Surgical Treatment of Liver Metastases

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Approximately 50% to 60% of patients with colorectal cancer will develop hepatic metastases during the course of their illness, with 20% to 30% of patients having liver metastases at time of diagnosis. In nearly a quarter of these patients the liver is the only site of disease. Surgical resection of isolated hepatic metastases has been associated with a 27% to 37% 5-year survival and confers a survival advantage compared to patients not undergoing resection. Thorough preoperative and intraoperative evaluation is necessary to select appropriate surgical candidates who may benefit from resection. This article examines criteria useful in patient selection, and also reviews the management of recurrent hepatic metastases and the role of repeat hepatic resection.

AN ESTIMATED 135,400 persons developed colorectal cancer in 2001.[1] Fifty percent of patients with colorectal cancer will develop metastatic disease, and nearly 20% of patients have evidence of liver metastases at the time of diagnosis.[2] Due to the unique venous drainage of the gastrointestinal tract through the portal vein, the liver is the most common site of distant metastases. Of the patients who develop liver metastases, one quarter will have disease isolated to the liver and only 10% to 25% will be candidates for surgical resection.[3] An analysis of more than 1,500 autopsies in patients with colorectal cancer revealed that 44% had hepatic metastases and the liver was the sole site in nearly half of these patients (overall, 20%).[4]

NATURAL HISTORY

Understanding the benefit of surgical resection of colorectal cancer liver metastases requires knowledge of the natural history of these lesions. The outcome of untreated hepatic metastases is dismal, with a median survival of less than 12 months.[5-7] However, these studies are retrospective, with the majority of patients having advanced disease with a large tumor burden. Furthermore, these studies (reported in the 1960s and 1970s) were conducted without the advantage of modern imaging modalities.

No randomized trial comparing resection, chemotherapy, and observation in patients with potentially resectable liver metastases has been performed, although several retrospective studies have reviewed the outcome of patients treated nonoperatively who had potentially resectable hepatic metastases. Scheele et al[8] reviewed the outcome of 288 patients with resectable liver metastases as determined at the time of laparotomy, of which 62 patients did not undergo resection. In the resected group, a 5-year survival rate of 38% was observed in contrast to no 5-year survivors in the nonresected group. Furthermore, they noted that the outcome of patients with residual microscopic or minimal macroscopic disease after resection was similar to the group of patients who did not undergo resection. A series from the Mayo Clinic compared 141 resected patients with 70 patients not resected (all of whom were considered resectable) and reported similar findings.[9] They observed a 5-year survival rate of 25% for patients who were resected and only 2.5% for patients who were not resected. Wilson and Adson[10] compared the outcome of 120 patients (60 patients in each group) who were matched with regards to sex, age, size, and number of hepatic lesions. The outcome of patients was similar in this study, with no 5-year survivors in the group not resected and a 5-year survival of 25% for the resected group. Although these studies are limited because they are retrospective analyses, they strongly suggest a survival advantage for patients who undergo resection of colorectal liver metastases. This concept is widely accepted by the medical community, rendering the possibility of a prospective randomized trial unlikely, and potentially unethical.

LONG-TERM RESULTS

Multiple recent studies have demonstrated 5-year overall survival rates following hepatic resection for colorectal metastases ranging from 27% to 37% (Table 1).[11-15] A median survival of 30 to

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0093-7754/02/2902-0006$35.00/0

doi:10.1053/sonc.2002.31676

Table 1. Results of Hepatic Resection for Metastatic Colorectal Cancer

Study	Year	No. of Patients	5-Year Survival (overall)	Median Survival (mo)
Hughes et al[11]	1986	607	33%	—
Scheele et al[12]	1995	434	33%	40
Nordlinger et al[13]	1996	1,568	28%	—
Jamison et al[14]	1997	280	27%	33
Fong et al[15]	1999	1,001	37%	42
Iwatsuki et al[20]	1999	305	32%	—

40 months has been reported in these patients, in contrast to a median survival of 12 to 18 months for patients treated with chemotherapy only (5-flourouracil–based). Long-term follow-up of these patients has documented a 10-year survival rate of 20%.[14,16,17] Furthermore, the majority of patients (>70%) who are alive and disease-free after 5 years can expect to survive for another 5 years. Clearly, surgical resection of hepatic metastases significantly prolongs survival, and in a subset of patients is curative.

