Management of Hepatic Metastases

Michael A. Choti and Gregory B. Bulkley

Although the liver is the most common site of metastatic disease from a variety of tumor types, isolated hepatic metastases most commonly occur from colorectal cancer and, less frequently, from neuroendocrine tumors, gastrointestinal sarcoma, ocular melanoma, and others. Complete evaluation of the extent of metastatic disease, both intrahepatically and extrahepatically, is important before considering treatment options. Based on a preponderance of uncontrolled studies for hepatic metastatic colorectal carcinoma, surgical resection offers the only potential for cure of selected patients with completely resected disease, with 5-year survival rates of 25% to 46%. Systemic and hepatic arterial infusion chemotherapy may be useful treatment options in patients with unresectable disease and possibly as an adjuvant treatment after liver resection. Other techniques of local tumor ablation, including cryotherapy and radiofrequency ablation, although promising, remain unproved. Management of hepatic metastases from neuroendocrine tumors and other noncolorectal primary tumors should be individualized based on the patient’s clinical course, extent of disease, and symptoms. Copyright © 1999 by the American Association for the Study of Liver Diseases

As many as 50% of the patients with a primary malignancy will eventually develop metastases in the liver, a percentage greater than for any other organ, including the lung. Although primary tumors that drain principally into the portal circulation are more likely than others to develop hepatic metastases, many tumors arising in other sites, such as the breast and lung, also commonly develop hepatic metastases. Although the liver represents a common site of spread from many of these solid tumors, isolated hepatic metastases most commonly occur from colorectal and neuroendocrine tumors. Other less common malignancies also can metastasize predominantly to the liver. For most other solid malignancies, the pattern of metastatic disease is most often that of generalized dissemination.

Colorectal Metastases

Cancer of the colon and rectum is the third most commonly diagnosed cancer in the United States. An estimated 131,600 new cases will have been discovered in 1998, comprising 11% of new cancer diagnoses.1 An estimated 56,500 deaths will occur from colorectal cancer that year, comprising 10% of all cancer deaths.1 Although mortality from large-bowel cancer has been improving over the past 30 years, largely because of improvements in early detection, diagnosis, and treatment, approximately 50% of the patients with colorectal cancer eventually die of their neoplastic disease.1 The liver is the most commonly involved organ in patients with metastatic colorectal cancer. Approximately 20% of these patients have clinically recognizable liver metastases at the time of their primary diagnosis.1,2 After resection of a primary colorectal cancer in the absence of apparent metastatic disease, approximately 50% of the patients will subsequently manifest metastatic liver disease. Given these figures, one can expect that at least 30,000 patients per year in the United States will develop metastatic colorectal cancer confined to the liver.

Although it is now uncommon not to treat this form of metastatic colorectal cancer, several earlier studies have reported the natural history of patients untreated for liver metastases.2-5 Although the survival of such patients can be quite variable, only approximately 20% survive for 3 years, and few will live beyond 5 years from the time of the detection of the liver metastases.2,6 It is clear from these reports that survival time in these patients is related to the extent of liver involvement. The median survival of untreated patients with a soli-
tary metastasis is approximately 17 months compared with less than 6 months in those with multiple bilobar disease.3

Metastatic Neuroendocrine Tumors

The potential for developing liver metastases from neuroendocrine tumors depends on the tumor type. Appendiceal carcinoid tumors and insulinomas rarely develop liver metastases, whereas small-bowel carcinoid tumors and other islet cell tumors, including gastrinoma and glucagonoma, develop hepatic metastatic disease in up to 40% of the cases.7 One important feature that is unique to many metastatic neuroendocrine tumors is their potential for the production of functioning hormones. These functional metastases result in clinical syndromes that can often become extremely debilitating. Metastatic islet cell tumors may develop syndromes characteristic of the tumor type. Metastatic carcinoid tumors can result in the systemic production of vasoactive peptides, including serotonin, and consequent carcinoid syndrome.

Liver metastases from carcinoid and islet cell tumors are often slow growing, and prolonged survival is often possible, even with untreated bilobar and multicentric disease.8-13

Hepatic Metastases From Other Sources

The incidence and pattern of hepatic metastases from noncolorectal, nonendocrine tumors is less well documented. Primary gastrointestinal malignancies, such as those of the pancreas, stomach, or gallbladder, although frequently metastasizing to the liver, rapidly develop disseminated disease and carcinomatosis, as well. Few of these patients present with resectable disease limited to the liver and, as a group, their survival is poor. For these metastases, systemic therapies comprise the principle treatment options offered to these patients. Therapy directed specifically to the liver in these cases is limited to unusual situations when local symptoms develop. Other less common malignancies can also show a pattern of liver-predominant metastases. These include gastrointestinal stromal tumors (leiomysarcoma) and ocular melanoma. Other tumor types, including renal cell carcinoma, Wilm's tumor, and breast cancer, although they do not metastasize principally to the liver, can occasionally develop isolated liver metastases.

