Surgical Management of Liver Metastases From Colorectal Cancer

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Abstract

Surgical resection remains one of the major curative treatment options available to patients with colorectal liver metastases. Surgery and chemotherapy form the backbone of the treatment in patients with colorectal liver metastases. With more effective chemotherapy regimens being available, the optimal timing and sequencing of treatments are important. A multidisciplinary approach with the involvement of medical oncologists and surgical oncologists from the beginning is crucial. Identification of the clinical and molecular prognostic factors may help personalize the treatment approaches for these patients. This article provides an overview of the surgical management of colorectal liver metastases.

INTRODUCTION

Colorectal cancer is the third most common cancer and the third leading cause of mortality among men and women. In 2015, there will be an estimated 132,700 new cases and an estimated 49,700 deaths from colorectal cancer.[1] Approximately 30% to 50% of patients with this disease will develop liver metastases at the time of presentation or later during the course of their disease.[2,3] The focus of this article is to discuss the surgical management of liver metastases in the context of other treatment options available to these patients. Surgical resection can be curative in a subset of patients with limited disease and favorable biology.

TREATMENT OPTIONS

The treatment of patients with metastatic colorectal cancer is multidisciplinary, involving surgeons (surgical oncologist, hepatobiliary surgeons, and colorectal surgeons), medical oncologists, radiation oncologists, radiology, interventional radiologists and oncologists, gastroenterologists, and ancillary staff. These patients should be discussed in a tumor-board fashion and surgeons should be involved early in their care.

Several treatment options are available for patients with colorectal liver metastases, with chemotherapy and surgical resection forming the backbone of treatment in these patients. There have been several advancements in the field of chemotherapy, with three major classes of drugs being used: cytotoxic chemotherapy, including fluorouracil with leucovorin, capecitabine, irinotecan, and oxaliplatin; angiogenesis inhibitors, including bevacizumab, ziv-aflibercept, and regorafenib; and epidermal growth factor receptor (EGFR) inhibitors, including cetuximab and panitumumab.

These drugs have been studied extensively in phase III randomized clinical trials.[4] In the United States, unless otherwise contraindicated, patients receive multidrug regimens, including infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX)/fluorouracil, leucovorin, and irinotecan (FOLFIRI) with or without angiogenesis inhibitors or EGFR inhibitors, on the basis of their expanded *RAS* (*KRAS/NRAS/HRAS/BRAF*) mutational profile, as first-line therapy. Given its

ASSOCIATED CONTENT

See accompanying commentaries on pages 40 and 42

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increased toxicity, fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) may be considered in highly select patients in whom a high response rate is desired and an aggressive approach is warranted.

Recent trials, including FIRE-3, PEAK, and Cancer and Leukemia Group B (CALGB)/Southwest Oncology Group (SWOG) 80405,[5-7] have attempted to compare anti-EGFR regimens with anti–vascular endothelial growth factor (VEGF) regimens. Anti-EGFR regimens were associated with higher response rates in the FIRE-3 and PEAK trials and a statistically significant increase in median overall survival (OS) in the first-line setting (anti-EGFR *v* anti-VEGF OS: FIRE-3, 28.7 months *v* 25 months; PEAK, 34.2 months *v* 24.3 months).

Further discussion regarding the chemotherapeutic options is beyond the scope of this article.

SURGICAL TREATMENT

Hepatic Resection

Hepatic resection remains one of the major curative treatment options available to patients with liver metastases. Decision making for these patients can be complex and several factors must be considered, including medical tolerability and technical and oncologic feasibility. Evaluation for medical fitness remains paramount before embarking on any treatment option in these patients.

Preoperative Imaging to Evaluate the Extent of Disease

A high-quality, preoperative, triple-phase computed tomography (CT) scan with thin cuts or a contrast-enhanced dynamic magnetic resonance imaging (MRI), preferably with liver-specific contrast agents such as gadoxetate disodium, is paramount to preoperative evaluation of liver metastases in these patients.[8] In addition, a complete staging work-up, including colonoscopy and chest CT in patients who had CT of the abdomen and pelvis, or chest, abdomen, and pelvis CT in patients who were evaluated by liver MRI, is essential for evaluation of extrahepatic disease. The role of positron emission tomography/CT in colorectal liver metastases remains controversial, and recent studies have questioned its routine use.[9] The two goals of preoperative imaging are to identify the extent of liver metastasis, and to determine the presence of any extrahepatic disease. Figure 1 shows how proper imaging can improve the detection of liver metastases.