PROGNOSTIC FACTORS

Despite the apparent benefit of surgical resection of hepatic metastases, this is only applicable to a minority of patients. The majority of patients will develop recurrent disease during the course of their illness.[11,18] Furthermore, as many as 20% of patients have evidence of metastatic disease within 6 months of resection.[19] Many investigators have identified a variety of prognostic factors that predict outcome following hepatic resection that could be used to enhance results by optimizing patient selection. Table 2 provides a compilation of these prognostic factors from several reports.[12-15,19-23]

Extrahepatic Disease

One of the most critical elements in the evaluation of potential surgical candidates is determining the extent of metastatic disease. The presence of extrahepatic disease is often considered a contraindication to hepatic resection. In evaluating the data, it is important to understand the investigator's definition of extrahepatic disease. In general, the presence of extrahepatic disease (even if completely resected) is associated with decreased survival.[14,15,20] In a review of 1,001 patients treated at Memorial Sloan-Kettering Cancer Center, patients with extrahepatic disease had a 5-year survival rate of 18% (median duration, 29 months), compared to 38% in patients without

Table 2. Negative Prognostic Factors Affecting Overall Survival Following Hepatic Resection of Colorectal Metastases

Study	Age	Primary Tumor Stage	No. of Lesions	Size	Satellite Lesions	Bilobar	Margins (<1 cm)	Disease-Free Interval	Preoperative CEA	Extra-hepatic Disease
Fong et al[15]		+	+ (>1)	+ (>5 cm)			+	+ (<1 yr)	+	+
Iwatsuki et al[20]			+ (>2)	+ (>8 cm)		+	+	+ (<30 mo)		+
Lise et al[19]		+	+ (>1)	+ (>3 cm)			+			
Cady et al[22]			+ (>3)		+		+		+	
Nordlinger et al[13]	+	+	+ (>3)	+ (>5 cm)			+	+ (<2 yr)	+	
Jamison et al[14]										+
Wanebo et al[23]			+ (>3)			+				
Scheele et al[12]		+		+ (>5 cm)	+			+*		
Doci et al[21]		+								

* Synchronous disease.

extrahepatic disease.[15] Patients with involvement of adjacent structures by direct extension constituted the majority of patient in the extrahepatic subset. The presence of noncontiguous extrahepatic disease is also associated with decreased survival.[24] The presence of an anastomotic recurrence of the primary tumor should not dissuade the physician from resecting any hepatic metastases, as long as complete resection of both sites is possible.

In the case of portal, hepatic, or celiac lymph node metastases (which is the drainage of the liver), the perihepatic lymph node metastases are believed to be the result of "remetastasis" or metastases from the liver metastases.[25,26] In a retrospective review of more than 850 patients in the Registry of Hepatic Metastases, metastatic lymphadenopathy (portal and celiac nodes) was documented in 24 patients (3%). This subset of patients had markedly decreased survival with no 5-year survivors reported, despite resection of the hepatic and lymph node metastases.[24] The finding of positive portal or celiac nodes is considered a contraindication to liver resection.

The lung is the second most common site of metastatic spread from colorectal cancer. A small minority of patients will develop isolated pulmonary and hepatic metastases, both of which are resectable. Information regarding outcome of combined resections in this highly selected patient population is limited. Nevertheless, a median survival of 2 years and a 5-year survival rate of 30% following hepatic and pulmonary metastectomies have been reported.[27,28] The presence of malignant thoracic lymph nodes, a short disease-free interval, and a high preoperative carcinoembryonic antigen (CEA) level have been associated with poor prognosis.[27-29]

