Review Article

Liver-directed therapies in metastatic colorectal cancer

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Abstract: Colorectal cancer (CRC) is a major health concern in the United States (US) with over 140,000 new cases diagnosed in 2012. The most common site for CRC metastases is the liver. Hepatic resection is the treatment of choice for colorectal liver metastases (CLM), with a 5-year survival rate ranging from 35% to 58%. Unfortunately, only about 20% of patients are eligible for resection. There are a number of options for extending resection to more advanced patients including systemic chemotherapy, portal vein embolization (PVE), two stage hepatectomy, ablation and hepatic artery infusion (HAI). There are few phase III trials comparing these treatment modalities, and choosing the right treatment is patient dependent. Treating hepatic metastases requires a multidisciplinary approach and knowledge of all treatment options as there continues to be advances in management of CLM. If a patient can undergo a treatment modality in order to increase their potential for future resection this should be the primary goal. If the patient is still deemed unresectable then treatments that lengthen disease-free and overall-survival should be pursued. These include chemotherapy, ablation, HAI, chemoembolization, radioembolization (RE) and stereotactic radiotherapy.

Keywords: Colorectal cancer (CRC); liver metastases; hepatectomy; radiofrequency ablation (RFA); portal vein embolization (PVE)

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Introduction

Colorectal cancer (CRC) is a major health concern in the United States (US) with over 140,000 new cases diagnosed in 2012 (1). Worldwide CRC is the second leading cause of cancer deaths (2). However, there has continued to be a decline in the death rates due to increased screening, prevention, and improved treatment options. The 1-year and 5-year survival rates are 83.2% and 64.3% respectively (1). However, once there has been metastasis to distant organs the 5-year survival drops to 11.7% (1). The most common site for CRC metastases is the liver. Approximately 25% of patients have hepatic metastases at their initial presentation, and another 30% develop metastases during the course of their disease (2). Hepatic disease accounts for two-thirds of CRC deaths (2,3), emphasizing the importance of understanding the multidisciplinary and multimodality treatment options for colorectal liver metastases (CLM). Surgical resection remains the gold standard for curative resection with several modalities available to extend the resection criteria and additional modalities to extend survival and provide palliation when the patient is not a resection candidate.

Surgical resection

Hepatic resection is the treatment of choice for CLM, with a 5-year survival rate ranging from 35% to 58% in modern series (4-14). The most common indication for hepatectomy in western populations is CLM (15). The morbidity and mortality rates of hepatic resection in modern series are less than 30% and less than 3% respectively (2,4,13,16-18). There have been multiple risk factors that have been reported to independently predict survival after resection. These factors include age, primary tumor stage, preoperative carcino embryonie antigen (CEA) level, disease-free interval, hepatic

tumor size, number of metastases, margin of resection, and presence of extrahepatic disease (4,12,19). These factors are important to identify the 10-20% of patients with hepatic metastases that are eligible for resection (3,17,20).

In 1999, Fong *et al.* developed a clinical prognostic score, identifying seven factors with a significant impact on survival following resection of colorectal metastases (12). The first two of these factors were positive margin and the presence of extrahepatic disease both of which predicted a risk of death 1.7 times greater than baseline. The authors concluded that those two should be relative contraindications to resection. The other five factors were disease-free for less than 12 months, number of tumors >1, pre-op CEA >200, lymph node-positive primary and size of tumor >5 cm. A scoring system was devised with 1 point for each of the five factors. The 5-year survival rate for patients with 0 points was 60% *vs.* the rate for patients with 5 points was only 14%. They concluded that those with a score of 0-2 have a highly favorable outcome, those with a score of 3-4 have a much more guarded prognosis and resection should be planned only in the context of adjuvant therapies. In patients with a score of 5, resection without effective adjuvant therapy or outside of adjuvant trials would be highly questionable. The prognostic score still remains valid but the 5-year survival of even patients with a score of 5 has improved to 31% in a more recent analysis (21). The improvement is likely related to numerous factors including more effective chemotherapy and adjunct procedures to extend the indications for resection. In the more recent analysis the only patients that derived no benefit from resection were those with ≥8 metastases combined with an inflammatory tumor response (21).

While most studies traditionally looked at clinicopathologic factors like those described above to determine which patients will benefit from liver resection, the focus has now shifted to whether complete intrahepatic and extrahepatic disease resection can be obtained, while maintaining sufficient hepatic reserve (22).

The definition of complete intrahepatic resection has been based on a general consensus that a 1 cm margin should be obtained. More recently the exact definition of an adequate margin has been more closely evaluated. Based on a number of studies it appears that with modern chemotherapy the width of the margin does not impact overall survival (OS) as long as it is negative (4,23-27).

The ability to remove all disease from the liver safely with a negative margin is dependent on the future liver remnant (FLR). The FLR should be calculated in a standardized fashion for all patients in whom the expected FLR is ≤40% (28). There is no consensus as to the minimal FLR at which liver surgery can be done safely (28). Suggested guidelines are in a patient without cirrhosis or underlying liver disease, ≥20% of the total liver volume must remain (2,3,29,30). In patients with extensive steatosis or chemotherapy a volume of >30% has been proposed, and patients with cirrhosis should have a FLR of >40% prior to hepatic resection (2,3). Studies looking specifically at extended liver resections show that the complication rate, intensive care unit stay, and hospital stay are all prolonged in patients with an FLR ≤25% (28-30). Another method to assess safety of resection is FLR to body weight ratio rather than percentage of total liver volume. A FLR to body weight ratio of ≤0.5%, puts the patient at considerable risk for hepatic dysfunction and mortality (31).

Extra-hepatic disease

Long-term post-hepatectomy survival is possible in selected patients with extra-hepatic disease (EHD). Multiple studies show long term survival is possible with complete resection of EHD with survival based on the EHD site. Lung metastases with CLM have the best survival, pedicular lymph nodes and peritoneal disease have a somewhat lower OS, and multiple sites and para-aortic or celiac nodes have a dismal prognosis (32,33). OS is significantly lower in the EHD group compared with patients without EHD, but a 5-year OS of 19-38% compares favorably with rates much less than 5% when treated by chemotherapy alone (32-36). A recent review analyzed 22 studies with 1,142 patients with EHD and CLM, morbidity and mortality were 28% and 1% respectively, similar to isolated CLM resection series. The review found a median overall 5-year survival with an R0 resection of 25% (range, 19-36%). As previously noted survival varies by EHD site with a median 5-year OS for lung of 27% (range, 0-33%), porta-caval nodes 17% (range, 0-27%), peritoneal metastases 8% (range, 0-30%), and multiple sites 7% (range, 0-28%) (36). The significantly better survival associated with lung metastases must keep in mind that in these patients, the liver resection and lung resections were likely staged, allowing for potential selection bias as the patients who progressed in the lung were excluded. Looking specifically at CLM and peritoneal disease a recent multi-institutional study of 523 patients with peritoneal disease from CRC, of which 77 had CLM found no that CLM did not impact OS for the entire group but did have a significant impact on the group

that had an R0 resection of the peritoneal disease. Based on this the authors felt that liver metastases could be a relative contraindication if associated with a high peritoneal index (37). In summary, resection of CLM with EHD can result in long term survival in highly selected patients when complete resection of disease is possible.

