Can Metastatic Colorectal Cancer Be Cured?

This article reviews the main issues that must be considered in metastatic colorectal cancer from the surgical oncology and medical oncology perspectives, respectively.

Introduction

In 2012, colorectal cancer (CRC) continues to be a major public health problem. In the United States this year, there will be an estimated 147,000 new cases diagnosed and nearly 50,000 deaths resulting from this disease.[1] Worldwide, approximately 1 million new cases of CRC are diagnosed each year, with nearly 500,000 deaths attributed to this disease annually. About 25% of patients present with metastatic disease, and of this group, 50% to 75% will have disease confined to the liver.[2-4] In patients who present initially with early-stage disease, up to 50% will eventually develop metastatic disease, with the liver being the most common site. Another 10% to 20% of patients will present with disease involving the lung and other less common sites of metastatic involvement, including the peritoneum, ovaries, adrenal glands, bone, and brain.[5,6]

When metastatic disease is limited to an organ-specific site, an important consideration is whether the disease is resectable at the time of initial diagnosis or whether it is initially deemed to be unresectable but may become resectable with the up-front use of chemotherapy. With the integration of chemotherapy and surgical resection, overall 5-year survival rates on the order of 30% to 40% can now be achieved. A multidisciplinary, team-based approach involving surgeons, medical oncologists, radiologists, and other healthcare professionals is required to determine the optimal timing and sequence of surgery and chemotherapy.

This article reviews the multidisciplinary approach to patients who have organ-limited metastatic CRC (mCRC), with the main focus being on liver-limited disease. In particular, the surgical and chemotherapy aspects of disease management will be discussed.

Surgical Considerations for Patients With Metastatic Disease

Historically, the setting of liver-limited metastases from CRC has been one of the few examples of curative metastasectomy in oncology. Even before the development of effective chemotherapy agents, surgical resection of limited hepatic metastases was associated with prolonged survival and cures.[7] Several important prognostic factors, such as disease-free interval, number and size of metastases, presence of extrahepatic disease, and stage of the primary cancer, have all helped to define the expected cure rate for hepatic metastasectomy. For patients with metastases defined by the most favorable prognostic categories, cure rates of 24% have been achieved with surgery alone.[8] The indications for surgical metastasectomy were for patients with disease limited to the liver, a total of four or fewer metastases, unilobar involvement, tumors of less than 5 cm in their greatest diameter, and a disease-free interval of at least 6 months.[9-12] It is, therefore, not surprising that the development of more effective chemotherapy has led to a significant improvement in overall survival and cure rates, as well as an expansion of the indication for metastasectomy. This indication has evolved into resection of any disease that allows for adequate hepatic residual volume for liver regeneration and survival, assuming there has been a response to neoadjuvant chemotherapy.[13] In the past, surgeons were appropriately concerned that resection of visible disease would be followed by rapid recurrence from microscopic metastases in the residual liver. However, incorporation of effective neoadjuvant and/or conversion chemotherapy, as will be discussed in this article, provides greater confidence that micrometastatic disease can be eliminated and that removal of gross disease can lead to long-term cure. In addition, as hepatic surgery has become safer and easier for the patient, there is now wider acceptance of incorporating hepatic resection into a multimodality strategy to prolong survival.

The options for local and regional treatment of hepatic metastases have become broad, and include
surgical resection, local ablation therapy, hepatic arterial infusion therapy, transarterial chemoembolization, radiofrequency therapy, and isolated hepatic perfusion.[14,15] Each of these approaches has been associated with long-term cures, although surgical resection and local ablation strategies have been the most effective. The goal for surgical resection is to achieve a negative microscopic margin. Given the concern about microscopic extension beyond the visible tumor, a 1-cm margin around the tumor is ideal. Numerous coagulation devices exist to enhance the safety of parenchymal transection by limiting blood loss. Minimally invasive approaches, such as laparoscopic and robotic assistance, have become commonplace, and they are associated with reduced blood loss, shortened hospital stay, and decreased narcotic usage postoperatively.[16,17] For patients undergoing multimodality therapies, minimally invasive surgery may also improve quality of life during treatment and decrease the recovery time necessary before adjuvant chemotherapy is administered. The options for resection include extended lobectomy, lobectomy, segmentectomies, and nonanatomic wedge resections. Many surgeons remove the least amount of liver tissue feasible to preserve the anatomy for future resections, if necessary, while others prefer formal anatomic resections in order to provide the best chance of a negative margin. These two approaches have not been directly compared in a randomized trial; however, retrospective data suggest that the ability to achieve a negative margin, as opposed to the specific type of resection, determines long-term prognosis.[18]

