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Surgical management of colorectal cancer metastases to the liver: multimodality approach and a single institutional experience

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SUMMARY

Over the past 30 years, the treatment of metastatic colorectal cancer to the liver has undergone major changes. Once considered terminal and incurable, the prognosis of patients with colorectal hepatic metastases has seen dramatic improvements using modern multimodality therapy and now long-term survival and even cure are possible in some patients. Despite the advances seen in systemic therapy, hepatic resection offers the longest survival potential and remains the only curative option. Based on long-term outcomes and the improved safety of hepatic resection using modern operative techniques and critical care support, an aggressive locoregional approach to colorectal hepatic metastasis has become the standard of care. This article focuses on the management of colorectal hepatic metastases and highlights the importance of multimodality therapy. We also report our 18-year experience treating patients with hepatic resection for colorectal metastases.

Colorectal cancer remains the third most common cancer diagnosis in the USA and approximately 5% of Americans will develop colorectal cancer in their lifetime [1]. Colorectal cancer is also the third leading cause of cancer-related deaths in the USA with over 51,000 people dying each year of the disease [1]. The liver is the most common site of colorectal metastasis [2] and over half of all colorectal cancer patients will develop colorectal hepatic metastases (HM) during their lifetime [3]. As many as 25% will have synchronous HM at the time of diagnosis [4,5] and 36–57% of patients will develop HM during follow-up after surgical resection for their primary tumor [5,6]. Unfortunately, only 10–25% of colorectal HM are resectable when diagnosed [7,8]. Even after curative hepatic resection, recurrence commonly occurs within 24 months and by 5 years, 70% of patients with resected colorectal HM will develop recurrent disease [6,9–12].

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Median survival of untreated colorectal HM ranges between 4.5 and 7.8 months [9,13] and very few patients survive 5 years [9,13,14]. Prognosis in untreated patients has been associated with the extent of liver involvement, the presence of extrahepatic disease, performance status, carcinoembryonic antigen (CEA) level and liver function tests [4,13,14]. These outcomes represent patients who were deemed unresectable at the time. However, in one study, median survival was 14.2 months in untreated patients who, in retrospect, could have undergone surgical resection using more current resection criteria [9].

Over the past three decades, significant improvement in outcomes has been seen in patients with metastatic colorectal cancer treated with multimodality therapy. While surgical resection has become the keystone of multimodality therapy and offers the best chance for long-term survival, many adjunct therapies are now available. This review discusses the diagnostic assessment of colorectal HM and the multimodality management of initially unresectable, as well as resectable, disease. It also summarizes the perioperative and long-term outcomes recently reported using modern therapies.

Determining hepatic resectability

Despite the many treatment options for colorectal HM, surgical resection remains the only potentially curative therapy for patients with colorectal HM. Patient selection for hepatic resection is paramount to prevent devastating postoperative complications, such as hepatic insufficiency, and to avoid unnecessary operations in patients with unresectable extrahepatic disease. The criteria for hepatic resectability have expanded over time and many more patients are now candidates or can become candidates for hepatic resection. For example, extrahepatic disease is no longer an absolute contraindication for hepatic resection. When possible, surgical resection of synchronous or metachronous lung metastases can lead to long-term survival [15], which further underscores the importance of a multimodality team approach.

Currently, three main criteria are used to determine hepatic resectability of colorectal HM [16]: the ability to preserve two contiguous hepatic segments; preservation of adequate vascular inflow and outflow as well as biliary drainage; and the ability to preserve adequate future liver remnant (FLR). Tumor involvement of the inferior vena cava, hepatic vein confluence and/or hilar structures can make the hepatic disease unresectable. Most often, however, patients present with diffuse, multifocal, bilobar metastases, which makes resection impossible to preserve an adequate FLR consisting of 2 adjacent segments. In patients with extensive hepatic involvement, CT scan or MRI volumetric analysis can be used to estimate the functional volume of the FLR. The FLR limit for safe hepatic resection depends on the degree of chronic liver dysfunction in a given patient. Patients with normal liver parenchyma should have an FLR of >20% to prevent hepatic insufficiency following hepatectomy. Owing to chemotherapy-associated hepatic steatosis, steatohepatitis and sinusoidal injury, patients who receive extensive preoperative chemotherapy should have an FLR of 30% prior to resection, while patients with chronic liver disease, such as fibrosis/cirrhosis, require an FLR of 40% [17].

In addition to FLR, indocyanine green (ICG) clearance tests can be used following preoperative chemotherapy in patients with colorectal HM to assess the degree of chemotherapy-associated hepatic dysfunction and can therefore be used to estimate preoperative risk. ICG is a water-soluble compound that is taken up by hepatocytes and excreted in bile. Thus, the ICG clearance rate is a dynamic marker for hepatic function. In a recent study [18], preoperative chemotherapy for colorectal HM was associated with lower ICG plasma disappearance rates and longer ICG retention rates. In addition, patients with impaired ICG plasma disappearance rates ($< 18\%/min$) had more postoperative complications (34.1 vs 8.3%; $p = 0.001$). ICG clearance tests also correlated to the incidence and degree of steatohepatitis and sinusoidal injury seen on histopathology. Currently, this test is mainly used in Europe and Asia.

