

CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

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Locoregional Therapy for Liver Metastases in Colorectal Cancer



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H&O How often does colorectal cancer (CRC) metastasize to the liver?

AK The exact frequency has been controversial for a long time. Current data suggest that approximately 20% of patients with newly diagnosed CRC already have tumor in the liver, and liver metastases will develop over the course of the disease in 10% to 20% of the patients who do not have them at diagnosis. So, approximately 30% to 40% of all patients with CRC will have to deal with tumor in the liver at some point. That percentage represents approximately 40,000 to 50,000 patients per year.

H&O What is the standard treatment for a patient with CRC that has metastasized to the liver?

AK Treatment varies depending on when the metastasis occurs. For the 20% of patients who have liver metastases at initial diagnosis, the gold standard treatment begins with a discussion of the case at a multidisciplinary tumor board. There, the decision is made whether first to resect the primary tumor or first to give chemotherapy. The purpose of neoadjuvant chemotherapy is to shrink tumors in the liver and elsewhere enough to allow curative surgical resection of both the liver and primary tumors during the next few months.

For patients in whom liver metastases develop after their CRC has been treated, the approach is highly specialized. If a patient's disease is considered incurable because metastases have spread beyond the liver, perhaps to the lungs or the para-aortic lymph nodes, we consider a liver-sparing approach. We do not wish to undertake a major surgery to remove an entire lobe of a patient's liver if we will be leaving behind significant extrahepatic

tumor. In these patients, the best approach is to employ multiple-agent chemotherapy to decrease all metastases, which results in liver-dominant residual disease. Liver-directed therapies may then be able to render the patient tumor-free. In other patients, liver-dominant metastases are the immediate problem. In this situation, we ask, What can we do to render this liver as tumor-free as possible?

Although most patients with CRC in whom hepatic metastases develop are not able to receive potentially curable therapy, controlling disease in the liver can still lead to major improvements in overall survival, progression-free survival, and quality of life. That is why our multidisciplinary CRC tumor board generally recommends a variety of liver-directed procedures whenever possible.

In the 1990s and early 2000s, surgical resections for hepatic metastases were limited to patients with up to 4 tumors in 1 lobe. That approach was well supported by the data we had at that time. Over the last decade, however, most surgical oncologists began to decide on eligibility for resection of CRC liver metastases on the basis of the amount of residual functional liver volume rather than on the number of lesions. Surgeons now have many more tools at their disposal to resect tumors appearing in both sides of the liver, and they are better able to use a combination of resection and ablation that leaves behind enough normal functional liver.

H&O What are the various approaches to locoregional therapy besides resection?

AK The most commonly used ablative techniques are radiofrequency ablation (RFA), microwave ablation,

external beam radiation therapy, and intra-arterial radiotherapy. RFA and microwave ablation create a thermal injury that causes permanent tissue damage in the tumor and a small rim of normal liver adjacent to the tumor. With these techniques, local control of tumors that are up to 3 cm in diameter is excellent and approaches that of surgical resection.

In the external radiation approach, which is known as stereotactic body radiotherapy (SBRT), between 1 and 5 large individual daily fractions of radiotherapy are administered that target only the hepatic metastasis and

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spare normal liver. The size, location, and other eligibility factors are similar to those for RFA and microwave ablation, but SBRT can treat larger-diameter tumors successfully. SBRT is also effective at controlling lesions that are adjacent to large vessels, whereas heat sink can make RFA ineffective in these lesions.

Intra-arterial radiation therapy is also termed *radioembolization* and *selective internal radiotherapy* (SIRT). The radioactive element, which is yttrium 90, is securely embedded within microspheres that are 25 to 40 μm in diameter. SIRT is an outpatient procedure in which radioactive particles are delivered via the hepatic artery, which feeds metastatic tumors. The microparticles are permanently embedded in the tumor and deliver high doses of radiation locally in the tumor mass. With the type of radiation decay (beta) used, high-energy radiation travels only a few millimeters away from the sphere. Therefore, normal liver adjacent to the tumor is not subjected to radiation injury.

Another approach to intra-arterial treatment is to deliver chemotherapy by hepatic arterial infusion (HAI). This is not very commonly used at present, but in the past it demonstrated significant efficacy with acceptable toxicity in prospective studies. Whether radiation or chemotherapy is being delivered via the hepatic artery, arterial blood flows preferentially to liver metastases compared with normal liver. Metastatic tumors are efficient at taking up the therapeutic agent because cytokines have caused an excessive and abnormal

proliferation of arterial vessels. The arterial density in and around metastatic lesions can be up to 200 times higher than in normal liver parenchyma. This is a key factor exploited by intra-arterial therapies.

H&O Which patients are candidates for locoregional therapy?