Evaluation of the Patient With Hepatic Metastases

To choose the extent of evaluation required for a patient with liver metastases, one must consider the available treatment options. In patients for whom further treatment is not being considered, an exhaustive evaluation for the extent of disease may be unwarranted. In patients for whom systemic chemotherapy is being considered, an evaluation should facilitate monitoring of the response to treatment at all sites. In those who are candidates for surgical resection, it is important to exclude the presence of extrahepatic disease, particularly recurrence at the primary site.

When evaluating the patient for extrahepatic disease, computed tomography (CT) is the imaging modality used most frequently. Abdominal CT will often show other intraabdominal disease, whereas chest CT is the most sensitive for identifying pulmonary metastases, detecting 95% of the lesions greater than 1 cm in diameter.14-17 Even in patients with normal chest radiograph results, chest CT should be strongly considered before resection of liver metastases. The ability of CT to detect extrahepatic disease within the abdominal cavity or pelvis is less, with a sensitivity reported between 22% and 41%.18-20 Moreover, false-positive results are seen in up to 45% of the cases, particularly within a previously irradiated pelvis.21

Other imaging modalities have shown potentially increased sensitivity for the detection of extrahepatic disease. Whole-body position emission tomography, using fluoro-deoxyglucose (FDG-PET) with 18F as the position emitting isotope, has a sensitivity as high as 92% to 100%, with a specificity of 85% to 100%.22-27 Schiepers et al25 reported a 93% sensitivity with FDG-PET compared with 60% with CT. Radioimmunodetection with monoclonal antibodies may also be useful in select cases. In some reports, indium 111 CYT-103 (OncoScint, Cytogen, Princeton, NJ) appeared to be more sensitive than CT in detecting lesions outside the liver.28-30 Similarly, scintigraphy with technetium 99m-labeled anti–carcinoembryonic antigen (CEA) monoclonal antibody has shown promising preliminary results.31,32 However, these newer imaging modalities have yet to significantly improve the clinical outcome in patients with metastatic colorectal cancer. The cost, limited availability, and unclear utility of these techniques currently
limit their routine use for the detection of recurrent colorectal cancer.

When a patient is considered for hepatic resection, a careful evaluation of the extent of intrahepatic and perihilar nodal disease is also important. Multiple bilobar metastases, involvement of hilar structures, or the presence of periporal or celiac nodal disease often preclude resection. Not infrequently, patients considered preoperatively to be candidates for resection are found at operation to be unresectable because of previously unrecognized additional hepatic lesions. The preoperative CT of the liver has largely supplanted ultrasonography as the most commonly used initial imaging modality for the detection of liver metastases. The sensitivity and specificity of CT within the liver can vary widely, depending on equipment and contrast enhancement methods. Whereas CT detects the presence or absence of liver metastases in approximately 85% of the cases,33 the accuracy of detecting any individual lesion is less than 70%, particularly when it is less than 1 cm in diameter.33,34 Although helical (spiral) scanning has significantly improved the capability of CT to detect liver tumors,34-38 its sensitivity for detecting lesions smaller than 1 cm remains less than 60%.34 Diagnostic hepatic angiography has a limited role in the preoperative management of liver metastases. CT arteriportography (CTAP) is a variation of hepatic CT imaging performed after the selective injection of contrast material into the celiac and/or superior mesenteric arteries.35,39,40 With this technique, selective enhancement of the liver image occurs through the portal venous circulation; therefore, arterially supplied liver metastases appear hypodense. Although the sensitivity of this approach has been reported to exceed 85% for detecting individual lesions,41-43 CTAP has several drawbacks. Flow artifacts within the liver can appear as defects, resulting in a higher incidence of false-positive findings.42,44,45 Consequently, some studies have reported positive predictive values as low as 63% for this approach.18 Because of this low specificity, some patients could be denied the potential benefits of complete resection. Moreover, CTAP is more invasive than other imaging modalities, requiring femoral arterial puncture. The associated morbidity, expense, and lower specificity have, therefore, limited the use of CTAP for preoperative evaluation in many institutions.

Magnetic resonance imaging (MRI) is being used more commonly for the evaluation of the liver. In addition to the ability to detect lesions within the liver, MRI can provide information about the vascular anatomy of the liver, which may be important in planning hepatic surgery. MRI angiography can also show hepatic or portal venous patency and assess tumor extension into major vascular structures. Another advantage provided by MRI is the lower incidence of false-positive results compared with CT or CTAP. In cases in which the nature of a particular lesion is unclear, MRI can characterize it more accurately.46,47 Overall, the sensitivity of MRI without contrast enhancement for detecting liver neoplasm(s) is approximately 85% overall and 75% for detecting individual lesions.20,48 With the addition of contrast agents such as gadolinium, as well as the development of newer liver-specific contrast agents that use supraparamagnetic iron oxide particles, MRI may soon be able to detect even smaller liver metastases.49-51

**Treatment**

After the patient has been evaluated for the location and extent of disease, a number of therapeutic options are available. These include systemic chemotherapy, surgical resection, other local ablative procedures, such as cryosurgery and intratumoral ethanol injection, and regional chemotherapy.

