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Selection of Patients for Resection of Hepatic Colorectal Metastases: Expert Consensus Statement

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PREOPERATIVE IMAGING OF HEPATIC COLORECTAL METASTASES

Surgical resection has been shown to be the best treatment option for cure in patients with hepatic metastases from primary colorectal cancer, particularly when complete resection can be accomplished. The 5-year survival rates in such patients have almost doubled from about 30% to about 60% during the past two decades.[1,2] Among other factors, this improved survival has been attributed to better preoperative imaging techniques that have improved patient selection.

The goals of preoperative imaging studies are: (1) to define number and extent of hepatic metastases in the segmental and lobar distribution in order to facilitate surgical planning and (2) to identify extrahepatic disease, including nodal metastases, peritoneal implants, regional or local recurrent or residual disease, and other sites of hematogenous spread such as pulmonary metastases.

Computed Tomography

The quality of computed tomography (CT) has continued to improve over the past two decades, with faster scan speed and better image resolution in the z-axis direction allowing scan coverage for the abdomen and pelvis or for the chest within a single breath hold. This improvement allows for better lesion detection, particularly in high-contrast organs such as the lung and peritoneal fat. Intravenous contrast enhancement with iodinated contrast agents remains essential for lesion detection and characterization, particularly in the liver.

Meta-analyses of studies over the past two decades have shown that the average sensitivity of lesion detection of hepatic metastases from colorectal cancer has increased from 52.3% when a nonhelical scanning technique was used to 63.8% when helical CT was used.[3,4] Recent studies with multidetector helical scanners have increased sensitivity of lesion detection to between 70% and 95%.[3,5] However, lesions smaller than 1 cm remain problematic because of high false negative rate of about 10% and nonspecificity of lesions. Moreover, there is no clear

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evidence that scanning at thinner slice thickness (below 5 mm) will improve lesion detection. In addition, the total amount of iodine used for intravenous (IV) contrast enhancement only minimally improves the detection rate (from 61% to 64%).[3]

The strength of CT, particularly multidetector helical CT, is its superior image resolution throughout the whole body, providing excellent vascular, segmental, and lobar anatomic detail. Those with anatomic knowledge can take this advantage and provide excellent anatomic information for surgical planning. One weakness of CT includes low sensitivity in detecting extrahepatic metastases, particularly in regions with low contrast to distinguish a tumor from the surrounding tissue, such as the periportal region, and serosal deposits on hepatic surface or bowel wall. Another limitation of this imaging modality is lack of sensitivity and specificity for detection and characterization of lesions smaller than 1 cm.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) produces images with better contrast-to-noise ratio than does CT. With proper scanning technique, lesions are easier to detect. Higher magnetic field strength and faster speed allow imaging the liver with contrast enhancement within a single breath hold on a routine basis. Liver-specific contrast agent, such as superparamagnetic iron oxide (SPIO), which improves contrast between liver and lesion, has also become widely available.

Meta-analyses of published data have shown that the average sensitivity of detection of hepatic metastases improved from 60% (noncontrast MR) to 73% when SPIO contrast was used and 78% when gadolinium-based contrast was used.[3,4,6–8] One study has shown lesion detection rates as high as 97% with SPIO contrast agent.[7]

The strength of MRI is its better image contrast for lesion detection and lesion characterization in the liver because several classes of contrast agents, including liver-specific agents, are available. The limitations of MRI are the relatively long scan time and multiple imaging sequences that are needed for complete evaluation, as well as low sensitivity for detecting extrahepatic disease.

Positron Imaging Tomography

[F18]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) has been shown to improve lesion detection of metastases in patients with recurrent or metastatic colorectal cancer, particularly for extrahepatic disease. Meta-analyses of publications have shown an average sensitivity of about 75% in detecting hepatic metastases, but FDG-PET imaging improved detection of extrahepatic disease and changed the treatment plan on the average of 29%.[3,4,9] These three meta-analyses all concluded that FDG-PET is the most sensitive imaging method of detecting hepatic colorectal metastases. A recent study with PET/CT has shown improvement of sensitivity of lesion detection over PET alone from 75% to 89%.[10] Based upon these findings, it is recommended that FDG-PET and, if possible PET/CT, be used routinely in preoperative evaluation of patients with suspected or proven hepatic colorectal metastases when resection is being considered. Where economic factors limit the use of this test, PET/CT can be selectively directed toward patients with higher risk scores, as the probability of obtaining a result that will affect management increases as risk goes up.

