World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v6.i7.453

World J Hepatol 2014 July 27; 6(7): 453-463
ISSN 1948-5182 (online)

REVIEW

Colorectal hepatic metastasis: Evolving therapies

Francisco Igor B Macedo, Tafadzwa Makarawo

Francisco Igor B Macedo, Tafadzwa Makarawo, Department of Surgery, Providence Hospital and Medical Centers, Southfield, MI 48075, United States
Author contributions: Macedo FI and Makarawo T contributed equally in all steps of this paper.
Correspondence to: Francisco Igor B Macedo, MD, Department of Surgery, Providence Hospital and Medical Centers, 16001 W Nine Mile Rd, Southfield, MI 48075, United States. franciscoigor.macedo@stjohn.org
Telephone: +1-786-9994754 Fax: +1-786-9994754
Received: November 28, 2013 Revised: February 23, 2014
Accepted: May 31, 2014
Published online: July 27, 2014

Abstract

The approach for colorectal hepatic metastasis has advanced tremendously over the past decade. Multidrug chemotherapy regimens have been successfully introduced with improved outcomes. Concurrently, adjunct multimodal therapies have improved survival rates, and increased the number of patients eligible for curative liver resection. Herein, we described major advancements of surgical and oncologic management of such lesions, thereby discussing modern chemotherapeutic regimens, adjunct therapies and surgical aspects of liver resection.

Key words: Colorectal cancer; Hepatic metastasis; Hepatectomy; Survival; Chemotherapy; 5-fluorouracil leucovorin and oxaliplatin

Core tip: The management of colorectal hepatic metastasis is complex, and should involve a multidisciplinary tumor board involving specialized medical and surgical oncologists. Although liver resection still remains as the key step in the management of liver metastasis, the introduction of new chemotherapeutic regimens and recent adjunct therapies, including radiofrequency ablation, cryotherapy and radioembolization improved patient care, and prolonged survival in patients with unresectable disease.

Macedo FI, Makarawo T. Colorectal hepatic metastasis: Evolving therapies. *World J Hepatol* 2014; 6(7): 453-463 Available from: URL: http://www.wjgnet.com/1948-5182/full/v6/i7/453.htm DOI: http://dx.doi.org/10.4254/wjh.v6.i7.453

INTRODUCTION

Colon cancer is the third most common malignancy in the United States, and comprising around 10% of all cancer-related mortality[1]. Most disease-related mortality is associated with metastatic disease. Approximately 25% of patients is diagnosed with metastases at initial presentation, and around 50% will present metastases during the clinical management of the disease[2,3]. The survival for untreated colorectal hepatic metastasis (CHM) are dismal with medial survival estimated in only 6 to 9 mo[4].

Although liver resection still remains as the most important modality in the treatment of CHM, the introduction of recent adjunct therapies, including radiofrequency ablation (RFA), cryotherapy and radioembolization improved patient care, and prolonged survival in patients with unresectable disease. Concurrently, the evolution of chemotherapy with the introduction of multidrug therapy optimized response rates, and expanded the number of surgical candidates for curative liver resection. Herein, we describe the current management of CHM, thereby discussing major advancements in chemotherapeutic regimens, adjunct therapies and surgical technique, and describe paradigm changes in resectability and outcomes.

DETERMINATION OF STRATEGY

The management of CHM is complex, and should involve a multidisciplinary tumor board including oncologists, radiologists, colorectal and hepatobiliary surgeons. Clinical and laboratory suspicion of metastasis should be routinely confirmed by radiological imaging. Options

available include computed tomography (CT), ultrasound, fluorodeoxyglucose-positron emission tomography (PET), and magnetic resonance imaging (MRI). Multi-detector CT is widely available, and is routinely used for detection of CHM[5]. MRI is being used more commonly, and provides better visualization of liver lesions as compared to CT by some experts[6]. PET scan is usually associated with CT (PET-CT), and is superior to CT or MRI for identification of equivocal lesions, metastases, and local recurrence, prior to resection of metastatic disease[7-10].

Several prognostic factors should be considered during definition of therapeutic strategy, including: staging of the primary tumor, interval diagnosis between the primary and metastatic lesions, number and size of metastases, presence of surgical margins and extrahepatic recurrence, and elevated biochemical markers such as carcinoembrionic antigen, alkaline phosphatase, and albumin[11-15]. The most important decision for definition of the therapeutic plan is defined based on resectability of metastatic disease. Patients should be stratified as suitable for resection, potentially resectable after chemotherapy and/or adjunct therapies, and those with unresectable disease.

MANAGEMENT OF RESECTABLE DISEASE

Liver resection continues to be the most crucial step in the management of CHM, potentially offering definitive treatment to a subset of patients. The use of chemotherapy is used as an adjunct therapy, thereby enhancing the 5-year survival at approximately 37%-58%[16,17]. Assessment of resectability is based on the volume of future remnant liver with adequate vascular inflow and outflow and biliary drainage[18]. For patients with normal liver function, 20% of remnant tissue is required, whereas in the presence of steatosis and cirrhosis, 30% and 40% of residual liver is necessary, respectively. Negative margins of 1-cm is associated with improved outcomes, and is currently recommended by most experts[19,20]. Contraindications to resection include uncontrollable extrahepatic disease, extensive lymph node involvement, including retroperitoneal or mediastinal nodes, bone or central nervous system metastases[21]. Local predictors of unresectability are determined by hepatic vascular involvement, and bilaterally, that would leave an inadequate functional liver remnant. Perioperative combination with chemotherapy with 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) regimen given 3 mo prior and 3 mo following resection of metastases enhances survival by 8% at 3 years[22]. Neoadjuvant chemotherapy for patients with resectable liver metastases is still under investigation, and currently, remains controversial. Another topic of major debate is regarding the timing of the colectomy relative to the hepatectomy in cases of synchronous CHM. Typically, the primary colorectal cancer (CRC) is resected first, however in select cases where the liver disease is marginally resectable and primary CRC is small, the liver resection may be considered as initial approach to avoid progression of CHM. Combined resections are associated with shorter hospital stay and less morbidity, with similar 5-year survival and technically more challenging[23].

MANAGEMENT OF POTENTIALLY RESECTABLE DISEASE

Initially unresectable liver metastases can become resectable after being downsized by neoadjuvant chemotherapy, and, in such cases, resection may be advocated. Bismuth *et al*[24] reported the first experience with downstaging of unresectable lesions to resectable. They found similar outcomes to those patients with initially resectable lesions[25]. Nuzzo *et al*[26] found similar operative complications, and 3-year overall survival between initially resectable patients and those with initially unresectable but downstaged lesions. Subsequent reports showed conversion rates between 30%-50% with the combination of hepatic artery infusional fluoxuridine with systemic chemotherapy[27,28]. In these patients, response to initial chemotherapy appears to be a predictor of outcome[29].

Initial experience with addition of a vascular endothelial growth factor (VEGF) or epidermal growth factor receptor (EGFR) target agent (bevacizumab or cetuximab, respectively) is associated with higher resection rates in patients with initially unresectable disease. Resection is usually performed 5-8 wk after the last chemotherapy cycle with cetuximab or bevacizumab, respectively. The decision for resectability in these patients is often challenging, and involves a multidisciplinary team, depending on the experience of hepatobiliary surgeon and assessment for sufficient remnant liver. Many surgeons and oncologists would offer resection as soon as the lesion has become resectable, whereas others usually continue chemotherapy for 4 to 9 mo regardless of the response[30].

