The management of hepatic metastases has become more and more complex, and the role of the surgical oncologist in directing care has become increasingly important. Patients with metastatic colorectal cancer represent the majority in whom resection may be indicated, but other tumor types are also appropriately resected in some cases. Diagnostic methods are increasingly sensitive and provide improved delineation of extrahepatic disease and the relationship of metastatic tumors to the relevant normal anatomy of the liver. Intraoperative ultrasonography and laparoscopy are two areas that are especially relevant to the hepatic surgeon. Multimodality therapy is often employed in the management of metastatic disease in the liver. In addition to resection, radiation, and chemotherapy, modern treatment algorithms involve a variety of novel therapies, including embolization, hepatic artery infusion of chemotherapy, cryotherapy, and radio-frequency ablation. Despite the multitude of therapeutic options, resection of metastatic disease to the liver remains the most effective therapy in selected patients and is potentially curative, unlike other modalities.

The range of treatments available for the management of liver metastases has underlined the importance of instituting a multidisciplinary planning conference in any institution that treats a significant volume of patients with hepatic metastases. Such a forum allows for the appropriate selection of the best therapy for individual patients. In a subset of patients, resection is indicated. Increasingly, resection is combined with other modalities to provide the best management of hepatic metastatic disease. For example, experience is increasing regarding the efficacy of resection followed by adjuvant chemotherapy or hepatic artery infusion therapy or of resection combined with cryoablation of unresectable lesions. The purpose of this chapter is to review the data supporting resection in different tumor types. In addition, the indications, applications, and limitations of hepatic resection for metastatic disease will be presented.

**COLORECTAL CANCER METASTASES**

Hepatic metastases from colorectal cancer (CRC) are identified at some point in nearly half of all patients with this disease. A large body of evidence supports the role of resection in the management of CRC metastatic to the liver in selected patients. Resection is accepted as the treatment of choice when all hepatic disease can be removed and when there is no evidence of extrahepatic metastatic disease. In the appropriate setting, resection results in a 30 to 40 percent 5-year survival rate, which is much greater than that observed with chemotherapy alone. Thus, although no prospective comparison of resection with chemotherapy has been performed, resection has emerged as the most effective treatment, based on markedly improved survival in several large series.

Recognition of the biologic and technical factors that govern success or failure is expected to allow improved application of hepatic resection for CRC. Additionally, enhanced approaches to assessing dis-
ease extent preoperatively have resulted in better patient selection and improved planning of resection for complex cases. Improvements in radiologic imaging technology and the use of laparoscopy minimize unnecessary laparotomies. Furthermore, clinically identified risk factors may help identify those patients who will benefit from neoadjuvant, adjuvant, or alternative therapies. Toward that end, we have developed a scoring system designed to give the clinician a better estimate of the likelihood of success following hepatic resection (see below).

**Epidemiology**

Colorectal cancer is the second leading cause of mortality from cancer in the United States. Approximately 150,000 new cases of CRC are treated annually, and approximately half of these patients will develop hepatic metastases in the course of their disease. Roughly half of this group will have recurrence in the liver, with the liver as the first or only site of disease recurrence. In a select subset of patients, the hepatic disease can be resected completely, which improves survival and which may provide a cure for 25 to 40 percent of patients (Fig. 4–1). Although this group represents a small proportion of all patients with CRC, it is a relevant population to study because of the relatively high incidence of CRC, which is second only to lung cancer in cancer-related mortality. Thus, the number of resectable cases of hepatic colorectal metastases is approximately equal to the number of cases of retroperitoneal sarcomas or resectable pancreatic cancers seen in the United States every year.

Metastases from CRC most commonly develop within 2 years of resection of the primary tumor and are usually asymptomatic; rarely, patients may complain of vague upper abdominal pain. Hepatic metastases associated with CRC may occur regardless of the initial stage of the primary tumor although node-positive primary lesions are more likely to precede hepatic metastasis. Up to 25 percent of hepatic metastases may be identified synchronously with the primary tumor. Biologically, patients treatable by hepatic resection represent an exclusive group. The development of small-volume metastatic disease or small numbers of metastases isolated to the liver is an uncommon phenomenon. Other gastrointestinal tumors such as esophageal, gastric, and pancreatic tumors do not display this favorable pattern; consequently, hepatic resection has never been found to be a useful therapeutic option in these diseases. Ultimately, biologic factors, rather than technical prowess, are the reason that hepatic resection has emerged as a successful strategy in large numbers of patients with CRC metastases. Further improvements in results can be expected as the understanding of the biology of metastasis increases and as existing and novel therapies are applied in a thoughtful manner.

**Diagnosis**

A variety of modalities, including laboratory tests, radiologic examinations, and laparoscopy, are relevant in diagnosing patients with CRC hepatic metastases. These studies are done to initially identify

![Figure 4–1. The proportion of patients amenable to resection of colorectal cancer (CRC) liver metastases is small.](image-url)
hepatic metastases, determine suitability of resection, and as follow-up after resection. In general, laboratory tests are done to screen for metastases. Serial carcinoembryonic antigen (CEA) level assessment is useful for detecting recurrence in many patients. Radiology has been progressively refined such that ultrasonography (US), computed tomography (CT), and (to a lesser extent) magnetic resonance imaging (MRI) provide the cornerstone of identification and assessment of CRC metastasis. Nuclear medicine scans such as CEA scans and OncoScint scanning have not proved useful and are not done routinely. Positron emission tomography (PET) may prove useful, but its role remains to be defined. Finally, laparoscopy has increasingly found application in the assessment of resectability.

**Screening for Hepatic Metastases**

Controversy exists as to the most appropriate manner in which to follow patients after resection of primary CRC. Some clinicians advocate frequent follow-up with laboratory tests and radiologic examinations while others tend to be more nihilistic, concluding that follow-up does not affect outcome and is not cost-effective.\(^7\)–\(^10\) Some randomized studies have indicated that rigorous follow-up does not affect overall outcome. A number of attempts have been made to resolve the issue of whether follow-up after resection of primary CRC has a beneficial effect. Table 4–1 lists several studies that evaluate the utility of close follow-up. Most of the trials did not find increased surveillance to be beneficial. However, the studies appear to be inadequately sized to determine anything other than gross differences between patients followed intensively and those followed less intensively or not at all.

