DOI:10.1111/j.1477-2574.2012.00557.x HPB

ORIGINAL ARTICLE

Selection for hepatic resection of colorectal liver metastases: expert consensus statement

Reid B. Adams[1], Thomas A. Aloia[2], Evelyne Loyer[3], Timothy M. Pawlik[4], Bachir Taouli[5] & Jean-Nicolas Vauthey[2]

[1]Division of General Surgery, University of Virginia School of Medicine, Charlottesville, VA, Departments of [2]Surgical Oncology and [3]Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX, [4]Department of Surgery, Johns Hopkins University, Baltimore, MD, and [5]Department of Radiology, Mount Sinai Medical Center, New York, NY, USA

Abstract

Hepatic resection offers a chance of a cure in selected patients with colorectal liver metastases (CLM). To achieve adequate patient selection and curative surgery, (i) precise assessment of the extent of disease, (ii) sensitive criteria for chemotherapy effect, (iii) adequate decision making in surgical indication and (iv) an optimal surgical approach for pre-treated tumours are required. For assessment of the extent of the disease, contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI) with gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) is recommended depending on the local expertise and availability. Positron emission tomography (PET) and PET/CT may offer additive information in detecting extrahepatic disease. The RECIST criteria are a reasonable method to evaluate the effect of chemotherapy. However, they are imperfect in predicting a pathological response in the era of modern systemic therapy with biological agents. The assessment of radiographical morphological changes is a better surrogate of the pathological response and survival especially in the patients treated with bevacizumab. Resectability of CLM is dependent on both anatomic and oncological factors. To decrease the surgical risk, a sufficient volume of liver remnant with adequate blood perfusion and biliary drainage is required according to the degree of histopathological injury of the underlying liver. Portal vein embolization is sometimes required to decrease the surgical risk in a patient with small future liver remnant volume. As a complete radiological response does not signify a complete pathological response, liver resection should include all the site of a tumour detected prior to systemic treatment.

Received 26 July 2012; accepted 29 July 2012

Correspondence

Jean-Nicolas Vauthey, Anderson Cancer Center, 1515 Holcombe Blvd, Unit 444, Houston, TX 77030, USA. Tel: 1 713 792 2022. Fax: 1 713 745 1921. E-mail: jvauthey@mdanderson.org

Pre-therapeutic imaging evaluation of colorectal liver metastases

Adequate pretreatment imaging is critical for patients with suspected colorectal cancer (CRC) liver metastases for diagnosis, staging, pre-surgical and treatment planning, and post-treatment evaluation. The goals of pre-operative imaging in patients with CRC liver metastases are to: (i) define the number and segmental/lobar distribution, (ii) determine surgical resectability and (iii) identify any extra-hepatic disease.[1]

Imaging techniques and results in CRC liver metastases

Options available for hepatic imaging include ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI) and fluorodeoxyglucose-positron emission tomography (FDG-PET). The modality of choice will be dictated by local availability and expertise, the limitations and purpose of the study and prior imaging results.

US and contrast-enhanced US

Transabdominal US plays a limited role in the diagnosis of CRC liver metastases, given its limited sensitivity of 50–75%[2] and its operator-dependent nature. However, it may be the initial imaging choice in centres with expertise. The addition of intravenous (i.v.)

Proceedings of the Consensus Conference on Multidisciplinary Treatment of Colorectal Cancer Liver Metastases sponsored by the Americas Hepato-Pancreato-Biliary Association and co-sponsored by the Society of Surgical Oncology, the Society for Surgery of the Alimentary Tract and the University of Texas M.D. Anderson Cancer Center held in San Francisco, CA, USA; January 18, 2012.

contrast improves sensitivity by about 20%, results similar to those seen with MDCT (multi-detector CT).[2–4] The use of perflubutane ultrasound microbubbles (Sonazoid; Amersham Health, Princeton, NJ, USA) improves detection and characterization of focal liver lesions.[5] Liver lesions are detected with higher sensitivity using Sonazoid-enhanced US compared with CECT (contrast-enhanced CT), especially for small tumours.[6,7] However, US contrast agents are not Food and Drug Administration approved in the United States.

The best reference standard for the detection of liver metastases is intra-operative US (IOUS) combined with surgical exploration, typically performed at the time of hepatic surgery.[8,9] IOUS often alters the pre-operative surgical plan.[10] In a comparison between IOUS and helical CT on 250 patients undergoing surgical resection, IOUS detected additional tumours in 27% of patients.[11] Even improvements in cross-sectional imaging did not alter the beneficial role of IOUS, which altered surgical management in 20% of patients in two different time periods to account for improvements in CT scanning.[12] However, advances in MDCT and MRI ultimately may reduce the utility of IOUS.[13,14] More recent results advocate the use of contrast-enhanced IOUS (CE-IOUS) based on a study of 60 patients with CRC.[15] CE-IOUS had greater sensitivity compared with CT/MR and IOUS (96.1% vs. 76.7% and 81.5%, respectively). Similar to transabdominal ultrasound, a limitation of IOUS is its operator dependence.

Multidetector row CT (MDCT)

MDCT is routinely used for the detection of CRC liver and lung metastases.[16] MDCT offers high temporal and spatial resolution, is widely available and relatively inexpensive. Contrast enhancement with a bolus-tracking technique is required for optimization of arterial and portal venous phase imaging and the detection of lesions. The arterial phase of enhancement is typically obtained 20–30 s after the injection of contrast, whereas the portal venous phase is obtained at approximately 60 s. Generally, CRC metastases are hypovascular, more evident during portal venous phase imaging,[17] appearing hypodense compared with normal liver parenchyma, often demonstrating rim enhancement that subsequently washes out on later phases.[13] Arterial phase imaging using a high contrast injection rate is useful for surgical planning as it delineates vascular anatomy and the relationship of intrahepatic lesions to these structures.

Liver metastases have a variable appearance on unenhanced CT, with the majority being hypointense. Calcifications may occur with mucinous adenocarcinoma.[18] A limitation of CT is the patient exposure to ionizing radiation and the potential for reactions to iodinated contrast. A second common limitation is the inability to adequately characterize sub-centimetre lesions, which are too small to accurately differentiate as metastatic or benign, even in patients with known primary malignancies.[19,20]

MRI

Recent technological advances in hardware and software, together with the development of a variety of MR contrast agents have made MRI the most accurate imaging technique for detection and characterization of liver masses, including metastases.[21–23] MRI does not use ionizing radiation, offers higher contrast resolution and the possibility of performing multiparametric imaging, combining T1, T2, and diffusion-weighted imaging (DWI) with dynamic multiphasic contrast imaging. State of the art MRI now routinely offers thin 3D T1-weighted dynamic acquisitions.[24] In addition, 3T MRI offers higher spatial resolution compared with 1.5T MRI, owing to the improved signal-to-noise ratio. CRC liver metastases are generally hypointense on T1W pre-contrast, slightly T2 hyperintense, with restricted diffusion (bright on high *b*-value diffusion with low apparent diffusion coefficient, except in necrotic metastases[25]). After gadolinium contrast injection, CRC metastases generally display a hypovascular enhancement pattern, with internal enhancement on portal venous or late venous phase images.[26] Perilesional enhancement in the form of circular or wedge-shaped enhancement may also be seen.[27] Compared with CT, MRI has the potential advantage of increased lesion conspicuity given the number of different imaging sequences employed.[25] DWI also improves liver lesion conspicuity compared with T2W sequences.[28,29]

Several i.v. contrast agents with differing performance characteristics are available to improve detection and characterization of liver lesions.[30] Extracellular gadolinium chelates such as gadopentetate dimeglumine (Gd-DTPA, Magnevist; Bayer Healthcare Pharmaceuticals, Berkeley, CA, USA) are used routinely in abdominal MRI. Hepatobiliary agents such as gadobenate dimeglumine (Gd-BOPTA; Multihance, Bracco Diagnostics, Princeton, NJ, USA) or gadoxetate disodium (Gd-EOB-DTPA, Eovist or Primovist; Bayer Healthcare Pharmaceuticals) can improve characterization of small liver lesions as they are taken up by normal liver parenchyma, but excluded from metastatic lesions.[31,32] Shimada *et al.*[33] assessed detection of small metastatic lesions ($\leq$2 cm), using a 3T system, showing an area under the curve (AUC) of 0.958–0.966 for Gd-EOB-DTPA and 0.881–0.906 for DWI (for two observers). Lowenthal *et al.*[34] demonstrated superiority of Gd-EOB-DTPA enhanced MRI for the detection of CRC metastases (detection rate 94.4% and 100% for 2 observers) compared with DWI (78.3% and 97.5%). The delayed hepatocyte phase images after administration of Gd-EOB-DTPA have the disadvantage of missing small hepatic lesions near small vascular structures; these are better detected with DWI.[35,36] Recently, Koh *et al.* showed the combination of DWI and Gd-EOB-DTPA-enhanced T1 weighted imaging significantly improved the detection of CRC liver metastases, over each technique alone.[36] The primary limitations of MRI are costs, contra-indications, and access to specialized techniques and the expertise to interpret them.