The strength of PET imaging is its high sensitivity in detecting metastatic lesions, particularly when CT and PET interpretation can be combined.[10] However, limitations of FDG-PET are largely due to lower spatial resolution than CT and MRI, poor sensitivity for detection of lesions less than 1 cm and mucinous lesions, and the nonspecificity of positive findings.

In addition to the potential for improved lesion detection, the intensity of FDG uptake as assessed by PET scanning may correlate with tumor behavior and patient outcome. In other malignancies, such as lung cancer[11] and in esophageal cancer,[12] the intensity of FDG uptake is an independent predictor of clinical outcome. Active investigation is ongoing to determine if FDG uptake would also correlate to prognosis of patients with hepatic colorectal metastases and whether response to chemotherapy as detected by PET scanning may also correlate with outcome.

Impact of Imaging Studies on Treatment Planning and Outcome

There are few data that assess the impact of each imaging study on resection rates of hepatic metastases. Compared with historical data over the past two decades, few publications have shown an improvement in resectability rate from about 30% when no CT or early generation CT was used compared with approximately 80% when high-quality CT or MRI are routinely used for preoperative imaging.[13] During the past decade, PET imaging has been shown to change the treatment plan in patients who were considered resectable by standard CT or MRI in

about 10%–24% of cases because of additional disease within and outside the liver.[10,14–16]

Consensus Statement:

1. In patients being considered for surgical therapy of hepatic colorectal metastases, a high-quality cross-sectional imaging study, either contrast-enhanced CT or MRI, should be performed to evaluate hepatic colorectal metastases before surgery. MRI, however, is inferior to CT in the evaluation of extrahepatic disease.
2. FDG-PET appears to improve patient selection and should be considered as part of preoperative evaluation of resectability.
3. Response to chemotherapy may impact the sensitivity of preoperative imaging studies at identifying all sites of disease.

PROGNOSTIC VARIABLES IN THE EVALUATION OF PATIENTS WITH HEPATIC COLORECTAL METASTASES

Surgical resection has been proven to be a safe and effective treatment for hepatic colorectal metastases. Resections can be accomplished with an operative mortality well less than 5%, even for resections of up to 80% of the liver.[17–21] Such resections result in 5-year survival for over one third of the patients, even in the era prior to established adjuvant chemotherapy,[22–24] and provide 5-year survival in nearly 60% of patients with modern adjuvant treatments.[1,2,25]

Adoption of hepatic resection as standard treatment for colorectal cancer suddenly converted a stage IV cancer that was uniformly fatal within months of diagnosis into a heterogeneous population of patients with highly variable outcomes. This brought about a need for defining a classification system that segregated patients according to prognosis to (1) allow comparisons of results from various institutions and time periods, (2) help guide selection of therapies, including resections, ablations, and adjuvant therapies, and (3) allow for stratification of patients in clinical trials.

Clinical Prognostic Variables

Many investigators have attempted to classify patients according to clinical variables. Characteristics of the primary tumor presentation that have been most commonly associated with adverse outcome have been male gender,[26,27] stage of the primary,[28,29] regional nodal positivity,[30] and synchronous presentation of the primary with hepatic metastases.[31] Clinical characteristics of liver metastases most often associated with poor outcome are short disease-free interval between primary cancer and hepatic metastases,[19,29,32] multiple tumors,[29,32] bilateral tumors,[33] high preoperative carcinoembryonic antigen,[24,29] and large size of tumor.[12,17,29,34] Certain operative and pathologic characteristics of liver metastases have also been associated with poor outcome, including nonanatomic resections,[35] positive resection margins,[29,36] extrahepatic disease,[29,32,33,36–38] and satellite lesions.[39,40]

Clinical Scoring Systems

A number of investigators have attempted to synthesize these data on prognostic variables into a scoring system for stratifying patients with hepatic colorectal metastases. Cady and Stone proposed the use of a scoring system with number of tumors, disease-free interval, carcinoembryonic antigen (CEA) level, and tumor margin as variables.[41] Gayowski, Iwatsuki, and colleagues proposed using number and size of tumors and lobar distribution of metastases.[22] Nordlinger and colleagues, after analysis of a large multicenter database, proposed for use as variables number, size, disease-free interval, CEA level, stage of primary, age, and margin.[24]