The literature that examines follow-up is of limited quality, and the follow-up schemes that are examined vary widely. The randomized studies that decry the use of follow-up are composed of relatively few patients with resectable disease.\(^7\) Even in a relatively large study such as that by Kjeldsen and colleagues, the number of patients developing recurrence (\(n = 91\)) is small, and the number of patients eligible for radical reoperation, including liver resection, is even smaller (\(n = 14\)); this study would not detect a survival difference of 20 percent or less.\(^11\) Moreover, these studies do not routinely make a point of applying follow-up strategies to high-risk individuals (ie, those who would be most likely to develop recurrent disease and to benefit from recognition and resection of such).

Thus, although patients amenable to hepatic resection are a distinct minority, it is likely that some form of follow-up aimed at identifying hepatic metastases is justified. Some patients who would subsequently develop unresectable lesions because of tumor size or location may be identified at an early and resectable stage with rigorous follow-up. A definitive study to determine the most efficacious and cost-effective approach to follow-up after primary CRC resection has yet to be done.\(^11\) It is interesting that a large majority of patients report a preference for follow-up even if follow-up has demonstrated only a relatively small increase in lives saved.\(^12\)

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Intensity of Follow-up</th>
<th>Number of Patients</th>
<th>Median Observation (mo)</th>
<th>Overall Recurrence Rate (%)</th>
<th>Radical Reoperation in Recurrent Cases (%)</th>
<th>5-year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ohlsson(^13) (1995)</td>
<td>Minimal</td>
<td>54</td>
<td>82</td>
<td>33</td>
<td>17</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>Intense</td>
<td>53</td>
<td>—</td>
<td>32</td>
<td>29</td>
<td>75</td>
</tr>
<tr>
<td>Makela(^14) (1995)</td>
<td>Regular</td>
<td>54</td>
<td>&gt; 60</td>
<td>39</td>
<td>14</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Intensified</td>
<td>52</td>
<td>—</td>
<td>42</td>
<td>22</td>
<td>59</td>
</tr>
<tr>
<td>Kjeldsen(^11) (1997)</td>
<td>Infrequent</td>
<td>307</td>
<td>&gt; 60</td>
<td>26</td>
<td>7</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Frequent</td>
<td>290</td>
<td>—</td>
<td>26</td>
<td>22*</td>
<td>70</td>
</tr>
<tr>
<td>Schoemaker(^8) (1998)</td>
<td>Regular</td>
<td>158</td>
<td>&gt; 60</td>
<td>NR</td>
<td>NR</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Aggressive</td>
<td>167</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>76</td>
</tr>
<tr>
<td>Pietra(^15) 1998</td>
<td>Regular</td>
<td>103</td>
<td>&gt; 60</td>
<td>19</td>
<td>10</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Intensive</td>
<td>104</td>
<td>—</td>
<td>25*</td>
<td>65</td>
<td>73*</td>
</tr>
</tbody>
</table>

\(^*\)\(p < .05.\)

NR = not reported.
Carcinoembryonic antigen (CEA) is a glycoprotein that is found on the surface of CRC cells and that can be secreted into the bloodstream. Used as a screening tool, an elevated CEA level serves to prompt further investigation with radiologic studies. Several studies have shown that elevated CEA is highly sensitive for the identification of hepatic metastases. Although some authors have argued that only a small number of patients benefit from surveillance of CEA levels, other investigators have concluded that CEA-based follow-up strategies are efficacious and cost-effective. A study from the Mayo Clinic found that patient survival nearly doubled when hepatic metastases were identified on the basis of CEA elevation rather than tumor-related symptoms. Because CEA-based strategies are associated with survival benefit, the American Society of Clinical Oncology (ASCO) recommendations indicate that CEA levels should be assessed every 2 to 3 months in patients with stage 2 or 3 CRC for at least 2 years after diagnosis (Table 4–2). Unfortunately, CEA-based strategies are of limited benefit in the 30 percent of patients whose tumors do not secrete CEA as these patients are not expected to manifest an elevation in CEA level, even with progression of disease.

In addition to its utility in identifying hepatic metastases, CEA level is predictive of prognosis following hepatic resection; high levels of CEA are associated with worse outcomes. There is little evidence that other biochemical tests such as alkaline phosphatase or transaminase tests contribute to the early identification of resectable tumors or to the prediction of outcomes following resection.

Presently, there are no firm guidelines regarding the use of radiologic investigations to screen for