Synchronous CLM

A subset of EHD is the patient with synchronous presentation of CRC and CLM. Studies are divided on whether synchronous CLM is associated with worse survival than metachronous metastases (38). In resectable patients the decision is whether colon and hepatic resections should occur as a single combined procedure or staged. There are three options including staged resection with colon first, staged with liver first, or simultaneous resection. The concern with simultaneous resection has been increased morbidity and mortality associated with the combined operation. However, recent studies have shown simultaneous resection to be similar in morbidity, and perioperative mortality to staged resection (39-42). A recent multicenter international analysis compared simultaneous resections to staged (colon first and liver first) in over 1,000 patients and found no significant difference in morbidity, mortality or long-term oncologic outcomes between any of the three sequences (39). In addition, a recent meta-analysis confirmed no difference in oncologic outcome between staged and simultaneous resection, and a shorter hospital length of stay and lower morbidity with simultaneous resection (40). Retrospective studies have also shown that complications and mortality are similar between staged and simultaneous procedures even in the setting of major hepatectomy (39-41). Simultaneous resection appears safe in selected patients but most studies addressing staged versus simultaneous resection have a high degree of selection bias given that patients expected to have higher complication rates will generally be offered staged resection. In selected patients the simultaneous resection of the primary colon tumor and hepatic metastasis may be the preferred approach, as it avoids a second surgery, permits earlier completion of surgical therapy, allowing more prompt initiation of adjuvant therapy (41). According to a recent expert consensus the priority in staged resection may be given to colorectal-first or liver-first strategies based on concern for complications related to the primary tumor, such as obstruction, perforation, or bleeding, or the progression of marginally resectable CLM during treatment of the primary (38). The decision to do simultaneous resections is based on the overall complexity of both procedures and the patient's comorbidities (38). The liver-first sequence is most suited to rectal cancers so that the liver metastases are not left untreated during the radiation portion of treatment to the rectum (38). During the simultaneous procedure the liver resection is typically done first so that it may be done with low central venous pressure (38). Whichever order of procedures is used, R0 resections need to be obtained at both sites. If liver metastases are not resectable, resection of the primary tumor does not improve survival (42) and should only be used in patients with symptoms that are not controlled with less invasive techniques.

Adjuncts to improved resectability

When the FLR is anticipated to be marginal there are several options for improving the FLR. These options include systemic chemotherapy, portal vein embolization (PVE), two-stage hepatectomy, and associating liver partition with portal vein ligation (PVL) for staged hepatectomy (ALPPS)/*in situ* split procedure.

Systemic chemotherapy

For patients with unresectable disease, systemic chemotherapy remains the standard first-line therapy. For patients with initially unresectable CLM, systemic chemotherapy offers the possibility of reducing the tumor burden to an extent where resection becomes possible (38). In patients with disease initially determined to be anatomically unresectable, modern preoperative chemotherapy allows complete resection in 12.5-32.5% of patients (43,44). These regimens include FOLFOX (folinic acid, fluorouracil, and oxaliplatin) and FOLFIRI (folinic acid, fluorouracil, and irinotecan) most commonly and more recently the use of the monoclonal antibodies bevacizumab or cetuximab in combination with chemotherapy to increase response rates (45).

Steatosis and steatohepatitis have been associated with the use of fluorouracil and irinotecan. Sinusoidal dilation and congestion can be seen with prolonged use of oxaliplatin. Both steatohepatitis and sinusoidal injury, but not steatosis, have been associated with increased perioperative morbidity with liver resection (45-50). Steatohepatitis has been associated with increased mortality (47). The increase in morbidity appears to be related to duration

of therapy with increased risks with greater than six cycles (45,48). Scoggins *et al.* found no difference in morbidity or mortality with neoadjuvant chemotherapy with a median chemotherapy duration of 4.2 months (51). Steatohepatitis is also more frequently seen in obese patients with neoadjuvant chemotherapy. Bevacizumab does not appear to be increase complication rates when added to standard chemotherapy regimens but studies stop the drug for an average of 6-8 weeks prior to surgery (52,53). There is some data that bevacizumab may be protective when combined with oxaliplatin against development of sinusoidal injury (46). There are no published studies regarding the direct effect on chemotherapy-induced liver injury of the anti-epidermal growth factor receptor (EGFR) monoclonal antibodies cetuximab and panitumumab (46).

Because approximately two-thirds of patients have a recurrence following resection of colorectal metastases preoperative systemic chemotherapy has been examined in resectable colorectal metastases as well. The EORTC Intergroup trial 40,983 randomized patients with resectable colorectal metastases to six cycles of perioperative chemotherapy with FOLFOX or surgery and found improved 3-year progression free survival (PFS) for neoadjuvant chemotherapy (49). The study was not powered to adequately assess for a survival benefit but a follow up study showed no difference in OS between the two groups (17). Retrospective studies show variable results based on prognostic factors. Adam *et al.* looked at metachronous solitary lesions and found increased morbidity with no improvement in survival (54). Zhu *et al.* found that patients with more than two poor prognostic factors had a survival advantage with neoadjuvant therapy (55). Malik *et al.* examined more than 600 patients retrospectively and found no difference in disease free survival (DFS) or OS between neoadjuvant versus upfront surgery (56). Reddy *et al.* in a large multi-center retrospective study, examined patients with resectable synchronous colorectal metastases. They found that post-hepatectomy chemotherapy but not preoperative chemotherapy increased OS (57). The variability in these findings has led to differences in expert consensus varying from resection should be performed as soon as feasible, and the duration of neoadjuvant therapy should be carefully considered to most patients regardless of resectability should receive chemotherapy upfront (3,58).

PVE

PVE has been used in pre-operative management of patients with marginal FLR to increase the safety of resection in these patients. The physiologic response is referred to as the atrophy-hypertrophy complex (AHC) and is likely related to increased flow within the portal vein to the non-embolized lobe (59,60). PVE can be performed under conscious sedation by interventional radiology under sonographic and fluoroscopic guidance (30,61). Resection typically occurs 3-6 weeks following embolization. This time frame is based studies showing it takes at least 3 weeks to reach the steady state of liver regeneration (62). The hypertrophy of the FLR reduces the risk of postoperative liver failure and allows potentially curative extended hepatectomy in a group of patients that otherwise would be only marginal candidates for resection based on a small FLR. PVE has been reported to result in a 7-27% increase in the % FLR (30,61,63). With PVE the functional capacity as measured by indocyanine green excretion and 99mTc-GSA scintigraphy appears to improve to a greater extent and sooner than hypertrophy (64,65). PVE is safe, with complication rates less than 10% in most series (61,62,66). PVE results in a greater than 60% resection rate and an R0 resection in greater than 70% of resected patients (30,62,63,67). Liver surgery following PVE can be accomplished safely with morbidity of 19-55% and perioperative mortality of 1-7% (61,63,67-69).

There is a concern that tumors could have increased growth rates following PVE in both the embolized and non-embolized lobes. The hypothesis states that by increasing hepatic artery and portal blood flow there is an increase in local growth factors, leading to tumor growth (70,71). Several studies have indeed demonstrated this in colorectal metastases (15,70-72). The addition of chemotherapy between PVE and resection has shown success in slowing tumor progression, and improving long-term survival for PVE patients (15). Given the proposed etiology of the increased growth rate Bevacizumab has been examined for its potential impact on tumor growth following PVE with a decrease in the tumor growth rate but it did not reach statistical significance (71). Initially it was thought that if a patient continued their neoadjuvant chemotherapy there would be impediment of liver hypertrophy. However, this has more recently been shown to be false, with chemotherapy having no negative effects on the amount of hepatic hypertrophy (73).