**Systemic Chemotherapy**

The choice of systemic chemotherapeutic agents and their efficacy varies with respect to the tumor type. For colorectal cancer, a variety of cytotoxic agents have been tested in patients with advanced disease in the liver and elsewhere. The most useful agent currently available is fluorouracil (5-FU). 5-FU alone, administered either as a bolus or by continuous infusion, results in response rates from 15% to 29%.52-55 Leucovorin (LV), a modulator of fluoropyrimidine metabolism, has been used in combination with 5-FU in an attempt to enhance its specific efficacy and thereby reduce host toxicity. In most reported series, the combination of 5-FU and LV has produced a response rate significantly better than 5-FU alone (Table 1). A recent metaanalysis of nine reported randomized trials involving 1381 patients indicated an increased response rate (23%) with combination therapy compared with that for 5-FU alone (11%).56 However, there was no impact on the median survival
time of approximately 12 months. More recently, irinotecan, a topoisomerase I inhibitor, has been approved for use in patients with advanced colorectal cancer in whom 5-FU/LV therapy has failed. Although no randomized trials with irinotecan have been reported to date, phase II studies have shown activity against colorectal cancer, with observed response rates of 15% to 32%.57-60 The precise role of systemic chemotherapy in patients with metastatic colorectal cancer confined to the liver remains unclear. Although objective responses can be observed in a substantial minority of patients, these regimens have not prolonged survival and have produced few long-term survivors.

Systemic therapy for metastatic neuroendocrine cancer is of limited benefit. Doxorubicin and streptozocin in combination have been shown to achieve partial response rates for metastatic islet cell carcinoma of up to 69%.61 Systemic chemotherapy for metastatic carcinoid tumors appears less effective. Moreover, significant toxicity is seen with these regimens, and the duration of response is short, thus limiting their usefulness. Octreotide, a somatostatin analogue, has been reported to significantly reduce symptoms associated with some functional metastatic disease and to thereby improve quality of life.62 However, prolongation in survival has not been reported with octreotide.

**Surgical Resection**

In 1963, Woodington and Waugh63 first reported a 20% 5-year survival rate in 20 patients undergoing liver resection for a variety of malignancies, including colon, stomach, gallbladder, pancreas, and melanoma. Since that time, there has been an increasing acceptance of this approach to treat liver metastases, particularly in light of the poor outcome obtained with other treatment modalities. A more accurate understanding of liver structure, based on functional segmental anatomy, as well as advances in operative technique and postoperative care, have resulted in the capability to perform this operation with low morbidity and mortality.

Preoperative and intraoperative assessment before hepatic resection. Before considering liver resection, a thorough preoperative evaluation is essential. As previously discussed, careful evaluation with imaging modalities is needed to determine the extent and resectability of disease within the liver and to

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**NOTE.** Modified from Choti MA, Bulkley GB. Schiff’s Diseases of the Liver, Fig 57-3 (in press).

Abbreviations: NCOG, Northern California Oncology Group; GITSG, Gastrointestinal Tumor Study Group; NCCTG, North Central Cancer Treatment Group; GOIRC, Italian Oncology Group for Clinical Research; SWOG, Southwest Oncology Group.

*Statistically significant.
†For high-dose leucovorin only.
‡For low-dose leucovorin only.
§Includes patients without measurable disease.
exclude extrahepatic disease. The goal of the preoperative evaluation is to identify the best candidates for resection and discriminate between those who will be found at operation to have unresectable disease, thereby avoiding unnecessary laparotomy in the latter group. The performance status of the patient must also be considered. Whereas age alone is not a contraindication to resection,64 comorbid diseases, including significant cardiac and pulmonary conditions, increase perioperative morbidity and mortality and may preclude major surgical resection.