Several techniques have been recently introduced aiming at downsizing metastatic disease and improving resectability, including radioembolization, intra-arterial chemotherapy, and local ablation techniques, especially radiofrequency ablation. These adjunct modalities will be discussed separately.

MANAGEMENT OF UNRESECTABLE DISEASE

The majority of patients with CRC and concurrent metastasis has unresectable disease. However, due advances in systemic therapy, the survival of these patients is progressively improving[31]. The median survival is improved, estimated in up to 24 mo.

The approach for unresectable metastatic disease with synchronous CRC is still controversial. Resection of the bowel cancer initially is associated with precise definition of nodal and peritoneal status, prevention of local complications, the theoretical advantage of reduced total-body tumor load as well as psychological benefits for the patient[11]. However, the chemotherapy-first approach

is considered better by other experts due to the avoidance of postoperative morbidity and mortality, potential downstaging of unresectable CHM to resectability, and data showing equivalent survival benefits[11].

Monoclonal therapy against VEGF and EGFR should be considered especially in refractory cases, and will be further discussed in this review. For non-curative therapy of CHM, in addition to using the standard FOLFOX or FOLFIRI chemotherapy regimens, single agent strategies have been used with survival benefits as evidenced by the MRC FOCUS (using 5-FU-LV) and CAIRO (using capecitabine) trials[32-34].

TREATMENT MODALITIES

Resection

Surgery is the key step in the management of patients with CHM and represents the only chance for cure. Resection of CHM is considered a relatively safe operation with an operative mortality less than 5% by most recent series[30,35,36]. In high volume centers, median hospital stay ranges between 5 and 10 d for minor and major resections[36,37]. With increased outcomes, hepatectomies are now safely performed in elderly patients[38].

In cases of multiple, bilateral CHM, surgical options include: parenchyma-sparing approaches, and two-stage hepatectomy. In a two-stage operation, a portion of the liver disease is removed, and the contralateral portal vein is occluded, followed by 1 to 3 mo interval to allow for hypertrophy of the remaining liver and a curative-intent, second-stage hepatectomy. In such cases, the portal vein is occluded intraoperatively or subsequently by percutaneous embolization. Most experts perform minor segment resection first followed by resection of major liver. The minor-first approach spares the patient with progressive disease to undergo a major hepatectomy.

Within 2 years, most patients developed a recurrence[11,39]. Approximately 40% of them are eligible to undergo reoperation. The 5-year survival after first and second hepatectomies was 47% and 32%, respectively[40].

The experience with laparoscopic resection of CHM is yet minimal. Buell *et al*[41] and Mala *et al*[42] demonstrated tumor clearance, feasibility and safety of laparoscopic liver resection in 31 and 42 patients with CHM, respectively[41,42]. Long-term outcomes compared to open approach remains unknown.

CHEMOTHERAPY

Although chemotherapy plays a vital role in managing resectable and unresectable CHM, the timing of delivery is still controversial. For resectable disease, delivery of chemotherapy may be offered before colon resection (pre-operative), after colon resection but before liver resection (peri-operative) or after both resections (post-operative).

Pre- and peri-operative chemotherapy for resectable disease

For patients with potentially resectable CHM, response to chemotherapy has become an important adjunct in deciding whether to proceed with surgery. Typically, most tumors either reduce in size or remain unchanged following chemotherapy[22,43-46].

The recommended approach of delivering neoadjuvant chemotherapy to patients with resectable CHM consists of a 2-3 mo course of FOLFOX in order to limit chemotherapy-induced liver injury[46]. Chemotherapy application is considered safe to be used in patients with intact colorectal tumors[47]. In order to avoid difficulties locating both colorectal tumors and CHM that respond well to systemic chemotherapy, it would be prudent to mark the lesions before initiation of therapy, typically done using India ink tattoo or metallic coils placed by interventional radiology[48]. The disadvantages of pre-operative chemotherapy application include the development of new extrahepatic lesions[49] as well as a possible increased incidence of post-operative sequelae[22].

Adjuvant chemotherapy

The application of 5-FU-based chemotherapy post-CHM resection is established in most clinical practice despite prospective data limited to only two studies[50-52]. Pooled analysis of these two trials demonstrated a trend towards longer disease-free survival but no difference in median progression-free survival or overall survival. At present, there is no role for irinotecan-containing chemotherapy regimen (FOLFIRI) following hepatic resection with no benefit demonstrated when compared to 5-FU based regimens[53].

The application of systemic chemotherapy for CHM is associated with hepatotoxicity, a sequelae that has been recognized to increase the risk of peri- and post-operative mortality for CHM resection candidates. Amongst these hepatotoxic sequelae are hepatic steatosis seen in 30%-47% of patients on 5-FU[17], non-alcoholic steatohepatitis (NASH) in 12%-25% of patients on irinotecan[18] and sinusoidal dilation in 78% of patient on oxaliplatin[37]. The impact of these hepatotoxic effects is somewhat varied, although it is clear that the irinotecan-associated NASH appears to be the most significant with established evidence of increased post-operative mortality due to liver failure. Although previously the recognition of these adverse reactions was the domain of oncologists, the significant impact on post-operative outcomes has made it imperative for surgeons to be mindful of them too before considering operative intervention.

MOLECULAR TARGETED THERAPIES

Monoclonal antibodies against VEGF and EGFR have added an additional therapeutic option for treatment in select patients when used in combination with chemotherapy. Evidence of the therapeutic benefit of this treatment modality was initially found using the anti-VEGF monoclonal antibody, bevacizumab, with findings of improved survival when used in combination with therapy of IFL (irinotecan, 5-FU and leucovorin)[54]. Additional studies have demonstrated similar benefits in response

rate, disease-free progression and overall survival of using bevacizumab in combination with 5-FU/LV alone and FOLFOX in the first-line and second-line settings respectively[29]. Bevacizumab has, however, been associated with a number of complications, most notably gastrointestinal perforation, risk of bleeding and wound healing problems. As a result, the use of this modality requires careful monitoring, with treatment withheld for 6-8 wk prior to resection[55,56].

Panitumumab and cetuximab are EGFR inhibitors that have also demonstrated benefits in treating patients with metastatic CRC. Benefits have particularly been found using cetuximab in chemorefractory patients, improving survival compared to standard therapies[57]. Indeed, similar to bevacizumab, cetuximab appears to have superior effects when used in combination with[29]. It also appears that EGFR inhibitors are most effective for non-mutated (wild-type) K-ras colorectal tumors[55]. The side-effect profile for anti-EGFR antibodies is less extensive, limited to acneiform rash and hypomagnesemia and allergic reactions with cetuximab only[29] and no significant hepatotoxic effects seen thus far.

ADJUNCT THERAPIES

With the role of surgical resection for CHM widely accepted, the roles of non-operative liver directed therapies continue to evolve. With numerous new adjunctive therapies coming to the fore in recent years producing encouraging outcomes (including downstaging of CHM and increasing survival), the decision to integrate these options into current practice is challenging. Broadly speaking, there are three non-operative, liver directed therapies in use; intra-arterial therapies, ablative therapies, and radiotherapies.

