

# Rational treatment planning for isolated, potentially curable liver metastases

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The liver is a frequent site of metastatic colorectal disease. Surgical resection remains the gold standard for treating isolated liver metastasis, but only 5%–10% of patients are eligible for resection. Chemotherapy is the treatment of choice for unresectable disease. Clinical trials with newer agents and combinations as well as drug delivery via the hepatic artery have shown that initially unresectable disease can become resectable with chemotherapy. Because of the high rate of recurrence after resection, chemotherapy is also used in the adjuvant setting to improve outcomes. The role of adjuvant therapy in resectable liver metastases is unclear. Neoadjuvant therapy now is being considered in patients with resectable liver metastases to decrease the size of the tumor prior to surgery. The timing and sequence of chemotherapy and surgery are important considerations in this setting and need to be defined. Additionally, the potential for liver toxicity associated with neoadjuvant chemotherapy needs to be weighed against the benefit of therapy.

**P**atients with colorectal cancer (CRC) frequently develop liver metastases, as venous drainage from the colon and rectum flows via the portal vein to the liver. Approximately 15% of patients with CRC present with liver metastases at the time of diagnosis. In addition 60% of patients who develop metastatic disease during the course of their disease will have metastases to the liver.<sup>1</sup>

The gold standard for treating isolated CRC metastases in the liver is surgical resection. Patients who are candidates for surgical resection of liver metastases may have prolonged survival or even a cure. Recent studies have reported 5-year survival rates of up to 58% after curative resection of hepatic CRC metastases.<sup>2–5</sup> This is an improvement compared with the approximate 38% 5-year survival rate seen in the late 1990s.<sup>6,7</sup> Advances in surgery and the implementation of multimodality approaches that involve new chemotherapeutic options (in the neoadjuvant and adjuvant settings), hepatic arterial infusion (HAI), conformal irradiation, preoperative portal vein embolization, local ablative therapy with radiofrequency ablation or cryosurgery, and staged resection are factors contributing to improved survival after resection of liver metastases.<sup>1,8</sup>

Only 5%–10% of patients with CRC with liver metastases are eligible for liver resection.<sup>9</sup> Extrahepatic disease, involvement of nonresectable structures such as liver veins, and insufficient remaining liver tissue render liver metastases unresectable in most cases.<sup>10</sup> In patients with unresectable metastases, chemotherapy is the treatment of choice. In this setting, chemotherapy often is used with palliative intent, and more recently it has been used in an attempt to render the metastases resectable.<sup>11</sup>

This article discusses the role of systemic chemotherapy for resectable and unresectable liver metastases in patients with CRC.

## Role of neoadjuvant chemotherapy in unresectable liver metastases

The possibility of downstaging unresectable liver metastases to the point of resectability and improving survival with neoadjuvant systemic chemotherapy initially was shown in several retrospective

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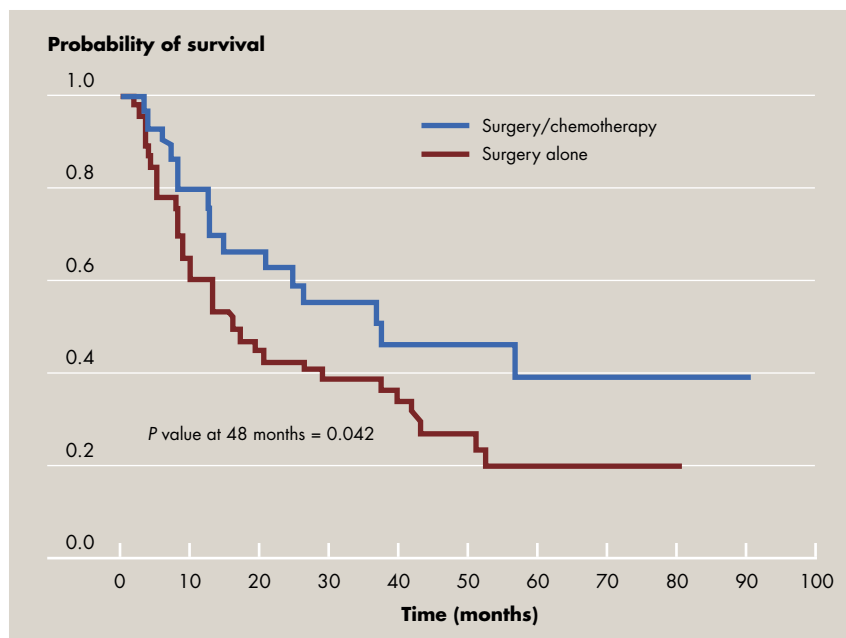
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analyses of chemotherapy trials. These analyses have reported resectability rates ranging from 1%–22%.<sup>1</sup> In the largest retrospective review of 1,104 patients with unresectable disease who received neoadjuvant therapy (mainly FOLFOX, a combination of oxaliplatin [Eloxatin] with infusional 5-fluorouracil [5-FU] and leucovorin [LV]), metastases became resectable in 12.5% of patients; the 5-year survival rate among these patients was 34%—similar to that achieved in patients with initially resectable disease.<sup>11</sup>

