The liver is a frequent site of metastatic disease, especially for cancers of the gastrointestinal tract. Since venous drainage from the colon and rectum flows via the portal vein to the liver,[1] it is not surprising that patients with colorectal cancer frequently develop liver metastases. Approximately 15% of patients will have liver metastases at the time of diagnosis, and another 60% of patients who develop metastatic disease will have metastases to the liver. For many years, the approach to patients with hepatic metastases was nihilistic. In the past 2 decades, improvements in systemic chemotherapy, in modalities to detect liver metastases, and in surgical techniques for hepatic resection, have improved the survival of these patients.

**Systemic Chemotherapy**

**TABLE 1**

Randomized Trials of First-Line Chemotherapy for Metastatic Colorectal Cancer

For 4 decades, fluorouracil (5-FU) plus leucovorin (LV) were the only drugs available to treat metastatic colorectal cancer, yielding a response rate of 20% to 30% and a median survival of 11 to 12 months. A number of new agents are now available, including irinotecan (Camptosar), a topo-isomerase inhibitor, and oxaliplatin (Eloxatin), a platinum compound with in vivo and in vitro activity against colon cancer cell lines and the ability to synergize with 5-FU.[2,3] Randomized trials using irinotecan with 5-FU/LV vs 5-FU/LV alone[4,5] produced an increase in response rate and survival ([Table 1](#)). When irinotecan/5-FU/LV (IFL) was compared to oxaliplatin plus 5-FU/LV (FOLFOX), the response rate was increased from 35% to 45%, and survival was increased from 15 to 19.5 months for the IFL and FOLFOX groups, respectively.[6] That said, 5-FU given by continuous infusion is more effective than bolus 5-FU; therefore, when 5-FU administration was changed to infusion (ie, FOLFIRI rather than IFL), the regimen of irinotecan/5-FU/LV became more effective and produced results similar to those seen with FOLFOX.[7]
Second-Line Therapy: Systemic Therapy in Previously Treated Colorectal Cancer Patients

In the past few years, targeted agents have become available: bevacizumab (Avastin), a monoclonal antibody to vascular endothelial growth factor, and cetuximab (Erbitux), an antibody to epidermal growth factor receptor. The addition of bevacizumab to IFL increased response rates and survival (35% to 45%, and 15.6 to 19.5 months, for IFL vs bevacizumab/IFL, respectively). For almost 4 decades, the 2-year survival for metastatic colorectal patients treated with 5-FU or 5-FU/LV was 25%; with these new agents, 2-year survival rates have increased to 30%-39%, with a marked improvement in overall survival (Table 1).

In the second-line setting, even with the new agents, results are less impressive. Irinotecan is associated with a response rate of 5% to 14% and a median survival of 9.9 months.[9] FOLFOX administered to irinotecan-refractory patients produces a 9.9% response rate, with a median survival of 9.8 months (Table 2).[10] After progression on irinotecan, cetuximab alone can produce a 10% response rate, which increases to 23% when this agent is combined with irinotecan.[11] Second-line bevacizumab combined with FOLFOX increased survival to 12 months from 10 months for FOLFOX alone (Table 2).[12]

Hepatic Arterial Infusional Chemotherapy

To further improve on results, adding direct liver perfusion with chemotherapy might be useful. The first trials compared hepatic arterial infusion (HAI) alone to systemic chemotherapy. The rationale for HAI is based on the following facts: (1) liver metastases are perfused almost exclusively by the hepatic artery, whereas the normal liver is perfused by the portal vein,[13] (2) certain drugs are largely extracted by the liver during the first pass, allowing for minimal systemic toxicity,[14] and (3) the liver is often the first and only site of metastatic disease.[15] Therefore, aggressive treatment of metastases confined to the liver by resection or hepatic infusion may yield prolonged survival for some patients.

Regional therapy can be delivered using a hepatic arterial port or a totally implantable pump. Early studies with catheters produced clotting and bleeding that did not allow for long-term hepatic infusion with reliable patency.[16] Studies in Europe still use the catheters rather than pumps, perhaps explaining the inferior results in the European trials.

Randomized Trials

TABLE 3

Randomized Trials of Hepatic Arterial Infusion vs Systemic Chemotherapy for Unresectable Liver Metastases

Ten randomized studies have compared HAI to systemic chemotherapy (Table 3).[17-26] Almost all the studies showed an increase in response rate. Only the English trial that used HAI 5-FU failed to increase response rate.
Why did the superior response rates seen with HAI not translate into improved survival in the earlier trials? Most of these trials were too small, and a number of them allowed crossover to HAI at the time of progression on systemic chemotherapy, potentially diluting statistical results that might have demonstrated a survival benefit. Two earlier European studies demonstrated an increase in survival with HAI, but appropriate systemic therapy was not always used.

Two recent European trials did not show an increase in survival—the first being the Medical Research Council and European Organization for Research and Treatment of Cancer (EORTC) study,[26] which randomized patients to HAI 5-FU/LV via a port rather than a pump (using 5-FU rather than floxuridine [FUDR]) vs systemic 5-FU/LV. In this study, 37% of the patients assigned to the HAI arm did not receive treatment and 29% had to stop treatment. No differences were seen in response rate at 12 weeks (22% vs 19%, for HAI and systemic therapy, respectively), and no differences were seen in toxicity, progression-free survival (PFS), or survival. The study was not analyzed to look at the patients who actually received treatment.