Intraoperative exploration and evaluation of the extent of disease in the abdominal cavity and liver are critical before proceeding with surgical resection. If the site of the primary tumor is intraabdominal, this area should be inspected and palpated, if possible, to rule out local or regional recurrence. Special attention should be paid to the pelvis and cul de sac. Bimanual and bidigital palpation of the liver is performed after inspection and palpation of the peritoneal surfaces and periportal nodal region. Nodal involvement in the periportal area is associated with a significantly poorer long-term outcome and should, in most cases, preclude curative resection. In one study, only a 4% 5-year survival rate was achieved despite the presence of (resected) regional nodes.65

Intraoperative ultrasonography (IOUS) is the most sensitive modality currently available for detecting liver metastases. Its overall sensitivity is reported to be 98% to 100%.49,66,67 With this technique, the ultrasound probe is applied directly to the surface of the liver. By improving the ability to detect clinically occult metastases, patients with multiple bilobar metastases may be spared unnecessary hepatic resection. IOUS may also contribute to improved survival by helping detect and excise otherwise occult residual disease. IOUS also facilitates the careful examination of intrahepatic vascular structures and their relationship to the hepatic tumors, often allowing for safer and more accurate resection. Findings from IOUS have been found to alter the operative management in 15% to 49% of patients with liver metastases.41,67 However, improvements in long-term outcome after liver resection attributable to the routine use of IOUS have yet to be definitively shown.

Laparoscopic evaluation of the liver and abdominal cavity just before laparotomy may identify additional patients who have unresectable disease, reducing the number of patients undergoing unnecessary full surgical exploration.68,69 With recent refinements in laparoscopic ultrasonographic devices, IOUS can now complement visual laparoscopic assessment. In one report, diagnostic laparoscopy with laparoscopic ultrasonography identified additional disease and thereby avoided unnecessary laparotomy in 18% of the patients with upper gastrointestinal malignancies in general.69 For patients with isolated hepatic metastases determined to be resectable by preoperative studies, the role of laparoscopy before surgical exploration has yet to be defined.

Results of liver resection for colorectal metastases. Overall, the perioperative mortality for liver resection of colorectal metastases is less than 5% in most reported series (Table 2). In experienced hands, even major resections (hepatic lobectomy or extended hepatic lobectomy), which are performed in approximately half the cases, result in perioperative mortality rates of less than 8%.70-74 The potential for adverse outcome and the complexity of these operations justify the recommendation that major liver resection be performed at centers and by surgeons with more than occasional experience.

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with such procedures. A recent report analyzing the short-term outcome for liver resections in the state of Maryland indicated a clear relationship between hospital procedure volume and postoperative mortality. The inhospital mortality rate was 1.5% in the high-volume group (defined as more than 15 resections per year) compared with a 9.6% mortality rate in centers performing less than eight resections per year. Although operative mortality should be uncommon, significant complications have been reported in up to 30% of the patients. Although cardiac complications are rare, pulmonary complications occur in 5% to 22% of the patients. The morbidity associated specifically with liver resection includes hemorrhage, perihepatic abscess, bile leak and/or fistula, pleural effusion, and hepatic failure.

The overall 5-year survival rate reported after hepatic resection for metastatic colorectal cancer in most series ranges from 25% to 46% (Table 2). In these reports, the median survival was as high as 28 to 38 months. In one multicenter retrospective review, Hughes et al reported 859 patients undergoing hepatic resection for colorectal metastases from 24 institutions in North America and Europe between 1948 and 1985. In this group, the actuarial 5-year survival was 33%, with a 5-year disease-free survival rate of 21%. All currently published studies reporting the results of hepatic resection are retrospective in design and contain no control groups of untreated patients. However, given the favorable results of resection, which appear substantially better than those in either untreated patients or those treated with systemic chemotherapy, a trial randomizing patients to no resection is probably not ethical and resection should be recommended to all eligible patients.

Although surgical resection results in prolonged survival and perhaps cure in some patients, the majority will eventually develop recurrent disease. For this reason, many investigators have attempted to identify factors that might improve patient selection, thereby improving the long-term outcome of those undergoing resection. These prognostic factors can be divided into four categories: (1) patient-related factors, (2) primary tumor factors, (3) features of the metastases, and (4) technical factors.

Patient-related factors that relate to the individual's general health should be considered when surgical resection is anticipated. Patients with significant comorbid disease should be excluded. In most studies, advanced age (>70 years) is not associated with a poorer prognosis. However, Hughes et al. reported a significantly better prognosis in women (40% 5-year survival rate) than in men (23%), whereas other studies have failed to detect a difference. The stage of the primary colorectal tumor appears to correlate with long-term outcome, and a similar correlation has been seen with the histological grade of the primary tumor. In their multicenter series, Hughes et al reported a 5-year survival rate of 47% after hepatic resection of tumors that had been initially node-negative primary tumors, compared with 23% for primary node-positive tumors. However, these differences are small and do not appear to preclude liver resection.

