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Expanding Criteria for Resectability of Colorectal Liver Metastases

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Identify the criteria for hepatic resection of colorectal metastases.
2. Describe strategies for expanding the number of patients who may potentially benefit from hepatic resection.
3. List the factors associated with poor prognosis following hepatic resection.

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ABSTRACT

Surgical resection is the treatment of choice in patients with colorectal liver metastases, with 5-year survival rates reported in the range of 40%–58%. Over the past 10 years, there has been an impetus to expand the criteria for defining resectability for patients with colorectal metastases. In the past, such features as the number of metastases (three to four), the size of the tumor lesion, and a mandatory 1-cm margin of resection dictated who was “resectable.” More recently, the criteria for resectability have been expanded to include any patient in whom all disease can be removed with a negative margin and who has adequate hepatic volume/reserve. Specifically, instead of resectability being defined by what is removed, decisions concerning resectability now center around what will remain after resection. Under this new paradigm, the number of patients with resectable disease can be expanded by increasing/preserving hepatic reserve (e.g., portal vein embolization, two-stage hepatectomy), combining resection with ablation, and decreasing tumor size (preoperative chemotherapy). The criteria for resectability have also expanded to include patients with extrahepatic disease. Rather than being an absolute contraindication to surgery, patients with both intra- and extrahepatic disease should potentially be considered for resection based on strict selection criteria. The expansion of criteria for resectability of colorectal liver metastases requires a much more nuanced and sophisticated approach to the patient with advanced disease. A therapeutic approach that includes all aspects of multidisciplinary and multimodality care is required to select and treat this complex group of patients. The Oncologist 2008;13:51–64

INTRODUCTION

The incidence of colorectal cancer is approximately 150,000 new cases per year in the U.S. [1]. Approximately one half of these patients either present with hepatic metastases or develop them during the course of their disease [2]. These hepatic metastases are discovered synchronously in

15%–25% of patients [3–5], while 20%–25% of patients metachronously develop hepatic tumors [6–8]. In 30%–50% of patients with either synchronous or metachronous liver metastases, the liver is the only site of metastatic disease [9]. Thus, 10,000–15,000 patients per year are candidates for local therapy for colorectal metastases [8].

Although ablative therapies are frequently used, resection of liver metastases, when possible, remains the preferred therapy for potential cure [10]. The overall 5-year survival rates are in the range of 35%–58% in the major series reporting on the results of hepatectomy with curative intent [10–19]. Patients with untreated metastatic colorectal cancer have a short median survival time of approximately 12 months [20–24]. Although the progress of developing effective agents has accelerated, the median survival time of unresected patients is still in the range of 16–24 months, and survival beyond 5 years is uncommon [25–36]. Given that surgical resection remains the best chance for cure, there has been considerable interest in expanding the criteria for resectability of patients with colorectal metastasis using other adjunctive and adjuvant approaches.

**Old Paradigm: Traditional Factors Associated with Resectability**

Previously, clinicopathologic factors were used to define the appropriateness of attempting hepatectomy for colorectal metastases. These factors concentrated on the lesions to be removed and patient factors rather than the liver that would remain. In a 1986 publication by Ekberg et al. [37], the authors proposed several general contraindications to hepatectomy for metastatic colorectal cancer. These criteria included: four or more metastases within the liver, additional extrhepatic metastatic disease, large size of hepatic metastases, and the inability to achieve a resection margin of at least 1 cm. Multiple subsequent studies from other groups then corroborated some or all of these findings. With time, these clinicopathologic factors were used to determine which patients with colorectal liver metastases had “resectable” disease.

Subsequently, these studies were criticized both on clinical and methodological grounds. One major problem is that only a small number of patients who actually met all the “unresectable” criteria were included in the analyses. Additionally, most of these studies used only univariate (log-rank) analyses, which do not adjust for competing risk factors that may have affected survival. Systemic chemotherapy and the availability of adjunctive techniques such as radiofrequency ablation (RFA) and portal vein embolization (PVE) have greatly changed our management of patients. These new techniques make the application of these older data to current paradigms of treatment problematic. Community physicians, oncologists, and even some surgeons still use these factors to determine resectability of patients with colorectal metastases and fail to refer potentially resectable patients.

