

Current approaches for liver-only metastases in colorectal cancer

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The liver is the most common site of metastatic disease in patients with colorectal cancer (CRC). However, only 5%–10% of patients with CRC have metastatic lesions that are amenable to curative resection. Current management of patients with potentially downstageable unresectable CRC metastases involves an aggressive multimodality approach led by an interdisciplinary team of surgeons, medical oncologists, pathologists, and diagnostic radiologists. Efforts to increase the proportion of patients eligible for curative resection have led to improvements in prognostic factors for patient selection, advancements in surgical techniques, and implementation of multimodality approaches involving neoadjuvant chemotherapy, hepatic arterial infusion, preoperative portal vein embolization, local ablative therapy through radiofrequency ablation or cryosurgery, and staged resection. This article focuses on the use of neoadjuvant chemotherapy for hepatic CRC metastasis and patient selection criteria for resection of these metastases.

The liver is the most common, and often the only, site of metastatic disease in patients with colorectal cancer (CRC).¹ However, only 5%–10% of all patients with CRC have metastatic disease restricted to the liver that is amenable to curative resection.² The usual criteria for unresectability include the presence of extrahepatic disease, involvement of nonresectable structures such as liver veins, and insufficient remaining liver tissue.³

Analysis of data from 456 consecutive patients who underwent liver surgery from 1985 to 1991 at Memorial Sloan-Kettering Cancer Center showed a 5-year survival rate of 38%, median survival duration of 46 months, perioperative mortality rate of 2.8%, and perioperative morbidity rate of 24%.¹ Long-term survival of patients with CRC following curative resection of hepatic CRC metastases has significantly improved in the past 2 decades. Choti and colleagues reported 5-year median survival rates of 31% for 93 patients who were operated on between 1984 and 1992 and 58% among 133 patients who had operations between 1993 and 1999.⁴ Possible reasons for this improved survival include the use of new preoperative and intraoperative imag-

ing, increased use of chemotherapy, and improved salvage surgery. It should be noted, however, that a number of patients in the new cohort were only followed for 2 years, and a longer follow-up is needed to evaluate the actual increase in survival.

Efforts to increase the proportion of patients eligible for curative resection have led to improved prognostic factors for patient selection, advances in surgery, and implementation of multimodality approaches that involve new therapeutic options, such as neoadjuvant chemotherapy, hepatic arterial infusion (HAI), conformal radiation, preoperative portal vein embolization, local ablative therapy with radiofrequency ablation (RFA) or cryosurgery, and staged resection.^{5–7} Advances in surgical techniques for hepatic resections include the use of intraoperative ultrasonography to define lesions that might be missed by preoperative imaging or bimanual palpation; improved hemorrhage control through the use

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of new vascular occlusion techniques, low central venous pressure anesthesia, and innovative devices for parenchymal transection; and controlled anatomic hepatectomy with the Glissonian technique.²

Current approaches in the management of colorectal liver metastases are more aggressive than they were 20 years ago, when hepatic resection was recommended only in patients with a maximum of three lesions, a clear margin of 10 mm, and no extrahepatic disease. This article focuses on the use of neoadjuvant chemotherapy for liver-only metastases in CRC and the evolution of criteria for selection of patients who are likely to benefit from resection of hepatic metastases.

The National Comprehensive Cancer Network (NCCN) practice guidelines for CRC recommend upfront resection or neoadjuvant therapy for patients with stage IV CRC or recurrent disease and resectable synchronous liver metastases (Figure 1).⁸ The NCCN panel also suggests considering systemic therapy with FOLFOX (5-fluorouracil [5-FU], leucovorin [LV], and oxaliplatin [Eloxatin] every 2 weeks) or FOLFIRI (5-FU/LV plus irinotecan [Camptosar] every 2 weeks) in combination with bevacizumab (Avastin) or HAI for patients with unresectable liver metastases to attempt to reduce the hepatic disease burden and make resection feasible. Several studies have attempted to evaluate the effectiveness of neoadjuvant therapy in converting nonresectable colorectal hepatic metastases to resectability. Although there are no prospective randomized trials comparing liver resection with chemotherapy alone, the curative potential of liver resection is widely accepted. However, in extensive retrospective studies of chemotherapy, the 5-year survival rate is below 5%.