Features of the hepatic metastatic disease, including the number, size, and location of the metastases, are correlated with prognosis in some series. In the report by Hughes et al, the 5-year survival rates for one, two, three, or four or more metastases were 37%, 34%, 9%, and 18%, respectively. Rosen et al also found a trend toward a poorer prognosis with an increasing number of metastases. Other reports, however, failed to find significant differences in survival related to the number of metastases. Overall, these data suggest that although the prognosis appears worse with an increased number of metastases, long-term survival can be achieved, at least in selected patients, with resection of even four or more metastases. The presence of synchronous liver metastases or a short disease-free interval between the time of primary diagnosis and detection of metastatic disease is also associated with a poorer outcome. Hughes et al reported that patients with a disease-free interval of greater than 1 year had a 5-year survival rate of 42% compared with 24% in patients for whom the disease-free interval was less than 1 year. Other studies also show a similar trend toward improved survival with a longer disease-free interval. Involvement of celiac or periportal lymph nodes draining the liver at the time of liver resection is associated universally with poor outcome. In all reports examining this factor, there were almost no survivors at 5 years.

Technical factors at the time of surgery can impact on the prognosis. These are of particular significance because they may be avoidable. A positive histological surgical resection margin has been clearly associated with poor long-term sur-
survival.\textsuperscript{70,72,73} The optimal width of the negative surgical margin, however, is more controversial. Some investigators reported an improved survival when clearance margins were 1 cm or greater,\textsuperscript{72,77} whereas others have shown no differences provided the margin is grossly negative.\textsuperscript{76} The type of resection performed (wedge resection, segmentectomy, or lobectomy) and the technique of parenchymal dissection does not appear to affect long-term outcome.\textsuperscript{70,77,78} An association between the number of blood transfusions administered during hepatic resection and long-term prognosis has been difficult to show. In one study, transfusions were associated with poorer prognosis by univariate analysis, but this difference was not seen with multivariate analysis.\textsuperscript{78} Certainly, the association between blood transfusion and other factors, including the extent of disease, confound the capability to analyze this parameter.

Therefore, a variety of factors appear to be associated with differences in prognosis, including the stage of the primary tumor, number of hepatic metastases, disease-free interval, and resection margin. However, patients should not be excluded from an attempt at curative resection solely on the basis of one or more of these poor prognostic factors. The presence of extrahepatic disease, including periportal nodal disease, or lack of control of the locoregional disease, however, is generally considered a contraindication to resection. In patients with metastatic disease confined to the liver in whom surgical resection can completely and safely remove all evident disease with negative margins, surgical resection should be strongly considered.

Liver resection for noncolorectal metastases. The role of liver resection for hepatic metastases from noncolorectal tumors has not been as well studied as that for metastases from colorectal primary tumors.\textsuperscript{89-92} Wolf et al\textsuperscript{79} reviewed 151 cases of liver resection for noncolorectal carcinoma from multiple institutions. They found a 40% 5-year survival rate in patients with Wilms tumor and carcinoid metastases. From other primary sites, the 5-year survival rate was 15%. Selected patients with neuroendocrine metastases specifically, because of the slow tumor growth and often significant symptoms related to hormone production and tumor bulk, may benefit from aggressive complete surgical resection and even (incomplete) cytoreductive surgery. The Mayo Clinic group reported on 74 patients who underwent resection for metastatic neuroendocrine tumors.\textsuperscript{80} In this uncontrolled study, they found a 4-year survival rate of 73%. A study from Johns Hopkins retrospectively compared patients undergoing liver resection to a group of unresectable patients with similar tumor burdens confined to the liver.\textsuperscript{81} In this report, the 5-year actuarial survival was significantly higher in the resected group (73% vs 29%), but this, of course, largely reflects patient selection. Even when all disease cannot be resected, uncontrolled reports suggest that when it is symptomatic or when greater than 90% of disease can be resected, palliative or cytoreductive surgery may also be of benefit in patients with hepatic metastases from neuroendocrine primary tumors.\textsuperscript{82}

The role of liver resection in nonneuroendocrine metastases is less clear. Several small retrospective series have reported 5-year survival rates of 0% to 37\%,\textsuperscript{79,83-85} Harrison et al\textsuperscript{83} reported the best outcome in patients with genitourinary and gynecologic primary tumors, compared with those with soft tissue metastases and nonsarcomatous gastrointestinal primary tumors. Others suggest that gynecologic malignancies are not candidates for liver resection because of the poor long-term survival.\textsuperscript{79} In patients with visceral leiomyosarcoma, melanoma, and malignancies of the kidney, adrenal, and breast in whom isolated liver metastases are found, liver resection should be considered. Because in these diseases metastases confined to the liver are uncommon, careful imaging, including of the lung, brain, and bone, should be performed before any surgical therapy is considered.

Resection of recurrent hepatic metastases. Although hepatic resection has become the treatment of choice for patients with isolated liver metastases from colorectal cancer, more than 60% of the patients will develop recurrent disease after liver resection,\textsuperscript{89-92} and half of these will initially recur only within the liver.\textsuperscript{89,90,93-95} As the safety and efficacy of liver resection has been increasingly accepted, repeat resections are also more commonly being performed. Although re-resections only account for 3% to 11% of all liver resections in experienced centers,\textsuperscript{94-97} the number of repeat resections at major centers may be increasing. Bismuth et al\textsuperscript{93} reported a significant increase in the percent of liver resections that are repeat resections at their institution from 6\% (6 of 105) from 1983 to 1989 compared with 28\% (49 of 177) from 1990 to 1994.