**Tumor Number**

Previous studies have placed an inordinate emphasis on the association between the number of hepatic metastases and survival. For example, both Cady et al. [3] and Ekberg et al. [37] reported no disease-free survivors at 48 months, and Hughes et al. [38] reported a 5-year survival rate of only 18% for patients with four or more metastases. Many surgeons interpreted these data to indicate four or more lesions as a relative contraindication to hepatic resection, even though this survival rate exceeds what is reported following pancreaticoduodenectomy for pancreatic cancer or transhiatal esophagectomy for esophageal cancer. More recently, in an era of better adjuvant therapy and imaging modalities, Altendorf-Hofmann and Scheele [8] reported the lack of a survival difference between patients who had one to three metastases and patients who had four or more metastases as long as they underwent an R0 (i.e., microscopically negative) resection (Fig. 1). In another series of 159 patients with four or more metastases who had a median of five hepatic metastases resected, Pawlik et al. [39] reported 5-year disease-free and overall survival rates of 22% and 51%, respectively. That study demonstrated that response to preoperative chemotherapy was a much more robust factor in predicting long-term survival than the number of hepatic metastases. Specifically, analysis revealed that patients who failed to have a measurable reduction in tumor size following neoadjuvant chemotherapy had over a 2.5 times higher risk for cancer-related death following surgical treatment. These data suggest that higher tumor numbers should not be used to deny patients a potentially curative resection.

**Tumor Size**

Tumor size has been studied as a prognostic factor and results have been mixed. Some studies [10, 14, 40] have reported tumor size to be important in regard to prognosis, whereas numerous other studies [9, 13, 41, 42] have failed to demonstrate this association. Given theses conflicting results, the size of hepatic metastases cannot be accepted as a criterion for determining which patients should be taken to the operating room. Size may negatively impact the surgeon’s ability to gain negative margins or to leave an adequate remnant, but if a patient is potentially resectable they should not be denied the opportunity to have their disease completely resected. Additionally, tumor size may be a function of when the tumor is found during the disease...
course, rather than a true predictor of biological aggressiveness.

**Surgical Margin <1 cm**

Surgical margin status has long been held as an important criterion for resectability and continues to be so. Cady et al. [43] reported that a surgical margin <1 cm was associated with a significantly shorter disease-free survival duration. Many centers adopted the “1 cm rule” as a minimal margin to obtain at the time of hepatic resection. They have suggested that an anticipated surgical margin <1 cm is an absolute or relative contraindication to surgery. The status of the surgical margin has been shown to be important in long-term outcomes following resection of colorectal liver metastases. Multiple studies [8, 13, 44, 45] have shown that a negative resection margin decreases local recurrence rates and improves survival. Complete removal of all macroscopic disease with negative microscopic resection margins is a very strong determinant of long-term outcome in all studies. In a study by Altendorf-Hofmann and Scheele [8], the median survival time of patients who underwent an R1 or R2 resection was only 14 months, compared with 44 months for those patients who underwent an R0 resection (Fig. 2a) [8].

In a more recent study by Choti et al. [13], patients who had a positive microscopic resection margin had a median survival time of only 24 months, compared with 46 months for patients with a negative surgical margin. In that study, a positive surgical margin was associated with a 3.5 times higher relative risk for disease-specific death. Given the overwhelming significance of a clear margin, then what is an acceptable negative microscopic margin? Early studies [43, 46] suggested that patients with a margin ≥10 mm had better outcomes than those with microscopically clear but closer margins. On multivariate regression analysis with adjustment for other confounding risk factors, these findings have not been corroborated. Rather, more recent studies [8, 44] have shown that survival was not associated with the width of the negative surgical margin as long as they were completely microscopically negative.

Pawlik et al. [44] reported on 557 patients in whom the influence of surgical margin status on survival and site of
recurrence following curative hepatic resection was specifically evaluated. In that study, patients were classified according to the width of the resection margin, defined as the shortest distance from the edge of the tumor to the line of transection. A positive margin was defined as the presence of exposed tumor along the line of transection detected by histologic examination, and margin recurrence was defined as evidence of new tumor involving the parenchymal transection line. On final pathologic analysis, margin status was positive in 45 patients and negative by 1–4 mm in 129, 5–9 mm in 85, and at least 1.0 cm in 298. Among the 45 patients with a positive margin, the diagnosis of positive margin was made postoperatively in 34 patients and intraoperatively in 11 patients. Of the patients who recurred, only 21 patients, or 4%, developed a recurrence at the site of the surgical margin. Among these 21 patients, only four had the surgical margin as the sole site of recurrence. With regard to factors predictive of pattern of recurrence, patients with a positive surgical margin had a higher overall recurrence rate, 51%, compared with about 40% for patients with a negative surgical margin. However, patients with a negative margin, regardless of the margin width, had similar overall recurrence rates. Only a positive surgical margin was associated with surgical margin recurrence. The 5-year survival rate was 17% for patients with a positive margin, compared with 64% for patients with a negative surgical margin. The width of the surgical margin did not significantly affect survival in patients with negative margins. That is, no significant difference in survival was seen in patients with a negative surgical margin, regardless of the width of the margin (Fig. 2B). Furthermore, on multivariate analysis, margin status was not a significant predictor of survival.