INTRA-ARTERIAL THERAPIES

The role of intra-arterial therapies continues to evolve. The delivery of intra-arterial therapies uses the principal that hepatic metastases deriving their blood supply from hepatic arteries[58,59]. Therefore, intra-arterial therapy enhances drug delivery to hepatic tumors, maximizing local tumor therapy and limiting systemic therapy with its side-effects.

Hepatic arterial infusion chemotherapy

The hepatic arterial infusion (HAI) modality delivers chemotherapy directly to the liver *via* intra-abdominal catheters or infusion pumps cannulating the gastroduodenal artery[60,61]. An intimate understanding of hepatobiliary anatomy by surgeons is required to avoid placement of these catheters within aberrant anatomy leading to organ underperfusion with associated peptic ulceration, pancreatitis or biliary sclerosis[62]. The complex technical skills for correct placement of these infusion pumps requires experience often attainable at high volume centers. The delivery of HAI may be initiated as soon as the first post-operative week provided the patient has recovered well. In the United States, the chemotherapeutic agent most commonly used for HAI is fluoxuridine (FUDR) due to its high uptake by the liver limiting systemic toxic effects[63], although the low toxicity benefit may be lost by concomitant systemic chemotherapy use[64]. Dexamethasone has been delivered in conjunction with FUDR HAI-therapy, reducing biliary sclerosis, increasing tumor response rate and patient survival[65]. In Europe, 5-FU based HAI chemotherapy has also been used with some success.

HAI in unresectable disease

The role of HAI chemotherapy in unresectable disease is yet to be defined. This is largely due to inconclusive evidence from trials regarding patient outcomes[66]. On one hand, HAI has been found to produce higher tumor response rates than systemic therapy alone, but on the other no significant survival advantage has been found *via* the numerous randomized trials performed so far[67]. The application of combination therapy of HAI and systemic chemotherapy as second-line therapy following failed conventional chemotherapy[68] or to downstage initially unresectable CHM[28] have been suggested roles for HAI.

HAI as adjuvant therapy

The evidence supporting adjuvant HAI-therapy is even less established. To date, there has only been evidence from a single RCT that demonstrated a significant survival advantage applying HAI chemotherapy over systemic chemotherapy in the adjuvant setting[69]. This subject is therefore under ongoing scrutiny in current studies assessing HAI chemotherapy *vs* modern chemotherapy regimens.

Radioembolization

Radioembolization (or selective internal radiation therapy; SIRT) delivers high-energy beta-emitting radiation locally to CHM, delivering its effects specifically on tumor vasculature and minimizing collateral hepatic damage[70]. At present, this modality is delivered *via* two forms; Yttrium-90 (^{90}Y)-labeled resin microspheres (SIR-Spheres®; Sirtex Medical, Sydney, Australia) and ^{90}Y-labeled glass microspheres (Therasphere®; MDS Nordion, Ottawa, Canada). Radioembolization therapy is performed by injecting radioactive microspheres designed to embolize into small vessels around the metastases *via* branches of the hepatic artery, usually using a percutaneous femoral approach and fluoroscopic monitoring[71].

The current benefits with radioembolization using ^{90}Y microspheres have been reduced tumor load of unresectable CHM particularly if refractory to conventional chemotherapy. Indeed, combing radioembolization with chemotherapy has produced longer tumor suppression compared to chemotherapy alone[72]. The results of the recently ended SIRFLOX trial evaluating the efficacy of first-line therapy of FOLFOX6 combined with SIR-Spheres® *vs* FOLFOX6 alone will hopefully provide ad-

ditional evidence in favor of this treatment strategy in patients with unresectable CHM[73,74].

Further, trials have also demonstrated similar benefits of ^{90}Y microspheres used in combination with other treatment modalities like HAI therapy, demonstrating a superior time to progression compared to HAI alone[73,74].

The evidence supporting the use of ^{90}Y glass microspheres in CHM is less extensive with limited research demonstrating CHM tumor regression in upto 88% of patients with chemo-refractory tumors treated with ^{90}Y glass microspheres[75]. The further assessment of ^{90}Y-glass microspheres as salvage therapy continues to be evaluated with an ongoing phase Ⅲ multicenter randomized trial (EPOCH trial) which will hopefully provide corroborative evidence in support of this modality[17]. The long-term toxicity effects of radioembolization techniques are yet to elucidated.

Chemoembolization

Chemoembolization [or transcatheter arterial chemoembolization (TACE)] is a form of transarterial therapy that also utilizes the principal of liver tumors' predominantly arterial supply, allowing for regional therapy to the tumors. Similar to HAI, TACE is delivered using selective angiographic techniques by injection of chemotherapeutic drug combined with embolic material resulting in selective ischemic and chemotherapeutic effects on the CHM[76].

At present, there is no standard approach to delivering TACE therapy, although the application of a newer approach, drug-eluting beads composed of irinotecan (DEBIRI®; Biocompatibles United Kingdom Ltd, Farnham, United Kingdom) is gaining wider acceptance through ongoing clinical trials[77-79]. Irinotecan is preferentially used in this modality due to its properties allowing for application to the beads. Administration of DEBIRI® occurs *via* a selective arterial catheter, depositing the beads adjacent to the CHM tumors. This allows for slow release of irinotecan locally to the tumors.

Although DEBIRI® is presently not approved by the United States Food and Drug Administration, there are promising early results on its efficacy and safety. Available clinical trials suggest that DEBIRI® treatment may be associated with a median survival time of 15-25 mo, which is broadly equivalent to the outcomes achieved for unresectable CHM with the use of best-practice systemic chemotherapy[76]. In addition, the majority of patients that had responded to TACE treatment had failed first-line chemotherapy regimens[76]. Further evidence from additional trials[78,80-82] have also found successful downstaging of unresectable CHM to resectable status with most trials describing minimal toxicity effects[76].

It must be mentioned that the majority of the available trials to date have methodological flaws, and their conclusions must be interpreted with caution. To address the lack of high-quality randomized comparative trials assessing DEBIRI® use, there is ongoing research to evaluate its benefits when used in combination with systemic chemotherapy.

ABLATION TECHNIQUES

Ablation techniques aim to induce local destruction of the CHM. At present, the exact role of ablative techniques in the treatment of CHM is unclear, although there have been suggestions that its roles may include to reduce tumor size minimizing the extent of liver resection required, adjunctive therapy for patients either unfit for surgery or with unresectable disease. Ablative approaches can be subdivided into cryoablation, RFA and microwave ablation.

Cryoablation

Cryoablation was the first thermal ablative modality attempted to treat unresectable hepatic malignancies[83]. Cryoablation (or cryosurgery) is induced by local delivery of liquid nitrogen or argon on a probe tip to the CHM, resulting in tumor destruction by intracellular ice crystals that form from the rapid cooling. The "iceball" that forms around the tip of the probe can be measured by real-time intraoperative ultrasound although there has been some suggestion that the tissue furthest away from the tip may not be cooled sufficiently to cause tissue destruction[17].