Hepatic lymph node involvement is considered a relative contraindication by most hepatic surgeons. In a prospective study, Jaeck *et al.* performed hepatic lymph node dissection in 160 patients and found worse 3-year survival in the 17 patients with positive lymph nodes compared with those without hepatic nodal involvement (19 vs 62%; $p < 0.001$) [19]. Survival was also dependent on the location of the hepatic lymph node involvement. The 3-year survival was significantly worse when the nodal metastases involved the common hepatic artery and celiac axis compared with being limited to the hepatoduodenal ligament and/or retropancreatic nodes (0 vs 38%; $p < 0.001$). Another larger study [20] confirmed the negative prognosis of hepatic lymph node involvement. The 5-year survival was twice as long when hepatic lymph nodes were not involved (53 vs 18%; $p = 0.004$). Again, celiac and para-aortic lymph node invasion were associated with no long-term survival. Based on these and other studies, hepatic resection for colorectal HM with lymphadenectomy is reasonable in patients with nodal disease involving the hepatoduodenal ligament but is not indicated when disease has spread to more distant lymph nodes.

Preoperative evaluation & imaging

Most patients with colorectal HM are asymptomatic and are diagnosed during their initial staging evaluation or during surveillance imaging after primary resection. Tumor markers, such as CEA and CA19–9, can be elevated in some patients even before metastatic disease is detectable on standard imaging; however, the sensitivity of detecting colorectal HM is only 80% for CEA [21] and 48% for CA19–19 [22]. Despite their low sensitivity, these markers still carry prognostic value and, when elevated, can be used during surveillance to detect early recurrence. It is also important to assess for undiagnosed liver insufficiency by history and physical examination, liver function tests and occasionally liver biopsy. Steatohepatitis and chemo-related liver injury can limit the extent of liver resection and can increase the patients' risk for postoperative hepatic failure [23].

Determining hepatic resectability begins with high-quality imaging, often using multiple modalities, to: establish the diagnosis of and locate metastatic lesions; define hepatic anatomy for surgical planning; assess the postoperative hepatic remnant; and rule out unresectable extrahepatic disease. Multidetector helical CT scans are most commonly used for staging assessments, evaluating response to chemotherapy or other adjuvant treatments, and during surveillance for recurrent disease. The sensitivity of CT scans in detecting

colorectal HM is 64–84% with a specificity of 95% [24,25]. CT imaging can not only diagnose hepatic lesions but also define the relevant vascular and biliary anatomy essential for surgical planning. Additionally, CT-guided biopsy is occasionally required when imaging characteristics are indeterminate. Patients who are treated with extensive chemotherapy can develop steatohepatitis, which can decrease the accuracy of identifying small metastatic lesions. In most cases, MRI offers little advantage over CT imaging (sensitivity of 76–88% and specificity of 93%) [24,25], except for identifying lesions of less than 10 mm and distinguishing metastases from primary liver malignancies or benign lesions. Although rarely necessary, CT and MRI angiography can further define vascular anatomy and has largely replaced invasive hepatic angiography. Likewise, MR cholangiopancreatography can define intrahepatic biliary anatomy but is not normally necessary.

The role of PET imaging is less clear in colorectal HM. Some studies report that combining PET with CT scans increases the sensitivity for diagnosing metastases [24,25] and is more sensitive than CT alone in detecting hepatic recurrence after hepatectomy [26]. The most significant clinical advantage of PET/CT, however, is whole body screening for extrahepatic disease and is therefore helpful in selecting patients who are most likely to benefit from hepatic resection [26]. Similarly to CT scans, PET imaging is less sensitive when detecting subcentimeter lesions [27] but can be used to evaluate systemic treatment response [28].

Ultrasound is also useful at detecting colorectal HM. In addition, duplex ultrasound can accurately define the relationship of metastases to hilar and vascular structures. More important, however, is the utilization of intraoperative ultrasound. Used either laparoscopically or open, intraoperative ultrasound can detect lesions not seen on CT imaging or MRI and can significantly change the surgical plan in as many as 30% of patients [29,30]. In addition, the vascular structures can be clearly identified in relation to the metastatic lesion(s) in order to plan the surgical resection.

Finally, staging laparoscopy is often helpful when imaging is suspicious for extrahepatic disease, such as involved lymph nodes or peritoneal dissemination, or when hepatic anatomy needs to be further clarified by intraoperative ultrasound to determine resectability [31]. In such cases, diagnosing unresectable disease prior to laparotomy can decrease the morbidity of surgery and shorten the delay to receiving systemic chemotherapy.

The efficacy of modern systemic chemotherapy

Significant advances in the systemic treatment of colorectal HM have been seen using multi-drug chemotherapy regimens. 5-fluorouracil has long been the backbone of systemic therapy for colorectal metastases. Early studies showed a significant survival advantage when 5-fluorouracil was using in combination with leucovorin [32]. This multidrug strategy has been expanded with the advent of new chemotherapy agents. Today, standard regimens such as fluorouracil, leucovorin and oxaliplatin (FOLFOX) and fluorouracil, leucovorin and irinotecan (FOLFIRI) have improved median overall survival (OS) to 15–20 months [33–35]. Finally, adding biological agents, such as bevacizumab or cetuximab, to standard chemotherapy regimens can add 2–5 months to median survival [36–38]. Still, few patients

achieve a complete response and 5-year survival is 1% at best [39]. The availability of multiple effective combination regimens allows reasonable second and third line options for patients who develop recurrent or progressive disease [40]. Unfortunately, the data evaluating the effectiveness of chemotherapy as an alternative to surgical resection in resectable disease are extremely limited. In fact, no randomized controlled trials exist comparing chemotherapy with surgical resection for colorectal HM; however, systemic chemotherapy can play a vital role in the preoperative and adjuvant management of colorectal HM, as discussed below.