It is clear that patients should be evaluated for resection based on the ability to resect all metastases with negative histologic margins (along with preservation of adequate hepatic function). Patients should not be denied a potentially curative resection based on the prediction that a 1-cm margin will not be obtainable.

**Extrahepatic Disease**

The presence of extrahepatic disease (exclusive of the primary lesion and associated locoregional nodes) is accepted to portend a worse prognosis following liver resection of colorectal metastases. Patients with extrahepatic disease have a significantly shorter overall survival time than patients with liver-only disease. As such, the presence of extrahepatic disease has traditionally almost universally been accepted as a contraindication to hepatic resection of colorectal metastases. From Altendorf-Hofmann A, Scheele J. A critical review of the major indicators of prognosis after resection of hepatic metastases from colorectal carcinoma. Surg Oncol Clin N Am 2003;12:165–192, xi, with permission.

More recently, in the late 1980s and 1990s, other groups [10, 14, 40] reported 5-year survival rates of 10%–20%. Interpretation of these studies should be done cautiously for multiple reasons. In many of these studies, direct invasion of adjacent structures was considered extrahepatic disease. Although technically this may be true, direct invasion of a hepatic metastasis into an adjacent resectable structure does not connote the same risk as a separate site of extrahepatic metastasis. Many of these studies included too few patients with extrahepatic disease to allow appropriate statistical analysis. Lastly, all of these studies were carried out before the current era of more active chemotherapy agents and more robust adjunctive techniques.

**NEW PARADIGM: SHIFTING FOCUS ON HOW RESECTABILITY IS DEFINED**

Based on the currently available data, the prognostic importance of clinicopathologic factors in deciding who is “resectable” is at best inconsistent and conflicting. Conventional clinicopathologic factors, although perhaps generally instructive with regard to prognosis, should not be used to define resectability criteria in patients with colorectal liver metastases. Rather, current data have precipitated a shift in the definition of resectability from criteria based on the characteristics of the metastatic disease (e.g., number, size, etc.) to new criteria based on whether a macroscopic and microscopic complete or R0 resection of the liver lesion, as well as any extrahepatic disease, can be performed. In addition, decisions on resectability are contingent on whether an adequate liver remnant will be left following surgery. This notion of resectability represents a paradigm shift. Instead of resectability being defined by what is removed, decisions concerning resectability now center around what
will remain after resection, with a particular focus on the lack of residual disease as well as the volume and function of the residual liver (Fig. 4). In this new paradigm, resectability is defined by four main criteria:

1. The disease needs to be completely resected. An R0 resection of both the intra- and extrahepatic disease sites must be feasible.
2. At least two adjacent liver segments need to be spared.
3. Vascular inflow and outflow, as well as biliary drainage to the remaining segments, must be preserved.
4. The volume of the liver remaining after resection (i.e., the future liver remnant) must be adequate (which usually means at least 20% of the total estimated liver volume for normal parenchyma, 30%–60% if the liver is injured by chemotherapy, steatosis, or hepatitis [47], or 40%–70% in the presence of cirrhosis, depending on the degree of underlying hepatic dysfunction).

These new criteria of resectability depend less on dogmatic parameters such as tumor number, size, or location and more on clinical judgment. As such, in difficult or borderline cases, resectability should be assessed by an experienced hepatobiliary surgeon.

Armed with this new definition of resectability, we are faced with the challenge of answering the question: how can we increase the number of patients with resectable disease? In general, there are three broad strategies: (a) increase/preserve hepatic reserve, (b) combined modality local therapy, and (c) decrease tumor size.

**INCREASING THE NUMBER OF PATIENTS WHO HAVE RESECTABLE DISEASE**

**Increase/Preserve Hepatic Reserve**

**PVE**
In general, 20% of the total liver volume appears to be the minimum safe volume that can be left following extended resection in patients with a normal underlying liver. However, the cutoff threshold for the future liver remnant (FLR) may need to be greater in those patients with underlying liver injury secondary to steatosis or steatohepatitis (30% FLR) or cirrhosis (40% FLR). Computed tomography (CT) or magnetic resonance imaging can now provide an accurate, reproducible method for preoperatively measuring FLR volume [48]. The right liver (right lobe) accounts for about two thirds of the total liver volume, and the left liver (left lobe) accounts for about one third. Often, patients with multiple hepatic colorectal metastases are treated with resection of the right hemiliver plus segment IV (termed extended right hepatectomy or right trisectionectomy). On average, this procedure removes 84% of the total liver volume in the absence of compensatory hypertrophy resulting from tumor growth [49]. There is, however, considerable variability in the lobar and segmental intrahepatic volumetric distribution. To avoid operating on patients with a low-volume FLR, any patient who fails to show compensatory hypertrophy as a result of tumor growth and who has an FLR \(<20%\) (or 30% in patients with a very fatty liver) should be considered for PVE to induce hypertrophy of the contralateral liver lobe [50].