A German cooperative group[17] randomized patients to HAI FUDR, HAI 5-FU/LV, or systemic 5-FU/LV. Tumor response rates were 43.2%, 45%, and 19.7%, and development of extrahepatic disease was 40.5%, 12.5%, and 18.3% for the HAI FUDR, HAI 5-FU/LV, and systemic 5-FU/LV groups, respectively. Toxicity data indicated that 5-FU/LV therapy was much more toxic than FUDR. A port was used, rather than a pump, and the FUDR regimen was different from what was used in the American studies in that the dosage was reduced from 0.2 to 0.15 mg/kg/d after three cycles rather than adjusting for patient toxicity. The median survival was 12.7, 18.7, and 17.6 months for the HAI FUDR, HAI 5-FU/LV, and systemic 5-FU/LV groups, respectively. Only 66% of patients randomized to HAI FUDR were treated, but all were included in the survival analysis. Eight patients in the HAI FUDR group died before ever receiving treatment, perhaps explaining the very low survival with HAI FUDR.

The Cancer and Leukemia Group B (CALGB)[18] trial differs from the other HAI studies in that it included the use of dexamethasone in the HAI arm.[27] HAI FUDR, dexamethasone plus LV was compared to systemic bolus 5-FU/LV. No crossover was allowed. The HAI group had a significant increase in survival (24.4 months, vs 20 months in the systemic group, \( P = .0034 \)). The time to hepatic progression was better in the HAI arm (9.8 vs 7.3 months, \( P = .034 \)) but the time to extrahepatic progression was better in the systemic arm (14.8 vs 7.7 months in the HAI group, \( P < .029 \)). The toxicities were as expected, with a significant increase in diarrhea and neutropenia for the systemic arm and a significant increase in biliary toxicity for the HAI arm (18% vs 0%). A quality-of-life assessment was performed as part of the study, and the HAI group experienced improvement in this parameter, as measured at 3 and 6 months.

Differences between the CALGB study[18] and the European studies might explain differences in the outcomes. The CALGB study used pumps instead of ports, and HAI therapy included FUDR with dexamethasone to decrease toxicity.[27] Survival was based on intent to treat in all three studies, and the actual number of patients treated was much lower in the European studies—66% in the German study and 63% in the English study—while it was 86% in the CALGB study. The CALGB study did demonstrate that regional therapy alone can improve survival over systemic 5-FU/LV with a survival similar to that seen with newer agents. Randomized studies of HAI therapy vs the new therapies have not been conducted. In the future, studies comparing HAI or HAI plus new agents vs the new agents alone would be appropriate.

**Second-Line Therapy**

**TABLE 4**

![Hepatic Arterial Infusion in Previously Treated Patients: Second-Line](image-url)
Therapy

HAI-based therapy in patients refractory to systemic chemotherapy has produced much higher response rates in small single-institution studies (Table 4). A trial using HAI FUDR/LV/dexamethasone[28] in both chemotherapy-naive and previously treated patients produced response rates of 72% and 52%, and median survivals of 23 and 13.5 months for the chemotherapy-naive and previously treated patients, respectively. HAI FUDR/dexamethasone plus mitomycin administered through the pump sideport, produced a 70% response rate in previously treated patients, with a median survival of 19 months from the start of HAI therapy after progression on systemic 5-FU/LV.[29]

A phase I study of HAI FUDR combined with systemic irinotecan in previously treated patients (45% had previously received irinotecan) reported a response rate of 74%, a time to disease progression of 8.1 months, and a median survival of 20 months.[30] A total of 13 of the 16 patients with prior irinotecan exposure responded to this regimen. Systemic oxaliplatin plus 5-FU/LV or oxaliplatin plus irinotecan with concurrent HAI FUDR/dexamethasone in 36 previously treated patients (74% had received prior irinotecan) produced response rates of 86%, with a median survival of 36 months, and a 1-year survival of 80%.[31] These and other small studies (Table 4) suggest that a benefit may be derived from HAI plus systemic therapy as second-line therapy, and randomized studies exploring the use of HAI plus systemic therapy vs new agents alone in the second-line setting should be performed.

Toxicity of Hepatic Arterial FUDR Infusion

The most common problems with HAI therapy are hepatic toxicity and gastric ulcerations. Myelosuppression, nausea, vomiting, and diarrhea do not occur with HAI FUDR. If diarrhea does occur, shunting to the bowel should be suspected.[32] Clinically, biliary toxicity is manifested as elevations of aspartate transaminase, alkaline phosphatase, and bilirubin.[28] In early stages of the disease, hepatic enzyme elevations will return to normal when the drug is withdrawn and the patient is given a rest period, whereas in more advanced cases, it does not resolve. Therefore, careful monitoring of liver function tests is necessary to avoid this toxicity. The bile ducts derive their blood supply almost exclusively from the hepatic artery,[33] and thus are also perfused with high doses of chemotherapy during HAI treatment. HAI 5-FU causes fewer biliary problems and more arteritis.[34] In patients who develop jaundice, an endoscopic retrograde cholangiopancreatogram (ERCP) may demonstrate lesions resembling idiopathic sclerosing cholangitis in 5% to 29% of patients treated. The strictures may be focal and present at the hepatic duct bifurcation, and therefore drainage procedures either by ERCP or by transhepatic cholangiogram may be helpful. Duct obstruction from metastases or bile duct strictures from surgery can also be causes of elevated bilirubin and must be ruled out before concluding that the elevation in liver function tests is due to HAI therapy.

Liver Resection

Since autopsy series show that in one-third of patients dying from colorectal cancer, the liver is the only site of metastatic disease, surgical resection of liver metastases has been encouraged when possible. More than 20 large series show that liver resections are possible with reasonable mortality and morbidity, producing an average 5-year survival of about 30%.[35-41] No randomized studies of liver resection vs systemic chemotherapy have been performed. Historically, however, the median survival for patients with liver metastases is about 6 to 12 months. Even with the newer therapies, the 2-year survival rate is generally less than 40%, and this drops rapidly at 3 and 4 years. In contrast, patients with liver metastases who have undergone resection generally have a 2-year survival of around 60% to 70% and a 5-year survival of 25% to 30%.