Resection after first-line systemic chemotherapy

Results of trials with novel regimens as first-line therapy for pa-

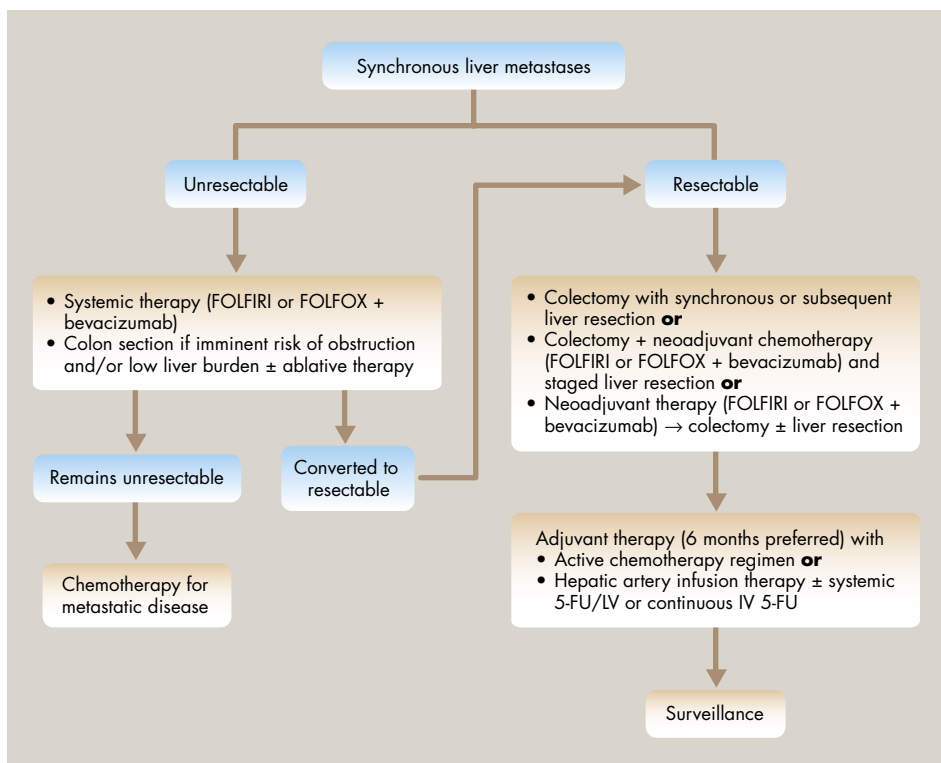


FIGURE 1 Summary of National Comprehensive Cancer Network practice guidelines for patients with colon cancer and synchronous liver metastatic disease. These recommendations are based on category 2B (on a scale of 1 to 3, where 1 is the highest level recommendation) evidence indicating that the NCCN consensus on this recommendation was not uniform (but there were no major disagreements) based on lower-level evidence. From National Comprehensive Cancer Network.⁸

tients with metastatic CRC (mCRC) have shown that these new systemic chemotherapy regimens induce resectability in patients with metastases that were considered unresectable at study entry. Tournigand and coworkers reported that secondary surgeries to remove metastases occurred in 9 patients (9%) treated with FOLFIRI followed by FOLFOX versus 24 patients (22%) treated with FOLFOX followed by FOLFIRI.⁹ In a randomized comparison between FOLFOX4 (agents administered every 2 weeks until disease progression) and FOLFOX7 (6 cycles followed by maintenance without oxaliplatin for 12 cycles and reintroduction of oxaliplatin for 6 cycles), the drug regimens had similar safety and efficacy profiles and similar rates of secondary surgery to remove metastases.¹⁰ In the FOLFOX4 arm, 55 patients (17.7%)

underwent such surgery, with 11.3% achieving R0 resection, and in the FOLFOX7 arm, 47 patients (15.2%) had the surgery, and 9.4% underwent R0 resection. Median survival time for patients who had surgery was 38.9 months in the FOLFOX4 arm (vs 19.3 months for all patients in this arm) and 43.0 months in the FOLFOX7 arm (vs 21.2 months for all patients in this arm). In a trial reported by de Gramont and colleagues in which patients were randomized to infusional 5-FU/LV with or without oxaliplatin, 7 patients (3.3%) treated with infusional 5-FU/LV and 14 patients (6.7%) treated with FOLFOX4 had surgical resections to remove metastases.¹¹

When evaluating the addition of irinotecan to the weekly Arbeitsgemeinschaft für Internistische Onkologie (AIO) high-dose infusional

5-FU/LV regimen, Köhne and colleagues reported that 6 (3%) patients in the irinotecan plus AIO group and 14 (6%) patients in the AIO-alone group underwent secondary resection of metastasis.¹²