PET and PET/CT

F18-FDG-PET imaging detects metabolically active tumour cells. Optimal PET imaging is performed with concurrent CT, providing a metabolic map of glucose uptake throughout the entire body. PET is routinely used in the evaluation of patients with

malignancies, demonstrating high sensitivity and specificity for detection of liver metastases, with the advantage of detection of extrahepatic metastases, which can have profound implications for patient management.[37] PET and PET/CT are superior to CT or MRI for detection of extrahepatic metastases, local recurrence, or diagnosis of indeterminate hepatic lesions.[38–42] The use of i.v. contrast during the CT portion of a PET/CT examination improves the detection of CRC liver metastases.[43] However, PET is less effective for the diagnosis of small pulmonary nodules or the detection of intrahepatic recurrence especially in patients who have undergone chemotherapy.[44] Other limitations of PET/CT imaging include limited availability, cost and the uncertainty surrounding its utility and the timing of its use during treatment planning for CRC metastases.

Comparison between imaging modalities

Each imaging modality has specific advantages and disadvantages, related to cost, speed of acquisition, the use of ionizing radiation, the risk of contrast reaction, and local availability and expertise. Sensitivity and specificity reported for different imaging modalities depend on a number of factors. These include the number of patients, their tumour burden (high tumour burden patients will have many subcentimetre lesions, lowering overall sensitivity), the reference standard used (preferably histological examination of resected specimens), the prevalence of incidental benign lesions (which will affect the specificity), the contrast agent used for MRI (hepatobiliary agents, extracellular Gd chelates), previous chemotherapy and the presence of fatty liver.

Available evidence supports the use of MRI for the detection of CRC liver metastases based on two recent meta-analyses. Floriani *et al.*[45] compiled 25 articles and showed that sensitivity and specificity on a per-patient basis for US, CT, MRI and FDG-PET were 63.0% and 97.6%, 74.8% and 95.6%, 81.1% and 97.2, and 93.8% and 98.7%, respectively. On a per-lesion basis, sensitivity was 86.3%, 82.6%, 86.3% and 86.0%, respectively. MRI showed a better sensitivity than CT in per-patient and per-lesion analysis. In per-lesion analysis, the difference was higher when liver-specific contrast agents were administered. Niekel *et al.*[46] compiled 39 articles (3391 patients) and showed the following estimates of sensitivity per-lesion: CT 74.4%, MRI 80.3% and FDG PET 81.4%. Per-patient sensitivities were CT 83.6%, MRI 88.2% and FDG PET 94.1%. The per-patient sensitivity of CT was lower than that of FDG PET ($P = 0.025$). Specificity estimates were comparable. For lesions smaller than 10 mm, the sensitivity estimates for MRI were higher than those for CT. No differences were seen for lesions measuring at least 10 mm. In this meta-analysis, the use of liver-specific contrast material and MDCT scanners did not provide improved results. Data about FDG PET/CT were too limited for comparisons with other modalities. It was concluded that MRI was the preferred first-line modality for evaluating untreated CRC liver metastases.[46] Seo *et al.*[47] compared Gd-EOB-DTPA enhanced MRI (using 3T) with CE-PET/CT, and demonstrated a AUC of 0.94 vs. 0.81 for Gd-EOB-MRI vs. CE-PET/CT for all lesion sizes ($P < 0.001$), 0.92 vs. 0.60 for lesions ≤1 cm ($P < 0.001$) and 0.88 vs. 0.96 for lesions >1 cm ($P = 0.098$), respectively. It was concluded that Gd-EOB-enhanced MRI using a 3T system is more accurate than CE-PET/CT, especially for the detection of small (≤1.0 cm) lesions.

Finally, MRI is more sensitive for the detection of small CRC metastases (≤1 cm) compared with CT in the presence of chemotherapy associated steatosis.[48]

Consensus statement

1 The choice of imaging technique for pre-treatment assessment of colorectal liver metastases depends on local expertise and availability.
2 However, when the technical and interpretive expertise is available:
   a MRI combining Gd-EOB-DTPA delayed images and diffusion-weighted imaging has the best performance characteristics for detecting and characterizing liver lesions, particularly those < 1 cm in size. However, increased sensitivity may be associated with reduced specificity.
   b In patients with steatosis or changes secondary to preoperative chemotherapy, MRI is more sensitive for the detection of metastatic lesions and is the preferred imaging technique for these patients.
3 PET and PET/CT are useful for detecting extra-hepatic metastases and local recurrence. However, it is less effective for the diagnosis of small pulmonary nodules or the detection of small liver metastases.

Imaging evaluation of response

Imaging is the cornerstone of response evaluation in oncology. Established methods of evaluation rely on changes in tumour size as defined by the WHO and RECIST criteria.[49–51] The advent of targeted and locoregional therapies, however, are increasingly drawing attention to the shortcomings of this method while at the same time, advances in molecular imaging and image processing are opening up new opportunities for response evaluation.[52] Inconsistent agreement between the objective response and patient outcome underscores the need to establish better criteria.[53] Several sophisticated new methods exploring the response to treatment, such as perfusion CT and MRI, diffusion-weighted imaging and texture evaluation, are in the developmental stages.[52,54–58] In clinical practice, a tumour response in hepatic CRC metastasis can be evaluated from three different perspectives:

- a change in tumour size
- morphological changes unrelated to size
- functional imaging, using F18-FDG PET.

Change in tumour size

A change in tumour size is quantified and categorized into one of four groups used to judge the effect of the drug. The WHO crite-

ria, the first attempt at standardization, uses bidimensional measurements. In 2000, RECIST criteria were introduced to simplify data collection and increase standardization.[49] The RECIST criteria were revised in 2009 to clarify the evaluation of nodal disease, refine the definition of Progressive disease (PD) and further simplify data collection. The RECIST criteria use unidimentional measurement and are based on the sum of the maximal transverse diameters of up to five target lesions measured before and after treatment. The percentage difference between the two measurements is used to categorize treatment response. Broadly, partial response (PR) is defined by a decrease of at least 30% of the pretreatment sum. PD is defined by an increase of at least 20% and at least 5 mm in the sum, or a new lesion.[51] A complete response (CR) is defined by the disappearance of all lesions and stable disease (SD) by a lack of change.[51] It is extremely important to note that although radiological CR may reflect pathological CR, it is not always synonymous with pathological CR. Consequently, all metastatic sites identified on pre-chemotherapy imaging need to be resected.[59] This highlights the critical value of high-quality pre-chemotherapy scans.

A change in tumour size is a strong indicator of a response, but recent studies have questioned the clinical value of the categorical definitions of RECIST, and the choice of threshold values that were developed in an era when precise measurements were not feasible. The need for a 30% decrease in tumour size derives from historical data collected at a time when a precise measurement was impossible. Today, the available imaging techniques allow better estimation. Two recent studies show that an early decrease in size of 10% correlates better with outcome than the established 30% decrease by RECIST.[60,61] These results indicate the cut-off value and optimal time of evaluation need reappraisal.

Non-size-based morphological parameters

Increasingly, studies recognize morphological features as valid indicators of a response, particularly with targeted therapy. Features such as modification of the tumour texture, enhancement and margins are reflections of a response regardless of a change in tumour size.[51,62] This correlation was first observed with gastrointestinal stromal tumours (GIST), leading to establishment of the Choi criteria.[62] Similar changes occur in hepatic CRC metastases treated with bevacizumab-containing chemotherapy.[63] Hepatic CRC metastases typically are heterogeneous with poorly defined margins. Tumours with an optimal response to therapy become homogeneous with sharp margins lacking enhancement. They acquire a pseudocystic appearance. Comparison of the subjectively judged pretreatment and post-treatment morphological characteristics allows classification of patients into optimal, partial or non-responders. The morphological radiographical response correlates very well with the pathological response, is a better indicator of a minor pathological response (with more than 50% of viable tumour) than RECIST, and correlates with overall survival.[63] It is important to note these criteria have been described with high-quality CT,[63] but are not yet validated with MRI. These criteria need to be validated in independent studies.

Functional imaging with F18-FDG PET

Many authors advocate using F18-FDG PET for response evaluation in hepatic CRC metastases.[64] Although a metabolic response reflects tumour volume, the data are insufficient to support the routine use of F18-FDG PET for response assessment in metastatic CRC.[65] Importantly, the sensitivity of PET decreases after systemic chemotherapy[44] and PET, like CT, is not an accurate indicator of a complete pathological response.[66] The most recent publication on the subject indicates that PET can identify patients that will not benefit from treatment after only one cycle of chemotherapy.[67]

Consensus statement

1 The RECIST criteria are routinely used criteria; however, they are limited for assessing a response to systemic and locoregional therapy in hepatic CRC. Newer data demonstrate the need to reassess the response criteria.
2 Morphological assessment is a better surrogate of a pathological response and survival than the RECIST criteria in patients receiving bevacizumab. However, this needs to be validated in larger independent studies.
3 The role of PET in evaluating a treatment response in metastatic CRC is undefined. Therefore, its routine use in this circumstance is not indicated.