Limits of Resection

Historically, several criteria, which were based on size and number of metastases, expected margin of resection, and presence of extrahepatic disease, excluded patients from undergoing liver resection.[10] However, the availability of portal vein embolization, ablation techniques, two-stage hepatectomies, preoperative chemotherapy, and resections in the setting of extrahepatic metastases have led to a paradigm shift and an increase in number of complex resections.[11,12] In simplified terms, the focus of surgical resection has shifted from what is being removed to what is being left behind. The limits of technical resection include leaving behind at least two contiguous liver segments with adequate vascular inflow and outflow, adequate biliary drainage, and an adequate future liver remnant.

The terminology used for hepatic resection has been standardized.[13] Most experts consider removal of three or more segments as major hepatectomy.

Decision making before surgery involves evaluation for the following: number, size, and location of lesions and their relationship to inflow and outflow vessels; subtle radiologic signs such as fatty liver disease and signs of portal hypertension such as splenomegaly (low platelet count and impaired liver function tests can be an indicator of underlying liver damage); portal and retroperitoneal lymphadenopathy; peritoneal carcinomatosis; other areas of metastases, including lung, mediastinum, bone, etc; and size and function of the future liver remnant.

Evaluation of Future Liver Remnant Volume

Major or extended hepatectomy may lead to an inadequate future liver remnant that can be associated with significant risk of hepatic insufficiency and subsequent mortality. Although the risk of hepatic insufficiency is determined by several factors, the size of the future liver remnant continues to be one of the major determinants of postoperative hepatic failure.

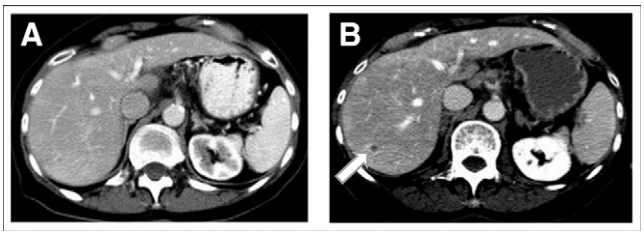

FIG 1. Role of appropriate imaging. An appropriately timed computed tomography (CT) scan with thin slices can enhance the detection of liver metastases. (A) Regular CT scan with thick slices. (B) Thin-cut CT scan with enhanced visualization of segment 7 lesion (arrow).

Precise measurements of hepatic volume are needed before operating on any patient who is likely to be left with an inadequate future liver remnant, because the size of the right and left hemilivers varies considerably among the patients.[14,15]

The size of the future liver remnant can be calculated using three-dimensional CT volumetry.[15] The size of the future liver remnant has been used as a surrogate to predict postoperative outcomes. In patients with normal liver function, a future liver remnant of at least 20% is recommended. For patients with cirrhosis and for those treated with systemic chemotherapy because of the underlying liver dysfunction, a larger future liver remnant size is recommended (40% for cirrhosis, 30% after systemic chemotherapy).[15]

Portal Vein Embolization

A small future liver remnant may increase the risk of post-hepatectomy liver failure; however, this can be avoided by inducing ipsilateral atrophy of the tumor-bearing liver and compensatory hypertrophy of the future liver remnant by selectively occluding the blood flow to the tumor-bearing part of the liver. Portal vein embolization is offered to patients with normal liver function and a future liver remnant of 25% to 30% and to those with compromised liver function, such as post-chemotherapy liver damage, cirrhosis/fibrosis, and cholestasis and a future liver remnant of 35% to 40%.[16] In the post–portal vein embolization period, the future liver remnant undergoes rapid hypertrophy in the ensuing 3 to 4 weeks. In patients who have diabetes and cirrhosis, the hypertrophy may be delayed, and an additional 3 to 4 weeks may be required to assess the complete response.[16] Figure 2 shows the increase in the volume of the remnant liver after portal vein embolization.

A recent meta-analysis by van Lienden et al[16] has shown that the mean technical success rate of the procedure is 99.3% and that 96.1% of patients undergo sufficient hypertrophy of the future liver remnant to allow resection. The mean increase in future liver remnant size is 37.9% (range, 20.5% to 69.4%). Chemotherapy does not seem to affect the hypertrophy, whereas patients with cirrhosis and fibrosis tend to undergo less hypertrophy than do patients with normal livers. Less than 1% of patients may develop severe complications in the form of severe cholangitis, liver abscesses, sepsis, or portal venous or mesentericoportal venous thrombosis precluding liver resection. The originally planned liver resection may not be possible in approximately 20% of patients because of intra-hepatic tumor progression, extrahepatic tumor spread, insufficient hypertrophy, major complications, or preoperative mortality or if the patient refuses.

