Advancements in the treatment of mCRC:
Improvements in the management of liver metastases

The role of chemotherapy in stage IV colorectal cancer: focus on combinations with biologic agents and conversion therapy
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New paradigm in the treatment of hepatic colorectal metastases: a surgeon’s perspective
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Introduction and statement of needs

In the past decade, great strides have been made in the treatment of colorectal cancer (CRC), specifically with regard to metastatic disease. Ten years ago, the median overall survival with the use of 5-fluorouracil (5-FU) and leucovorin (LV) was 11.3 months; now the trend for overall survival is more than double that. The approval of six new agents for the treatment of metastatic CRC has significantly contributed to this positive trend. The use of the three cytotoxic agents irinotecan, oxaliplatin (Eloxatin), and capecitabine (Xeloda) as well as the three targeted agents bevacizumab (Avastin), cetuximab (Erbitux), and panitumumab (Vectibix) is changing the paradigm of how advanced colorectal disease is treated.

With the advent of these agents, metastatic disease is now being seen more as a chronic and dynamic state of being with a diverse armamentarium of treatment options. Chemotherapy regimens that combine traditional cytotoxic agents with targeted therapy are the standard in first- and second-line treatments of metastatic CRC. Recommended first-line treatment regimens should include 5-FU and LV combined with oxaliplatin or irinotecan plus bevacizumab. There is also supportive evidence that bevacizumab is beneficial in the second-line setting. Cetuximab and panitumumab are approved for second-line treatment of metastatic disease.

Oxaliplatin, used in combination with infusional 5-FU/LV, is indicated for adjuvant treatment of stage III colon cancer patients who have undergone complete resection of the primary tumor and for treatment of advanced carcinoma of the colon or rectum. The Food and Drug Administration’s (FDA) approval in the metastatic setting was based on clinical studies with oxaliplatin plus infusional 5-FU with LV that demonstrated the statistically significant advantages of longer median survival, increased time to tumor progression, and a higher response rate compared with an irinotecan-based regimen. The FDA approval for the adjuvant setting is based on an improvement in disease-free survival after a follow-up of 4 years. Oxaliplatin use in the adjuvant and metastatic settings is the current standard of care.

Now that we have a complement of new therapeutic treatment combinations, neoadjuvant therapy with first- and second-line agents can be employed to move patients with liver metastases along the continuum of resectability. New chemotherapy regimens have increased tumor response rates, in some cases allowing resection of metastases that previously would not have been resectable. Phase III trials have combined oxaliplatin, irinotecan, and 5-FU and achieved response rates of 60%. Such response rates contribute tremendously to practitioners’ ability to successfully downsize the tumor burden in preparation for planned metastectomy. Evidence from clinical trials supports the advantages of neoadjuvant therapy, suggesting that down staging metastases to the point of resection may allow for a cure in some cases.

In conclusion, there is a shift in the treatment and prognosis for patients with metastatic CRC. Combinations of cytotoxic and targeted therapy are improving overall response rates and survival. Neoadjuvant therapy in the setting of metastatic disease is now allowing for a much-improved 5-year survival rate and increased hope for a cure. There is ongoing research on optimizing the therapeutic combinations with regard to maximizing response in conjunction with the surgical approach to metastatic disease.

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Intended audience

This activity has been developed for medical oncologists and other health professionals involved in the care of patients with metastatic colorectal cancer and liver metastases.

Program goals

- Review recent data on chemotherapy in metastatic CRC.
- Understand the potential roles of chemotherapy in treatment of liver metastases.
- Understand the role of resection in liver metastases and strategies for increasing the proportion of patients eligible for curative resection.

Educational objectives

After participating in this activity, participants should be able to:

- Discuss recent findings regarding chemotherapy regimens for treating metastatic CRC.
- Identify the roles that chemotherapy may play in treating liver metastases.
- Recognize the benefits of curative resection of liver metastases.
- Identify strategies for converting unresectable disease to resectable disease.

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The role of chemotherapy in stage IV colorectal cancer: focus on combinations with biologic agents and conversion therapy

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Recent findings in studies of chemotherapy in metastatic colorectal cancer include the apparent ability of the presence of mutated K-ras to predict the absence of response to epidermal growth factor receptor (EGFR) inhibitors, the lack of benefit of combining panitumumab and bevacizumab in first-line treatment, the benefits of maintenance therapy versus chemotherapy-free intervals, and the suggested benefit of continuing bevacizumab treatment beyond first disease progression. In the setting of liver metastases, recent data indicate a reduced risk of disease progression with perioperative chemotherapy in patients with resectable disease (albeit at the cost of increased postoperative complications) and potential roles for chemotherapy and biologic therapy in converting initially unresectable disease to resectable disease.

Over the past 25 years, the median overall survival (OS) in stage IV colorectal cancer (CRC) has improved from approximately 5 months to over 2 years as the chemotherapeutic agents irinotecan, capecitabine (Xeloda), and oxaliplatin (Eloxatin) joined 5-fluorouracil (5-FU) as active agents and as the biologic agents cetuximab (Erbitux), bevacizumab (Avastin), and panitumumab (Vectibix) have been integrated into treatment regimens. Ongoing analysis of trials evaluating various regimens containing 5-FU/leucovorin (LV), oxaliplatin, and irinotecan continues to suggest that patients receiving all three drugs, irrespective of which doublet is used first, have prolonged survival compared with patients receiving only doublets. The most recent advances involve the addition of biologic agents to the several active chemotherapeutic regimens now available.