PVE involves cannulating the left or right portal vein under fluoroscopic guidance and embolizing the appropriate vessel(s) using embolic material (e.g., coils, thrombin, polyvinyl alcohol, cyanoacrylate, or tris-acryl gelatin microspheres). The concept emerged from the recognition that tumor invasion of the portal vein causes contralateral lobar hypertrophy and ipsilateral atrophy. PVE is safe, with a complication rate in the range of 5%-8%. PVE has been shown to increase the size of the FLR from 8% to 16%, depending on the extent of the underlying liver disease (Fig. 5) [51–53]. PVE has been shown to increase both the size of
the FLR as well as the percentage of indocyanine green excretion and bile volume flow in the remnant liver [54]. In 2003, Farges et al. [53] published the results of a prospective study of PVE performed in patients undergoing right hepatectomy for either primary liver cancer or metastatic liver disease. They demonstrated significantly fewer postoperative complications when PVE was used to increase the FLR volume in patients with chronic liver disease whose anticipated FLR was <40%. In contrast, patients with normal liver function who underwent a right hepatectomy did not benefit from PVE. In general, PVE needs to be performed only in patients who have normal liver function who are being considered for an extended right hepatic resection; PVE is rarely necessary prior to extended left hepatectomy because the right posterior sector typically constitutes about 30% of the total liver volume [49, 55]. The selective use of PVE may enable safe and potentially curative hepatic resection in a subset of patients with advanced colorectal metastases who would otherwise have been marginal candidates for resection because of an inadequate FLR or significant underlying liver disease.

PVE is most useful as part of a multimodality approach that includes preoperative chemotherapy and surgery. Chemotherapy in conjunction with PVE does not appear to be detrimental to liver hypertrophy. Preoperative chemotherapy studies by both Elias and colleagues [56] and Bismuth and colleagues [57] included patients who underwent preoperative PVE to increase the size of the FLR.

Two-Stage Hepatectomy

In patients with multiple colorectal liver metastases in both sides of the liver, a two-stage hepatectomy may be the best therapeutic approach [58, 59]. Specifically, a two-stage hepatectomy approach may be the only potentially curative therapeutic approach in those patients with extensive bilateral colorectal liver metastases that cannot be resected with or without ablation in a single procedure while sparing an adequate FLR. Initial experience with the two-stage hepatectomy procedure without PVE was associated with a relatively high incidence of liver failure resulting from insufficient functional volume of the FLR and high mortality (9%–15%) [59, 61]. More recently, two-stage hepatectomy combined with PVE was reported with no operative mortality and acceptable morbidity [59]. Because of concern that nodules in the FLR after PVE may progress more rapidly than those in the nontumoral remnant hepatic parenchyma [61], metastases in the FLR (usually the left bilateral sectors) are usually resected in the first stage. PVE is then performed, if indicated, and the liver is allowed to hypertrophy for 3–4 weeks. Another advantage of performing a limited resection in the first stage is the preservation of a maximal amount of liver parenchyma that will hypertrophy after PVE to become the FLR. The components of the two stages should, however, be individualized, depending on the distribution of the tumor, liver volume, and other needed procedures. Similarly, as an alternative to PVE, portal vein ligation can sometimes be performed during the first-stage resection [62]. In the absence of any significant tumor progression, an extended hepatectomy (usually involving the right hemiliver) is performed as the second stage.

Adam et al. [58] have reported a 3-year survival rate of 35% in 13 patients undergoing two-stage hepatectomy. More recently, Jaeck et al. [59] reported 1- and 3-year survival rates of 70.0% and 54.4%, respectively, in 25 patients in whom a two-stage hepatic resection could be performed. The corresponding 1- and 3-year disease-free survival rates were 35.2% and 14.1%, respectively. In that study, the authors reported no operative mortality and postoperative morbidity rates of 15.1% and 56.0% after the first- and second-stage hepatectomies, respectively. A two-stage hepatectomy approach should be considered in patients with otherwise unresectable multiple bilateral hepatic metastases. A two-stage hepatectomy should only be performed, however, with curative intent, and the application of this strategy must be carefully considered to avoid posthepatectomy liver failure.

Combined Local Therapy: Resection Plus RFA

Methods for local ablation have been developed in recent years with the goal of increasing the number of patients eligible for liver-directed therapy. Combining hepatic resection with ablation can expand the number of patients who may be candidates for liver-directed surgical therapy, particularly as larger lesions that are less effectively treated with ablation can be resected and small lesions can be ablated [63]. Although tumor ablation should not be viewed as a replacement to resection, it does have applicability in patients who do not meet the criteria for resectability but are candidates for liver-directed therapy based upon the presence of liver-only disease.

