Review Article

Surgical treatment of colorectal liver metastases

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Abstract: The incidence of colorectal cancer is rising in China. Since nearly 50% of these patients will ultimately develop liver metastases, an understanding of the surgical management of hepatic metastases is important. Surgical strategies for the management of liver metastases have evolved in recent years and now include adjunctive procedures such as portal vein embolization and radiofrequency ablation, which can help increase the number of patients eligible for potentially curative surgical management. In addition, innovations in treatment sequencing, including the use of peri-operative chemotherapy and the liver-first approach to the management of synchronous liver metastases have helped improve outcomes in these patients. Along with such changes in surgical management come new risks, such as chemotherapy-induced liver damage, with which the surgeon must be prepared to contend.

Key Words: Chemotherapy-associated liver injury; radiofrequency ablation; reverse approach to synchronous colorectal liver metastasis; portal vein embolization

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Epidemiology and background

Colorectal cancer is the 3rd most common cancer worldwide (1) and the 5th most common cancer in Eastern Asia (2). The incidence is rising in China (3) and it ranks among the top 5 most common cancers in residents of Shanghai with an incidence of 56 cases per 100,000 residents (4). Approximately 40-50% of patients affected with colorectal cancer will develop liver metastases at some point during the course of their disease, making liver metastases the most common cause of death for these patients (3,5,6). Complete surgical resection offers the only hope of cure and long-term survival for these patients. Using contemporary multimodality therapy, 5-year survival rates of 47-58% have been achieved for the 20-30% of patients who are able to undergo surgical resection (3,7,8).

According the general international classification system, colorectal liver metastases are considered synchronous if they are discovered at the time of initial diagnosis of the primary tumor or within six months of resection of the primary tumor (9). Metastases discovered in the liver more than six months after resection of the primary cancer, on the other hand, are considered metachronous.

Imaging and staging work up

The Chinese Guidelines for the Diagnosis and Comprehensive Treatment of Hepatic Metastasis of Colorectal Cancer recommend that the initial staging work-up for patients with colorectal cancer include measurement of serum AFP, CEA, and CA 19-9 as well as an hepatic ultrasound and abdominal and pelvic computed tomography (CT) scan with contrast to categorize the number and location of liver metastases and exclude additional sites of metastatic disease (9). For patients with suspected liver metastases, the guidelines recommend a liver magnetic resonance imaging (MRI) scan for further evaluation. It should be noted that while MRI has higher sensitivity for detection of tumors within the liver, CT provides superior imaging of extrahepatic disease (10). In addition, the guidelines recommend against routine percutaneous biopsy of suspected liver metastases due to the risks of needle track seeding and false negative

results; however, incisional or excisional biopsy should be performed if any suspicious liver lesions are encountered during resection of the primary tumor.

Following resection of a primary colorectal tumor in a patient without known metastatic disease, the recommended imaging follow up includes liver ultrasound every 3-6 months for the first two years and then every 6 months for 5 years (9). For patients undergoing surveillance after resection for stage II or III disease, the guidelines also recommend annual chest, abdomen, and pelvis CT with contrast with use of liver MRI to confirm any lesions seen on CT that are suspicious for new liver metastases. In patients who have previously undergone resection of liver metastases, the guidelines suggest that CT of the chest, abdomen, and pelvis with contrast be performed every 3 months for 2 years and then every 6-12 months for an additional 5-7 years (9). For each of these patient groups evaluation of the CEA level should be performed every 3-6 months for two years and then every 6 months for an additional 3-5 years.

Positron emission tomography (PET)/CT is not recommended as part of the routine staging work up for colorectal cancer (9). A retrospective British study showed a similar sensitivity and specificity of liver MRI and PET/CT for the detection of liver metastases, with a greater accuracy of MRI for lesions less than a centimeter in size--although it should be noted that this study also found a benefit of PET/CT over contrast-enhanced CT scan for the detection of extrahepatic metastatic disease (11). Similarly, a U.S. study identified the use of PET imaging as an independent predictor of a lower rate of nontherapeutic laparotomy in patients with hepatic colorectal metastases (12). No studies, however, have shown a survival benefit associated with the use of PET/CT. PET/CT is also limited in its detection of tumors less than 1 cm and mucinous tumors. PET-positive lesions are nonspecific, particularly in settings where inflammation may be present. Additionally, prior treatment with chemotherapy may decrease the sensitivity of PET for detection of disease (10).

