

# Improving Resectability of Hepatic Colorectal Metastases: Expert Consensus Statement

Eddie K. Abdalla, MD,<sup>1</sup> René Adam, MD, PhD,<sup>2</sup> Anton J. Bilchik, MD, PhD,<sup>3</sup>  
Daniel Jaeck, MD,<sup>4</sup> Jean-Nicolas Vauthey, MD,<sup>1,6</sup> and David Mahvi, MD<sup>5</sup>

<sup>1</sup>The University of Texas M. D Anderson Cancer Center, Houston, TX USA

<sup>2</sup>Centre Hépatobiliaire, Hôpital Paul Brousse, Villejuif, France

<sup>3</sup>John Wayne Cancer Institute, Santa Monica, CA USA

<sup>4</sup>Centre de Chirurgie Viscérale et de Transplantation, Hautepierre Hospital, Strasbourg, France

<sup>5</sup>Department of Surgery, University of Wisconsin Medical School, Madison, WI USA

---

**Key Words:** Radiofrequency ablation—Preoperative chemotherapy—Liver resection—Portal vein embolization—Colorectal metastases.

---

## DOWNSTAGING OF UNRESECTABLE METASTASES AND TIMING OF LIVER RESECTION

Colorectal cancer is the third most common malignancy in Western countries.<sup>1,2</sup> Approximately 50% of patients with colorectal cancer develop hepatic metastases during the course of the disease.<sup>3–5</sup> The liver is the most common site of metastases of colorectal cancer, and hepatic metastases are responsible for death in at least two thirds of patients with colorectal malignancy.<sup>3,4</sup>

At present, the only accepted potentially curative standard treatment in patients with liver metastases of colorectal cancer is liver resection. After resection, the 5-year overall survival rate in selected patients is 37%–58% in recent series.<sup>6–11</sup> Although only 10%–20% of patients with hepatic colorectal metas-

tases are eligible for resection, the absolute number of patients amenable to resection is large and is growing with better imaging, better surgery, and improvements in systemic therapies to reduce the risk of both intrahepatic and extrahepatic recurrences.<sup>3,12–16</sup> For patients with liver metastases, a multidisciplinary team approach has become mandatory.

Advances made by chemotherapy have been the major determinant of new therapeutic approaches concerning primarily unresectable patients. Until recently, patients with unresectable hepatic colorectal metastases were treated with palliative chemotherapy, and almost no such patients survived for 5 years.<sup>17,18</sup> Recently, advances in chemotherapy have permitted resection in some patients with initially unresectable metastases.

Chemotherapy regimens based on 5-fluorouracil (5-FU) rarely provided sufficient intrahepatic tumoricidal effect to convert hepatic metastases from unresectable to resectable (response rate < 20%). However, novel chemotherapeutic regimens combining 5-FU, folinic acid, and oxaliplatin and/or irinotecan<sup>19–26</sup> have been associated with improved response rates (around 50%), allowing 10%–30% of patients with initially unresectable hepatic metastases to be rescued by liver surgery.<sup>13,14,22</sup> In addition, early results from trials evaluating several novel biologic agents, including cetuximab<sup>27</sup> and bevacizumab,<sup>26</sup> suggest that even more patients with initially unresectable disease may respond to primary

---

Received May 8, 2006; accepted June 22, 2006; published online September 6, 2006.

Address correspondence and reprint requests to: Jean-Nicolas Vauthey, MD; Department of Surgical Oncology, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 444, Houston, TX 77030, USA. Telephone: +1-713-7922022. Fax +1-713-7920722; E-mail: jvauthey@mdanderson.org

Proceedings of the Consensus Conference sponsored by the American Hepato-Pancreato-Biliary Association and cosponsored by the Society for Surgery of the Alimentary Tract and the Society of Surgical Oncology, held in San Francisco, CA, USA, January 25, 2006.

Published by Springer Science+Business Media, Inc. © 2006 The Society of Surgical Oncology, Inc.

treatment with combinations of systemic chemotherapy, with response rates of 70% or more.<sup>28,29</sup>

### **Long-term Outcomes Following Hepatic Resection in Patients Converted to Resectable Status by Systemic Chemotherapy**

Although numerous studies have been published describing response and resection rates following systemic and/or regional chemotherapy for patients with initially unresectable hepatic colorectal metastases,<sup>30</sup> only four of these studies have included long-term outcomes analyses.

The first of these studies<sup>13</sup> is a retrospective update of a single-institution experience first reported in 1996.<sup>31</sup> At the time of the 2004 update, the study cohort included 1,104 patients with anatomically unresectable disease. Following a mean of ten cycles of systemic chemotherapy (mainly chronomodulated oxaliplatin + 5-FU-based regimens), 12.5% of patients were converted to resectable status. In 93% of these cases, a curative hepatectomy was performed. Following hepatic resection, 5-year and 10-year overall survival rates were 33% and 23%, respectively, and disease-free survival rates were 22% and 17%, respectively. Poor prognostic factors included primary lesion in the rectum,  $\geq$  three metastases, size of the largest metastasis  $> 10$  cm, and CA 19-9 level  $> 100$  IU/l.

The second series is a phase II trial published by Zelek et al.<sup>32</sup> in 2003. This report included 31 patients with anatomically unresectable liver metastases treated with a combination of intravenous irinotecan, 5-FU, and folinic acid and hepatic arterial infusion of pirarubicin. This was a fairly toxic regimen (78% of patients had grades 3 or 4 of hematologic toxicity) that produced objective partial responses following a median of five cycles of treatment in 48% of patients based on World Health Organization (WHO) response criteria. Eleven patients (35%) subsequently underwent resection, and in nine (29%) of these cases, resection margins were negative. For the subset of patients with complete resections, median disease-free survival was 20.2 months and median overall survival had not been reached at the time of the report. Two- and 3-year overall survival rates for completely resected patients were 100% and 65%, respectively. The limited follow-up duration and a lack of events prevented analysis of prognostic factors that may have been associated with poor outcomes following hepatic resection.