Margins

Surgical management of hepatic metastases includes complete resection with a 1-cm microscopically negative margin when possible. Failure to achieve a negative margin is associated with a worse prognosis.[13,15,19,20,22] The Gastrointestinal Tumor Study Group demonstrated that patients with positive resection margins (noncurative) had a significantly shorter median survival compared to those with negative resection margins (curative).[30] Further analysis revealed that patients with "noncurative" resections had a life expectancy similar to that of patients with unresectable disease. In a review of 350 patients undergoing "potentially curative" resections, Scheele et al observed that noncurative resections, palliative resections (macroscpic tumor left), and patients with unresectable lesions had similar survival curves that were significantly shorter when compared to patients with potentially curative resection.[12] Furthermore, they reported that patients with minimally negative microscopic margins (1 to 9 mm) had a decreased 5-year survival (34%) compared to patients with margins greater than 10 mm (41%) ($P = .009$). A similar survival benefit was detected in the Registry of Hepatic Metastases, that is, a 5-year survival of 47% when the margin was greater than 1 cm versus 23% when the margin was $\leq$ 1 cm ($P < .01$).[24] The presence of positive margins may also adversely impact hepatic recurrence. In a multi-institutional analysis of patterns of recurrence, Hughes et al[11] documented a significant increase in hepatic recurrence in patients with positive margins (68%) versus those with negative margins (41%) ($P < .001$). Of all the technical factors analyzed by Cady et al, the only significant variable to affect outcome was resection margin.[22] They also observed improved survival in patients with negative margins $\geq$ 1 cm versus negative margins less than 1 cm. The importance of a complete resection cannot be overemphasized.

Primary Tumor Stage

In general, patients with lymphatic spread from their primary colorectal cancer have a decreased survival rate compared to patients without lymphatic spread, and are candidates for adjuvant chemotherapy.[31] The stage of the primary cancer is a prognostic factor for liver resection. Patients whose primary colorectal cancer was stage II (Dukes' B) have an improved outcome compared to patients with stage III (Dukes' C) tumors.[12,13,15,19,21] In an analysis of 1,001 patients with resected colorectal hepatic metastases, the 5-year survival for node-negative patients was 41% compared to 32% for node-positive patients ($P = .05$).[15] Despite the reduced survival associated with node-positive tumors, patients with stage III (Dukes' C) colorectal cancer who develop resectable hepatic metastases should not be excluded from surgical therapy.

Number of Liver Metastases

Multiple investigators have shown that the number of metastatic lesions is probably a prognostic indicator of patient outcome following liver resection.[13,15,19,20,22,23] However, the number of lesions reported as a poor prognostic factor in these studies varies from one to four or more. Intuitively, increasing number of lesions suggests a more aggressive tumor biology and portends a worse outcome. This has been demonstrated clinically with decreasing survival when the number of lesions resected increases from one to four.[15,20] A review of the Hepatic Metastases Registry of 100 long-term survivors identified only a few 5-year survivors (<3%) who had four or more lesions resected.[16] More recent reports have observed a 5-year survival from 9% to 23% in patients with four or more lesions.[20,24,32] Weber et al[32] reviewed their experience with 155 patients who had had four or more lesions. Even in patients with nine to 20 metastases resected, a 5-year survival of 14% was reported. Multivariate analysis identified increasing number of metastases and positive resection margin as independent prognostic factors for decreased survival. Logically, as the number of metastases increases, complete resection with negative margins is more difficult, and nearly a quarter of the patients with nine to 20 metastases had positive resection margins. Although the number of lesions is a strong predictor of outcome, the number of metastases should not be considered an absolute contraindication to surgery. The inability to resect all gross disease with an acceptable negative margin needs to be taken into account, and 5-year survival remains superior to that of systemic chemotherapy.

Size of Metastases

Some studies have demonstrated that increasing tumor size (of largest metastasis) is a poor prognostic factor.[12,13,15,19,20] However, the size limit for developing prognostic scores is less agreed upon, as the size of the metastases evaluated in these series has ranged from greater than 3 cm to greater than 8 cm. The true impact of this variable is controversial, as several studies have failed to observe any influence on survival.[14,22,23] Currently, an absolute size limit for attempting curative surgical resection has not been determined.

Disease-Free Interval

Increasing disease-free interval has been reported to be associated with improved survival.[13,15,20] The intervals of time analyzed range from 12 months to 30 months. The development of hepatic metastases more than 2 to 3 years after the treatment for primary colorectal cancer represents a more indolent biological behavior, and is thus more likely to be associated with a better prognosis. Nonetheless, even patients with a disease-free survival of less than 12 months can achieve a durable survival. Interestingly, over half of the patients from two studies (N = 198) of long-term survivors (>5 years) had a disease-free interval of less than 12 months.[16,17]

Nearly 20% of newly diagnosed colorectal cancer patients will have synchronous hepatic metastases.[2] Scheele et al[12] observed a median survival of 27 months for patients with synchronous disease versus 37 months for metachronous disease, and a similar decrease in disease-free survival was also noted (13 *v* 23 months, respectively). In a retrospective review, Rosen et al[33] reported that, of 120 patients who presented with stage IV colorectal cancer, patients with resectable hepatic metastases had a survival advantage over patients who were not resected (median survival, 30 months *v* 10 months, respectively). In contrast to the development of delayed hepatic metastases, the presentation of synchronous metastases, particularly multiple, suggests an aggressive biologic behavior.