Despite the potentially increased technical diffi-
difficulties of repeat liver resection, operative mortality is similar to that of initial hepatectomy (Table 3). Postoperative complications range from 15% to 32%, somewhat higher when compared with initial resections.$^{94-96}$ This higher morbidity is in part the result of increased risk for bleeding related to perihepatic adhesions and the frequent limited ability to achieve selective vascular control.

The selection criteria of patients for re-resection for colorectal liver metastases are similar to those for initial resection. Patients should not have medical contraindications to liver surgery, have technically resectable recurrent hepatic disease, and not have unresectable extrahepatic disease. Preoperative imaging should be performed, as for the evaluation before initial resection.

Earlier reports of the long-term outcome of patients after repeat liver resection for metastatic colorectal disease were largely confined to case reports and small single-institution series. More recently, several larger series and multicellular reports show 5-year survival rates of between 16% and 41% (Table 3). Although uncontrolled and retrospective, survival rates after repeat resection are similar to those after initial resection. Certainly, this is related to careful patient selection. Regardless, the current data justify the use of repeat liver resection performed in experienced centers, in carefully selected patients with colorectal cancer. For noncolorectal metastases, as with initial resections, the benefit of repeat liver resection is unproved.

Role of total hepatectomy with orthotopic liver transplantation. Orthotopic liver transplantation has a very limited role in the management of hepatic metastatic disease.$^{90}$ This is largely because of the high likelihood of developing recurrent disease in the immunosuppressed patient. Only in metastatic neuroendocrine tumor is total hepatectomy with transplantation considered. In some of these cases, hepatectomy can be performed in conjunction with upper abdominal exenteration or pancreaticoduodenectomy.$^{90}$ Two recent studies have reported median survivals of 30 and 55 months after hepatic transplantation for neuroendocrine metastases.$^{100,101}$ Moreover, liver transplantation has been shown to be effective at controlling symptoms from secreting (symptomatic) neuroendocrine tumors, with an improvement in quality of life in selected patients with bulky metastatic disease limited to the liver.$^{99}$ However, postoperative mortality remains high in most reports,$^{100,101}$ and limited donor liver availability severely limits the capability to offer this form of therapy for any metastatic disease.

Adjuvant therapy after liver resection. Because adjuvant chemotherapy has been effective in patients at high risk for relapse after resection of primary colorectal cancer, there has been an increased interest in offering patients adjuvant therapy after resection of hepatic colorectal metastases. It is primarily considered in those patients who have not received prior chemotherapy, either as an adjuvant or for advanced disease. Although there are no published randomized controlled trials addressing this question, several retrospective studies have attempted to evaluate this problem. Hughes et al.$^{65,77}$ found that patients who received postoperative systemic chemotherapy appeared to have an improved survival. Other studies failed to find a significant difference.$^{102}$ Adjuvant regional hepatic chemotherapy has also been examined, principally with prospective, single-arm trials. Hepatic arterial, as well as portal venous, infusion has been studied with a variety of chemotherapeutic regimens.$^{103-105}$ Only one randomized trial has been performed

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<tr>
<td>Fong et al$^{94}$</td>
<td>1994</td>
<td>25</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Nordlinger et al$^{92}$</td>
<td>1994</td>
<td>130</td>
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<tr>
<td>Fernandez-Trigo et al$^{97}$</td>
<td>1995</td>
<td>170</td>
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<tr>
<td>Tuttle et al$^{147}$</td>
<td>1997</td>
<td>23</td>
<td>0</td>
<td>55%</td>
</tr>
<tr>
<td>Adam et al$^{148}$</td>
<td>1997</td>
<td>64</td>
<td>0</td>
<td>60%</td>
</tr>
</tbody>
</table>
examining the role of regional adjuvant therapy. Although the patient number was small, none of the 5 patients with adjuvant hepatic arterial infusion (HAI) therapy developed hepatic recurrence. There are at least three ongoing single- and multi-institutional, randomized, prospective trials evaluating the potential benefit of adjuvant chemotherapy after liver resection, delivered either systemically, regionally, or in combination.

Cryosurgery and Other Forms of Local Hepatic Ablative Therapy

Although surgical resection may afford the only potential for cure in patients with hepatic metastases, many patients may not be candidates for surgical resection for a variety of reasons. Novel methods for local ablation have been developed with a goal of increasing the number of patients eligible for surgical resection. Hepatic cryosurgery is such an approach that has gained popularity in recent years. This technique relies on the destruction of a defined area within the liver by freeze/thawing, using probes cooled by liquid nitrogen to subzero temperatures. Although cryosurgery has been used in the past for the treatment of a variety of surface malignancies, recent advances in the ability to deliver cold probes deep within tissue using a closed-circuit, insulated system, as well as improvements in intrahepatic imaging using IOUS, have provided the capability for safe hepatic cryoablative.