The third study to report on outcomes after hepatic resection in patients with disease rendered resectable by chemotherapy is another phase II study, from Pozzo et al., published in 2004.<sup>22</sup> This group treated

40 patients deemed unresectable according to strict institutional policy criteria with a regimen containing irinotecan, folinic acid, and 5-FU. The mean number of cycles delivered was 15. By WHO response criteria, 48% of patients had an objective response. Sixteen patients (40%) underwent laparoscopic exploration, and 13 (33%) had their disease resected with negative margins. Median disease-free survival for patients who underwent surgery was 14.3 months, and all patients who underwent resection were alive at a median follow-up interval of 19 (range: 6–30) months. Prognostic factors were not investigated.

The final, and most recent, study to report outcomes data for patients with unresectable disease converted to resectable status by systemic therapy is from Alberts et al.<sup>33</sup> Their data were first reported in abstract form in 2001 and were updated in a formal report in October 2005. The patient cohort included 42 evaluable patients enrolled in a phase II trial of the North Central Cancer Treatment Group who were treated for unresectable colorectal liver metastases with the oxaliplatin-folinic acid-fluorouracil (FOLFOX4) regimen. Sixty percent of patients experienced a radiographic response, and 43% ultimately underwent hepatic resection. Fifteen patients had a complete resection, yielding a potentially curative resection rate of 37%. Unfortunately, within 2 years of hepatic resection, 11 (73%) of these 15 patients experienced a relapse, including more than 70% with recurrence in the liver. The reported median overall survival for patients who underwent hepatic resection was 26 months.

In addition to the prognostic factors mentioned above, another factor appears to influence long-term outcome after hepatic resection in patients treated with preoperative chemotherapy: the ability of chemotherapy to control the tumor just before liver surgery. In a recent study performed in 131 patients with more than three liver metastases,<sup>14</sup> Adam et al. demonstrated that tumor progression was an important adverse factor with respect to outcome following hepatic resection: 5-year survival rates were 8% in patients with progression during chemotherapy compared with  $> 30\%$  in patients with stable disease or objective tumor response to chemotherapy. Therefore, tumor progression during preoperative chemotherapy should be considered a relative contraindication to resection.

### **Timing of Surgery after Chemotherapy and Techniques to Improve Resectability**

In general, hepatic resection should be performed as soon as colorectal metastases become resectable.

The reasons are twofold: First, preoperative chemotherapy results in damage to the liver that may increase morbidity and mortality after hepatic resection.<sup>34,35</sup> Second, occasionally, preoperative chemotherapy results in a radiographic complete response (histologically confirmed in 7% or less) that jeopardizes the performance of an adequate liver resection.<sup>13</sup>

Advances in the surgical approach to patients with extensive liver involvement by primary tumor include: (1) preoperative portal vein embolization (PVE),<sup>36</sup> (2) liver resection combined with radiofrequency ablation (RFA) or cryosurgery,<sup>37</sup> and (3) two-stage hepatectomy.<sup>38</sup> By reducing the incidence of postoperative liver failure, optimizing the size of the future liver remnant (FLR) (preoperative PVE and two-stage hepatectomy), and permitting complete treatment of otherwise unresectable tumors (resection combined with RFA), these methods have increased the total number of patients who are candidates for hepatic resection.

Treatment of initially unresectable hepatic colorectal metastases has been characterized by remarkable advances over the past 15 years. Patients who years ago would only have been eligible for palliative chemotherapy now can take advantage of a variety of strategies available to render their disease surgically resectable, and in such patients who are ultimately able to undergo hepatic resection, long-term survival rates are 30%–35% at 5 years. These advances are the result of a strong collaboration between medical oncologists and surgeons. Development of new chemotherapy protocols has played a major role, offering the possibility of curative surgery to an increasingly large number of patients.

#### Consensus Statement

1. For patients with metastatic colorectal carcinoma isolated to the liver, hepatic resection is the only treatment associated with demonstrated long-term survival. All patients with resectable disease should be offered hepatic resection.
2. For patients with disease isolated to the liver that is deemed initially anatomically unresectable, preoperative chemotherapy permits complete resection in 15%–30% of patients.
3. In patients with initially unresectable hepatic colorectal metastases who undergo resection, the survival rate at 5 years (30%–35%) approaches the survival rate of patients who undergo upfront hepatic resection for initially resectable disease.
4. Preoperative chemotherapy results in damage to the liver that may increase morbidity and mortality after hepatic resection. Occasionally, preoperative chemotherapy results in a radiographic complete response (rarely histologically confirmed) that jeopardizes the performance of an adequate liver resection. For these reasons, the duration of neoadjuvant chemotherapy should be carefully considered, and resection should be performed as soon as hepatic metastases become technically resectable.
5. Radiological complete response is rarely associated with complete pathological response. Mapping and timing of resection are critical. Resection should encompass segments involved based on pre-chemotherapy imaging.