EGFR inhibitors

The epidermal growth factor receptor (EGFR) inhibitors cetuximab and panitumumab have shown activity in later-line treatment of stage IV CRC and have recently been evaluated in earlier-line treatment. In the CRYSTAL trial, reported at the 2007 American Society of Clinical Oncology (ASCO) meeting, patients with EGFR-expressing metastatic CRC were randomized to receive first-line FOLFIRI (5-FU, LV, irinotecan; n = 599) or FOLFIRI plus cetuximab (n = 599), with the primary endpoint being progression-free survival (PFS; on independent review). FOLFIRI plus cetuximab was associated with a marginally significant reduction in the risk of disease progression (hazard ratio [HR], 0.851; P = 0.0479), with a median PFS of 8.9 months versus 8.0 months. Overall response rates were 46.9% with FOLFIRI plus cetuximab, including complete response (CR) in 0.5% and partial response (PR) in 46.5% (stable disease [SD] in 37.4%), compared with 38.7% with FOLFIRI (P = 0.0038), including CR in 0.3% and PR in 38.4% (SD in 46.7%). Although neither the benefit in PFS nor that in overall response rate is remarkable, the late divergence of the PFS curves strongly indicates that a subset of patients benefited from the addition of cetuximab. And, indeed, this appears to be the case.

One of the potentially significant advances in the past year has been the finding that EGFR inhibitors do not inhibit the Ras pathway of signal transduction in the presence of K-ras mutation, with only wildtype K-ras appearing to be under control of signaling from the EGFR. As shown in a recent trial of panitumumab as last-line treatment in metastatic CRC, panitumumab treatment was associated with a significant 55% reduction in the risk of disease progression compared with best supportive care in patients with wildtype K-ras mutation (P < 0.0001) and no benefit in those with mutated K-ras (Figure 1). Mutated K-ras was present in approximately 45% of patients, suggest-
ing that, in the last-line setting, this percentage of patients stands no chance of benefit from EGFR inhibition. An assay for K-ras status is expected to be available commercially in the United States in the current year.

**Anti-VEGF agents**

The efficacy of antivascular endothelial growth factor (VEGF) therapy was demonstrated in a trial reported several years ago. In this study, the addition of bevacizumab (n = 402) to IFL (irinotecan, bolus 5-FU, LV; n = 411) in the first-line treatment of metastatic CRC resulted in significant improvements in median OS (20.3 months vs 15.6 months; P = 0.000004), PFS (10.6 months vs 6.2 months; P < 0.00001), overall response rate (45% vs 35%; P = 0.0036), and duration of response (10.4 months vs 7.1 months; P = 0.0014).4

We know from the BICC-C trial that FOLFIRI is a better irinotecan-containing regimen than IFL in first-line treatment. In the phase III period 1 of this trial, FOLFIRI (n = 144) was associated with a significant prolongation of PFS compared with modified IFL (mIFL; n = 141) and CapeIRI (capecitabine and irinotecan; n = 145); there was a median PFS of 7.6 months versus 5.9 months (P = 0.0009) and 5.8 months (P = 0.0049),6 and OS was 23.1, 17.6, and 18.9 months, respectively. Bevacizumab was added to FOLFIRI (n = 57) and mIFL (n = 60) in the recently reported BICC-C phase II period 2; FOLFIRI plus bevacizumab resulted in PFS of 11.2 months and OS of 28.0 months, compared with 8.3 months and 19.2 months, respectively, for mIFL.6

On the basis of these findings, FOLFIRI plus bevacizumab has become one of the standard therapies in first-line treatment of metastatic CRC. However, most practitioners use FOLFIRI rather than FOLFIRI in metastatic disease, likely reflecting the experience that FOLFOX is easier to use in the first several cycles, and FOLFIRI has been associated with more diarrhea and hair loss. Nevertheless, there are few data available on the comparative efficacy of FOLFOX and FOLFIRI, and FOLFOX carries the disadvantage of cumulative neurotoxicity that can impede the delivery of treatment.

The effects of adding bevacizumab to FOLFOX were assessed in the Roche NO16966 trial, conducted mostly outside the United States. The trial was initially designed as a comparison of FOLFOX4 versusXELOX (capecitabine and oxaliplatin), with the protocol being amended after phase III data on bevacizumab became available to a 2 × 2 placebo-controlled design, including XELOX plus placebo (n = 350) or bevacizumab (n = 350) and FOLF-OX4 plus placebo (n = 351) or bevacizumab (n = 350).7 XELOX plus placebo or bevacizumab was noninferior to FOLFOX4 plus placebo or bevacizumab with regard to PFS (8.0 months vs 8.5 months; HR, 1.04 with an upper limit of 95% confidence interval (CI) < 1.23 [noninferiority margin]), PFS with XELOX or FOLFOX4 plus bevacizumab was significantly increased versus XELOX or FOLFOX4 alone (9.4 months vs 8.0 months; HR, 0.83; P = 0.0023). However, whereas the addition of bevacizumab to XELOX significantly increased PFS compared with XELOX alone (9.3 months vs 7.4 months; HR, 0.77; P = 0.0026), the addition of bevacizumab to FOLFOX4 did not significantly increase PFS (9.4 months vs 8.6 months; HR, 0.89; P = not significant).

