Chemotherapy for Colorectal Cancer Liver Metastases

STEVEN R. ALBERTS,a LAWRENCE D. WAGMANb

aMayo Clinic, Rochester, Minnesota, USA; bSt. Joseph Hospital, Center for Cancer Prevention and Treatment, Orange, California, USA

Key Words. Chemotherapy • Colorectal cancer • Liver metastases • Oxaliplatin • 5-fluorouracil

Disclosure: Employment/leadership position: None; Intellectual property rights/inventor/patent holder: None; Consultant/advisory role: Lawrence D. Wagman, Medwaves, Inc., San Diego, CA; Honoraria: Lawrence D. Wagman, Angiodynamics; Research funding: Steven R. Alberts, Bristol-Myers Squibb, Pfizer, Sanofi-Aventis; Ownership interest: None; Expert testimony: None; Other: None. The article discusses the neoadjuvant use of drugs manufactured or provided by Roche, Merck, and Sanofi-Aventis. The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the authors, planners, independent peer reviewers, or staff managers.

ABSTRACT

Colorectal cancer (CRC) is a highly prevalent malignant disease in industrialized nations. The annual incidence of invasive CRC in the U.S. is among the highest in the world, and the liver is the only metastatic site in approximately one third of patients. Without treatment, patients with metastatic disease have a poor prognosis; however, long-term survival benefits and even cure have been reported in patients undergoing surgical resection of metastases. In addition, advances in chemotherapy, imaging, and surgical techniques have increased the proportion of patients who are eligible for resection. Combination therapy with fluorouracil and leucovorin has been the mainstay of treatment for metastatic CRC; however, the introduction of newer agents, such as oxaliplatin and irinotecan, and targeted agents, such as cetuximab and bevacizumab, has yielded improvements in response rates (RRs) and survival. Maximizing the exposure of hepatic metastases to high target concentrations of cytotoxic drugs using hepatic arterial infusion (HAI) increases RRs further than with systemic chemotheraphy; however, the impact of HAI on survival is unclear. As the goals of chemotherapeutic treatment for metastatic CRC increasingly shift from palliation to prolongation of survival, improvement in RRs, and downsizing of tumors in order to enable or optimize resection, treatment in a multidisciplinary environment involving a medical oncologist, radiologist, and surgical oncologist with hepatobiliary expertise will become central to deciding the best course of therapy and timing of surgery. The Oncologist 2008;13:000–000

INTRODUCTION

Colorectal cancer (CRC) is the second most prevalent malignant disease in industrialized countries, with approximately 2.8 million people alive who were diagnosed with the disease between 1997 and 2002 [1]. The annual incidence of invasive CRC in the U.S. remains among the highest in the world, with an age-adjusted rate of 50.6 per 100,000 population for the years 2001–2005 [2]. The major cause of death in patients with CRC is distant metastasis. Depending on the stage of the primary tumor, liver metastases are seen in 20%–70% of patients with CRC, and lung metastases are seen in 10%–20% of patients with CRC [3].

Correspondence: Steven R. Alberts, M.D., M.P.H., Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55901, USA. Telephone: 507-284-8965; Fax: 507-284-1803; e-mail: alberts.steven@mayo.edu Received June 27, 2008; accepted for publication August 17, 2008. ©AlphaMed Press 1083-7159/2008/$30.00/0 doi: 10.1634/theoncologist.2008-0142

The Oncologist 2008;13:000–000 www.TheOncologist.com
The liver is the only metastatic site in around one third of patients [4].

Without treatment, the outlook for patients with metastatic CRC is very poor, with a median survival time in the region of 1 year [5, 6]. However, surgical resection of metastases can produce long-term survival and cure in some patients. Large patient series have shown that liver resection is possible with reasonable mortality and morbidity, and may achieve 5-year survival rates of approximately 27%–41% [7]. In 1984, a series of 252 patients with biopsy-proven, unresected hepatic metastases from CRC was reported by Wagner and colleagues to achieve 5-year survival rates of 25% and 2% for patients with resected and unresected disease, respectively [8]. More recent data from Canada show a survival rate of 43% at 5 years after liver resection for metastatic CRC [9]. Furthermore, in well-selected patients, there is an estimated 17%–25% chance of cure after hepatectomy (survival >10 years after liver resection), even in the presence of poor prognostic factors [10].