Definition of resectability

After confirmation of medical fitness for general anaesthesia and major abdominal surgery, the eligibility for resection in patients with CRC metastases is determined by two domains: oncological and technical. From an oncological perspective, evaluation for extrahepatic disease and the response to pre-operative systemic therapy are the main considerations. From a technical perspective, resection is the preferred treatment option if all viable tumours can be removed with negative margins, while leaving an adequate functional liver remnant.

Oncological resectability

From an oncological perspective, in the era of effective systemic therapy, the goal of complete resection of all viable disease in patients with CRC liver metastases is critical as they are the most likely to benefit from this approach. This applies to extirpation of both intra- and extrahepatic disease.

Extrahepatic disease

All patients with CRC liver metastases require adequate pre-operative staging for the biochemical and radiological presence, location, multiplicity, volume and resectability of extrahepatic disease. Excluding the case of synchronous disease at the primary tumour site, the most common sites of extrahepatic disease

include recurrent colorectal involvement, intra-abdominal lymph node involvement and lung metastases.[68] Several previous studies report long-term post-hepatectomy survival in highly selected patients with clinically apparent extrahepatic disease.[68–74] These studies have defined clinical variables associated with poor outcomes including a positive resection margin,[68,71,72] extrahepatic disease site,[72–74] number of metastases[68,72,73] and an unanticipated intra-operative diagnosis.[71,72] In particular, regarding extrahepatic disease sites, patients with isolated lung metastases or periportal adenopathy have the best 5-year survivals (30–40%).[72] Those with limited volume peritoneal disease have intermediate 5-year survivals (15–30%), whereas patients with aortocaval adenopathy or multiple sites of disease rarely benefit from liver resection (5-year survivals <15%).[75] Furthermore, whether these variables are present or absent, posthepatectomy recurrence in patients with extrahepatic disease is nearly universal, ranging from 84% to 95%.[71–73,75]

These data suggest that patients harbouring limited extrahepatic disease amenable to surgical resection (e.g. isolated portal lymphadenopathy) or with reasonable expectations for long-term control with adjuvant therapies (e.g. small volume lung disease) and who have responded to pre-operative systemic therapy could be considered for hepatic resection. When the extrahepatic disease burden is not resectable or controllable, a hepatic metastasectomy is contraindicated.

Response to systemic therapy

When patients are treated with pre-operative systemic therapy prior to a hepatic resection, the patient and surgeon benefits by observing the biological behaviour of the tumour. Although uncommon with modern systemic therapy regimens, patients occasionally (5–15%) will progress during administration of systemic therapy, demonstrating growth of known lesions and/or development of new lesions.[76] Considering the potency of current therapy, disease progression represents a marker for aggressive tumour biology. Allen *et al.* in 2003[77] and Adam *et al.* in 2004[78] recognized the association between progression during pre-operative systemic therapy and poor post-hepatectomy survival. The previous study by Adam *et al.* indicated that in patients with > 3 liver metastases who progressed on chemotherapy the 5-year survival after liver resection was only 8%.[78] A more recent study challenges this concept,[79] finding no relationship between the pre-operative therapy response and survival. However, only 44% of patients in this study received modern therapy regimens compared with 85% in the Adam study.

Progression in the form of development of new lesions, regardless of location, is the strongest predictor of poor post-hepatectomy outcomes.[78] When patients progress in the form of new lesions during pre-operative chemotherapy, additional considerations include confirmation that the patient received a modern chemotherapy regimen, performance of tumoural genetic testing (i.e. K-ras and B-raf) and administration of second-line systemic therapy.[80] In contrast, the prognostic impact of progression in the form of pre-existing intrahepatic lesion growth during pre-operative chemotherapy is unclear, suggesting that patients with this pattern of progression and anatomically resectable lesions may remain candidates for a hepatectomy.

Technical resectability

Assessment of technical resectability requires a multifaceted analysis of liver anatomy, histology and function, best analyzed in a multidisciplinary setting with input from hepatobiliary surgeons, radiologists, hepatologists and pathologists. The previously proposed definition of technical resectability mandating 'a margin negative removal of all viable tumours leaving a minimum of two contiguous segments of hepatic parenchyma with adequate vascular inflow and outflow and adequate biliary drainage' has served the surgical community well.[1] More recently, the ability to accurately predict the future liver remnant volume and function has optimized the selection of patients with resectable CRC metastases.

Assessment of adequate postoperative (remnant) liver volume

Liver volumetry permits quantification of the anticipated future liver remnant (FLR) volume.[81,82] This allows patient stratification for the risk of liver failure after a major hepatectomy. Additionally, FLR assessment can guide selection of candidates who may benefit from portal vein embolization (PVE).[83–87] Studies confirm FLR hypertrophy after PVE, allowing a major hepatectomy in patients who were previously technically unresectable because the FLR was too small. This approach also lowers the risk of post-operative liver insufficiency for patients with borderline FLR volumes.[85,87–89] These data support the concept that patients with a normal liver, in general, will tolerate a reduction in liver volume to 20%. Those with chemotherapy-induced liver injury require a FLR volume of approximately 30% and those with cirrhosis require at least a 40% residual volume.[81,90,91]

Assessment of remnant liver function

The FLR volume after a major hepatectomy does not account for all the factors contributing to early post-operative liver insufficiency and mortality. In addition to the volume, function of the FLR has evolved as an important factor for consideration. Thus, technical resectability takes into account liver anatomy, FLR volume and function. Eastern countries use ICG excretion as a critical assay to assess liver function,[84,92] and consequently, resectability. ICG excretion is not widely available in the West, thus surgeons have relied more on laboratory assessments of liver function, such as solitary values (e.g. serum bilirubin) or aggregate scores (e.g. model for end-stage liver disease[93]). For patients with abnormal liver laboratories and/or imaging, a liver biopsy may confirm the presence of histological abnormalities. This information is combined with clinical expertise to decide whether the patient's liver function is sufficient to support a hepatectomy. With increased utilization of pre-operative systemic chemo-

therapy,[94] and the epidemics of obesity[95] and viral hepatitis,[96] it has become increasingly hazardous to perform a major hepatectomy in the absence of an objective measure of FLR function.

One of the few accurate tests available for the assessment of the functional and regenerative capacity of the FLR is PVE.[81–84] The FLR's ability to hypertrophy in response to PVE is a highly reliable indicator of the function of the remnant liver. Therefore, hypertrophy should be considered another criteria for resectability in patients with marginal FLR volumes.[85,86] Furthermore, recent data indicates a high risk of post-operative liver failure for patients with marginal FLR volumes when the FLR does not hypertrophy after PVE by at least 5 percentage points. Although the liver continues to hypertrophy over time after PVE, patients without adequate hypertrophy within 10 weeks of a technically successful PVE should be approached with extreme caution.[85]

Resectional strategies

The suitability of a surgical strategy for the treatment of CRC metastases is evaluated by its safety and oncological efficacy. With limited liver tumour burden, including small volume and anatomically favourably positioned bilateral metastases, a one-stage strategy involving one or more simultaneous partial to lobar hepatic resections is safe and effective.[97–102] When extensive bilobar metastases are present, several surgical strategies are available. The most frequently utilized is a two-stage strategy with initial resection of tumours within the future liver remnant contralateral to planned PVE, followed by percutaneous PVE and a subsequent ipsilateral second-stage resection. The percutaneous technique of PVE is more effective at inducing liver hypertrophy than simple portal ligation.[103,104] For patients who are candidates for this approach and complete the second stage, long-term survivals are equivalent to patients with more limited disease treated with a conventional single-stage strategy.[103]

Several recent publications describe novel approaches to treat patients with extensive bilobar CRC metastases.[105–108] While innovative, current experience with these techniques is limited and the data available regarding the safety and oncological profile are insufficient to advocate any of these as valid resectional strategies.

Margin status

The acceptable margin width necessary when resecting CRC liver metastases has been debated for decades. Prior to effective systemic therapy, studies identified a survival advantage when a negative margin width of 1 cm was achieved and a consensus developed that this margin width was not only optimal, but defined resectability.[109–111] Recent studies that include patients treated with pre-operative systemic therapy, consistently have found that the resection margin width, as long as no tumour cells are microscopically present at the margin, does not impact long-term survival.[112–116] Two recent detailed analyses provide the genetic and pathological bases for this argument.[117,118]

Several authors hypothesize that surgical transection techniques and effective chemotherapy minimize the impact of a sub-centimeter margin on long-term outcomes. One group suggests the prognostic distinction between R0 and R1 (microscopically positive margin) is diminishing in the current era of systemic chemotherapy.[119] Unfortunately, more definitive conclusions regarding optimal and acceptable margins of resection are confounded by differences in study patient populations, including the per cent of patients receiving modern pre-operative chemotherapy.