To many, the absence of benefit in adding bevacizumab to FOLFOX was surprising. Although the explanation could include a ceiling effect on response in first-line therapy (ie, that PFS was about as prolonged as it could be in this setting using FOLFOX alone), it is more likely that the results reflect the fact that patients receiving FOLFOX had their treatment completely interrupted when oxaliplatin-related neurotoxicity occurred after several months of therapy.

The relatively recent OPTIMOX studies8,9 provide a valuable clinical lesson by showing that the practice of treating to disease progression and continuing a form of active therapy if
other components of chemotherapy must be interrupted for toxicity is associated with substantial benefit over chemotherapy-free intervals. In OPTIMOX-2 (n = 202), for example, patients received mFOLFOX7 followed by maintenance therapy with 5-FU/LV and then mFOLFOX7 or mFOLFOX7 with a completely chemotherapy-free interval followed by mFOLFOX7. This phase II trial showed striking yet nonsignificant improvements in PFS (36 weeks vs 29 weeks; \( P = 0.08 \)) and OS (26 weeks vs 19 months; \( P = 0.0549 \)) with maintenance treatment.9 The addition of bevacizumab to FOLFOX therapy in which maintenance therapy is continued—rather than the cessation of all treatment in case of neurotoxicity, for example—may show a larger benefit than that observed in the Roche NO16966 trial.

Combining EGFR and angiogenetic inhibitors

Outcomes in the BOND trials in last-line treatment of metastatic CRC suggested benefit of combining EGFR and angiogenetic inhibitors. Compared with time to disease progression (TTP) in patients receiving cetuximab plus irinotecan in the BOND-1 trial (4.1 months), TTP was increased with cetuximab plus bevacizumab (5.6 months) and with cetuximab/irinotecan/bevacizumab (7.9 months) in the phase II BOND-2 trial (OS of 8.6 months in BOND-1, compared with 10.2 months and 18.0 months, respectively in BOND-2).10,11 These data encouraged evaluation of the combination of panitumumab and bevacizumab in first-line treatment.

In the PACCE trial, patients were assigned to oxaliplatin-based chemotherapy (investigator’s choice; n = 800) or irinotecan-based chemotherapy (investigator’s choice; n = 200) and then randomized to receive bevacizumab or bevacizumab plus panitumumab. A limited update in the oxaliplatin-based cohort, with data as of April 2007, showed that PFS was significantly reduced in the panitumumab/bevacizumab group (9.0 months vs 10.5 months; HR, 1.29; 95% CI, 1.05–1.58).12

An interim analysis of OS at the April 2007 data cutoff showed a median OS of 18.8 months in the panitumumab/bevacizumab group, with median survival not yet being reached in the bevacizumab group (HR, 1.44; 95% CI, 1.10–1.88). It is unclear why the addition of another active drug resulted in poorer outcome in this setting; however, such adverse effects as skin toxicity, diarrhea, dehydration, hypokalemia, nausea, and infections were significantly increased in the panitumumab/bevacizumab group compared with the bevacizumab group (Table 1). It may be that resultant treatment discontinuations or interruptions prevented the combination group from being on treatment for long enough to derive benefit.

Although the PACCE trial provides no rationale for combining bevacizumab and panitumumab in first-line therapy, the ongoing CALGB/SWOG (Cancer and Leukemia Group B/Southwest Oncology Group) Intergroup Trial 80405 is examining the addition of bevacizumab, cetuximab, or the combination to patients receiving first-line FOLFIRI or FOLFOX (investigator’s choice) in a target population of nearly 2,300 patients. Another problem for this and other trials assessing EGFR inhibitors is the issue of K-ras mutation. CALGB 80405 is not yet testing for K-ras mutation; it is conceivable, though, that the trial will be amended soon if results to be presented at ASCO 2008 confirm mutated K-ras as a negative predictive factor for cetuximab. An additional important issue that would be raised by confirmation of the dependence of response to EGFR inhibitors on the presence of wildtype K-ras mutation is the need for additional effective treatments in those with mutated K-ras.

### How long should biologic agents be continued?

Potentially important information on the continuation of bevacizumab after disease progression has come from the BRiTE Registry, involving patients who received bevacizumab-containing regimens for first-line treatment of metastatic CRC.13 Among 1,953 evaluable patients, 1,445 had experienced first disease

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<td>Grade 3</td>
<td>Grade 4</td>
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<td>Pulmonary embolism</td>
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From Hecht et al12
progression at the time of analysis (932 deaths, median follow-up of 19.6 months); of the 1,445 patients, based on physician decision (no randomization), 253 received no post-progression treatment, 531 received postprogression treatment excluding bevacizumab, and 642 received bevacizumab beyond disease progression. Some patients (19) received bevacizumab monotherapy and were excluded from the analysis.

As shown in Table 2, median OS and OS after first disease progression were substantially longer in patients continuing to receive bevacizumab after disease progression than patients who did not receive bevacizumab at any time point beyond first progression. On multivariate analysis, use of bevacizumab beyond disease progression was associated with a significantly reduced risk of death (HR, 0.48; P < 0.001), and no treatment beyond disease progression was associated with a significantly increased risk of death (HR, 2.01; P < 0.001) compared with treatment beyond disease progression that did not include bevacizumab.

The potential benefit of continuing bevacizumab beyond disease progression is now being evaluated in the SWOG/NCCCTG/NCIC S0600/iBET second-line trial (open since June 2007). In this trial, a target population of 1,200 patients with metastatic CRC pretreated with oxaliplatin-based regimens plus bevacizumab is being randomized to receive FOLFIRI/ce-tuximab, FOLFIRI/ cetuximab/bevacizumab 5 mg/kg, or FOLFIRI/cetuximab/bevacizumab 10 mg/kg, with a primary endpoint of OS.