Miscellaneous

Other possible predictors of outcome include age,[13] presence of satellite lesions,[12,22] bilobar distribution,[20,23] and preoperative CEA level.[13,15,22] The prognostic significance of an elevated CEA level was reported by Cady et al, who observed no long-term disease-free survivors (>36 months) in patients with a CEA level greater than 200 ng/mL.[22] This finding was confirmed by Fong et al, who documented a 5-year survival rate of 24% in patients with a CEA level greater than 200 ng/mL compared to 38% when the CEA level was less than 200 ng/mL ($P = .003$).[15] The significance of satellite lesions is less conclusive secondary to the lack of a uniform definition of satellitosis.

No prognostic factors should be used to exclude an attempt at curative resection, with the exception of involved portal nodes and unresectable extrahepatic disease (see Table 3).

Table 3. Contraindications for Resection of Hepatic Colorectal Metastases

Presence of unresectable extrahepatic disease
Inability to preserve an adequate reserve of functional hepatic tissue
Presence of portal or celiac lymph node metastases

PREOPERATIVE EVALUATION

The preoperative evaluation for potential candidates of hepatic resection for colorectal metastases includes an assessment of their underlying medical condition, determining extent of extrahepatic disease, and the resectability of liver metastases.

Medical Condition

Technical advances in liver surgery and improvements in perioperative care during the last three decades have permitted patients who are otherwise medically fit to undergo hepatic resection with minimal morbidity and mortality. Operative risk assessment is similar to other major abdominal procedures, but particular attention to pulmonary and cardiac complications should be noted. The development of a sympathetic right pleural effusion postoperatively is common and usually well tolerated in patients with normal pulmonary reserve. Additionally, major hepatic resections can be associated with dramatic fluid fluctuations, which can compromise cardiac function in patients with underlying heart disease. Routine measurement of hepatic parenchymal function is not indicated, as most patients with colorectal metastases do not have underlying liver disease. The presence of hepatomegaly, ascites, or jaundice should raise the suspicion of massive replacement of liver parenchyma with tumor. In the absence of cirrhosis or fatty liver, as much as 75% of the liver can be resected without significantly increasing the risk for postoperative liver failure.

Extent of Extrahepatic Disease

Most patients with extrahepatic disease do not benefit from surgical resection of their hepatic metastases. Therefore, preoperative evaluation to determine the presence of extrahepatic disease is necessary to identify patients who can be spared an unnecessary abdominal exploration. The most common sites of extrahepatic disease are lung, colon (anastomosis), and peritoneal, portal, and celiac lymph nodes.

A detailed history and physical examination along with complete blood cell count and serum chemistry panel are performed. Unexplained or recent complaints of bone pain warrant investigation with a bone scan; however, the yield of routine bone scans is low and is not justified. Evaluation for lung metastases is performed with a routine chest radiograph and the presence of suspicious lesions is further investigated with computed tomography (CT) scan of the chest. Percutaneous biopsy, thoracoscopy, and thoracotomy are utilized if histologic confirmation of pulmonary metastases is necessary. The routine use of chest CT scans for detecting pulmonary metastases is of questionable value. A recent study described 100 patients with normal chest radiographs and resectable hepatic metastases who underwent chest CT scans.[34] Abnormal lesions detected on CT scans were evaluated by thoracotomy and thoracoscopy prior to liver resection. Of the 100 patients with negative chest radiographs, 11 had abnormal CT scans, with four patients having malignant lesions of the lung (three metastatic colorectal cancers and one primary lung cancer). The authors conclude that the low positive yield (4%) and the low positive predictive value (36%) in the setting of a negative chest radiograph do not warrant the use of routine chest CT in the evaluation of patients with hepatic metastases.