<table>
<thead>
<tr>
<th>Table 4–2. AMERICAN SOCIETY OF CLINICAL ONCOLOGY GUIDELINES FOR FOLLOW-UP AFTER CURATIVE RESECTION OF COLORECTAL CANCER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Carcinoembryonic Antigen (CEA)</strong></td>
</tr>
<tr>
<td>If resection of liver metastases would be clinically indicated, it is recommended that postoperative serum CEA testing be performed every 2 to 3 months in patients with stage 2 or 3 disease for ≤ 2 years after diagnosis. An elevated CEA level, if confirmed by retesting, warrants further evaluation of metastatic disease but does not justify the institution of systemic therapy for presumed metastatic disease.</td>
</tr>
<tr>
<td><strong>2. History and Physical Examination</strong></td>
</tr>
<tr>
<td>There are no data that directly address the contribution of the history and physical examination to outcomes of colorectal cancer (CRC) surveillance. However, the expert panel suggests that a clinical history and pertinent physical examination be performed every 3 to 6 months for the first 3 years and annually thereafter.</td>
</tr>
<tr>
<td><strong>3. Liver Function Test (LFT)</strong></td>
</tr>
<tr>
<td>The data are sufficient to advise against the regular monitoring of any LFTs after primary therapy for CRC.</td>
</tr>
<tr>
<td><strong>4. Fecal Occult Blood Test (FOBT)</strong></td>
</tr>
<tr>
<td>The data are sufficient to recommend against periodic FOBTs in surveillance for CRC.</td>
</tr>
<tr>
<td><strong>5. Computed Tomography (CT)</strong></td>
</tr>
<tr>
<td>The data are sufficient to recommend against routine CT scanning in the follow-up of CRC.</td>
</tr>
<tr>
<td><strong>6. Chest X-Ray (CXR)</strong></td>
</tr>
<tr>
<td>Data are sufficient to advise against routine yearly CXRs in the follow-up of CRC. They may be ordered to diagnose abnormalities prompted by elevated CEA levels or for patients who have symptoms suggestive of a pulmonary metastasis.</td>
</tr>
<tr>
<td><strong>7. Colonoscopy</strong></td>
</tr>
<tr>
<td>All patients should have a colonoscopy for the pre- or perioperative documentation of a cancer- and polyp-free colon. The data are sufficient to recommend colonoscopy every 3 to 5 years to detect new cancers and polyps. Routine annual colonoscopies are not recommended for all patients.</td>
</tr>
<tr>
<td><strong>8. Flexible Proctosigmoidoscopy (for Rectal Cancer)</strong></td>
</tr>
<tr>
<td>Combined chemotherapy and pelvic radiation represent the standard treatment for stage 2 and 3 rectal cancer. For patients who do not receive pelvic radiation, either because they could not or because they refused treatment, direct imaging of the rectum at periodic intervals is suggested. For patients who have received pelvic radiation, direct imaging of the rectum (except colonoscopy every 3 to 5 years) is not suggested. All patients with rectal cancer should have a colonoscopy for the pre- or perioperative documentation of a cancer- and polyp-free colon.</td>
</tr>
<tr>
<td><strong>9. Pelvic Imaging</strong></td>
</tr>
<tr>
<td>Data are sufficient to recommend against routine pelvic imaging in asymptomatic patients who have received surgical resection and radiation for rectal cancer.</td>
</tr>
<tr>
<td><strong>10. Complete Blood Cell (CBC) Count</strong></td>
</tr>
<tr>
<td>The expert panel recommends against routine monitoring of CBC for CRC surveillance.</td>
</tr>
</tbody>
</table>

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metastatic disease following colorectal resection for cancer. The ASCO recommendations do not include standard follow-up with imaging following primary resection. The argument is that CT or US rarely detects recurrence before CEA levels are elevated. However, this fails to address the issue of non-CEA-secreting tumors, and it is likely that selected patients benefit from periodic imaging.

Liver US is a versatile tool in the evaluation of the patient with suspected hepatic colorectal metastases. This modality has the advantage of being inexpensive, widely available, noninvasive, and sensitive for the definition of hepatic metastases. Its limitations include an inability to specifically characterize solid lesions as metastases as opposed to other benign lesions. Moreover, US is operator dependent and is not as easily interpreted by nonradiologists as are other cross-sectional imaging techniques. Despite this, it remains the most widely used screening method worldwide for detection of hepatic metastases. Computed tomography is more sensitive and less operator dependent than US. Nonetheless, CT involves increased expense, the use of radiation, and the risk of nephrotoxic and allergic reactions, thus limiting its application as a routine screening tool.

The ideal radiologic approach to screening for hepatic CRC metastases remains to be established. Any algorithms used should be sensitive and cost-effective, and should have an impact on patient outcome. At present, approximately 25 percent of clinicians routinely follow up patients by using radiologic tests designed to detect metastases. Although the evidence does not exist to fully recommend follow-up investigations after primary colorectal resection for cancer, neither does existing evidence exclude imaging as being worthwhile at some interval in selected patients.

Unlike follow-up after resection of the primary lesion, follow-up imaging (CT or US) after hepatic resection is indicated for patients undergoing successful hepatic resection for CRC metastases. Although a majority of lesions will recur at hepatic and extrahepatic sites and be incurable, there is the occasional opportunity to successfully resect recurrent hepatic disease in some patients. Studies have confirmed long-term survival in some patients after repeat hepatic resection.

Determining Resectability

The majority of patients with hepatic metastases have unresectable disease either because of the extent of disease in the liver or because of the presence of extrahepatic disease. In general, radiologic examinations are the primary tools that guide decisions regarding resectability, and the CT scan is the most widely used study because it can define the relationship of the tumor to its surrounding vascular and biliary structures, reveal the extent of disease within the liver, and allow assessment of extrahepatic disease. Imaging studies with enhanced and non-enhanced views are critical to obtain maximal assessment of the liver parenchyma. The spiral or helical CT scan allows the rapid acquisition of data with decreased artifact as well as decreased requirements for intravenous contrast. This technique is associated with a reduction in partial-volume averaging and a consequently improved detection of smaller metastases. Computed tomographic arteriopography (CTAP) is a more invasive procedure but represents the “gold standard” for the detection and preoperative assessment of liver metastases. This procedure involves the injection of contrast into the mesenteric circulation and the acquisition of image data during the portal phase, when the liver parenchyma tends to be more vascular compared to the surrounding tumor that is supplied by the hepatic arterial system. This technique is particularly sensitive for the detection of lesions less than 2 cm in size; overall, it detects hepatic metastases at a rate of greater than 90 percent (Fig. 4–2). The arteriograph obtained during this procedure is also of value in patients who will undergo placement of a hepatic artery infusion pump. Information obtained during this stage of the study is valuable for identifying aberrant arterial anatomy. As noninvasive imaging modalities (MRI and CT) advance, they will likely supplant angiography for this purpose.