Despite the clear benefits of surgery, conventionally only about 10%–20% of patients have had metastases that are considered to be resectable at presentation [11]. Fortunately, advances in chemotherapy, regional treatment, imaging, and surgical techniques are radically changing the management of liver metastases from CRC; patients who were eligible only for palliative chemotherapy a few years ago now have options that may improve their chances of long-term survival [11].

## WHICH PATIENTS HAVE RESECTABLE DISEASE?

Recent opinion recommends that evaluation for resectability requires review by an expert team, which should include a skilled surgeon, a medical oncologist, and a radiologist [7]. Perceptions of resectability vary among surgeons, and this variability was highlighted by a multicenter study in which predefined criteria for unresectability were applied. Subsequent central review showed that 10% of patients who met the criteria for resection did not undergo surgery [7].

Broadly, patients without extrahepatic disease and those with good liver function and in good general condition may be eligible for hepatic resection [6]. Classic contraindications for surgery, such as more than four metastases, extrahepatic disease, and a resection margin <1 cm, have been revised in recent years. It has been suggested that the absolute contraindications should include unresectable extrahepatic disease, >70% liver involvement (six segments), liver failure, and insufficient fitness to undergo surgery [12]. Following a recent consensus conference, a definition of resectability was proposed that included the ability to achieve complete resection (negative margin), preserve two contiguous liver segments with adequate vascular inflow and outflow, and preserve an adequate future liver remnant (>20% healthy liver) [13]. Modifications of the required size of the remaining liver have been prepared and include the use of preoperative chemotherapy (30%) and underlying cirrhosis (40%).

The use of scoring systems may also help to identify patients likely to have recurrent metastatic disease after surgery [14, 15]. For example, analysis of records for 1,001 consecutive patients who underwent liver resection as a component of their treatment for metastatic CRC between 1985 and 1998 showed that a preoperative scoring system that included the negative factors of a node-positive primary tumor, a disease-free interval from primary to metastatic disease of <12 months, more than one hepatic metastasis, the largest hepatic metastasis >5 cm, and a carcinoembryonic antigen level >200 ng/l was highly predictive (p < .0001) of survival [14].

## DISEASE STAGING

Accurate staging is required to rule out extrahepatic disease, select curable patients, and confirm the suitability of patients for surgery. Staging of metastatic disease includes radiologic (triple-phase computed tomography scan or magnetic resonance imaging) and functional (positron emission tomography scan) imaging. A review of imaging techniques is beyond the scope of this review, but has been well summarized elsewhere [16, 17].

## CHEMOTHERAPY FOR PATIENTS WITH LIVER METASTASES FROM CRC

For many years, fluorouracil (5-FU) in combination with leucovorin (LV) was the standard therapy for metastatic CRC, yielding a response rate (RR) of 20%–30% and median survival time of 11–12 months [4]. Newer systemic chemotherapy regimens incorporating the platinum agent oxaliplatin and the topoisomerase inhibitor irinotecan have increased both RRs and overall survival (OS) [18–28]. First-line chemotherapy regimens that include oxaliplatin or irinotecan have yielded RRs of 33%–62% [18–28]. The inclusion of targeted agents with chemotherapy has further improved outcomes. Cetuximab added to oxaliplatin or irinotecan regimens increased the RR from 33% to 49% [28], and the addition of bevacizumab to irinotecan increased the RR from 35% to 45% [22]. A median OS time >20 months is now seen [22, 27]. The objectives of chemotherapy in CRC with metastases to the liver have accordingly shifted from palliation to maximization of benefit through prolongation of survival, improving RRs, and downsizing tumors to enable or optimize resection. The recent recognition of
the role of KRAS in predicting response to cetuximab will help to further select patients that may benefit from the use of an epithelial growth factor inhibitor such as cetuximab [29].

**Initially Unresectable Disease**

Increasing evidence supports the ability of chemotherapy to downsize tumors and enable surgery that was not initially possible. Three reports describe the ongoing experience of a group in France [30–32] and demonstrate that patients with initially unresectable disease who undergo curative liver surgery after a response to chemotherapy have a survival duration similar to that of patients who undergo primary resection.