More recently, Fong et al. [22] performed an analysis of a large, single-institution series, examining independent predictors of poor outcome. Seven parameters that were found to be independent predictors of prognosis are: (1) extrahepatic disease, (2) positive surgical margin, (3) nodal metastases for primary cancer, (4) short disease-free interval, (5) tumor size greater than 5 cm, (6) more than one liver metastases, and (7) CEA over 200 ng/ml. Extrahepatic disease is a relative contraindication to resection, and no surgeon should go to the operating room expecting a positive margin. Furthermore, the first two of these data are not available preoperatively. Thus, using the last five criteria, a clinical risk score system was created. This prognostic scoring system has been verified by independent investigators.[42] Certainly, this scoring system reflects the likelihood of disseminated disease at the time of presentation. Whether it will translate into good patient stratification for long-term outcome in the era of modern chemotherapy awaits studies with long-term follow-up. However, it has also been shown that this scoring system predicts resectability and therefore yield of diagnostic modalities.[43,44]

Thus, this scoring system may be useful in aiding selection of expensive preoperative staging modalities such as FDG-PET scanning[43] and laparoscopy.[44]

Molecular Markers for Prognosis Prediction

Attempts to use molecular markers to predict outcome have taken two approaches. Investigators have attempted to find molecular markers of tumor aggressiveness and tumor hypermetabolism or proliferation, such as p53, Ki67, glucose transporter-1 protein (GLUT-1), or p27 in colorectal cancer.[45] Recently, human telomerase reverse transcriptase (hTERT) has been shown to be superior to Ki67 and several known clinical predictors of outcome in a multicenter study of patients who underwent resection of hepatic colorectal metastases.[46] Investigators have used molecular markers that predict response to systemic therapies, such as thymidylate synthase or vascular endothelial growth factor receptor (VEGFR).[47,48] The wide use of molecular markers is hindered at present by inconsistencies in some assays, cost, and technical difficulties in wide deployment. Also, with evolving therapeutic options, the importance of molecular markers is also evolving. For example, it is clear that thymidylate synthase levels correlate to response to fluoropyrimidines such as 5-FU but do not correlate to response to newer agents such as camptothectin-11 (CPT-11).[49] It has also become apparent that metastatic tumors residing in different sites in the same patient can have very different molecular profiles,[50] complicating interpretation of data obtained from biopsies of a single site. Even with all of these uncertainties, active, promising investigations are ongoing. Although no molecular marker is currently used as part of a standard panel of criteria for patient assessment, it is likely that some molecular determinants will be incorporated into standard clinical assessment of these patients in the future.

Response to Preoperative Chemotherapy

There are emerging data suggesting that response to chemotherapy may be an important predictor of outcome in patients with hepatic colorectal metastases. Allen and colleagues recently examined patients with hepatic metastases discovered synchronously with the primary tumor. Patients who have tumors stable or responsive to neoadjuvant 5-FU-based chemotherapy had significantly better long-term survival than those who progressed.[51] In another study, Adam et al.[52] examined the outcome of 93 patients who were converted from unresectable to resectable by systemic chemotherapy. The 5-year survival following liver resection was 34%, indicating that even patients with incurable disease can be converted by response to chemotherapy to a favorable outcome. It is likely that "response to therapy" will become a prognostic variable formally used in the routine evaluation of patients with metastatic colorectal cancer.

Consensus Statement:

1. Clinical and pathologic factors can predict risk of recurrence and survival in patients following liver resection of hepatic colorectal metastases.
2. Clinical scoring systems based on preoperative clinical parameters have proven to be useful in predicting systemic dissemination of disease, resectability, and yield of diagnostic modalities.
3. While some molecular and biologic markers appear to correlate to prognosis, these factors must still be considered investigational as prognostic modalities.
4. Response to preoperative chemotherapy is emerging as a favorable clinical parameter that should be considered when considering hepatectomy in patients with multiple colorectal metastases.