The contraindications to PVE are largely relative and include tumor invasion of the portal vein (presumably flow has already been diverted), portal thrombosis, severe portable hypertension, uncorrectable coagulopathy, renal failure, and biliary dilation not amenable to drainage in the FLR (2,3).

Imaging should be performed 3-6 weeks after PVE to assess the amount of hypertrophy, determine the patient's new FLR, and determine if resection for cure is possible.

Two-stage hepatectomy

Two-stage hepatectomy can accomplish complete resection of disease that is initially unresectable, resulting in improved survival over comparative patients treated with chemotherapy only (74). This approach usually begins with 4-6 cycles of systemic chemotherapy. Repeat imaging is obtained and patients with response or stable disease undergo the first-stage resection. The first-stage resection usually involves resection of all metastases from the future FLR in the form of minor resections that avoid hilar dissection or mobilization of the contralateral liver (75). Often PVE is necessary at this stage to increase FLR prior to the second-stage resection. Resecting all disease in the FLR prior to PVE also avoids the increased tumor growth rate seen following PVE (70). After 4-6 weeks, typically with or without chemotherapy, repeat imaging is obtained to assess for liver regeneration and second-stage resection then follows (38). Morbidity following the first procedure is 11-17% with negligible mortality (74,76,77). It is important to minimize morbidity after this first stage to ensure the subsequent resection because there is no benefit of just the first stage for survival (74). The second stage resection is completed in 76-87% of patients who undergo the first stage (74,76,77). The R0 resection rate for the second stage procedure is 58-79% (74,77).The 3-year OS ranges from 50% to 84% for patients completing both stages of resection (74,76,77). This survival is a reflection of both selection of favorable biology and complete resection of metastatic disease (74).

Associating liver partition with PVL for staged hepatectomy (ALPPS)/in situ split procedure

ALPPS or the *in situ* split procedure is an alternative to PVE for increasing the FLR. This is a novel procedure in its developmental stage with promising initial results (78). The first stage is surgical exploration, right PVL, and *in situ* splitting (ISS) of the liver parenchyma to the right of the falciform ligament for proposed extended right hepatectomy or along Cantile's line for right hepatectomy. Computed tomography (CT) volumetry is performed about a week later followed shortly by the second operation performed where completion of the resection of the involved liver is performed (78-83).

The increase in FLR with ALPPS ranges form 63-87% (79-83). The morbidity ranges from 53-71% with a mortality of 0-22% (79-83). The reported mortality after ALPPS is significantly higher in some series than the 4.7-5.6% reported after extended hepatectomy in recent series (79,81,82,84-86). This increased mortality will likely decrease as the technique and indications are further developed (78). A particularly high rate of morbidity and mortality is seen in hilar cholangiocarcinoma patients with preoperative cholestasis and colonized bile, with some authors questioning the indication in these patients (81,82). Given the novel nature of the technique there are no long-term oncologic outcome studies.

The advantage of ALPPS over PVE is the short interval to completion surgery. This short interval may prevent tumor progression. The shorter interval also adds a technical advantage over the more traditional two-stage hepatectomy. There should be fewer adhesions, a faster recovery for the patient, and the ability for the patient to start adjuvant therapy sooner. ALPPS also addresses the most common causes of failure to undergo resection following PVE, disease progression and failure of FLR to hypertrophy (63,87). When compared to PVE the hypertrophy of the FLR generally occurs in less than 10 days compared to over 3 weeks for PVE (29,62,70,78-82). The reason this procedure appears to work much more efficiently than PVE is due to the ISS, allowing complete devascularization of segment IV and preventing formation of collaterals between the left lateral and right lobes (79).

In patients who have insufficient hypertrophy after PVE, ALPPS can still be evaluated as an option in order to convert the patient to resectability. Patients who had insufficient PVE followed by *in situ* liver transection showed rapid growth within 3 days with a mean volume increase of 63% (80).

Unresectable disease

Ablative therapies

Ablative therapies include radiofrequency ablation (RFA), microwave ablation (MWA) and cryoablation. Thermal ablation delivers extreme temperatures to hepatic colorectal metastases causing immediate cell death (38). The advantages of ablation therapies are the ability to spare liver parenchyma; utilization of percutaneous and laparoscopic modalities; it does not limit future therapeutic options; and low morbidity

rates (38,88). The ablative techniques generate and maintain enough temperature change to cause irreversible thermal damage to the tumor and a margin of normal liver tissue in a process called coagulative necrosis (89). RFA is the most common ablation therapy used to treat CLM (89,90). These methods are limited by the size of the lesion in relation to the probe and have largely been used for patients with unresectable disease or significant comorbidities precluding resection.

RFA

During RFA an electrode is placed within the tumor under radiologic guidance. Radiofrequency, or thermal energy, is used to destroy the tumor and a margin of normal surrounding parenchyma. Specifically, high-frequency alternating current causes thermal coagulation and protein denaturation. At 60° Celsius there is immediate cell death, and ablation zones are created in excess of this threshold (38).

RFA can be performed percutaneously, laparoscopically, or during laparotomy. RFA has been most effective for smaller lesions (<3 cm) that are amenable to coverage by a single probe (91-94). For larger lesions it is necessary to apply multiple overlapping RFA probe applications to achieve adequate ablation. Visualizing a sphere and then attempting to cover the surface of that sphere with additional overlapping burns shows the difficulty of this. Open or laparoscopic placement of the probe allows better placement than percutaneous and offers the additional advantage of exploration and intra-operative ultrasound of the liver, which can demonstrate occult peritoneal and hepatic disease (88,89,95). RFA has some limitations to placement within the liver. Placement near major vessels runs the risk of an inadequate ablation secondary to the flow in the vessels conducting the heat energy away from the target. This "heat sink" phenomenon can be overcome by temporary vascular occlusion such as a "Pringle" maneuver (96). RFA should not be performed adjacent to major biliary structures, particularly within 1 to 2 cm of the hepatic hilum due to the risk for bile duct stricture and fistula (13).

The data regarding oncologic outcome of RFA is based on two, phase II trials and a large number of retrospective series. The median survival following RFA for CLM ranges from 24-45.3 months with a 5-year OS of 18-33% (88,93,97-103). This compares to a median survival of 41-80 months and a 5-year OS of 48-71% in resection of CLM (13,97,99,102-104). The local recurrence rate even in the best cases (4-16.1%) is inferior to margin recurrences of 0.9-5% for resected CLM (13,92,93,97-100,105,106). The improved outcome of resection when compared to RFA retrospectively is related to more advanced disease in RFA performed for unresectable CLM and hepatectomy may remove occult parenchymal micrometastases (91).