The first report was a retrospective study in 330 initially inoperable chemotherapy-naïve patients, of whom 53 were able to undergo surgery after downsizing of metastases using a chronomodulated regimen of oxaliplatin plus 5-FU and LV [30]. The survival rate was 40% at 5 years, there was no operative mortality, and repeat surgery was possible for hepatic recurrence in 15 cases (Table 1).

In another retrospective study, oxaliplatin plus 5-FU and LV (a chronomodulated regimen in 83% of patients) yielded a 50% 5-year survival rate in 58 patients who underwent complete resection [31]. Across all 151 patients in that study, the size of the liver metastases decreased by >50% in 89 patients (59%).

Adam et al. [32] more recently reported data from a consecutive series of 1,439 patients managed over 11 years, of whom 1,104 initially had unresectable disease. After a mean of 10 courses of mostly oxaliplatin-based chemotherapy, resection was possible in 138 patients (12.5%) (Table 1); 75% of resections were major hepatectomies and 93% were potentially curative. The operative mortality rate was 0.7% at 2 months. The 10-year survival rate was 23%. Among the 335 patients who underwent primary surgery without chemotherapy, the 10-year survival rate was 30% ($p = .01$). Four preoperative risk factors predicting poor outcome were identified: rectal primary, three or more metastases, maximum tumor size $>10$ cm, and carcinoembryonic antigen level $>100$ UI/L.

Most recently, Baize et al. [33] identified 39 patients with unresectable metastases from 82 patients with advanced CRC, of whom 11 underwent surgery after oxaliplatin-based chemotherapy (Table 1). Among the patients who underwent surgery, the progression-free survival (PFS) duration was 14 months, compared with 6 months for the 28 patients who did not undergo surgery ($p < .002$). The median OS times were 60 months and 18.5 months in the two groups, respectively ($p < .0001$).

Subgroup analyses of recent phase III trials of oxaliplatin-containing regimens also show promising rates of secondary resection. In the OPTIMOX-1 (Optimized 5-FU-Oxaliplatin Strategy) study, which compared two first-line regimens of oxaliplatin plus 5-FU and LV (FOLFOX4 and “stop and go” FOLFOX7) in 620 patients with unresectable metastases from CRC, chemotherapy allowed resection in 101 patients (16%) [34]. An R0 (radical) resection was possible for 71 patients, and R1 and R2 resections were each performed in 15 patients. Patients who had an R0 or R1 resection had a median OS time of 51 months with FOLFOX4 and 38 months with FOLFOX7. In a retrospective analysis of data from the large Intergroup N9741 trial [35], the rate of curative resection was significantly higher with oxaliplatin-based regimens than with irinotecan in combination with 5-FU and LV (IFL) (FOLFOX4, 2.4%; irinotecan plus oxaliplatin, 2.9%; IFL, 0.9%; $p = .02$). In a study of 74 patients with unresectable metastatic CRC who were treated

<table>
<thead>
<tr>
<th>Study</th>
<th>n of patients (resected/initial)</th>
<th>Regimen</th>
<th>Resection rate (%)</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bismuth et al. [30]</td>
<td>53/330</td>
<td>5-FU + LV + OXA (chronomodulated)</td>
<td>16</td>
<td>–</td>
<td>3-yr, 54%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-yr, 40%</td>
<td></td>
</tr>
<tr>
<td>Giacchetti et al. [31]</td>
<td>58/151</td>
<td>5-FU + LV + OXA (83% chronomodulated)</td>
<td>38</td>
<td>–</td>
<td>5-yr, 50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-yr, 40%</td>
<td>Median, 48 mos</td>
</tr>
<tr>
<td>Adam et al. [32]</td>
<td>138/1,104</td>
<td>5-FU + LV + OXA or IRN or both (87% chronomodulated)</td>
<td>12.5</td>
<td>5-yr, 22%</td>
<td>5-yr, 33%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10-yr, 17%</td>
<td>10-yr, 23%</td>
</tr>
<tr>
<td>Baize et al. [33]</td>
<td>11/39</td>
<td>5-FU + LV + OXA</td>
<td>28</td>
<td>Median, 14 mos</td>
<td>3-yr, 73%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10-yr,</td>
<td>Median, 60 mos</td>
</tr>
</tbody>
</table>