Local ablative approaches have provided an alternative to surgical resection for patients with mCRC. These approaches include radiofrequency ablation (RFA), microwave ablation, cryotherapy, and focused radiotherapy (eg, using the CyberKnife). RFA is a reliable technique to ablate metastases up to 5 cm in size. However, it has limited efficacy in centrally located tumors in which proximity to the main portal triads or hepatic veins may cause bile duct injury, extensive hepatic necrosis, or inadequate tumor cell death adjacent to the vessels. The potential advantages of these local strategies over surgical resection include enhanced safety, outpatient percutaneous treatment options, and the ability to preserve hepatic parenchyma. The local recurrence rate after local ablative procedures is clearly higher than with surgical resection, with rates as high as 34% having been reported.[19] The local recurrence rate at the site of ablation is influenced by the size and location of the metastatic lesions, as well as the use of percutaneous vs laparoscopic approaches. Although local recurrence can often be salvaged with repeat ablation or resection, for patients with limited comorbidities in whom the goal is curative intent, surgical resection is the preferred and most reliable method for actual cure. A meta-analysis of nonrandomized studies comparing RFA with surgical resection demonstrated an improvement in 5-year survival for patients treated with hepatic resection.[20]

### TABLE 1

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<th>Prognostic Factors for Cure After Surgical Resection</th>
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The curative potential of surgical resection for hepatic metastases from CRC varies depending on a number of important prognostic factors (Table 1). Nomograms for predicting cancer-related survival have been developed, and may be helpful when considering the utility of resection.[21] A patient’s risk for morbidity and mortality also plays a significant role in defining the eventual treatment strategy. Surgical resection is still associated with a defined mortality rate of 2.8% (0 to 6.6%), which is influenced, in large part, by the health of the background liver.[22,23] Liver failure is the most common cause of death after hepatectomy, and as discussed below, this complication is influenced by the specific type and cumulative dose of chemotherapy received. The indications for surgical resection are currently based on feasibility and safety in patients who have responded to chemotherapy. It is critically important for the surgical resection to leave 20% to 25% of functioning liver volume (future liver remnant [FLR]) in patients with a normal background liver, and 40% of liver volume in patients whose background liver is diseased from previous chemotherapy.[24] Preoperative planning CT scans, including residual volume calculations, are essential when planning...
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an extended or bilobar resection.[25]
To date, more than 750 series of hepatic metastasectomy for metastatic CRC have been reported in the literature. The actuarial 5-year survival rate for patients who underwent R0 resections (negative margins) was 30% when combining 16 well-reported series of more than 100 patients with follow-up greater than 2 years (15% to 67%).[22] While 5-year survival was historically considered a cure for this disease, because of advances in systemic chemotherapy an increasing number of patients are now living with their disease beyond 5 years. A single-institution study of 455 patients revealed a median overall survival of 33 months, with 5- and 10-year actuarial survival rates of 34% and 25%, respectively.[26] In that study, 124 patients were identified as actual 5-year survivors (27%), and of this group 59 were found to be 10-year survivors. This finding suggests ongoing disease-related mortality beyond the 5-year time-frame, with actual cure rates of 10% to 15%. Randomized clinical data suggest an improvement in disease-free survival when systemic chemotherapy is incorporated as part of a combined neoadjuvant and postoperative adjuvant approach, as will be discussed in detail in this article.

With the extended indications for hepatic metastasectomy in the presence of active systemic chemotherapy, larger resections can now be safely and effectively performed. Commonly used techniques include staged resections for bilobar disease and preoperative portal vein occlusion to achieve compensatory hypertrophy and safer extended resections.[27,28] While there appear to be impressive actuarial 5-year survival rates in these series of extensive surgical resections, it is expected that the true cure rate will be much lower. When looking at patients with initially unresectable colorectal liver metastases who were treated with chemotherapy and then resected, 16% of this group were considered cured, with a disease-free interval of more than 5 years after metastasectomy.[29] On multivariate analysis, the main predictors of cure included maximum size less than 3 cm, no more than three metastatic lesions, and complete pathologic response.