Several prospective trials have addressed resectability after neoadjuvant chemotherapy in patients with initially unresectable liver metastases. In these trials, resectability rates of 10%–37.5% have been reported.<sup>1</sup> The higher resectability rates in these series could be attributed to the use of newer, more effective chemotherapy agents and combinations, including FOLFOX and irinotecan (Camptosar) combined with infusional 5-FU/LV (FOLFIRI).

In an attempt to increase resectability rates and improve outcomes, HAI has been used in combination with or without systemic chemotherapy. In these studies, resectability rates of 12%–47% have been achieved.<sup>1</sup> In a study of 51 patients with unresectable disease treated with HAI, 5-FU, and systemic tegafur/uracil (UFT), 31 patients were candidates for resection after preoperative chemotherapy, but only 24 agreed to surgery. The 3- and 5-year survival rates were 58% and 42%, respectively, for the resected group, but for those patients who did not have resection, the 3- and 5-year survival rates were 25% and 0%, respectively.<sup>12</sup>

Although neoadjuvant chemotherapy has increased the number of patients eligible for resection and improved survival outcomes for patients with previously unresectable liver metastases, an important concern is its potential for liver toxicity (steatosis, steatohepatitis, and sinusoidal inju-



**FIGURE 1** Adjuvant hepatic arterial infusion and systemic chemotherapy improve disease-free survival following surgery for liver metastases in patients with colorectal cancer. Adapted, with permission, from Kemeny et al<sup>19</sup>

ry).<sup>13–15</sup> Chemotherapy-induced liver toxicity may preclude the feasibility of liver resection and increase postoperative complications and mortality. Steatohepatitis, in particular, has been associated with increased 90-day mortality after hepatic surgery.<sup>16</sup>

### Role of postoperative adjuvant chemotherapy in resected liver metastases

Approximately 60%–70% of patients with CRC who undergo resection of liver metastases will have a recurrence of their metastatic disease. Approximately one half of the recurrences will occur in the liver, and this may be the only site of recurrence for many patients.<sup>7</sup> Clinical trials assessing the potential role of chemotherapy after liver resection have been performed in an attempt to reduce the rate of recurrence and increase survival. However, the benefit of chemotherapy in this setting is unclear because of the lack of large prospective or randomized trials. Recently, two studies have attempted to address this issue.

A meta-analysis of two prematurely terminated phase III trials showed an almost significant improvement ( $P = 0.059$ ) in progression-free survival with adjuvant chemotherapy after resection of liver or lung metastases ( $n = 138$ ; median, 2.20 years; 95% confidence interval [CI], 1.72–3.95 years) over surgery alone ( $n = 140$ ; median, 1.55 years; 95% CI, 1.22–2.15 years).<sup>17</sup> Median overall survival, however, was not statistically significant between the two treatments, likely because of the lack of statistical power. In a retrospective study of 146 patients with CRC, adjuvant systemic chemotherapy after resection of liver or lung metastases has been associated with a longer survival probability (hazard ratio, 2.049; 95% CI, 1.149–3.656;  $P = 0.015$ ).<sup>18</sup>

Given the high proportion of CRC patients with liver-only recurrence, several large randomized trials have assessed intrahepatic therapy using HAI of floxuridine (FUDR) or 5-FU compared with either liver resection alone or systemic therapy. In one of the two trials that compared HAI

with surgery alone, HAI FUDR alternating with systemic 5-FU after surgery showed a recurrence-free benefit over surgery alone. As shown in Figure 1, the 4-year recurrence-free rate was significantly longer with HAI plus systemic therapy versus resection alone (45.7% and 25.2%, respectively;  $P = 0.04$ ).<sup>19</sup> However, this trial was not designed to assess an overall survival benefit. In the second trial, comparing HAI 5-FU/LV with surgery alone, no benefit was seen over surgery alone.<sup>20</sup>