**Role of chemotherapy in liver metastases**

In multimodality management of CRC liver metastases, chemotherapy plays a role in the neoadjuvant setting in patients with initially resectable metastases by facilitating surgery, allowing predictive/prognostic biologic information to be obtained (eg, allowing a determination of whether a patient will respond to similar therapy postoperatively), and providing early systemic therapy in patients with a poor prognosis. For patients with unresectable metastases, conversion chemotherapy can permit a significant proportion to subsequently undergo R0 resection through tumor downsizing. Adjuvant chemotherapy may include both local and systemic treatments.

**Perioperative chemotherapy**

Benefits of perioperative chemotherapy in patients with resectable metastases have been suggested by findings in the EORTC (European Organization for Research and Treatment of Cancer) 40983 trial, in which 364 patients were randomized to undergo surgery alone versus 6 cycles of neoadjuvant FOLFOX4, surgery, and 6 cycles of adjuvant FOLFOX4. Perioperative chemotherapy was associated with a higher rate of postoperative complications than surgery alone (25.2% vs 15.9%; P = 0.04), including higher rates of biliary fistula, elevated bilirubin levels, and intra-abdominal infection but no increase in postoperative mortality. However, postoperative mortality was low and did not differ between both treatment arms. Among all eligible patients, perioperative chemotherapy (n = 171) was associated with an absolute 8.1% increase in 3-year PFS compared with surgery alone (n = 171; 36.2% vs 28.1%; HR, 0.77; P = 0.041; Figure 2).

**Conversion chemotherapy**

In terms of conversion therapy, it is known that the resectability rate in patients with initially unresectable metastases corresponds with the response rate to chemotherapy (Figure 3). Thus, response is an important objective in conversion treatment, even though most patients are not symptomatic with liver metastases at the time of diagnosis. Recent trials demonstrating shrinkage of liver metastases with chemotherapy include the EORTC 40983 trial previously noted, in which the 6 cycles of preoperative FOLFOX4 resulted in tumor downsizing, and a phase III trial in Italy in which up-front FOLFOXIRI (FOLFOX plus irinotecan) improved secondary resection rates in patients with unresectable disease.

In terms of the potential role of biologic agents in this regard, trials of bevacizumab that have shown tumor shrinkage include the AVF2107g trial (10% increase in overall response rate over IFL alone); TREE-2; the E3200 trial (12% increase over FOLFOX alone); and the Roche NO16966 trial, which found a higher rate of resectability with bevacizumab compared with placebo. Cetuximab trials that have shown tumor shrinkage include CRYSTAL (8% increase in overall response rate over FOLFIRI alone), CALGB 80203 (8% increase over FOLFIRI;
20% increase over FOLFOX), and the EPIC trial (12% increase over irinotecan in second-line treatment).

In the CRYSTAL trial, for example, the addition of cetuximab to FOLFIRI allowed more patients to undergo surgery with curative intent (6% vs 2.5%) in the total patient population (n = 599 in each group), with more having no residual tumor after resection (4.3% vs 1.5%). Among patients with liver metastases only (n = 134 for FOLFIRI alone; n = 122 for FOLFIRI/cetuximab), more patients in the cetuximab group had no residual tumor after resection (9.8% vs 4.5%). Among all patients in the Roche NO16966 trial, the addition of bevacizumab to XELOX or FOLFOX increased the secondary liver resection rate to 8.4% from 6.1% with XELOX/FOLFOX alone; among patients with liver metastases only, the addition of bevacizumab to XELOX/FOLFOX (n = 177) increased the proportion of patients undergoing secondary liver resection to 18.2% from 12.8% with XELOX/FOLFOX alone (n = 178).

There is some concern over wound complications with the use of bevacizumab prior to surgery. Kesmodel et al. analyzed complications in hepatic surgery in patients receiving neoadjuvant bevacizumab for CRC according to whether the last dose of bevacizumab was ≤ 60 days (median 49 days; n = 40) or > 60 days (median 74 days; n = 35). They found no significant differences in overall complication rates (55% vs 46%; P = 0.43), wound complications (33% vs 29%; P = 0.70), or hepatobiliary complications (8% versus 3%; P = 0.39). Although the optimal time to surgery after bevacizumab treatment is unknown, there is some evidence to suggest that a 6-week interval is sufficient.

The potential for toxicity must be considered in conversion therapy. For example, 5-FU may be associated with hepatic steatosis (yellow liver), which is associated with increased postoperative morbidity. Irinotecan may cause a nonalcoholic steatohepatitis (“yellow liver” or “orange liver”), particularly in obese patients, which can affect hepatic reserve and increase postoperative morbidity and mortality. Oxaliplatin may cause hepatic sinusoidal obstruction syndrome (“blue liver”), which does not appear to be associated with an increased risk of postoperative death.
Overall, the role of FOLFOX in conversion therapy is better established than that of FOLFIRI, with the former having been studied more extensively and having a better toxicity profile. The potential utility of FOLFOXIRI in this setting requires further study, and an EORTC trial examining the regimen is under way. The duration of preoperative therapy should be limited to 3–4 months, with the goal being treatment to resectability rather than treatment to best response. Thus, treatment requires close interaction with surgeons to determine when the optimal conditions for resectability are achieved in each patient. The reduced duration of preoperative surgery also reduces the risk or extent of hepatotoxicity that could compromise resection or its outcome.