Cryotherapy applications

Cryoablation application appears to vary between institutions. In general, its primary use has been for the ablation of unresectable CHM. Despite initial thoughts that cryoablation could be used in patients with resectable CHM, high tumor recurrence following cryosurgery has tempered this enthusiasm. So far, previous research has demonstrated a modest 5 year survival of 26% but also low mortality rates of less than 5% following cryotherapy for CHM[84]. Cryoablation used in combination with surgery has also been shown to produce similar survival benefits to surgery alone in patients with initially unresectable CHM[85].

The application of cryotherapy to the remnant liver resection margins (edge cryotherapy) remains undecided. Although some authors have reported the decreased application of edge cryotherapy due to report higher complication rates than hepatic resection alone[17], other institutions have reported positive outcomes with this approach, finding potential cure of up to 13% of advanced unresectable CHM compared with resection alone.

Additional benefits of cryosurgery include its facility in treating bilobar CHM or recurrent hepatic tumors following resection in addition to evidence from animal models that shows decreased secretion of factors that stimulate growth of occult micrometastases following cryotherapy compared to post-surgical resection[86]. One of the shortcomings of cryoablation is its poor ability to destroy tumors next to larger blood vessels due to the "heat-sinking" effect[87], resulting in recurrence rates as high as 44%. Another disadvantage of this modality is that for unclear physiologic reasons, patients may suffer from a systematic

inflammatory response (cryoshock phenomenon)[82,88,89] associated with periprocedural deaths[88,89].

RFA

By far, the most extensively evaluated ablative approach is RFA. RFA is the most widely applied ablative modality due to ease and safety of application and inexpense of equipment[17]. This modality is applied by placing needles within and adjacent to CHM through which alternating electrical current is delivered at radiofrequency range generating heat to desiccate the tumors[90,91].

Application

Although RFA is in widespread use across many institutions internationally, a paucity of randomized controlled trials up to now has prevented the development of a consistent approach to its use. Indeed, to date, there are no RCTs comparing surgical resection with RFA in resectable CHM, a study that at present seems inconceivable and unethical considering established survival data from surgical resection. At present, most evidence from the retrospective studies available comparing RFA and resection has demonstrated the inferiority of RFA compared to surgical resection with increased local recurrence rates (16%-60% *vs* 0%-24%) and worse long-term survival[91,92].

At present, RFA is being used to treat unresectable CHM only, with no extrahepatic metastatic disease[93]. Tumors amenable to successful treatment with RFA have typically been solitary CHM or a few which are not close to large hepatic vessels[93]. Tumor size in particular has been limited to 3-cm due to the circumferential rim of ablation currently delivered by ablation probes being approximately 4-cm in diameter, a limitation that may be addressed with advancement of the technology. Overlapping ablations can be used to treat larger tumors although this has been associated with less successful complete ablation[94]. The presence of large blood vessels limits RFA efficacy because their high blood flow acts a "heat sink", protecting adjacent cells from thermal ablation[17].

RFA is delivered *via* open, laparoscopic or percutaneous approaches[93]. The application of ultrasound, CT and MRI are particularly important to guide the needle in the percutaneous approach while intraoperative ultrasound is an additional adjunct used to directly visualize the tumor in the operative approaches. It appears at present that RFA *via* laparotomy is associated with the lowest recurrence rate followed by laparoscopy, and finally by percutaneous approach. The trade-off of using the least invasive percutaneous approach must be weighed up against poor tumor visualization increasing the potential for recurrence. The surgical approaches are typically applied at the time of primary or hepatic metastasis tumor resection.

In addition to the aforementioned advantages of RFA, it has a relatively lower morbidity profile of < 10% independent of the approach used for delivery being surgical or percutaneous[95]. Amongst the complications that have been seen, thermal injury (bowel and biliary injury), mechanical (biliary and vessel injury) and septic (abscess and peritonitis) have been the most widely reported. A more infrequent presentation of post-ablative syndrome where patients suffer from self-limiting constitutional upset including malaise, febrile episodes, myalgia, nausea and vomiting has also been reported[93].

Microwave ablation

Microwave ablation (MWA) is a more recently developed technique used for CHM. MWA is applied *via* a microwave probe delivered into the tumor *via* image-guided percutaneous, or ultrasound guided surgical approaches. *Via* these probes, microwave radiation between 900 MHz and 2.4 GHz is delivered that causes polarized water molecules within the tissue to oscillate generating friction that produces heat that destroys tissue by coagulative necrosis[96].

MWA application

As this modality is relatively new, the evidence of its efficacy is limited and has included too many different liver tumor types particularly hepatocellular carcinoma. The exact application of MWA for CHM is therefore still unclear. Although reported local recurrence rates have been extremely variable ranging from 3% to 50%, encouraging evidence from the largest series reported rates as low as 3% and 6%[97,98]. Further research would therefore provide the evidence to define its role as an ablative therapy in CHM management.

The purported advantages of MWA have been the more extensive nature of tissue destruction created by the heating mechanism generated by this technique. This mechanism also appears to be less prone to the "heat-sink" effect seen with RFA therapy[99]. There has also been suggestion that intra-operative hepatic inflow occlusion (Pringle maneuver) increases the size of ablated lesions[100]. Further, there appears to be reduced occurrence of charring using MWA and it creates larger ablation zones up to 6 cm away more rapidly than RFA[96]. Interestingly, there is now growing interest over a further method of cell death induced by microwaves characterized by normal-looking but non-viable cells. If indeed this is correct, this would have important implications in the post-procedure observation of the ablated tumors, requiring likely routine histopathology to differentiate seemingly viable tumor from completely ablated ones.

The complication rates from MWA range from 6% to 30%, most often associated with cases where laparotomy and additional procedures had been performed[90,97,98]. There are at present concerns of potential inadvertent injury to surrounding organs due to the higher energy generated by this modality.

STEREOTACTIC BODY RADIOTHERAPY

Stereotactic body radiotherapy (SBRT) is another newer technology that has generated growing interest for use in ablating CHM[101]. Unlike external beam radiation therapy (EBRT) which had previously been abandoned for use

in liver tumors due to the narrow therapeutic window between tumoricidial and hepatoxic effects, SBRT uses more modern technology that allows for safe treatment delivery in lung and liver with hypofractionation[101].

Application

SBRT is based on techniques used in stereotactic radiosurgery for brain tumors[101]. In this modality, the tumor location is identified using four-dimensional imaging that maps the target area accounting for patient movements during breathing. Gold seeds called fiducials are then placed within the tumor, which guide treatment. Using the predetermined tumor coordinates, high-dose radiation is delivered over a relatively shorter duration compared to conventional EBRT.

Although encouraging evidence of tumor local control rates as high as > 90% have been demonstrated in lung tumors using SBRT[102,103], its application in liver tumors specifically CHM is still under scrutiny with few well-designed studies presently available in current literature. The optimum radiation dosage is also undetermined, although it appears that a higher dose of up to 60 Gy is most effective, eliminating high local progression rates seen at lower doses[104], maximizing tumor response rate (up to 90%) and 2-year local control rate of 100%.

Although the treatment is focused, it does not eliminate surrounding toxicity. Specifically, acute gastrointestinal and liver toxicity in addition to chest wall pain have been reported side effects of the therapy. In addition, and more importantly, although there is some early evidence of local tumor control with SBRT, it is not yet been demonstrated to significantly impact survival.