In a trial that compared HAI and systemic therapy with systemic therapy alone, patients were randomized after liver resection to receive treatment with HAI FUDR plus dexamethasone and systemic 5-FU (with or without LV) or systemic chemotherapy alone.<sup>21</sup> Patients who received HAI plus systemic chemotherapy had a significantly increased 2-year survival rate compared with patients who received systemic therapy alone (86% vs 72%;  $P = 0.03$ ). An update of this study at a median follow-up of 10 years revealed a 10-year survival rate of 41% for the group receiving HAI plus systemic therapy versus 27% for the group receiving systemic therapy alone.<sup>22</sup> Overall median survivals were 68.4 months for HAI plus systemic therapy compared with 58.8 months for systemic therapy alone. Median time to hepatic recurrence has not been reached in the combination arm but was 32.5 months for patients receiving systemic therapy

### Clinical commentary

Neoadjuvant chemotherapy helps the oncologist assess the biology of the tumor and determine which patients will likely benefit from metastasectomy. Data demonstrate a poor outlook for patients with disease that progresses on neoadjuvant therapy.

The decision regarding surgery should be made as soon as the biology of the tumor can be assessed, generally after 2 or 3 months. If the lesion is deemed to be resectable, the patient should be referred early for surgery. Waiting too long risks liver damage and increased operative complications.

If the response to chemotherapy is good, the same chemotherapy can be given for several cycles after surgery. If the response is poor, an alternative chemotherapy regimen should be used. I do use adjuvant chemotherapy after resection. Because high-risk patients with stage III CRC are known to benefit from adjuvant treatment, patients with stage IV disease who are rendered disease-free by surgery are likely to benefit as well.

A flaw in the European Organization for Research and Treatment of Cancer (EORTC) trial 40983, which evaluated pre- and postoperative FOLFOX versus surgery alone, is that patients in the control group never received chemotherapy.<sup>23</sup> Therefore, the interpretation of that study in the context of contemporary management of metastatic CRC is difficult. However, it does suggest that potential cures are not being sacrificed by the use of neoadjuvant chemotherapy.

—Alan P. Venook, MD

alone ( $P \leq 0.01$ ). Median progression-free survival was 31 months for HAI plus systemic therapy compared with 17 months for systemic therapy alone ( $P = 0.02$ ).

### Role of neoadjuvant chemotherapy in resectable liver metastases

The improved survival associated with neoadjuvant chemotherapy in unresectable liver metastases has prompted investigations into the benefit of neoadjuvant chemotherapy in resectable liver metastases. A recent

trial evaluated pre- and postoperative FOLFOX4 ( $n = 182$ ) versus surgery alone ( $n = 182$ ) in patients with CRC and potentially resectable liver metastases. Preliminary results indicate a decrease in lesion size in response to preoperative chemotherapy.<sup>23</sup> Because the size of metastases at the time of surgery has an impact on survival, it is hoped that preoperative chemotherapy will improve survival. This possibility will be verified when disease-free survival and survival rates are available for this study.

Reduction of lesion size or complete disappearance of lesions in response to chemotherapy does not preclude resection after chemotherapy. Even after the absence of lesions is determined by computed tomography (CT), microscopic or macroscopic disease may persist. In a study by Benoist et al,<sup>24</sup> persistent macroscopic or microscopic residual disease or early recurrence in situ was observed in 55 (83%) of 66 liver metastases, despite CT imaging showing a complete re-

TABLE 1

Complication rates associated with neoadjuvant bevacizumab following hepatic surgery in patients with CRC and liver metastases

Complication	Bevacizumab therapy		P value	Interval from bevacizumab to surgery		P value
	Yes (n = 82)	No (n = 45)		≤ 60 days (n = 41)	> 60 days (n = 36)	
Any	41 (50%)	19 (42%)	0.40	23 (56%)	16 (44%)	0.31
Hepatobiliary	4 (5%)	5 (11%)	0.20	3 (7%)	1 (3%)	0.39
Wound	23 (28%)	11 (24%)	0.66	13 (32%)	10 (28%)	0.71

CRC = colorectal cancer

Adapted from Kesmodel et al<sup>25</sup>

sponse. Thus, resection after chemotherapy is necessary in most patients.