Abbreviations: 5-FU, 5-fluorouracil; IRN, irinotecan; LV, leucovorin; OS, overall survival; OXA, oxaliplatin; PFS, progression-free survival.
with FOLFOXIRI (oxaliplatin and irinotecan with LV and bolus plus infusional 5-FU), 19 patients (26%) were able to undergo a potentially curative resection [36]. The median OS time was 36.8 months for patients who underwent resection, compared with 22.2 months for the 34 patients who responded to chemotherapy but who did not undergo surgery (p = .0114). In a phase III study of 283 patients conducted by the Hellenic Oncology Research Group, the addition of oxaliplatin to FOLFIRI (irinotecan with LV and bolus plus infusional 5-FU) increased the resection rate of lung and liver metastases from 4% to 10% (p = .08); among patients who underwent surgery after FOLFOXIRI, 86% had an R0 resection [37]. FOLFOXIRI also conferred superior resection rates and survival over FOLFIRI in a phase III trial in 244 previously untreated patients with no prior chemotherapy [38, 39]. The overall RRs to FOLFIRI and FOLFOXIRI were 34% and 60%, respectively (p < .0001), enabling radical secondary resection in a greater proportion of patients in the FOLFOXIRI arm than in the FOLFIRI arm (Fig. 1).

Phase II studies of pre- or postoperative chemotherapy with curative intent have yielded encouraging responses and good resection rates (Table 2) [40, 41]. Notably, the study by Alberts et al. [40] enrolled patients with liver metastases considered to be not optimally resectable.

The addition of targeted agents to chemotherapy may further improve RRs and secondary resection rates [42–44]. As shown in Table 2, the addition of the epidermal growth factor receptor (EGFR) inhibitor cetuximab to FOLFLEX4 or the vascular endothelial growth factor (VEGF) inhibitor bevacizumab to capcitabine plus oxaliplatin has resulted in overall RRs of up to 74% and potentially curative surgery in up to 89% of patients.

However, when a decision is made to use an EGFR inhibitor it has become increasingly clear that the status of the KRAS gene within the tumor should be assessed first. Mutations of KRAS and its downstream signaling can adversely affect response to EGFR inhibitors. The currently available information shows that approximately 40%–45% of patients with advanced CRC have mutations within KRAS, making this a potential major determinant of treatment outcome for patients receiving EGFR inhibitors. Retrospective analyses of trials using either cetuximab or panitumumab have shown that there is essentially no response to treatment with one of these antibodies in patients with mutated KRAS, whereas those with wild-type KRAS are likely to respond. In a trial of 463 patients evaluating the potential efficacy of panitumumab in last line therapy, 427 had available KRAS data, of whom 43% had mutated KRAS [45]. For patients with wild-type KRAS, 17% responded and 34% had stable disease, compared with zero responders and 12% with stable disease in the mutated KRAS group. When the treatment arms were combined, the OS time was longer in patients with wild-type KRAS than in patients with mutated KRAS (hazard ratio, 0.67; 95% confidence interval [CI], 0.55–0.82).

The National Surgical Adjuvant Breast and Bowel Project (NSABP) is currently planning a trial of patients carefully selected specifically for “conversion” from unresectable to resectable using an EGFR inhibitor. With the newly gained knowledge on KRAS this trial will use analysis of KRAS status for treatment assignment.

While it is clear that progressive improvements are being made in downsizing tumors, this approach can negatively impact the quality of life of patients undergoing this approach. Given the potential greater toxicity of therapy to downsize metastases compared with what may be used in a palliative setting, it is important that patients be carefully evaluated for this type of approach. Patients should be assessed as to their ability to undergo chemotherapy as well as surgery.