Systemic Chemotherapy

Long-term cures are exceedingly rare when patients with organ-limited mCRC are treated with chemotherapy alone. In a retrospective review of 2751 patients with metastatic CRC, during a median follow-up of 10.3 years, only 6 (0.24%) were found to be free of disease after having received chemotherapy alone.[30] It is now well established that a multimodality strategy results in a much higher chance of long-term cure. In patients with organ-limited disease, chemotherapy is administered in three main settings, which include neoadjuvant therapy, conversion therapy, and adjuvant therapy. Neoadjuvant therapy refers to chemotherapy given to patients with potentially resectable disease, while conversion therapy refers to chemotherapy given to patients deemed to have initially unresectable disease. Adjuvant chemotherapy is use of chemotherapy following an R0 surgical resection, with the intent of preventing disease recurrence.

Neoadjuvant Chemotherapy

Up to 20% to 30% of patients with liver-limited mCRC may have potentially resectable disease at the time of initial presentation. However, because a large proportion of patients experience recurrence of their disease either in the liver or systemically, chemotherapy has been integrated in their up-front care to improve upon the potential benefit of surgery.

Several clinical trials have specifically evaluated the role of neoadjuvant therapy for patients with potentially resectable liver metastases. In a single-arm trial involving 20 patients, neoadjuvant therapy with a weekly administration of FOLFOX (fluorouracil [5-FU], leucovorin/folinic acid [LV], and oxaliplatin [Eloxatin]) resulted in a partial or complete response in all patients enrolled.[31] A total of 16 patients underwent a potentially curative resection, with 7 developing recurrence during the median follow-up period of 23 months. A phase II trial of neoadjuvant therapy investigated bevacizumab (Avastin) plus CapOx, the combination of capecitabine (Xeloda) and oxaliplatin.[32] In this study, 56 patients received 6 cycles of therapy prior to surgical resection, and a remarkably high objective response rate of 73% was observed. A total of 52 of the 56 patients were able to undergo an R0 resection, with complete pathologic response occurring in nearly 10% of patients. Given concerns over the potential risks of bleeding or wound-healing complications, bevacizumab was not given with the last cycle of chemotherapy prior to surgery. This study is important as it showed that bevacizumab could be safely administered to patients with no increased risk of intraoperative bleeding or wound-healing complications. Moreover, it was estimated that normal liver regeneration occurred in all but one patient.

The European Organisation for Research and Treatment of Cancer (EORTC) randomized phase III trial
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40983 investigated use of perioperative FOLFOX4 chemotherapy in patients with up to four resectable liver metastases. In this study, patients were randomized to surgery alone or to receive 6 cycles of FOLFOX4 before surgery and 6 cycles of FOLFOX4 after surgery.[33] The overall response rate was 43% in patients receiving chemotherapy. Of note, surgery was performed in 83% of patients randomized to chemotherapy and in 84% of patients randomized to surgery alone, providing evidence that use of initial chemotherapy did not compromise the ability of patients to undergo surgical resection. While there was an increased risk of postoperative complications in patients receiving neoadjuvant chemotherapy, these events were reversible and not associated with an increased risk of mortality. When the entire group of randomized patients was considered, a 7.3% increase in progression-free survival (PFS) at 3 years was observed in patients receiving chemotherapy, although this difference did not reach statistical significance. However, in the group of patients who underwent surgical resection, a significant 9.2% improvement in 3-year PFS was, in fact, observed.

Adam et al examined the influence of the response to neoadjuvant chemotherapy on the eventual outcome in patients following surgical resection of multiple liver metastases.[34] In this retrospective analysis of 131 patients, 44% underwent hepatectomy after achieving an objective tumor response, 30% went to surgical resection after tumor stabilization, and 26% were surgically resected after tumor progression. Five-year survival was significantly lower in the group of patients who had evidence of tumor progression, compared with patients who had evidence of tumor response (8% vs 37%). Of note, patients with stable disease on neoadjuvant chemotherapy had only a slightly worse prognosis with respect to 5-year survival, compared with responders (30% vs 37%). Disease-free survival in patients who progressed on neoadjuvant chemotherapy was only 3%, compared with rates of 21% and 20% for patients with tumor response or stable disease, respectively. Based on this study, it is clear that tumor progression before surgery is associated with extremely poor clinical outcome, and in this setting, hepatic resection should be avoided in patients who are deemed to be nonresponders to preoperative chemotherapy.