Early experiences with ablation of metastases involved hepatic cryosurgery, which relied on the destruction of a defined area within the liver by at least two cycles of freezing/thawing using probes cooled by liquid nitrogen or argon gas to subzero temperatures. Ice crystals form within the treated cells leading to their destruction. Probably because of the smaller size of the equipment, speed of use, lower cost, and fewer hepatic parenchymal complications (e.g., liver fracturing, etc.), RFA was more recently adopted as the most commonly applied ablation method. Other interstitial local ablative approaches have also been applied to liver metas-
tases, including therapeutic high-intensity ultrasound ablation [64, 65], laser thermotherapy [66, 67], and yttrium-90 seed implants [68], but these have not gained widespread acceptance. More recently, thermal ablation using microwave emitting devices has been gaining in popularity [69, 70].

RFA involves the localized application of conductive thermal energy to destroy tumor cells. Specifically, alternating electric current in the range of radiofrequency waves (460 kHz) is applied from a generator through a needle electrode placed directly into the tumor [71]. As the temperature within the tissue becomes elevated beyond 50–60°C, proteins are denatured, cells are destroyed, and a zone of necrosis surrounding the electrode develops [72]. A variety of probe designs are available, including multielectrode deployable devices, cooled parallel probes, and saline infusion probes. These designs allow the capability of increasing the speed and size of the zones of ablation. Tumors \( \leq 4 \) cm in diameter can typically be ablated with a single placement of a multielectrode array, creating a spherical burn of up to 5–6 cm in diameter [73]. Larger tumors require multiple deployments of the needle electrode. Treatment should be planned such that the zones of coagulative necrosis overlap to ensure complete destruction of the tumor as well as a rim of nonmalignant tissue. Tumors abutting major vascular structures can be safely ablated because the blood within these vessels acts as a heat sink to protect the vascular endothelium from thermal injury while allowing complete coagulative necrosis of the tissue surrounding the vessel wall [73, 74]. However, the presence of heat sinks from large vessels may result in incomplete ablation and higher local recurrence. RFA should not, however, be applied to lesions near the hilum; although the blood vessels can tolerate the heat generated from RFA, not, however, be applied to lesions near the hilum; although tissue surrounding the vessel wall [73, 74]. However, the presence of heat sinks from large vessels may result in incomplete ablation and higher local recurrence. RFA should not, however, be applied to lesions near the hilum; although the blood vessels can tolerate the heat generated from RFA, the large bile ducts in this area can be damaged, resulting in biliary strictures [73].

Tumor ablation should not be viewed as a replacement for resection, but more as a supplement or extension of localized therapy in unresectable patients [11, 73, 75]. In general, patients with resectable colorectal liver metastasis should undergo resection, not ablation. The main indication for ablation is in patients who do not meet the criteria for resectability, but are candidates for liver-directed therapy based upon the presence of liver-only disease. As with the criteria for resectability, only those patients in whom complete margin-negative ablation can be achieved should be considered for this therapy. As with resection, incomplete or cytoreductive therapy should not be advocated outside a clinical trial.

Combining hepatic resection with ablation expands the number of patients who may be candidates for liver-directed surgical therapy, particularly as larger lesions that are less effectively treated with ablation can be resected and small lesions can be ablated. Adding RFA to hepatic resection has been reported to be well tolerated, with a perioperative morbidity and mortality comparable to those seen following resection alone [75]. Procedure-related complications were infrequent, with a complication rate <10% [75, 76]. Complications from RFA included bleeding, fever, pain, biliary fistulae, and hepatic abscess [73, 75, 76]. Local recurrence following RFA is highly dependent on tumor size as well as location within the liver. While some studies [11, 76–79] have reported recurrence or persistence of metastatic disease at the site of the RFA to be <10%, other studies have reported local recurrence rates as high as 47% [80, 81]. Survival following ablation is also difficult to interpret, because many patients who undergo this therapy are characterized by a number of poor prognostic factors (e.g., “unresectable” disease, multiple tumors, bilobar location, etc.), thereby making comparisons with patients who have undergone complete surgical resection difficult. In general, studies with isolated RFA show a median survival duration of about 30–35 months and a 3-year survival rate of 20%–36% [75, 82–84]. In a recent study comparing recurrence and outcome following hepatic resection, RFA, and combined resection and RFA for colorectal liver metastases, Abdalla et al. [11] reported a significantly worse disease-free and overall survival rate for patients treated with RFA. Some investigators, however, have questioned whether patient selection for RFA may lead to biased analytical comparisons. While prospective data are still needed to assess the comparability of RFA versus resection, RFA should continue to be used in combination with resection as a means to achieve complete extirpation/destruction of all tumor-bearing liver in otherwise unresectable patients.