#### PVE AND EVALUATION OF THE FUTURE LIVER REMNANT (FLR)

PVE is a minimally invasive preoperative procedure advocated as a means for reducing risk for postoperative complications by increasing the mass of anticipated FLR. The rationale for PVE is that the increase in volume of the FLR, as a result of PVE, appears to improve liver function, as indicated by increased biliary excretion,<sup>39,40</sup> increased technetium-99m-galactosyl human serum albumin uptake,<sup>41</sup> and improvement in postoperative liver function tests following extended hepatectomy in patients undergoing PVE compared with no PVE.<sup>42</sup> The goal of PVE is to redistribute portal flow toward the segments of liver that will remain after surgery. PVE usually is performed percutaneously under sonographic and fluoroscopic guidance with the patient under conscious sedation in the interventional radiology suite.

#### Measurement of the FLR

The aim of “measurement” of the FLR is therefore not simply to assess the actual volume of the FLR but rather to predict the function of the FLR after removal of the tumor-bearing liver. Several methods for liver volume determination have been proposed. Most utilize computed tomography (CT) combined with three-dimensional (3D) CT volumetry.<sup>42,43</sup> With these methods, FLR volumes can be calculated accurately and reproducibly with errors of less than  $\pm 5\%$ .<sup>44,45</sup>

The FLR is generally standardized to total liver volume (TLV) and expressed in terms of percentage

of TLV that will remain after resection. It is possible to directly measure TLV using CT. However, direct measurement of TLV may not be relevant to surgical planning for two reasons. First, in patients with large tumors and in patients with liver disease, TLV is altered. Second, subtraction of tumor volume(s) from TLV results in additive mathematical errors in volume calculation.<sup>46</sup>

An alternative, accurate, and reproducible approach is to estimate TLV using a formula that relies on the linear correlation between TLV and body weight or body surface area.<sup>42,47,48</sup> A recent meta-analysis that compared 12 TLV formulas<sup>49</sup> revealed that the least biased and most precise formula for predicting TLV is  $-794.41 + 1,267.28 \times \text{body surface area}$ .<sup>47</sup> Using the standardized FLR measurement in which FLR volume equals CT-measured FLR volume  $\bar{Y}$  calculated TLV, a correlation between the standardized FLR volume and postoperative outcome has been established.<sup>42,50,51</sup>

### Indications and Contraindications for PVE

Indications for PVE depend on factors that impact the FLR volume needed for adequate post-hepatectomy liver function in an individual patient. Presence or absence of underlying liver disease, patient size (large patients require larger liver remnants than do smaller patients), and the extent and complexity of the planned resection must be considered in the setting of the patient's comorbidities, such as diabetes, that may affect hepatic regeneration. The volumetry technique detailed above integrates assessment of the actual FLR volume with patient size so that the standardized FLR volume can be used to determine the need for PVE based on the presence and extent of liver disease.

The FLR volume limit for safe resection varies from patient to patient. Guidelines have evolved from analysis of outcomes after extended hepatectomy. In patients with an otherwise normal liver, PVE is indicated when the standardized FLR volume is  $\leq 20\%$ . This cut-off point was determined by analysis of complications in 42 patients with normal underlying liver who underwent extended right hepatectomy.<sup>51</sup> The complication rate was increased, and intensive care unit stay and hospital stay were prolonged in patients with an FLR volume  $\leq 20\%$  compared with those with an FLR volume  $> 20\%$ . No patient died in the series. Analysis of the distribution of segmental volume variations in patients with normal liver underscores the need for systematic volumetry before extended hepatectomy: the left lateral bisegment (II

and III) contributes  $\leq 20\%$  of TLV in  $> 75\%$  of patients in the absence of compensatory hypertrophy.<sup>52</sup>

Among patients who receive extensive chemotherapy prior to hepatic resection, liver injury can occur.<sup>35,53,54</sup> Although the clinical significance of chemotherapy-related liver injury is not well defined, it has been proposed that in patients who have received preoperative systemic chemotherapy, PVE is indicated when the FLR volume is  $\leq 30\%$  of TLV.<sup>13,55</sup> In patients with hepatic fibrosis/cirrhosis, data suggest that PVE is indicated when the FLR is  $\leq 40\%$  of TLV.<sup>56-58</sup>

Contraindications to PVE include FLR volume larger than the cut-off volumes specified above and tumor invasion of the portal vein to be resected because in such cases, portal flow is already diverted. Relative contraindications to PVE include tumor extension to the FLR, uncorrectable coagulopathy, biliary dilatation in the FLR (if the biliary tree is obstructed, drainage is recommended), portal hypertension, and renal failure.

### Technical Details of PVE

The optimal extent of PVE before extended right hepatectomy is debated. Some propose embolization of the right portal vein only, leaving the portal veins supplying segment IV patent even if there is tumor involvement of this segment.<sup>58-60</sup> While PVE before extended right hepatectomy results in the desired hypertrophy of the FLR, it also increases the volume of segment IV; full diversion of portal flow to segments II and III  $\pm$  I ensures the maximal stimulus for hypertrophy of the true FLR.<sup>61,62</sup> Segment IV hypertrophy is not desired for extended right hepatectomy because hypertrophy increases the parenchymal transection surface across this segment. A modified PVE technique in which embolization is extended to segment IV prior to extended right hepatectomy using small particles and coils has been shown to be safe and also to result in the best hypertrophy rate (69% FLR volume increase), increasing resection rates (86%) compared with other techniques.<sup>63,64</sup>

Incomplete embolization of tumor-bearing liver may have oncologic consequences. Although tumor growth in the nonembolized liver has been noted after right PVE, tumor size changes before and after PVE have not been reported, so the effects of PVE on tumor growth rate are not known.<sup>65,66</sup> Analysis of patients with disease deemed unresectable despite PVE showed that after embolization of the entire tumor-

bearing liver, changes in tumor size did not affect resectability.<sup>67</sup> Chemotherapy administration after PVE and before resection does not appear to retard hepatic regeneration. Thus, the technical aspects of PVE<sup>64,68,69</sup> are of great importance to maximize hypertrophy and to minimize the risk of tumor growth in the interval between PVE and hepatic resection.<sup>63,64</sup>

### Outcomes from PVE Studies to Date

Systematic use of standardized FLR volumetry and PVE according to the guidelines above was validated in a large series (127 consecutive extended hepatectomies).<sup>50</sup> In this series, 31 patients (24%) underwent PVE prior to resection; postoperative liver insufficiency occurred in six patients (5%) and was transient in all of them. The postoperative complication rate was 31%, and only one postoperative death occurred (0.8%).