The role of biologic agents in conversion therapy is evolving. If bevacizumab is used as part of a regimen in conversion therapy, it should be discontinued 6 weeks before planned surgery. Cetuximab could be a valid option in this setting (likely only in those patients with a wildtype K-ras mutation), but it is not yet approved for first-line treatment.

Conclusion

Medical therapy for advanced CRC has seen major advances in the past several years and will continue to evolve, particularly in the field of biomarker-dependent treatment decisions. The year 2008 will see the CRC subclassified according to the K-ras mutation status, with immediate consequences for routine practice. In terms of conventional chemotherapy, FOLFOX and FOLFIRI can be considered equally effective with regard to their use as palliative treatment. The role of FOLFOX, however, is better established in a potentially curable situation with limited metastatic disease where chemotherapy is used to increase the rate of surgical resectability of metastases.

References


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Approximately 25,000–30,000 patients with advanced colorectal cancer (CRC) in the United States have liver-only metastases, with approximately 30%–40% of patients with advanced disease having liver-only metastases at the time of recurrence and approximately 20%–30% having liver-only metastases at the time of initial evaluation.\(^1,2\) Curative (R0) resection in patients with liver metastases is associated with dramatically improved survival compared with partial (R1/R2) resection.\(^3\) Advances in imaging technology, surgical techniques, and systemic chemotherapy have brought steady improvements in median and 5-year survival rates in patients undergoing resection, with 5-year overall survival (OS) exceeding 50%–60% in patients undergoing curative resection in series reported in the past several years.

Thus, the goal of surgery should be complete removal of all metastatic disease. Several issues should be confronted in attempting to provide curative resection for the greatest proportion of patients. (1) How do we select patients for resection? (2) How can we expand the role of liver resection to those with disease that is initially considered to be unresectable; and (3) What is the role of adjuvant or neoadjuvant chemotherapy for patients undergoing hepatic resection?

**Defining resectability**

The definition of “resectable” for liver metastases is a moving target. The definition traditionally has been based on consideration of prognostic factors (Table 1). The paradigmatic shift under way in defining resectability in this setting can be viewed as a movement away from “what comes out” toward “what stays in.” That is, the decision regarding whether disease is resectable has come to rely less on clinicopathologic factors such as the number of metastases, the size of metastases, and more on whether all known disease can be removed while leaving adequate remnant liver.

A difficulty for surgeons and multidisciplinary teams in this regard is that resectability was easier to determine with the older paradigm, whereas now decisions often have to be made on a highly individualized basis. For example, Figure 1 shows scans of a patient with bilateral metastases, which might appear to be unresectable based on the distribution of lesions and their proximity to the vascular pedicles; it also shows another patient with a single tumor that would require...
extended right hepatectomy that would not appear to leave sufficient remnant liver to maintain function during liver regeneration. However, with sufficient preoperative planning, which may involve a multidisciplinary approach and extensive high-quality imaging studies, both cases represent potentially resectable disease.

**TABLE 1**

Prognostic factors in patients with CRC liver metastases

- Number of metastases
- Resection margin status
- High preoperative carcinoembryonic antigen level
- Size of largest tumor
- Stage of primary tumor
- Disease-free interval
- Synchronous disease
- Extrahepatic disease
- Periportal node status
- Newer factor: response to preoperative chemotherapy

CRC = colorectal cancer

**Strategies for rendering more patients eligible for liver surgery**

Approaches to increasing the number of patients with resectable disease include tumor downsizing, increasing hepatic reserve, and using such techniques as radiofrequency ablation (RFA) in combination with resection.

*Tumor downsizing*

The prospect of converting initially unresectable metastases to resectable disease has improved over the past several years with the addition of irinotecan and oxaliplatin (Eloxatin) and, most recently, bevacizumab (Avastin), cetuximab (Erbitux), and panitumumab (Vectibix) to the options in metastatic CRC. In several studies, oxaliplatin administered in combination with infusional fluorouracil (5-FU; FOLFOX) or irinotecan given in combination with infusional 5-FU and leucovorin (FOLFIRI) has been associated with response rates of approximately 50% and median OS of 20–22 months; the addition of bevacizumab or cetuximab to such regimens has produced response rates of approximately 70% and OS of 24 months or more.6–8

Figure 2 shows an example of a patient in whom disease was initially unresectable, because the tumor in the right lobe involved hepatic veins near the vena cava and the portal pedicles extending across to the left lobe; resection would result in insufficient inflow and outflow. In this patient, conversion chemotherapy resulted in marked reduction in tumor size and retraction of the tumor away from vascular structures in the left lobe, facilitating a safe, margin-negative resection of disease via right hepatectomy.

Currently, it is estimated that approximately 20%–25% of patients with liver metastases present with initially resectable tumors and that resection can be made possible through tumor downsizing in approximately 10%–20% of those with initially unresectable disease. As noted, the benefits of curative resection are significant, with recent series indicating OS of 50%–60% or more at 5 years and disease-free survival of 15% at 10 years. In an older series of more than 1,400 patients with liver metastases at Paul Brousse Hospital in Paris, France, between 1988 and 1999, 23% had initially resectable disease; of those with initially unresectable disease, 13% were able to have surgery after chemotherapy, with 33% of all patients undergoing resection.7 For patients with initially resectable disease and for those with initially unresectable disease who subsequently underwent resection, OS rates were 48% and 33%, respectively, at 5 years and 30% and 23%, respectively, at 10 years.