Three clinical questions remain, is RFA equal to resection in resectable CLM, can RFA extend the pool of patients offered resection for cure, and is there benefit of RFA in addition to chemotherapy for unresectable CLM (91)? The first question is the most difficult to answer. Numerous authors have used retrospective comparison of resected CLM to unresectable CLM treated with RFA as evidence that RFA is inferior regarding local control (13,97,102,103). These are obviously different patient populations (deemed unresectable, failed chemotherapy, and/or are unable to tolerate a liver resection) and comparing retrospective data on RFA versus resection to conclude that RFA is inferior is flawed (93,102,106). However, local recurrence is universally higher for RFA studies and this is associated with decreased survival. This data supports continued use of resection as the "gold standard" for resectable CLM. Some authors have suggested that the increased local recurrence rate can be overcome by repeat applications via a minimally invasive technique in select patients similar to the development of the breast conservation therapy model (88,107). The ultimate role for RFA will be defined by recognizing that RFA and resection have different strengths and weakness inherent, different indications might highlight the advantages of each technique (96).

The question of benefit in using RFA to extend the pool of resectable patients was addressed with a Phase II prospective trial. The EORTC 40004 trial looked at 52 patients with unresectable CLM treated with a combination of RFA and resection. They achieved a 43% 5-year OS (106). Karanicolas *et al.* also recently reviewed their experience with the use of ablation combined with resection in unresectable bilateral CLM with poor prognostic factors and found a 56% 5-year OS (108). This data supports the use of RFA in addition to resection in an attempt at curative resection in otherwise unresectable disease. The use of RFA can potentially obviate the need for a two-stage hepatectomy. This allows sooner recovery, initiation of adjuvant therapy and avoiding the risks of progression between stages.

The question of benefit of the addition of RFA to chemotherapy for the treatment of unresectable CLM was addressed with the CLOCC trial (chemotherapy plus local ablation *vs.* chemotherapy alone). The trial randomized 119 patients to chemotherapy or chemotherapy plus RFA.

The PFS was significantly better at 16.8 months in the patients undergoing RFA when compared to 9.9 months in the chemotherapy alone group (99). The trial was hampered by slow accrual and was not ultimately powered to evaluate OS and so we do not know if the PFS translates into OS.

MWA

MWA has been introduced as a rapid method of delivering high temperatures to a large hepatic area. An electrode is placed into the tumor under ultrasound or CT guidance. The microwave coagulator then generates and transmits microwave energy. Coagulative necrosis causes cellular death and destroys the tissue. MWA induces rapid oscillation in water molecules leading to coagulation necrosis of the tumor, making its effects less dependent on tissue variations (107,109,110). This has some advantages over RFA and could allow safer applications, and potentially resulting in lower local recurrence and complication rates (107). The shorter wavelength of microwave allows more rapid heating and less loss of energy across different densities of tissues. This theoretically addresses two shortcomings of RFA, the heat sink effect near major vessels and the incomplete burn of larger lesions secondary to charring. These benefits have been seen when examining animal models (111-115). MWA offers a potential benefit for patients with lesions >3 cm, because the desiccation and charring seems to be of less importance when using MWA in comparison to RFA (111). However in a recent multi-center trial despite a low local recurrence rate of 6% the greatest impact on recurrence free survival was a lesion ≥3 cm. mirroring findings in RFA studies (116). MWA has not been nearly as well studied, as RFA and the theoretical benefits have not been clearly shown to translate to improved clinical outcome to date.

Cryoablation

Cryoablation involves liquid nitrogen or argon gas being delivered into the liver tumor, guided by ultrasound. Ice crystal formation during rapid freezing causes destruction of cellular structure and kills the tumor cells. Cryoablation has fallen out of favor, because of a higher complication rate and recurrence rate than RFA (117,118). The higher complication rate is marked by the potentially fatal complication of cryoshock manifested by hypothermia, coagulopathy, respiratory failure and renal failure (89).

Hepatic artery infusion

Hepatic artery infusion (HAI) is directed chemotherapy via a pump attached to a catheter which gets implanted through the gastroduodenal artery. The tip of the catheter is positioned at the gastroduodenal-hepatic artery junction. This therapy can be used in combination with systemic chemotherapy, along with resection or RFA if performed via laparotomy or laparoscopy. Chemotherapy given via the hepatic artery decreases toxicity given the knowledge that liver metastases are perfused almost exclusively by the hepatic artery, opposed to normal liver tissue that receives its blood supply predominantly from the portal circulation (119). This directed therapy allows an increased amount of cytotoxic drugs without increasing the systemic side effects. Given the high hepatic extraction rate for FUDR, almost a full dose of systemic chemotherapy can be given concurrently without increasing toxicity (120).

Phase I and II HAI studies show response rates in the liver between 52% and 75% in previously treated patients and even higher in chemotherapy naïve patients (121-123). HAI can be used to convert unresectable CLM to resectable. The combination of HAI and systemic chemotherapy has shown response rates in excess of 90% with 24-47% of patients going on to resection (121,124). The conversion to resectable was even greater at 53-57% in the chemotherapy naïve patients including patients with extensively involved liver (121,124). HAI has been studied in the adjuvant setting in patients with a high risk for recurrence following resection of CLM and increased DFS significantly but not OS (125). Pump complications after catheter placement occur in approximately 20% of patients; however, approximately half can be salvaged and still used for treatment (126). Biliary sclerosis is a long-term complication that can usually be managed by insertion of a biliary stent, without affecting OS.

Chemoembolization

Transarterial chemoembolization (TACE) can be performed in conventional method using either emulsions of ethiodized oil, which are embolic particles, in combination with chemotherapy solution, or as drug-eluting beads loaded with irinotecan (DEBIRI-TACE). There have been no studies comparing the two, so which method to give is usually institutional preference. DEBIRI was first reported in 2006 (127). The toxicity data suggests a more severe post-embolization syndrome compared to radioembolization (RE), with 40% reporting right upper quadrant pain, 80% fever, 27% nausea, and increased transaminases in 70% of patients (128). However, despite these symptoms,

therapeutic response was achieved in 78% of patients, and over 90% of patients report an improvement in their well-being for over 4 months, with a median duration of response lasting 6 months, and a median survival of 25 months (128). A recent prospective study randomizing patients with colorectal metastases who failed standard chemotherapy to DEBIRI versus FOLFIRI chemotherapy. The DEBIRI group had a significantly improved median survival of 22 months compared to 15 months for the FOLFIRI group (129).

RE

RE is the best studied of the embolization techniques for CLM. RE can be performed with microspheres labeled with the β emitter yttrium-90 (^{90}Y). There are two commercially available microspheres, one composed of a biocompatible resin (SIR-Spheres; SIRTex Medical, Ltd., Sydney, Australia) and the other composed of glass (TheraSphere; MDS Nordion, Inc., Ontario, Canada). Portal vein compromise is a contraindication for the SIR-Spheres (130). The most common adverse effect for both is gastrointestinal toxicity (131). The first step in minimizing this toxicity is performing arteriography of the celiac and superior mesenteric arterial distribution and skeletonizing the hepatic arterial vasculature. Gastrointestinal ulceration results from microspheres diverting via extrahepatic arteries supplying the gastrointestinal tract. A technetium 99 ($Tc^{99\,m}$) macroaggregated albumin (MAA) scan is also used in pretreatment evaluation to determine the presence and extent of any arteriovenous shunts and identify non-target organs, such as the gastrointestinal tract, or the lungs. A lung shunt fraction (LSF) is calculated based on imaging and dose reduction needs to be considered if the LSF is between 10-20% (130). Toxicity is usually mild and resolves in 1 to 4 weeks but symptoms include fatigue, abdominal pain, nausea, and anorexia (130). The response rates are 12.9-35.5% with 24-65% achieving stable disease (132-136). The median OS following ^{90}Y is 10.2-12.6 months (132-137). This is achieved in patients who have failed chemotherapy.