Others have confirmed that FLR volume predicts postoperative liver function and the post-hepatectomy clinical course. In a retrospective analysis of outcome following resection of colorectal liver metastases, Shoup et al.<sup>70</sup> found that FLR volume  $\leq 25\%$  was an independent predictor of complications and prolonged hospital stay. Elias et al.<sup>36</sup> demonstrated that patients considered to have unresectable tumors because of inadequate FLR volume at presentation could undergo complete resection after PVE, with a 5-year overall survival rate of 29%. Azoulay et al.<sup>55</sup> showed that the 5-year overall survival rate after resection in patients with colorectal liver metastases who required PVE (40%) was similar to that in patients who did not require PVE (38%).

### Consensus Statement

1. Volumetry to evaluate the FLR volume is indicated if major hepatic resection (resection involving more than four segments) is planned or if the patient has underlying liver disease.
2. Preoperative PVE may be indicated when the standardized FLR volume is  $\leq 20\%$  of TLV in patients with normal liver;  $\leq 30\%$  of TLV in patients who have received extensive chemotherapy; and  $\leq 40\%$  of TLV in patients with hepatic fibrosis or cirrhosis.
3. Imaging is indicated 3–4 weeks after PVE to reassess liver volume and hypertrophy.
4. The benefits of PVE are clearly established prior to major hepatectomy in selected subsets of patients

with and without chronic liver disease. There is no role for a new randomized trial of PVE.

### RFA OF HEPATIC COLORECTAL METASTASES

As stated previously, hepatic resection is the only curative option for patients with hepatic colorectal metastases. Unfortunately, many hepatic tumors are considered unresectable because they are multiple or inaccessible.<sup>71</sup> Options for patients with unresectable disease include systemic therapy, local ablative techniques (percutaneous ethanol injection, microwave tumor coagulation, interstitial laser photocoagulation, cryosurgical ablation, or RFA), and hepatic-directed therapy (hepatic artery ligation, chemoembolization, and hepatic artery infusion).

Over the past decade, the generation of heat within a lesion by a radiofrequency current has become the preferred method of local ablation because it can effectively destroy tumors with few complications.<sup>72–75</sup> In 1996, the U.S. Food and Drug Administration (FDA) approved RFA for generic tissue ablation; in 2000, RFA was approved for ablation of unresectable hepatic colorectal metastases.

RFA can be performed in the operating room via celiotomy or laparoscopy or in the radiology suite by using a percutaneous approach. RFA can be performed with other modes of liver-directed therapy, such as resection and hepatic artery perfusion, and it can be used in conjunction with systemic therapy. RFA is associated with low morbidity, and retreatment for persistent or recurrent disease is feasible.<sup>75</sup> RFA continues to evolve; new technology has increased the potential field of ablation and simplified the technique. More recently, microwave ablation has been introduced as a rapid method of delivering high temperatures to a large area of the liver, possibly reducing local recurrence rates.

### Indications

RFA has mainly been used for unresectable hepatocellular carcinoma or unresectable metastatic disease confined to the liver. Because tumors may be deemed unresectable on the basis of size, number, location, or doubling time, the preoperative work-up must include imaging to look for other sites of disease, document response to prior therapies, and

determine the nature of the disease. Some patients have resectable disease but limited hepatic reserve; for example, a patient with hepatic recurrence after previous hepatectomy may not have sufficient hepatic reserve to permit additional resection. In patients with bilobar disease, resection of larger lesions and RFA of smaller lesions may completely eradicate the tumor while preserving hepatic reserve. Finally, in patients who have multiple comorbid factors and are at high risk for complications of general anesthesia, a less invasive approach such as percutaneous RFA may be preferable to hepatic resection.

### Local Recurrence and Survival Rates after RFA

Local recurrence rates after RFA are difficult to interpret across studies. Some authors report recurrences after complete ablation verified by early postoperative images obtained with CT or magnetic resonance imaging (MRI) whereas others do not confirm complete response by postoperative imaging and report recurrences based on follow-up imaging. Some investigators also report rates of recurrence within the whole liver rather than only at the site of ablation. The length of follow-up also affects recurrence rate.

Bowles et al.<sup>72</sup> evaluated 76 patients undergoing RFA of 328 tumors. Sixteen patients underwent repeated ablation for recurrences or new lesions. There were 30 recurrences at the site of a prior ablation. Patients with large tumors, tumor vascular invasion, and hepatic dysfunction had a significantly higher recurrence rate. Solbiati et al.<sup>75</sup> evaluated 117 patients undergoing percutaneous RFA of hepatic colorectal metastases and found that time to local recurrence and frequency of recurrence were influenced by lesion size. Similarly, others found that tumor size significantly influenced local recurrence of metastatic disease, independent of RFA technique.<sup>73,74</sup> No study has shown that differences in technique influence the rate of recurrence after a complete response.