Early reported series of hepatic cryosurgery for colorectal hepatic metastases suggest that this technique is both feasible and safe. These results, however, are too preliminary to draw conclusions about long-term efficacy. Ravikumar et al reported no deaths in the first 25 patients treated at the New England Deaconess Hospital. Twenty-eight percent of the patients remained disease-free at a median follow-up of 2 years. Morris et al reported a 75% relapse rate at 6 months, as determined by CEA levels. The efficacy of cryosurgery may depend on the tumor type and the ability to achieve complete freezing of the lesion, with adequate margins. Adam et al reported on 44 patients undergoing cryosurgery for hepatic malignancies, either alone or in combination with resection. Although they found no differences in survival between groups, local recurrence was significantly greater in patients with metastatic colorectal cancer compared with patients with primary liver cancer. Nonresectional ablative approaches, such as cryosurgery, may also have a role in the treatment of neuroendocrine tumors. Because neuroendocrine metastases are often multiple, bilobar, and functional, hepatic cryosurgery may be particularly useful with unresectable liver disease. In one report, cryosurgery was shown to be effective in alleviating the symptoms associated with hormonal secretion by neuroendocrine metastases.

Currently, cryosurgical ablation is considered an investigational form of therapy for the treatment of metastatic cancer. The efficacy of this approach, either in unresectable patients or as an alternative or adjuvant to resection, should be evaluated in the setting of formal clinical trials.

A variety of other interstitial local approaches have been applied to liver metastases, including microwave, radiofrequency, and focused high-intensity ultrasound ablation. The use of local irradiation using yttrium seed implants has also been reported. Intratumoral ethanol injection, a therapy that has gained wide acceptance for unresectable hepatocellular cancer, is less effective in ethanol metastatic lesions, which are denser and result in with less capacity for diffusion. Whereas some of these approaches are promising and may afford less invasive methods of local tumor ablation, their role in the treatment of metastatic disease has yet to be defined.

As with hepatocellular cancer, arterial embolization with or without chemotherapy can provide a palliative treatment option in some patients with metastatic liver disease, particularly in hypervascular metastases, such as from neuroendocrine tumors, melanoma, and adrenal cancer. Two small clinical trials have shown a reduction in tumor size and relief of symptoms in a majority of patients with hepatic neuroendocrine metastases undergoing chemoembolization. Significant responses are rarely seen and survival benefit has not been shown with chemoembolization therapy and, therefore, it should be limited to selected patients with symptomatic disease.

Hepatic Arterial Infusion (HAI) Chemotherapy

Chemotherapy delivered systemically to treat hepatic metastases may be limited by the inability to deliver high concentrations of drug to tumor cells without systemic toxicity. For this reason, there is a rationale for regional chemotherapy. The normal liver derives its blood supply from both the hepatic
arterial and portal venous vessels. Macroscopic hepatic tumors, however, derive most of their afferent blood supply from the hepatic artery.\textsuperscript{120-123} Directing a high-dose infusion of chemotherapy into the hepatic artery therefore increases the concentration of drug to which the tumor is exposed, proportional to the hepatic parenchyma, as well as to the body as a whole, and should thereby improve the therapeutic index. Drugs such as floxuridine (FUDR), an active metabolite of 5-FU, that are rapidly metabolized within the liver on the first pass are the most commonly used regional chemotherapeutic agents.

Several randomized trials have compared the results of continuous hepatic arterial infusion (HAI) to systemic chemotherapy in patients with unresectable liver metastases (Table 4). These have reported significantly higher response rates with HAI (42\% to 62\% v 10\% to 21\%).\textsuperscript{124-129} True survival rates were difficult to evaluate in these studies because of inadequate sample sizes, crossover study designs, or inadequately administered systemic chemotherapy. Only one study reported a statistically significant improvement in 2-year survival with HAI (23\% v 13\%).\textsuperscript{129} This trial, however, has been criticized because most of the control patients did not receive systemic chemotherapy. The results of seven of these randomized trials were recently examined by metaanalysis, comparing HAI with systemic chemotherapy.\textsuperscript{130} This confirmed a greater response rate with HAI therapy, as well as suggesting a trend toward improved survival for those receiving regional therapy. A more recent phase II study evaluated the combination of hepatic arterial FUDR with regional LV and dexamethasone and found response rates as high as 72\%,\textsuperscript{131} significantly higher than those for any of the systemic 5-FU/LV chemotherapeutic regimens. In this study, the 2-year survival rate was 66\%. Moreover, HAI with this drug combination showed response rates of 50\% even in those patients in whom tumors had been previously refractory to 5-FU–based systemic chemotherapy.\textsuperscript{124}