Unresectable metastases

As previously stated, less than 25% of patients with colorectal HM are resectable at the time of diagnosis [7,8]. However, with modern chemotherapy and surgical technology, the number of patients who become surgical candidates has grown significantly. Several strategies are available and it is imperative that patients with colorectal HM, especially when initially deemed unresectable, be evaluated and managed by a multidisciplinary team. Preoperative chemotherapy, portal vein embolization (PVE), two-stage hepatectomy and radiofrequency ablation are well accepted strategies used to downstage tumor burden and/or improve resectability.

Downstaging chemotherapy

As highlighted above, the efficacy of modern combination chemotherapy regimens has improved dramatically in recent years. Clinical response rates now range between 50 and 70% [33,37,41,42] and, while complete responses are rare (3–9%) [42–44], up to a third of unresectable patients can be downstaged to the point where rescue hepatic resection is feasible [41,44]. Several studies [41,44,45] have reported similar 5-year disease-free survival (DFS) and 5-year OS (16–22% and 33–42%, respectively) in patients who achieved an R0 resection following preoperative chemotherapy compared with patients who undergo resection immediately after diagnosis. Chemotherapy-associated liver injury, as discussed in detail below under preoperative chemotherapy, must be taken into account prior to surgical resection when using various regimens to downstage hepatic disease as a larger FLR is generally needed following chemotherapy.

Portal vein embolization

When preoperative liver volumetric measurements predict an inadequate FLR, PVE can be used prior to major hepatectomy to improve FLR and thereby decrease the risk of postoperative liver dysfunction. PVE is designed to redirect portal venous blood flow from the involved segments of liver to the FLR. This induces atrophy in the embolized portions of liver and stimulates hypertrophy of the FLR. The triggers for liver hypertrophy are poorly understood but result in the clonal expansion of hepatocytes, which enhances hepatic function, rather than simply an increase in volume of existing hepatocytes [46].

PVE is well tolerated with minor complications occurring in less than 10% of patients [46,47]. In patients with normal liver function, virtually all patients attain some amount of liver hypertrophy after PVE with an average FLR increase of 9–16% [46,48–50] within 4–8

weeks. The response rate to PVE is less for patients with dysfunctional liver disease (86%); however, the average FLR increase still approaches 10% [48,49]. Importantly, 70–85% of previously unresectable patients will go on to have hepatic resection following PVE [47,48]. Most studies report comparable or lower morbidity and mortality rates following hepatectomy in patients who received PVE to those who did not [46,47,49]. For example, transient liver failure occurs in only 2.5% of patients, and less than 1% of patients die from liver failure after PVE and subsequent hepatic resection [47]. Furthermore, long-term survival rates are similar after hepatectomies not requiring PVE and are significantly better than in patients who do not undergo hepatic resection [51].

Two-stage hepatectomy

Two-stage hepatectomy has become another treatment strategy for unresectable, bilobar HM. In the two-stage approach, clearance of all HM in the FLR is performed during the first operation, followed by a period of observation to allow liver hypertrophy. Intraoperative portal vein ligation or postoperative PVE is usually performed to promote liver hypertrophy and patients are treated with systemic chemotherapy to control disease progression and potentially shrink the remaining metastatic lesions. Once sufficient hypertrophy has been achieved to obtain a curative resection with minimal risk of postoperative liver insufficiency, a second curative hepatectomy is performed.

When the two-stage hepatectomy strategy is planned, 70–75% of patients will complete the second stage and achieve a curative resection [52,53], while the remaining patients experience disease progression or insufficient liver hypertrophy preventing a curative second hepatectomy. The median interval between liver resections is approximately 3 months [52,53], but can be as short as 1 month. In most cases the second stage operation involves a more extensive resection and is consequently associated with longer operative times, more intraoperative blood loss, longer hospitalizations and more postoperative morbidity [52,53]. Recent studies have reported a median OS of approximately 40 months, with 5-year OS rates between 32 and 42% following successful two-stage hepatectomy [52,53]. Compared with patients who undergo one-stage hepatectomy, similar operative morbidity and long-term survival has been achieved using the two-stage approach [53,54] making it an attractive strategy in select unresectable patients.

Supplementary/alternative therapy options

Radiofrequency ablation

Radiofrequency ablation (RFA) has emerged as an important adjunct to hepatic resection for colorectal HM and can be used in combination with hepatectomy when curative resection is technically unattainable due to tumor characteristics or patient comorbidities. In addition, RFA has been used as an alternative for hepatic resection in patients with small, solitary lesions or in patients who have unresectable disease or are poor surgical candidates. In a large prospective study, Siperstein *et al.* reported a median OS of 24 months and 5-year survival of 18% in 234 patients who were treated with RFA for colorectal HM [55]. Likewise, Veltri *et al.* [56] reported procedure-related complications in 11% of 122 patients

undergoing RFA and a local recurrence rate of 26% with median recurrence-free survival (RFS) and OS of 9 and 32 months, respectively [56].

Unfortunately, there are no randomized studies contrasting RFA to resection. However, several comparative studies have suggested the superiority of resection over RFA. Abdalla *et al.* compared outcomes in patients treated with resection alone, resection plus RFA and RFA alone and reported 4-year survival of 65, 36 and 22%, respectively ($p < 0.001$) [57]. In addition, hepatic recurrence was much more common in patients treated with RFA alone compared with resection alone (44 vs 11%; $p < 0.001$). There is clear selection bias in these types of studies making conclusive recommendations impossible; however, most oncology providers agree that RFA is inferior to resection but can play an invaluable role in the management of unresectable disease.