There are very few reports of survival rates following RFA. Studies that report survival data differ in patient selection criteria, follow-up time, tumor type, and RFA approach, which make them difficult to compare. The 3-year survival rate following RFA for hepatic colorectal metastases was 37% in a study by Abdalla et al.<sup>10</sup> and 46% in a study by Solbiati et al.<sup>75</sup> In both studies, > 50% of patients had only one tumor ablated. Solbiati et al.<sup>75</sup> ablated liver lesions in 13 patients who had extrahepatic metastases whereas Abdalla et al.<sup>10</sup> ablated liver lesions in pa-

tients with localized hepatic disease only. These two studies also differed in the method of RFA: Solbiati et al.<sup>75</sup> used a percutaneous approach whereas Abdalla et al.<sup>10</sup> performed RFA via an open approach. Some patients in the Solbiati study also underwent placement of a hepatic arterial infusion pump, which may explain the slightly better outcome.

### RFA versus Hepatic Resection

There is no prospective randomized controlled trial of RFA versus resection for the treatment of primary liver carcinoma or hepatic metastases. One retrospective study of 358 patients with colorectal liver metastases compared resection, RFA plus resection, RFA alone, and laparotomy with biopsy.<sup>10</sup> RFA was used for cure when complete resection was not possible. All patient-related and tumor-related factors known to influence outcome were similar among the groups although in a non-randomized study, selection bias cannot be ruled out, favoring RFA. The rate of recurrence was 84% after RFA alone, 63% after RFA plus resection, and 52% after resection alone. Local recurrence (in the area treated) was more common after RFA plus resection (9%) than after RFA alone (5%) or resection alone (2%). The 3-year overall survival rate was 73% after resection, 43% after RFA plus resection, and 37% after RFA alone. Patients who underwent RFA had a survival advantage over patients who underwent biopsy with or without chemotherapy.

Resection remains the first choice for patients with disease confined to the liver, in part because recent data demonstrate higher local recurrence rates after RFA than after resection. However, RFA holds promise for improving the treatment of hepatic malignancies. It is a useful adjunct to resection, and it may be a successful alternative to resection when extensive disease and limited hepatic reserve, bilobar disease, or medical conditions would preclude laparotomy. The survival advantage of RFA may be decreasing as outcome with chemotherapy improves—the median survival in patients with advanced metastatic disease treated with chemotherapy is currently reported to be > 20 months. The potential advantage of adding RFA to chemotherapy is being evaluated in a randomized phase III study of RFA combined with chemotherapy versus chemotherapy alone [the Chemotherapy + LOCAL ablation versus Chemotherapy (CLOCC) trial, European Organization for Research and Treatment of Cancer (EORTC) trial 40004]. Outcome data from this trial and large multicenter trials comparing RFA and

resection will help establish a comprehensive algorithm for multimodal management of patients with hepatic colorectal metastases.

### Consensus Statement

1. Resection, not RFA, is the treatment of choice for patients with resectable hepatic malignancies.
2. RFA is a local therapy option in selected patients who are not candidates for resection.
3. Recurrence rates after RFA are higher than those after resection; survival rates after RFA are lower than those after resection.
4. Patients with tumors larger than 3 cm have high local recurrence rates after RFA and are not optimal candidates for this procedure.
5. Open or laparoscopic RFA is preferable because of superior probe placement with intraoperative ultrasound and the ability to detect other tumors.
6. All patients considered for RFA of hepatic colorectal metastases should be evaluated by a multidisciplinary team including a surgeon with hepatobiliary expertise.

### RESECTION OF EXTRAHEPATIC DISEASE AND HILAR LYMPH NODE METASTASES

One of the main clinicopathologic characteristics of colorectal liver metastases is their tendency to spread to regional lymph nodes and contiguous or distant organs. Currently, liver resection constitutes the gold-standard treatment in patients presenting with resectable hepatic colorectal metastases provided that a complete macroscopic resection can be achieved. In the early 1990s, the best candidates for liver resection were patients with fewer than four liver metastases, each nodule < 5 cm in diameter, and onset of metastasis > 12 months after colorectal primary tumor resection. While extrahepatic disease was once considered an absolute contraindication for liver resection, today, selected patients with extrahepatic disease may be offered curative resection.

In selected patients with hepatic colorectal metastases associated with limited resectable extrahepatic disease (either hilar pedicle lymph node involvement or resectable peritoneal carcinomatosis), an aggressive surgical resection can offer hope for long-term survival. However, in such patients, surgery represents cytoreductive therapy, and a complete cure can only be obtained by means of a multidisciplinary approach including chemotherapy (systemic and in selected cases intraperitoneal).

Extrahepatic disease can be either extra-abdominal or intra-abdominal. The most common forms of intra-abdominal extrahepatic disease are hepatic pedicle lymph node metastases and peritoneal carcinomatosis.

### Hepatic Pedicle Lymph Node Involvement

The incidence of hepatic pedicle lymph node metastases ranges from 3% to 33% in patients with hepatic colorectal metastases. In patients with hepatic pedicle lymph node involvement, the reported 5-year survival rate after resection of colorectal liver metastases ranges from 5% to 42%.<sup>76,77</sup> A prospective study evaluated whether hepatic pedicle lymph node dissection could improve the outcome in such patients.<sup>76</sup> This study found that the survival rate was significantly lower among patients with than among those without hepatic pedicle lymph node metastases. However, the survival rate after hepatic pedicle lymph node dissection was significantly higher among patients with node involvement limited to area 1 (hepatoduodenal ligament and retropancreatic nodes) than among patients with involvement of area 2 (common hepatic artery and celiac axis nodes). Finally, the study found that hepatic pedicle lymph node involvement was significantly more frequent in patients with more than three metastases, when the metastasis was located in segments IV and V, with a solitary resectable peritoneal deposit, or with poorly differentiated adenocarcinoma. The best strategy for patients presenting with hepatic colorectal metastases and hepatic pedicle lymph node involvement is not well defined, and the role of aggressive treatment of hepatic pedicle lymph node involvement, even when a curative resection can be achieved, is still a matter of discussion.