Although not useful for pre-operative staging, intra-operative ultrasound is an important component of the surgical management of patients with hepatic metastases from colorectal cancer. Intra-operative ultrasound has been shown to detect tumors not seen on helical CT scan in as many as 27% of patients undergoing resection of primary or metastatic liver tumors, with even higher rates of detection of unsuspected lesions in patients with increasing numbers of tumors (13). For this reason, intra-operative ultrasound should be utilized at the time of liver resection for cancer.

Resectability and operability

Operability refers to a patient's ability to tolerate a liver resection (14) and includes factors such as comorbidities and baseline performance status. The resectability of a tumor has do with both technical and oncologic factors (14). Tumors are technically resectable when all metastases can be removed with negative margins with sparing of at least two adjacent segments of liver, and with preservation of adequate blood inflow and outflow, biliary drainage, and remnant parenchyma (generally accepted as at least 20% of estimated total liver volume) (10,15).

Oncologic factors which have previously been considered at least relative contraindications to the surgical treatment of liver metastases include the presence of four or more metastases and the presence of extrahepatic sites of metastases (16,17). Two recent retrospective studies have shown that long-term survival is possible even for patients with four or more metastases if complete resection can be accomplished (18,19). In one of these studies, even though the presence of multiple tumor nodules was independently associated with a lower rate of overall survival, it was not associated with disease-free survival (18). In the other study patients with four or more colorectal liver metastases had a 5-year actuarial disease-free survival rate of 21.5% with an overall survival rate of 50.9% after treatment with multimodality therapy (19). Additionally recent studies have shown favorable survival for patients with liver metastases and limited sites of resectable extrahepatic disease, including lung (20), limited peritoneal disease, and portal lymph nodes (21,22). Patients who develop new liver metastases or new sites of extrahepatic disease while on chemotherapy, however, should not be considered for resection unless a response to other therapy can be demonstrated (14).

Response to therapy

Emerging data suggest that the pathologic response to chemotherapy may represent an important endpoint that is highly correlated with overall survival (23,24). Four to nine percent of patients treated with neoadjuvant oxaliplatin or irinotecan-based chemotherapy may achieve a pathologic complete response (23,24), which has been shown on multivariate analysis to be an independent predictor of improved overall survival, overwhelming other previously established predictors of survival such as disease-free

interval, tumor size, and tumor multiplicity, with a hazard ratio of 4.8 for patients with a major pathologic response (defined as 49% or fewer viable tumor cells) (23). In addition, morphologic response to chemotherapy as seen on CT scan has been shown to correlate with overall survival (25). A study from the M.D. Anderson Cancer Center defined the "optimal" morphologic response as the presence of homogeneous low attenuation lesions with a thin, sharply defined interface between the tumor and the surrounding liver parenchyma and showed that patients treated with bevacizumab were significantly more likely to achieve such a response than those not treated with bevacizumab (47% *vs.* 12%) (25). The patients in the optimal morphologic response group had overall 3- and 5-year survival rates of 82% and 74%, respectively, *vs.* 60% and 45% (P<0.001) for those with a suboptimal response (25).

Synchronous metastases and treatment sequencing

Liver metastases are discovered synchronously with the primary tumor in approximately 25% of patients (26) and can be approached via three different strategies. The Chinese Guidelines for treatment of hepatic metastasis of colorectal cancer recommend either synchronous resection of both the primary and metastatic tumors or two-stage resection with resection of the primary tumor followed by resection of the hepatic metastases either with or without systemic chemotherapy in between the two operations (9). Classically, resection of the primary tumor followed by liver resection for the metastatic disease has been the approach taken to synchronous disease. There are several disadvantages to this approach, however, including the potential for progression of the metastatic disease prior to any systemic therapy, complications from the colorectal resection which may significantly delay or even preclude all together systemic therapy and/or resection of the liver metastases, and a substantial interval between presentation and administration of systemic therapy for stage IV disease. For these reasons, two alternative strategies have also been utilized. The first of these is simultaneous resection of both the primary tumor and the liver metastases. Several studies have shown the feasibility of this approach and have suggested that it can be accomplished without an increase in postoperative morbidity or mortality rates (26-29). Such an approach, however, is typically recommended for patients who either require a low-risk colon resection (e.g., right hemicolectomy) or a limited liver resection (e.g., wedge resection) if a more complex colorectal resection is required (10).

