Review Article

Patient selection for hepatic resection for metastatic colorectal cancer

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KEY WORDS Cancer; colorectal; non-hepatic; metastasis

J Gastrointest Oncol 2012;3:3-10. DOI: 10.3978/j.issn.2078-6891.2012.001

Introduction

The most common site of hematogenous metastasis from colorectal cancer is the liver. Approximately one half of patients with colorectal cancer develop liver metastasis during the course of their disease (1). Hepatic resection for liver metastasis remains the only potentially curative therapy, with 5 year survival rates of approximately 50% (2) and an actual 10-year cure rate approaching 20% (3). Additionally, effective systemic and regional chemotherapy combined with resection can result in long-term survival without cure (4). Therefore, the goals and indications for hepatic resection include both the possibility of cure and prolongation of life. This report focuses on factors which we feel are important for properly selecting patients to undergo surgical therapy. The initial patient consultation focuses on 3 areas: I. the patient's ability to tolerate the operation, II. determining technical resectability and III. predicting whether removal of liver disease will improve long-term survival.

Operative morbidity and patient selection

Operative mortality for liver resections performed for metastatic colorectal cancer has decreased substantially over the past 3 decades to <5% in most series and is approximately 1% in high volume centers (2,5-15). Reported major complication rates are greater than 20% in most series and are therefore an important issue (16-20). Patient selection plays a critical role in minimizing mortality and morbidity following hepatic resection. Pre-existing comorbidities contribute substantially to surgical morbidity and mortality. Therefore, one goal of the preoperative evaluation should be to exclude patients with prohibitive operative risks and to identify patients with manageable conditions that can be medically optimized before operation.

Advanced age is not a contraindication to hepatic resection which is now routinely performed in elderly patients with acceptable morbidity and mortality (21,22). Some centers have demonstrated that the American Society of Anesthesiology (ASA) and Acute Physiology and Chronic Health Evaluation (APACHE) scores can be useful in predicting complications (23,24). Although such surrogates of physiological conditions can help predict complications in this patient population, they fail to provide guidelines for managing co-morbid conditions in the perioperative setting. Performance status and frailty are very important predictors of perioperative outcome (25,26) and are routinely evaluated at the preoperative visit. Patients are evaluated for their co-morbid conditions by appropriate sub-specialty services and risk stratified. Patients must be fit for a major laparotomy (in most cases), the metabolic consequences of a hepatic resection and the attendant substantial physical recovery.

All patients being considered for a hepatic resection should be assessed for preoperative liver dysfunction. Although most patients with colorectal cancer do not have underlying chronic liver disease, exposure to chronic chemotherapy can result in hepatic steatosis, steatohepatitis, sinusoidal obstruction syndrome and even portal hypertension (27-31). Steatosis and steatohepatitis

No potential conflict of interest.

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Submitted Dec 05, 2011. Accepted for publication Jan 12, 2012.
Available at www.thejgo.org

ISSN: 2078-6891

also frequently occur in the general population but are likely exacerbated with chemotherapy treatment. Chemotherapy associated steatohepatitis (CASH) results from chronic liver damage which can make surgical resection risky due to higher rates of postoperative liver dysfunction. There is evidence that CASH increases the risk of postoperative complications after hepatic resection for metastatic colorectal cancer (28-30). The assessment of liver function can be complex and unfortunately, blood tests are not reliable predictors of liver function. Nonetheless, all patients should have liver chemistries, a complete blood count and a prothrombin time measured prior to surgery. These laboratory values combined with a clinical evaluation are used to calculate a Child-Pugh classification (32). We routinely perform hepatic resections on Child-Pugh class A patients with acceptable morbidity and mortality, but generally consider class B and C patients as prohibitively high operative risk. A more critical assessment is to assess the patient for portal hypertension. Patients with significant portal hypertension have a very high risk of mortality associated with hepatic resection and are generally not considered candidates (33). Splenomegaly, thrombocytopenia (<100K/mcl) and varices on endoscopy or on CT scan are all indicative of portal hypertension. If there is doubt about the presence of portal hypertension, a more direct measurement of portal pressures can be obtained with a hepatic vein wedge pressure (34). Cross-sectional imaging should be reviewed carefully for signs of steatosis, cirrhosis and portal hypertension. MRI is effective for determining the degree of steatosis by decomposing the liver signal into its fat and water components (35). CT is effective at identifying varices and splenomegaly which are indicative of portal hypertension (36). No single test can reliably predict which patients have adequate hepatic reserve to tolerate a resection. However, with a comprehensive investigation of chemotherapy history, liver function tests, platelet count, Child-Pugh score, and imaging findings in conjunction with the extent of resection required the operative risk can be reasonably estimated. In patients with evidence of liver dysfunction related to chronic chemotherapy, morbidity can be minimized by decreasing the volume of resected liver with parenchymal sparing resection techniques or by increasing the volume of the future liver remnant (FLR) utilizing portal vein embolization (PVE). (see below)