MANAGEMENT OF PRIMARY COLORECTAL CANCER WITH SYNCHRONOUS COLORECTAL HEPATIC METASTASES

The best timing for surgical resection of synchronous colorectal liver metastasis and the primary tumor has not been well defined. Conventionally, most investigators have recommended a staged approach, with initial resection of the primary tumor followed 2–3 months later by the liver resection.[18,53] Proponents of this approach cite increased morbidity associated with the combined procedure. More recently, with advances in surgical and perioperative care, several studies have reported that simultaneous resection of colon and liver tumors results in morbidity, length of hospital stay, and perioperative mortality comparable to staged resection.[54–61] In addition, because a second laparotomy can be avoided, simultaneous resection of the primary colon tumor and hepatic metastasis may be preferred, as it permits earlier completion of surgical therapy thereby allowing more prompt initiation of adjuvant therapy.[59] The final decision whether to perform a simultaneous or staged resection, however, should be individualized. Simultaneous resection may be more appropriate in patients who require either an

uncomplicated colon resection combined with a liver resection or in those patients who require a more complex colorectal resection combined with a limited liver resection. Patients who require both a complex colorectal and major hepatic resection are probably best managed with a staged approach. Ultimately, the decision whether to perform a staged or simultaneous resection needs to be based on the experience of the surgeon, the estimated time necessary to perform both operations, and the flow of the case intraoperatively.

Integrating adjuvant therapy into the surgical management of the primary tumor and synchronous resectable hepatic metastases adds an additional level of complexity. In patients who are not symptomatic, initial chemotherapy can be considered. Alternatively, adjuvant or neoadjuvant chemotherapy can be administered either following complete resection (either staged or simultaneous) or between staged resections. Similarly, in patients with primary rectal cancer, the addition of neoadjuvant or adjuvant radiation therapy is impacted by the patient's local stage and symptoms. In all such cases, management and integration of surgical and adjuvant therapies of resectable stage IV patients should be individualized.

Consensus Statement:

1. Patients with primary colorectal tumors who present with synchronous resectable liver metastases should be considered for aggressive curative-intent therapy when appropriate.
2. Either staged or simultaneous resections of the primary tumor and liver metastases can be considered depending on the variable factors, including complexity of resections, symptoms, comorbid disease, and available surgical expertise.
3. Integration of adjuvant and/or neoadjuvant therapy in patients with resectable stage IV disease is not well defined based on the available evidence. The use and timing of these therapies should be individualized and planned as part of a multidisciplinary approach.

EVALUATION OF RESECTION MARGIN AND DEFINITION OF RESECTABILITY

Surgical margin status has been shown to be important in long-term outcomes following resection of colorectal liver metastases. Multiple studies have shown that a negative resection margin decreases local recurrence rates and improves survival.[1,62] In a study by Scheele et al.,[63] the median survival of patients who underwent an R1 or R2 resection was only 14 months compared with 44 months for those who underwent an R0 resection. In a more recent study by Choti et al.,[1] patients who had a positive microscopic resection margin had a median survival of only 24 months compared with 46 months for patients with a negative surgical margin. In this study, positive surgical margin status was associated with a 3.5 increase in relative risk of disease-specific death. Similarly, Pawlik et al.[62] reported that a positive resection margin was associated with a significantly higher risk of surgical margin recurrence and decreased overall survival.

Given the importance of a clear surgical margin, the question then arises as to what constitutes a minimally acceptable negative microscopic margin. Several earlier series concerning liver resection for hepatic colorectal metastases have reported that one should attain at least a 1-cm margin,[64,65] and if not possible, this should be a relative contraindication to surgery.[66] Cady et al.[65] reported that a surgical margin less than 1 cm was associated with a significantly shorter disease-free survival. As a result, many centers adopted the ''1-cm rule'' as a minimal margin to obtain at the time of hepatic resection.[67,68] These findings, however, have not been corroborated in multivariate regression analyses adjusted for other confounding risk factors.[62]

In fact, other investigators[62,69] more recently reported that the actual width of the surgical margin has no effect on survival as long as the margin is microscopically negative. Altendorf-Hofmann and Scheele[69] noted that while patients with a microscopically positive margin had a worse prognosis compared with patients who had a microscopically negative margin, survival was not associated with the width of the negative surgical margin. Similarly, Pawlik et al.[62] noted that the width of a negative surgical margin did not affect survival, recurrence risk, or site of recurrence following hepatic resection of colorectal metastases. In this study, patients with a positive surgical margin had a higher overall risk of recurrence (51%) compared with patients who had a negative surgical margin (40%); however, patients with a negative margin—regardless of the width of the surgical margin—had similar overall recurrence rates. The 5-year survival rate was 17% for patients with a positive surgical margin compared with 64% for patients with a negative surgical margin. The width of the surgical margin did not significantly affect survival in patients with negative margins.[62]