Surgical Advances

Recent advances in surgery have made liver resection a possibility for more patients. One technique, portal vein embolization,[42] removes the blood supply to the affected liver and thereby induces hypertrophy of the nondiseased portion that will remain after liver resection. If small remnant parts of the liver can undergo hypertrophy, larger resections of diseased areas can be done. The use of intraoperative ultrasonography allows the surgeon to find lesions missed by other modalities and also helps define the relationship of the tumor to hepatic vasculature.[43] Improved vascular clamping techniques,[44] controlled anatomic resection,[45] and other new strategies are outlined in a review by Khatri et al.[46] The use of radiofrequency ablation to small lesions in the remaining liver
also extends liver resection options to more patients. Some reports have stated that even patients with positive nodes or small lung metastases can undergo liver resection with better outcomes than those seen with chemotherapy alone,[46] but these data are not widely accepted.

**Patient Selection**

There is no consensus for determining which patients are suitable for resection. A computer program (the OncoSurge model) was developed to aid in selecting these patients.[47] A panel of 16 experts from oncology, radiology, and liver surgery developed hypothetical patient profiles to decide when resection should be done first, chemotherapy should be done first followed by possible resection, or resection should be absolutely contraindicated. This consensus panel decided that absolute contraindications were unresectable extrahepatic disease, more than 70% liver involvement, liver failure, and being surgically unfit. Factors that did not influence treatment strategy were age, primary tumor stage, timing of metastasis detection, past blood transfusion, liver resection type, preresection carcinoembryonic antigen (CEA), or previous hepatectomy. They also suggested that patients with bilobar disease or more than four metastases receive resection only after tumors were shrunk with chemotherapy.

**Prognostic Indicators**

A number of published studies have attempted to identify prognostic factors associated with poorer outcomes, and two large series have developed a scoring system.[48,49] At Memorial Sloan-Kettering Cancer Center (MSKCC), for the 1,001 patients undergoing liver resection, the most important factors adversely affecting survival were size of tumor (> 5 cm), disease-free interval (< 12 months), number of tumors (> 1), lymph node-positive primary, and preoperative CEA (> 200 ng/mL). Giving 1 point for each of these factors, a score was obtained that correlated with survival. For scores of 0, 1-2, 3, and 4-5, the predicted 5-year survival rates were 60%, 42%, 20%, and 18%, respectively.[48] Nordlinger et al.[49] reviewed data on 1,568 patients who underwent liver resection for colorectal metastases. The 2- and 5-year survival rates of 64% and 28% were affected by age, size of the largest metastases, CEA level, stage of the primary, disease-free interval, number of liver nodules, and resection margin. Giving 1 point to each of these risk factors, the investigators calculated scores that divided the patients into three risk groups: 0-2, 3-4, and 5-7 with corresponding 2-year survival rates of 79%, 60%, and 43%, respectively.

The Liver Met Survey is an international Internet-based registry that includes 2,122 patients. In a recent report on this registry, the overall 5- and 10-year survival rates were 42% and 26%. The 5-year survival rates for three or fewer vs more than three nodules were 48% vs 24% (P = .0001). Another factor that affected survival was whether the tumor was unilateral or bilateral. In this review, preoperative chemotherapy did not benefit patients with solitary metastases (5-year survival rate: 45% vs 58%), whereas for patients with more than five metastases, the 5-year survival rate was 22% and 12% for patients with and without prior chemotherapy.[50]

**Is Neoadjuvant Chemotherapy Useful?**

<table>
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<td>Resectability Rate After Systemic Chemotherapy: Retrospective Studies</td>
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The use of new effective systemic chemotherapy has increased the possibility of obtaining a response and thus making liver metastases resectable. Several systemic chemotherapy studies have retrospectively evaluated resectability after chemotherapy (Table 5). The first retrospective reviews were written by Bismuth et al.[51] and Giacchetti et al.[52] Adam and colleagues.[53] from the same
group, reviewed the records of 1,104 patients with unresectable disease who received mainly FOLFOX as neoadjuvant therapy; 12.5% became resectable, and the 5-year survival rate of these patients was 34%—similar to what could be obtained with patients who were initially resectable. TABLE 6

Prospective Trials Evaluating Neoadjuvant Systemic Chemotherapy for Unresectable Disease: Resectability Rate

Recently, several trials were designed to address resectability after chemotherapy (Table 6), but variations in patient selection makes it difficult to compare these studies. The Mayo Clinic trial considered patients to be unresectable if they had (1) involvement of all three major hepatic veins, portal vein bifurcation, or the hepatic vena cava; (2) involvement of the main right or main left portal vein and the main hepatic vein of the opposite lobe; (3) disease requiring more than a right or left trisegmentectomy; or (4) six or more metastatic lesions distributed diffusely in both lobes of the liver. In the presence of any of the above, patients were treated with preoperative oxaliplatin/5-FU/LV. Of 44 patients, 17 (38%) became suitable for resection, but after resection, 73% had a recurrence in the liver. Median survival was 26 months.[54] A retrospective review of these data demonstrated that 10% of patients were actually resectable prior to neoadjuvant therapy. Pozzo et al treated 40 patients who had unresectable disease in a nonrandomized trial using neoadjuvant FOLFIRI.[55] Their criteria for unresectability were (1) six metastases or three per lobe, (2) size > 5 cm for one lesion if six metastases were present, or (3) contiguity with two hepatic veins, inferior vena cava, or liver hilum. Overall, 32% of patients were able to undergo liver resection after chemotherapy. With a median follow-up of 30 months, the disease-free survival of resected patients is presently 28 months, and overall survival has not been reached. Other trials evaluating neoadjuvant chemotherapy are listed in Table 6.