The availability of new and more effective agents, such as the targeted antiangiogenic agent bevacizumab (Avastin), has fueled additional research to assess the benefit of the newer agents in the preoperative setting for the management of resectable liver disease. Bevacizumab has improved response rates and survival when used with chemotherapy in patients with metastatic CRC. However, an increase in postoperative wound complications has been reported with bevacizumab. A review of records of 82 patients who received neoadjuvant bevacizumab and chemotherapy and 45 patients who received chemotherapy alone before surgery for CRC liver metastases showed that neither bevacizumab nor the interval between bevacizumab use and surgery affected the surgical complication rate (Table 1).<sup>25</sup> Preliminary data from a prospective study, First BEAT, suggest that metastasectomies are feasible after treatment with chemotherapy plus bevacizumab; stopping bevacizumab 6–8 weeks before surgery was not associated with bleeding complications.<sup>26</sup>

### Roundtable discussion

*The roundtable discussion on key issues in rational treatment planning for isolated, potentially curable liver metastases was moderated by Dr. Charles Blanke. Participants included Drs. Al Benson III, Charles Fuchs, and Axel Grothey.*

*Dr. Blanke:* It is nice to have a situation in which a large fraction of patients with metastatic disease have the potential for a cure. The cure rate, even with surgery alone, has historically been around 25%, and with recent phase II trials of systemic therapy, we have seen rates approaching 50%. However, there are a number of questions surrounding this patient population and the proposed therapy:

- Should patients with potentially resectable metastases go to the oper-

ating room first? Or should neoadjuvant systemic therapy be considered? Can we predict who will do best or worst with resection?

- If we are going to use neoadjuvant systemic therapy, what will the endpoint be? Will it be a number of cycles or time based? Or should we just treat the disease until maximum response?

- Can neoadjuvant therapy damage the liver? This is a hot issue right now, and this question comes up with both some types of chemotherapy and targeted biologic agents.

- Is radiofrequency ablation as good as surgery for potentially resectable metastasis? What do we do with our highly successful systemic therapy when all gross disease disappears? Should we wait or resect anyway?

- Do we need postoperative therapy? And should we base our decision on the final pathology as we do with sarcoma treatment?

- And, of course, should we ever use HAI?

### What is the role of HAI?

*Dr. Blanke:* I feel that HAI plus old-fashioned chemotherapy (eg, 5-FU or FUDR) alone is better than chemotherapy alone. But, when newer chemotherapy is used, such as FOLFOX and biologics, it is not known whether HAI will add benefit. HAI is better than systemic therapy in terms of hepatic disease-free survival, and a recent update suggested it is also better in terms of progression-free survival.<sup>27</sup>

*Dr. Fuchs:* I don't necessarily agree that HAI plus chemotherapy is better than chemotherapy alone. No overall survival benefit has been shown.

*Dr. Grothey:* HAI can be hampered by feasibility issues. In most centers, I would consider HAI still experimental. We need to test its role further. We do have an ongoing trial, "Oxaliplatin and Capecitabine with or without an Hepatic Arterial Infusion with Floxuridine in Treating Pa-

tients Who Are Undergoing Surgery and/or Ablation for Liver Metastases due to Colorectal Cancer" (National Surgical Adjuvant Breast and Bowel Project protocol C-09), designed to help answer this question.

*Dr. Blanke:* HAI is extraordinarily difficult to do without the experience gained by doing it every day or at least every week. It is very easy to cause biliary sclerosis.

*Dr. Grothey:* Today, our various systemically active chemotherapy regimens have so dominated our medical treatment that the need for HAI is much less than it was when we had only 5-FU to treat patients with metastatic CRC.

*Dr. Blanke:* True. However, recent papers by Nancy Kemeny and colleagues look at more modern agents, such as irinotecan.<sup>28</sup> Certainly that group believes it still shows a benefit. However, I don't think there is any role for it outside of a clinical trial right now.

### What is your approach to the patient with resectable liver lesions? Should neoadjuvant therapy be given?

*Dr. Blanke:* At our institution, these patients usually undergo surgery first.

*Dr. Grothey:* It depends on when I see the patient. If a patient presents with a solitary metastasis in the right lobe 3 years after resection of a primary sigmoid cancer, for example, the tumor has been able to generate only one metastasis in 3 years. A rational approach is to refer this patient for resection first. However, if a patient presents with synchronous liver metastasis at the time the primary tumor is detected, little information about the biology of the tumor is known. For this patient, I would tend to use neoadjuvant chemotherapy—to get information about tumor biology, shrink the extent of the disease, and potentially treat micrometastatic disease away from the site of the primary tumor.

*Dr. Blanke:* I agree.