AK A patient's eligibility for surgical resection is often very difficult to predict. It depends on many factors—the patient, the clinical course, underlying hepatic function, anatomic and physiologic issues, and the particular surgeon's skill and approach. This was made clear in the CLIMB study (An EORTC-ESSO Prospective Colorectal Liver Metastasis Database With an Integrated Quality Assurance Program), which was a prospective randomized trial of resection of liver metastases in CRC that included surgeons throughout Europe. It was difficult for the surgeons in the study to decide on a protocol for determining precisely who would or would not undergo resection. But in general, we want to begin treatment with resection or with an approach that combines resection and intraoperative ablation of all hepatic metastases.

Ablative techniques assist patients who are unable or unwilling to undergo major surgery. Although level 1 evidence to support this approach is limited, our multidisciplinary team favors less-invasive approaches in patients who have fewer, smaller tumors. RFA/microwave ablation is often a first choice for patients with 1 or 2 small hepatic tumors that are approachable and do not adhere to large blood vessels. If tumors occur in areas where RFA/microwave ablation will not be very effective, or if a tumor is more than 3 cm in diameter, we consider SBRT. If the number or location of metastases precludes SBRT, the preferred approach is intra-arterial radiotherapy with SIRT.

H&O Are there any other approaches to locoregional therapy?

AK Another approach to ablative therapy is irreversible electroporation, in which needles are placed around the tumor to deliver a high-voltage direct current. This technique is especially good for tumors near blood vessels, where RFA and microwave ablation are less effective owing to heat loss. Electroporation is a major procedure that requires a great deal of expertise on the part of the surgeon/interventional radiologist. It is not available at many centers, but it is another one of the tools in the toolbox.

H&O What else goes into deciding on the best approach for a patient?

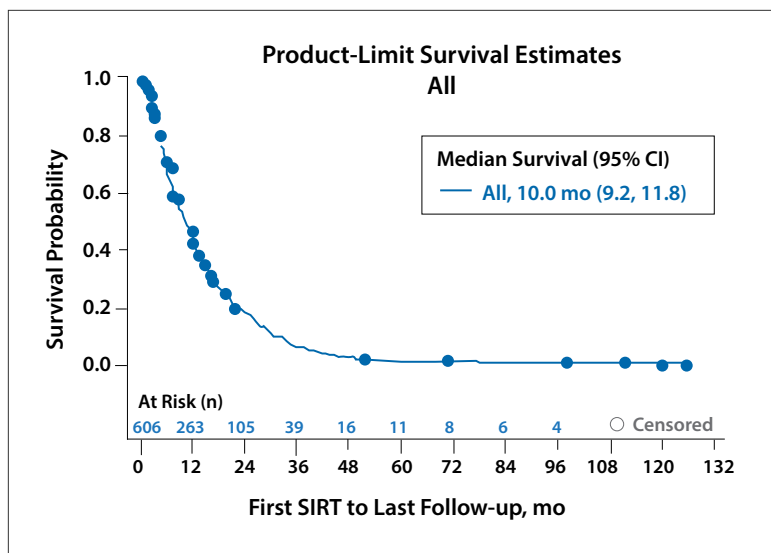


Figure. Kaplan-Meier survival curve for 606 patients with liver metastases due to colorectal cancer from the MORE (Metastatic Colorectal Cancer Liver Metastases Outcomes After Radioembolization) study, with follow-up through December 2016. Patients received chemotherapy initially, then selective internal radiotherapy (SIRT) with yttrium 90 resin microspheres as salvage treatment for chemotherapy-insensitive progressive metastases. mo, months; SIRT, selective internal radiotherapy.

AK At the initial diagnosis of CRC, the intent is to provide cure if possible. If we are not likely to achieve cure, can we prolong life and quality of life? For patients with incurable disease, a thoughtful and disciplined approach to sequencing liver-directed therapies will often provide excellent additional benefit beyond best-practice chemotherapy. The approach shifts in patients who have recurrent disease in the liver, or in whom liver metastases develop later. In these cases, we always begin by considering resection. If resection is not an option, we move on to ablation with radiation or RFA. The main consideration of therapy is preservation of at least 700 cc of functional liver.

In summary, for RFA/microwave ablation, the tumor should be no larger than 3 cm, should not be lying on a blood vessel, and should not be on the surface of the liver or within 1 cm of the stomach, duodenum, or large bile ducts. Similar but less stringent constraints apply in SBRT. We can treat very large tumors, and we can treat multiple tumors (usually not more than 3) as long as 700 cc of the liver is protected from radiation. When tumors are within 1 cm of the stomach or the duodenum, however, the radiation dose must be reduced.