Combined, these studies support a consensus that resectability of CRC liver metastases be based on a minimal goal of achieving a margin-negative resection. Therefore, patients with hepatic metastases, regardless of the anatomic distribution or relationship to critical structures, should be considered resectable if the margin is expected to be a grossly and microscopically negative margin in a patient with a sufficiently sized FLR.

Conclusions

Published experience supports determination of resectability in patients with CRC liver metastases based on an adequate imaging evaluation and consideration of both oncological and technical aspects. From an oncological perspective, patients with limited and favourably located extrahepatic disease that is durably controllable with a second treatment modality and patients with minimal progression of existing disease during administration of pre-operative systemic therapy may still benefit from a hepatic resection and should be considered resectable.

From a technical perspective, the ability to remove all viable metastasis with negative microscopic margins, leaving a minimum of two contiguous segments of hepatic parenchyma with adequate vascular inflow and outflow, adequate biliary drainage and adequate functional regenerative capacity defines resectability. Any surgical approach with a proven record of safety and long-term oncological benefit that adheres to these principles is valid as a resectional strategy.

Consensus statement

Oncological criteria of resectability

1 Prior to considering resection of CRC hepatic metastases, pre-treatment radiological staging is required to assess for the presence and extent of intra- and extrahepatic disease.
2 Patients harbouring limited extrahepatic disease amenable to surgical resection or with reasonable expectations for long-term control with adjuvant therapies may be considered for a hepatic resection.
3 Patients with significant progression of metastatic disease (growth in more than three existing liver metastases and/or the development of multiple new lesions) during treatment with optimal pre-operative chemotherapy should have a surgical resection deferred until achieving disease control with second-line systemic or regional therapies.

Technical criteria of resectability

1 Resectability includes the expectation that a margin-negative resection (i.e. R0) can be achieved.
2 The technical feasibility of a hepatic resection should be based on four criteria related to the liver remnant after resection:
   a the anticipated ability to preserve two contiguous segments
   b the anticipated ability to preserve adequate vascular inflow, outflow and biliary drainage
   c the anticipated ability to preserve adequate FLR volume (20% in normal liver and 30% in pretreated liver with chemotherapy)
   d the demonstrated ability of the FLR to adequately function based on the appropriate regenerative response after PVE in patients with a marginal FLR volume and/or underlying liver disease.

Management of the disappearing metastasis

A subset of patients with CRC liver metastasis will be treated with pre-operative chemotherapy. Pre-operative chemotherapy can be used to treat patients with unresectable liver metastasis or in the neoadjuvant setting before surgery for resectable liver metastasis.[76,77,120,121] New chemotherapeutic and targeted agents have higher response rates than previous systemic agents.[59,122] The pathological response to pre-operative chemotherapy is strongly predictive of prognosis after a resection,[123]; however, the fate of patients with a complete radiological response is unclear.[59] The entity 'disappearing' metastases describes the complete radiological response after effective chemotherapy leading to several institutional reports describing their experiences with this situation.[59,122,124–127] Disappearing metastases become a problem when they are outside of the field of planned surgery. As such they should be defined as 'missing' metastases. It is best to avoid the problem of 'missing' liver metastasis by early involvement of the liver surgeon, preferably before the initiation of chemotherapy. In addition, limiting the duration of chemotherapy to a fixed, short course (e.g. in the neoadjuvant setting) or a response adequate to allow surgical resection (e.g. 'conversion' chemotherapy) is desirable. Placing fiducials or coils to mark small metastases at risk of becoming 'missing' before chemotherapy assists intra-operative localization of DLM.[128]

The incidence of disappearing liver metastasis (DLM) ranges from 5% to 38%.[59,122,124–127] A complete radiological response depends, however, on the quality and completeness of pre-operative imaging.[129] Until recently, contrast-enhanced multi-slice CT has been the primary imaging modality for CRC liver metastasis with sensitivities ranging from 60% to 90%.[15,130–132] However, pre-operative chemotherapy can cause steatosis or steatohepatitis, limiting the accuracy, interpretation, and consequently, the utility of CT for evaluating CRC liver metastasis.[133–135] Recent reports indicate MRI is superior to a CT scan for pre-operative characterization of CRC liver metastasis and the response to therapy after preoperative chemotherapy.[132] Auer *et al.* note that the inability to observe DLM on MRI is strongly associated (OR, 4.7; $P = 0.005$) with a true complete response at histology.[122] In this study, of the seven DLM detected at the site of its disappearance, six were detected by MRI. In a meta-analysis evaluating varying pre-operative imaging modalities, Bipat *et al.* note that MRI is more accurate than CT for detecting lesions after pre-operative chemotherapy.[130] These data support using MRI to evaluate patients with DLM as the best imaging technique to assess for residual disease and delineate those patients with a 'true' radiological complete response.

Among patients with DLM an extensive search for the lesions, including full mobilization of the liver, palpation and intra-operative ultrasound, is essential at the time of surgery.[136] Contrast-enhanced intra-operative ultrasonography is more sensitive for detecting DLM, finding an additional 10%–15% DLM vs. palpation and unenhanced ultrasonography.[136] The ability to detect DLM at the time of surgery ranges from 27% to 45%.[59,122,124,127] Benoist *et al.* report observing macroscopic disease among 24% of patients in spite of a pre-operative CT scan (in this study, metastases were evaluated only on CT-scan) showing a complete response.[59] More recently, van Vledder *et al.* report intra-operative detection of DLM in 45% of patients undergoing surgery.[127] The variability in detecting DLM at the time of surgery is undoubtedly multifactorial, but the most likely contributor is the quality of the pre-operative imaging. Specifically, the ability to detect the site of DLM is more common among patients without pre-operative MR imaging, suggesting these lesions are not 'true' complete responders, but rather are simply lesions undetected in the absence of MR imaging.[122,124,125]

The concordance between a complete clinical/radiological response and a complete pathological response is variable, ranging from 20% to 100%.[59,124–127] Benoist *et al.* reported viable tumour cells in 80% of pathologically examined specimens containing a DLM after short duration pre-operative chemotherapy and no targeted biological therapy.[59] van Vledder *et al.* reported a complete pathological response in 35% of DLM that were detected and resected. Others report a higher response, observing complete pathological responses in 58% of DLM, which were incorporated in the resection specimen, but not detected at the time of surgery.[127] Elias *et al.*[124] reported a pathological complete response of 45%, whereas Auer *et al.*[122] noted a complete response of 65%. The variability in complete pathological response rates probably is related to type and duration of chemotherapy.[129] For groups employing hepatic arterial infusion therapy, the incidence of a complete pathological response is much higher.[122,124,125] Specifically, Elias *et al.* reported a complete response rate of 86% among patients receiving hepatic arterial infusion therapy prior to surgery vs. 22% for those receiving systemic chemotherapy alone.[124,125] Collectively these data demonstrate that a complete radiological response is not equivalent to a complete pathological response.

In addition to a pathological response, DLM may result in a durable clinical response. In reviewing the literature, investigators

defined a durable clinical response as DLM without recurrence on follow-up imaging over a period of time (usually 1 year).[59,122,124,127] Previous reports indicate a higher incidence of recurrence for DLM left *in situ* when other resected DLM exhibit an incomplete pathological response.[129] Benoist *et al.* showed that a complete pathological response of 20% correlates with a similarly low durable clinical response of 25%.[59] van Vledder *et al.* reported 17 patients with unidentified, untreated DLM, who develop local recurrence at the initial site of disease in 10 (59%), with a median time to intra-hepatic recurrence of 11 months.[127] Again, similar to data on a pathological response, a durable clinical response is more likely after hepatic arterial therapy. Tanaka *et al.* reported nearly a 100% durable response after treatment with hepatic arterial infusion therapy.[126] Elias *et al.* used post-operative hepatic arterial infusion therapy achieving a durable response in 70% of patients.[124] Auer *et al.* reported that most lesions, when they recur, do so 10 to 20 months after cessation of chemotherapy.[122]

Not surprisingly, most studies report a higher rate of intrahepatic recurrence among patients with untreated DLM compared with those having complete resection of the DLM.[127] In several series, DLM recur in more than one-half of patients when the DLM are not resected.[59,127]A post-operative adjuvant hepatic arterial infusion results in a lower incidence of intrahepatic recurrence.[122,124–126] Overall 5-year survival for patients with DLM ranges from 40% to 80%.[59,122,124–127] Several reports find no statistically significant difference in overall survival among patients with some untreated DLM vs. those in whom all original DLM sites were excised.[127,129]