Preoperative cross sectional imaging and role of positron emission tomography (PET)

Every patient evaluated for hepatic resection for colorectal cancer should undergo cross-sectional imaging to evaluate the extent of both intra- and extrahepatic disease. We routinely obtain contrast-enhanced multidetector helical computed tomography (CT) imaging of the chest, abdomen and pelvis on patients being evaluated for hepatic resection. Although somewhat controversial, we obtain chest CT scans to rule out pulmonary metastasis because of its high degree of sensitivity (37) and potential to change management. However, a potential weakness of routinely obtaining chest CT scans is its lack of specificity and false positive rate of identifying non-specific small pulmonary nodules. These small pulmonary nodules are frequently under the resolution for PET scans, may be nearly impossible to biopsy percutaneously, and probably do not justify a thoracotomy or thoracoscopic procedure. Forty-three percent of patients selected for liver resection for colorectal metastases at our institution have subcentimeter pulmonary nodules of which one third ultimately proved to be metastatic disease (38). However, the presence of limited subcentimeter pulmonary nodules did not significantly impact 3-year DSS and should not necessarily preclude liver resection (38). The goal of hepatic imaging is to define the number, location, distribution and relation of the hepatic tumors to vascular and biliary structures. The standard CT scan to evaluate for liver metastasis is a triphasic scan with 2.5-5-mm slices. The arterial phase is useful to define arterial anatomy and identify co-existing benign lesions. However, colorectal metastases are not very vascular and therefore are best seen on the portal venous phase where they appear hypodense. The sensitivity of identifying liver metastasis with contrast enhanced multidetector CT scans approaches 80-90% (39-41). Superior image resolution of CT provides excellent vascular and anatomic detail which is useful in preoperative planning. However, CT lacks the sensitivity and ability to characterize lesions less than 1cm.

Contrast enhanced magnetic resonance imaging (MRI) is another useful imaging modality for assessing the extent of liver disease with an accuracy of 80-90% (42-44). MRI is most useful for evaluating equivocal lesions and differentiating metastasis from benign lesions. It may also be beneficial in defining relationships to the biliary tree with MRI cholangiopancreatography. We selectively use contrast enhanced MRI in order to characterize indeterminate liver lesions and for patients with steatosis from obesity, diabetes and previous chemotherapy. MRI is particularly useful in identifying 'disappearing' tumors while on chemotherapy since many of these tumors are not visible due to the development of hepatic steatosis (45). The strength of MRI is the ability to characterize small liver lesions using liver specific contrast agents such as EOVIST (gadolinium-EOB-DTPA) (46,47), but the low sensitivity for detecting extrahepatic disease limits our use as a first-line imaging modality.

Some centers have advocated for the routine use of positron emission tomography (PET). PET most frequently uses fludeoxyglucose (FDG), a glucose analogue which accumulates in glucose-avid rapidly metabolizing cancer cells and inflammatory cells. When comparing preoperative CT alone to combined PET and CT, Strasberg *et al.* reported an improved resectability rate from 86% to 95% with the addition of PET (48). These data are encouraging because PET-CT may identify otherwise radiologically occult extrahepatic disease and may improve long term survival by selection. However, it is important to note that all of these patients had high quality CT scans as well, so the utility of PET-CT alone for evaluating liver metastasis is limited because the sensitivity of PET in the liver for small lesions is poor. PET-CT is also limited by the non-specificity of positive lesions. A recent meta-analysis suggested PET-CT may be slightly more sensitive (91-100% versus 78-94%) and specific (75-100% versus 25-98%) than CT alone for hepatic colorectal metastases (49), but these results were based on only 5 studies. It is possible that expert radiologic review of high quality CT scans may abrogate the purported benefit of PET-CT. We currently use PET-CT selectively for patients at high risk of extrahepatic disease or indeterminate extrahepatic lesions, realizing that subcentimeter lesions may fall below the diagnostic threshold of detection.

Determining technical resectability

A negative resection margin is associated with a lower local recurrence rate and improved long-term survival (50). Scheele *et al.* demonstrated that patients who undergo an R0 resection have a three-fold increase in median survival compared to R1 or R2 resections (51). Similarly, another more recent study by Pawlik *et al.* demonstrated a significantly higher risk of liver recurrence and decreased overall survival with positive margins (50). The optimal resection margin is still debatable. One study reported a resection margin of ≥1cm being associated with improved disease-free survival, but other studies have demonstrated that the width of resection margin is not independently associated with improved oncologic outcome as long as the margin is microscopically negative (50,52). We studied 1019 patients undergoing hepatic resection for colorectal metastases and found that obtaining a >1cm margin was independently associated with improved outcome but subcentimeter resections are also associated with favorable outcomes (53). Therefore, a negative margin should be attainable for a patient to be deemed resectable and aiming for 1cm margins should be encouraged when possible. We speculate that obtaining a negative margin can be both a technical and biologic issue. Some tumors that appear to be resected with narrow gross margins are found to have pathologically negative margins, while other resections which appear to have wide gross margins are found to have microscopically positive margins. Although no data exist to support this, we believe this dilemma may be indicative of underlying tumor biology.