The second alternative strategy for the management of synchronous metastases is the reverse approach, whereby the liver resection is undertaken prior to the colorectal resection. This approach may include administration of neoadjuvant chemotherapy prior to any surgical resection and is feasible when the primary tumor is asymptomatic, without evidence of obstruction or bleeding. The major advantage to this approach is treatment of the metastatic disease prior to progression to an unresectable status (30,31). Progression of the primary tumor during the administration of systemic therapy is rare (32,33), but does require a change in treatment plan, so it is important that surveillance of the primary tumor be performed throughout the period of treatment for the metastatic disease. Once resection of the metastatic disease has been accomplished, focus can be turned to locoregional control of the primary tumor (i.e., resection for a colonic tumor or chemoradiation followed by resection for a locally advanced rectal tumor). In general, the decision regarding operative strategy for management of synchronous colorectal liver metastases should be prioritized based on whether the primary or metastatic tumor is causing symptoms, followed by which of the two sites presents the greatest oncologic risk. Evaluation of these factors is best undertaken by a multidisciplinary team at the outset of therapy.

Cautionary notes on neoadjuvant chemotherapy

Timing of surgery after chemotherapy

A Japanese study reported the results of sequential measurements of 15 minute indocyanine green retention (ICG R15) in patients following neoadjuvant chemotherapy. This study showed a significant improvement in the ICG R15 following the final dose of chemotherapy after a 2-week interval with further nonsignificant improvements at increasing time points up to 8 or more weeks after cessation of chemotherapy (34). Based on this data the authors concluded that resection should be delayed for at least 2-4 weeks following completion of chemotherapy. Another retrospective study of patients undergoing liver resection for colorectal metastases showed that receipt of 5 or fewer cycles of 5-FU-based preoperative chemotherapy was associated with a markedly lower rate of postoperative complications (19% *vs.* >40%) relative to patients receiving greater numbers of cycles (35).

Chemotherapy-induced liver injury

Several studies have described histologic changes in the livers of patients treated with certain chemotherapeutic agents. The first to be described of these was sinusoidal obstruction and veno-occlusive disease [the sinusoidal obstruction syndrome (36)] occurring in up to 78% of patients treated with oxaliplatin (37-40). These histologic changes do not seem to correlate with the total oxaliplatin dose received and may persist for months after chemotherapy (37,38). Although the presence of the sinusoidal obstruction syndrome has not been associated with increased rates of postoperative complications in most studies (38-40), in one French study it was associated with a longer length of hospital stay and a higher morbidity rate (41), and in another it was associated with an increased risk of transfusion (39).

Use of irinotecan has been associated with the development of steatohepatitis in approximately 20% of patients (38,40) and has been associated with higher rates of postoperative mortality (38), and may be correlated with higher rates of postoperative hepatic insufficiency (42). The development of steatohepatitis has also been shown to occur primarily in patients with a high body mass index (43), suggesting that rather than inducing steatohepatitis, irinotecan may cause progression of it (42). Increased rates of postoperative complications have also been correlated with longer durations of preoperative chemotherapy, with the most conservative cutoff occurring after 5 cycles of chemotherapy (35,39,41,44).

The effectiveness of modern chemotherapy regimens has resulted in a phenomenon known as disappearing liver metastases—metastases that become radiologically undetectable during neoadjuvant therapy. A retrospective study of patients treated with liver resection for colorectal metastases who had been treated with preoperative chemotherapy reported that almost 25% of patients had at least one liver metastasis that disappeared during treatment (45). In the patients whose missing tumors were not resected, nearly 60% eventually recurred at that site; however, the overall survival rates were not adversely impacted despite these local recurrences. Another retrospective study of disappearing metastases showed that persistent macroscopic disease was identified intraoperatively in 30% of the lesions, 80% of resected lesions without macroscopic evidence of residual disease had microscopic disease identified, and 74% of unresected lesions without macroscopic evidence of residual disease developed local recurrences with 1 year of surgery (46).