Strategies for tumor downsizing and resection need to be refined. We still do not know what circumstances indicate the greatest likelihood of optimal outcome in initially unresectable disease. For example, it is unclear whether all areas where the tumor...
initially existed should be resected. However, it is likely, for example, that removal of 3 visible tumors that have been reduced in size with chemotherapy portends a better outcome than removal of a sole remaining visible tumor in a patient who initially had 20 visible metastases. Furthermore, it is still unclear what role ablation might play in such a setting.

The optimal duration of conversion chemotherapy also remains uncertain. For example, should patients be treated until disease is resectable or to a maximal response? It is likely that residual visible disease is of benefit in marking sites that need to be resected to prevent recurrent disease. Similarly, it is unclear how to manage disease in the case of complete radiologic response; should all sites that were affected be resected, or should disease progression be awaited to determine the possibility of resection?

Increasing hepatic reserve

Strategies for increasing hepatic reserve to permit resection include utilization of staged resections and preoperative portal vein embolization. When conducting staged resections, resection of some disease in one hemiliver is performed, with the remainder of the disease being resected once sufficient liver regeneration has occurred to preserve function. Such a strategy may be used, for example, in cases in which metastases are present in both liver lobes and complete resection in both lobes would not leave sufficient remnant liver. When employing portal vein embolization, occlusion of the main vein to one lobe is performed percutaneously, resulting in atrophy of the affected lobe and compensatory hypertrophy of the other lobe, providing sufficient hepatic reserve to permit resection in the atrophied lobe. One can also consider portal vein ligation rather than embolization in cases when staged resection is being performed and additional hypertrophy is needed.

Figure 3 shows the case of a patient with a large tumor primarily confined to the right lobe of the liver. Preoperative calculations indicated that resection would leave less than 20% of the total estimated liver volume. With right portal vein embolization performed approximately 5 weeks before surgery, the right hemiliver atrophied and the left liver increased in volume; the future remnant liver after resection was calculated to be now 27% of the total liver volume. The patient subsequently underwent successful resection of the tumor.
Resection combined with RFA

Methods for local ablation have been developed in recent years to increase the number of patients eligible for liver-directed therapy. RFA involves the localized application of thermal energy to destroy tumor cells. Specifically, alternating electric current in the range of RF waves (460 kHz) is applied from a generator through a needle electrode placed directly into the tumor. As with the criteria for resectability, only those patients in whom complete ablation can be achieved should be considered for this therapy. As with resection, incomplete or cytoreductive therapy should not be advocated outside a clinical trial.

Combining hepatic resection with RFA can expand the number of patients who may be candidates for liver-directed surgical therapy, particularly because larger lesions that are less effectively treated with ablation can be resected and small lesions can be ablated. Although tumor ablation should not be viewed as a replacement to resection, it may be applicable to patients who do not meet the criteria for resectability but who are candidates for liver-directed therapy based upon the presence of liver-only disease.

Adding RFA to hepatic resection has been reported to be well tolerated, with a perioperative morbidity and mortality comparable to those seen following resection alone.10 Procedure-related complications are infrequent with this approach, with a complication rate lower than 10%.10 Local recurrence following RFA is highly dependent on tumor size as well as its location within the liver. Although some studies have reported recurrence or persistence of metastatic disease at the site of the RFA to be less than 10%, other studies have reported local recurrence rates as high as 47%.11,12 Survival following ablation is also difficult to interpret, as many patients who undergo this therapy are characterized by a number of poor prognostic factors, thereby making comparisons to patients who have undergone complete surgical resection difficult. In general, studies with isolated RFA show a median survival of about 30 to 35 months and a 3-year survival rate of 20%–36%.11

Role of neoadjuvant/adjuvant therapy for initially resectable metastases

Issues to be confronted in determining the role of preoperative and postoperative chemotherapies in patients with initially resectable liver metastases include the extent of risk/benefit in chemotherapy-naive patients and in patients who have received prior therapy for primary disease, appropriate chemotherapy regimens, the relative value of preoperative versus postoperative treatment, and the optimal duration of adjuvant therapy.

Chemotherapy is generally recommended in the chemotherapy-naive patient with resectable liver metastases, based both on the indications for and efficacy of CRC stage IV chemotherapy and on extrapolation from data on adjuvant therapy in stage III disease.13 The recently reported European Organization for Research and Treatment of Cancer (EORTC) 40983 trial showed benefit of perioperative chemotherapy consisting of 6 preoperative and 6 postoperative cycles of FOLFOX4 compared with surgery alone in 364 chemotherapy-naive patients with resectable liver metastases.14 As shown in Table 2, chemotherapy was associated with a marginally significant absolute 7% increase in 3-year progression-free survival in the intent-to-treat population, a significant 8% increase among all eligible patients, and a significant 9% increase among all patients actually undergoing resection.

This trial, however, leaves unanswered such important questions as why the observed benefit of chemotherapy was somewhat smaller than that observed in patients with stage III disease. For instance, the benefit of FOLFOX compared with 5-FU/Leucovorin in the MOSAIC (Multicenter International Study of Oxaliplatin/5-FU/Leucovorin in the Adjuvant Treatment of Colon Cancer) trial in stage III disease was greater than that seen with FOLFOX versus no chemotherapy in the EORTC 40983 trial. Whether this difference in outcome reflects different disease biology in stage IV disease versus stage III disease, variations in study designs, or some other factor remains unknown. An additional unanswered question is whether the findings in EORTC 40983 indicate benefits for preoperative therapy, postoperative therapy, or both.