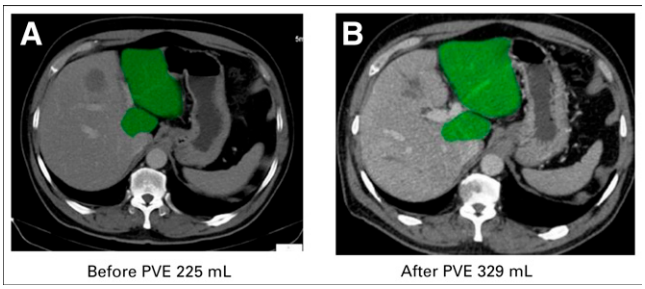

FIG 2. Liver hypertrophy after portal vein embolization (PVE). (A, before; B, after) Shaded area in green depicts increase in volume of the left lateral segment after PVE of the right side.

Portal vein embolization can be used as a stress test for the liver. Patients who undergo sufficient hypertrophy may do well with resection, whereas those with insufficient hypertrophy are more likely to experience complications and posthepatectomy liver failure. Similarly, any disease progression seen during the period of portal vein embolization indicates aggressive tumors to begin with, and resection may not change the course of the disease. Technical factors that can enhance hypertrophy after portal vein embolization include embolization of segment 4 branches during right portal vein embolization and the use of small spherical particles.[17] All three of the following criteria should be taken into consideration to prevent post-hepatectomy liver failure: absolute increase of 5%; kinetic growth rate of $\geq$ 2% per week of the future liver remnant; and overall size of future liver remnant ($>$ 30% after chemotherapy, $>$ 40% for early cirrhosis or fibrosis).

Margins of Resection

R0 resection margins are the goal of surgical resection. A positive margin increases the risk of local recurrence and compromises long-term survival. Older studies showed an advantage of a 1-cm resection margin over just achieving a negative margin; however, studies performed in the era of modern chemotherapy argue that the extent of the negative margin has minimal impact on the outcome. In addition, as more and more complex resections are being undertaken, a 1-cm margin is not always feasible. The goal of surgery is to achieve an R0 resection margin.[18-20]

Chemotherapy: Resectable Versus Unresectable Disease

The role of adjuvant therapy in patients with resectable liver metastases is controversial. EORTC 40983 randomly assigned

patients with resectable liver metastases to perioperative chemotherapy (FOLFOX4) versus surgery alone. The use of perioperative chemotherapy resulted in an improvement in progression-free survival; however, long-term data did not show any statistically significant benefit in OS.[21,22] The advantages of chemotherapy in patients with resectable disease remain controversial; however, most surgical oncologists recommend a short course of chemotherapy 2 to 3 months before surgical resection to assess tumor response to systemic therapy. Long periods of systemic therapy before resection can lead to two issues: chemotherapy-induced liver injury or steatohepatitis, and disappearing colorectal liver metastases.

In contrast to the treatment of resectable liver metastases, chemotherapy remains the mainstay of therapy for patients with unresectable liver metastases. With the advent of modern chemotherapy regimens, response rates to first-line chemotherapy using FOLFOX/FOLFIRI and biologic agents, such as VEGF inhibitor or EGFR inhibitors, are up to 60% to 70%, and median survival is up to 34 months in patients with metastases.[5-7,23] However, progression-free survival still averages 10 months, and response rates in the second-line setting average only 30%.[24] With modern chemotherapy, a subset of patients (approximately 15% to 40%) with unresectable disease may convert to resectable disease, and these patients have a long-term outcome comparable to those with an original diagnosis of resectable disease (ie, a 5-year survival of 30% to 40%).[25-30] Patients receiving chemotherapy who continue to have unresectable disease either because of lack of adequate response or because of progression of disease have a poor prognosis. In addition to the improved efficacy of systemic chemotherapy, factors that have contributed to the increase in secondary resection rates include portal vein embolization, two-stage hepatectomies, ablation techniques, expanding criteria for resection, and improved surgical and parenchymal transection techniques.

Two-Stage Hepatectomy

In patients presenting with unresectable bilobar liver metastases who respond to systemic chemotherapy, a two-stage hepatectomy approach has been proposed. Most of these patients have synchronous metastases at the time of presentation. In addition, one side of the liver is less affected than the other. In these patients, a limited resection could clear the less affected side of the liver before the patient undergoes a future contralateral liver resection. In the majority of these patients, systemic chemotherapy is administered initially, followed by a limited resection of the left side. Right portal vein and segment 4 branch embolization is used next to increase the size of the left lateral sector, and these patients then undergo an extended right hepatectomy. Figure 3 depicts an example of a patient who underwent this approach.