Resectable Disease: Neoadjuvant Therapy

The potential benefits of neoadjuvant chemotherapy in patients with resectable disease include the opportunity to test for chemoresponsiveness [46], the potential elimination of micrometastatic disease [7], and the possibility of tumor downsizing with a higher likelihood of a complete resection and/or reduced extent of resection [47].
addition, response to neoadjuvant chemotherapy has been highlighted as a potential prognostic indicator for survival, which may help to select suitable candidates for surgery [48]. Potential disadvantages of neoadjuvant chemotherapy include the possibility of hepatic damage (see below) and inducing a complete response that renders previously resectable patients unsuitable for surgery. In addition, Benoist et al. [49] described the high rate of recurrence of lesions (43 of 66, 65%) that were initially radiologically determined to be complete responses. Therefore, a mixed response of partial and complete responses may disrupt surgical planning for the complete resection or ablation of the originally identified lesions and result in a high rate of recurrence [49]. The ability to visualize the metastases at the time of surgery, either on a preoperative scan or directly in the operating room, permits a higher likelihood of a complete resection. A complete radiologic response may require that a large resection be performed to ensure all potential microscopic disease is resected and may also result in an incomplete resection through the lack of ability to visualize the metastases.

Neoadjuvant chemotherapy feasibility studies include two trials in which oxaliplatin-based chemotherapy was assessed in patients with resectable liver metastases [50, 51]. Good efficacy and manageable tolerability were noted with the MIROX strategy of giving six cycles of FOLFOX7 before surgery and six cycles of FOLFIRI thereafter in 22 patients (Table 3); the median OS time had not been reached at the time of reporting [51]. An intensive regimen of weekly high-dose 5-FU and LV with biweekly oxaliplatin also yielded high response and curative resectability rates in a small study of 20 patients [50] (Table 3).

In the large (n = 364) phase III European Organization for the Research and Treatment of Cancer (EORTC) 40983 study, perioperative FOLFOX4 (six cycles before and six cycles after surgery) was associated with a longer PFS time than with surgery alone among patients with resectable liver metastases [52, 53]. There was no evidence that chemotherapy prevented patients from undergoing surgery. Perioperative chemotherapy was observed to produce a longer PFS time among patients who underwent resection, although the benefit was slightly less evident when patients who were considered resectable upon imaging but were not ultimately operated upon were included in the analysis (Fig. 2).

### Adjuvant Therapy

The role of adjuvant chemotherapy after surgery for resection of liver metastases remains uncertain. A meta-analysis based on two phase III trials in which 138 patients received 5-FU and LV–based chemotherapy after radical resection and 140 patients underwent surgery without chemotherapy showed a nonsignificant trend toward a longer median PFS duration among patients who received adjuvant chemotherapy (2.20 years versus 1.55 years, respectively), but no significant difference in OS (5.09 years versus 3.91 years) [54]. In contrast, a multicenter, randomized trial of adjuvant 5-FU plus LV demonstrated a significant benefit in terms of disease-free survival (DFS) with adjuvant chemotherapy versus surgery alone [55]. In total, 173 patients who underwent radical resection of liver metastases were randomized to surgery with observation only or postoperative 5-FU and LV–based chemotherapy for 6 months. The 5-year DFS rate (primary endpoint) was 33.5% among patients who received adjuvant chemotherapy, compared with 26.7% for

---

**Table 2. Neoadjuvant chemotherapy with operative intent in patients with initially unresectable liver metastases from colorectal cancer: Results of phase II studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>n of patients</th>
<th>Regimen</th>
<th>Overall RR (%)</th>
<th>Radical (R0) resection rate (%)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberts et al. [40]</td>
<td>42</td>
<td>FOLFOX4</td>
<td>60</td>
<td>33.3</td>
<td>Median overall, 26 mos</td>
</tr>
<tr>
<td>Pozzo et al. [41]</td>
<td>40</td>
<td>FOLFIRI</td>
<td>47.5</td>
<td>32.5</td>
<td>All patients still alive after median follow-up of 19 mos</td>
</tr>
<tr>
<td>With targeted biologic agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Díaz-Rubio et al. [42]</td>
<td>42</td>
<td>FOLFOX4 + cetuximab</td>
<td>72</td>
<td>23.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Progression-free, 10.2 MOS (study ongoing)</td>
</tr>
<tr>
<td>Gruenberger et al. [43]</td>
<td>54</td>
<td>XELOX with or without bevacizumab</td>
<td>74&lt;sup&gt;b&lt;/sup&gt;</td>
<td>89</td>
<td>Data pending (study ongoing)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Total resections: Eight of these 10 patients had liver metastases only. Study is ongoing.

<sup>b</sup>Included a complete response rate of 11%.