In a phase III randomized trial of the survival benefit of bevacizumab added to irinotecan plus bolus 5-FU/LV (IFL), Hurwitz and colleagues reported that less than 2% of patients in both treatment groups underwent metastasectomy.¹³ Future trials should help determine if there is a role for bevacizumab in neoadjuvant therapy. Southwest Oncology Group (SWOG) trial 50408 is an ongoing phase II study of neoadjuvant capecitabine (Xeloda), oxaliplatin, and bevacizumab in patients with resectable colorectal hepatic metastases. A5961065 is a phase II trial of irinotecan, LV, infusional 5-FU, and bevacizumab in patients with CRC and unresectable hepatic metastases.

There is an increased risk of wound-healing complications after surgery in patients who had chemotherapy with bevacizumab.¹⁴ Karoui et al demonstrated how prolonged neoadjuvant therapy can affect postoperative morbidity.¹⁵ Patients who received no preoperative chemotherapy had a morbidity rate of 13.6%, and those who had < 5 cycles or > 10 cycles had a 19% and 61% rate of postoperative morbidity, respectively ($P = 0.02$). Although there is no consensus on the optimal waiting period between the last dose of chemotherapy and surgery, the NCCN suggests a minimum of 6 weeks between the last dose of bevacizumab and elective surgery.⁸ Others argue that because of bevacizumab's long half-life, it may be warranted to wait 8 weeks after the last dose of bevacizumab before hepatic resection.¹⁶

Given that cetuximab (Erbix) targets epidermal growth factor receptor (EGFR), which is not known to be involved in wound healing or angiogenesis, it follows that changes in surgery complication rates have not been re-

ported in the pivotal clinical trial with this agent.¹⁷ Similarly, preliminary results of a phase II trial of cetuximab plus FOLFIRI for first-line treatment of mCRC reported that 7 of 22 patients evaluable for efficacy underwent secondary surgery for metastases.¹⁸

Neoadjuvant therapy for nonresectable colorectal hepatic metastases

A number of studies have evaluated the role of neoadjuvant therapy in downstaging initially unresectable liver metastases to the point of resectability and improving survival in selected patient populations. Adam and colleagues reported on their 11-year experience with 1,439 consecutive patients with colorectal liver metastases treated at their institution.¹⁹ The main criteria for nonresectability were the presence of extrahepatic metastases and the inability to leave at least 30% healthy liver parenchyma after curative hepatectomy. According to these criteria, 1,104 patients whose liver disease was deemed unresectable were treated with chemotherapy (70% oxaliplatin, 7% irinotecan, and 4% both), primarily with chronomodulated infusional 5-FU/LV. These patients were monitored every four treatment courses, and responders were re-evaluated for surgery.

Following an average of 10 courses of chemotherapy, 138 responding patients (12.5%), including 41 of 52 patients who had extrahepatic tumors at diagnosis, underwent hepatic resection combined with portal embolization, ablative treatment, or second-stage hepatectomy (42 patients, 30%) and resection of extrahepatic tumor (41 patients, 30%). The authors reported 0.7% operative mortality within 2 months of surgery and 28% postoperative morbidity. After a mean follow-up of 48.7 months, 72% of patients had tumor recurrence. Overall survival (OS) for those patients whose hepatic resection was preceded by chemotherapy

was 52% at 3 years, compared with 66% for those patients who had primary extrahepatic resection; 5-year survival was 32% and 48% and 10-year survival was 23% and 30%, respectively.

A prospective study of 418 consecutive patients with liver-only CRC metastases at the M. D. Anderson Cancer Center in Houston identified 348 patients with potentially resectable hepatic metastases and 70 patients with unresectable disease (multiple metastases) who received chemotherapy alone (primarily 5-FU-based regional chemotherapy).²⁰ Patients with potentially resectable metastases undergoing resection alone ($n = 190$) had a longer median 5-year survival (58%; $P < 0.001$) compared with patients undergoing resection plus RFA ($n = 101$) or for those who had RFA alone ($n = 57$). Although the author did not provide 5-year survival for the two latter groups, reported 4-year survival rates were 65% for patients undergoing resection alone, 36% for those who had RFA plus resection, and 22% for those who had RFA alone ($P < 0.0001$). Patients in all three treatment groups had significantly longer median 4-year survival rates compared with those treated with chemotherapy alone ($P = 0.0017$).