Reduce Tumor Size
Whereas in the past, bolus 5-fluorouracil and leucovorin had reported response rates of only about 20%, over the past decade, additional chemotherapeutic and biologic agents have been found that have significantly greater activity against colorectal cancer. These newer agents have led not only to higher response rates, but also to a notable longer survival time for patients with traditionally nonresectable disease (Table 1). With combination therapies that include oxaliplatin and irinotecan, response rates >50% can be achieved. This superior efficacy of chemotherapy agents has led clinicians to treat a subset of previously unresectable patients and “convert” them so that they can undergo liver surgery following tumor downsizing. Specifically,
about 15%-20% of patients with initially unresectable disease (defined as either the inability to resect all tumor while leaving 20% of the total liver volume or by the concomitant presence of extrahepatic metastases) have significant tumor downsizing to the point that the metastatic disease can ultimately be considered resectable. As such, patients with extensive disease who respond to chemotherapy should be reassessed by a hepatic surgeon. By reconsidering the initial unresectability of patients, hepatic resection, and long-term survival, may be achieved in a subgroup of patients who otherwise would have a poor outcome [57, 85, 86]. Adam et al. [85] reported that rescue surgery for unresectable colorectal liver metastases downsized by chemotherapy resulted in a 5-year survival rate of 33%. Other investigators [87–89] have substantiated these findings, and resection of initially non-resectable liver metastases following systemic chemotherapy has become increasingly more common.

When treating patients with initially unresectable disease with preoperative chemotherapy, the question often arises as to whether one should treat to “maximal effect” or discontinue chemotherapy once the disease within the liver has been cytoreduced to the point where resection is feasible. In the setting of unresectable disease, the goal of preoperative chemotherapy is to convert the extent of intrahepatic disease from unresectable to resectable based on the criteria outlined above. As such, in general, preoperative chemotherapy should be stopped once the intrahepatic disease has been downsized to the point where hepatic resection is feasible. Not only does treating to maximal effect prior to surgery provide no measurable oncologic benefit, but prolonged courses of preoperative chemotherapy may also have a detrimental effect on the hepatic parenchyma. Some studies have associated the use of oxaliplatin with a higher incidence of hepatic sinusoidal obstruction [90], while others have suggested that irinotecan may be associated with steatosis [91, 92]. Fernandez et al. [91] reported that preoperative administration of oxaliplatin or irinotecan was associated with a higher risk for steatohepatitis, especially in the obese. Similarly, Vauthey et al. [93] reported that steatohepatitis was more common following preoperative treatment with irinotecan and was associated with a higher 90-day mortality rate following hepatic surgery. In aggregate, these data suggest that preoperative chemotherapy can potentially be a powerful tool to convert otherwise unresectable patients, but its use should be individualized to the specific circumstance. Chemotherapy that has effectively downsized previously unresectable lesions should not be continued indefinitely. Rather, the patient should be seen by the hepatic surgeon or surgical oncologist on a regular interval basis during chemotherapy. In this manner, the surgeon can help continually assess disease response/progression and reconsider resection if appropriate.

An important question arises when considering a patient for surgery following response to preoperative chemotherapy: do all the original sites of disease need to be resected or ablated in order to derive a survival benefit from local therapy? In general, the answer is yes. Benoist et al. [94] examined metastatic sites in which complete radiologic response was achieved. Of the 66 lesions evaluated, the authors reported persistent tumor on pathology in 83% of cases. Based on these data, resection should be performed on all original sites of disease. Local therapy of only residual sites following complete radiologic response of untreated sites should be considered cytoreductive therapy and avoided. These data serve to emphasize the importance of the surgeon reviewing all cross-sectional imaging prior to planned hepatic resection. In particular, it is critical to compare pretherapy imaging including both the CT and positron emission tomography (PET) scan with images obtained following chemotherapy. As noted, in general, all the original sites of disease that were noted on the initial pretherapy scans need to be resected or ablated, not just the residual disease seen on post-therapy imaging.

EXTRAHEPATIC DISEASE

The role of hepatic resection in the setting of extrahepatic disease was recently re-examined. Extrahepatic disease has traditionally been considered a contraindication to resection of hepatic colorectal cancer metastasis [9, 14, 15, 45]. However, improvements in morbidity and mortality rates following hepatectomy, as well as the advent of more effective systemic chemotherapy agents, have prompted several investigators [95–98] to attempt surgery for some of these patients. Local extension to adjacent structures, intraluminal biliary tumor thrombus, and locoregional recurrence should not be considered true extrahepatic disease, and none of these should be considered a contraindication to surgery when an R0 resection is feasible. In contrast, there has been significantly more controversy regarding hepatic resection for colorectal metastases in the presence of pulmonary metastases, hilar lymph node metastases, carcinomatosis, and metastasis of other extra-abdominal sites.