Abbreviations: FOLFIRI, irinotecan plus bolus and infusional 5-fluorouracil and leucovorin; FOLFOX4, oxaliplatin plus bolus and infusional 5-fluorouracil and leucovorin; RR, response rate; XELOX, capecitabine and oxaliplatin.

---
Table 3. Neoadjuvant chemotherapy in patients with initially resectable liver metastases from colorectal cancer: Results of feasibility studies of regimens based on oxaliplatin

<table>
<thead>
<tr>
<th>Study</th>
<th>n of patients</th>
<th>Regimen</th>
<th>Overall RR (%)</th>
<th>Resection rate (%)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taïeb et al. [51]</td>
<td>22</td>
<td>MIROX (6 cycles of FOLFOX7 before surgery + 6 cycles of FOLFIRI after surgery)</td>
<td>77a</td>
<td>95.5</td>
<td>Median disease-free, 21 mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2-yr overall, 89%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2-yr disease-free, 47%</td>
</tr>
<tr>
<td>Wein et al. [50]</td>
<td>20</td>
<td>High-dose weekly 5-FU + LV + biweekly oxaliplatin</td>
<td>100b</td>
<td>80</td>
<td>2-yr disease-free, 52%</td>
</tr>
</tbody>
</table>

aTwo complete and 15 partial responses.
bTwo complete and 18 partial responses.

Abbreviations: 5-FU, 5-fluorouracil; FOLFIRI, irinotecan plus bolus and infusional 5-fluorouracil and leucovorin; FOLFOX7, 2-weekly 5-fluorouracil by 46-hour infusion, leucovorin, and oxaliplatin; LV, leucovorin; RR, response rate.

Figure 2. Effect on progression-free survival (PFS) of perioperative FOLFOX4 versus surgery alone in patients with resectable colorectal cancer liver metastases [50]. Hazard ratios (95% confidence interval) corresponding to the absolute differences in PFS were 0.79 (0.62–1.02; p = 0.58), 0.77 (0.6–1.0; p = 0.41), and 0.73 (0.55–0.97; p = 0.025) for all, all eligible, and all resected patients, respectively.

Abbreviations: FOLFOX, oxaliplatin plus 5-fluorouracil and leucovorin.

those who received surgery alone (p = 0.28). A trend toward a higher 5-year OS rate for chemotherapy did not attain statistical significance (51.1% versus 41.1%; p = 0.13).

An ongoing phase III trial is evaluating adjuvant oxaliplatin plus capecitabine and bevacizumab versus oxaliplatin plus capecitabine alone (NCT00394992). A phase III trial of oxaliplatin plus capecitabine with hepatic arterial infusion (HAI) (see below) of floxuridine versus oxaliplatin plus capecitabine in patients with resected or ablated liver metastases failed to accrue sufficient patients and was closed recently (NSABP C-09; NCT00268463).

Hepatic Arterial Infusion

The rationale underlying HAI is the maximization of exposure of hepatic metastases to high target concentrations of cytotoxic drugs by localized infusion. Most randomized studies have shown higher RRs for HAI when compared with systemic chemotherapy, but the impact of HAI on survival is unclear, particularly when compared with optimal systemic regimens. A recent meta-analysis of seven randomized controlled trials in 1,098 patients showed median OS durations of 16.04 months and 12.64 months (p = .3) for HAI and systemic chemotherapy, respectively, in patients with unresectable liver metastases [56].

The Cancer and Leukemia Group B 9481 randomized trial compared floxuridine by HAI with systemic 5-FU and LV in 135 patients [57]. The median OS time (24.4 months versus 20.0 months; p = .0034), objective response rate (47% versus 24%; p = .012), and time to hepatic progression (9.8 months versus 7.3 months; p = .034) were all significantly better with HAI, and a quality of life assessment showed better physical functioning in the HAI group at 3 months and 6 months. Grade 3 or 4 neutropenia (2% versus 45%) and stomatitis (0% versus 24%) were significantly (p < .01) more frequent with systemic therapy, but elevated bilirubin was reported with HAI only (18.6% versus 0%; p < .01).