Perioperative chemotherapy

The use of perioperative chemotherapy in patients with resectable colorectal liver metastases was studied in a multicenter randomized trial—the EORTC Intergroup Trial 40983 (5). In this trial oxaliplatin-naïve patients were randomized to either 6 cycles of pre-operative and 6 cycles of post-operative FOLFOX4 or to surgery alone. The trial demonstrated that peri-operative chemotherapy increased the probability of 3-year progression-free survival by 35% (with a 7% absolute risk reduction) (5). Reversible post-operative complications were significantly more common in the peri-operative chemotherapy group (25% *vs.* 16%). A partial or complete response by RECIST criteria was seen in 40% of patients and on average the total tumor diameter decreased by about 25% (5).

A meta-analysis of randomized trials comparing surgery alone with peri-operative chemotherapy plus surgery in patients with stage IV colorectal cancer showed no evidence of a survival benefit for use of hepatic arterial chemotherapy, whereas the survival advantage for patients receiving peri-operative systemic chemotherapy approached significance (HR 0.74, P=0.08) (47). Both hepatic arterial chemotherapy (HR 0.78, P=0.01) and systemic peri-operative chemotherapy (HR 0.75, P=0.003) were associated with a significant recurrence-free survival benefit, however.

Functional liver remnant and portal vein embolization

A Japanese study of liver volumes in living transplant donors showed that in 25% of patients the left liver represents 30% or less of the total liver volume (48). For such patients, an extended right hepatectomy would carry a prohibitive risk of postoperative liver failure due to an inadequate functional liver remnant. The concept of portal vein embolization to induce hypertrophy of the functional liver remnant and thereby decrease the risk of postoperative liver insufficiency was first introduced by Makuuchi in 1990 to allow surgical resection in such patients (49). Since that time, additional studies have clarified the safety of and indications and techniques for the appropriate use of portal vein embolization. Preoperative portal vein embolization is typically recommended for patients with an anticipated functional liver remnant that is less than 20-25% of estimated total liver volume (50,51), with an expected average increase in volume of the remnant liver of 12% of the total liver volume (50). The rate of hypertrophy

has been shown to correlate with the degree of increase in the portal blood flow velocity in the nonembolized segment on postembolization day 1 (52). Portal blood flow in the nonembolized segments remains elevated for at least 14 days after embolization (52), providing the rationale for a 2-4 week waiting period between embolization and resection (50). The rate of hypertrophy after embolization is slower and the degree of hypertrophy is less in patients with cirrhosis (53) and diabetes (54,55). If an interventional radiology suite is unavailable for the performance of percutaneous portal vein embolization, then a transileocolic venous approach for embolization can be undertaken during laparotomy (49).

The technique of right portal vein ligation with in situ splitting (also known as ALPPS-associating liver partition and portal vein ligation staged hepatectomy) has been proposed as an alternate strategy for approaching the treatment of patients with a marginal or inadequate functional liver remnant (56). This technique involves two operations—the first during which the right portal vein is ligated and the hepatic parenchyma is completely (or nearly-completely) transected and a second (occurring after a variable period of delay, but during the same hospital stay) during which the resection is completed. Proponents of this approach feel that the hypertrophy achieved is more rapid and, perhaps, greater than that realized after portal vein embolization (57,58). Critics of the approach, however, feel that the high morbidity rate (68%), in-hospital mortality rate (12%), and lack of data on long-term oncologic outcomes should limit the use of this technique to clinical trials (56,59).

Repeat hepatectomy

Approximately 65-85% of patients who undergo liver resection for colorectal metastases will eventually develop a recurrence, of which 20-30% will be isolated to the liver (60). Repeat hepatic resection for recurrent liver metastases has been shown to have equivalent long-term survival without significant increases in perioperative morbidity or mortality in several studies, provided that a margin negative resection can be obtained (61-64).

(Metachronous metastases) - unresectable with downstaging

Retrospective studies have shown that use of contemporary chemotherapy regimens that include oxaliplatin and irinotecan can convert 12.5-38% of patients with initially unresectable liver metastases into surgical candidates (21,65). While such patients experience a high rate of recurrent disease (approximately 80% of patients will recur), 33-50% of them will be 5-year survivors and 23% of them will be 10-year survivors if an aggressive approach to resection of recurrent disease is used (21,65,66).