Oxaliplatin

In phase II or retrospective trials, treatment of unresectable colorectal liver metastases with oxaliplatin-based regimens resulted in complete resection in approximately 12% of patients studied (Table 1).^{19,21} Among 1,439 consecutive patients at Hôpital Paul Brousse in Villejuif, France, 1,104 (77%) patients whose colorectal cancer metastases were initially deemed unresectable received chemotherapy (70%, 5-FU/LV plus oxaliplatin; 7%, 5-FU/LV plus irinotecan; 4%, 5-FU/LV plus oxaliplatin and irinotecan).¹⁹ After an average of 10 courses of chemotherapy, 138 (12.5%) patients who were ini-

TABLE 1

Effectiveness of oxaliplatin and irinotecan-based neoadjuvant chemotherapy in downstaging patients with unresectable colorectal cancer liver metastases

Reference (study type; enrollment period)	Number of patients	Regimen	Results
Adam et al ¹⁹ (consecutive patient series; 1988–1999)	1,104	5-FU/LV + oxaliplatin (70% of patients) 5-FU/LV + irinotecan (7%) 5-FU/LV + irinotecan + oxaliplatin (4%)	<ul style="list-style-type: none"> • Surgery attempts: 138 (12.5%) • Complete resection: 93% • Follow-up: 48.7 mo • 5-year overall survival of surgery patients: 33% • 10-year overall survival of surgery patients: 23%
Alberts et al ²¹ (phase II; 1999–2001)	42	FOLFOX4 (biweekly oxaliplatin, 5-FU/LV)	<ul style="list-style-type: none"> • Response rate: 59% • Surgery attempts: 40% • Complete resection: 33% • Follow-up: 22 mo (range, 12–32 mo) • Overall survival: 26 mo • 3-year overall survival: 30% (95% CI, 19–48) • Survival of surgery patients: not reached (67% alive at 3 yr)
Kemeny et al ³² (phase I)	36	Group A: HAI (FUDR) + systemic oxaliplatin/irinotecan Group B: systemic 5-FU/LV + oxaliplatin	<ul style="list-style-type: none"> • Response rate: 90% in group A, 87% in group B • 89% previously treated • Complete resection: 7 (33%) of 21 patients in group A • Overall survival: 35.8 mo in group A, 22 mo in group B • 2-year overall survival: 65% in group A, 40% in group B
Delaunoy et al ⁴¹ (subgroup analysis of data from phase III trial; 24 patients resected out of 795 randomized (1999–2001))	24	FOLFOX4 (n = 264), IFL (n = 267), or IROX (n = 265)	<ul style="list-style-type: none"> • 22 of 24 resected patients had liver metastases • Complete resection: FOLFOX4, 11 patients (4.1%); IROX, 11 patients (4.2%); IFL, 2 patients (0.7%) • Median follow-up: 34 mo • Time to tumor progression of resected patients: 18.4 mo • Survival of resected patients: 42.4 mo
Ho et al ²² (phase II)	40	Irinotecan + 5-FU (22-h continuous infusion) + LV	<ul style="list-style-type: none"> • Follow-up: 27 mo • Response rate: 55% • Complete resection: 10% (n = 4) after a median of 8 cycles (range, 4–12 cycles) • Overall survival: 20 mo • After a median follow-up of 33 mo, 1 patient disease free, 3 others progressed • Principal toxicity: grade 3/4 neutropenia, observed in 50% of patients
Pozzo et al ^{23,24} (phase II; patient series; 2000–2003)	40	Irinotecan + 5-FU (48-h continuous infusion) + LV	<ul style="list-style-type: none"> • Follow-up: 30.4 mo • Response rate: 48% • Complete resection: 33% • Overall survival: 30.1 mo • Overall survival nonresected: 24 • Overall survival resected: not yet reached • Time to tumor progression: 14.3 mo • Time to tumor progression nonresected: 5.2 mo • Disease-free survival resected: 28.2 mo • Expected toxicity pattern
Masi et al ²⁶ (retrospective analysis of data collected from a phase I/II study and a phase II trial; 1999–2002)	74	Irinotecan + oxaliplatin + 5-FU (48-h chronomodulated continuous infusion) + LV (FOLFOXIRI)	<ul style="list-style-type: none"> • Follow-up: 34.4 mo • Response rate: 72% • Curative resection: 26% (n = 19) • Overall survival resected: 36.8 mo • Overall survival of responders who were not resected: 22.2 mo (n = 34) • 4-year survival resected: 37%

5-FU/LV = 5-fluorouracil/leucovorin; FOLFOX4 = oxaliplatin + infusional 5-FU/LV; IFL = irinotecan + bolus 5-FU/LV; IROX = irinotecan + oxaliplatin; HAI = hepatic arterial infusion; FUDR = floxuridine

tially unresectable underwent hepatic resection. Median 5-year OS rates were 33% for secondarily resected patients versus 48% for primary resected patients. Similarly, 10-year OS rates were 23% and 30%, respectively. Several patients underwent repeat hepatectomies (52 patients; 71 procedures) and extrahepatic resection (41 patients; 77 procedures) to treat disease recurrence.