HAI of oxaliplatin with i.v. LV and bolus and infusional 5-FU appears to be feasible in patients with unresectable liver metastases after systemic chemotherapy failure [58]. After a median of nine cycles of treatment, there were 24 partial responses (62%) among 39 assessable patients, allowing R0 resection in seven patients and radiofrequency ablation in one patient. However, other trials have shown no survival benefit for 5-FU and LV HAI [59, 60]. Problems with HAI are most commonly linked with hepatic toxicity and gastric ulceration [4]. In early reports, HAI floxuridine was associated with biliary toxicity, manifested as elevated levels of aspartate transaminase, alkaline phosphatase, and bilirubin [61]. These toxicities have been managed with close attention to the development of “transaminitis” and hyperbilirubinemia. Immediate emptying of the residual floxuridine in the pump and subsequent dose reductions
avoid the dangerous complications of sclerosing cholangitis. Careful skeletonization of the extrahepatic portion of the hepatic artery in the porta hepatis dramatically reduces, if not eliminates, common hepatic and bile duct strictures and gastroduodenal ulceration. Sclerosing cholangitis is also seen in patients undergoing HAI [4].

Two randomized trials of HAI following surgical resection of hepatic metastases from CRC previously reported evidence of clinical benefit. In a trial conducted at the Memorial Sloan-Kettering Cancer Center, patients were randomized to systemic chemotherapy alone versus systemic chemotherapy combined with HAI of 5-fluorouracil [62, 63]. Seventy-four patients were randomized to combined therapy and 82 were randomized to systemic therapy. A significant benefit was seen in patients receiving combined therapy, with a median survival time of 72.2 months in the combined therapy group, compared with 59.3 months for patients receiving systemic therapy alone. At 2 years, the rate of survival free of hepatic recurrence was 90% in the combined therapy group compared with 60% in the systemic therapy only group (p < .001). However, recurrence outside the liver was similar in both groups. In a separate study, patients with two to four resected hepatic metastases were randomized to resection alone versus HAI of 5-fluorouracil combined with systemic infusional 5-FU [64]. That trial also showed a markedly lower incidence of hepatic recurrence with HAI as well as a significantly longer recurrence-free survival time.

The potential benefit of a more active systemic regimen alternating with HAI was evaluated in a multicenter phase II trial (the North Central Cancer Treatment Group N9945 trial). Patients undergoing resection with or without ablation received four alternating cycles of HAI consisting of 5-fluorouracil and dexamethasone alternating with systemic capecitabine and oxaliplatin. Two additional cycles of systemic therapy were given. At the time of the initial analysis, the estimated 2-year survival rate was 86% (95% CI, 76%–97%) and the median time to progression was 32 months [65].

The clinical benefit of HAI in the setting of other available active systemic regimens requires further study. For the present time, the use of this modality should be restricted to experienced centers [66].

**Optimal Timing and Duration of Perioperative Chemotherapy**

The issue of the optimal timing and duration of perioperative chemotherapy remains largely unresolved. Treatment toxicity and tumor response.

**SafetY of Perioperative Chemotherapy**

Perioperative chemotherapy may cause liver damage, which has the potential to increase the risks of surgery, prevent liver resection, and impair functioning of the remaining hepatic tissue. Adverse effects of most concern in this setting are those causing vascular changes and chemotherapy-associated steatohepatitis. Vascular changes include sinusoidal dilation with erythrocytic congestion, sometimes accompanied by perisinusoidal fibrosis and fibrotic venular occlusion; this may result in sinusoidal obstruction syndrome, as seen in veno-occlusive disease [69].

Evidence suggests that oxaliplatin-based regimens are associated with a higher risk for hepatic vascular lesions [67, 69], whereas irinotecan-based regimens are associated with higher risks for steatosis and steatohepatitis [70]. Steatohepatitis tends to be seen more frequently in patients with a high body mass index [71] and is reported more frequently in U.S. studies [72], whereas vascular lesions are reported more commonly in Europe [66, 67]. It is therefore possible that chemotherapy does not cause steatosis as such but may aggravate it where it is already present.

Steatohepatitis has been associated with a higher 90-day mortality rate after surgery [70]. Pathologic review of 158 patients who received no preoperative chemotherapy and 248 patients who received neoadjuvant therapy for a median of 16 weeks showed more sinusoidal dilation with oxaliplatin-based regimens than with no chemotherapy (18.9% versus 1.9%), and more steatohepatitis with irinotecan-based regimens (20.2% versus 4.4%). A higher 90-day mortality rate was seen in patients with steatohepatitis (14.7% versus 1.6%; p = .001).