Because a complete pathological or durable clinical response for DLM occurs in only 20% to 40% of patients treated with systemic chemotherapy, surgical resection of CRC liver metastasis should include all original sites of disease. This recommendation is particularly pertinent when a major hepatectomy is not required and a limited resection has the potential to leave DLM *in situ*. In the situation of a mixed response to therapy, when some metastases disappear while other areas have residual macroscopic disease, the clinical approach is more controversial. While the recommendation is resection of all original sites of disease including the DLM, this is not always feasible. Resection of residual macroscopic disease while leaving DLM untreated may be reasonable in select patients, therefore, this approach is not considered an absolute contraindication to surgery.[129] Selective resection of residual macroscopic disease with or without some of the sites of DLM, while leaving other DLM sites untreated is appropriate only in a multidisciplinary setting. Prior to surgery, a chemotherapy break is valuable to allow a better evaluation as to whether, or which, DLM truly represent a durable clinical response off chemotherapy. The goal of such an approach is to extirpate all macroscopic or residual sites of disease while assuming that the untreated, non-recurrent DLM sites will remain quiescent. One should consider resuming systemic chemotherapy or hepatic arterial infusion therapy in the adjuvant setting with this approach.[129]

Consensus statement

1 A complete radiological response does not signify a complete pathological response as residual microscopic disease can be expected in up to 90% of patients with resected DLM treated with pre-operative systemic chemotherapy.
2 From a surgical perspective, not all 'disappearing' liver metastases and only those 'missing' (i.e. outside of planned resection field) are relevant.
3 Multidisciplinary assessment with appropriate imaging prior to chemotherapy would minimize the occurrence of 'missing' metastases.
4 In patients with metastases at risk of disappearing and missing at surgery, placement of a fiduciary marker by interventional radiology should be considered.
5 Because a complete pathological or durable clinical response for DLM occurs in only 20% to 40% of patients treated with systemic chemotherapy, surgical resection of CRC liver metastasis should include all original sites of disease.

Conflicts of interest

None declared.

References

1. Charnsangavej C, Clary B, Fong Y, Grothey A, Pawlik TM, Choti MA. (2006) Selection of patients for resection of hepatic colorectal metastases: expert consensus statement. *Ann Surg Oncol* 13:1261–1268. Epub 2006/09/02.
2. Konopke R, Kersting S, Bergert H, Bloomenthal A, Gastmeier J, Saeger HD *et al*. (2007) Contrast-enhanced ultrasonography to detect liver metastases: a prospective trial to compare transcutaneous unenhanced and contrast-enhanced ultrasonography in patients undergoing laparotomy. *Int J Colorectal Dis* 22:201–207.
3. Dietrich CF, Kratzer W, Strobe D, Danse E, Fessl R, Bunk A *et al*. (2006) Assessment of metastatic liver disease in patients with primary extrahepatic tumors by contrast-enhanced sonography versus CT and MRI. *World J Gastroenterol* 12:1699–1705. Epub 2006/04/06.
4. Larsen LP, Rosenkilde M, Christensen H, Bang N, Bolvig L, Christiansen T *et al*. (2007) The value of contrast enhanced ultrasonography in detection of liver metastases from colorectal cancer: a prospective double-blinded study. *Eur J Radiol* 62:302–307.
5. Sugimoto K, Shiraishi J, Moriyasu F, Saito K, Doi K. (2009) Improved detection of hepatic metastases with contrast-enhanced low mechanical-index pulse inversion ultrasonography during the liver-specific phase of sonazoid: observer performance study with JAFROC analysis. *Acad Radiol* 16:798–809. Epub 2009/04/28.
6. Hatanaka K, Kudo M, Minami Y, Maekawa K. (2008) Sonazoid-enhanced ultrasonography for diagnosis of hepatic malignancies: comparison with contrast-enhanced CT. *Oncology* 75 (Suppl. 1):42–47. Epub 2009/02/20.
7. Moriyasu F, Itoh K. (2009) Efficacy of perflubutane microbubble-enhanced ultrasound in the characterization and detection of focal liver lesions: phase 3 multicenter clinical trial. *AJR Am J Roentgenol* 193:86–95. Epub 2009/06/23.
8. Cervone A, Sardi A, Conaway GL. (2000) Intraoperative ultrasound (IOUS) is essential in the management of metastatic colorectal liver lesions. *Am Surg* 66:611–615. Epub 2000/08/05.

9. Foroutani A, Garland AM, Berber E, String A, Engle K, Ryan TL *et al*. (2000) Laparoscopic ultrasound vs triphasic computed tomography for detecting liver tumors. *Arch Surg* 135:933–938. Epub 2000/08/02.
10. Kruskal JB, Kane RA. (2006) Intraoperative US of the liver: techniques and clinical applications. *Radiographics* 26:1067–1084. Epub 2006/07/18.
11. Scaife CL, Ng CS, Ellis LM, Vauthey JN, Charnsangavej C, Curley SA. (2006) Accuracy of preoperative imaging of hepatic tumors with helical computed tomography. *Ann Surg Oncol* 13:542–546. Epub 2006/02/14.
12. Ellsmere J, Kane R, Grinbaum R, Edwards M, Schneider B, Jones D. (2007) Intraoperative ultrasonography during planned liver resections: why are we still performing it? *Surg Endosc* 21:1280–1283. Epub 2007/02/13.
13. Sahani DV, Kalva SP, Tanabe KK, Hayat SM, O'Neill MJ, Halpern EF *et al*. (2004) Intraoperative US in patients undergoing surgery for liver neoplasms: comparison with MR imaging. *Radiology* 232:810–814. Epub 2004/07/27.
14. Tamandl D, Herberger B, Gruenberger B, Schoppmann SF, Puhalla H, Schindl M *et al*. (2008) Adequate preoperative staging rarely leads to a change of intraoperative strategy in patients undergoing surgery for colorectal cancer liver metastases. *Surgery* 143:648–657. Epub 2008/04/26.
15. Ong KO, Leen E. (2007) Radiological staging of colorectal liver metastases. *Surg Oncol* 16:7–14. Epub 2007/05/15.
16. Kamel IR, Fishman EK. (2004) Recent advances in CT imaging of liver metastases. *Cancer J.* 10:104–120.
17. Soyer P, Poccard M, Boudiaf M, Abitbol M, Hamzi L, Panis Y *et al*. (2004) Detection of hypovascular hepatic metastases at triple-phase helical CT: sensitivity of phases and comparison with surgical and histopathologic findings. *Radiology* 231:413–420.
18. Scatarige JC, Fishman EK, Saksouk FA, Siegelman SS. (1983) Computed tomography of calcified liver masses. *J Comput Assist Tomogr* 7:83–89. Epub 1983/02/01.
19. Khalil HI, Patterson SA, Panicek DM. (2005) Hepatic lesions deemed too small to characterize at CT: prevalence and importance in women with breast cancer. *Radiology* 235:872–878.
20. Schwartz LH, Gandras EJ, Colangelo SM, Ercolani MC, Panicek DM. (1999) Prevalence and importance of small hepatic lesions found at CT in patients with cancer. *Radiology* 210:71–74. Epub 1999/01/14.
21. Braga L, Guller U, Semelka RC. (2004) Modern hepatic imaging. *Surg Clin North Am* 84:375–400. Epub 2004/04/06.
22. Patel J, Sigmund EE, Rusinek H, Oei M, Babb JS, Taouli B. (2010) Diagnosis of cirrhosis with intravoxel incoherent motion diffusion MRI and dynamic contrast-enhanced MRI alone and in combination: preliminary experience. *J Magn Reson Imaging* 31:589–600. Epub 2010/02/27.
23. Semelka RC, Cance WG, Marcos HB, Mauro MA. (1999) Liver metastases: comparison of current MR techniques and spiral CT during arterial portography for detection in 20 surgically staged cases. *Radiology* 213:86–91. Epub 1999/11/30.
24. Rofsky NM, Lee VS, Laub G, Pollack MA, Krinsky GA, Thomasson D *et al*. (1999) Abdominal MR imaging with a volumetric interpolated breath-hold examination. *Radiology* 212:876–884.
25. Pedro MS, Semelka RC, Braga L. (2002) MR imaging of hepatic metastases. *Magn Reson Imaging Clin N Am* 10:15–29. Epub 2002/05/10.
26. Danet IM, Semelka RC, Leonardou P, Braga L, Vaidean G, Woosley JT *et al*. (2003) Spectrum of MRI appearances of untreated metastases of the liver. *AJR Am J Roentgenol* 181:809–817.
27. Semelka RC, Hussain SM, Marcos HB, Woosley JT. (2000) Perilesional enhancement of hepatic metastases: correlation between MR imaging and histopathologic findings-initial observations. *Radiology* 215:89–94. Epub 2001/02/07.
28. Bruegel M, Gaa J, Waldt S, Woertler K, Holzapfel K, Kiefer B *et al*. (2008) Diagnosis of hepatic metastasis: comparison of respiration-triggered diffusion-weighted echo-planar MRI and five t2-weighted turbo spin-echo sequences. *AJR Am J Roentgenol* 191:1421–1429.
29. Parikh T, Drew SJ, Lee VS, Wong S, Hecht EM, Babb JS *et al*. (2008) Focal liver lesion detection and characterization with diffusion-weighted MR imaging: comparison with standard breath-hold T2-weighted imaging. *Radiology* 246:812–822. Epub 2008/01/29.
30. Gandhi SN, Brown MA, Wong JG, Aguirre DA, Sirlin CB. (2006) MR contrast agents for liver imaging: what, when, how. *Radiographics* 26:1621–1636.
31. Hammerstingl R, Huppertz A, Breuer J, Balzer T, Blakeborough A, Carter R *et al*. (2008) Diagnostic efficacy of gadoxetic acid (Primovist)-enhanced MRI and spiral CT for a therapeutic strategy: comparison with intraoperative and histopathologic findings in focal liver lesions. *Eur Radiol* 18:457–467. Epub 2007/12/07.
32. Kim YK, Lee JM, Kim CS, Chung GH, Kim CY, Kim IH. (2005) Detection of liver metastases: gadobenate dimeglumine-enhanced three-dimensional dynamic phases and one-hour delayed phase MR imaging versus superparamagnetic iron oxide-enhanced MR imaging. *Eur Radiol* 15:220–228.
33. Shimada K, Isoda H, Hirokawa Y, Arizono S, Shibata T, Togashi K. (2010) Comparison of gadolinium-EOB-DTPA-enhanced and diffusion-weighted liver MRI for detection of small hepatic metastases. *Eur Radiol* 20:2690–2698. Epub 2010/06/22.
34. Lowenthal D, Zeile M, Lim WY, Wybranski C, Fischbach F, Wieners G *et al*. (2011) Detection and characterisation of focal liver lesions in colorectal carcinoma patients: comparison of diffusion-weighted and Gd-EOB-DTPA enhanced MR imaging. *Eur Radiol* 21:832–840. Epub 2010/10/05.
35. Koh DM, Brown G, Riddell AM, Scurr E, Collins DJ, Allen SD *et al*. (2008) Detection of colorectal hepatic metastases using MnDPDP MR imaging and diffusion-weighted imaging (DWI) alone and in combination. *Eur Radiol* 18:903–910. Epub 2008/01/15.
36. Koh DM, Collins DJ, Wallace T, Chau I, Riddell AM. (2011) Combining diffusion-weighted MRI with Gd-EOB-DTPA-enhanced MRI improves the detection of colorectal liver metastases. *Br J Radiol* 85:980–989.
37. Erturk SM, Ichikawa T, Fujii H, Yasuda S, Ros PR. (2006) PET imaging for evaluation of metastatic colorectal cancer of the liver. *Eur J Radiol* 58:229–235.
38. Chen LB, Tong JL, Song HZ, Zhu H, Wang YC. (2007) (18)F-DG PET/CT in detection of recurrence and metastasis of colorectal cancer. *World J Gastroenterol* 13:5025–5029. Epub 2007/09/15.
39. Chua SC, Groves AM, Kayani I, Menezes L, Gacinovic S, Du Y *et al*. (2007) The impact of 18F-FDG PET/CT in patients with liver metastases. *Eur J Nucl Med Mol Imaging* 34:1906–1914. Epub 2007/08/24.
40. Schmidt GP, Baur-Melnyk A, Haug A, Utzschneider S, Becker CR, Tiling R *et al*. (2009) Whole-body MRI at 1.5 T and 3 T compared with FDG-