Magnetic resonance imaging of the abdomen occasionally gives additional information beyond that provided by high-quality CT. It is especially useful in differentiating hemangiomas from metastases and may accurately characterize lesions as hemangiomas in 84 to 95 percent of cases. Moreover, MRI is helpful in characterizing lesions
smaller than 2 cm in diameter. Hepatic colorectal metastases are usually dark on T1-weighted images, and 90 percent are hyperintense on T2-weighted images (Fig. 4–3, A). Lesions are particularly likely to be bright if they are vascular or necrotic. Gadolinium administration may help further define metastatic lesions (see Fig. 4–3, B). Hemangiomas have a distinctive appearance on MRI, demonstrating low attenuation on T1-weighted images whereas T2-weighted images are homogeneously hyperintense, producing a characteristic “lightbulb” sign (Fig. 4–4). The pattern of enhancement on T1-weighted images is especially useful for distinguishing hemangiomas from metastases. After administration of gadolinium, hemangiomas demonstrate a characteristic pattern of peripheral nodular enhancement. Compared to CT, MRI is expensive and less accessible, but it is useful for defining the lesions that are indeterminate on CT.

Additional techniques commonly used in preoperative hepatic imaging (including nuclear medicine scintigraphy, angiography, and direct cholangiography) have no role in the routine evaluation of the patient with colorectal hepatic metastases. The use-
fulness of positron emission tomography (PET) continues to be investigated, and its role remains to be defined.\textsuperscript{28–30} Positron emission tomography scanning uses 18F-FDG, a radiolabeled glucose analogue that is preferentially taken up by glucose-avid tissues such as tumors and is then phosphorylated by hexokinase and trapped within the cells. The PET scanner detects the increased radioactivity, which appears as a “hot spot” on the scan. Preliminary studies suggest that PET identifies liver metastases with 90 percent sensitivity and is superior to conventional methods in the detection of extrahepatic disease.\textsuperscript{31} In particular, PET affords an advantage in the detection of pulmonary metastases, normal-sized celiac nodes that contain metastases, and locoregional recurrence related to the primary cancer (Fig. 4–5). In a study from Memorial Sloan-Kettering Cancer Center, whole-body PET scanning was evaluated in a group of 40 patients with CRC metastatic to the liver who were being considered for curative treatment.

*Figure 4–4.* Dynamic MRI images of hemangioma. A, pre-contrast. B, post-contrast. C–D, delayed contrast. Note the peripheral nodular enhancement.
hepatectomy. All patients were known to be at high risk for extrahepatic disease, based on clinical factors. Whole-body PET scans were performed and the effect on clinical outcomes was studied. Findings on PET scanning influenced clinical management in 16 cases (40%) and led to a change in management in 9 patients (23%). Of importance, 6 individuals were spared laparotomy, and small foci (< 1 cm) of extrahepatic disease that precluded resection were discovered in 3 patients. In this study, PET detected 37 of 52 resected lesions. Lesion size greater than 1 cm was an important predictor of the ability of PET to detect lesions. At present, PET scans are expensive and not widely available; therefore, the utility of this technology requires further rigorous evaluation. Studies must demonstrate that the additional cost is justified by the added benefit of preventing unnecessary laparotomies.28,29

Despite improvements in imaging technology, a subset of patients are still found to be unresectable at laparotomy. Previous reports suggested that up to half of the patients submitted to operation for a potentially curative resection harbor radiologically occult unresectable disease identifiable only at exploration.32,33 Although the incidence of nontherapeutic laparotomy has decreased, exploration without resection remains a problem. In a recent audit of our experience, we found that, with careful radiologic assessment, we resected 79 percent of patients submitted to laparotomy, which is higher than the percentage indicated in most other published reports.34

Laparoscopic examination (with or without laparoscopic US) represents a further refinement of diagnosis prior to laparotomy and may further reduce the number of unnecessary laparotomies. Laparoscopy may identify unresectable disease that escapes radiologic detection. A growing number of authors report that staging laparoscopy (including laparoscopic US) performed under general anesthesia just prior to planned resection will identify 16 to 64 percent of patients with unresectable disease.35–38 Staging laparoscopy has been shown to involve no additional time in those patients with unresectable disease.39 Moreover, it is associated with less morbidity, shorter length of stay in hospital, decreased hospital costs, and a shorter time for the initiation of definitive therapy, compared to patients with unresectable disease who are subjected to laparotomy. This approach is particularly useful in identifying small peritoneal metastases, additional hepatic metastases, and unsuspected cirrhosis. Laparoscopy in this setting is less likely to identify lymph node metastases, vascular compromise, and extensive biliary involvement that might render a patient unresectable39 (Fig. 4–6). We recently evaluated our experience with staging laparoscopy in 103 patients with metastatic colorectal cancer thought to be resectable by radiographic criteria. Laparoscopy identified the majority of patients with unresectable disease and added 35 minutes of operating time in those who went on to laparotomy. Laparoscopy improved resectability from 75 to 87 percent. Ten patients were ultimately spared an unnecessary laparotomy.
Metastatic Liver Cancer

Intraoperative ultrasonography (IOUS), performed at laparotomy, has been an important tool for assessing resectability, and it remains in wide use. The sensitivity of open IOUS for detecting metastases is 96 percent, compared to 91 percent for CT portography. Moreover, IOUS may alter management in 10 to 48 percent of cases. In some cases, it causes the surgeon to change the planned resection because new lesions are identified or because unanticipated vascular involvement is detected. There is a significant learning curve for the novice using IOUS. However, once the surgeon gains facility with it, the technique is especially useful in clarifying the relationship of tumors to the portal structures and hepatic veins. This feature is particularly important when planning segmental or sectoral resections.

Figure 4–7. Outcome with staging laparoscopy in patients with hepatic colorectal cancer metastases. (HA = hepatic artery; preop = preoperative.) Reproduced with permission from Jarnagin WR, Bodniewicz J, Dougherty, E, et al. A prospective analysis of staging laparoscopy in patients with primary and secondary hepatobiliary malignancies. Ann Surg Oncol [In press].
radiologist is out of the radiology department but ensuring that the maximum benefit from the IOUS is obtained. Open US, like laparoscopic US, continues to be used routinely, but it is likely that the yield will continue to decrease as better imaging becomes widely available.