Alberts and colleagues, from the North Central Cancer Treatment Group (NCCTG), reported on a phase II trial of neoadjuvant FOLFOX4 in resectable patients, which resulted in complete resection in 33%. These patients had the longest median OS yet, with 67% of the patients still alive at 3 years.²¹

Irinotecan

Neoadjuvant therapy with irinotecan in combination with 22-hour infusional 5-FU/LV produced a 55% overall response rate and a 10% curative resection rate (after a median of 8 cycles) in 40 patients with previously untreated CRC liver metastases.²² Persistent bilobar disease (in 29 patients) was the most common reason for unresectability after chemotherapy. All four patients who had resection are alive after a median follow-up of 33 months, with only one patient remaining disease free.

Pozzo and colleagues reported a 48% response rate and a 33% complete resection rate in a phase II trial of neoadjuvant therapy with modified FOLFIRI (a 48-hour 5-FU continuous infusion).²³ With a median follow-up of 30.4 months, median OS was 30.1 months for all patients and 24 months for nonresponders. Median disease-free survival of resected patients was 28.2 months, and median OS had not been reached.²⁴

Oxaliplatin plus irinotecan

In a phase II trial of FOLFOXIRI (irinotecan, oxaliplatin, and LV with 48-hour continuous infusion 5-FU),

Masi and colleagues reported that eight (25%) patients with initially unresectable mCRC underwent radical resections.²⁵ In a more recent retrospective analysis of data, these authors reported a response rate of 72% with 19 (26%) of 74 patients undergoing curative resection.²⁶ With a median follow-up of 34.4 months, OS of patients who had resection is 36.8 months. This compares favorably only with the 22.2 months for responders who did not have resection. Patients who had resection achieved a 4-year survival rate of 37%.

Falcone and colleagues, from the Italian Gruppo Oncologico Nord Ovest (GONO), compared FOLFOXIRI and FOLFIRI in 422 patients with previously untreated mCRC.²⁷ Approximately one third of patients in both treatment groups had liver-only metastatic disease. The R0 surgical resection rate was 36% with FOLFOXIRI and 12% with FOLFIRI ($P = 0.017$). The FOLFOXIRI regimen caused more grade 2/3 neurotoxicity ($P < 0.0001$) and grade 3/4 neutropenia ($P = 0.0006$). OS data are still immature.

A few studies have shown that HAI chemotherapy can sometimes downstage nonresectable CRC liver metastases to resectable CRC liver metastases. In 1999, Link and colleagues reported performing secondary liver resections in 9 (12%) of 74 patients whose CRC liver metastases were deemed unresectable and who had received HAI with 5-FU/LV or 5-FU/LV plus mitoxantrone and mitomycin.²⁸

In another study, 5 (12%) of 43 patients receiving alternating HAI fluorodeoxyuridine (floxuridine, FUDR) and continuous infusion 5-FU underwent a liver resection.²⁹ Treatment of unresectable liver metastases with biweekly 5-FU/LV and irinotecan combined with HAI pirarubicin resulted in liver resection in 11 (35%) of 31 patients enrolled in a phase II trial.³⁰ Clavien et al treated 23 patients

with HAI FUDR, and 26% became resectable.³¹ In a phase I trial, treatment with concurrent HAI FUDR and systemic oxaliplatin and irinotecan led to liver resection in 7 (33%) of 21 patients with unresectable liver metastases.³² Systemic therapy had been administered to 89% of patients before entry into this trial.

Future studies need to use clearer definitions of absolute unresectability and document how borderline cases are evaluated. In addition, efforts need to focus on optimizing neoadjuvant regimens (systemic or HAI) to improve response while minimizing hepatic toxicity.