Preoperative evaluation of the colon and rectum is performed to detect the presence of a second primary or recurrent disease. A recent (within 1 year) colonoscopy is recommended to rule out intraluminal extension of recurrent tumor and for the detection of a metachronous primary colorectal cancer (which can occur in as many as 9% of patients).[35] CT has limited ability to detect peritoneal implants or low-volume locally recurrent disease.

Use of newer imaging modalities to assess the extent of metastatic disease has included positron emission tomography (PET). Studies comparing PET scans with conventional CT scans have demonstrated enhanced detection of both extrahepatic disease and liver metastases.[36,37] The increased sensitivity and specificity of PET has recently been confirmed by a meta-analysis.[38] The investigators

reported a sensitivity of 97% and a specificity of 76% of PET scan for detecting recurrent colorectal cancer. This imaging modality may prove useful in detecting occult disease in patients with an unexplained rise in their CEA level.[39,40] The use of PET scanning in the preoperative evaluation in patients with known liver metastases has recently been reported in two studies (N = 58 patients).[41,42] Occult extrahepatic disease was detected in 15 patients (26%) and management was altered in 16 (28%). Although promising, the disadvantages of PET scan are the expense and lack of availability.

Distribution of Liver Metastases

The role of hepatic imaging is to delineate the size, extent, and location of hepatic metastases, and their relationship to major vascular structures. CT is commonly utilized as it allows assessment of the liver as well as extrahepatic sites. With the use of intravenous contrast, hepatic metastases appear as hypoattenuated lesions during the portal venous phase.[43] The sensitivity of contrast-enhanced "spiral" CT scan has been reported between 50% and 80%, although the sensitivity declines dramatically for lesions less than 1 cm in diameter.[44,45]

The liver derives most of its blood supply from the portal vein. In contrast, liver metastases (>3 mm in size) are perfused almost exclusively by the hepatic artery.[46] In an effort to increase the sensitivity, CT arterial portography (CTAP) was developed in the attempt to take advantage of the dual blood supply to the liver. This technique involves the injection of contrast via a catheter in the superior mesenteric artery (SMA) and obtaining images during the portal venous phase, with metastases appearing as hypodense lesions. Overall sensitivity for detection of hepatic metastases using CTAP ranges from 85% to 94%.[44,47,48] The major limitations of CTAP are the invasive nature of the procedure (visceral arterial manipulation) and the cost. Furthermore, the frequent appearance of perfusion defects contributes to a false-positive rate of 15%.[49] However, if a chemotherapy pump is to be placed at the time of liver resection, an arteriogram is useful and CT portography can readily be done.

Magnetic resonance imaging (MRI) is another modality available for the preoperative assessment of patients with colorectal metastases. In addition to its ability to detect metastases, MRI provides excellent anatomical information with respect to major vascular involvement. MRI can also assist in differentiating metastases from other benign lesions such as benign cysts and hemangiomas. The recent advances in liver contrast agents, mangafodipir (Mn-DPDP) and ferumoxides, makes MRI a more versatile radiographic test. Mn-DPDP is composed of manganese bound to a pyridoxyl phosphate ligand and is taken up by hepatocytes, whereas metastases lack the ability to take up Mn-DPDP and appear hypointense compared with the enhanced liver parenchyma on T1-weighted images.[43] Ferumoxide, composed of iron oxide particles, is cleared by the reticular endothelium system (Kupffer cells), which metastases lack, and appear as enhanced lesions on T2-weighted images. Recently, ferumoxides-enhanced MRI has been shown to be as sensitive as CTAP in detecting liver metastases.[50]

LIVER RESECTION

Following preoperative assessment, candidates for surgical resection are further evaluated intraoperatively for any contraindications to resection.

Nomenclature

Liver resection is founded on the anatomic description by Couinaud,[51] who divided the liver into segments based on venous anatomy (Fig 1). The right and left hemilivers are supplied by the right and left portal vein, respectively. Further subdivision of the portal vein delineates the liver into eight segments. Major hepatic resections are based on this segmental anatomy. However, nomenclature used to describe major resection is not standardized and can vary from country to country and even from institution to institution, resulting in confusion when trying to analyze the literature. As a result, Strasberg has issued a plea for uniform terminology.[52]

Operative Considerations

The initial operative step is to exclude the presence of any contraindications to hepatic resection, such as the presence of extrahepatic disease or unresectable hepatic lesions. This is typically accomplished via an exploratory laparotomy through a subcostal or midline incision. Recently, interest