Radioembolization

Radioembolization, used in combination with systemic chemotherapy or hepatic artery infusion (HAI) chemotherapy, is another local therapeutic option for colorectal HM that has emerged within the past decade [58,59]. Radioembolization uses the intra-arterial delivery of microspheres loaded with the radionuclide yttrium-90 to target multiple tumors. These radioactive microspheres embolize within the tumor and deliver high local doses of radiation over 14 days. A Phase III trial of 74 patients with unresectable bilobar colorectal HM randomized patients to HAI with or without radioembolization [58]. Adding radioembolization was associated with a higher clinical response rate (50 vs 24%; $p = 0.03$) and longer median time to progression (12.0 vs 7.6 months; $p = 0.04$). To date, no clear survival benefit has been shown with the use of radioembolization in this patient population.

Transarterial chemoembolization

Based on successful results from randomized trials treating unresectable hepatocellular carcinoma, transarterial chemoembolization (TACE) has become another modality being used for colorectal HM. TACE combines intrahepatic chemotherapy with embolizing material that temporarily or permanently restricts blood flow to tumor-affected liver parenchyma, inducing tumor necrosis and prolonging drug transit time. Data supporting the use of TACE for colorectal HM are limited to several Phase II studies in the setting of unresectable disease [60–63], which have shown initial response rates from 63 to 80%. Progression generally occurs within 8 months and median survival is less than 1 year in most reports. A significant limitation of TACE is the extent of liver involvement making few patients eligible for TACE while being ineligible for resection. With response lasting only a few months and no proven survival benefit, the utilization of TACE in colorectal HM is currently in the palliative setting only, until further studies are performed.

Stereotactic body radiation therapy

While whole liver radiation therapy is limited because of the radiosensitivity of normal liver parenchyma, stereotactic body radiation therapy (SBRT) can deliver high doses of radiation to the target lesion(s) and limit the exposure to surrounding healthy tissue. The use of SBRT for unresectable colorectal HM is based on several small Phase I/II studies that report good local control rates [64–66] with a median time to local failure up to 16 months [65,66] and

median OS up to 29 months [64–66]. Prospective randomized trials are needed to define the role of SBRT in the context of other available treatments. SBRT has the greatest potential as an adjunct therapy for central hepatic lesions, as proximity to vascular structures is not an issue.

Resectable metastases: the role of perioperative chemotherapy

Even with resectable liver disease, it is well accepted that the remaining liver can harbor undetectable metastatic lesions and can lead to early postoperative hepatic recurrences. For this reason, the role of preoperative and postoperative chemotherapy in the setting of resectable disease has received significant attention in recent years. The EORTC Intergroup trial 40983 randomized patients to hepatic resection ± perioperative FOLFOX chemotherapy [67] and reported 3-year progression-free survival of 28.6% in the surgery-only group compared with 37.9% in the surgery plus chemotherapy group ($p = 0.023$). The study was not powered to detect differences in survival, nor was it designed to assess the efficacy of preoperative versus postoperative chemotherapy.

While there appears to be an advantage to perioperative systemic treatment for colorectal HM, the timing of chemotherapy in relation to surgery remains controversial. Recently we examined outcomes from 210 colorectal HM patients who underwent hepatectomy based on the systemic chemotherapy received. Despite the groups being similar in regards to age, gender, stage, lymph node status and largest tumor size we found a survival advantage for patients treated with postoperative chemotherapy. Median survival for patients who received postoperative, preoperative, perioperative (both preoperative and postoperative) and surgery alone was 48, 35, 39 and 29 months, respectively ($p = 0.04$) [68]. Clearly prospective, randomized studies are needed to determine the most efficacious timing of chemotherapy. This was attempted, however, in the NSABP C-11 trial, which was a Phase III multicenter, randomized study of perioperative versus postoperative chemotherapy for resectable colorectal HN. Unfortunately, this study closed early due to poor accrual.

Preoperative chemotherapy

Preoperative chemotherapy in the setting of resectable colorectal HM offers the potential advantages of: decreasing the hepatic tumor burden prior to resection; measuring tumor response to chemotherapy as a guide for postoperative therapy; avoiding futile surgery in patients with early progressive disease; and treating undetectable disease without delay of surgery. Response to preoperative chemotherapy is evaluated by serial imaging and tumor markers (when elevated prior to treatment). Response rates to preoperative chemotherapy are impressive – between 43 and 73% [67,69,70] – and correlate to a 26% average reduction in tumor size [67]. Patients who respond to preoperative chemotherapy also have improved progression-free survival and OS compared with nonresponders [43,70].

However, the potential advantages of pre-operative chemotherapy have minimal clinical relevance. Given the high response rate of current chemotherapy regimens, the need to assess response preoperatively is generally unnecessary and few unnecessary surgeries are avoided because progression while receiving preoperative therapy only occurs in 5–8% of patients [67,69,70] and only 2% of patients develop new lesions [67]. Furthermore, patients

who receive preoperative chemotherapy have more operative complications compared with patients who did not, as seen in the Intergroup 40983 trial where morbidity was 25 and 16%, respectively ($p = 0.04$) [67]. The increased operative morbidity may be related to chemotherapy-associated hepatic injury [71,72], which occurs in 23–51% of patients who receive preoperative chemotherapy [71–74]. Specifically, oxaliplatin is associated with increased rates of sinusoidal injury [71–73], while irinotecan can cause significant steatosis and steatohepatitis [72,74]. Finally, there is no proven survival benefit of preoperative chemotherapy over postoperative chemotherapy in the setting of resectable colorectal metastases. Given the increased perioperative risk associated with chemotherapy induced liver injury, the decision to use chemotherapy prior to hepatectomy must be individualized based on the clinical situation.