Neoadjuvant chemotherapy may be associated with complete disappearance of some or all of the hepatic metastases on imaging studies (approximately 18% of tumors will disappear completely).[35] Pathological complete response is associated with a high rate of long-term cure after surgical resection (5-year survival of 79%).[36] Controversy exists regarding the need to resect patients with complete radiographic responses, to achieve long-term cure. Up to 70% of these sites of complete radiographic response are associated with pathologic complete response or failure to recur at these sites.[36,37] The remaining 30% of patients are at risk of disease recurrence if resection is not performed. Thus, curative therapy should include resection of these regions, although the potential risk of disease recurrence at other sites must also be taken into consideration.

Conversion Therapy

The majority of patients will present with liver metastases from CRC that are unresectable or not optimally resectable based on their size, number, or location at the time of initial assessment. In this setting, conversion therapy is used in appropriately selected patients. The primary focus, therefore, is on achieving downsizing of the metastatic disease that is sufficient to allow surgical resection to be performed, but not with the goal of achieving a complete or even maximal response.

Adam and colleagues in France have had the largest experience in this area to date, and their work has provided important insights into the potential role of conversion therapy.[38-40] In their original series of 701 patients with initially unresectable liver metastases, treatment with oxaliplatin-based chemotherapy resulted in downsizing in nearly 15% of patients, and subsequent surgery. Based on 5-year follow-up after surgery, 22% of patients had no evidence of residual or recurrent disease. When stratified according to the underlying reasons for initial unresectability, the 5-year overall survival (OS) rates were 60% for patients with large tumors, 49% for those with poorly located tumors, and 34% for patients with multinodular tumors. In an expanded series of 1439 patients treated with a broader range of cytotoxic chemotherapy, the conversion rate was 12.5%, with a 5-year survival rate of 33%.

Folprecht and colleagues[41] conducted an interesting analysis of all published/presented clinical trials and retrospective studies of the rate of objective response and the subsequent rate of resection of initially unresectable metastases. They observed a strong correlation (r = 0.96) between response rates and the subsequent resection rate in patients with isolated liver disease. Moreover, their analysis confirmed that patient selection and efficacy of preoperative chemotherapy were strong predictors of potential resectability of liver metastases. Since this analysis, several
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In these studies, use of oxaliplatin- vs irinotecan-based chemotherapy has shown similar clinical outcomes.[42,43] Of note, approximately 20% to 30% of patients were able to undergo R0 surgical resection. Two trials have directly compared the clinical efficacy of FOLFOX plus irinotecan (FOLFOXIRI), an aggressive regimen that incorporates the three active cytotoxic agents, against that of FOLFIRI (5-FU, LV, irinotecan). Falcone et al randomized patients with mCRC to receive either FOLFOXIRI or FOLFIRI, and they reported a significant increase in R0 resection for the subgroup of patients with liver-only metastases who were randomized to the FOLFOXIRI arm.[44] The R0 resection rate was 36% in the FOLFOXIRI arm vs 12% in the FOLFIRI arm ($P = .017$). Despite the increased clinical activity of FOLFOXIRI, patients receiving this regimen experienced a significantly higher incidence of grade 3/4 toxicity in the form of myelosuppression and neurotoxicity. In contrast to the positive findings of the Falcone study, Souglakos et al observed a nonsignificant increase in overall response rate (43% vs 33.6%), conversion rate (10% vs 3.4%), and R0 resection rate (8.8% vs 3.4%).[45] A pooled analysis of the Falcone phase III study and two phase II studies reported an overall response rate of 70% with the FOLFOXIRI regimen and a 19% R0 resection rate. The 5-year disease-free survival (DFS) and OS were 29% and 42%, respectively.[46]

### TABLE 2

Select Trials Reporting Conversion of Unresectable Metastatic CRC to Resectable Metastatic Disease