Patient selection for hepatic resection

Adam and colleagues identified four independent preoperative predictive risk factors for decreased survival in patients who become resectable after neoadjuvant chemotherapy: rectal primary, ≥ 3 metastases, maximum tumor size > 10 cm, and CA 19-9 > 100 UI/L.¹⁹ Mean adjusted 5-year survival rates were 59% for patients with no risk factors, 30% for one factor, 7% for two factors, and 0 for patients with three or more factors. These authors observed that metastatic lymph nodes of the hepatic pedicle were the only type of concomitant extrahepatic disease that had a significant negative impact on survival. The same investigators also performed a subgroup analysis of patients who underwent liver resection for multiple colorectal liver metastases after systemic chemotherapy.³³ They reported that in this group of patients, long-term survival is possible with hepatic resection combined with neoadjuvant and postsurgery chemotherapy only if the metastatic disease is not progressing during chemotherapy administered before surgery. Allen and colleagues reported a similar conclusion in their retrospective study of patients referred for evaluation of clinically resectable

liver metastases following removal of primary CRC.³⁴

Definitions of resectability and unresectability

Table 2 lists absolute contraindications to resection with curative intent identified by an international consensus panel in the course of devising a computer-assisted therapeutic decision model (OncoSurge).³⁵ The purpose of this model is to aid general medical oncologists and surgeons in identifying optimal treatment strategies for individual patients with colorectal liver metastases.

In most studies the presence of extrahepatic metastases has been considered a clear contraindication to hepatic resection with curative intent. However, some recent studies suggest that some patients with extrahepatic metastases do benefit from resection. For example, Elias and colleagues reported a 28% 5-year median survival rate among 75 patients who underwent complete (R0) resections of extrahepatic disease coupled with hepatectomy for colorectal liver metastases.³⁶ The postoperative mortality rate was 2.7%, and the morbidity rate was 25%, with two patients requiring surgical treatment to manage complications. This was a retrospective analysis of a relatively small series of patients, but the authors found that after R0 resection, the 5-year survival rate of 28% for the 75 patients who had extrahepatic disease was similar to the 33% 5-year median survival of the 219 patients who did not have extrahepatic disease. The presence of multiple extrahepatic disease sites or more than five liver metastases were negative prognostic factors for surgery.

In a more recent study, the same group of investigators has proposed that the total number of hepatic and extrahepatic metastases is a more powerful prognostic indicator than the site of these metastases.³⁷

A group from the M. D. Anderson

TABLE 2

Absolute contraindications to resection with curative intent according to the OncoSurge model

Condition	Examples
Unresectable extrahepatic disease	<ul style="list-style-type: none"> • Peritoneal carcinomatosis • Multifocal lung metastases • Distant lymph nodes in the preaortic and celiac axis N2 nodal basin for liver, bone, or brain metastases
Extensive liver involvement	<ul style="list-style-type: none"> • Six liver segments involved • > 70% liver invasion or all three hepatic veins involved
Major liver insufficiency	
Child B or C liver cirrhosis with complications	
Patient status	<ul style="list-style-type: none"> • Unfit • Declines surgery

From Poston et al.³⁵

Cancer Center demonstrated the benefit of aggressive surgical treatment, consisting of liver resection with or without RFA, in 159 patients with four or more colorectal liver metastases.³⁸ This group of patients achieved 50.9% 5-year median OS and 21.5% 5-year disease-free survival following resection alone (in 29% of patients), RFA alone (7.5%), or RFA and resection (63.5%). The investigators reported that no response to neoadjuvant chemotherapy was a poor risk factor.

Neoadjuvant chemotherapy in patients with resectable liver metastases

Thus far, two studies have examined the effectiveness of oxaliplatin-based neoadjuvant chemotherapy in patients with resectable colorectal liver metastases. A German group tested the effects of neoadjuvant therapy with weekly oxaliplatin, LV, and a high-dose, 24-hour infusion of 5-FU in a small phase II trial involving patients with resectable colorectal liver metastases.³⁹ With a short follow-up of only 23 months, these authors reported that 16 (80%) of 20 patients had curative resection leading to a 2-year disease-free survival rate of 52% and an overall 2-year survival rate of

80%. More informative results are expected from the European Organization for the Research and Treatment of Cancer (EORTC) Intergroup randomized phase III study 40983, which is examining the risks and benefits of FOLFOX4 preoperative chemotherapy in 364 patients with resectable CRC liver metastases.⁴⁰ Interim results from this trial show that 80% of patients in the FOLFOX4 plus surgery group underwent resection, compared with 77% of patients in the surgery-alone group. Preoperative administration of FOLFOX4 appeared to be safe. Survival rates are expected in 2006.