The most common method of administering HAI chemotherapy relies on a catheter placed surgically, under direct vision, combined with the use of a subcutaneously implanted pump. Cholecystectomy is performed routinely at the time of pump placement to avoid chemical cholecystitis. Typically, the catheter tip is placed nonocclusively within the hepatic artery using the gastroduodenal artery as a conduit. Small branches of the hepatic artery distal to the catheter tip, which supply other portions of the gastrointestinal tract, are ligated. Whereas this approach requires a laparotomy, the more precise placement of the catheter results in fewer complications and allows for a much longer duration of infusion than percutaneous methods. Moreover, at the time of surgical exploration, the abdomen and liver can be evaluated more accurately for potentially resectable disease or for extraregional disease that may preclude any benefit of regional HAI therapy. Early postoperative complications of HAI therapy include arterial thrombosis, pump pocket hematoma, and infection. Misdirected infusion into the stomach or duodenum or incomplete hepatic perfusion can occur because of the lack of recognition of accessory hepatic or extraregional vessels.\textsuperscript{132} Careful attention to surgical technique has reduced such complications to less than 5\%.\textsuperscript{128,131} The most commonly seen late complications are related to hepatic and biliary chemotoxicity. Early on, alkaline phosphatase level elevations can be seen, which may return to normal

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>HAI Therapy</th>
<th>IV Therapy</th>
<th>Response Rate (%)</th>
<th>2-Year Survival (%)</th>
</tr>
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<tbody>
<tr>
<td>MSKCC, 1987\textsuperscript{125}</td>
<td>162</td>
<td>FUDR</td>
<td>FUDR</td>
<td>50% 20%</td>
<td>.001 25% 20% NS</td>
</tr>
<tr>
<td>NCOG, 1989\textsuperscript{126}</td>
<td>143</td>
<td>FUDR</td>
<td>FUDR</td>
<td>42% 10%</td>
<td>.0001 30% 20% NS</td>
</tr>
<tr>
<td>NCI, 1987\textsuperscript{127}</td>
<td>64</td>
<td>FUDR</td>
<td>FUDR</td>
<td>62% 17%</td>
<td>.003 22% 15% NS</td>
</tr>
<tr>
<td>Mayo Clinic, 1990\textsuperscript{128}</td>
<td>74</td>
<td>FUDR</td>
<td>5-FU</td>
<td>48% 21%</td>
<td>.02 — — —</td>
</tr>
<tr>
<td>France, 1992\textsuperscript{129}</td>
<td>168</td>
<td>FUDR</td>
<td>5-FU*</td>
<td>49% 14%</td>
<td>23% 13% &lt;.02</td>
</tr>
</tbody>
</table>

Abbreviations: HAI, hepatic arterial infusion; NS, no significance; IV, intravenous; FUDR, floxuridine; 5-FU, fluorouracil; MSKCC, Memorial Sloan-Kettering Cancer Center; NCOG, Northern California Oncology Center; NCI, National Cancer Institute.

*Left to the discretion of the physician.
after temporary withdrawal of the drug. Approximately 10% to 25% of the patients develop an elevated bilirubin level from chemical sclerosis of cholangitis. Although uncommon, this complication can be reversible, requiring biliary stenting. The precise mechanism of this hepatobiliary toxicity is unclear. Some investigators have proposed a drug-induced pericholangitis and fibrosis of biliary radicals, whereas others have suggested a hepatitis-like inflammatory injury. In up to 10% of the cases, some degree of anatomically identifiable biliary sclerosis can develop, most commonly at the site of the hepatic bifurcation.

**SUMMARY**

Metastatic disease is the most common malignant process affecting the liver. Although metastases can develop in the liver through hematogenous spread from most solid malignancies, certain tumor types have the propensity to develop liver-dominant disease and isolated liver metastases. These include primarily colorectal cancer and, less commonly, neuroendocrine tumors, gastrointestinal sarcomas, and others. There is a preponderance of uncontrolled studies strongly suggesting that surgical resection offers the only potential cure for colorectal cancer metastatic to the liver. Evidence is less clear for other primary tumor types. Careful preoperative evaluation of the liver, primary tumor, and extrahepatic sites is important to exclude unresectable disease and select those patients who may benefit most from resection. Potential strategies currently under investigation for improving outcomes include combining resection with adjuvant regional or systemic chemotherapy. For unresectable disease, other local ablative approaches, including cryoablation or regional chemotherapy as well as systemic chemotherapy may offer some benefit.

**References**

52. Ansfield F, Schroeder JM, Currell AR. Five years experience with 5-fluorouracil. JAMA 1962;181:295