PET-CT for the detection of tumour recurrence in patients with colorectal cancer. *Eur Radiol* 19:1366–1378. Epub 2009/02/05.

41. Truant S, Huglo D, Hebbar M, Ernst O, Steinling M, Pruvot FR. (2005) Prospective evaluation of the impact of [18F]fluoro-2-deoxy-D-glucose positron emission tomography of resectable colorectal liver metastases. *Br J Surg* 92:362–369. Epub 2005/01/27.

42. Votrubova J, Belohlavek O, Jaruskova M, Oliverius M, Lohynska R, Trskova K *et al*. (2006) The role of FDG-PET/CT in the detection of recurrent colorectal cancer. *Eur J Nucl Med Mol Imaging* 33:779–784. Epub 2006/03/28.

43. Badiee S, Franc BL, Webb EM, Chu B, Hawkins RA, Coakley F. (2008) Role of IV iodinated contrast material in 18F-FDG PET/CT of liver metastases. *AJR Am J Roentgenol* 191:1436–1439.

44. Glazer ES, Beaty K, Abdalla EK, Vauthey JN, Curley SA. (2010) Effectiveness of positron emission tomography for predicting chemotherapy response in colorectal cancer liver metastases. *Arch Surg* 145:340–345; discussion 345. Epub 2010/04/21.

45. Floriani I, Torri V, Rulli E, Garavaglia D, Compagnoni A, Salvolini L *et al*. (2010) Performance of imaging modalities in diagnosis of liver metastases from colorectal cancer: a systematic review and meta-analysis. *J Magn Reson Imaging* 31:19–31. Epub 2009/12/23.

46. Niekel MC, Bipat S, Stoker J. (2010) Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. *Radiology* 257:674–684. Epub 2010/09/11.

47. Seo HJ, Kim MJ, Lee JD, Chung WS, Kim YE. (2011) Gadoxetate disodium-enhanced magnetic resonance imaging versus contrast-enhanced 18F-fluorodeoxyglucose positron emission tomography/computed tomography for the detection of colorectal liver metastases. *Invest Radiol* 46:548–555. Epub 2011/05/18.

48. Kulemann V, Schima W, Tamandl D, Kaczirek K, Gruenberger T, Wrba F *et al*. (2011) Preoperative detection of colorectal liver metastases in fatty liver: MDCT or MRI? *Eur J Radiol* 79:e1–e6. Epub 2010/04/16.

49. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L *et al*. (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 92:205–216.

50. Jaffe CC. (2006) Measures of response: RECIST, WHO, and new alternatives. *J Clin Oncol* 24:3245–3251. Epub 2006/07/11.

51. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R *et al*. (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 45:228–247. Epub 2008/12/23.

52. Figueiras RG, Goh V, Padhani AR, Naveira AB, Caamano AG, Martin CV. (2010) The role of functional imaging in colorectal cancer. *AJR Am J Roentgenol* 195:54–66. Epub 2010/06/23.

53. Saltz LB, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R *et al*. (2008) Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 26:2013–2019. Epub 2008/04/19.

54. Taouli B, Koh DM. (2010) Diffusion-weighted MR imaging of the liver. *Radiology* 254:47–66. Epub 2009/12/25.

55. Goh V, Ganeshan B, Nathan P, Juttla JK, Vinayan A, Miles KA. (2011) Assessment of response to tyrosine kinase inhibitors in metastatic renal cell cancer: CT texture as a predictive biomarker. *Radiology* 261:165–171. Epub 2011/08/05.

56. Buijs M, Vossen JA, Hong K, Georgiades CS, Geschwind JF, Kamel IR. (2008) Chemoembolization of hepatic metastases from ocular melanoma: assessment of response with contrast-enhanced and diffusion-weighted MRI. *AJR Am J Roentgenol* 191:285–289. Epub 2008/06/20.

57. Cui Y, Zhang XP, Sun YS, Tang L, Shen L. (2008) Apparent diffusion coefficient: potential imaging biomarker for prediction and early detection of response to chemotherapy in hepatic metastases. *Radiology* 248:894–900. Epub 2008/08/20.

58. Koh DM, Scurr E, Collins D, Kanber B, Norman A, Leach MO *et al*. (2007) Predicting response of colorectal hepatic metastasis: value of pretreatment apparent diffusion coefficients. *AJR Am J Roentgenol* 188:1001–1008. Epub 2007/03/23.

59. Benoist S, Brouquet A, Penna C, Julie C, El Hajjam M, Chagnon S *et al*. (2006) Complete response of colorectal liver metastases after chemotherapy: does it mean cure? *J Clin Oncol* 24:3939–3945. Epub 2006/08/22.

60. De Roock W, Piessevaux H, De Schutter J, Janssens M, De Hertogh G, Personeni N *et al*. (2008) KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab. *Ann Oncol* 19:508–515. Epub 2007/11/14.

61. Suzuki C, Blomqvist L, Sundin A, Jacobsson H, Bystrom P, Berglund A *et al*. (2012) The initial change in tumor size predicts response and survival in patients with metastatic colorectal cancer treated with combination chemotherapy. *Ann Oncol* 23:948–954. Epub 2011/08/13.

62. Choi H, Charnsangavej C, Faria SC, Macapinlac HA, Burgess MA, Patel SR *et al*. (2007) Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. *J Clin Oncol* 25:1753–1759. Epub 2007/05/02.

63. Chun YS, Vauthey JN, Boonsirikamchai P, Maru DM, Kopetz S, Palavecino M *et al*. (2009) Association of computed tomography morphologic criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases. *JAMA* 302:2338–2344. Epub 2009/12/03.

64. de Geus-Oei LF, Vriens D, van Laarhoven HW, van der Graaf WT, Oyen WJ. (2009) Monitoring and predicting response to therapy with 18F-FDG PET in colorectal cancer: a systematic review. *J Nucl Med* 50 (Suppl. 1):43S–54S. Epub 2009/06/24.