Delaunoy and colleagues examined the experience of patients with inoperable metastatic disease enrolled in Intergroup study N9741 whose lesions were sufficiently downstaged to permit resection.⁴¹ After chemotherapy, 24 of 795 randomized patients had metastatic resection with curative intent. Neoadjuvant treatment of resected patients consisted of FOLFOX in 11 patients, irinotecan + oxaliplatin (IROX) in 11 patients, and IFL in 2 patients. Resections included 16 hepatectomies, 6 RFAs, and 2 lung resections. After a median follow-up of 34 months, 7 patients (29%) remained disease free, but all patients undergo-

TABLE 3

Randomized trials of hepatic arterial infusion (HAI) versus systemic therapy or control

Trial	Number of patients	Survival, %					
		2 years		3 years		5 years	
		HAI	Systemic or control	HAI	Systemic or control	HAI	Systemic or control
Kusunoki et al ⁴⁶	58	90	65	78	30	60	30
Tono et al ⁵³	19	78	50	78	50	78	50
Kemeny et al ⁴⁴	156	86	72	70	60	55	40
Lorenz et al ⁴²	201*	62	60	50	50	50	30
Kemeny et al ⁵	75†	75	75	70	70	60	70
lygidakis et al ⁴³	122	92	75	80	71	73	60

* Treated patients; not everyone randomized

† Patients entered into study; not everyone randomized

ing RFA had disease recurrence. OS in resected patients was 42.4 months, with four (80%) of five patients who received chemotherapy post resection remaining disease free.

Postoperative HAI

HAI as adjuvant therapy after liver resection has been evaluated in six randomized trials (Table 3).^{5,42-44} A trial performed at Memorial Sloan-Kettering Cancer Center randomized 156 patients at the time of liver resection from mCRC to receive 6 cycles of HAI (FUdR and dexamethasone) plus systemic chemotherapy (5-FU with or without LV) or systemic chemotherapy only.⁴⁴ The primary endpoint, 2-year median OS, was significantly higher in the HAI plus systemic chemotherapy group (86%) versus the systemic chemotherapy-only group (72%; $P = 0.02$). A recent report showed that at a median follow-up of 10.3 years, 5-year survival was 57% for the HAI-exposed group and 47% for the systemic chemotherapy-only group.⁴⁵ Similarly, 10-year survival was 41% for HAI and 27% for the systemic chemotherapy-only group.

An Eastern Cooperative Oncology Group (ECOG) Intergroup study preoperatively randomized patients with one to three potentially resectable liver metastases to receive no

further therapy ($n = 56$) or postoperative HAI (FUdR) plus intravenous (IV) continuous infusion 5-FU ($n = 53$).⁵ At surgery, some patients were found to be ineligible for the study treatment, thus leaving 45 eligible patients in the control group and 30 in the HAI group. The primary endpoint, 4-year recurrence-free survival, was significantly higher in the HAI plus systemic therapy group (46%) compared with that in the control group (25%; $P = 0.04$). This study was not powered to detect differences in OS.

In a German study, investigators randomized 226 patients with colorectal liver metastases to liver resection followed by adjuvant HAI (5-FU/LV) or liver resection only.⁴² After the first planned intent-to-treat interim analysis, a median survival of 34.5 months in the adjuvant HAI therapy group and 40.8 months in the control group were reported. Accrual to this study was terminated because this interim analysis showed that adjuvant HAI, at best, might have reduced the risk of death by 15% and, at worst, it might have doubled it. Confounding the interpretation of these results were several study flaws: only 77% of patients randomized to the HAI arm received their assigned therapy, and only 30% finished all courses of therapy; arterial ports (which increase

clot formation) were used rather than pumps; and 5-FU was used, which is less efficiently extracted by the liver than FUdR.⁴⁵

In another study, 143 patients were randomized after hepatic resection to adjuvant treatment with mitomycin, 5-FU/LV, and aldesleukin (IL-2, Proleukin) given by HAI and IV (group A) or to treatment with the same drugs given only IV (group B).⁴³ The HAI-containing group achieved a higher median 2-year survival rate (92% for group A vs 75% for group B) and 5-year survival rate (73% for group A vs 60% for group B). Median survival was longer in the HAI plus IV group (79 months) than in the IV-only group (66 months; $P = 0.04$).