In situations in which SBRT is not recommended, particularly when multiple tumors involve many segments, SIRT has the proven efficacy and safety advantage of being able to treat an unlimited number of tumors in both lobes. SIRT is a well-tolerated, outpatient treatment in which the incidence of grade 3 side effects is typically less than 10%. The potential downside of the intra-arterial approach is that as tumors get larger, SIRT is less likely to control them in a single treatment, so that repeated treatments are required to provide the best tumor control. If tumors respond after SIRT has been used but uncertainty

exists, a second SIRT procedure can be administered, or other options can be considered for the next treatment, including RFA and SBRT.

H&O How good are the results with the various approaches to locoregional therapy?

AK The best results are with surgery, which provides the most effective control of liver metastases and is the only technique proven to provide a cure in patients with CRC. We see a cure rate of approximately 40% in patients who undergo chemotherapy and have a complete resection of hepatic metastases.

For nonsurgical approaches, we do not report cure rates but rather rates of radiographic response, local control, hepatic progression-free survival, and overall survival. The local control rate is greater than 90% with RFA for tumors smaller than 3 cm, and it is also greater than 90% with SBRT in lesions from CRC primary tumors that are less than 6 cm in diameter.

The first clinical trial to evaluate RFA plus chemotherapy is the phase 2 CLOCC (Chemotherapy and Bevacizumab With or Without Radiofrequency Ablation in Treating Unresectable Liver Metastases in Patients with Colorectal Cancer; EORTC-NCRI CCSG-ALM Intergroup 40004) trial, presented at the 2015 annual meeting of the American Society of Clinical Oncology (ASCO) and recently published online in the *Journal of the National Cancer Institute*. This was an impressive effort by European groups to determine whether the addition of RFA to chemotherapy would benefit patients who have CRC with nonresectable liver lesions, which is the situation most frequently encountered in the patients we all see. This study of 119 patients

revealed much better progression-free survival in those who received RFA than in those who did not—16.8 vs 9.9 months ($P=.025$). That was something we suspected would be the case, but we appreciate having level 1 data to support this approach.

The thinking is that it does not matter whether you use RFA or SBRT to ablate a tumor; what is critical is rendering the liver tumor-free. That is highly beneficial to any patient who can go on to receive additional chemotherapy. For patients with unresectable disease, who comprise the vast majority of our patients, we mix and match our tools to get the best result. When RFA becomes untenable, we can use SBRT and get results that are just as good. If SBRT is not appropriate, we can use SIRT. This technique does not provide local control similar to that achieved with RFA or SBRT, but there is a much larger tumor burden with more advanced disease, and these patients have greater prior exposure to chemotherapy and antibody treatments. Even with all that, the reported response rates are 50% or higher, and overall survival is improved in salvage patients (those with progressive disease after third-line chemotherapy). Modest prospective and large retrospective reports, including one that I published with the Metastatic Colorectal Cancer Liver Metastases Outcomes After Radioembolization (MORE) study investigators in 2016, demonstrate consistent results with SIRT worldwide. Median overall survival in patients with chemotherapy-insensitive CRC metastases has improved from 5 or 6 months to approximately 9 to 12 months in the most recent results (Figure).

In the first-line therapy of liver-dominant CRC metastatic disease, the SIRFLOX study (FOLFOX Plus SIR-Spheres Microspheres Versus FOLFOX Alone in Patients With Liver Mets From Primary Colorectal Cancer) of 530 patients, which was presented at the ASCO meeting in 2015 and published in the *Journal of Clinical Oncology* in 2016, showed that the addition of SIRT to chemotherapy in the liver improved progression-free survival from 12.6 months to 20.5 months. No difference was seen in overall survival, but we should have more answers after the 2017 ASCO annual meeting, where we expect to hear the widely anticipated results of a meta-analysis of 3 studies—SIRFLOX, FOXFIRE (5-Fluorouracil, Oxaliplatin and Folinic Acid With or Without Interventional Selective Internal Radiation

Therapy As First-Line Treatment for Patients With Unresectable Liver-Only or Liver-Dominant Colorectal Cancer), and FOXFIRE Global. Each of these 3 studies has approximately 450 patients, and the meta-analysis will include approximately 1100 of them.

H&O Has the availability of modern chemotherapy and biologic agents increased the number of patients eligible for resection?

AK When I first began administering liver-directed treatments in 1999, I usually became involved in treating the liver at 6 to 8 months after a patient's initial diagnosis. Thanks to advances in modern chemotherapy and the availability of biologic agents in CRC, now I often do not see patients for hepatic therapy until 20 to 30 months after their original diagnosis. Many more patients are becoming eligible for liver-directed treatments, including resection, and they often receive more than 1 hepatic therapy over the course of their disease.

Disclosure

The Sarah Cannon Research Institute received a grant from Sirtex Medical to conduct a clinical trial of yttrium 90 resin microspheres.

Suggested Readings

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