However, the encouraging early results have lead to the assertion that SBRT be considered as an option in patients not offered surgery after chemotherapy to locally ablate their CHM[101].

CONCLUSION

The management of CHM is complex, and should involve a multidisciplinary tumor board involving specialized medical and surgical oncologists. Although overall survival has increased tremendously over the last 5 years with the introduction of adjunct therapies, more efficient chemotherapeutic regimens still need to be discovered. Concurrently, the criteria for resection is much more liberal and should be based on functional remnant liver volume. Even in situations where multiple, bilobar liver metastases are present, resection may be a considered option. Both basic studies and prospective trials are necessary to further understand the molecular aspects of colorectal hepatic metastasis, and therefore improve outcomes.

REFERENCES

1 **Parkin DM**, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *Cancer J Clin* 2005; **55**: 74-108 [PMID: 15761078 DOI: 10.3322/canjclin.55.2.74]

2 **Steele G**, Ravikumar TS. Resection of hepatic metastases from colorectal cancer. Biologic perspective. *Ann Surg* 1989; **210**: 127-138 [PMID: 2667471 DOI: 10.1097/00000658-198908000-00001]

3 **Mohammad WM**, Balaa FK. Surgical management of colorectal liver metastases. *Clin Colon Rectal Surg* 2009; **22**: 225-232 [PMID: 21037813 DOI: 10.1055/s-0029-1242462]

4 **Scheele J**, Stangl R, Altendorf-Hofmann A. Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. *Br J Surg* 1990; **77**: 1241-1246 [PMID: 2253003 DOI: 10.1002/bjs.1800771115]

5 **Kamel IR**, Fishman EK. Recent advances in CT imaging of liver metastases. *Cancer J* 2004; **10**: 104-120 [PMID: 15130270 DOI: 10.1097/00130404-200403000-00006]

6 **Braga L**, Guller U, Semelka RC. Modern hepatic imaging. *Surg Clin North Am* 2004; **84**: 375-400 [PMID: 15062651 DOI: 10.1016/S0039-6109(03)00227-5]

7 **Adams RB**, Aloia TA, Loyer E, Pawlik TM, Taouli B, Vauthey JN. Selection for hepatic resection of colorectal liver metastases: expert consensus statement. *HPB* (Oxford) 2013; **15**: 91-103 [PMID: 23297719 DOI: 10.1111/j.1477-2574.2012.00557.x]

8 **Chen LB**, Tong JL, Song HZ, Zhu H, Wang YC. (18)F-DG PET/CT in detection of recurrence and metastasis of colorectal cancer. *World J Gastroenterol* 2007; **13**: 5025-5029 [PMID: 17854148]

9 **Schmidt GP**, Baur-Melnyk A, Haug A, Utzschneider S, Becker CR, Tiling R, Reiser MF, Hermann KA. Whole-body MRI at 1.5 T and 3 T compared with FDG-PET-CT for the detection of tumour recurrence in patients with colorectal cancer. *Eur Radiol* 2009; **19**: 1366-1378 [PMID: 19190917 DOI: 10.1007/s00330-008-1289-y]

10 **Truant S**, Huglo D, Hebbar M, Ernst O, Steinling M, Pruvot FR. Prospective evaluation of the impact of [18F]fluoro-2-deoxy-D-glucose positron emission tomography of resectable colorectal liver metastases. *Br J Surg* 2005; **92**: 362-369 [PMID: 15672427 DOI: 10.1002/bjs.4843]

11 **Haddad AJ**, Bani Hani M, Pawlik TM, Cunningham SC. Colorectal liver metastases. *Int J Surg Oncol* 2011; **2011**: 285840 [PMID: 22312501 DOI: 10.1155/2011/285840]

12 **Fong Y**, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999; **230**: 309-318; discussion 318-321 [PMID: 10493478 DOI: 10.1097/00000658-199909000-00004]

13 **Nordlinger B**, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, Jaeck D. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Française de Chirurgie. *Cancer* 1996; **77**: 1254-1262 [PMID: 8608500]

14 **Schindl M**, Wigmore SJ, Currie EJ, Laengle F, Garden OJ. Prognostic scoring in colorectal cancer liver metastases: development and validation. *Arch Surg* 2005; **140**: 183-189 [PMID: 15724001 DOI: 10.1001/archsurg.140.2.183]

15 **Iwatsuki S**, Dvorchik I, Madariaga JR, Marsh JW, Dodson F, Bonham AC, Geller DA, Gayowski TJ, Fung JJ, Starzl TE. Hepatic resection for metastatic colorectal adenocarcinoma: a proposal of a prognostic scoring system. *J Am Coll Surg* 1999; **189**: 291-299 [PMID: 10472930 DOI: 10.1016/S1072-7515(99)00089-7]

16 **Choti MA**, Sitzmann JV, Tiburi MF, Sumetchotimetha W, Rangsin R, Schulick RD, Lillemoe KD, Yeo CJ, Cameron JL. Trends in long-term survival following liver resection for hepatic colorectal metastases. *Ann Surg* 2002; **235**: 759-766 [PMID: 12035031 DOI: 10.1097/00000658-200206000-00002]

17 **Abdalla EK**, Vauthey JN, Ellis LM, Ellis V, Pollock R, Broglio KR, Hess K, Curley SA. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg*