65. Bystrom P, Berglund A, Garske U, Jacobsson H, Sundin A, Nygren P *et al*. (2009) Early prediction of response to first-line chemotherapy by sequential [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography in patients with advanced colorectal cancer. *Ann Oncol* 20:1057–1061. Epub 2009/01/24.

66. Tan MC, Linehan DC, Hawkins WG, Siegel BA, Strasberg SM. (2007) Chemotherapy-induced normalization of FDG uptake by colorectal liver metastases does not usually indicate complete pathologic response. *J Gastrointest Surg* 11:1112–1119. Epub 2007/07/12.

67. Hendlisz A, Golfinopoulos V, Garcia C, Covas A, Emonts P, Ameye L *et al*. (2011) Serial FDG-PET/CT for early outcome prediction in patients with metastatic colorectal cancer undergoing chemotherapy. *Ann Oncol* 23:1687–1693.

68. Elias D, Liberale G, Vernerey D, Pocard M, Ducreux M, Boige V *et al*. (2005) Hepatic and extrahepatic colorectal metastases: when resectable, their localization does not matter, but their total number has a prognostic effect. *Ann Surg Oncol* 12:900–909.

69. Elias D, Ouellet JF, Bellon N, Pignon JP, Pocard M, Lasser P. (2003) Extrahepatic disease does not contraindicate hepatectomy for colorectal liver metastases. *Br J Surg* 90:567–574. Epub 2003/05/08.

70. Jaeck D, Nakano H, Bachellier P, Inoue K, Weber JC, Oussoultzoglou E *et al*. (2002) Significance of hepatic pedicle lymph node involvement in patients with colorectal liver metastases: a prospective study. *Ann Surg Oncol* 9:430–438.

71. Carpizo DR, Are C, Jarnagin W, Dematteo R, Fong Y, Gonen M *et al*. (2009) Liver resection for metastatic colorectal cancer in patients with concurrent extrahepatic disease: results in 127 patients treated at a single center. *Ann Surg Oncol* 16:2138–2146. Epub 2009/06/06.

72. Pulitano C, Bodingbauer M, Aldrighetti L, de Jong MC, Castillo F, Schulick RD *et al*. (2011) Liver resection for colorectal metastases in presence of extrahepatic disease: results from an international multi-institutional analysis. *Ann Surg Oncol* 18:1380–1388. Epub 2010/12/08.

73. Adam R, de Haas RJ, Wicherts DA, Vibert E, Salloum C, Azoulay D *et al*. (2011) Concomitant extrahepatic disease in patients with colorectal liver metastases: when is there a place for surgery? *Ann Surg* 253:349–359. Epub 2010/12/24.

74. Elias D, Gilly F, Boutitie F, Quenet F, Bereder JM, Mansvelt B *et al*. (2010) Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. *J Clin Oncol* 28:63–68. Epub 2009/11/18.

75. Chua TC, Saxena A, Liauw W, Chu F, Morris DL. (2011) Hepatectomy and resection of concomitant extrahepatic disease for colorectal liver metastases – a systematic review. *Eur J Cancer* 48:1757–1765.

76. Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P *et al*. (2008) Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 371:1007–1016.

77. Allen PJ, Kemeny N, Jarnagin W, DeMatteo R, Blumgart L, Fong Y. (2003) Importance of response to neoadjuvant chemotherapy in patients undergoing resection of synchronous colorectal liver metastases. *J Gastrointest Surg* 7:109–115; discussion 116–117.

78. Adam R, Pascal G, Castaing D, Azoulay D, Delvart V, Paule B *et al*. (2004) Tumor progression while on chemotherapy: a contraindication to liver resection for multiple colorectal metastases? *Ann Surg* 240:1052–1061; discussion 1061–1064.

79. Neumann UP, Thelen A, Rocken C, Seehofer D, Bahra M, Riess H *et al*. (2009) Nonresponse to pre-operative chemotherapy does not preclude long-term survival after liver resection in patients with colorectal liver metastases. *Surgery* 146:52–59. Epub 2009/06/23.

80. Adam R, Aloia T, Levi F, Wicherts DA, de Haas RJ, Paule B *et al*. (2007) Hepatic resection after rescue cetuximab treatment for colorectal liver metastases previously refractory to conventional systemic therapy. *J Clin Oncol* 25:4593–4602. Epub 2007/10/11.

81. Abdalla EK, Denys A, Chevalier P, Nemr RA, Vauthey JN. (2004) Total and segmental liver volume variations: implications for liver surgery. *Surgery* 135:404–410.

82. Vauthey JN, Chaoui A, Do KA, Bilimoria MM, Fenstermacher MJ, Charnsangavej C *et al*. (2000) Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. *Surgery* 127:512–519.

83. Makuuchi M, Thai BL, Takayasu K, Takayama T, Kosuge T, Gunven P *et al*. (1990) Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. *Surgery* 107:521–527.

84. Uesaka K, Nimura Y, Nagino M. (1996) Changes in hepatic lobar function after right portal vein embolization. An appraisal by biliary indocyanine green excretion. *Ann Surg* 223:77–83.

85. Ribero D, Abdalla EK, Madoff DC, Donadon M, Loyer EM, Vauthey JN. (2007) Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome. *Br J Surg* 94:1386–1394.

86. Wicherts DA, de Haas RJ, Andreani P, Sotirov D, Salloum C, Castaing D *et al*. (2010) Impact of portal vein embolization on long-term survival of patients with primarily unresectable colorectal liver metastases. *Br J Surg* 97:240–250. Epub 2010/01/21.

87. Kubota K, Makuuchi M, Kusaka K, Kobayashi T, Miki K, Hasegawa K *et al*. (1997) Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. *Hepatology* 26:1176–1181.

88. Abdalla EK, Barnett CC, Doherty D, Curley SA, Vauthey JN. (2002) Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. *Arch Surg* 137:675–680; discussion 680–681.

89. Farges O, Belghiti J, Kianmanesh R, Regimbeau JM, Santoro R, Vilgrain V *et al*. (2003) Portal vein embolization before right hepatectomy: prospective clinical trial. *Ann Surg* 237:208–217.

90. Abdalla EK, Hicks ME, Vauthey JN. (2001) Portal vein embolization: rationale, technique and future prospects. *Br J Surg* 88:165–175.

91. Vauthey JN, Pawlik TM, Abdalla EK, Arens JF, Nemr RA, Wei SH *et al*. (2004) Is extended hepatectomy for hepatobiliary malignancy justified? *Ann Surg* 239:722–730; discussion 730–732.

92. Imamura H, Sano K, Sugawara Y, Kokudo N, Makuuchi M. (2005) Assessment of hepatic reserve for indication of hepatic resection: decision tree incorporating indocyanine green test. *J Hepatobiliary Pancreat Surg* 12:16–22. Epub 2005/03/09.

93. Schroeder RA, Marroquin CE, Bute BP, Khuri S, Henderson WG, Kuo PC. (2006) Predictive indices of morbidity and mortality after liver resection. *Ann Surg* 243:373–379. Epub 2006/02/24.

94. Aloia T, Sebagh M, Plasse M, Karam V, Levi F, Giacchetti S *et al*. (2006) Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases. *J Clin Oncol* 24:4983–4990.

95. Balzan S, Nagarajan G, Farges O, Galleano CZ, Dokmak S, Paugam C *et al*. (2010) Safety of liver resections in obese and overweight patients. *World J Surg* 34:2960–2968. Epub 2010/08/17.

96. El-Serag HB, Mason AC. (1999) Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 340:745–750. Epub 1999/03/11.

97. Rees M, Tekkis PP, Welsh FK, O'Rourke T, John TG. (2008) Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. *Ann Surg* 247:125–135. Epub 2007/12/25.

98. Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P *et al*. (1996) Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. *Cancer* 77:1254–1262.

99. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. (1999) Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 230:309–318; discussion 318–321.

100. Wei AC, Greig PD, Grant D, Taylor B, Langer B, Gallinger S. (2006) Survival after hepatic resection for colorectal metastases: a 10-year experience. *Ann Surg Oncol* 13:668–676. Epub 2006/03/09.

101. Kato T, Yasui K, Hirai T, Kanemitsu Y, Mori T, Sugihara K *et al*. (2003) Therapeutic results for hepatic metastasis of colorectal cancer with special reference to effectiveness of hepatectomy: analysis of prognostic factors for 763 cases recorded at 18 institutions. *Dis Colon Rectum* 46 (10 Suppl.):S22–S31. Epub 2003/10/08.

102. Scheele J, Altendorf-Hofmann A, Grube T, Hohenberger W, Stangl R, Schmidt K. (2001) Resektion colorectaler Lebermetastasen. Welche Prognosefaktoren bestimmen die Patientenselektion? [Resection of colorectal liver metastases. What prognostic factors determine patient selection?]. *Chirurg* 72:547–560. Epub 2001/06/01.