### Peritoneal Carcinomatosis

In a large series of patients, investigators from the Gustave Roussy Institute<sup>78,79</sup> evaluated whether resection of extrahepatic disease could improve the outcome of patients with resectable hepatic colorectal metastases. They showed that the survival rate was significantly lower for patients with extrahepatic disease than for those without extrahepatic disease. However, they also showed that a 5-year survival rate ranging from 12% to 37% could be obtained in selected patients with extrahepatic disease depending on the type of disease (lung metastasis, primary colorectal recurrence, retroperitoneal or hepatic pedicle lymph node involvement, peritoneal carcino-

matosis, or miscellaneous). Interestingly, among patients presenting with extrahepatic disease, the survival rate was significantly higher in patients with fewer than five liver metastases, in patients who received neoadjuvant chemotherapy, and in those in whom a complete resection could be achieved. Therefore, resection of intra-abdominal extrahepatic disease during hepatectomy for colorectal liver metastases should be performed provided a negative resection margin is achieved.

### Consensus Statement

1. Extrahepatic disease (except the primary colorectal tumor) is typically a contraindication to resection.
2. The rationale for resection of resectable extrahepatic disease associated with hepatic colorectal metastases has been based on the lack of nonsurgical curative therapies.
3. The incidence of hepatic pedicle lymph node involvement in patients with hepatic metastases is 3%–33% and correlates with the extent of liver disease.
4. No data convincingly demonstrate that resection of portal nodes confers a survival advantage. The presence of positive nodes in the paraaortic or celiac zone is associated with an extremely poor prognosis.
5. Extrahepatic disease in the lung that is resectable with a complete resection and local recurrence in the bowel should be resected in patients undergoing hepatic resection.
6. Resection of low-volume peritoneal carcinomatosis has not been demonstrated to improve survival and should only be performed in the context of a clinical trial.

### REFERENCES

1. Rastogi T, Hildesheim A, Sinha R. Opportunities for cancer epidemiology in developing countries. *Nat Rev Cancer* 2004; 4:909–17.
2. Bouvier AM, Remontet L, Jouglu E, et al. Incidence of gastrointestinal cancers in France. *Gastroenterol Clin Biol* 2004; 28:877–81.
3. Geoghegan JG, Scheele J. Treatment of colorectal liver metastases. *Br J Surg* 1999; 86:158–69.
4. Welch JP, Donaldson GA. The clinical correlation of an autopsy study of recurrent colorectal cancer. *Ann Surg* 1979; 189:496–502.
5. Faivre J, Manfredi S, Bouvier AM. [Epidemiology of colorectal cancer liver metastases]. *Bull Acad Natl Med* 2003; 187:815–22.
6. Yamamoto J, Shimada K, Kosuge T, et al. Factors influencing survival of patients undergoing hepatectomy for colorectal metastases. *Br J Surg* 1999; 86:332–7.
7. Minagawa N, Nakayama Y, Hirata K, et al. Correlation of plasma level and immunohistochemical expression of vascular endothelial growth factor in patients with advanced colorectal cancer. *Anticancer Res* 2002; 22:2957–63.
8. Ercolani G, Grazi GL, Ravaoli M, et al. Liver resection for multiple colorectal metastases: influence of parenchymal involvement and total tumor volume, vs number or location, on long-term survival. *Arch Surg* 2002; 137:1187–92.
9. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. *Ann Surg* 2002; 235:759–66.
10. Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg* 2004; 239:818–25.
11. Mann CD, Metcalfe MS, Leopardi LN, Maddern GJ. The clinical risk score: emerging as a reliable preoperative prognostic index in hepatectomy for colorectal metastases. *Arch Surg* 2004; 139:1168–72.
12. Adam R, Lucidi V, Bismuth H. Hepatic colorectal metastases: methods of improving resectability. *Surg Clin North Am* 2004; 84:659–71.
13. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg* 2004; 240:644–57.
14. Adam R, Pascal G, Castaing D, et al. Tumor progression while on chemotherapy: a contraindication to liver resection for multiple colorectal metastases?. *Ann Surg* 2004; 240:1052–61.
15. Fusai G, Davidson BR. Management of colorectal liver metastases. *Colorectal Dis* 2003; 5:2–23.
16. Fong Y. Surgical therapy of hepatic colorectal metastasis. *CA Cancer J Clin* 1999; 49:231–55.
17. Stangl R, Altendorf-Hofmann A, Charnley RM, Scheele J. Factors influencing the natural history of colorectal liver metastases. *Lancet* 1994; 343:1405–10.
18. Giacchetti S, Itzhaki M, Gruia G, et al. Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin and surgery. *Ann Oncol* 1999; 10:663–9.
19. Ong SY. Neoadjuvant chemotherapy in the management of colorectal metastases: A review of the literature. *Ann Acad Med Singapore* 2003; 32:205–11.
20. Rougier P, Guimbaud R, Mitry E, Vaillant JN. [Chemotherapy with curative intent before (neoadjuvant) or after (adjuvant) surgery for colorectal cancer liver metastases]. *Bull Acad Natl Med* 2003; 187:881–92.
21. Masi G, Allegrini G, Cupini S, et al. First-line treatment of metastatic colorectal cancer with irinotecan, oxaliplatin and 5-fluorouracil/leucovorin (FOLFOXIRI): results of a phase II study with a simplified biweekly schedule. *Ann Oncol* 2004; 15:1766–72.
22. Pozzo C, Basso M, Cassano A, et al. Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients. *Ann Oncol* 2004; 15:933–9.
23. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; 18:2938–47.
24. Rougier P, Van Cutsem E, Bajetta E, et al. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *Lancet* 1998; 352:1407–12.
25. Levi F, Zidani R, Misset JL. Randomised multicentre trial of chronotherapy with oxaliplatin, fluorouracil, and folinic acid in