In the past, resection of hepatic colorectal metastases was not attempted in patients who had more

than three or four metastases, hilar adenopathy, metastases within 1 cm of major vessels such as the vena cava or main hepatic veins, or extrahepatic disease. Earlier studies that established certain clinicopathologic factors as being contraindications for surgery have subsequently been criticized on both clinical and methodologic grounds. Methodologically, these studies were problematic because only a small number of patients who actually met all the "exclusion" criteria were included in the analyses. Additionally, most early studies reported only univariate or log-rank analyses while failing to control for competing risk factors. Clinically, data are problematic because many of these early studies were carried out prior to the era when new, more active chemotherapy agents, as well as new techniques such as portal vein embolization (PVE) and radiofrequency ablation, were available.

More recent studies demonstrate that patients with "traditional" adverse clinicopathologic factors can achieve long-term survival following hepatic resection and therefore should not be excluded from surgical consideration. This has therefore precipitated a shift in the definition of resectability from criteria based on the characteristics of the metastatic disease (tumor number, size, etc.) to new criteria based on whether a complete (margin-negative) resection of the liver lesion can be performed. Currently, hepatic colorectal metastases should be defined as resectable when it is anticipated that disease can be completely resected, two adjacent liver segments can be spared, adequate vascular inflow and outflow and biliary drainage can be preserved, and the volume of the liver remaining after resection (i.e., the "future liver remnant") will be adequate (at least 20% of the total estimated liver volume).[21,70] This definition of resectability represents a paradigm shift. Instead of resectability being defined by what is removed, decisions regarding resectability should now focus on what will remain following resection. Concern for the future liver remnant is particularly pertinent during preoperative evaluation of patients for an extended hepatectomy (resection of ≥ five liver segments), as some patients may be excluded from the benefit of a potentially curative resection because the anticipated liver remnant may be too small.

In general, 20% of the total liver volume appears to be the minimum safe volume that can be left following extended resection in patients with normal underlying liver. CT or MRI can now provide an accurate, reproducible method for preoperatively measuring the volume of the future liver remnant.[70] To avoid operating on patients with low-volume future liver remnants, any patient who fails to show compensatory hypertrophy as a result of tumor growth and who has a future liver remnant of less than 20% should be considered for PVE to induce hypertrophy of the contralateral liver lobe.[71]

Another factor that has almost universally been well accepted as a contraindication to liver resection is the presence of extrahepatic disease. In Adson's[38] initial report in 1984, he noted that no patient with extrahepatic disease survived beyond 5 years. As such, extrahepatic disease has long been regarded as an absolute exclusion criteria for hepatic resection. The advent of more effective systemic chemotherapy agents, as well as improvements in imaging modalities to more accurately identify the true extent of extrahepatic disease, has prompted some investigators to advocate for surgical resection for patients with extrahepatic disease. Elias et al.[72] have reported that the 5-year survival rates following hepatectomy for hepatic colorectal metastases and simultaneous resection of extrahepatic disease with curative intent was 29%. As such, the presence of extrahepatic disease should not be considered an absolute contraindication to hepatic resection. However, patients with extrahepatic disease must be selected carefully. In general, resection should only be considered following documentation of stable/responsive disease after treatment with systemic chemotherapy in situations where complete (margin-negative) resection is feasible. Management of patients with simultaneous intra- and extrahepatic disease involves complex clinical decision making and therefore should be carried out in a multidisciplinary setting.

Consensus Statement:

1. In patients undergoing liver resection for hepatic colorectal metastases, a positive surgical margin is associated with a higher local recurrence and worse overall survival and should be avoided whenever possible.
2. While a wide (> 1-cm) resection margin should remain the goal when performing a liver resection, an anticipated margin of less than 1 cm should not be used as an exclusion criterion for resection.
3. Assessment of resectability of hepatic colorectal metastases should focus on the ability to obtain a complete resection (negative margins).
4. The feasibility of hepatic resection should also be based on three criteria related to the remaining liver following resection: (1) the ability to preserve two contiguous hepatic segments, (2) preservation of adequate vascular inflow and outflow as well as

biliary drainage, and (3) the ability to preserve adequate future liver remnant (> 20% in a healthy liver).

5. The presence of extrahepatic disease should no longer be considered an absolute contraindication to hepatic resection provided the patient is carefully selected and a complete (margin-negative) resection of both intra- and extrahepatic disease is feasible.

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