Improving Outcomes

TABLE 7

Initially Unresectable Disease: Resectability After HAI With or Without Systemic Therapy

How can we improve outcomes for unresectable patients? The use of targeted agents such as cetuximab or bevacizumab may be helpful. Rougier et al treated 23 patients with cetuximab and FOLFIRI, and 7 (30%) became resectable.[56] Would adding HAI therapy improve results? In a phase I study of oxaliplatin/irinotecan plus HAI chemotherapy in 44 clearly unresectable patients, 34% became resectable (70% of patients were receiving this treatment as second- or third-line therapy).[31] The median survival of the entire group is 36 months, and median survival for the resected group has not been reached (Table 7). In a Japanese study of 51 patients with unresectable disease with HAI 5-FU and systemic UFT (tegafur/uracil), 31 patients were judged to be resectable after preoperative chemotherapy, but only 24 agreed to surgery. The 3- and 5-year survivals were 58% and 42% for the resected group, but for
those patients who did not have resection, the 3- and 5-year survivals were 25% and 0%.[57] Using all three active agents may increase resectability. The Gruppo Oncologico Nord Ovest (GONO) randomized 244 patients to FOLFIRI or FOLFIRI plus oxaliplatin (FOLFOXIRI). In patients with only liver metastases, the resection rate was 12% and 36% for the FOLFIRI and FOLFOXIRI regimens, respectively.[58]

Predicting Poor Outcomes

Adam,[53] in a retrospective review of 131 patients who underwent liver resection after preoperative -systemic chemotherapy, found in a multivariate analysis that tumor progression on chemotherapy, elevated CA 19-9, and an increase in the number of metastases were all predictors of poor outcome. Even if metastases disappear on CT, they may remain viable. In a review by Nordlinger et al on 586 patients[59] treated at their institution, 38 patients had disappearance of at least one lesion on CT. Pathologic examinations of sites that were considered to have a complete response showed that in 12 of 15 (80%) of these lesions, there were still viable tumor cells on pathologic examination. Areas where there was a complete response (although they could not be resected at the time of surgical exploration) were closely followed. Of these 31 sites, 23 (74%) developed a recurrence. Clearly, this analysis shows that further postresection therapy needs to be given to these patients if sites are left intact at the time of liver resection.

Toxicity of Neoadjuvant Chemotherapy

As use of preoperative chemotherapy increases, reports are emerging about liver toxicity associated with this strategy. Investigators have found an increased incidence of steatosis, sinusoidal abnormalities, veno-occlusive disease, and steatohepatitis in this setting. In the Rubbia-Brandt[60] report on 153 patients undergoing liver resection, 51% of the 87 patients who received chemotherapy prior to resection had sinusoidal dilation, while 66 patients treated with surgery alone did not. Of 43 patients who had received prior oxaliplatin, 34 (78%) showed striking sinusoidal alterations, and 48% had veno-occlusive fibrosis.

Kooby reported on 325 patients with fatty livers undergoing resection at MSKCC. They compared this group to 160 patients with normal livers. Men and those with higher body mass index were more likely to have steatosis. Patients treated with preoperative chemotherapy were more likely to have steatosis (66%), with marked steatosis being an independent predictor of complications following hepatic resection.[61]

M. D. Anderson researchers reported no increase in preoperative deaths from neoadjuvant irinotecan in 2003.[62] However, they recently reported a 20% incidence of steatohepatitis in patients receiving preoperative irinotecan vs 4.4% in those who received no prior chemotherapy, and an 18.9% incidence of sinusoidal dilation in those receiving preoperative oxaliplatin vs 1.9% in those receiving no prior chemotherapy. Moreover, patients with steatohepatitis had an increased 90-day mortality (14.7% vs 1.6%, \( P = .001 \)).[63]

Timing of Surgery and Chemotherapy

In making decisions about the timing of liver resection and pre- or postoperative chemotherapy, there are a number of factors to be considered. For patients with clearly resectable disease, resection can be done first followed by adjuvant therapy, or chemotherapy can be given prior to resection (Table 8). The advantages of preoperative chemotherapy include (1) a decrease of micrometastatic disease, (2) the ability to see if disease is responsive to a particular regimen, and (3) a decrease in tumor size. The disadvantages comprise (1) toxicity to the liver, (2) the possibility of progression, and (3) the possibility of spread to hepatic lymph nodes and a complete response make it difficult to find where to resect.

For patients with borderline resectability, chemotherapy can be done first but only for short periods of time, and as soon as response is noted, surgery should be performed rather than extending chemotherapy for a long period of time. Adam reported that prolonged chemotherapy (> 12 cycles) was related to longer hospital stays after liver resection. For clearly unresectable disease, patients should enter protocols that are addressing the question of how best to decrease liver metastases to allow resection.

In patients with synchronous colorectal cancer, there are those who advocate for simultaneous resection of both the primary and the metastatic disease. In one study of 39 consecutive patients with synchronous disease, only the histologic grade of the tumor was a predictor of survival.[64] In a retrospective series of 71 patients with five or more bilobar liver tumors, improved survival was seen.
with neoadjuvant therapy.[65] In a neoadjuvant study on patients with synchronous colon and liver metastases, 16 of 20 had a liver resection after chemotherapy with irinotecan/oxaliplatin/LV/5-FU. This was followed by primary resection 3 to 8 weeks later. The 2-year survival rate in these patients was 79%.[66] If the primary is in the rectum, other considerations come into play such as the need for preoperative treatment to shrink the tumor and avoid the need for a colostomy.

Ongoing Trials

Studies have begun to address the question, "Is neoadjuvant chemotherapy useful for resectable liver metastases?" The EORTC study is looking at pre- and postoperative FOLFOX vs observation. These investigators have randomized 364 patients with potentially resectable liver metastases to six cycles of FOLFOX before and after surgery, or surgery alone.[67] The primary endpoint is disease-free survival, and the study has limited accrual to patients with up to four metastases.