Outcomes of Resection

Natural History of Colorectal Cancer Metastases

An understanding of the impact of surgical resection in patients with hepatic CRC metastases requires an understanding of the natural history of colorectal metastases to the liver (Table 4–3). Although a randomized study comparing survival in treated and untreated patients has never been done, a number of retrospective studies have addressed the issue of outcomes in patients with unresected liver metastases. Survival after resection is better than that for untreated hepatic metastases, even when only the most favorable unresected cases are considered. Median survival in patients with unresectable disease consistently ranges from 3 to 21 months, and 5-year survival is rare, occurring in less than 2 percent of patients. Survival is most dependent on the extent of hepatic involvement: the more extensive the involvement, the worse the survival. Some authors have attempted to identify retrospectively patients who are not offered resection but who have potentially resectable disease, as determined from data in the clinical record. Wood and colleagues identified 13 patients with disease inferred to be resectable from a total of 126 patients with hepatic metastases. Survival was markedly better in this group of 13, compared to those with unresectable disease. The 1-year survival was 77 percent, compared to 15 percent in the unresectable group; 3-year survival was 23 percent, compared to 0 percent; and 5-year survival was 8 percent. Similarly, a report from the Mayo Clinic compared 141 patients who had resections of CRC hepatic metastases with 70 patients who had potentially resectable tumors treated nonoperatively. Five-year survival in the resection group was 25 percent, compared to 2.5 percent in the unresected group. Scheele compared three groups: 183 patients with resected metastases, 62 patients who had resectable lesions that were not removed, and 921 patients with unresectable disease. The 5-year survival in the resected group was 38 percent while there were no 5-year survivors in the nonoperated groups. Moreover, patients in the resectable but nonoperated group had a median survival of 14 months, compared to 6.9 months for the unresectable group. Conceding the limitations of these retrospective studies, it appears that a patient with disease that is potentially resectable probably has a more favorable tumor biology and a better prognosis than a patient with unresectable disease. However, these data also strongly suggest that resection improves survival, even in the group with favorable biology. Extended survival is associated only with resection, and 5-year survivors represent less than 3 percent of patients in all series of unresected colorectal hepatic metastases.

Alternative Treatments

Extensive experience in treating metastatic CRC with chemotherapy has been obtained over the past two decades. Regimens including 5-fluorouracil (5-FU) with or without the modulation of folinic acid (leucovorin) have been the mainstay of chemotherapy in stage 4 disease. Despite progress in understanding the best timing of dose administration and the emergence of new active agents against metastatic CRC, there are no data to suggest that systemic
chemotherapy is curative in stage 4 disease.\textsuperscript{44,45} Historically, large trials of chemotherapy based on 5-FU have shown overall response rates of 20 to 40 percent and hepatic response rates of 20 to 30 percent. Complete responses are extremely rare, and median survival typically ranges from 10 to 14 months.\textsuperscript{46} Although these results apply to the large group of patients that includes those with predominantly unresectable disease, there is no evidence to suggest that response rates are better in the subset of patients with resectable disease. The contention that the excellent results obtained by resection are solely the result of selection bias is deflated when one considers that 5-year survivors, including disease-free survivors, are not uncommon after resection but are exceedingly rare in untreated or chemotherapy-treated patients.\textsuperscript{18,47,48} We recently reported 96 actual 5-year survivors after hepatic resection. In this group, 74 percent of patients were disease free at 5 years and had a 10-year actuarial survival of 78 percent.\textsuperscript{48} Thus, the benefit of resection is clearly established.\textsuperscript{49}

Additional approaches, including hepatic artery infusion of chemotherapy and novel ablative therapies (cryotherapy and radio-frequency ablation [RFA]), have established roles in the management of CRC metastases in the liver, but no data exist to sug-

\textbf{Figure 4–9.} \textit{A,} Intraoperative ultrasonography examination of the liver. \textit{B,} Intraoperative ultrasonography demonstrates a large metastasis (M) compressing the middle hepatic vein (HVM). The inferior vena cava (IVC) is also shown.
suggest that any of these modalities should supplant resection as the treatment gold standard. The application of cryotherapy and RFA remain limited by tumor size and location. Lesions adjacent to major vascular structures cannot be completely ablated. The potential advantage of RFA is that it is more suited to percutaneous application. On the other hand, RFA is more limited by tumor size than is cryotherapy, and following the progress of the ablation by US is more difficult and imprecise. Cryotherapy should be reserved for those patients who cannot undergo resection although it may have a role in selected cases as an adjunct to resection\textsuperscript{57,58} (Fig. 4–11). Cryotherapy combined with hepatic artery infusion,\textsuperscript{59} cryotherapy for close resection margins,\textsuperscript{60} cryotherapy-assisted resections,\textsuperscript{61} and combined resection and cryotherapy for multiple lesions are examples of novel ways in which resection may be complemented with emerging ablative technologies. Details of these approaches are discussed in other chapters. The increasing complexity of decision making in these cases underscores the benefit of a multidisciplinary planning conference to optimize the planning of treatment for individual patients.\textsuperscript{62}

### Table 4–3. LARGE SERIES EXAMINING THE NATURAL HISTORY OF UNRESECTED UNTREATED COLORECTAL CANCER METASTASES

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Patients</th>
<th>Median Survival (months)</th>
<th>5-yr Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pestana</td>
<td>353</td>
<td>9.0</td>
<td>3</td>
</tr>
<tr>
<td>Cady</td>
<td>269</td>
<td>13.0</td>
<td>1</td>
</tr>
<tr>
<td>Lahr</td>
<td>175</td>
<td>6.1</td>
<td>1</td>
</tr>
<tr>
<td>Wagner</td>
<td>252</td>
<td>19.0</td>
<td>2</td>
</tr>
<tr>
<td>Scheele</td>
<td>921</td>
<td>6.9</td>
<td>0</td>
</tr>
<tr>
<td>Stangl</td>
<td>484</td>
<td>7.5</td>
<td>1</td>
</tr>
<tr>
<td>Rougier</td>
<td>318</td>
<td>5.7</td>
<td>—</td>
</tr>
</tbody>
</table>