External beam

External beam radiation therapy (EBRT) has not been used historically on liver tumors given the small therapeutic window between benefit and liver toxicity (38). Stereotactic radiotherapy, originally developed in neurosurgical practice, allows delivery of highly focused ionizing radiation with extreme precision. The technique is termed stereotactic body radiotherapy (SBRT) (138). The local control rates in the liver at 1 and 2 years for SBRT are 67-100% and 55-92% respectively (139-141). The median survival ranges from 20.5-34 months (139,140). Chang *et al.* also showed that local control for colorectal metastases is dose-dependent, with an 18-month local control of 84% for total doses ≥42 Gy versus 43% for total doses <42 Gy (141). Based on this the authors recommend 3 fractions with a total dose of 42 Gy.

Conclusions

Surgical resection remains the treatment of choice for resectable CLM. There are a number of options for extending resection to more advanced patients including systemic chemotherapy, PVE, two stage hepatectomy, ablation and HAI. There are few phase III trials comparing these treatment modalities, and choosing the right treatment is patient dependent. Treating hepatic metastases requires a multidisciplinary approach and knowledge of all treatment options as there continues to be advances in management of CLM. If a patient can undergo a treatment modality in order to increase their potential for future resection this should be the primary goal. If the patient is still deemed unresectable then treatments that lengthen disease-free and overall-survival should be pursued.

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References

1. Siegel R, DeSantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 2012;62:220-41.
2. Donadon M, Ribero D, Morris-Stiff G, et al. New paradigm in the management of liver-only metastases from colorectal cancer. Gastrointest Cancer Res 2007;1:20-7.
3. Abdalla EK, Adam R, Bilchik AJ, et al. Improving resectability of hepatic colorectal metastases: Expert consensus statement. Ann Surg Oncol 2006;13:1271-80.
4. Pawlik TM, Scoggins CR, Zorzi D, et al. Effect of surgical margin status on survival and site of recurrence after

hepatic resection for colorectal metastases. Ann Surg 2005;241:715-22, discussion 722-4.
5. Scheele J, Stangl R, Altendorf-Hofmann A, et al. Indicators of prognosis after hepatic resection for colorectal secondaries. Surgery 1991;110:13-29.
6. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg 2002;235:759-66.
7. Hughes KS, Rosenstein RB, Songhorabodi S, et al. Resection of the liver for colorectal carcinoma metastases. A multi-institutional study of long-term survivors. Dis Colon Rectum 1988;31:1-4.
8. Adson MA, van Heerden JA, Adson MH, et al. Resection of hepatic metastases from colorectal cancer. Arch Surg 1984;119:647-51.
9. Gayowski TJ, Iwatsuki S, Madariaga JR, et al. Experience in hepatic resection for metastatic colorectal cancer: Analysis of clinical and pathologic risk factors. Surgery 1994;116:703-10; discussion 710-1.
10. Jenkins LT, Millikan KW, Bines SD, et al. Hepatic resection for metastatic colorectal cancer. Am Surg 1997;63:605-10.
11. de Jong MC, Mayo SC, Pulitano C, et al. Repeat curative intent liver surgery is safe and effective for recurrent colorectal liver metastasis: Results from an international multi-institutional analysis. J Gastrointest Surg 2009;13:2141-51.
12. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: Analysis of 1001 consecutive cases. Ann Surg 1999;230:309-18; discussion 318-21.
13. Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg 2004;239:818-25; discussion 825-7.
14. Jamison RL, Donohue JH, Nagorney DM, et al. Hepatic resection for metastatic colorectal cancer results in cure for some patients. Arch Surg 1997;132:505-10; discussion 511.
15. Fischer C, Melstrom LG, Arnaoutakis D, et al. Chemotherapy after portal vein embolization to protect against tumor growth during liver hypertrophy before hepatectomy. JAMA Surg 2013;148:1103-8.
16. Gur I, Diggs BS, Wagner JA, et al. Safety and outcomes following resection of colorectal liver metastases in the era of current perioperative chemotherapy. J Gastrointest Surg 2013;17:2133-42.
17. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): Long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol 2013;14:1208-15.
18. Fernandez FG, Drebin JA, Linehan DC, et al. Five-year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET). Ann Surg 2004;240:438-47; discussion 447-50.
19. Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. association francaise de chirurgie. Cancer 1996;77:1254-62.
20. Bowles BJ, Machi J, Limm WM, et al. Safety and efficacy of radiofrequency thermal ablation in advanced liver tumors. Arch Surg 2001;136:864-9.
21. Malik HZ, Prasad KR, Halazun KJ, et al. Preoperative prognostic score for predicting survival after hepatic resection for colorectal liver metastases. Ann Surg 2007;246:806-14.
22. Gall TM, Frampton AE, Krell J, et al. Optimizing unresectable colorectal liver metastases for surgery--no limits, any benefits? J Gastrointest Surg 2013;17:2185-7.
23. Hamady ZZ, Cameron IC, Wyatt J, et al. Resection margin in patients undergoing hepatectomy for colorectal liver metastasis: A critical appraisal of the 1cm rule. Eur J Surg Oncol 2006;32:557-63.
24. Lordan JT, Karanjia ND. 'Close shave' in liver resection for colorectal liver metastases. Eur J Surg Oncol 2010;36:47-51.
25. Figueras J, Burdio F, Ramos E, et al. Effect of subcentimeter nonpositive resection margin on hepatic recurrence in patients undergoing hepatectomy for colorectal liver metastases. evidences from 663 liver resections. Ann Oncol 2007;18:1190-5.
26. Mbah NA, Scoggins C, McMasters K, et al. Impact of hepatectomy margin on survival following resection of colorectal metastasis: The role of adjuvant therapy and its effects. Eur J Surg Oncol 2013;39:1394-9.
27. Muratore A, Ribero D, Zimmitti G, et al. Resection margin and recurrence-free survival after liver resection of colorectal metastases. Ann Surg Oncol 2010;17:1324-9.
28. Vauthey JN, Chaoui A, Do KA, et al. Standardized measurement of the future liver remnant prior to extended liver resection: Methodology and clinical associations. Surgery 2000;127:512-9.
29. Vauthey JN, Pawlik TM, Abdalla EK, et al. Is extended