Presently, in the group receiving preoperative chemotherapy, 7.7% progressed prior to surgery and 11% were not able to undergo resection. In the control group, 4% were not able to undergo resection. However, the actual number of patients who were resected was similar in both groups. It is too early to look at the disease-free survival and survival rates in this trial. The Southwest Oncology Group (SWOG) will conduct a study of neoadjuvant CapeOx (capecitabine/oxaliplatin) and bevacizumab.

For clearly unresectable disease, studies are asking how we can best decrease hepatic metastases to make them resectable. The North Central Cancer Treatment Group (NCCTG) and National Surgical Adjuvant Breast and Bowel Project (NSABP) are conducting a phase II trial of FOLFOX and cetuximab, Pfizer has initiated a study of FOLFIRI and bevacizumab, and MSKCC has a trial of HAI plus systemic chemotherapy with bevacizumab. Finally, Gercor is exploring FOLFOX and bevacizumab with or without erlotinib (Tarceva).

Is Adjuvant Therapy With HAI Useful Post-Liver Resection?

Once metastases grow beyond 3 mm, they obtain their blood supply from arterial circulation, whereas normal hepatocytes receive blood flow from the portal vein. After hepatic resection of liver metastases, residual disease, if present, may be 2 to 3 mm in diameter, and therefore derive its blood supply from the hepatic artery.

Four large randomized trials addressed the question of whether adjuvant therapy with HAI is useful after liver resection. At MSKCC,[68] patients were randomized after liver resection to HAI FUDR plus dexamethasone and systemic 5-FU with or without LV or systemic chemotherapy alone. The endpoint was 2-year survival. Patients were stratified according to the number of liver metastases (1, 2-4, > 4) and type of chemotherapy (none, 5-FU ± levamisole, or 5-FU + LV). Numerous other parameters, including molecular markers, were comparable in both treatment groups. The study found that the 2-year survival rate was significantly increased with HAI + systemic chemotherapy to 86%, vs 72% with systemic therapy alone ($P = .03$).

An update with a median follow-up time of 10 years revealed a 10-year survival rate of 41% for the HAI-plus-systemic therapy group and 27% for the systemic therapy-alone group. Overall median survivals were 68.4 vs 58.8 months for the HAI + systemic group vs systemic alone, respectively. Median time to hepatic recurrence has not been reached in the combination arm, but was 32.5 months for patients receiving systemic therapy alone ($P \leq .01$). Median progression-free survival was 31 vs 17 months for HAI plus systemic therapy vs systemic therapy alone, respectively ($P = .02$).[69]TABLE 9

| Adjuvant Therapy After Liver Resection: Randomized Trials of Hepatic Arterial Infusion vs Systemic Therapy or Control |

The Eastern Cooperative Oncology Group (ECOG) and SWOG conducted a prospective trial of hepatic
resection alone vs resection followed by HAI (FUDR) and systemic infusional 5-FU.[70] Only patients with three or fewer hepatic metastases were enrolled, and 109 patients were randomized prior to resection. Because randomization was done prior to resection, 29 patients were found to be ineligible at the time of liver resection. For the 75 patients who actually entered the study, 4-year disease-free survival was significantly longer with HAI plus systemic therapy vs resection alone (58% and 34%, respectively, \( P = .039 \)). The primary endpoint of the study was disease-free survival, and the study was not powered for overall survival. The 5-year survival rate was 58% for the HAI-plus-systemic treatment group and 40% for the resection-only group (Table 9).

In a German multicenter, randomized trial[71] of hepatic resection alone vs hepatic resection plus adjuvant HAI 5-FU/LV, patients were stratified according to number of liver metastases (1-2, 3-6) and the site of the primary tumor (colon or upper rectum, mid or lower rectum). A total of 113 patients were assigned to each group. Despite initial randomization, only 87 (77%) were actually treated in the HAI-plus-systemic therapy group for various reasons including extrahepatic disease and technical complications. Chemotherapy data were available for 73 (64.6%) of the 113 patients randomized, and only 34 (30%) patients completed the assigned protocol, possibly due to the use of ports and 5-FU therapy. No survival advantage was seen. In the secondary analysis comparing the "actually treated" patients (n = 87) to those receiving no therapy (n = 114), median survival was 44.8 vs 39.7 months, respectively. Median time to progression in the liver doubled in the group receiving HAI 5-FU/LV (44.8 vs 23.3 months), and median time to any progression was 20 vs 12.6 months, respectively.

A prospective randomized study from Greece used intraoperative randomization to regional liver therapy plus systemic therapy vs systemic therapy alone.[139] The regional group received mitomycin, 5-FU/LV, and interleukin-2 (Proleukin) via a hepatic arterial catheter and also received the same drugs by a systemic route. The systemic group received the same drugs without HAI therapy. A total of 143 patients were randomized, 5 died during the postoperative period, and 16 were lost to follow-up, leaving 122 in the follow-up groups. The 2-year survival rates were 80% and 71%, and 5-year survival rates were 73% and 60%, in the regional-plus-systemic vs systemic-alone groups, respectively (\( P = .004 \)). Five-year freedom from hepatic recurrence was also significantly increased in the regional-plus-systemic group (82% vs 49%, \( P < .001 \)).

Tono et al[138] randomized 19 patients to continuous infusion of 5-FU, 500 mg/d for 4 days via HAI for 6 weeks. Though this was a small study, there was an increase in 3-year disease-free survival—66.7% for the regional group and 20% for the control group (\( P = .045 \)). The 5-year survival rate was 77.8% for the regional group vs 50% for the control group.