Postoperative chemotherapy

The practice of using postoperative chemotherapy following hepatic resection for colorectal HM is largely based on extrapolated data using postoperative therapy in stage III disease with positive lymph nodes. However, there have been two Phase III trials assessing the benefit of postoperative fluorouracil plus leucovorin for colorectal HM compared with surgery alone [75,76]. Both trials closed prematurely due to slow accrual but did show a nonsignificant trend of improved outcomes using postoperative therapy. Mitry *et al.* combined the data from these trials, totaling 278 patients, and reported a median DFS of 27.9 months in the chemotherapy group compared with 18.8 months in the surgery alone group ($p = 0.058$) and a median OS of 62.2 months compared with 47.3 months, respectively ($p = 0.095$) [77]. On multivariate analysis, postoperative chemotherapy was associated with less risk of recurrence ($p = 0.026$) and better OS ($p = 0.046$).

In another large comparison study [78], data from 792 patients from two international cancer centers were analyzed based on the administration of postoperative chemotherapy. The use of postoperative chemotherapy was associated with a median OS of 47 months and a 5-year OS of 37% compared with 36 months and 31% in patients receiving surgery alone ($p = 0.007$). It is important to note that these studies were performed prior to the widespread use of oxaliplatin and irinotecan combination therapy. A recent Phase III trial compared postoperative fluorouracil/leucovorin with or without irinotecan in the setting of resected colorectal HM and failed to show a significant difference in DFS or OS between the two regimens [79]. Owing to this study, patients are generally offered an oxaliplatin-based regimen as postoperative therapy after resection of colorectal HM.

HAI chemotherapy

Chemotherapy delivered by HAI has been extensively researched in the postoperative setting but results have been inconsistent. In an intergroup study, 75 patients were randomized to HAI plus systemic chemotherapy following curative resection for colorectal HM or to surgery alone and found 4-year RFS rates of 46 and 25%, respectively ($p = 0.04$); however, there was no difference in median OS (64 vs 49 months; $p = 0.60$) [80]. In another clinical trial evaluating postoperative HAI plus systemic chemotherapy versus postoperative systemic chemotherapy alone, Kemeny *et al.* reported 2-year survival free of hepatic

progression of 90% using combined therapy compared with 60% using chemotherapy alone ($p < 0.001$) and 2-year survival of 86 versus 72%, respectively ($p = 0.03$) [81].

These outcomes conflict with results from a German Cooperative on Liver Metastases randomized trial, which closed prematurely due to an interim analysis showing reduced survival in patients treated with postoperative HAI and systemic chemotherapy compared with liver resection alone (35 vs 41 months; $p = 0.15$) [82]. Furthermore, a meta-analysis combined seven prospective trials and reported a nonsignificant 2-year survival benefit of 9.6 months (95% CI: 2.2–21.4; $p = 0.11$) with the use of HAI.

HAI has also been studied in the setting of unresectable disease. A meta-analysis combining data from ten randomized controlled trials found that HAI is associated with improved tumor response rates compared with systemic chemotherapy alone in unresectable colorectal HM (43 vs 18%; relative risk: 2.26; 95% CI: 1.80–82.84; $p < 0.0001$) but that this did not correspond to an improvement in median OS (15.9 vs 12.4 months; HR: 0.90; 95% CI: 0.76–71.07; $p = 0.24$) [83]. While HAI chemotherapy appears to have a beneficial locoregional effect, patients continue to have high rates of extrahepatic recurrence, which explains the lack of a clear survival advantage. In addition, complications relating to hepatic artery pump are frequent and the complexity of administration limits its clinical utility. More successful studies comparing this approach with modern multi-drug systemic regimens are required before HAI can be used routinely in the postoperative or unresectable setting.

Recurrent hepatic metastases

Despite a multimodality approach, hepatic recurrence following liver resection for colorectal HM is common. Recurrent disease is generally found by surveillance imaging or by increasing tumor markers. When recurrence is diagnosed or suspected, a full workup should be initiated to characterize the extent of disease, including evaluation for extrahepatic metastases. Treatment options for recurrence are dictated by the individual clinical situation and guided by the same principles discussed above. Again surgical resection offers the only possibility of cure and, when appropriate, multimodality therapies can be used again to eliminate known disease. However, in a patient with a prior hepatectomy, the surgical options may be more limited. A short period of observation or a trial of systemic chemotherapy to evaluate the true extent of disease may also be reasonable.

In a large multi-institutional study, de Jong *et al.* reported on 1669 patients who underwent curative surgical treatment of colorectal HM [6]. Half of the patients had recurred within 2 years with a median RFS of 23.0 months. Intrahepatic recurrence with or without concomitant extrahepatic disease occurred in 37.6% of patients at the time of last follow-up. In a follow-up study from the same group [84], 246 out of 645 patients with recurrent colorectal HM underwent repeat hepatectomy with or without RFA. Perioperative morbidity (21.0%) and mortality (0.4%) following repeat hepatectomy were similar following the initial resection (22.5 and 0%, respectively). Following a second hepatic resection, median survival was 42.0 months and 5-year survival was 32.6%. These outcomes are similar to other reports [85] and suggest that repeat hepatectomy is feasible and beneficial in select patients.