*Dr. Fuchs:* I agree that synchronous lesions are ones for which I would feel strongly about using neoadjuvant therapy. For patients who have long disease-free intervals, I often go to surgery first because there is less concern about concomitant disease elsewhere. However, we really don't know that the patient with a long disease-free interval isn't carrying some occult disease beyond where we're looking during resection.

#### **What neoadjuvant therapy would you recommend if you were going to use it?**

*Dr. Fuchs:* I use chemotherapy plus bevacizumab because, from my perspective, we're treating stage IV disease and ought to use the best available therapy. I do stop administering bevacizumab 4–6 weeks before surgery, usually closer to 6 weeks.

*Dr. Grothey:* I use a FOLFOX-based chemotherapy regimen. However, we recently saw that FOLFOX plus bevacizumab did not produce higher response rates than FOLFOX alone in the NO16966 trial.<sup>29</sup> Perhaps we should be using a cetuximab (Erbix)–based regimen, which we know from CALGB (Cancer and Leukemia Group B) 80203 does increase response rates when combined with FOLFOX and FOLFIRI or even FOLFOXIRI.<sup>10,30</sup>

*Dr. Blanke:* The best correlation with final outcome may be response rate, and that's the key point in selecting a regimen. We're not worrying about long-term survival because the surgery takes care of most of that. I use FOLFOX with bevacizumab at this time, as well, but I think about it.

#### **Does anybody have any concerns about neoadjuvant chemotherapy and steatohepatitis?**

*Dr. Fuchs:* The retrospective analysis by Vauthey et al<sup>16</sup> suggested that irinotecan was associated with a higher rate of steatohepatitis; how-

ever, it did not show a link between irinotecan and perioperative complications and mortality. It's difficult to draw conclusions about irinotecan from this analysis.

*Dr. Blanke:* The patient database dated back to 1992. Chemotherapy usage in the patients analyzed might have been higher, or perhaps the imaging was poorer, or the patients may have had more underlying liver disease.

*Dr. Grothey:* It would be helpful to have some validation of this retrospective analysis from M. D. Anderson, or perhaps from looking at the patients in another trial, like BICC-C (first-line irinotecan/fluoropyrimidine combinations with or without celecoxib [Celebrex]), where irinotecan was used.

#### **Is there a set amount of therapy we should give in the neoadjuvant setting?**

*Dr. Grothey:* The data from OP-TIMOX-1 showed that 3 months of a FOLFOX7-based regimen, which uses a high dose of oxaliplatin, was sufficient to induce maximum activity of the chemotherapy.<sup>31</sup> I don't think we have to shoot for a maximum response. We have to make these metastases resectable; not seeing anything on scans doesn't mean that the disease is gone. We should talk to the surgeon and decide the best timing for surgery.

*Dr. Fuchs:* Part of our interest is to have some time—perhaps 3 months—where we can feel assured that additional metastatic disease won't be evolving. I agree that the biggest response from chemotherapy is probably achieved in 3 months.

#### **Should we take a patient to surgery who has five or more lesions spread across the liver?**

*Dr. Blanke:* If the area where the tumors are present can be removed, then the surgery should be done. Obviously, an entire liver cannot be removed, and the patient would not be a candidate for a transplant. We

know that multiple metastases, although probably an adverse prognostic factor, do not absolutely predict against long-term survival, especially with the use of the best systemic therapy.

*Dr. Fuchs:* I would try to treat neoadjuvantly and resect if possible. Obviously, this approach is one I would not have contemplated a decade ago.

*Dr. Grothey:* Even if only some patients are long-term survivors after surgery, this approach is better than a completely palliative approach.

#### **Does radiofrequency ablation of colorectal liver metastases, with or without surgery, contribute a benefit beyond that achieved with chemotherapy?**

*Dr. Benson:* It is an important question, because radiofrequency ablation data in the recent literature suggest that the local recurrence rate can be significant.

*Dr. Blanke:* Absolutely.

*Dr. Benson:* The problem is that there is a large variation in the size of the lesions treated (with this technique). This is an area where we need good prospective data. We know that there is a great deal of variability. Multiple lesions are treated one way or the other. What is the impact of that over time?

*Dr. Blanke:* I agree.

#### **Should adjuvant therapy be used after liver resection?**

*Dr. Grothey:* We do not have any prospective clinical trials showing that this approach increases overall or disease-free survival. But, we all assume that this is what we would do because we translate patients with high-risk stage III disease into the resected stage IV situation. I do believe patients with resected stage IV disease should have adjuvant chemotherapy—even outside a trial.

*Dr. Blanke:* I agree now, but 10 years ago, I might have said something different. Seriously, thinking evolves.

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