Although the association of perioperative chemotherapy with liver injury is accepted, the clinical significance of this effect remains uncertain. Safety data from the EORTC 40983 study, which compared surgery alone with perioperative chemotherapy comprising oxaliplatin plus 5-FU and LV in 364 patients, showed very low mortality rates (~1%)
Chemotherapy for Colorectal Cancer Liver Metastases

in both treatment arms, with an acceptable rate of reversible complications [51].

Few data pertaining to the safety of targeted biologic agents in the perioperative setting are available, but there is concern that the use of bevacizumab may increase the risk for wound-related complications [73, 74]. Bevacizumab has been associated with a higher risk for organ perforation, bleeding, and decreased wound healing. VEGF is important in hepatic regeneration, and the use of VEGF inhibitors may therefore impair this process in patients undergoing surgery [74]. A review of wound-healing complications after cancer surgery in patients treated with 5-FU–containing chemotherapy showed complication rates of 1.3% (3 of 230 patients) when bevacizumab was added to chemotherapy and 0.5% (1 of 194 patients) with the control [73]. The authors concluded that the addition of bevacizumab to therapy caused no relevant increase in the rate of wound-healing complications.

**RADIOFREQUENCY ABLATION FOR LIVER METASTASES**

Nonsurgical ablative techniques are now being used more frequently for the treatment of liver metastases. Of the various techniques available, radiofrequency ablation (RFA) is the one most commonly used. However, long-term outcomes related to the use of RFA for potentially resectable liver metastases remain uncertain. In a recent review of the literature, no 5-year survival data could be identified in published studies for resectable liver metastases, while the 5-year survival rate for unresectable metastases was in the range of 14%–55% [75]. While RFA appears to have an important role in augmenting surgical resection or providing an option for patients unable to undergo surgical resection, it does not appear that RFA provides an outcome comparable with that of surgery overall. However, a subgroup of patients may exist in which RFA may provide outcomes similar to surgery, but with the lack of randomized trials this remains uncertain. Further work is needed to clarify the role of RFA in the treatment of liver metastases from CRC.

**CONCLUSIONS**

The potential of chemotherapy to render unresectable liver metastases resectable is now a clinical reality. Studies have shown that oxaliplatin-based preoperative chemotherapy achieves high RRs and makes resection possible in a clinically relevant proportion of patients. Looking forward, further research is required to establish the best endpoint for new clinical trials in this setting [76]. OS is a long-term outcome and can be influenced by many factors. Possible alternatives include the best response, resection rate, and relapse-free survival rate after response [76]. As patients with metastatic CRC increasingly receive chemotherapy with curative intent, treatment in a multidisciplinary environment will become central to achieving optimal outcomes; a medical oncologist, radiologist, and skilled hepatobiliary surgeon should be involved in deciding the best course of therapy and timing of surgery. In this context, computerized decision models (including OncoSurge) are in development and will need to be validated for decision making [12, 77]. Emerging chemotherapeutic regimens, targeted biologic agents, and new surgical and radiation techniques create challenges for maintaining the timeliness of these tools. Clearly, there has been remarkable progress in therapy for CRC that has metastasized to the liver, and the prospect of long-term survival is becoming a reality for an increasing proportion of patients.

**AUTHOR CONTRIBUTIONS**

Manuscript writing: Steven Alberts, Lawrence Wagman
Final approval of manuscript: Steven Alberts, Lawrence Wagman

The authors take full responsibility for the content of the paper but thank Samantha Richer, Ph.D., from Adelphi Communications, supported by Sanofi-Aventis, US, for her assistance in preparing the initial draft of the manuscript and collating the comments of authors.

**REFERENCES**


44 Adam R, Aloia T, Lévi F et al. Hepatic resection after rescue cetuximab...
Chemotherapy for Colorectal Cancer Liver Metastases


65 Alberts SR, Mahoney MR, Donohue J et al. Systemic capcitabine and oxaliplatin administered with hepatic arterial infusion (HAI) of fluorouridine (FUDR) following complete resection of colorectal metastases (M-CRC) confined to the liver: A North Central Cancer Treatment Group (NCCTG) phase II Intergroup Trial. J Clin Oncol 2006;24:152s.