Neoadjuvant therapy

In general, a number of advantages can be cited for the use of neoadjuvant therapy in initially resectable disease. The chemotherapy course allows time

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**TABLE 2**

Progression-free survival (PFS) in patients receiving perioperative chemotherapy versus surgery alone in the EORTC 40983 trial in patients with resectable liver metastases

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>3-Year PFS, chemotherapy vs surgery alone (absolute difference)</th>
<th>Hazard ratio (95% confidence interval)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>All patients</td>
<td>182 182</td>
<td>35.4% vs 28.1% (+7.2%)</td>
<td>0.79 (0.62–1.02)</td>
<td>0.058</td>
</tr>
<tr>
<td>Eligible patients</td>
<td>171 171</td>
<td>36.2% vs 28.1% (+8.1%)</td>
<td>0.77 (0.60–1.00)</td>
<td>0.041</td>
</tr>
<tr>
<td>All resected patients</td>
<td>151 152</td>
<td>42.2% vs 33.2% (+9.2%)</td>
<td>0.73 (0.55–0.97)</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Adapted from Nordlinger et al.14
Advancements in treating mCRC: Improvement in managing liver metastases

for other metastatic sites to declare themselves prior to surgery and allows for earlier therapy for occult micrometastatic disease. Response to neoadjuvant treatment also provides an in vivo gauge of chemoresponsiveness, facilitating postoperative chemotherapy planning. One example of how determination of chemoresponsiveness to neoadjuvant therapy might influence management follows. In patients receiving 4 cycles of preoperative FOLFOX plus bevacizumab, responders would be continued on FOLFOX/bevacizumab following resection, whereas those with disease progression may consider FOLFIRI/bevacizumab following resection. Another advantage of neoadjuvant therapy is that response may permit a smaller resection and improve the likelihood of margin-negative resection.

Response to neoadjuvant chemotherapy may also be an important prognostic factor, in addition to the traditional clinicopathologic prognostic factors previously mentioned. Outcome in patients with ≥ four initially resectable metastases in the Paul Brousse Hospital series was studied. The result was based on whether preoperative chemotherapy was associated with disease progression, stable disease, or partial response, with survival rates being markedly higher in those with response or stable disease versus those with disease progression.

Disadvantages of neoadjuvant therapy include the potential for tumors to progress to unresectable status during treatment (probably a rare phenomenon), chemotherapy-associated hepatotoxicity that may preclude or complicate resection, and the fact that response may hinder identification and removal of all sites of metastatic disease. With regard to toxicity, “blue liver” due to sinusoidal dilatation may occur in perhaps 10% of patients, most often in association with oxaliplatin treatment; this toxicity is not associated with a marked increase in surgical complication rates. However, “yellow liver” due to steatosis/steatohepatitis, which is frequently observed in obese or diabetic patients receiving 5-FU or irinotecan chemotherapy, may be associated with a poorer outcome.

Bevacizumab, which is commonly used in preoperative regimens, has not been associated with a significant increase in postoperative complications if it is stopped 6–8 weeks prior to surgery and held for a similar period after surgery. In a study at Memorial Sloan-Kettering Cancer Center comparing outcomes in 32 patients receiving preoperative bevacizumab versus 32 not receiving bevacizumab, there were no significant differences in the rates of overall postoperative complications (40.6% vs 37.5%) or grade 3/4 adverse events (6.2% vs 9.4%), with bevacizumab being associated with a numerically but not significantly greater frequency of wound complications (18.7% vs 6.2%; \( P = 0.29 \)).

From a surgical standpoint, too good of a response to neoadjuvant therapy at times may be problematic. Although tremendous response to chemotherapy may be desirable in some cases, the ability to identify all initial sites at the time of surgery could result in failure to remove these sites and increased risk of recurrence. Figure 4 shows the changes in the patient shown in Figure 1 (left, before chemotherapy; right, after chemotherapy). Most metastases are not visible after chemotherapy, complicating decisions regarding resection.

**FIGURE 4** Effect of preoperative chemotherapy in the patient shown in Figure 1 (left, before chemotherapy; right, after chemotherapy). Most metastases are not visible after chemotherapy, complicating decisions regarding resection.
by evaluating 66 hepatic lesions that disappeared on CT scan after chemotherapy. Persistent macroscopic disease was found at surgery in 20 of the 66 lesions (30%). Of 15 nondetected sites that were resected, 12 (80%) had viable tumor. Of 31 nondetected sites left in place, 23 (71%) had recurrent disease within 1 year. Overall, 83% of lesions with complete response had residual disease. Such findings emphasize the need to limit the duration of preoperative therapy, with the objective of achieving a partial response that still permits surgeons to identify and remove affected areas.

An approach to resection and integration of chemotherapy

Liver metastases in CRC may be considered to fall into four categories with regard to resectability, with management differing for each category: (1) initially resectable disease by a standard approach; (2) initially resectable disease that requires an extended approach—ie, staged resection, preoperative portal vein embolization, or resection plus RFA; (3) initially unresectable disease but likely convertible with response to chemotherapy; and (4) initially unresectable disease and likely not convertible. A rational approach to integrating chemotherapy into treatment of patients with resectable liver metastases based on available information is to consider neoadjuvant therapy in patients with marginally unresectable disease, multiple metastases, or stage IV presentation, as well as in patients with extrahepatic disease. Resection before chemotherapy may be indicated in patients with marginally resectable disease (eg, in a caudate lobe or other location where disease progression would render the disease unresectable), in obese or diabetic patients in whom major hepatectomy is required, and in previously treated patients.