Brouquet et al[31] reported that 72% of the patients selected for this approach were able to complete the second stage of the procedure. Progression of the disease was the main cause (61%) for noncompletion of the second stage. After a median follow-up of 50 months, 5-year survival was 51% in the two-stage hepatectomy group compared with 15% in those treated by chemotherapy alone. Lam et al[32] performed a systematic review on the topic and included 10 studies with a total of 459 patients in their quantitative analysis. Seventy-seven percent of the patients were able to undergo the planned second stage, and the median survival of this cohort was 37 months. In selected patients with unresectable bilobar colorectal liver metastases, a two-stage hepatectomy seems to be safe. The duration of preoperative and interval chemotherapy between the two stages varies among institutions and must be decided on a case-by-case basis.

There are several different possibilities for treatment sequencing: (1) chemotherapy, hepatectomy (first stage), hepatectomy (second stage), then chemotherapy; (2) chemotherapy, hepatectomy (first stage), portal vein embolization, hepatectomy (second stage), then chemotherapy; and (3)

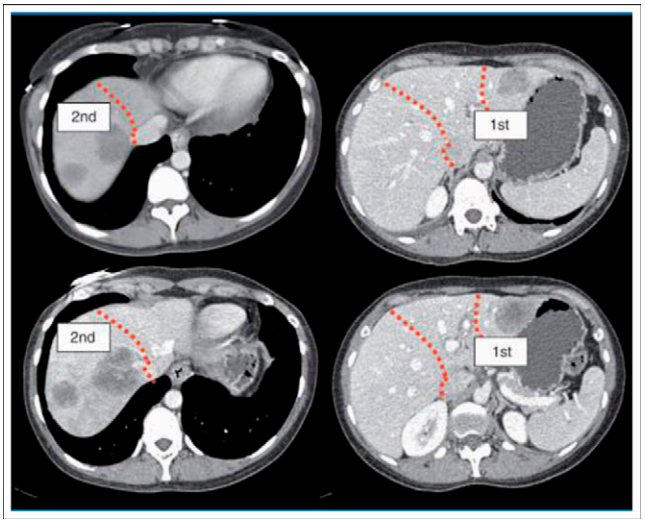

FIG 3. Two-stage hepatectomy. Minor disease is resected first, followed by contralateral portal vein embolization to maximize future liver remnant before major hepatectomy.

chemotherapy, hepatectomy (first stage), portal vein embolization, chemotherapy (second stage), hepatectomy, then chemotherapy.

Chemotherapy-Associated Liver Injury or Steatohepatitis

The majority of patients receive chemotherapy before liver resection, with FOLFOX and FOLFIRI forming the backbone of modern-day chemotherapy. Longer durations of chemotherapy are being used to increase cure rates in resectable cases and for conversion therapy (ie, to convert unresectable to resectable disease); however, the use of more than eight cycles of chemotherapy leads to chemotherapy-associated liver injury, without increasing response rates.[33] Therefore, longer durations of chemotherapy should be avoided, and liver surgeons should be involved from the beginning in the multidisciplinary care of patients with colorectal liver metastases. The goal of chemotherapy should be to facilitate resection rather than to maximize the response before resection.[34]

Oxaliplatin is associated with sinusoidal damage, which can appear as blue liver intraoperatively. Therefore, a longer duration of oxaliplatin therapy can give rise to portal hypertension, often noted on the preoperative CT scan as splenomegaly and ascites.[34] In addition, blue liver leads to increased perioperative blood loss without increasing mortality. Irinotecan is associated with steatohepatitis, especially in patients with obesity and diabetes, resulting in yellow liver.[35] Irinotecan-associated steatohepatitis has been shown to increase the risk of posthepatectomy liver failure; however, more recent data suggest that morbidity is not influenced by the type of chemotherapy used.[36,37]

Disappearing Liver Metastases

The response rates to modern chemotherapy have increased, resulting in complete radiographic response in some patients; the lesions in these cases are termed disappearing liver metastases. The incidence of disappearing liver metastases varies from 7% to 24%.[11,38] Approximately 10% to 50% of these lesions can be detected in the operating room. Disappearing liver metastases are more likely to occur in patients with smaller tumors or multiple tumors and in those undergoing an increasing number of cycles of chemotherapy. The incidence of disappearing liver metastases varies with the imaging modality used. MRI with the appropriate contrast medium has the highest sensitivity and specificity.[8] Limiting the duration of chemotherapy to less than 3 months also helps limit the number of disappearing liver metastases.