2004; **239**: 818-825; discussion 825-827 [PMID: 15166961 DOI: 10.1097/01.sla.0000128305.90650.71]
18 **Charnsangavej C**, Clary B, Fong Y, Grothey A, Pawlik TM, Choti MA. Selection of patients for resection of hepatic colorectal metastases: expert consensus statement. *Ann Surg Oncol* 2006; **13**: 1261-1268 [PMID: 16947009 DOI: 10.1245/s10434-006-9023-y]
19 **Cady B**, Jenkins RL, Steele GD, Lewis WD, Stone MD, McDermott WV, Jessup JM, Bothe A, Lalor P, Lovett EJ, Lavin P, Linehan DC. Surgical margin in hepatic resection for colorectal metastasis: a critical and improvable determinant of outcome. *Ann Surg* 1998; **227**: 566-571 [PMID: 9563547 DOI: 10.1097/00000658-199804000-00019]
20 **Scheele J**, Stang R, Altendorf-Hofmann A, Paul M. Resection of colorectal liver metastases. *World J Surg* 1995; **19**: 59-71 [PMID: 7740812 DOI: 10.1007/BF00316981]
21 **Garden OJ**, Rees M, Poston GJ, Mirza D, Saunders M, Ledermann J, Primrose JN, Parks RW. Guidelines for resection of colorectal cancer liver metastases. *Gut* 2006; **55** Suppl 3: iii1-iii8 [PMID: 16835351 DOI: 10.1136/gut.2006.098053]
22 **Nordlinger B**, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Collette L, Praet M, Bethe U, Van Cutsem E, Scheithauer W, Gruenberger T. 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**: 1007-1016 [PMID: 18358928 DOI: 10.1016/S0140-6736(08)60455-9]
23 **Hillingsø JG**, Wille-Jørgensen P. Staged or simultaneous resection of synchronous liver metastases from colorectal cancer--a systematic review. *Colorectal Dis* 2009; **11**: 3-10 [PMID: 18637099 DOI: 10.1111/j.1463-1318.2008.01625.x]
24 **Bismuth H**, Adam R, Lévi F, Farabos C, Waechter F, Castaing D, Majno P, Engerran L. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Ann Surg* 1996; **224**: 509-520; discussion 520-522 [PMID: 8857855 DOI: 10.1097/00000658-199610000-00009]
25 **Adam R**, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, Giacchetti S, Paule B, Kunstlinger F, Ghémard O, Levi F, Bismuth H. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg* 2004; **240**: 644-657; discussion 657-658 [PMID: 15383792]
26 **Nuzzo G**, Giuliante F, Ardito F, Vellone M, Pozzo C, Cassano A, Giovannini I, Barone C. Liver resection for primarily unresectable colorectal metastases downsized by chemotherapy. *J Gastrointest Surg* 2007; **11**: 318-324 [PMID: 17458605 DOI: 10.1007/s11605-006-0070-2]
27 **Clavien PA**, Selzner N, Morse M, Selzner M, Paulson E. Downstaging of hepatocellular carcinoma and liver metastases from colorectal cancer by selective intra-arterial chemotherapy. *Surgery* 2002; **131**: 433-442 [PMID: 11935134 DOI: 10.1067/msy.2002.122374]
28 **Kemeny NE**, Melendez FD, Capanu M, Paty PB, Fong Y, Schwartz LH, Jarnagin WR, Patel D, D'Angelica M. 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**: 3465-3471 [PMID: 19470932 DOI: 10.1200/JCO.2008.20.1301]
29 **Van Cutsem E**, Nordlinger B, Cervantes A. Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment. *Ann Oncol* 2010; **21** Suppl 5: v93-v97 [PMID: 20555112 DOI: 10.1093/annonc/mdq222]
30 **Ito K**, Govindarajan A, Ito H, Fong Y. Surgical treatment of hepatic colorectal metastasis: evolving role in the setting of improving systemic therapies and ablative treatments in the 21st century. *Cancer J* 2010; **16**: 103-110 [PMID: 20404606 DOI: 10.1097/PPO.0b013e3181d7e8e5]
31 **Schwarz RE**, Berlin JD, Lenz HJ, Nordlinger B, Rubbia-Brandt L, Choti MA. Systemic cytotoxic and biological therapies of colorectal liver metastases: expert consensus statement. *HPB* (Oxford) 2013; **15**: 106-115 [PMID: 23297721 DOI: 10.1111/j.1477-2574.2012.00558.x]
32 **Falcone A**, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, Crinò L, Benedetti G, Evangelista W, Fanchini L, Cortesi E, Picone V, Vitello S, Chiara S, Granetto C, Porcile G, Fioretto L, Orlandini C, Andreuccetti M, Masi G. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol* 2007; **25**: 1670-1676 [PMID: 17470860 DOI: 10.1200/JCO.2006.09.0928]
33 **Seymour MT**, Maughan TS, Ledermann JA, Topham C, James R, Gwyther SJ, Smith DB, Shepherd S, Maraveyas A, Ferry DR, Meade AM, Thompson L, Griffiths GO, Parmar MK, Stephens RJ. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. *Lancet* 2007; **370**: 143-152 [PMID: 17630037 DOI: 10.1016/S0140-6736(07)61087-3]
34 **Koopman M**, Antonini NF, Douma J, Wals J, Honkoop AH, Erdkamp FL, de Jong RS, Rodenburg CJ, Vreugdenhil G, Loosveld OJ, van Bochove A, Sinnige HA, Creemers GJ, Tesselaar ME, Slee PH, Werter MJ, Mol L, Dalesio O, Punt CJ. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. *Lancet* 2007; **370**: 135-142 [PMID: 17630036 DOI: 10.1016/S0140-6736(07)61086-1]
35 **Fernandez FG**, Drebin JA, Linehan DC, Dehdashti F, Siegel BA, Strasberg SM. 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**: 438-447; discussion 447-450 [PMID: 15319715 DOI: 10.1097/01.sla.0000138076.72547.b1]
36 **Kato T**, Yasui K, Hirai T, Kanemitsu Y, Mori T, Sugihara K, Mochizuki H, Yamamoto J. Therapeutic results for hepatic metastasis of colorectal cancer with special reference to effectiveness of hepatectomy: analysis of prognostic factors for 763 cases recorded at 18 institutions. *Dis Colon Rectum* 2003; **46**: S22-S31 [PMID: 14530655]
37 **Minagawa M**, Makuuchi M, Torzilli G, Takayama T, Kawasaki S, Kosuge T, Yamamoto J, Imamura H. Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: long-term results. *Ann Surg* 2000; **231**: 487-499 [PMID: 10749608 DOI: 10.1097/00000658-200004000-00006]
38 **Fong Y**, Blumgart LH, Fortner JG, Brennan MF. Pancreatic or liver resection for malignancy is safe and effective for the elderly. *Ann Surg* 1995; **222**: 426-434; discussion 434-437 [PMID: 7574924]
39 **de Jong MC**, Pulitano C, Ribero D, Strub J, Mentha G, Schulick RD, Choti MA, Aldrighetti L, Capussotti L, Pawlik TM. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. *Ann Surg* 2009; **250**: 440-448 [PMID: 19730175]
40 **de Jong MC**, Mayo SC, Pulitano C, Lanella S, Ribero D, Strub J, Hubert C, Gigot JF, Schulick RD, Choti MA, Aldrighetti L, Mentha G, Capussotti L, Pawlik TM. 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**: 2141-2151 [PMID: 19795176 DOI: 10.1007/s11605-009-1050-0]
41 **Buell JF**, Thomas MT, Rudich S, Marvin M, Nagubandi R, Ravindra KV, Brock G, McMasters KM. Experience with more than 500 minimally invasive hepatic procedures. *Ann Surg* 2008; **248**: 475-486 [PMID: 18791368]

42 **Mala T**, Edwin B, Rosseland AR, Gladhaug I, Fosse E, Mathisen O. Laparoscopic liver resection: experience of 53 procedures at a single center. *J Hepatobiliary Pancreat Surg* 2005; **12**: 298-303 [PMID: 16133696 DOI: 10.1007/s00534-005-0974-3]

43 **Chua TC**, Saxena A, Liauw W, Kokandi A, Morris DL. Systematic review of randomized and nonrandomized trials of the clinical response and outcomes of neoadjuvant systemic chemotherapy for resectable colorectal liver metastases. *Ann Surg Oncol* 2010; **17**: 492-501 [PMID: 19856028 DOI: 10.1245/s10434-009-0781-1]

44 **Adam R**, Pascal G, Castaing D, Azoulay D, Delvart V, Paule B, Levi F, Bismuth H. Tumor progression while on chemotherapy: a contraindication to liver resection for multiple colorectal metastases? *Ann Surg* 2004; **240**: 1052-1061; discussion 1061-1064 [PMID: 15570210 DOI: 10.1097/01.sla.0000145964.08365.01]

45 **Gallagher DJ**, Zheng J, Capanu M, Haviland D, Paty P, Dematteo RP, D'Angelica M, Fong Y, Jarnagin WR, Allen PJ, Kemeny N. Response to neoadjuvant chemotherapy does not predict overall survival for patients with synchronous colorectal hepatic metastases. *Ann Surg Oncol* 2009; **16**: 1844-1851 [PMID: 19224284 DOI: 10.1245/s10434-009-0348-1]