**Resection of Colorectal Hepatic Metastases**

Numerous reports have shown that selected patients benefit from resection, resulting in 5-year survival in 20 to 40 percent of patients and disease-free survival in up to 30 percent of patients. Moreover, technical advances and the increasing application of multimodality management to hepatic CRC metastases have expanded the group of patients in whom surgical therapy may be appropriate. Long-term survival and cure are now possible for patients previously considered unresectable.\textsuperscript{1}

Our approach to resection is described elsewhere in this book. It should be stressed, however, that care-
ful study of the technical and anesthetic issues regarding hepatic resection is a key component of successful surgical outcome. The widespread application of surgery to CRC metastatic to the liver is largely due to the effectiveness of resection and the safety with which it can be accomplished. Briefly, we use low–central venous pressure anesthesia and vascular inflow and outflow control before parenchymal transection. Wedge resections are avoided in favor of segmental resections based on hepatic anatomy. With this general approach, we can achieve a median blood loss of less than 700 cc, with 38 percent of patients requiring transfusion during or within 24 hours of surgery and only 53 percent of patients requiring any blood products (packed red blood cells, frozen fresh plasma, or platelets) at any time during hospitalization. The safety of hepatic resection is further reflected by the declining median hospital stay. For the last 1,001 patients who underwent major hepatectomy at Memorial Sloan-Kettering Cancer Center, the median length of stay was 11 days.2 The mortality rate in this large group was 2.8 percent, which has remained stable despite the increasingly large scope of resection.

Despite improvements in liver surgery, complications are not uncommon and may be seen in up to 30 percent of cases. The most common liver-related complications (in addition to general surgical complications) seen after any major resection include hemorrhage, bile leak or fistula, abscess, and liver failure (Table 4–4).1 If treated rapidly and appropriately, most complications do not lead to a poor outcome; indeed, most major centers report mortality rates of less than 5 percent, and most perioperative deaths result from sepsis, hemorrhage, or liver failure. The dramatic improvement in mortality rates over the past decades is due primarily to an improved understanding of hepatic anatomy and to refinements in technique and perioperative management.

Table 4–5 lists large series containing 100 or more patients treated by resection and highlights the

![Figure 4-11. Technique of cryotherapy-assisted resection. A, The cryoprobe and the “freeze ball.” B, C, Cryoprobe and freeze ball are used to guide subsegmental resection of colorectal cancer liver metastasis.](image-url)
5-year survival rates. Of importance, the majority of patients treated with liver resection will develop recurrence. Experience with resection has shown that strategy and technique are ultimately limited by biologic factors. Technical issues that affect patient outcome have been better described than have biologic factors, which are difficult to modulate presently.

An important goal of the ongoing investigation into the natural history of this disease is to better delineate patients who will benefit from resection and to distinguish them from patients with disease that is likely to recur even after complete resection.31 With identification of the latter group, it would be possible to use adjuvant therapies with resection to eradicate microscopic residual disease and improve results.

Several studies have identified a number of factors that influence outcome after hepatic resection for CRC metastases. The “tumor biology” is presently defined by standard clinical and pathologic features of patients and their cancers. This relatively simple approach may change in the near future as various molecular markers are rigorously studied.64,65 Patient factors limiting the application of hepatic resection are few. Medically infirm patients are not considered for hepatic resection although age alone is not a contraindication. We and others have demonstrated that excellent results can be achieved in older patients, with acceptable mortality.66 Most studies show no effect of the sex of the patient on outcome.1

Factors related to the primary tumor help define the tumor biology and influence outcome.1,2 The site of the initial tumor does not have an impact on outcome. There is an adverse relationship between the presence of lymph node metastases associated with the primary tumor and survival following the resection of subsequent liver metastases.1,2 Most studies suggest that liver metastases diagnosed synchronously with the primary tumor have a worse outcome, compared to those metastases diagnosed metachronously. Furthermore, analysis of some series suggests that longer disease-free intervals are associated with a better outcome.1

The characteristics of metastases in the liver also shed light on the biology of the disease. The number of metastases in the liver affects outcome: patients with solitary metastases fare better than those with multiple metastases. Nonetheless, the presence of multiple metastases or bilateral disease is not a contraindication to resection. Although resection of hepatic metastases was initially reserved for patients with solitary metastases, it is now evident that multiple metastases can be resected with the expectation of good results for patients with bilobar and unilobar metastases.3,43 Tumor size and CEA levels have also been identified as prognostic factors. Complete excision, with negative margins, of all disease is the most significant predictor of outcome.2,15

There are now sufficient data to identify factors associated with a high risk of recurrence following hepatic resection.2 Despite this, no single factor should be used to deny resection, because resection affords the possibility of cure and because there is a lack of effective alternatives. In otherwise healthy patients, extrahepatic disease and the inability to resect all disease safely are the generally accepted contraindications. However, even this has been challenged as selected patients with limited metastatic disease to the lungs and liver may also benefit from resection of all disease at both sites. Despite these caveats, it is clear that some patients will benefit more than others from resection. In an effort to identify such patients, we have devised a clinical-risk score that includes five preoperative factors that are independent predictors of survival. This system was
devised after review of clinical, pathologic, and outcome data for 1,001 consecutive patients undergoing liver resection for metastatic CRC.\textsuperscript{2} This group included 237 trisegmentectomies, 394 lobectomies, and 370 resections of less than a lobe. In this group, the operative mortality was 2.8 percent, the 5-year survival rate was 37 percent, and the 10-year survival rate was 22 percent. Multivariate analysis identified seven factors as significant predictors of poor outcome: (1) positive hepatic resection margins, (2) extrahepatic disease, (3) a node-positive primary tumor, (4) a disease-free interval from primary cancer to metastasis of < 12 months, (5) multiple hepatic tumors, (6) the largest hepatic tumor being > 5 cm in diameter, and (7) a CEA level > 200 ng/mL. The last five of these features can be easily identified preoperatively and serve as the basis of a clinical-risk scoring system.\textsuperscript{2} Each adverse factor is worth 1 point, and the final clinical-risk score is the sum. We have shown that this scoring system significantly predicted survival, which was 74 months (median) in patients with a score of 0 and 22 months in patients with a score of 5 (Table 4–6).\textsuperscript{2}