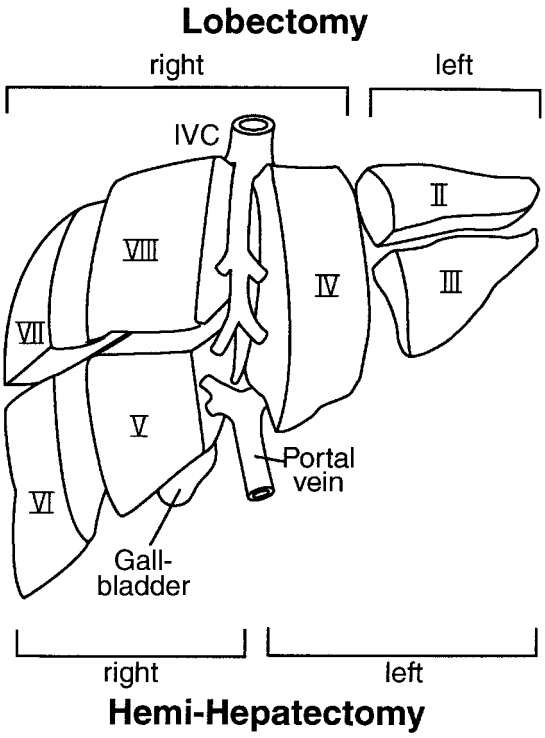

Fig 1. Schematic representation of the segmental anatomy of liver as described by Couinaud.[51] Segments of liver resected by either right or left lobectomy and hemihepatectomy are depicted.

in minimal access surgery has led to the increasing use of laparoscopy for staging patients with hepatic tumors.[53-56] Diagnostic laparoscopy prior to liver resection has demonstrated factors precluding curative resection (detection of peritoneal disease and additional hepatic tumors) in 25% to 48% of patients deemed resectable during preoperative evaluation. The false-negative rate of laparoscopy (finding unresectable disease at laparotomy after a negative laparoscopy) has been reported to be less than 15%.[27,54] The percentage of patients who successfully underwent hepatic resection after staging laparoscopy (83% to 93%) is significantly greater than patients undergoing operative assessment without laparoscopy (58% to 66%). In an effort to increase the yield of staging laparoscopy, Jarnagin et al[57] propose applying a clinical scoring system based on the characteristics of the primary tumor and hepatic metastases. Patients with a low score had a 12% chance of having occult disease versus 42% for patients with a high score (Table 4). In general, staging laparoscopy can prevent an unnecessary laparotomy, which results in shorter hospital stay and earlier return to normal activity.

After excluding the presence of extrahepatic disease, including sampling of portal and celiac lymph nodes, the next step is to thoroughly assess the extent of hepatic metastases. Intraoperative ultrasound (IOUS) examination of the liver is considered to be the most sensitive method. This imaging modality can provide information regarding number of metastases, as well as relationship to major vascular structures. Occult metastases can be identified in approximately 15% to 25% of patients evaluated with IOUS,[58,59] even when highly sensitive imaging modalities such as CTAP are used to evaluate patients preoperatively.[60] In addition, IOUS has been reported to change the operative management in as many as 15% of patients.[59,61] Cady et al[22] have suggested that the routine use of IOUS has increased their ability to obtain negative resection margins, which as mentioned previously is one of the most important prognostic variables. The development of ultrasound instrumentation for minimal access surgery permits thorough examination of the liver via laparoscopic ultrasound probes, with several studies reporting useful staging information obtained with this imaging technique.[53,62,63]

The use of anatomical (based on segmental anatomy) versus nonanatomical (wedge) resection in the management of colorectal hepatic metastases is controversial. Regardless of which resection technique is used, a surgical margin of 1 cm or more is desired. Limited nonanatomical resections

Table 4. Criteria Used in Clinical Risk Score to Determine Yield of Resectability With the Use of Diagnostic Laparoscopy Prior to Resection of Colorectal Hepatic Metastases [57]

Risk factor (each factor is 1 point)
Lymph node positive primary tumor (stage III)
Disease free interval <12 months
CEA >200 ng/mL
More than 1 metastasis*
Size of largest metastases >5 cm*
Likelihood of detecting radiographically occult disease:
Score ≤2, 12%
Score >2, 42%
P value, .001