46 **Karoui M**, Penna C, Amin-Hashem M, Mitry E, Benoist S, Franc B, Rougier P, Nordlinger B. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. *Ann Surg* 2006; **243**: 1-7 [PMID: 16371728 DOI: 10.1097/01.sla.0000193603.26265.c3]

47 **Abdalla EK**, Bauer TW, Chun YS, D'Angelica M, Kooby DA, Jarnagin WR. Locoregional surgical and interventional therapies for advanced colorectal cancer liver metastases: expert consensus statements. *HPB* (Oxford) 2013; **15**: 119-130 [PMID: 23297723 DOI: 10.1111/j.1477-2574.2012.00597.x]

48 **Zalinski S**, Abdalla EK, Mahvash A, Vauthey JN. A marking technique for intraoperative localization of small liver metastases before systemic chemotherapy. *Ann Surg Oncol* 2009; **16**: 1208-1211 [PMID: 19214636 DOI: 10.1245/s10434-009-0328-5]

49 **Mitry E**, Fields AL, Bleiberg H, Labianca R, Portier G, Tu D, Nitti D, Torri V, Elias D, O'Callaghan C, Langer B, Martignoni G, Bouché O, Lazorthes F, Van Cutsem E, Bedenne L, Moore MJ, Rougier P. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. *J Clin Oncol* 2008; **26**: 4906-4911 [PMID: 18794541 DOI: 10.1200/JCO.2008.17.3781]

50 **Langer B**, Bleiberg H, Labianca R, Shepherd L, Nitti D, Marsoni S. Fluorouracil (FU) plus l-leucovorin (l-LV) versus observation after potentially curative resection of liver or lung metastases from colorectal cancer (CRC): results of the ENG (EORTC/NCIC CTG/GIVIO) randomized trial. *Proc Am Soc Clin Oncol* 2002; **21**: 592

51 **Portier G**, Elias D, Bouche O, Rougier P, Bosset JF, Saric J, Belghiti J, Piedbois P, Guimbaud R, Nordlinger B, Bugat R, Lazorthes F, Bedenne L. Multicenter randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: FFCD ACHBTH AURC 9002 trial. *J Clin Oncol* 2006; **24**: 4976-4982 [PMID: 17075115 DOI: 10.1200/JCO.2006.06.8353]

52 **Reddy SK**, Zorzi D, Lum YW, Barbas AS, Pawlik TM, Ribero D, Abdalla EK, Choti MA, Kemp C, Vauthey JN, Morse MA, White RR, Clary BM. Timing of multimodality therapy for resectable synchronous colorectal liver metastases: a retrospective multi-institutional analysis. *Ann Surg Oncol* 2009; **16**: 1809-1819 [PMID: 18979139 DOI: 10.1245/s10434-008-0181-y]

53 **Ychou M**, Hohenberger W, Thezenas S, Navarro M, Maurel J, Bokemeyer C, Shacham-Shmueli E, Rivera F, Kwok-Keung Choi C, Santoro A. A randomized phase III study comparing adjuvant 5-fluorouracil/folinic acid with FOLFIRI in patients following complete resection of liver metastases from colorectal cancer. *Ann Oncol* 2009; **20**: 1964-1970 [PMID: 19567451 DOI: 10.1093/annonc/mdp236]

54 **Hurwitz H**, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; **350**: 2335-2342 [PMID: 15175435 DOI: 10.1056/NEJMoa032691]

55 **Normanno N**, Tejpar S, Morgillo F, De Luca A, Van Cutsem E, Ciardiello F. Implications for KRAS status and EGFR-targeted therapies in metastatic CRC. *Nat Rev Clin Oncol* 2009; **6**: 519-527 [PMID: 19636327]

56 **Kabbinavar F**, Hurwitz HI, Fehrenbacher L, Meropol NJ, Novotny WF, Lieberman G, Griffing S, Bergsland E. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. *J Clin Oncol* 2003; **21**: 60-65 [PMID: 12506171]

57 **Jonker DJ**, O'Callaghan CJ, Karapetis CS, Zalcberg JR, Tu D, Au HJ, Berry SR, Krahn M, Price T, Simes RJ, Tebbutt NC, van Hazel G, Wierzbicki R, Langer C, Moore MJ. Cetuximab for the treatment of colorectal cancer. *N Engl J Med* 2007; **357**: 2040-2048 [PMID: 18003960 DOI: 10.1056/NEJMoa071834]

58 **Lucke B**, Breedis C, Woo ZP, Berwick L, Nowell P. Differential growth of blood-borne metastatic tumors in liver and lung (experiments with rabbit V-2 carcinoma). *Am J Pathol* 1951; **27**: 729-730 [PMID: 14846956]

59 **Ackerman NB**. The blood supply of experimental liver metastases. IV. Changes in vascularity with increasing tumor growth. *Surgery* 1974; **75**: 589-596 [PMID: 4840805]

60 **Ensminger WD**. Intrahepatic arterial infusion of chemotherapy: pharmacologic principles. *Semin Oncol* 2002; **29**: 119-125 [PMID: 11951209 DOI: 10.1053/sonc.2002.31679]

61 **Allen PJ**, Stojadinovic A, Ben-Porat L, Gonen M, Kooby D, Blumgart L, Paty P, Fong Y. The management of variant arterial anatomy during hepatic arterial infusion pump placement. *Ann Surg Oncol* 2002; **9**: 875-880 [PMID: 12417509 DOI: 10.1007/BF02557524]

62 **Stratmann SL**. Hepatic artery chemotherapy in the management of colorectal metastases. *Proc* (Bayl Univ Med Cent) 2002; **15**: 376-379 [PMID: 16333468]

63 **Sigurdson ER**, Ridge JA, Kemeny N, Daly JM. Tumor and liver drug uptake following hepatic artery and portal vein infusion. *J Clin Oncol* 1987; **5**: 1836-1840 [PMID: 3681370]

64 **Kemeny N**, Capanu M, D'Angelica M, Jarnagin W, Haviland D, Dematteo R, Fong Y. Phase I trial of adjuvant hepatic arterial infusion (HAI) with floxuridine (FUDR) and dexamethasone plus systemic oxaliplatin, 5-fluorouracil and leucovorin in patients with resected liver metastases from colorectal cancer. *Ann Oncol* 2009; **20**: 1236-1241 [PMID: 19233901 DOI: 10.1093/annonc/mdn769]

65 **Kemeny N**, Seiter K, Conti JA, Cohen A, Bertino JR, Sigurdson ER, Botet J, Chapman D, Mazumdar M, Budd AJ. Hepatic arterial floxuridine and leucovorin for unresectable liver metastases from colorectal carcinoma. New dose schedules and survival update. *Cancer* 1994; **73**: 1134-1142 [PMID: 8313315 DOI: 10.1002/1097-0142(19940215)73:4<1134::AID-CNCR2820730403>3.0.CO;2-V]