Second-line chemotherapy

For patients with marginally resectable or unresectable liver metastases from colorectal cancer who do not respond to first line chemotherapy, a switch to second-line chemotherapy may result in a response to therapy. The question of whether or not liver resection is reasonable in such patients if they respond to second-line chemotherapy has been addressed in a retrospective analysis (67). This study showed that 1-, 3-, and 5-year survival rates of 83%, 41%, and 22%, respectively, with 1- and 3-year disease-free survival rates of 37% and 11%, respectively, can be achieved in this setting with reasonable postoperative morbidity and mortality rates.

Biological agents

Biological agents, such as vascular endothelial growth factor (VEGF) inhibitors and epidermal growth factor receptor (EGFR) inhibitors in combination with cytotoxic chemotherapy frequently have activity in patients with metastatic colorectal cancer. There is emerging evidence from phase II and III randomized clinical trials that chemotherapy regimens that include biological agents may improve the ability to convert unresectable liver metastases into resectable ones (68).

Randomized controlled trials comparing FOLFOX or FOLFIRI with or without the vascular endothelial growth factor inhibitor bevacizumab have shown that the addition of bevacizumab significantly increases the duration of survival, the progression-free survival, and rates of response in both previously treated and previously untreated patients with metastatic colorectal cancer (69,70). The addition of bevacizumab to FOLFOX has been shown in a retrospective study to result in a lower percentage of viable tumor cells, although not a higher complete pathologic response rate, in resected specimens, and a decrease in the frequency and severity of sinusoidal obstruction syndrome was also noted (71). Similar results were obtained in another retrospective study where bevacizumab was

shown to result in decreased severity of the sinusoidal obstruction syndrome, but not to improve the likelihood of response according to RECIST criteria (72). No published randomized controlled trials of bevacizumab have measured rates of resection as a pre-specified endpoint.

Cetuximab is a monoclonal antibody that blocks the EGFR, which is frequently present on colon cancer cells (73). A randomized phase II trial of cetuximab plus either FOLFOX or FOLFIRI in patients with unresectable liver metastases from colorectal cancer showed high rates of partial or complete clinical response by RECIST criteria (68% *vs.* 57%, P=NS) (74). A retrospective analysis of the data from this study showed that partial or complete responses were significantly more likely in patients with KRAS-wide type tumors (70%) *vs.* those with KRAS-mutations (41%), and that chemotherapy with cetuximab increased the baseline resectability rate from 32% to 60% (P<0.0001) (74). A randomized phase III trial of FOLFIRI with and without cetuximab in patients with metastatic colorectal cancer (including, but not limited to patients with liver metastases) showed that the rates of surgery for metastases (7% *vs.* 3.7%) and the rates of R0 resection (4.8% *vs.* 1.7%, P=0.002) were higher in the group receiving cetuximab, although these were not pre-specified endpoints of the study (75). In addition, other EGFR inhibitors, such as panitumumab, have been shown to have activity in patients with metastatic colorectal cancer whose tumors are KRAS-wild type (76), and may eventually show similar rates of conversion to resectability.

Radiofrequency ablation

The EORTC 40004 study, a randomized phase II trial, randomized patients with unresectable liver metastases to either systemic therapy or systemic therapy plus radiofrequency ablation (RFA) (77). This study reported a non-significant improvement in 30-month overall survival and a significantly improved 3-year progression-free survival rate in the patients treated with RFA plus chemotherapy.

A retrospective German study has suggested that RFA may result in equivalent disease-free and overall survival to surgical resection for patients with a small number of metastases <5 cm in diameter (78). The RFA and surgery groups in this study were well-matched except for a significantly larger median tumor diameter in the surgery group (3 *vs.* 5 cm). The incidence of local recurrence was significantly higher and the time to progression was significantly shorter in the group treated with RFA; however, a higher rate of salvage therapy in the RFA group resulted in similar disease-free survival rates (78).

In contrast, another retrospective study concluded that RFA, alone or in combination with hepatectomy, results in significantly poorer overall survival (4-year survival of 22% *vs.* 65%) (7). This study also demonstrated higher rates of local recurrence in the group of patients treated with RFA relative to those treated with resection. While the role of radiofrequency ablation in the management of patients with liver metastases from colorectal cancer is still being defined, it is at the very least a useful adjunctive procedure in certain situations where resection is not technically feasible or would leave a patient with a marginal/inadequate functional liver remnant.

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