In a nonrandomized study from Japan,[72] 58 patients who had radical resection of metastatic colorectal carcinoma could select whether they wanted HAI plus systemic therapy, or systemic therapy alone after surgery. The HAI therapy was 5-FU, 600 mg/m²/d for 2 days, with oral UFT, 200 mg twice daily for 5 days vs oral UFT alone. The 5-year survival was significantly increased for the HAI-plus-systemic therapy group (59% vs 27%, \( P < .001 \)). The investigators also found a significant reduction in hepatic recurrence—7% for HAI plus systemic therapy vs 57% for systemic therapy alone (\( P < .001 \)). Another small Japanese study of 38 patients involved two groups, one receiving HAI 5-FU infusion for 3 weeks and the other, no further treatment after hepatic resection. The 4-year survival rate was 100% vs 47% for the HAI and control groups, respectively (\( P = .05 \)).

A meta-analysis by Clancy et al[73] suggested no increase in survival when 1- and 2-year survivals were reported. However, looking at these same studies and reporting 3- and 5-year survivals show different results (Table 9).

**Newer Agents**

Some phase I and phase II studies testing the new systemic chemotherapy agents with HAI as adjuvant therapy after liver resection have been completed. A phase I study at MSKCC of systemic irinotecan and HAI FUDR/dexamethasone arrived at an irinotecan dose of 200 mg/m² every other week with concurrent HAI therapy.[74] The hepatic arterial dose (FUDR 0.12 mg × kg × 30 ÷ pump flow rate) was administered over 14 days with dexamethasone. In this adjuvant trial of systemic irinotecan and HAI FUDR/dexamethasone study, with a median follow up time of 5.2 years, the 2-year survival rate is 89% and the 5-year survival rate is 58%.

Another phase I trial used escalating systemic doses of oxaliplatin/5-FU/LV and HAI therapy.[75] With a minimum follow-up time of 26.9 months for the adjuvant systemic oxaliplatin/5-FU/LV-plus-HAI FUDR/dexamethasone trial, the 2-year survival rate is presently 98% and 5-year survival is 90%, but this may change with longer follow-up. At the Mayo Clinic, 5-FUDR plus dexamethasone has been added to systemic oxaliplatin and capecitabine. The FUDR dose is 0.2 mg/kg/d, not divided by the
flow rate. Presently, the 2-year survival rate is 86%.[76]
New studies to address the usefulness of adjuvant therapy after liver resection include the National Surgical Adjuvant Breast and Bowel Project (NSABP) study of HAI plus systemic oxaliplatin plus capecitabine vs systemic oxaliplatin plus capecitabine alone. A trial at MSKCC is addressing the question of the safety of bevacizumab given with HAI plus systemic therapy after liver resection in a randomized study of HAI and systemic therapy with or without bevacizumab (Table 8).

**Is Adjuvant Systemic Chemotherapy Alone Useful After Liver Resection?**

Two new randomized studies have addressed the utility of systemic therapy after liver resection. In the ENG study (EORTC/NCIC CTG/GIVIO), 128 patients were randomized to receive 5-FU and LV chemotherapy for 8 weeks vs no further therapy (control) after liver or lung resection. No significant differences were seen between the two groups in terms of overall or disease-free survival (39 vs 20 months for the treated and control groups, respectively). The 4-year survival rates were 57% and 47% for the treated and control groups.[77]

A European intergroup study (FFCD) randomized 173 patients to systemic 5-FU/LV vs no further treatment after liver resection. The 5-FU and LV were given by the bolus method on a monthly schedule. The 2-year disease-free survival (endpoint) was 50.4% for those receiving chemotherapy and 38.1% for the control group ($P = .058$). Negative prognostic factors were synchronous disease, multiple metastases, stage III tumor, preoperative hypertension, postoperative complications, and an elevated preoperative CEA. Median survival was 62 vs 46 months for the 5-FU/LV group vs control group. The 2- and 5-year survival rates were 81% and 51% for the chemotherapy group and 82% and 41% for the control group.

A trial combining the two European studies to increase power demonstrated that there was no significant difference in progression-free survival or survival between postoperative systemic chemotherapy with 5-FU/LV vs control after curative resection.[141] Progression-free survival was 27.9 vs 18.8 months ($P = .058$) and overall survival was 62.2 vs 47.3 months ($P = .095$) for the chemotherapy vs surgery-alone groups, respectively. Patient characteristics in this study included only one metastasis in 68% of patients, and more than a 1-year disease-free interval in 57% of patients. These factors clearly can affect results, as seen in this analysis, where disease-free survival was 27 months for a single metastasis and 16.8 months for two or more metastases ($P = .036$) and overall survival was 64.5 months for one metastasis vs 40 months for two or more metastases. In the MSKCC study of adjuvant HAI therapy plus systemic 5-FU/LV after liver resection, 36% of patients had only one metastasis, while 19% had more than four metastases, and only 20% had a disease-free interval greater than 1 year.[68]

A small study of 29 patients addressed the efficacy of systemic irinotecan post-hepatic resection.[142] The 2-year overall survival rate in this study was 85%. The patients were in a better-risk category, with 62% having only one metastasis, 79% with a disease-free interval > 1 year, and 62% with a surgical margin > 1 cm. The median disease-free survival was 45 months. The initial dose of irinotecan (350 mg/m$^2$) had to be lowered to 300 mg/m$^2$, and in patients older than 70, those who had received prior radiation therapy, and those with 60% of their liver resected, it was lowered to 250 mg/m$^2$ every 3 weeks. Current studies of systemic therapy are addressing the use of new agents alone or with molecular-targeted agents.