Is there an optimal cytotoxic chemotherapy regimen for conversion therapy? To date, there has been a significant absence of randomized trials directly comparing the various chemotherapy regimens in patients with liver-limited disease. In reviewing the literature, it appears that irinotecan- and oxaliplatin-based regimens yield approximately the same rate of conversion, on the order of 20% to 30%. While FOLFOXIRI appears to result in higher conversion rates, in the 40% to 60% range, and higher R0 surgical resections, this treatment regimen is clearly associated with increased toxicity and should be used only in certain select patient populations. Upon review of the recent National Comprehensive Cancer Institute (NCCN) guidelines, several regimens are currently recommended, and they include FOLFIRI, FOLFOX, CapOx, and FOLFOXIRI.[47]

The introduction of targeted therapies with either the antiangiogenic agent bevacizumab or the epidermal growth factor receptor (EGFR) inhibitors cetuximab (Erbitux) and panitumumab (Vectibix) has improved the clinical efficacy of chemotherapy in patients with mCRC. As a result, combination regimens incorporating these agents have now been evaluated in clinical trials for patients with liver-limited metastases.

The addition of the anti–vascular endothelial growth factor (VEGF) antibody bevacizumab to either FOLFOX or to capecitabine and oxaliplatin (XELOX/CapOx) vs the cytotoxic chemotherapy regimens alone was investigated in a randomized phase III trial in advanced mCRC.[48] Unfortunately, there was only a slightly higher incidence of R0 surgical resection with bevacizumab (8.4%) vs chemotherapy alone (6.1%).

The anti-EGFR antibodies cetuximab and panitumumab have been approved for use in patients with mCRC.[49] Subsequent studies have shown that these agents are active only in patients with wild-type KRAS tumors. KRAS mutations occur in up to 30% to 40% of patients with CRC, and they typically involve codon 12 or 13. In general, KRAS mutations lead to resistance to antibody therapy. However, recent studies have suggested that the G13D mutation in codon 13 may still allow for sensitivity to anti-EGFR antibody therapy, in sharp contrast to mutations in codon 12.

Retrospective analyses of clinical trials in mCRC have provided insights into the potential role of cetuximab in the treatment of liver-limited disease. In a phase II trial of FOLFOX plus cetuximab, 37 of the 43 patients enrolled had liver involvement, and in 17 of these patients, the liver was the only site of metastatic disease.[50] An objective response was seen in 34 of the 37 patients; 10 of these patients underwent surgical resection of their metastases, including 8 patients with liver metastases. In a series of 151 patients with unresectable mCRC liver metastases refractory to systemic chemotherapy, the addition of cetuximab to combination chemotherapy allowed 27 patients to
undergo surgical resection, and of this group, 25 underwent potentially curative hepatectomy.[51] Of note, this group included a majority of patients who were deemed to have either technically unresectable or marginally resectable disease. Moreover, the incorporation of cetuximab with chemotherapy conferred significant clinical benefit, with median progression-free survival (PFS) and OS of 13 and 20 months, respectively.

Several single-arm phase II trials have investigated the combination of cetuximab with either irinotecan- or oxaliplatin-based regimens. Min et al reported a radiologic response rate of 39%, with 30% of patients treated with FOLFIRI plus cetuximab able to undergo resection of their liver metastases.[52] Nearly identical results were observed with the combination of FOLFOX and cetuximab, which yielded an R0 resection rate of 29%.[53]

Two recent randomized studies have investigated the safety and efficacy of cetuximab in combination with either FOLFIRI[54] or FOLFOX.[55] The addition of cetuximab to FOLFIRI significantly increased the overall response rate (59% vs 43%; \( P = .004 \)) in patients with wild-type KRAS when compared with FOLFI RI alone, and this resulted in a higher number of patients able to undergo R0 surgical resection (4.3% vs 1.5%). An exploratory analysis revealed a two-fold higher rate of R0 surgical resection in patients with liver-limited disease (9.8% vs 4.5%).[54] Similar findings were reported by Bokemeyer et al[55] with the combination of cetuximab plus FOLFOX4. The overall response rate increased from 37% to 61% in patients with wild-type KRAS and in those treated with the combination vs FOLFOX4 alone. This improvement in response rate in patients treated with the combination was associated with an increase in the R0 resection rate from 2.4% to 4.7%.