hepatectomy for hepatobiliary malignancy justified? Ann Surg 2004;239:722-30; discussion 730-2.
30. Abdalla EK, Barnett CC, Doherty D, et al. Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. Arch Surg 2002;137:675-80; discussion 680-1.
31. Truant S, Oberlin O, Sergent G, et al. Remnant liver volume to body weight ratio > or =0.5%: A new cut-off to estimate postoperative risks after extended resection in noncirrhotic liver. J Am Coll Surg 2007;204:22-33.
32. Adam R, de Haas RJ, Wicherts DA, et al. Concomitant extrahepatic disease in patients with colorectal liver metastases: When is there a place for surgery? Ann Surg 2011;253:349-59.
33. Pulitanò C, Bodingbauer M, Aldrighetti L, et al. Liver resection for colorectal metastases in presence of extrahepatic disease: results from an international multi-institutional analysis. Ann Surg Oncol 2011;18:1380-8.
34. Giacchetti S, Itzhaki M, Gruia G, et al. Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin and surgery. Ann Oncol 1999;10:663-9.
35. Masi G, Cupini S, Marcucci L, et al. Treatment with 5-fluorouracil/folinic acid, oxaliplatin, and irinotecan enables surgical resection of metastases in patients with initially unresectable metastatic colorectal cancer. Ann Surg Oncol 2006;13:58-65.
36. Chua TC, Saxena A, Liauw W, et al. Hepatectomy and resection of concomitant extrahepatic disease for colorectal liver metastases--a systematic review. Eur J Cancer 2012;48:1757-65.
37. Elias D, Gilly F, Boutitie F, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: Retrospective analysis of 523 patients from a multicentric french study. J Clin Oncol 2010;28:63-8.
38. Abdalla EK, Bauer TW, Chun YS, et al. Locoregional surgical and interventional therapies for advanced colorectal cancer liver metastases: expert consensus statements. HPB (Oxford) 2013;15:119-30.
39. Mayo SC, Pulitano C, Marques H, et al. Surgical management of patients with synchronous colorectal liver metastasis: A multicenter international analysis. J Am Coll Surg 2013;216:707-16; discussion 716-8.
40. Chen J, Li Q, Wang C, et al. Simultaneous vs. staged resection for synchronous colorectal liver metastases: A metaanalysis. Int J Colorectal Dis 2011;26:191-9.
41. Martin RC 2nd, Augenstein V, Reuter NP, et al. Simultaneous versus staged resection for synchronous colorectal cancer liver metastases. J Am Coll Surg. 2009;208:842-50; discussion 850-2.
42. Huh JW, Cho CK, Kim HR, et al. Impact of resection for primary colorectal cancer on outcomes in patients with synchronous colorectal liver metastases. J Gastrointest Surg 2010;14:1258-64.
43. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: A model to predict long-term survival. Ann Surg 2004;240:644-57; discussion 657-8.
44. Pozzo C, Basso M, Cassano A, et al. Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients. Ann Oncol 2004;15:933-9.
45. Reissfelder C, Brand K, Sobiegalla J, et al. Chemotherapy-associated liver injury and its influence on outcome after resection of colorectal liver metastases. Surgery 2014;155:245-54.
46. Robinson SM, Wilson CH, Burt AD, et al. Chemotherapy-associated liver injury in patients with colorectal liver metastases: A systematic review and meta-analysis. Ann Surg Oncol 2012;19:4287-99.
47. Vauthey JN, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol 2006;24:2065-72.
48. Nakano H, Oussoultzoglou E, Rosso E, et al. Sinusoidal injury increases morbidity after major hepatectomy in patients with colorectal liver metastases receiving preoperative chemotherapy. Ann Surg 2008;247:118-24.
49. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC intergroup trial 40983): A randomised controlled trial. Lancet 2008;371:1007-16.
50. Karoui M, Penna C, Amin-Hashem M, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. Ann Surg 2006;243:1-7.
51. Scoggins CR, Campbell ML, Landry CS, et al. Preoperative chemotherapy does not increase morbidity or mortality of hepatic resection for colorectal cancer metastases. Ann Surg Oncol 2009;16:35-41.
52. Kesmodel SB, Ellis LM, Lin E, et al. Preoperative bevacizumab does not significantly increase postoperative complication rates in patients undergoing hepatic surgery

for colorectal cancer liver metastases. J Clin Oncol 2008;26:5254-60.
53. Wicherts DA, de Haas RJ, Sebagh M, et al. Impact of bevacizumab on functional recovery and histology of the liver after resection of colorectal metastases. Br J Surg 2011;98:399-407.
54. Adam R, Bhangui P, Poston G, et al. Is perioperative chemotherapy useful for solitary, metachronous, colorectal liver metastases? Ann Surg 2010;252:774-87.
55. Zhu D, Zhong Y, Wei Y, et al. Effect of neoadjuvant chemotherapy in patients with resectable colorectal liver metastases. PLoS One 2014;9:e86543.
56. Malik HZ, Farid S, Al-Mukthar A, et al. A critical appraisal of the role of neoadjuvant chemotherapy for colorectal liver metastases: A case-controlled study. Ann Surg Oncol 2007;14:3519-26.
57. Reddy SK, Zorzi D, Lum YW, et al. Timing of multimodality therapy for resectable synchronous colorectal liver metastases: A retrospective multi-institutional analysis. Ann Surg Oncol 2009;16:1809-19.
58. Nordlinger B, Van Cutsem E, Gruenberger T, et al. Combination of surgery and chemotherapy and the role of targeted agents in the treatment of patients with colorectal liver metastases: Recommendations from an expert panel. Ann Oncol 2009;20:985-92.
59. Kim RD, Kim JS, Watanabe G, et al. Liver regeneration and the atrophy-hypertrophy complex. Semin Intervent Radiol 2008;25:92-103.
60. Abdalla EK, Hicks ME, Vauthey JN. Portal vein embolization: Rationale, technique and future prospects. Br J Surg 2001;88:165-75.
61. Ratti F, Soldati C, Catena M, et al. Role of portal vein embolization in liver surgery: single centre experience in sixty-two patients. Updates Surg 2010;62:153-9.
62. Ribero D, Abdalla EK, Madoff DC, et al. Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome. Br J Surg 2007;94:1386-94.
63. Abulkhir A, Limongelli P, Healey AJ, et al. Preoperative portal vein embolization for major liver resection: A meta-analysis. Ann Surg 2008;247:49-57.
64. Uesaka K, Nimura Y, Nagino M. Changes in hepatic lobar function after right portal vein embolization. an appraisal by biliary indocyanine green excretion. Ann Surg 1996;223:77-83.
65. Hirai I, Kimura W, Fuse A, et al. Evaluation of preoperative portal embolization for safe hepatectomy, with special reference to assessment of nonembolized lobe function with 99mTc-GSA SPECT scintigraphy. Surgery 2003;133:495-506.
66. Madoff DC, Hicks ME, Abdalla EK, et al. Portal vein embolization with polyvinyl alcohol particles and coils in preparation for major liver resection for hepatobiliary malignancy: Safety and effectiveness--study in 26 patients. Radiology 2003;227:251-60.
67. Wicherts DA, de Haas RJ, Andreani P, et al. Impact of portal vein embolization on long-term survival of patients with primarily unresectable colorectal liver metastases. Br J Surg 2010;97:240-50.
68. Azoulay D, Castaing D, Smail A, et al. Resection of nonresectable liver metastases from colorectal cancer after percutaneous portal vein embolization. Ann Surg 2000;231:480-6.
69. Shindoh J, Tzeng CW, Aloia TA, et al. Portal vein embolization improves rate of resection of extensive colorectal liver metastases without worsening survival. Br J Surg 2013;100:1777-83.
70. Elias D, De Baere T, Roche A, et al. During liver regeneration following right portal embolization the growth rate of liver metastases is more rapid than that of the liver parenchyma. Br J Surg 1999;86:784-8.
71. Simoneau E, Aljiffry M, Salman A, et al. Portal vein embolization stimulates tumour growth in patients with colorectal cancer liver metastases. HPB (Oxford) 2012;14:461-8.
72. Pamecha V, Davidson B. Portal vein embolization prior to extensive resection for colorectal liver metastases. Ann Surg Oncol 2009;16:3214.
73. Covey AM, Brown KT, Jarnagin WR, et al. Combined portal vein embolization and neoadjuvant chemotherapy as a treatment strategy for resectable hepatic colorectal metastases. Ann Surg 2008;247:451-5.
74. Brouquet A, Abdalla EK, Kopetz S, et al. High survival rate after two-stage resection of advanced colorectal liver metastases: Response-based selection and complete resection define outcome. J Clin Oncol 2011;29:1083-90.
75. Adam R, Miller R, Pitombo M, et al. Two-stage hepatectomy approach for initially unresectable colorectal hepatic metastases. Surg Oncol Clin N Am 2007;16:525-36, viii.
76. Jaeck D, Oussoultzoglou E, Rosso E, et al. A two-stage hepatectomy procedure combined with portal vein embolization to achieve curative resection for initially unresectable multiple and bilobar colorectal liver metastases. Ann Surg 2004;240:1037-49; discussion 1049-51.
77. Tsim N, Healey AJ, Frampton AE, et al. Two-stage