Prognostic systems such as this serve mainly to provide the clinician with a more sophisticated means of assessing the potential benefit of resection. Staging patients in this way allows a more cogent discussion between doctor and patient with respect to the risks and benefits of surgery. In addition, it may delineate those patients who make up a high-risk group and who may be served well by adjuvant therapy. Most important, this system can be used to stratify patients in clinical trials. It should be stressed that this system is meant not to exclude individuals from hepatic resection that represents a potentially curative option, but rather to assess the risk of recurrence and to perhaps select those who should receive additional treatment.

The presence of extrahepatic disease is generally an indication that the patient has diffuse disease and is therefore unlikely to benefit from hepatic resection. However, this tenet has been challenged in the context of pulmonary and liver metastases from CRC.\textsuperscript{72} At Memorial Sloan-Kettering Cancer Center, we have shown that resection of pulmonary and hepatic CRC metastases is associated with extended survival in highly selected patients. A review of 81 patients showed extended survival in a group of patients with hepatic and pulmonary metastatic CRC. With a median follow-up of 3.7 years from resection of the first metastasis and a median follow-up of 2.5 years once a liver and a lung resection had been performed, median survival was 6.0 and 3.8 years, respectively.\textsuperscript{72} This report represents a highly selected group but shows that some patients can be salvaged.

Recurrent disease after hepatic resection generally portends a poor outcome, but some patients may be appropriate for repeat resection. Recurrence of CRC develops in 56 to 78 percent of patients after partial hepatectomy; in approximately half of these patients, the disease is isolated to the liver.\textsuperscript{48} A select few will be eligible for repeat resection after they are shown to have no extrahepatic disease.\textsuperscript{19–23} This procedure may be more technically difficult due to the presence of adhesions and to hypertrophy of the liver remnant. Nonetheless, when done in experienced units, the morbidity and mortality of repeat resection is similar to that of primary resection. In a series of long-term survivors, 43 percent were rendered disease free following repeat hepatectomy for recurrent hepatic CRC. A multi-institutional study

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Risk factors are node-positive primary; disease-free interval < 12 months; > 1 tumor; size > 5 cm; carcinoembryonic antigen level > 200 ng/mL. Each risk factor equals 1 point in scoring.
of 170 patients demonstrated that a 3-year survival of 37 percent and a 5-year survival of 26 percent following resection can be expected in this group.19

Technical surgical advances have had an impact on prognosis following resection of CRC metastases. These advances specifically relate to the safety of resection and to the achievement of negative margins. The need to achieve negative surgical margins cannot be overemphasized. Resection that leaves a positive margin generally results in recurrence although occasional long-term survivors have been reported.3,18,40,47,48 The Gastrointestinal Tumor Study Group showed that curative resection resulted in significantly longer median survival (37 vs 21 months) compared to palliative resection, which yielded results similar to those in unresected patients.73 Although some authors have maintained that margins of at least 1 cm are necessary, we have found that this is not necessarily the case and that negative histologic margins of any depth are acceptable and associated with good outcome.3,18,47

Anatomic resections afford the best chance of achieving negative margins. Lobar and extended lobar resections have typically been used to achieve this end. However, techniques of segmental resection also allow resection of multiple lesions while preserving liver parenchyma.40 This has allowed a more aggressive approach to bilobar disease. We have shown that segmental resections are associated with a much lower incidence of positive histologic margins and consequently with better survival.75 Wedge resection, therefore, should be discouraged for all but the smallest, most peripheral lesions. This has implications for the patient with liver metastases discovered incidentally at operation for primary CRC. In general, attempts at resection in such a context should be avoided, with a plan for further postoperative imaging to fully assess disease extent.

The remarkable regenerative capacity of the liver enables the hepatic surgeon to perform resections of up to 80 percent of hepatic parenchyma in a normal liver without causing hepatic failure. Nonetheless, there are scenarios in which performing extended hepatectomy can be expected to cause hepatic failure if the remnant liver is too small or is abnormal (fatty, fibrotic, or cirrhotic). This is particularly worrisome in the case of a small deep lesion that would require sacrificing a large amount of normal liver tissue. Recently, some investigators reported their experience with preoperative portal vein embolization in an effort to overcome this limitation. With this technique, the portal vein supplying the parenchyma to be resected is embolized before operation. After 2 to 4 weeks, compensatory hypertrophy of the uninvolved side of the liver occurs, thus reducing the amount of functional parenchyma resected.74,75 It is hoped that by inducing hypertrophy of the liver remnant preoperatively, the risk of postoperative hepatic failure will be lowered (Fig. 4–12). It must be emphasized, however, that experience with portal vein embolization is limited, that the indications are not clearly defined, and that no prospective comparison studies have been performed. It remains to be seen whether this technique will find a role in patients with metastatic CRC, especially given the low operative mortality in most large centers.