Determining technical resectability should focus on preserved structures rather than those which require resection. This is a critical issue because the risk of hepatic resection is directly related to the relative volume of hepatic parenchyma resected. Hepatic metastases are considered technically resectable when a negative resection margin is anticipated, all hepatic disease can be resected and/or ablated, two adjacent liver segments can be spared, vascular inflow, outflow and biliary drainage can be preserved, and a sufficient liver remnant (FLR) will remain (>20% of the total estimated liver volume) (54-57).

For non-diseased livers >20% of normal total liver appears to be a safe FLR (58,59). However, greater FLRs of 30-40% are probably necessary for patients on chronic chemotherapy or for diseased livers with significant steatosis (60). CT and MRI can accurately determine the volume of the FLR and both are utilized at our institution selectively, particularly for patients with small FLRs, underlying steatosis and those treated with long-term chemotherapy. One often underappreciated strategy for such patients is the use of parenchymal sparing resection techniques. The use of segmental and sub-segmental resections and intraoperative thermal ablation can often spare a patient an unnecessary large volume resection. For patients that require a major hepatic resection with an inadequate FLR volume based on cross-sectional imaging, pre-operative portal vein embolization (PVE) contralateral to the FLR is performed, followed by repeat volume measurements. Our goal for PVE is to achieve an approximately 10% increase in FLR. Failure to induce hypertrophy is either indicative of a technical failure and requiring repeat PVE, or represents a diseased liver without regenerative capacity for which resection has a high likelihood of postoperative liver failure. It has been suggested that the existence of bilobar disease is a relative contraindication to PVE because of potential contralateral tumor growth. Some feel that this situation is best approached with a 2-stage hepatectomy with PVE after the first stage of resection (61,62). However, PVE appears safe and effective in combination with concomitant chemotherapy (63) and we currently perform PVE while patients remain on chemotherapy.

Predicting oncologic outcome

The ultimate decision on whether to resect colorectal liver

metastasis assumes technical resectability, but must take into account the predicted oncologic outcome and potential clinical benefit. The presence of liver metastases defines the patient as stage IV by the American Joint Committee on Cancer staging system. However, cure is still achievable because the liver is frequently the only site of metastatic disease. The benefit of hepatic resection for metastatic colorectal cancer has never been tested in a randomized trial. However, 5-year survival for patients with colorectal liver metastasis treated with systemic chemotherapy alone is rare and cure essentially does not occur. Five-year survival after hepatic resection is 41-58% (2,8,11,15) and 10 year disease-free cure rates approach 20%. Therefore, a regional approach to liver disease is clearly indicated and improves survival. However, predicting which patients will benefit based on diverse clinical and pathological features can be difficult.

The ideal predictive scoring system would use preoperatively available factors to predict which patients derive no benefit from surgical resection and should be treated with systemic chemotherapy alone. Unfortunately, such an ideal predictor has been elusive. Fong *et al.* developed an effective clinical risk score (CRS) based on a retrospective multivariable analysis that identified 5 preoperatively available variables to predict outcome following hepatic resection. One point each was assigned for node positive disease, disease-free interval <12 months, number of tumors >1, preoperative CEA level >200 ng/dL, and size of tumor >5 cm (7). CRS is useful in predicting survival as well as the likelihood of disseminated disease and resectability (64). However, patients with a high CRS have a predicted 5-year survival of approximately 20% and documented 10 year cures. Patients with one or multiple negative prognostic factors still benefit from hepatic resection (65) as evidenced by documented long-term survival and cure (3).

Patients with ≥4 liver metastases, or evidence of extrahepatic disease were not offered hepatic resection in the past. However, the number of metastasis is no longer a contraindication to liver resection (52,66,67). Many of the early studies failed to perform multivariate analysis and thus confounding variables were not considered. We believe that although recurrence rates are very high after resection of ≥4 metastases, the associated long-term survival and small potential for cure (5-10%) justify surgical resection in selected patients. Several recent studies indicate that although the presence of extrahepatic disease portends a worse survival , complete resection of both the hepatic and extrahepatic metastases can result in long-term survival. Although highly selected patients with limited and completely resected extrahepatic disease experience long-term survival, recurrence rates in this group of patients approach 100%. We therefore, feel that patients with extrahepatic disease must be carefully selected with the use of neoadjuvant chemotherapy, extensive imaging and should be extensively counseled about the nearly universal recurrence rates after operation (68-71). In general, these patients should have a single site of resectable disease, limited hepatic disease and stable or responsive disease on systemic chemotherapy before considering resection.