resection for bilobar colorectal liver metastases: R0 resection is the key. Ann Surg Oncol 2011;18:1939-46.
78. de Santibañes E, Clavien PA. Playing Play-Doh to prevent postoperative liver failure: the "ALPPS" approach. Ann Surg 2012;255:415-7.
79. Schnitzbauer AA, Lang SA, Goessmann H, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg 2012;255:405-14.
80. Knoefel WT, Gabor I, Rehders A, et al. In situ liver transection with portal vein ligation for rapid growth of the future liver remnant in two-stage liver resection. Br J Surg 2013;100:388-94.
81. Ratti F, Cipriani F, Gagliano A, et al. Defining indications to ALPPS procedure: technical aspects and open issues. Updates Surg 2014;66:41-9.
82. Li J, Girotti P, Konigsrainer I, et al. ALPPS in right trisectionectomy: A safe procedure to avoid postoperative liver failure? J Gastrointest Surg 2013;17:956-61.
83. Alvarez FA, Ardiles V, Sanchez Claria R, et al. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): Tips and tricks. J Gastrointest Surg 2013;17:814-21.
84. Mullen JT, Ribero D, Reddy SK, et al. Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. J Am Coll Surg 2007;204:854-62; discussion 862-4.
85. Aloia TA, Fahy BN, Fischer CP, et al. Predicting poor outcome following hepatectomy: analysis of 2313 hepatectomies in the NSQIP database. HPB (Oxford) 2009;11:510-5.
86. Kishi Y, Abdalla EK, Chun YS, et al. Three hundred and one consecutive extended right hepatectomies: Evaluation of outcome based on systematic liver volumetry. Ann Surg 2009;250:540-8.
87. van Lienden KP, van den Esschert JW, de Graaf W, et al. Portal vein embolization before liver resection: A systematic review. Cardiovasc Intervent Radiol 2013;36:25-34.
88. Hammill CW, Billingsley KG, Cassera MA, et al. Outcome after laparoscopic radiofrequency ablation of technically resectable colorectal liver metastases. Ann Surg Oncol 2011;18:1947-54.
89. Nicholl MB, Bilchik AJ. Thermal ablation of hepatic malignancy: Useful but still not optimal. Eur J Surg Oncol 2008;34:318-23.
90. Tanis E, Nordlinger B, Mauer M, et al. Local recurrence rates after radiofrequency ablation or resection of colorectal liver metastases. analysis of the european organisation for research and treatment of cancer #40004 and #40983. Eur J Cancer 2014;50:912-9.
91. Stang A, Fischbach R, Teichmann W, et al. A systematic review on the clinical benefit and role of radiofrequency ablation as treatment of colorectal liver metastases. Eur J Cancer 2009;45:1748-56.
92. Pawlik TM, Izzo F, Cohen DS, et al. Combined resection and radiofrequency ablation for advanced hepatic malignancies: Results in 172 patients. Ann Surg Oncol 2003;10:1059-69.
93. Siperstein AE, Berber E, Ballem N, et al. Survival after radiofrequency ablation of colorectal liver metastases: 10-year experience. Ann Surg 2007;246:559-65; discussion 565-7.
94. Veltri A, Sacchetto P, Tosetti I, et al. Radiofrequency ablation of colorectal liver metastases: Small size favorably predicts technique effectiveness and survival. Cardiovasc Intervent Radiol 2008;31:948-56.
95. Wood TF, Rose DM, Chung M, et al. Radiofrequency ablation of 231 unresectable hepatic tumors: Indications, limitations, and complications. Ann Surg Oncol 2000;7:593-600.
96. Leblanc F, Fonck M, Brunet R, et al. Comparison of hepatic recurrences after resection or intraoperative radiofrequency ablation indicated by size and topographical characteristics of the metastases. Eur J Surg Oncol 2008;34:185-90.
97. Aloia TA, Vauthey JN, Loyer EM, et al. Solitary colorectal liver metastasis: Resection determines outcome. Arch Surg 2006;141:460-6; discussion 466-7.
98. Oshowo A, Gillams A, Harrison E, et al. Comparison of resection and radiofrequency ablation for treatment of solitary colorectal liver metastases. Br J Surg 2003;90:1240-43.
99. Ruers T, Punt C, Van Coevorden F, et al. Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: A randomized EORTC intergroup phase II study (EORTC 40004). Ann Oncol 2012;23:2619-26.
100. Abitabile P, Hartl U, Lange J, et al. Radiofrequency ablation permits an effective treatment for colorectal liver metastasis. Eur J Surg Oncol 2007;33:67-71.
101. Solbiati L, Livraghi T, Goldberg SN, et al. Percutaneous radio-frequency ablation of hepatic metastases from colorectal cancer: Long-term results in 117 patients. Radiology 2001;221:159-66.
102. White RR, Avital I, Sofocleous CT, et al. Rates and