* Based on preoperative imaging.

have been associated with positive margins in up to 30% of patients.[8] Scheele et al have reported a significant survival benefit with the use of anatomical versus atypical ("wedge") resection, with 5-year survival rates of 37% versus 20%, respectively.[12] While others have reported no difference in outcome between these two techniques,[13,64,65] one series has reported improved prognosis with nonanatomical resection.[21] However, meaningful comparison of outcome by the extent of resection is difficult, as patients with small tumors amenable to limited resection may have a more favorable prognosis.[66] The Registry of Hepatic Metastases indicates that patients with a solitary lesion greater than 4 cm had markedly improved outcomes following anatomical resection.[24]

Complications

Multiple large series have demonstrated the safety of hepatic resection for colorectal metastases, and these are summarized in Table 5. Overall, the postoperative mortality rate is less than 4%, with the majority of deaths due to perioperative hemorrhage, infection, and liver failure.[12,13,20,22,67,68] With proper patient selection, liver failure occurs in less than 5% of patients despite aggressive surgical resection.[12,22,67,68] Postoperative morbidity occur in less than a quarter of the patients and includes complications common to all major abdominal operations.[12,13,20,22,67,68] Complications related to liver resection include perihepatic abscess, bile leak, bile fistula, and sympathetic plueral effusion (which may require drainage in as many as 10% of patients). Several centers have tried to determine predictive factors for the development of postoperative complications and they include major hepatic resections, tumor size greater than 5 cm, combined resection of primary colorectal cancer and hepatic resection, and intraoperative blood loss.[13,65,68] With careful patient selection and preoperative evaluation, most patients can tolerate hepatic resection with minimal risk of mortality and acceptable morbidity.

RESECTION OF RECURRENT COLORECTAL METASTASES

Despite careful selection of patients for resection of colorectal metastases, a significant percentage of patients will develop recurrent disease. The liver is the most common site of recurrence (50% to 60% of patients) and may be the only site in as many as 40% of patients who recur.[11,18] With the decreasing morbidity of liver resection during the last three decades, there has been increasing enthusiasm for performing repeat hepatic resection in a select group of patients who have isolated liver recurrences. Among these patients, comparable survival rates to patients undergoing initial hepatic resection have been reported (Table 6).[69-75]

In a retrospective multicenter analysis of 170 patients from 20 centers in Europe and the United States, a 5-year survival rate of 32% was reported.[72] This was accomplished with an acceptable postoperative complication rate (20%), which is similar to the morbidity rate reported by other centers.[71,74] Although no mortality data were documented in this review, multiple series have reported a perioperative mortality rate of 5% or less.[69-71,73-75]

Many series have attempted to identify significant prognostic factors for survival after repeat

Table 5. Mortality and Morbidity Following Liver Resection for Colorectal Metastases

Study	Mortality (30-day postoperative)	Morbidity	Hepatobiliary Complications*	Infectious Complications
Scheele et al[12]	4%	16%	8%	3%
Iwatsuki et al[20]	1%†	8%	—	—
Nordlinger et al[13]	2%	23%	—	—
Cady et al[22]	4%	—	3%	6%
Fong et al[67]	3%	24%	4%	6%
Doci et al[68]	2%	18%	6%	8%

* Hepatobiliary complications include liver failure, biliary fistulas and bile duct injuries.
† 60-day mortality.

Table 6. Outcome After Repeat Hepatic Resection for Recurrent Colorectal Metastases

Reference	Year	No. of Patients	Perioperative Mortality	Overall Survival	Median Survival (mo)
Que and Nagorney[69]	1994	21	5%	43% (4 year)	41
Fong et al[70]	1994	25	0	44% (2 year)	30
Nordlinger et al[71]	1994	116	1%	33% (3 year)	24
Fernandez-Trigo et al[72]	1995	170	NS	32% (5 year)	34
Tuttle et al[73]	1997	23	0	32% (5 year)	40
Adam et al[74]	1997	64	0	41% (5 year)	46
Yamamoto et al[75]	1999	90	0	31% (5 year)	31

hepatic resection. However, these studies are retrospective, contain few patients, and span many years, so interpretation should be performed with caution. Not surprisingly, the same factors that predict favorable outcome after initial resection apply to repeat resection, and include complete extirpation of metastases with negative microscopic margins,[72,74,75] absence of extrahepatic disease (including regional lymphadenopathy),[75] disease-free interval of more than 1 year from time of initial resection to the development of recurrent disease,[74] and the presence of fewer than four lesions.[75]