Historic perspective of early surgical outcomes

While hepatic resection is now standard of care for resectable colorectal HM based on significant long-term outcomes, early reports were associated with considerable operative morbidity and mortality. In 1990, Vetto *et al.* reported outcomes on 58 patients who underwent hepatectomy for colorectal HM at the National Cancer Institute [86]. Mean anesthesia time was 448 minutes, mean estimate blood loss was 3663 ml and mean hospital stay was 17.5 days. Perioperative morbidity and mortality were 62 and 3%, respectively. These outcomes were common at the time as other early experiences of hepatic resection for HM reported operative morbidity of 13–46% and postoperative mortality up to 8.3% [87–89]. Despite the perioperative complications, long-term outcomes were encouraging, especially since systemic therapy at the time was largely ineffective.

Fortunately, over the past 20–30 years advances in surgical technique, patient selection and critical care management have led to more acceptable morbidity and mortality after hepatic surgery [90,91] and have improved long-term survival [90,92]. House *et al.* recently evaluated trends in perioperative and long-term outcomes after hepatic resection for colorectal HM in 1600 patients treated between 1985 and 2004 [90]. The patients were divided into two groups (era 1: 1985–1998; era 2: 1999–2004) based on the approximate time when oxaliplatin and irinotecan became widely used. Between the two eras, overall morbidity was unchanged (44%) but 90-day operative mortality decreased from 2.5 to 1% ($p = 0.04$). Median operative blood loss decreased significantly (from 600 to 500 ml; $p < 0.01$), as well as median length of stay (from 8 to 7 days; $p = 0.01$). There was also a significant improvement in 5-year disease-specific survival in era 2 compared with era 1 (51 vs 37%; $p < 0.01$) but only a trend towards improved 5-year RFS (33 vs 27%; $p = 0.16$).

Currently, operative mortality from hepatic resection for HM is less than 1% at high-volume centers and complications are becoming more manageable and less frequent. Several perioperative factors have been influential in these improved outcomes. Specifically reduced blood loss, lower transfusion rates and parenchyma-sparing resections are independent predictors for lower morbidity and mortality after hepatic surgery [93,94]. A better understanding of intrahepatic anatomy, intraoperative ultrasound, the focus on low central venous pressures during surgery, the introduction and refinement of surgical staplers, dissecting and coagulating devices and vascular control techniques have allowed hepatectomies to be performed with less blood loss and liver ischemia now than compared with 20 years ago.

Recent perioperative & long-term outcomes

Advances in liver surgery and other multimodality treatments have made hepatic resection for colorectal HM not only standard of care, but relatively safe, with consistently impressive long-term results. It remains the only reasonable curative option. While randomized trials establishing hepatic resection as the gold standard for colorectal HM do not exist, many large multi-institutional experiences have confirmed the operative safety and long-term outcomes of hepatic resection for metastatic colorectal cancer (Table 1). Wei *et al.* reported results of 423 hepatectomies performed over a 10-year period on 395 patients [11]. A third

of the patients presented with synchronous disease and 40% had stage III cancer. The majority of patients (65%) underwent a hemihepatectomy or greater with a median operative time and blood loss of 278 min and 1 l, respectively. Postoperative morbidity was 20% and mortality was 1.7%. Median DFS was 19 months and 5-year DFS was 27% while median OS was 53 months and survival at 5 and 10 years was 47 and 28%, respectively.

Similarly, Figueras *et al.* reported on 545 liver resections for colorectal HM in 501 patients [95]. In total, 63% of the patients had stage III disease at presentation. They reported a mortality of 4% due to acute myocardial infarction, urinary sepsis, liver failure, anastomotic leakage from synchronous bowel resection, pulmonary embolism, pneumonia and stroke. A blood transfusion was required in 16% of patients and 13% had positive surgical margins. The median postoperative hospital stay was 9 days. Postoperative complications occurred in 35% of patients with the most common event being biliary fistula (9%) followed by transient hepatic insufficiency (8%), wound infection (8%), intra-abdominal abscess (7%) and others (14%). Median DFS was 17 months and DFS at 5 and 10 years was 27 and 26%, respectively. Median OS was 44 months with a 3-, 5- and 10-year OS of 60, 42 and 30%, respectively.

Rees *et al.* reported that approximately 60% of their 929 patients underwent greater than or equal to a hemihepatectomy for colorectal HM [12]. The median operating room time was 240 minutes and the median blood loss was 345 ml. Postoperative morbidity and mortality was 26 and 1.6%, respectively. Median length of hospital stay was 9 days. Final resection margins were negative in 84% of patients. Median cancer-specific survival was 43 months and overall cancer-specific survival at 5 and 10 years was 36 and 23%, respectively.

In a recent multi-institutional international study, Nathan *et al.* evaluated conditional survival from 949 patients who underwent liver resection for colorectal HM [92]. Most patients presented with synchronous HM (53%) and had T3/4 disease (87%). Negative margins were achieved in 91% of patients and 90-day mortality was 0.9%. They reported a median OS of 52 months with a 3-, 5- and 10-year OS of 65, 45 and 22%, respectively. This study also reported a 5-year conditional survival of 50% in patients who already survived 5 years compared with the 10-year OS of 22%. Finally, a recent study examined 612 patients who underwent liver resection for HM and had a minimum follow-up of 10 years [96]. At 10 years, 102 patients were alive, 99 of whom had no evidence of disease, suggesting a cure rate after liver resection for colorectal HM of at least 17%.