patterns of recurrence for percutaneous radiofrequency ablation and open wedge resection for solitary colorectal liver metastasis. J Gastrointest Surg 2007;11:256-63.
103. Hur H, Ko YT, Min BS, et al. Comparative study of resection and radiofrequency ablation in the treatment of solitary colorectal liver metastases. Am J Surg 2009;197:728-36.
104. Park IJ, Kim HC, Yu CS, et al. Radiofrequency ablation for metachronous liver metastasis from colorectal cancer after curative surgery. Ann Surg Oncol 2008;15:227-32.
105. Ahmad A, Chen SL, Kavanagh MA, et al. Radiofrequency ablation of hepatic metastases from colorectal cancer: Are newer generation probes better? Am Surg 2006;72:875-9.
106. Evrard S, Rivoire M, Arnaud J-, et al. Unresectable colorectal cancer liver metastases treated by intraoperative radiofrequency ablation with or without resection. Br J Surg 2012;99:558-65.
107. Stättner S, Primavesi F, Yip VS, et al. Evolution of surgical microwave ablation for the treatment of colorectal cancer liver metastasis: review of the literature and a single centre experience. Surg Today 2014. [Epub ahead of print].
108. Karanicolas PJ, Jarnagin WR, Gonen M, et al. Long-term outcomes following tumor ablation for treatment of bilateral colorectal liver metastases. JAMA Surg 2013;148:597-601.
109. Gravante G, Ong SL, Metcalfe MS, et al. Hepatic microwave ablation: A review of the histological changes following thermal damage. Liver Int 2008;28:911-21.
110. Skinner MG, Iizuka MN, Kolios MC, et al. A theoretical comparison of energy sources--microwave, ultrasound and laser--for interstitial thermal therapy. Phys Med Biol 1998;43:3535-47.
111. Andreano A, Huang Y, Meloni MF, et al. Microwaves create larger ablations than radiofrequency when controlled for power in ex vivo tissue. Med Phys 2010;37:2967-73.
112. Andreano A, Brace CL. A comparison of direct heating during radiofrequency and microwave ablation in ex vivo liver. Cardiovasc Intervent Radiol 2013;36:505-11.
113. Garrean S, Hering J, Saied A, et al. Ultrasound monitoring of a novel microwave ablation (MWA) device in porcine liver: Lessons learned and phenomena observed on ablative effects near major intrahepatic vessels. J Gastrointest Surg 2009;13:334-40.
114. Bhardwaj N, Strickland AD, Ahmad F, et al. A comparative histological evaluation of the ablations produced by microwave, cryotherapy and radiofrequency in the liver. Pathology 2009;41:168-72.
115. Bhardwaj N, Dormer J, Ahmad F, et al. Microwave ablation of the liver: A description of lesion evolution over time and an investigation of the heat sink effect. Pathology 2011;43:725-31.
116. Groeschl RT, Pilgrim CH, Hanna EM, et al. Microwave ablation for hepatic malignancies: a multiinstitutional analysis. Ann Surg 2014;259:1195-200.
117. Bilchik AJ, Wood TF, Allegra D, et al. Cryosurgical ablation and radiofrequency ablation for unresectable hepatic malignant neoplasms: A proposed algorithm. Arch Surg 2000;135:657-62; discussion 662-4.
118. Pearson AS, Izzo F, Fleming RY, et al. Intraoperative radiofrequency ablation or cryoablation for hepatic malignancies. Am J Surg 1999;178:592-9.
119. Bierman HR, Byron RL JR, Kelley KH, et al. Studies on the blood supply of tumors in man. III. Vascular patterns of the liver by hepatic arteriography in vivo. J Natl Cancer Inst 1951;12:107-31.
120. Karanicolas PJ, Metrakos P, Chan K, et al. Hepatic arterial infusion pump chemotherapy in the management of colorectal liver metastases: Expert consensus statement. Curr Oncol 2014;21:e129-36.
121. Kemeny NE, Melendez FD, Capanu M, et al. Conversion to resectability using hepatic artery infusion plus systemic chemotherapy for the treatment of unresectable liver metastases from colorectal carcinoma. J Clin Oncol 2009;27:3465-71.
122. Kemeny N, Conti JA, Cohen A, et al. Phase II study of hepatic arterial floxuridine, leucovorin, and dexamethasone for unresectable liver metastases from colorectal carcinoma. J Clin Oncol 1994;12:2288-95.
123. Kemeny N, Seiter K, Niedzwiecki D, et al. A randomized trial of intrahepatic infusion of fluorodeoxyuridine with dexamethasone versus fluorodeoxyuridine alone in the treatment of metastatic colorectal cancer. Cancer 1992;69:327-34.
124. Goéré D, Deshaies I, de Baere T, et al. Prolonged survival of initially unresectable hepatic colorectal cancer patients treated with hepatic arterial infusion of oxaliplatin followed by radical surgery of metastases. Ann Surg 2010;251:686-91.
125. Goéré D, Benhaim L, Bonnet S, et al. Adjuvant chemotherapy after resection of colorectal liver metastases in patients at high risk of hepatic recurrence: a comparative study between hepatic arterial infusion of oxaliplatin and modern systemic chemotherapy. Ann Surg 2013;257:114-20.
126. Allen PJ, Nissan A, Picon AI, et al. Technical complications and durability of hepatic artery infusion pumps for unresectable colorectal liver metastases: An institutional

experience of 544 consecutive cases. J Am Coll Surg 2005;201:57-65.
127. Aliberti C, Tilli M, Benea G, et al. Trans-arterial chemoembolization (TACE) of liver metastases from colorectal cancer using irinotecan-eluting beads: Preliminary results. Anticancer Res 2006;26:3793-5.
128. Aliberti C, Fiorentini G, Muzzio PC, et al. Trans-arterial chemoembolization of metastatic colorectal carcinoma to the liver adopting DC bead(R), drug-eluting bead loaded with irinotecan: Results of a phase II clinical study. Anticancer Res 2011;31:4581-7.
129. Fiorentini G, Aliberti C, Tilli M, et al. Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: Final results of a phase III study. Anticancer Res 2012;32:1387-95.
130. Wang DS, Louie JD, Sze DY. Intra-arterial therapies for metastatic colorectal cancer. Semin Intervent Radiol 2013;30:12-20.
131. Murthy R, Brown DB, Salem R, et al. Gastrointestinal complications associated with hepatic arterial yttrium-90 microsphere therapy. J Vasc Interv Radiol 2007;18:553-61; quiz 562.
132. Cosimelli M, Golfieri R, Cagol PP, et al. Multi-centre phase II clinical trial of yttrium-90 resin microspheres alone in unresectable, chemotherapy refractory colorectal liver metastases. Br J Cancer 2010;103:324-31.
133. Cianni R, Urigo C, Notarianni E, et al. Selective internal radiation therapy with SIR-spheres for the treatment of unresectable colorectal hepatic metastases. Cardiovasc Intervent Radiol 2009;32:1179-86.
134. Jakobs TF, Hoffmann RT, Dehm K, et al. Hepatic yttrium-90 radioembolization of chemotherapy-refractory colorectal cancer liver metastases. J Vasc Interv Radiol 2008;19:1187-95.
135. Kennedy AS, Coldwell D, Nutting C, et al. Resin 90Y-microsphere brachytherapy for unresectable colorectal liver metastases: Modern USA experience. Int J Radiat Oncol Biol Phys 2006;65:412-25.
136. Nace GW, Steel JL, Amesur N, et al. Yttrium-90 radioembolization for colorectal cancer liver metastases: a single institution experience. Int J Surg Oncol 2011;2011:571261.
137. Bester L, Meteling B, Pocock N, et al. Radioembolization versus standard care of hepatic metastases: Comparative retrospective cohort study of survival outcomes and adverse events in salvage patients. J Vasc Interv Radiol 2012;23:96-105.
138. Hiraki M, Nishimura J, Ohtsuka M, et al. Impact of stereotactic body radiotherapy on colorectal cancer with distant metastases. Oncol Rep 2014;31:795-9.
139. Rusthoven KE, Kavanagh BD, Cardenes H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. J Clin Oncol 2009;27:1572-8.
140. van der Pool AE, Mendez Romero A, Wunderink W, et al. Stereotactic body radiation therapy for colorectal liver metastases. Br J Surg 2010;97:377-82.
141. Chang DT, Swaminath A, Kozak M, et al. Stereotactic body radiotherapy for colorectal liver metastases: A pooled analysis. Cancer 2011;117:4060-9.

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