A trial of 114 patients with initially nonresectable liver-limited metastases randomized patients to receive cetuximab in combination with either FOLFOX6 or FOLFIRI. R0 resection rates of 38% and 30% were observed, respectively, with an overall R0 resection rate of 34%.[56] In a retrospective analysis of response according to KRAS status with the two arms of the trial combined, the clinical response rate in patients with wild-type KRAS was 70% compared with 41% for those with mutant KRAS. This study provides further evidence of the strong association between high tumor response rate and increased rate of liver metastasectomy.

PRIME (the Panitumumab Ran-domized Trial in Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy) was designed to evaluate the efficacy and safety of panitumumab plus FOLFOX4 vs FOLFIRI4 alone as initial treatment for mCRC. The addition of panitumumab to FOLFOX4 chemotherapy significantly improved the overall response rate (57% vs 48%; \( P = .02 \)) and median PFS in patients with wild-type KRAS tumors (9.6 vs 8.0 months; \( P = 0.01 \)), which translated into a nonsignificant increase in median OS from 19.7 to 23.9 months.

In terms of surgical resection, metastasectomy of any site was attempted in 10.5% of patients treated with the combination regimen as opposed to 9.4% of patients treated with chemotherapy alone. However, the R0 resection rate was higher in patients with wild-type KRAS tumors and liver-limited disease (28% vs 18%) who were treated with panitumumab plus FOLFOX4. At the time of the most recent analysis, median OS had not been reached in patients who underwent R0 liver resection, in contrast to a median OS of 23.6 months in those who were unable to undergo complete surgical resection.[57]

**Adjuvant Chemotherapy**

To date, only a limited number of clinical trials have investigated the role of adjuvant chemotherapy following surgical resection of organ-limited metastases. Two randomized phase III trials were conducted to determine the potential role of adjuvant chemotherapy with 5-FU/ LV vs surgery alone.[58,59] Both trials showed a nonsignificant trend for improvement in DFS. Unfortunately, both studies closed prematurely due to slow patient enrollment. As a result, neither study had sufficient statistical power to demonstrate the predefined difference in OS. A pooled analysis of the individual data from these two trials was subsequently conducted by Mitry et al to improve the statistical power of the survival analysis. This analysis showed a marginally significant trend toward improved progression-free survival for patients receiving chemotherapy (27.9 vs 18.8 months).[60] This study is important as it provides proof of concept for the potential role of adjuvant chemotherapy in patients who have undergone curative resection of liver or lung metastatic disease. Unfortunately, a randomized phase III trial was unable to document the benefit of the FOLFIRI regimen as adjuvant therapy following surgical resection of liver metastases when compared with infusional 5-FU/LV.[61]

What should the recommendations be for adjuvant chemotherapy following surgical resection? Although definitive clinical data are lacking, the current approach would be to offer adjuvant therapy with an oxaliplatin-based regimen, whether it be FOLFOX or XELOX, for a defined 3- to 4-month
period. As is the case for the adjuvant treatment of early-stage colon cancer, there is presently no role for a biologic agent, such as bevacizumab or the anti-EGFR antibodies cetuximab and panitumumab, in oxaliplatin-based chemotherapy. Further support for this approach comes from the recently published NCCN clinical practice guidelines for adjuvant therapy of resected metastatic disease, which recommend a shortened course of cytotoxic chemotherapy, as would be offered for patients with resected stage III colon cancer. [47]

**Limitations of Chemotherapy**

**FIGURE 1**

Comparison of Survival of a Group of Patients With Colorectal Metastases to the Liver and a Second Group With Carcinomatosis

The role of chemotherapy is to enhance the outcomes of surgery and/or permit potentially curative resection to be performed. Unfortunately, chemotherapy has potential disadvantages, which relate to direct toxic effects on the liver, leading to an increased risk of potential postoperative complications. There is now a large body of evidence showing that systemic chemotherapy can result in nonalcoholic fatty liver disease and sinusoidal injury. The chemotherapy-associated liver disease ranges from steatosis to steatohepatitis (CASH).[62] Steatosis resulting from chemotherapy and/or any other etiology has been shown to lead to a higher rate of complications following hepatic resection. However, the development of CASH appears to hold greater significance.[63] Of note, CASH appears to be more closely associated with the use of irinotecan-based chemotherapy and to occur more commonly in patients with higher body mass index.[64] The development of CASH has been associated with a higher postoperative mortality rate related primarily to postoperative liver failure. In one series, the 90-day mortality rate in patients with steatohepatitis was 14.7% vs 1.6% for those who did not have steatohepatitis.[65] In contrast to treatment with irinotecan, oxaliplatin-based chemotherapy has been typically associated with liver sinusoidal injury.[62,65,66] In more severe cases, perisinusoidal fibrosis, sinusoidal obstruction, and portal hypertension have been observed. In contrast to CASH, the development of sinusoidal dilation has not been associated with an increased risk of perioperative morbidity and mortality.[67,68]