Prognostic factors

Several studies have analyzed independent prognostic factors associated with survival in patients with colorectal HM who undergo hepatic resection. Reported prognostic factors include: age [11,97,98], primary tumor differentiation [12,97], lymph node status [12,97,99,100], preoperative CEA level [12,98–100], multiple metastases [11,12,95,98–100], large metastases [12,95,98,99], extrahepatic disease [12,90,95,99], positive surgical margin [11,12,90,98,99], disease-free interval of less than 12 months [98,99], resection at a high volume center [97], postoperative chemotherapy [95,97] and response to preoperative chemotherapy [43,101].

Several authors have used prognostic factors to develop scoring systems designed to predict outcomes preoperatively [12,98–100,102]. While these scoring systems can have prognostic value, some studies have questioned their validity [92]. Notably, in a study of 102 actual 10-year survivors, Tomlinson *et al.* found a significant number of patients who possessed poor prognostic factors, including bilobar metastases (25%), tumor size >5 cm (35%), disease-free interval <12 months (36%), multiple metastatic lesions (39%) and node-positive primary (50%) [96]. This observation suggests that poor prognostic factors should not necessarily preclude patients from liver resection.

Wake forest experience

We recently reviewed our own experience treating colorectal HM with surgical resection. From December 1991 to September 2010, 181 patients with colorectal HM were treated with hepatic resection. Patient demographics and perioperative variables are shown in Table 2. The majority of our patients (55%) underwent a minor hepatectomy consisting of 3 hepatic segments.

The remaining patients underwent a major hepatectomy: 65 patients (36%) received a hemihepatectomy or the equivalent of four resected segments and 17 patients (9%) underwent an extended hepatectomy consisting of a hemihepatectomy plus additional wedge or segmental resection(s). In addition to their hepatectomy, 16 patients (9%) underwent simultaneous colorectal resection for their primary tumor and RFA was performed in 12 patients (7%) to treat unresected tumors. A negative-margin was achieved in 94% of resections.

Operative morbidity was 37% while 30-day mortality was 3.3%. The breakdown of postoperative complications by grade according to the Clavien–Dindo classification is shown in Figure 1 [103]. Major complications (grade III–V) occurred in 38 patients (21%). The most common grade III complication was a perihepatic abscess requiring percutaneous or operative drainage (15 patients). Other grade III complications included biloma or biliary leak [4], postoperative bleeding [2], pleural effusion [2], splenic abscess [1] and fascial dehiscence [1]. A total of seven patients had a grade IV complication; three developed respiratory failure (pneumonia, ARDS and air embolus) and four developed septic shock (catheter-related bloodstream infection, pneumonia [2] and anastomotic leak from a simultaneous left hemicolectomy). Of the seven postoperative deaths, two were caused by multisystem organ failure secondary to pneumonia, while the remaining deaths were due to hepatic failure, cerebrovascular accident, bowel perforation, intraoperative blood loss and pulmonary embolism. Five of the seven mortalities underwent major hepatectomies with a mean estimated blood loss of 1700 ml.

With a median follow-up of 57 months, median RFS and median OS were 16.6 and 44.9 months, respectively. RFS at 1, 3 and 5 years was 58, 28 and 18%, while 1-, 3-, 5- and 10-year OS was 88, 61, 35 and 14%, respectively. Kaplan–Meier curves for RFS and OS are shown in Figure 2. Univariate analysis found that largest lesion > 6.5 cm ($p = 0.026$), preoperative chemotherapy ($p = 0.011$) and the presence of extrahepatic disease ($p < 0.001$) were associated with shorter RFS. Likewise higher T stage ($p = 0.028$) and largest lesion

6.5 cm ($p = 0.010$) were associated with worse OS. On multivariate analysis, preoperative chemotherapy ($p = 0.01$), extrahepatic disease ($p = 0.002$) and largest lesion ≥ 6.5 cm ($p = 0.004$) were independently predictive of earlier recurrence while the presence of extrahepatic disease ($p = 0.05$), higher T stage ($p = 0.02$) and largest lesion ≥ 6.5 m ($p = 0.008$) were independently predictive of worse survival.

At last follow-up, 114 patients (63%) of patients had developed a recurrence (Table 3). Liver-only was the most common site of recurrence (33%), followed by lung (26%) and multiple simultaneous sites (19%). All other sites of recurrence occurred in less than 10% of patients. A total of 30 patients were lost to follow-up after their recurrence. Of the remaining 84 patients, 20 (24%) were able to undergo a second curative operation, 5 patients (6%) were salvaged with RFA and 5 patients (6%) had a radiographic complete response to chemotherapy. The median time to second recurrence in these patients was 21 months. All analyses were performed using SAS® 9.2 (SAS Institute Inc., NC, USA).

Conclusion & future perspective

Hepatic metastasis from colorectal cancer is a common and complex disease but, fortunately, advances in systemic therapy, surgical technique and multimodality management strategies have turned this terminal cancer into a manageable disease with good long-term outcomes and even cure in a subset of patients. Liver resection for colorectal HM has become the standard of care and aggressive measures should be undertaken when possible to render patients disease-free. While early hepatic surgery was associated with high morbidity and mortality, operative outcomes are much more acceptable today with mortality rates close to 1%.