It is likely that we are approaching the limits of what can be achieved with resection of hepatic metastases. Two challenges for the future are to select patients for resection in the best manner and to determine which patients are at prohibitive risk of recurrence following operation. High-risk individuals may be better served by a strategy that also addresses their risk of micrometastatic disease. Although there is no standard approach to neoadjuvant chemotherapy in high-risk patients, there are data to recommend that approach.74 Some authors have found that patients initially deemed unresectable became subsequently resectable following a course of aggressive chemotherapy.44 More recent approaches to aggressive adjuvant therapy following hepatic resection include hepatic arterial infusion (HAI) and systemic therapy after resection of hepatic metastases from CRC. Kemeny and colleagues have reported that HAI with floxuridine and dexamethasone followed by systemic 5-FU and leucovorin produces better 2-year survival and disease-free survival than systemic therapy alone.76 Finally, the emergence of a newer systemic chemotherapy that has improved activity over chemotherapy based on 5-FU may mean that these agents (eg, CPT-11, oxaliplatin) will find an application in liver resection for CRC. Indeed, trials are under way to test these drugs in this setting.
Summary

Colorectal metastases to the liver are common, and the surgical oncologist is frequently called upon to make a decision about the merits of resection. In general, this decision should be made only after a careful review of the patient’s history and relevant imaging studies. Nearly all patients with metastases found incidentally at operation should undergo resection of the primary tumor, followed by appropriate postoperative radiologic evaluation. The exception is the patient with the solitary peripheral metastasis that may be removed with a wedge resection if there is no evidence of further disease on palpation and intraoperative ultrasound examination. In patients with no evidence of extrahepatic disease and no medical contraindications, our practice is to offer resection if it is technically possible to remove all disease, with negative margins. Resection can be offered irrespective of the patient’s age and the number, location, and size of metastases. Selected patients may benefit from a period of watchful waiting and (possibly) chemotherapy prior to resection of their metastatic disease if aggressive tumor biology is suspected. In addition, patients who are determined to be at high risk of recurrence may be offered neoadjuvant chemotherapy or other therapy aimed at reducing this risk (eg, HAI chemotherapy). Finally, it must be emphasized that hepatic resection can provide long-term survival even in patients with poor prognostic factors.

NONCOLORECTAL NON-NEUROENDOCRINE METASTASES

As most reports are anecdotal, the role of liver resection for patients with noncolorectal non-neuroendocrine liver metastases is not well defined. There are two large published series. Over a 15-year period at Memorial Sloan-Kettering Cancer Center, 96 patients with such tumors underwent hepatic resection. Symptoms were present in 56 percent of patients. Operative procedures included 32 wedge resections, 44 lobectomies, and 20 extended resections. In 30 patients, another organ resection was performed concomitantly. There were no operative deaths. With a median follow-up of 20 months, the overall actuarial survival was 37 percent at 5 years, which is similar to that following resection for metastatic CRC at our institution. Predictors of survival included a disease-free interval greater than 36 months, curative resection, and tumor histology. The best results were achieved in patients with genitourinary tumors (n = 34) who had a 60 percent

Figure 4–12. Top row shows scans before preoperative portal vein embolization demonstrating a flow in the portal vein branch of the segment to be resected. Flow is abolished following portal vein embolization. Additionally, evidence of hepatic parenchymal hypertrophy is seen in the bottom row images after preoperative portal vein embolization.
5-year survival, with 7 (2 adrenal, 3 renal, 1 testicular, and 1 ovarian) actual 5-year survivors. Hepatectomy was performed in 41 patients with soft-tissue tumors (7 melanomas [1 ocular], 7 breast cancers, and 27 sarcomas), with a 5-year survival of 26 percent. Two-thirds of the sarcomas were leiomyosarcomas; the median survival for these patients was 31 months. Resection of gastrointestinal primaries (n = 7) resulted in a median survival of 21 months but no 5-year survivors. Patients with an unknown primary tumor (n = 8) did particularly poorly; all died of disease within 1 year. Similar results were reported in a series of 120 resections for noncolorectal non-neuroendocrine liver metastases. The overall 5-year survival rate was 36 percent; it was 20 percent for breast cancers (n = 35), 46 percent for testicular cancers (n = 20), and > 20 percent for gynecologic tumors. Patients with sarcomas, gastrointestinal malignancies, melanomas, head and neck tumors, and unknown primaries all had poor outcomes.

In other reports, 15 patients with Wilms’ tumor had a median survival of 24 months; at 5 years, there were 4 survivors after resection. In a study of 13 patients with metastatic melanoma to the liver, there was a median survival of 10 months, and only 1 person survived for 5 years. Ocular melanoma represents an important subgroup with a more favorable prognosis. Ocular melanoma has a propensity to metastasize to the liver, which is often the first site of recurrence in some patients. In 19 patients with ocular melanoma who underwent complete resection of all gross liver disease and who received postoperative intra-arterial chemotherapy, there was a median survival of 22 months. However, 16 patients had recurrences at a mean of 14 months.

Resection of noncolorectal non-neuroendocrine liver metastases is rarely indicated. However, in highly selected patients with a long disease-free interval, resection may be reasonable, and prolonged survival may be achieved. A period of observation prior to surgery may reveal the biology of the tumor to determine the suitability of resection (i.e., some patients’ cancer may rapidly progress during a short period of observation, indicating that their tumors are biologically unfavorable and not amenable to benefit from surgical resection). Hepatectomy may be indicated to palliate symptoms, accurately stage or diagnose a patient, or debulk disease prior to adjuvant therapy. Concomitant resection of extrahepatic disease may also be necessary. Patients with testicular or ovarian liver metastases appear to have the best outcome after partial hepectectomy and should be considered for resection to remove residual disease after systemic chemotherapy. Patients with metastatic disease from other primary lesions (melanoma, breast, and gastrointestinal) should be approached with caution, given the high rates of recurrence in these patients. Patients with metastatic sarcoma may benefit more from hepatic resection than previously reported. Given the lack of effective alternative treatments, this group of patients is difficult to manage. Chemotherapy and other interventions have not proven effective. Furthermore, transplantation in these patients should not be considered; less than half of 27 patients in one study survived 1 year.

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80. DeMatteo RP, Minnard EA, Kemeny N, et al. Surgical resection of both hepatic and pulmonary metastases in patients with CRC. (submitted)