Complete pathologic response is seen in approximately two thirds of resected disappearing liver metastases. However, if left in situ, more than one half of these lesions will recur.[38-41] Factors associated with true pathologic response are seen in patients who undergo hepatic artery infusion therapy, have normalization of carcinoembryonic antigen (CEA), underwent MRI as preoperative imaging, have no steatosis, and have a body mass index less than 30.[38] Rubbia-Brandt et al[42] reported that pathologic tumor regression corresponds to fibrosis overgrowth and a decrease in necrosis. The degree of tumor regression predicts disease-free survival and OS, independent of the neoadjuvant chemotherapy used. Oxaliplatin-containing regimens are associated with higher tumor regression compared with irinotecan-containing regimens. However, complete sterilization of the tumor after chemotherapy is rare ($< 5\%$), which further supports the notion of the resection of disappearing liver metastases.

The management of disappearing liver metastases remains controversial. Resection is the usual recommended treatment, if resection of all original sites of disappearing liver metastases is feasible. If the original sites cannot be resected, it is reasonable to resect macroscopic disease and leave disappearing liver metastases in situ because more than one half of these tend to recur within a year. A recent study suggests that surveillance of disappearing liver metastases after systemic chemotherapy was more beneficial and cost effective among patients older than 60 years and with multiple factors predictive of true complete, pathologic response, such as normalization of CEA, hepatic artery infusion therapy, body mass index $\leq$ 30 kg/m^2, and diagnosis of disappearing liver metastases made through MRI.[11]

Survival

Overall, 5-year survival after resection in patients with colorectal liver metastases varies from 40% to 60% in large series, and 10-year survival is up to 30% in some series.[12,43] Two large series of more than 2,000 patients reported a 5-year survival of approximately 40%.[20,44]

Resection can be curative in a subset of patients with limited disease and favorable biology; however, more than two thirds of these patients will have recurrences, and most of these tend to occur within the first 2 years. Patient selection is the key. Several prognostic models have been devised to act as adjunctive tools for patient selection, postoperative prognostication, and further substratification for use of adjuvant therapy. The clinical risk

score proposed by Fong et al[45] in 1999 remains one of the most commonly used prognostic scoring systems for resection of colorectal liver metastases.[46] Some of the scoring systems proposed by others have been discussed in detail elsewhere.[46] Nodal status of the primary tumor, disease-free interval, CEA levels, liver tumor burden, and the presence of extrahepatic disease remain some of the common factors included in these scoring systems.

Poor predictors include an increasing number and size of the metastatic tumors, positive nodal status of the primary tumor, short disease-free interval, and high CEA.[46] Lack of tumor regression after chemotherapy also portends poor prognosis.[46] Recently, molecular factors, such as the presence of *KRAS* mutation and *BRAF* mutation, have been associated with poor prognosis.[47,48]

Morbidity and Mortality

Analyses of the American College of Surgeons–National Surgical Quality Improvement Project database have reported a 30-day mortality of 2.5% and a major morbidity rate of 19.6%. A subset analysis of patients with metastatic disease has reported an even lower 30-day mortality (1.3%). Single-center series have reported lower mortality and morbidity rates after liver resections, including liver resections for colorectal liver metastases.[49]

Other approaches being used for the treatment of colorectal liver metastases include ablation with or without resection, embolization strategies (transarterial chemoembolization, especially with drug-eluting beads loaded with irinotecan), transarterial radioembolization or selective internal radiotherapy, hepatic artery infusion pump therapy, and stereotactic radiation. Discussion of these modalities is beyond the scope of this article.

In conclusion, chemotherapy and resection remain the backbone of treatment of colorectal liver metastases. Because the number of options available in the armamentarium is increasing, a multidisciplinary approach is recommended. Medical oncologists and surgical oncologists should see the patients from the beginning of their treatment for optimal sequencing of treatment planning. Quality of life should always be kept in mind. All treatments should be accompanied by best supportive care, and, in cases of disease progression, functional status decline, inability to tolerate treatment, and patient wishes, best supportive care should be pursued. JOP

Authors' Disclosures of Potential Conflicts of Interest

Disclosures provided by the authors are available with this article at jop.ascopubs.org.

Author Contributions

Conception and design: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Surgical Management of Liver Metastases From Colorectal Cancer

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