The importance of multimodality therapy in the management of colorectal HM implemented by a qualified team of subspecialists cannot be overstated. As such, patients with colorectal HM should be referred to high-volume centers where multimodality treatment is available. The improvements in perioperative and long-term outcomes in patients with colorectal HM have been the result of the general acceptance of multimodality therapy and intensive research efforts. This effective collaboration among oncology healthcare providers has led to expanded criteria for hepatic resection, new techniques and technologies, wider use of perioperative chemotherapy and aggressive treatments for recurrent and extrahepatic disease. In the coming years, additional research and experience will further define the most efficacious multimodality approaches to specific clinical scenarios leading to even better long-term outcomes in patients with colorectal HM.

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Practice points

- Over the past few decades advances in systemic chemotherapy regimens, surgical technique, patient selection criteria, critical care support and medical/surgical technologies have significantly improved outcomes in patients with colorectal liver metastases.
- A multimodality approach, with surgical resection as the keystone, is essential when treating patients with colorectal liver metastases and now offers a 5-year survival between 35 and 50% with apparent cure in a subset of patients.
- Hepatic resection for colorectal liver metastases is considered the standard of care when feasible and is now associated with acceptable rates of operative morbidity and mortality.

Figure 1.
Morbidity of 181 colorectal hepatic metastases patients following hepatic resection.

Figure 2. Kaplan–Meier curves for recurrence-free survival and overall survival in 181 patients who underwent hepatic resection for colorectal hepatic metastases
OS: Overall survival; RFS: Recurrence-free survival.

Table 1

Perioperative and long-term outcomes in patients treated with hepatic resection for metastatic colorectal cancer in recently reported series.

Study (year)	Patients (n)	Major morbidity (%)	30-day mortality (%)	Median RFS (months)	5-year RFS (%)	Median OS (months)	5-year OS (%)	Ref
Wei <i>et al.</i> (2006)	395	20	1.7	19	27	53	47	[11]
Wang <i>et al.</i> (2007)	923	–	–	–	–	–	22	[97]
Figueras <i>et al.</i> (2007)	501	35 [†]	4.0	17	27	44	42	[95]
Tomlinson <i>et al.</i> (2007)	612	–	–	–	–	44	17 (10-year OS)	[96]
Minagawa <i>et al.</i> (2007)	369	–	–	–	–	–	38	[100]
	229	–	–	–	–	–	44	
Rees <i>et al.</i> (2008)	929	26 [†]	1.5	23	24	43	36	[12]
House <i>et al.</i> (2010)	563	20	0.5	23	33	64	51	[90]
Nathan <i>et al.</i> (2010)	949	–	0.9 [‡]	–	–	52	45	[92]
Wake Forest (2012)	181	21	3.3	17	18	45	35	

[†] Reported morbidity (major morbidity not specified).

[‡] Reported as 90-day mortality.

–: Not reported; OS: Overall survival; RFS: Recurrence-free survival.

Table 2

Demographic characteristics of 181 colorectal cancer patients treated with hepatic resection.

Variable	n (%) [†]
Age (years), median ± SD (range)	61 ± 11 (30–88)
Gender:	
▪ Female	▪ 97 (54)
▪ Male	▪ 84 (46)
ECOG performance status:	
▪ 0	▪ 139 (77)
▪ 1	▪ 39 (21)
▪ 2	▪ 3 (2)
Primary site:	
▪ Colon	▪ 133 (73)
▪ Rectum	▪ 48 (27)
Presentation:	
▪ Synchronous	▪ 82 (45)
▪ Metachronous	▪ 99 (55)
Disease-free interval (months) [‡] , median (range)	18 (4–160)
T stage:	
▪ T1	▪ 4 (3)
▪ T2	▪ 25 (17)
▪ T3	▪ 104 (72)
▪ T4	▪ 12 (8)
N stage:	
▪ N0	▪ 62 (38)
▪ N1	▪ 52 (32)
▪ N2	▪ 48 (30)
Preoperative chemotherapy:	
▪ Yes	▪ 70 (39)
▪ No	▪ 110 (61)
Resection type:	
▪ Major	▪ 82 (45)
▪ Minor	▪ 99 (55)
Operative time (h), median (range)	5.0 (1.5–16)
Estimated blood loss (ml), median (range)	600 (30–5000)
Red blood cell transfusion:	

Variable	n (%) [†]
■ Yes	■ 47 (26)
■ No	■ 132 (74)
Length of stay (days), median (range)	6 (2–93)
Margin status:	
■ Negative	■ 170 (94)
■ Positive	■ 11 (6)
Bilobar disease:	
■ Yes	■ 42 (23)
■ No	■ 139 (77)
Number of liver lesions, median (range)	1 (1–7)
Largest lesion (cm), median (range)	3.5 (0.2–16)
Postoperative chemotherapy:	
■ Yes	■ 105 (63)
■ No	■ 63 (37)

[†] Unless otherwise stated.

[‡] Only includes patients presenting with metachronous disease.

ECOG: Eastern Cooperative Oncology Group; SD: Standard deviation.

Table 3

Sites of recurrence following hepatic resection for colorectal hepatic metastases.

Site of recurrence	Number of patients, n (%)
Total	114 (100)
Liver	37 (32.5)
Lung	30 (26.3)
Lymph nodes	9 (7.9)
Peritoneum	3 (2.6)
Bone	3 (2.6)
Brain	2 (1.8)
Local (primary site)	2 (1.8)
Second colorectal primary	2 (1.8)
Unknown	2 (1.8)
Pancreas	1 (0.9)
Thyroid	1 (0.9)
Multiple sites	22 (19.3)