We generally view liver resections for metastatic colorectal cancer as either potentially curative or operations with very high or nearly universal recurrence where controlling liver disease may prolong survival. Patients without evidence of extrahepatic disease, <4 metastases and in whom a negative resection margin is achievable are resected with curative intent. In patients with ≥4 metastases the operation is still considered potentially curative but recurrence rates are high. If technically resectable, these patients are offered resection but we are more likely to treat with a brief course of chemotherapy prior to resection. Patients with resectable extrahepatic disease, and those in which a margin is likely to be positive on final pathology have a nearly universal rate of recurrence but may still benefit from resection. Unfortunately, margin status is not completely predictable based on preoperative imaging and therefore this issue cannot reliably be used to exclude patients from resection. Nonetheless, if the margin is very likely to be involved due to tumor abutment of vascular structures that must be preserved we feel it is reasonable to treat with systemic and/or regional chemotherapy prior to resection in hope of achieving response and decreasing the chance of a positive margin. Concurrent resection of all extrahepatic disease in well selected patients is associated with the possibility of long-term survival at our institution but patients are highly selected. Currently, we restrict such resections to patients with limited, resectable single sites of extrahepatic disease who have stable or responsive disease on chemotherapy (71).

There are numerous reasons to justify the use of preoperative systemic chemotherapy. Preoperative chemotherapy may increase the R0 resection rate while preserving remnant liver parenchyma, treat unrecognized microscopic disease and be used as a test of chemoresponsiveness. Modern chemotherapy with fluorouracil (FU), leucovorin and oxaliplatin or irinotecan have improved response rates over the last decade and offer the possibility of converting unresectable to resectable disease. Studies have demonstrated meaningful conversion rates between 14-41% with systemic chemotherapy alone (9,72). Our institution offers hepatic artery infusional (HAI) therapy with floxuridine and dexamethasone

combined with systemic chemotherapy for patients with extensive liver disease not amenable to resection. When systemic chemotherapy is combined with HAI, 47% of initially deemed unresectable patients were eventually converted to resectable at our institution with promising long-term outcomes (73).

Using neoadjuvant chemotherapy for resectable disease (<4 metastases, no extrahepatic disease and technically resectable with clear margins) is debatable. Many argue that progression on chemotherapy portends a poor prognosis after resection and neoadjuvant chemotherapy is a strategy to identify such patients. Adam *et al.* retrospectively reviewed 131 patients treated with neoadjuvant chemotherapy who underwent liver resection and found that 5-year survival was significantly worse in the group of patients that progressed on chemotherapy versus responders (8% *vs.* 37%) (74). However 24% of patients had extrahepatic disease, all had 4 or more hepatic metastases and 25% were on 2nd or 3rd line chemotherapy. These data simply do not apply to patients with straightforward resectable disease. We recently reviewed 111 patients with synchronous colorectal liver metastases who were all initially deemed resectable and received neoadjuvant chemotherapy and found that response to therapy did not correlate with overall survival (75). Given the low rates of progression on modern chemotherapy (5-10%), the associated hepatotoxicity and the fact that progression does not necessarily translate into poor outcome we do not favor neoadjuvant chemotherapy for resectable disease.

Conclusion

Proper selection of patients for hepatic resection metastatic colorectal cancer demands a multidisciplinary approach in order to identify patients with prohibitive risks and medically optimize comorbidities prior to surgery. Cross-sectional imaging is crucial to determine technical resectability and identify extrahepatic disease. The definition of resectability has evolved over the past 3 decades to include multiple hepatic tumors, <1cm margins, limited extrahepatic disease and should now focus on complete extirpation of disease with preservation of anatomic structures. Currently, hepatic disease is deemed resectable when 2 contiguous liver segments with adequate inflow, outflow and biliary drainage can be preserved and adequate liver remnant volume will remain. The presence of limited and resectable extrahepatic disease no longer precludes surgical resection. We favor upfront hepatic resection in patients presenting with potentially curative and resectable disease (<4 metastases, no extrahepatic disease and technically resectable with clear margins) and reserve neoadjuvant chemotherapy for patients with a high likelihood of recurrence as defined above. When experienced surgeons properly select patients, hepatic resections can be performed safely and effectively in this diverse patient population.

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Cite this article as: Weiss MJ, D'Angelica MI. Patient selection for hepatic resection for metastatic colorectal cancer. J Gastrointest Oncol 2012;3:3-10. DOI: 10.3978/j.issn.2078-6891.2012.001