**Cryoablation**

Cryoablation is a freeze-thaw process that can induce cellular destruction. With this method, a cryoprobe is intraoperatively inserted into the lesion, liquid nitrogen is applied, and repeated freezing and thawing causes intra- and extracellular ice crystals, which destroy the tumor. One of the problems with cryoablation is that not all tumor cells may be destroyed. For example, in a study by Morris and Ross, 75% of patients treated with cryoablation developed an elevated CEA within 6 months.[78] In a large series of patients undergoing cryoablation, the actuarial 1-, 3-, and 5-year survival rates were 82%, 32%, and 13%, respectively. Cryoablation has been used in association with liver resection in cases where all disease cannot be resected. In one trial, the 3-year survival of 75 patients who underwent resection plus cryotherapy was similar to that of 32 patients who underwent resection alone.[79] Similar results were obtained by Rivoire et al, who reported a 4-year survival rate of 36% in patients receiving cryotherapy after preoperative chemotherapy.[80] In a study examining systemic irinotecan and HAI FUDR plus dexamethasone in previously treated patients, eight patients also received cryotherapy because resection was not possible. The 2-year survival rate was 80% for the patients receiving cryotherapy.
with HAI plus systemic therapy.[30]

Complications of cryoablation include biliary fistulae, coagulopathy, myoglobinuria, hepatic abscesses, and pleural effusions. A survey of a number of hospitals using cryoablation found a mortality rate of 1.5%, with the most common reason for mortality being cryoshock (18%) or liver failure (12%).[81]

**Radiofrequency Ablation**

Heat can be used to kill tumor cells; one such method is radiofrequency ablation (RFA). High-frequency attenuating currents result in ionic agitation, which induces heat and coagulative necrosis. RFA electrodes can be guided into position by sonogram, computed tomography (CT), or magnetic resonance imaging (MRI), or can be used intraoperatively. RFA has advantages over cryoablation because of the lower cost of equipment, less time involved, and the small size of the electrodes permitting use of RFA without laparotomy. A major obstacle to its use is the size of the lesion, because as heat is generated within the tumor, charring of the tissues can decrease the conduction of heat. Patients with lesions smaller than 3 cm are good candidates.

**Clinical Trials**

A large multicenter Italian study of 423 patients treated with RFA reported 3- and 5-year survival rates of 47% and 24%, respectively,[82] which is similar to outcomes seen in surgical series. Similar results were obtained in another series of 25 patients, where resection was not performed because the lesion was close to a major vessel or there were medical comorbidities. The 3-year survival rate with RFA alone was 52%.[83] Elias et al used RFA instead of repeat resections for the treatment of recurrence after liver resection in 47 patients. They found that this increased the percentage of local cures and decreased the need for resection.[84]

Livraghi et al evaluated the role of RFA in 88 patients who were waiting for resection. A total of 53 patients had complete tumor ablation by RFA, and 16 (30%) remained tumor-free. Among these 53 patients with complete ablation, 98% were spared surgical resection—44% because they remained tumor-free and 56% because they developed additional metastases. Lesions in 35 (40%) of the 88 patients demonstrated local tumor recurrence. Several underwent surgical resection, whereas 15 developed unresectable disease.[85]

In a study from the Cleveland Clinic, 135 patients underwent RFA because they were not good candidates for surgical resection, and 80% of these patients had already received chemotherapy. The study was designed to look at the predictors of survival after RFA. The median overall survival was 28.9 months. Predictors of survival included size of the lesion and baseline CEA values. A median survival of 38 months was found for lesions < 3 cm, 34 months for lesions 3 to 5 cm, and 21 months for lesions > 5 cm (P = .03). The survival was also influenced by baseline CEA values, with median survivals of 34 and 16 months for CEAs < 200 ng/mL vs > 200 ng/mL (P = .01). In the Cox proportional hazards model, only the size of the largest lesion (> 5) was found to be a significant predictor of survival.[86]

In another investigation of 179 patients, size was also an important predictor. For patients with a lesion size ≤ 2.5 cm vs > 4.1 cm, the local recurrence rate was 28% and 68%, respectively.[87] In a series of 418 patients who underwent their first laparotomy at M. D. Anderson Cancer Center for the treatment of liver metastases from colorectal cancer, 348 were treated with intent to cure: 190 had resection only, 101 had RFA and resection, and 57 had RFA alone. Recurrences were lowest with resection (52%) vs 64% for RFA and resection, and 84% for RFA alone. Liver-only recurrence after RFA was 44%. The 4-year survival rate was 65% for resection, 36% for resection and RFA, and 22% for RFA alone.[88] A multivariate analysis of these patients found that the type of procedure (ie resection, RFA and resection, or RFA alone) influenced survival, with the RFA-alone group having the lowest survival. Of course, RFA was usually a component of therapy when resection was not possible, especially in cases were the anatomic distribution of tumors made complete resection impossible. Therefore, this is not a true comparison of RFA vs resection. However, the 3-year survival rate for patients with a single metastasis treated by resection or RFA was 80% vs 40%, respectively, suggesting that RFA cannot replace resection.

The combination of RFA and HAI has shown feasibility in small studies. In an M. D. Anderson study on 50 patients, 32% remained tumor-free at a 20-month median follow-up. Recurrence at the site of RFA was seen in 10% and new liver metastases in 30%.[89] Kainuma et al treated nine patients with bilobar disease using RFA and regional chemotherapy with 5-FU, doxorubicin, and cisplatin.[90] The local recurrence rate was 55%, and the 2-year survival rate was 39%. Martin treated 21 patients with
RFA and HAI FUDR. With a median follow-up time of 24 months, the median survival is 30 months.[91] No trial is presently open to address the question of HAI or HAI and systemic therapy with RFA, vs RFA alone.