A smaller study in Japan of patients undergoing adjuvant therapy after liver resection showed that patients receiving 5-FU HAI therapy ($n = 30$) achieved a higher 5-year survival rate and lower hepatic recurrence rate compared with 28 patients given oral tegafur and uracil (UFT).⁴⁶ In a phase I/II trial, HAI FUdR and dexamethasone combined with IV irinotecan showed promise as an HAI-based posthepatectomy adjuvant treatment.⁴⁷

Postoperative systemic chemotherapy

Mackay and colleagues evaluated the safety and efficacy of adjuvant single-agent irinotecan in 29 patients following complete resection of hepatic CRC metastases.⁴⁸ As expected, the most common toxicities were nausea (grade 3, 10%), vomiting (grade 3, 14%), diarrhea (grade 3/4, 17%), and neutropenia (grade 3/4, 21%). With a median follow-up of 27.9 months, the preliminary estimated median relapse-free survival was 45.2 months. Duration of chemotherapy was the only statistically significant predictor of relapse-free survival. In univariate analyses, expression of p53, p27, and microsatellite instability in metastases did not

reach significance as predictive factors for relapse-free survival.

In a phase II study, patients with resectable hepatic or extrahepatic mCRC were treated with 6 cycles of FOLFOX7 before ($n = 25$) or after surgery ($n = 22$).⁴⁹ All but one patient underwent an R0 resection. There were no drug-related deaths, febrile neutropenia, or bleeding. The most common grade 3/4 toxicities were neutropenia (13%) and thrombocytopenia (11%). At the time the study was published in early 2005, the 2- and 3-year OS rates were 89% and 62%, respectively, and 2- and 3-year disease-free survival rates were 47% and 32%, respectively. Portal vein and systemic therapy after liver resection produced a 3-year survival of 42% and a 3-year disease-free survival of 19%.⁵⁰

Conclusion

Decades of institutional experience have shown that surgical resection of metastatic disease plays an important role in the long-term survival of some patients with mCRC. Recent experience with neoadjuvant therapy indicates that this therapy helps downstage liver metastases in some initially unresectable patients to the point that curative resection is feasible. The roles of RFA, cryosurgery, and HAI are also undergoing scrutiny. Until now, data guiding clinical practice in this arena came from retrospective studies of patient series and nonrandomized phase II trials. Ongoing and future randomized studies will address whether neoadjuvant regimens incorporating new agents benefit patients with resectable liver metastases, as well as patients with initially nonresectable liver metastases.

In the United States, the Cancer and Leukemia Group B (CALGB) trial C80405 is comparing FOLFOX and FOLFIRI with cetuximab and/or bevacizumab in patients with previously untreated mCRC. This trial, with a planned accrual of 2,300 patients, includes as a secondary ob-

jective the determination of whether patients with unresectable disease become eligible for resection following chemotherapy. As a follow-up to Taieb et al,⁴⁹ the Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR) trial C02-1 is testing FOLFOX4 versus sequential FOLFOX7 and FOLFIRI (6 courses of each) in patients with CRC and completely resected liver metastases or metastases considered resectable at second-look surgery.

The management of patients with potentially downstageable unresectable hepatic mCRC centers on a multimodality approach involving an interdisciplinary team of surgeons, medical oncologists, pathologists, and diagnostic radiologists. Neoadjuvant chemotherapy needs to be carefully monitored because of its potential to cause toxicities that would preclude the feasibility of liver resection. Such toxicities include development or worsening of steatosis, impairment of hepatic regeneration associated with antiangiogenesis agents, and development of blue-liver syndrome associated with chemotherapy-induced vascular disease.⁵¹ Close communication is necessary among medical oncologists, surgeons, and patients to ensure that patients whose hepatic mCRC is potentially resectable are referred for surgery early in the treatment continuum, before they become ineligible for surgery because of accumulated hepatic toxicity.⁵² In addition, enrollment in clinical trials should be encouraged.

In the future, definitive protocols will define when to administer chemotherapy within the treatment continuum and for what duration. Currently, it is not clear whether neoadjuvant therapy will benefit patients who have clearly resectable disease. Until randomized studies demonstrate this, it may be better to resect the tumor first and then to administer chemotherapy to avoid toxic effects on the liver. It is clear, however, that systemic chemo-

therapy can downstage unresectable disease in some patients to the point that resection is an option. If, however, patients fail to respond to first-line therapy, the chance of resection seems to be higher with regional hepatic therapy combined with systemic therapy than with systemic therapy alone. This concept requires additional evaluation in large, randomized studies. However, until these results are available, evidence from small studies suggests that HAI and systemic therapy increase the chance of resection in this setting. Based on current findings, medical oncologists and surgeons can meet the challenge of selecting the best treatment options for each patient that will result in improved outcomes.

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