Conclusion

Liver resection for CRC metastases is an increasingly safe and effective therapy. Surgical assessment and intraoperative planning are important to achieve safe and complete (R0) resection. Current methods for increasing the ability to offer liver resection include preoperative chemotherapy, staged resection, preoperative portal vein embolization, and ablative strategies. Perioperative chemotherapy may play a role in the optimal treatment of initially resectable disease, but the sequencing of chemotherapy and surgery remains unclear.

In the near future, we are likely to see expanding use of liver resection for non–CRC hepatic metastases, particularly as systemic chemotherapy improves. Minimally invasive approaches for resection, including laparoscopic resection, may be considered more often, as may the application of other locoregional strategies, including RFA, either instead of or in combination with resection. The role of locoregional therapies for cytoreduction is less clear. Further studies are needed to define their role.

References


ABOUT THE AUTHOR

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Self-assessment questions

1. The presence of mutant K-ras in metastatic CRC appears to predict:
   a. Response to panitumumab but not cetuximab
   b. Response to cetuximab but not panitumumab
   c. Response to all EGFR inhibitors
   d. Nonresponse to EGFR inhibitors

2. The NO16966 trial showed:
   a. Superiority of FOLFOX4/bevacizumab vs XELOX/bevacizumab
   b. Superiority of FOLFOX4 or XELOX plus bevacizumab vs FOLFOX4 or XELOX alone
   c. Superiority of XELOX/bevacizumab vs FOLFOX4 alone
   d. None of the above

3. The PACCE trial showed:
   a. PFS benefit of the addition of panitumumab to mIFL
   b. No benefit of the addition of panitumumab/bevacizumab vs bevacizumab to oxaliplatin-based chemotherapy
   c. Improved PFS with the addition of panitumumab/bevacizumab vs bevacizumab to oxaliplatin-based chemotherapy
   d. Improved OS with the addition of panitumumab/bevacizumab vs bevacizumab to oxaliplatin-based chemotherapy

4. Data from the BRiTE registry show:
   a. Improved survival with first-line use of bevacizumab
   b. Prolonged time to progression with first-line use of bevacizumab
   c. Improved survival with use of bevacizumab beyond progression
   d. All of the above

5. The EORTC 40983 trial in patients with liver metastases showed:
   a. Improved 3-year PFS with perioperative chemotherapy
   b. Improved PFS with neoadjuvant therapy
   c. Improved PFS with adjuvant therapy
   d. Reduced postoperative complications with chemotherapy

6. It is currently estimated that what proportion of patients with liver metastases present with initially resectable disease?
   a. < 10%
   b. 50%–60%
   c. 20%–25%
   d. 10%–15%

7. Approaches to increasing the proportions of patients with resectable liver metastases include:
   a. Conversion chemotherapy
   b. Staged resection
   c. Preoperative portal vein embolization
   d. All of the above

8. Potential advantages to neoadjuvant therapy in the setting of initially resectable liver metastases do not necessarily include:
   a. Achievement of radiologic complete response
   b. Indication of chemoresponsiveness that may aid decisions on future therapy
   c. Earlier therapy for occult micrometastatic disease
   d. Prognostic value of response

9. A recent study of outcome for hepatic lesions that became undetectable by CT after chemotherapy showed:
   a. Persistent macroscopic disease at surgery in 30%
   b. Recurrent disease in 71% at 1 year for CT-undetected lesions left in place
   c. Overall, residual disease in 83% of lesions with complete response
   d. All of the above

10. A rationale approach to integrating neoadjuvant chemotherapy into treatment of patients with resectable liver metastases includes:
    a. Neoadjuvant therapy in patients with marginally unresectable disease, multiple metastases, or stage IV presentation
    b. Neoadjuvant therapy in marginally resectable disease, previously treated patients, or obese or diabetic patients requiring major hepatectomy
    c. Both of the above
    d. None of the above
CME answer sheet and evaluation form

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All information is confidential.

CME Post-Test Answer Sheet
Circle the single, most appropriate answer for each question on page 15

| 1. a b c d | 5. a b c d |
| 2. a b c d | 6. a b c d |
| 3. a b c d | 7. a b c d |
| 4. a b c d | 8. a b c d |

Please turn this form over and complete the evaluation on page 17.
Course Evaluation
Please evaluate the effectiveness of this educational activity by circling your choice on a scale of 1 to 5, with 1 being the lowest and 5 the highest.

Discuss recent findings regarding chemotherapy regimens for treating mCRC. 1 2 3 4 5
Identify the roles that chemotherapy may play in treating liver metastases. 1 2 3 4 5
Recognize the benefits of curative resection of liver metastases. 1 2 3 4 5
Identify strategies for converting unresectable disease to resectable disease. 1 2 3 4 5
How do you rate the overall quality of the activity? 1 2 3 4 5
How do you rate the educational content of the activity? 1 2 3 4 5

After participation in this activity, have you decided to change one or more aspects in the treatment of your patients? □ Yes □ No
If yes, what change(s) will you make? __________________________________________________________
If no, why not? __________________________________________________________

Was the presented information fair, objective, balanced, and free of bias in the discussion of any commercial product or service? □ Yes □ No
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Suggested authors for future activities: ____________________________________________________________________

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