The lungs are the second most frequent site of metastatic disease, accounting for roughly 20%-25% of the metastases in patients who have undergone curative resection of their colorectal primary. Approximately 5%-10% of patients who present with metastatic disease have a combination of liver and lung metastases, and therefore there has been interest in how this subset of patients should be treated. In the past, multiple studies [99–101] have reported favorable long-term survival rates after resection of local-
ized lung-only disease. More recently, however, several centers have reported their results for patients undergoing combined lung and liver resection [102–105]. These studies have reported 5-year survival rates >30%. In fact, Shah et al. [105] reported a 5-year survival rate that exceeded 74%. In that study, although the median disease-free survival duration after initial metastasectomy was only 20 months, the median overall survival time was 87 months. Roughly half of the patients underwent repeat resections for recurrence, with the mean number of metastasectomies being 2.6 per patient. There were no perioperative deaths. The authors demonstrated that an aggressive surgical approach, even with serial metastasectomies, can lead to significant long-term survival in a highly select group of patients—perhaps those patients with a good response to chemotherapy and longer disease-free intervals.

Prognosis following resection of pulmonary and liver metastases does not appear to be affected by synchronous versus metachronous presentation. Several studies have reported no significant difference in survival between patients who present with simultaneous disease and those who present with synchronous disease [105, 106]. Thus, patients should not be denied a chance at curative hepatectomy simply because of a history of pulmonary metastases, assuming all sites can be resected. There are, however, a number of factors that do appear to be associated with a particularly poor prognosis. Patients with bilateral disease or who have more than six pulmonary metastases were 50%–70% more at risk for disease-specific death than other patients. Thus, particular attention must be paid when considering these high-risk patients for combined liver and lung resection.

Unlike pericolic nodal disease, hilar lymph nodes are felt to be “metastases from metastases” and are associated with a poor outcome. Because of this, some investigators have traditionally considered hilar nodal metastasis as a contraindication to hepatic resection of colorectal liver disease. Although early studies [37, 107] reported few, if any, long-term survivors with hilar lymph node metastases, more recent studies [98, 108, 109] have reported long-term survival in some patients with hilar nodal metastases and have concluded that this patient population may still benefit from hepatic resection.

When considering patients with hilar lymph node involvement, the location of the nodal metastases may be important. Jaeck [109] distinguished two areas of hilar lymph node involvement: the hepatoduodenal-retropancreatic area and common hepatic artery/celiac axis region. Whereas patients with positive hilar lymph nodes in the region of the hepatic artery/celiac axis had a very poor prognosis, some patients with hilar lymph node metastases involving the hepatoduodenal or retropancreatic area achieved long-term survival. Specifically, the 3-year survival rate following hepatectomy in patients with involvement of the hepatic pedicle lymph nodes limited to the hepatoduodenal-retropancreatic area was 38%, compared with 0% for patients with involvement of the common hepatic artery/celiac axis area [110]. Another critical factor may relate to whether the hilar lymph nodes are macroscopically positive. Although patients with microscopic involvement may derive a benefit from hepatic resection, gross involvement of the hilar nodes should be considered a relative contraindication to resection.

Peritoneal carcinomatosis is a common type of extrahepatic disease in patients with colorectal liver metastasis, representing about one third of the cases of extrahepatic disease. Although usually a particularly grave indicator of poor prognosis, some centers have reported success with debulking and intraperitoneal chemotherapy [111, 112]. However, such therapy is not the standard of care and, in general, liver resection is not indicated in the presence of diffuse carcinomatosis. Specifically, patients who are found to have unsuspected extrahepatic disease at the time of laparotomy have a poor long-term prognosis [98]. Thus, in most cases, incidental peritoneal disease found at laparotomy would contraindicate hepatic resection.

Elias et al. [98] reported that the 5-year survival rate following hepatectomy for colorectal liver metastasis and simultaneous resection of extrahepatic disease with curative intent was 29%. The distribution of extrahepatic disease included hilar lymph nodes, peritoneal carcinomatosis, retroperitoneal nodes, and lung metastasis. No statistically significant difference in outcome was found relating to the site of extrahepatic disease; however, the study was small and lacked statistical power. Patients with peritoneal carcinomatosis or extrahepatic disease at multiple sites did tend to have a worse survival than patients with single-site extrahepatic disease [98]. In contrast, patients with only pulmonary metastasis as the type of extrahepatic disease had a particularly good outcome following complete metastasectomy of both liver and lung disease [99, 101, 113, 114].