**Peritoneal Carcinomatosis**

While this review has focused on liver-limited metastatic disease, cures have also been reported after pulmonary metastasectomy, isolated nodal recurrences, and ovarian metastases.[69-71] While these are highly selected cases, they are worthy of consideration for patients with favorable tumor biology and/or for those who are responsive to chemotherapy. A growing field of interest has been the surgical management of peritoneal metastases from CRC, using cytoreductive surgery and intraoperative chemoperfusion with mitomycin C or oxaliplatin, combined with hyperthermia (HIPEC).[72,73] This interest stems from early randomized trials with this treatment strategy in gastric cancer and a randomized trial in mCRC from the Netherlands.[74,75] This mCRC carcinomatosis trial demonstrated an improvement in median survival in patients receiving intraoperative HIPEC, compared with systemic 5-FU/LV (22.3 months vs 12.6 months). Patients whose tumors could be completely resected from the peritoneum followed by HIPEC had an actuarial 3-year survival of 95%. A follow-up report on this trial demonstrated an overall actual 5-year survival of 45% in the HIPEC arm for patients with all disease resected.[76] A recent report from France noted a 5-year survival of 26% in patients receiving HIPEC with oxaliplatin for colorectal peritoneal carcinomatosis.[77] A number of series have compared surgical cytoreduction and HIPEC for peritoneal carcinomatosis vs surgical resection of hepatic metastases from mCRC, demonstrating similar survival curves (Figure 1).[78-80] This finding suggests that an aggressive combined-modality
approach for peritoneal carcinomatosis may have a defined cure rate. Presently, most centers combine surgical cytoreduction and HIPEC with neoadjuvant and postoperative adjuvant systemic chemotherapy, such as has been described for liver-limited metastatic disease.

**REFERENCE GUIDE**

**Therapeutic Agents Mentioned in This Article**

- Bevacizumab (Avastin)
- Capecitabine (Xeloda)
- Cetuximab (Erbitux)
- 5-Fluorouracil (5-FU)
- Irinotecan
- Leucovorin (folinic acid)
- Mitomycin C
- Oxaliplatin (Eloxatin)
- Panitumumab (Vectibix)

*Therapeutic agents are listed in alphabetical order by generic name. Trade name trade names are listed only if a drug is not available generically and is marketed as no more than two trademarked or registered products. More familiar alternative generic designations may also be included parenthetically.*

**Conclusions**

When limited to a specific organ site, mCRC is potentially curable. To date, nearly all of the clinical studies have focused on liver-limited disease, but similar results are now being reported for patients with disease limited to the lungs, ovaries, and peritoneum. It is clear that a multidisciplinary team-based approach is required for the optimal care of this particular subset of patients. The development of an individual treatment plan comes from a careful discussion and ongoing communication among a multidisciplinary team of specialists, including surgeons, medical oncologists, and radiologists. With the appropriate integration of chemotherapy plus biological agents and surgery, up to 30% to 40% of patients with organ-limited metastatic disease can be cured. While the costs of the three biological agents—cetuximab, panitumumab, and bevacizumab—are not insignificant, the clinical evidence is now well-established that their incorporation with cytotoxic chemotherapy regimens in the neoadjuvant and conversion settings has greatly facilitated curative resection of liver-limited metastatic disease. However, further improvements are needed to enhance the clinical outcome of the remaining 60% to 70% of patients.
Further refinements in whole-body and hepatic imaging should provide for a more accurate selection of the subset of patients who would benefit most from resection and would identify the presence of minimal residual disease following surgery. Finally, clinical trials are needed to develop novel cytotoxic agents and biologic/targeted agents that can be used in both the preoperative and postoperative settings to reduce the risk of local and systemic recurrence.

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