- metastatic colorectal cancer. International Organization for Cancer Chronotherapy. *Lancet* 1997; 350:681–6.
26. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; 350:2335–42.
  27. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004; 351:337–45.
  28. Rubio ED, Tabernero J, Cutsem EV et al. Cetuximab in combination with oxaliplatin/5-fluorouracil (5-FU)/folinic acid (FA) (FOLFOX-4) in the first-line treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer: An international phase II study. *American Society of Clinical Oncology (ASCO)* 2005; Abstract No: 3535.
  29. Hoff PM, Eng C, Adinin RB et al. Preliminary results from a phase II study of FOLFIRI plus bevacizumab as first-line treatment for metastatic colorectal cancer (mCRC) *American Society of Clinical Oncology (ASCO)* 2006; Abstract No: 252.
  30. Folprecht G, Grothey A, Alberts S, et al. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. *Ann Oncol* 2005; 16:1311–9.
  31. Bismuth H, Adam R, Levi F, et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Ann Surg* 1996; 224:509–20.
  32. Zelek L, Bugat R, Cherqui D, et al. Multimodal therapy with intravenous biweekly leucovorin, 5-fluorouracil and irinotecan combined with hepatic arterial infusion pirarubicin in non-resectable hepatic metastases from colorectal cancer (a European Association for Research in Oncology trial). *Ann Oncol* 2003; 14:1537–42.
  33. Alberts SR, Horvath WL, Sternfeld WC, et al. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. *J Clin Oncol* 2005; 23:9243–9.
  34. Karoui M, Penna C, Amin-Hashem M, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. *Ann Surg* 2006; 243:1–7.
  35. Vauthey JN, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in ninety-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol* 2006; 24:2065–72.
  36. Elias D, Cavalcanti A, de Baere T, et al. [Long-term oncological results of hepatectomy performed after selective portal embolization]. *Ann Chir* 1999; 53:559–64.
  37. Pawlik TM, Izzo F, Cohen DS, et al. Combined resection and radiofrequency ablation for advanced hepatic malignancies: results in 172 patients. *Ann Surg Oncol* 2003; 10:1059–69.
  38. Adam R, Laurent A, Azoulay D, et al. Two-stage hepatectomy: A planned strategy to treat irresectable liver tumors. *Ann Surg* 2000; 232:777–85.
  39. Ijichi M, Makuuchi M, Imamura H, Takayama T. Portal embolization relieves persistent jaundice after complete biliary drainage. *Surgery* 2001; 130:116–8.
  40. Uesaka K, Nimura Y, Nagino M. Changes in hepatic lobar function after right portal vein embolization. An appraisal by biliary indocyanine green excretion. *Ann Surg* 1996; 223:77–83.
  41. Hirai I, Kimura W, Fuse A, et al. Evaluation of preoperative portal embolization for safe hepatectomy, with special reference to assessment of nonembolized lobe function with 99mTc-GSA SPECT scintigraphy. *Surgery* 2003; 133:495–506.
  42. Vauthey JN, Chaoui A, Do KA, et al. Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. *Surgery* 2000; 127:512–9.
  43. Denys A, Madoff DC, Doenz F, et al. Indications for and limitations of portal vein embolization before major hepatic resection for hepatobiliary malignancy. *Surg Oncol Clin N Am* 2002; 11:955–68.
  44. Soyer P, Roche A, Elias D, Levesque M. Hepatic metastases from colorectal cancer: influence of hepatic volumetric analysis on surgical decision making. *Radiology* 1992; 184:695–7.
  45. Heymsfield SB, Fulenwider T, Nordlinger B, et al. Accurate measurement of liver, kidney, and spleen volume and mass by computerized axial tomography. *Ann Intern Med* 1979; 90:185–7.
  46. Abdalla EK, Hicks ME, Vauthey JN. Portal vein embolization: rationale, technique and future prospects. *Br J Surg* 2001; 88:165–75.
  47. Vauthey JN, Abdalla EK, Doherty DA, et al. Body surface area and body weight predict total liver volume in Western adults. *Liver Transpl* 2002; 8:233–40.
  48. Urata K, Kawasaki S, Matsunami H, et al. Calculation of child and adult standard liver volume for liver transplantation. *Hepatology* 1995; 21:1317–21.
  49. Johnson TN, Tucker GT, Tanner MS, Rostami-Hodjegan A. Changes in liver volume from birth to adulthood: A meta-analysis. *Liver Transpl* 2005; 11:1481–93.
  50. Vauthey JN, Pawlik TM, Abdalla EK, et al. Is extended hepatectomy for hepatobiliary malignancy justified?. *Ann Surg* 2004; 239:722–32.
  51. Abdalla EK, Barnett CC, Doherty D, et al. Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. *Arch Surg* 2002; 137:675–80.
  52. Abdalla EK, Denys A, Chevalier P, et al. Total and segmental liver volume variations: implications for liver surgery. *Surgery* 2004; 135:404–10.
  53. Kooby DA, Fong Y, Suriawinata A, et al. Impact of steatosis on perioperative outcome following hepatic resection. *J Gastrointest Surg* 2003; 7:1034–44.
  54. Behrns KE, Tsiotos GG, DeSouza NF, et al. Hepatic steatosis as a potential risk factor for major hepatic resection. *J Gastrointest Surg* 1998; 2:292–8.
  55. Azoulay D, Castaing D, Krissat J, et al. Percutaneous portal vein embolization increases the feasibility and safety of major liver resection for hepatocellular carcinoma in injured liver. *Ann Surg* 2000; 232:665–72.
  56. Shirabe K, Shimada M, Gion T, et al. Postoperative liver failure after major hepatic resection for hepatocellular carcinoma in the modern era with special reference to remnant liver volume. *J Am Coll Surg* 1999; 188:304–9.
  57. Kubota K, Makuuchi M, Kusaka K, et al. Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. *Hepatology* 1997; 26:1176–81.
  58. Farges O, Belghiti J, Kianmanesh R, et al. Portal vein embolization before right hepatectomy: prospective clinical trial. *Ann Surg* 2003; 237:208–17.
  59. de Baere T, Roche A, Vavasseur D, et al. Portal vein embolization: utility for inducing left hepatic lobe hypertrophy before surgery. *Radiology* 1993; 188:73–7.
  60. Capussotti L, Muratore A, Ferrero A, et al. Extension of Right Portal Vein Embolization to Segment IV Portal Branches. *Arch Surg* 2005; 140:1100–3.
  61. Nagino M, Nimura Y, Kamiya J, et al. Right or left trisegment portal vein embolization before hepatic trisegmentectomy for hilar bile duct carcinoma. *Surgery* 1995; 117:677–81.
  62. Nagino M, Kamiya J, Kanai M, et al. Right trisegment portal vein embolization for biliary tract carcinoma: technique and clinical utility. *Surgery* 2000; 127:155–60.
  63. Madoff DC, Abdalla EK, Gupta S, et al. Transhepatic ipsilateral right portal vein embolization extended to segment IV: improving hypertrophy and resection outcomes with spherical particles and coils. *J Vasc Interv Radiol* 2005; 16:215–25.