Toxicity from RFA is clearly outlined in a series by de Baere et al, involving 312 patients who underwent RFA (226 of these procedures were done percutaneously). Toxicities included liver abscesses (n = 7), portal vein thrombosis (n = 3), pleural effusion (n = 5), colon perforation (n = 1), and renal insufficiency (n = 1).[92]

**Role of RFA**

In conclusion, presently there are no data supporting the use of RFA in resectable lesions in patients who are able to undergo resection. RFA may have a role during surgical resection when one side of the liver is resected and limited disease exists on the other side that cannot be resected but can be ablated. In patients who have undergone a resection and develop a small recurrence and/or for whom repeat surgery is not indicated, percutaneous or laparoscopic RFA can be used if the lesion can be reached easily and is not close to large vessels. The presence of blood vessels near the tumors causes conduction of thermal energy away from the tumor, and this “heat sink” in effect spares killing the tumor near the blood vessel.[93]

Whether techniques such as cryoablation and RFA are more useful than chemotherapy, or should be used in combination with chemotherapy, is not known and new trials will hopefully address this question. A European study being conducted by the EORTC is exploring the use of RFA and chemotherapy vs chemotherapy alone.

**Radiation Therapy**

In the past, radiation therapy has not been an effective modality for the treatment of colorectal cancer, because the liver is quite sensitive to radiation and when doses greater than 3,500 cGy are used, radiation toxicity is common. Recently, new strategies in administering radiation therapy have made such treatment more effective. These include three-dimensional (3D) conformal radiation with or without simultaneous administration of radio-sensitizing chemotherapy agents, antibody-directed radioablation, radioembolization, and interoperative interstitial radiation.

Conformal 3D treatment planning, in which beams can enter the patient from almost any angle, can substantially reduce irradiation to the normal liver.[94,95] In one study, 22 patients with localized unresectable colorectal cancer metastatic to the liver were treated with HAI FUDR (0.2 mg/kg/d) combined with up to 72.6 Gy.[96] An objective response rate of 50% was reported, with the remaining patients showing stable disease. The overall median survival was 20 months.[97] A more recent trial in 128 patients (47 with colorectal cancer) used 60 Gy of radiation with HAI FUDR. These patients had hepatic lesions too large to be treated by RFA. Approximately 60% of the colorectal cancer patients responded. The median survival was 15.8 months for the whole group and 17.2 months for the colorectal group. Grade 3 and 4 toxicity was seen in 21% and 9% of patients, consisting mostly of liver function abnormalities, upper gastrointestinal bleeding, and hematologic complications.[98]

Delivering high-dose localized radiation to part of the liver can be performed by using a single large dose of radiation.[99,100] This technique has sometimes been referred to as “stereotactic” radiation, although current methods of liver treatment lack the precision in setup and tumor localization typical of stereotactic brain irradiation. Doses of 8 to 30 Gy have been delivered in a single fraction to small tumors. In a phase I/II study by Herfarth et al, 37 patients with 60 tumors (4 primary liver tumors and a median tumor size of 10 cm), showed local tumor control in 81% at 18 months after therapy.[100] Another method of delivering high-dose localized radiation is through the use of yttrium-90 microspheres that can be infused into the hepatic artery.[101-103] A randomized trial showed that the combination of microspheres and HAI FUDR was superior to HAI alone in the treatment of colorectal cancer confined to the liver. The overall response rate and median time to progression were increased in the group receiving microspheres (44% vs 18%, P < .01; and 16 vs 10 months, P < .001).[104] The problem with the study is the low response rate seen with FUDR alone. A single high dose of radiation can be administered to localized hepatic metastases by employing a high-dose-rate iridium-192 afterloader placed at the time of laparotomy.[105] A relative disadvantage of this approach is that sources can be placed only at the time of a laparotomy. Radiation can be combined with either systemic or regional chemotherapy. The fluoropyrimidines have been shown to be radiation sensitizers.[106-108] In a study comparing microspheres containing yttrium-90 plus 5-FU/LV or 5-FU/LV alone, the median survival was 29 and 13 months,
Conclusions

With the introduction of more effective diagnostic and therapeutic techniques, the treatment of liver metastases has become more challenging and rewarding. We now have a much clearer view of the extent of liver metastases and the presence of extrahepatic metastases. The use of MRI, CT, and positron-emission tomography (PET) can often help distinguish benign from metastatic liver lesions. In deciding how best to treat a patient with liver metastases, a multi-disciplinarian approach is useful. Input from medical oncologists, diagnostic interventional radiologists, and hepatobiliary surgeons can ascertain whether the patient is resectable and whether resection should be done before or after chemotherapy.

In most patients who are clearly resectable, resection should be performed first. Unless studies now being conducted show a benefit to preoperative chemotherapy, it should not be done routinely unless patients are on protocol. If preoperative chemotherapy is performed in resectable patients, it should be done for short periods of time, ie, ≤ 3 months. After liver resection, adjuvant therapy should be administered. Patients should enter protocols addressing the usefulness of new drugs, molecular-targeted agents, or HAI therapy, either alone or in combination after resection. Since most recurrences occur during the first 2 years, follow-up of patients postresection should be frequent—every 3 months in the first 2 years, and then every 4 to 6 months for another 3 years. Patients with unresectable hepatic metastases should be treated with FOLFIRI or FOLFOX with or without bevacizumab or cetuximab, in countries where it is available, or with HAI plus irinotecan and/or oxaliplatin. If patients experience major tumor reduction, subsequent resection may be possible. RFA plus chemotherapy vs chemotherapy alone is also being evaluated in unresectable patients. In patients who show disease progression on first-line therapy, second-line therapy with systemic therapy alone or with HAI may produce responses that might enable a patient to become resectable. Adjuvant therapy after liver resection is necessary. Trials have already demonstrated benefit, and further trials have been designed to determine which type of therapy will be most efficacious.

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