherapeutic regimens that may increase the ability to convert a patient from unresectable to resectable status are also being studied. Investigators are also evaluating systemic and targeted therapies, specifically looking at such agents in conjunction with liver-directed therapies.

Suggested Readings

- Alsina J, Choti MA. Liver-directed therapies in colorectal cancer. *Semin Oncol.* 2011;38:561-567.
- Pwint TP, Midgley R, Kerr DJ. Regional hepatic chemotherapies in the treatment of colorectal cancer metastases to the liver. *Semin Oncol.* 2010;37:149-159.
- Lau KN, Swan RZ, Sindram D, Martinie JB, Iannitti DA. Hepatic tumor ablation: application in a community hospital setting. *Surg Oncol Clin N Am.* 2011;20:455-466.