64. Madoff DC, Abdalla EK, Vauthey JN. Portal vein embolization in preparation for major hepatic resection: evolution of a new standard of care. *J Vasc Interv Radiol* 2005; 16:779–90.
65. Elias D, De Baere T, Roche A, et al. During liver regeneration following right portal embolization the growth rate of liver metastases is more rapid than that of the liver parenchyma. *Br J Surg* 1999; 86:784–8.
66. Kokudo N, Tada K, Seki M, et al. Proliferative activity of intrahepatic colorectal metastases after preoperative hemihepatic portal vein embolization. *Hepatology* 2001; 34:267–72.
67. Abdalla EK, Smith DL, Madoff DC et al. Portal vein embolization of the entire tumor-bearing liver prior to major hepatectomy is not associated with significant tumor growth. *HPB* 2004;6:6 - Abstract No. 18.
68. Madoff DC, Hicks ME, Abdalla EK, et al. Portal vein embolization with polyvinyl alcohol particles and coils in preparation for major liver resection for hepatobiliary malignancy: safety and effectiveness—study in 26 patients. *Radiology* 2003; 227:251–60.
69. Madoff DC. Portal vein embolization using polyvinyl alcohol and coils in preparation for major liver resection in patients with advanced hepatobiliary malignancy. *J Vasc Interv Radiol* 2001; 12:S39.
70. Shoup M, Gonen M, D'Angelica M, et al. Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. *J Gastrointest Surg* 2003; 7:325–30.
71. Cady B, Jenkins RL, Steele GD Jr., et al. Surgical margin in hepatic resection for colorectal metastasis: a critical and improvable determinant of outcome. *Ann Surg* 1998; 227:566–71.
72. Bowles BJ, Machi J, Limm WM, et al. Safety and efficacy of radiofrequency thermal ablation in advanced liver tumors. *Arch Surg* 2001; 136:864–9.
73. Wood TF, Rose DM, Chung M, et al. Radiofrequency ablation of 231 unresectable hepatic tumors: indications, limitations, and complications. *Ann Surg Oncol* 2000; 7:593–600.
74. Bleicher RJ, Allegra DP, Nora DT, et al. Radiofrequency ablation in 447 complex unresectable liver tumors: lessons learned. *Ann Surg Oncol* 2003; 10:52–8.
75. Solbiati L, Livraghi T, Goldberg SN, et al. Percutaneous radiofrequency ablation of hepatic metastases from colorectal cancer: long-term results in 117 patients. *Radiology* 2001; 221:159–66.
76. Jaeck D, Nakano H, Bachellier P, et al. Significance of hepatic pedicle lymph node involvement in patients with colorectal liver metastases: a prospective study. *Ann Surg Oncol* 2002; 9:430–8.
77. Laurent C, Sa Cunha A, Couderc P, et al. Influence of post-operative morbidity on long-term survival following liver resection for colorectal metastases. *Br J Surg* 2003; 90:1131–6.
78. Elias D, Ouellet JF, Bellon N, et al. Extrahepatic disease does not contraindicate hepatectomy for colorectal liver metastases. *Br J Surg* 2003; 90:567–74.
79. Elias D, Liberale G, Vernerey D, et al. Hepatic and extrahepatic colorectal metastases: when resectable, their localization does not matter, but their total number has a prognostic effect. *Ann Surg Oncol* 2005; 12:900–9.