Despite the lack of prospective data, long-term survival after repeat liver resection for metastatic colorectal cancer is achievable. In a review of 96 five-year survivors from Memorial Sloan-Kettering Cancer Center, nearly 20% of patients were rendered disease-free after undergoing repeat liver resections.[17] Several tertiary referral centers have reported favorable outcome after multiple resection, with some patients having as many as four resections.[71,74,75] Although these patients' tumors may be biologically more favorable, repeat hepatic resections can safely provide durable survival in a select group of patients.

SURGICAL MANAGEMENT OF UNRESECTABLE METASTASES

The majority of patients with colorectal cancer metastatic to the liver are unresectable. The main determinants of resectability include extent of tumor burden in liver, involvement of major vascular structures, and presence of extrahepatic disease. Treatment of patients who are not candidates for surgical resection is often limited to chemotherapy, which produces tumor regression in a minority of patients and rarely results in long-term survival. A small number of centers have reported their experience with the administration of chemotherapy followed by hepatic resection in patients who were initially considered unresectable by conventional criteria.[76-79] In the largest series, Bismuth et al[79] described 330 patients with unresectable metastases treated with systemic chemotherapy (5-fluorouracil, folinic acid, and oxaliplatin). After treatment (mean, 8 months), 53 patients (16%) were observed to have sufficient tumor response that permitted liver resection with curative intent. They report a 5-year survival of 40% after resection. Subset analysis revealed a 5-year survival of only 14% for the group of patients who were deemed unresectable due to the presence of extrahepatic disease. Overall, the experience using chemotherapy to downstage hepatic metastases is limited. Little is known regarding which regimen will be most effective, or regarding the optimal mode and duration of delivery. The use of neoadjuvant therapy in the setting of resectable hepatic metastases has not been evaluated and cannot be justified outside the scope of a clinical trial. Nevertheless, patients receiving chemotherapy for metastatic disease should be periodically re-evaluated for resection, as this is the only potentially curative treatment.

ADJUVANT THERAPY

Even with complete surgical resection of colorectal liver metastasis, extrahepatic and intrahepatic recurrences are common. The use of regional therapy to deliver high doses of therapeutic agents to the liver without significant systemic effects, hepatic arterial infusion (HAI), is a very attractive strategy for the management of undetected micro-

scopic residual disease. This approach has been the subject of many reports and is discussed in great detail elsewhere in this issue.

In contrast, the use of systemic chemotherapy in the postoperative setting has not been thoroughly investigated. In a review of 82 patients from four trials, Lorenz et al[80] did not detect any survival advantage with the use of adjuvant chemotherapy following liver resections. However, the small sample size and the experimental design of these studies preclude any meaningful conclusion. Nevertheless, two recent retrospective studies have reported favorable outcomes following use of adjuvant therapy (5-fluorouracil–based regimens) in comparison to controls.[81,82] In these two studies, the method of adjuvant chemotherapy administration included systemic or regional. Clearly, a multicenter prospective randomized study will be required to thoroughly address this issue. Even so, many clinicians justify using adjuvant chemotherapy following liver resection on the basis of the efficacy of adjuvant therapy in stage III disease.[31]

SUMMARY

Isolated colorectal hepatic metastases amenable to surgical resection occur in a minority of patients with colorectal cancer. However, in patients in whom resection is possible, a survival benefit for complete extirpation of all gross disease with negative margins exists when compared to no resection. Identifying which subset of patients would most likely benefit requires accurate preoperative and intraoperative assessment. Contraindications to surgery include the presence of unresectable extrahepatic disease, the involvement of portal nodes, and the inability to preserve adequate functional hepatic tissue. Liver resection is tolerated well, with low mortality and morbidity. A significant portion of patient will develop recurrent disease or systemic metastases. Some patients with recurrent hepatic disease may be candidates for repeated liver resection with the potential for a durable survival. To diminish the risk of recurrence following hepatic resection of colorectal metastases, the use of adjuvant chemotherapy seems attractive, but the contribution of chemotherapy has yet to be determined.

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