Not only is the site of the extrahepatic disease important with regard to prognosis, but perhaps more important is the adequacy of the resection. As with liver resection itself, the ability to achieve a complete macro- and microscopic resection of all known disease is critical to long-term outcome. In a study by Elias et al. [98], of those patients who underwent resection of both intra- and extrahepatic metastases, the 5-year survival rate was 28% in those patients who had an R0 resection, but was only 7% in those patients who had an R1 or R2 resection. These data serve to empha-
size that hepatic resection in the setting of extrahepatic disease is warranted only when an R0 resection is feasible. Patients with disease not amenable to a complete resection should not be offered combined metastasectomies of intra- and extrahepatic disease. For those patients who can have a complete microscopic resection, there are data to suggest that long-term survival may be similar in patients with isolated liver metastases and in those with liver metastases with extrahepatic disease, when the extent of disease was similar. In the multivariate analysis from Elias et al. [98], the site of the metastatic disease had less prognostic importance than the overall number of resected lesions, regardless of site. Not surprisingly, patients with more overall metastases have a worse survival than patients with fewer lesions—reflecting the worse overall tumor biology found in those patients with multiple lesions. However, in the study by Elias et al. [98], when the number of lesions was controlled for, patients with and without extrahepatic disease had similar overall survival times.

In addition to the extent of resection and the number of metastatic lesions, perhaps the most critical factor in helping to determine a patient’s eligibility for hepatic resection in the presence of extrahepatic disease is the response to preoperative chemotherapy. Adam et al. [85] reported that the prognosis following hepatic resection is dependent on the response to preoperative chemotherapy. Specifically, long-term survival is rare in patients who have disease progression while on chemotherapy. While patients who progress on chemotherapy have only an 8% reported 5-year survival rate following hepatic resection, those patients who respond to chemotherapy have reported 5-year survival rates of 37% [85]. Thus, the use of preoperative therapy may help to define those patients who will benefit from an aggressive surgical approach and those who may not (including those patients with extrahepatic disease). Whereas liver resection in patients with progressive disease on chemotherapy may not be warranted, an aggressive surgical approach may be appropriate in patients who have stabilization or responsive disease.

Therefore, based on the available data, a general treatment algorithm can be proposed. Patients with intra- and extrahepatic disease should initially be treated with systemic chemotherapy. Patients with progressive disease are not candidates for surgery and should receive additional chemotherapy and palliative support. Patients with stable or responsive disease should be evaluated for surgery. Those in whom an R0 resection is not possible are also not candidates for surgery and should go on to receive more chemotherapy. However, patients in whom an R0 resection is possible should be offered surgical resection followed by adjuvant chemotherapy. Patients with simultaneous hepatic and extrahepatic colorectal metastases do, however, need to be well selected for surgery. PET/CT can often be useful in evaluating the full extent of metastatic disease [115].

CONCLUSION

In summary, the criteria for resectability of colorectal liver metastases have been significantly revised and expanded over the course of the last decade. Clinicopathologic factors such as the tumor number, tumor size, presence of extrahepatic disease, or width of the resection margin should no longer be used to categorically exclude patients from consideration for surgical resection. Rather, assessment of resectability should take into account the ability to obtain an R0 resection of all known disease—whether it be intra- or extrahepatic. The feasibility of hepatic resection should be determined chiefly using three criteria: (a) the ability to preserve two contiguous hepatic segments, (b) the preservation of vascular inflow and outflow as well as biliary drainage, and (c) the ability to preserve an adequate FLR. In those patients with extensive disease and limited hepatic reserve, PVE or a two-stage hepatectomy approach can sometimes permit surgical resection. Similarly, the use of preoperative chemotherapy can be associated with conversion of some patients from unresectable to resectable. Preoperative chemotherapy may also be useful in the treatment of patients with intra- and extrahepatic disease. In this setting, preoperative chemotherapy can reduce disease volume so that an R0 resection is more feasible, but perhaps more importantly, preoperative chemotherapy can help assess the underlying biology of the patient’s disease. Although the criteria for resectability of colorectal liver metastases have been expanded to include patients with both intra- and extrahepatic disease, these patients must be very well selected. Patients with extensive extrahepatic disease, or those who progress on systemic chemotherapy, should probably not be considered for hepatic resection. The expansion of criteria for resectability of colorectal liver metastases requires a much more sophisticated approach to the patient with advanced disease. Patients require ongoing repeat evaluations by a surgeon with expertise in hepatic resection. Ultimately, a therapeutic approach that includes all aspects of multidisciplinary and multimodality care is required to select and treat this complex group of patients.

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