103. Brouquet A, Abdalla EK, Kopetz S, Garrett CR, Overman MJ, Eng C *et al*. (2011) High survival rate after two-stage resection of advanced colorectal liver metastases: response-based selection and complete resection define outcome. *J Clin Oncol* 29:1083–1090. Epub 2011/01/26.

104. Jaeck D, Bachellier P, Nakano H, Oussoultzoglou E, Weber JC, Wolf P *et al*. (2003) One or two-stage hepatectomy combined with portal vein embolization for initially nonresectable colorectal liver metastases. *Am J Surg* 185:221–229. Epub 2003/03/07.

105. Aloia TA, Vauthey JN. (2011) Management of colorectal liver metastases: past, present, and future. *Updates Surg* 63:1–3. Epub 2011/02/19.

106. de Santibanes E, Alvarez FA, Ardiles V. (2012) How to avoid postoperative liver failure: a novel method. *World J Surg* 36:125–128. Epub 2011/11/03.

107. Torzilli G, Donadon M, Palmisano A, Marconi M, Procopio F, Botea F *et al*. (2009) Ultrasound guided liver resection: does this approach limit the need for portal vein embolization? *Hepatogastroenterology* 56:1483–1490. Epub 2009/12/03.

108. Torzilli G, Procopio F, Botea F, Marconi M, Del Fabbro D, Donadon M *et al*. (2009) One-stage ultrasonographically guided hepatectomy for multiple bilobar colorectal metastases: a feasible and effective alternative to the 2-stage approach. *Surgery* 146:60–71. Epub 2009/06/23.

109. Hughes KS, Simon R, Songhorabodi S, Adson MA, Ilstrup DM, Fortner JG *et al*. (1986) Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of patterns of recurrence. *Surgery* 100:278–284. Epub 1986/08/01.

110. Shirabe K, Takenaka K, Gion T, Fujiwara Y, Shimada M, Yanaga K *et al*. (1997) Analysis of prognostic risk factors in hepatic resection for metastatic colorectal carcinoma with special reference to the surgical margin. *Br J Surg* 84:1077–1080. Epub 1997/08/01.

111. Jaeck D, Bachellier P, Guiguet M, Boudjema K, Vaillant JC, Balladur P *et al*. (1997) Long-term survival following resection of colorectal hepatic metastases. Association Francaise de Chirurgie. *Br J Surg* 84:977–980. Epub 1997/07/01.

112. Pawlik TM, Scoggins CR, Zorzi D, Abdalla EK, Andres A, Eng C *et al*. (2005) Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. *Ann Surg* 241:715–722; discussion 722–724. Epub 2005/04/26.

113. Hamady ZZ, Cameron IC, Wyatt J, Prasad RK, Toogood GJ, Lodge JP. (2006) Resection margin in patients undergoing hepatectomy for colorectal liver metastasis: a critical appraisal of the 1cm rule. *Eur J Surg Oncol* 32:557–563. Epub 2006/04/04.

114. Lordan JT, Karanjia ND. (2010) 'Close shave' in liver resection for colorectal liver metastases. *Eur J Surg Oncol* 36:47–51. Epub 2009/06/09.

115. Figueras J, Burdio F, Ramos E, Torras J, Llado L, Lopez-Ben S *et al*. (2007) Effect of subcentimeter nonpositive resection margin on hepatic recurrence in patients undergoing hepatectomy for colorectal liver metastases. Evidences from 663 liver resections. *Ann Oncol* 18:1190–1195. Epub 2007/04/17.

116. Muratore A, Ribero D, Zimmitti G, Mellano A, Langella S, Capussotti L. (2010) Resection margin and recurrence-free survival after liver resection of colorectal metastases. *Ann Surg Oncol* 17:1324–1329. Epub 2009/10/23.

117. Kokudo N, Miki Y, Sugai S, Yanagisawa A, Kato Y, Sakamoto Y *et al*. (2002) Genetic and histological assessment of surgical margins in resected liver metastases from colorectal carcinoma: minimum surgical margins for successful resection. *Arch Surg* 137:833–840. Epub 2002/07/03.

118. Ng JK, Urbanski SJ, Mangat N, McKay A, Sutherland FR, Dixon E *et al*. (2008) Colorectal liver metastases contract centripetally with a response to chemotherapy: a histomorphologic study. *Cancer* 112:362–371.

119. de Haas RJ, Wicherts DA, Flores E, Azoulay D, Castaing D, Adam R. (2008) R1 resection by necessity for colorectal liver metastases: is it still a contraindication to surgery? *Ann Surg* 248:626–637. Epub 2008/10/22.

120. Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D *et al*. (2004) Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg* 240:644–657; discussion 657–658. Epub 2004/09/24.

121. Meric F, Patt YZ, Curley SA, Chase J, Roh MS, Vauthey JN *et al*. (2000) Surgery after downstaging of unresectable hepatic tumors with intra-arterial chemotherapy. *Ann Surg Oncol* 7:490–495. Epub 2000/08/18.

122. Auer RC, White RR, Kemeny NE, Schwartz LH, Shia J, Blumgart LH *et al*. (2010) Predictors of a true complete response among disappearing liver metastases from colorectal cancer after chemotherapy. *Cancer* 116:1502–1509. Epub 2010/02/02.

123. Blazer DG, 3rd, Kishi Y, Maru DM, Kopetz S, Chun YS, Overman MJ *et al*. (2008) Pathologic response to preoperative chemotherapy: a new outcome end point after resection of hepatic colorectal metastases. *J Clin Oncol* 26:5344–5351.

124. Elias D, Youssef O, Sideris L, Dromain C, Baton O, Boige V *et al*. (2004) Evolution of missing colorectal liver metastases following inductive chemotherapy and hepatectomy. *J Surg Oncol* 86:4–9. Epub 2004/03/30.

125. Elias D, Goere D, Boige V, Kohneh-Sharhi N, Malka D, Tomasic G *et al*. (2007) Outcome of posthepatectomy-missing colorectal liver metastases after complete response to chemotherapy: impact of adjuvant intra-arterial hepatic oxaliplatin. *Ann Surg Oncol* 14:3188–3194. Epub 2007/08/21.

126. Tanaka K, Takakura H, Takeda K, Matsuo K, Nagano Y, Endo I. (2009) Importance of complete pathologic response to prehepatectomy chemotherapy in treating colorectal cancer metastases. *Ann Surg* 250:935–942. Epub 2009/12/03.

127. van Vledder MG, de Jong MC, Pawlik TM, Schulick RD, Diaz LA, Choti MA. (2010) Disappearing colorectal liver metastases after chemotherapy: should we be concerned? *J Gastrointest Surg* 14:1691–1700. Epub 2010/09/15.

128. Zalinski S, Abdalla EK, Mahvash A, Vauthey JN. (2009) A marking technique for intraoperative localization of small liver metastases before systemic chemotherapy. *Ann Surg Oncol* 16:1208–1211. Epub 2009/02/14.

129. Gaujoux S, Goere D, Dumont F, Souadka A, Dromain C, Ducreux M *et al*. (2011) Complete radiological response of colorectal liver metastases after chemotherapy: what can we expect? *Dig Surg* 28:114–120. Epub 2011/05/05.

130. Bipat S, van Leeuwen MS, Comans EF, Pijl ME, Bossuyt PM, Zwinderman AH *et al*. (2005) Colorectal liver metastases: CT, MR imaging, and PET for diagnosis – meta-analysis. *Radiology* 237:123–131.

131. Regge D, Campanella D, Anselmetti GC, Cirillo S, Gallo TM, Muratore A *et al*. (2006) Diagnostic accuracy of portal-phase CT and MRI with mangafodipir trisodium in detecting liver metastases from colorectal carcinoma. *Clin Radiol* 61:338–347. Epub 2006/03/21.

132. van Kessel CS, van Leeuwen MS, van den Bosch MA, Borel Rinkes IH, Mali WP, Westers P *et al*. (2011) Accuracy of multislice liver CT and MRI for preoperative assessment of colorectal liver metastases after neoadjuvant chemotherapy. *Dig Surg* 28:36–43. Epub 2011/02/05.

133. Peppercorn PD, Reznek RH, Wilson P, Slevin ML, Gupta RK. (1998) Demonstration of hepatic steatosis by computerized tomography in patients receiving 5-fluorouracil-based therapy for advanced colorectal cancer. *Br J Cancer* 77:2008–2011.

134. Vauthey JN, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM *et al*. (2006) Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol* 24:2065–2072.

135. Pawlik TM, Olino K, Gleisner AL, Torbenson M, Schulick R, Choti MA. (2007) Preoperative chemotherapy for colorectal liver metastases: impact on hepatic histology and postoperative outcome. *J Gastrointest Surg* 11:860–868.

136. Chami L, Lassau N, Malka D, Ducreux M, Bidault S, Roche A *et al*. (2008) Benefits of contrast-enhanced sonography for the detection of liver lesions: comparison with histologic findings. *AJR Am J Roentgenol* 190:683–690. Epub 2008/02/22.