66 **Mocellin S**, Pilati P, Lise M, Nitti D. Meta-analysis of hepatic arterial infusion for unresectable liver metastases from colorectal cancer: the end of an era? *J Clin Oncol* 2007; **25**: 5649-5654 [PMID: 18065736 DOI: 10.1200/JCO.2007.12.1764]

67 **Kemeny NE**, Niedzwiecki D, Hollis DR, Lenz HJ, Warren RS, Naughton MJ, Weeks JC, Sigurdson ER, Herndon JE, Zhang C, Mayer RJ. Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481). *J Clin Oncol* 2006; **24**: 1395-1403 [PMID: 16505413 DOI: 10.1200/JCO.2005.03.8166]

68 **Kemeny N**, Gonen M, Sullivan D, Schwartz L, Benedetti F, Saltz L, Stockman J, Fong Y, Jarnagin W, Bertino J, Tong W,

Paty P. Phase I study of hepatic arterial infusion of floxuridine and dexamethasone with systemic irinotecan for unresectable hepatic metastases from colorectal cancer. *J Clin Oncol* 2001; **19**: 2687-2695 [PMID: 11352961]

69 **Kemeny N**, Huang Y, Cohen AM, Shi W, Conti JA, Brennan MF, Bertino JR, Turnbull AD, Sullivan D, Stockman J, Blumgart LH, Fong Y. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 1999; **341**: 2039-2048 [PMID: 10615075 DOI: 10.1056/NEJM199912303412702]

70 **Kennedy AS**, Nutting C, Coldwell D, Gaiser J, Drachenberg C. Pathologic response and microdosimetry of (90)Y microspheres in man: review of four explanted whole livers. *Int J Radiat Oncol Biol Phys* 2004; **60**: 1552-1563 [PMID: 15590187 DOI: 10.1016/j.ijrobp.2004.09.004]

71 **Gulec SA**, Pennington K, Wheeler J, Barot TC, Suthar RR, Hall M, Schwartzentruber D. Yttrium-90 microsphere-selective internal radiation therapy with chemotherapy (chemoSIRT) for colorectal cancer liver metastases: an in vivo double-arm-controlled phase II trial. *Am J Clin Oncol* 2013; **36**: 455-460 [PMID: 22643569 DOI: 10.1097/COC.0b013e3182546c50]

72 **Wasan H**, Kennedy A, Coldwell D, Sangro B, Salem R. Integrating radioembolization with chemotherapy in the treatment paradigm for unresectable colorectal liver metastases. *Am J Clin Oncol* 2012; **35**: 293-301 [PMID: 21278562 DOI: 10.1097/COC.0b013e3182005747]

73 **Gray B**, Van Hazel G, Hope M, Burton M, Moroz P, Anderson J, Gebski V. Randomised trial of SIR-Spheres plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. *Ann Oncol* 2001; **12**: 1711-1720 [PMID: 11843249 DOI: 10.1023/A:1013569329846]

74 **Cosimelli M**, Golfieri R, Cagol PP, Carpanese L, Sciuto R, Maini CL, Mancini R, Sperduti I, Pizzi G, Diodoro MG, Perrone M, Giampalma E, Angelelli B, Fiore F, Lastoria S, Bacchetti S, Gasperini D, Geatti O, Izzo F. Multi-centre phase II clinical trial of yttrium-90 resin microspheres alone in unresectable, chemotherapy refractory colorectal liver metastases. *Br J Cancer* 2010; **103**: 324-331 [PMID: 20628388 DOI: 10.1038/sj.bjc.6605770]

75 **Lewandowski RJ**, Thurston KG, Goin JE, Wong CY, Gates VL, Van Buskirk M, Geschwind JF, Salem R. 90Y microsphere (TheraSphere) treatment for unresectable colorectal cancer metastases of the liver: response to treatment at targeted doses of 135-150 Gy as measured by [18F]fluorodeoxyglucose positron emission tomography and computed tomographic imaging. *J Vasc Interv Radiol* 2005; **16**: 1641-1651 [PMID: 16371530 DOI: 10.1097/01.RVI.0000179815.44868.66]

76 **Richardson AJ**, Laurence JM, Lam VW. Transarterial chemoembolization with irinotecan beads in the treatment of colorectal liver metastases: systematic review. *J Vasc Interv Radiol* 2013; **24**: 1209-1217 [PMID: 23885916 DOI: 10.1016/j.jvir.2013.05.055]

77 **Fiorentini G**, Aliberti C, Tilli M, Mulazzani L, Graziano F, Giordani P, Mambrini A, Montagnani F, Alessandroni P, Catalano V, Coschiera P. 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**: 1387-1395 [PMID: 22493375]

78 **Martin RC**, Scoggins CR, Tomalty D, Schreeder M, Metzger T, Tatum C, Sharma V. Irinotecan drug-eluting beads in the treatment of chemo-naive unresectable colorectal liver metastasis with concomitant systemic fluorouracil and oxaliplatin: results of pharmacokinetics and phase I trial. *J Gastrointest Surg* 2012; **16**: 1531-1538 [PMID: 22528576 DOI: 10.1007/s11605-012-1892-8]

79 **Fiorentini G**, Poddie DB, Cantore M, Giovanis P, Guadagni S, De Giorgi U, Cariello A, Dazzi C, Turci D. Locoregional therapy for liver metastases from colorectal cancer: the possibilities of intraarterial chemotherapy, and new hepatic-directed modalities. *Hepatogastroenterology* 2001; **48**: 305-312 [PMID: 11379296]

80 **Bower M**, Metzger T, Robbins K, Tomalty D, Válek V, Boudný J, Andrasina T, Tatum C, Martin RC. Surgical downstaging and neo-adjuvant therapy in metastatic colorectal carcinoma with irinotecan drug-eluting beads: a multi-institutional study. *HPB* (Oxford) 2010; **12**: 31-36 [PMID: 20495642 DOI: 10.1111/j.1477-2574.2009.00117.x]

81 **Thirion P**, Michiels S, Pignon JP, Buyse M, Braud AC, Carlson RW, O'Connell M, Sargent P, Piedbois P. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: an updated meta-analysis. *J Clin Oncol* 2004; **22**: 3766-3775 [PMID: 15365073 DOI: 10.1200/JCO.2004.03.104]

82 **Seifert JK**, Junginger T, Morris DL. A collective review of the world literature on hepatic cryotherapy. *J R Coll Surg Edinb* 1998; **43**: 141-154 [PMID: 9654872]

83 **Ng KM**, Chua TC, Saxena A, Zhao J, Chu F, Morris DL. Two decades of experience with hepatic cryotherapy for advanced colorectal metastases. *Ann Surg Oncol* 2012; **19**: 1276-1283 [PMID: 21913018 DOI: 10.1245/s10434-011-2025-4]

84 **Seifert JK**, Springer A, Baier P, Junginger T. Liver resection or cryotherapy for colorectal liver metastases: a prospective case control study. *Int J Colorectal Dis* 2005; **20**: 507-520 [PMID: 15973545 DOI: 10.1007/s00384-004-0723-0]

85 **Rivoire M**, De Cian F, Meeus P, Négrier S, Sebban H, Kaemmerlen P. Combination of neoadjuvant chemotherapy with cryotherapy and surgical resection for the treatment of unresectable liver metastases from colorectal carcinoma. *Cancer* 2002; **95**: 2283-2292 [PMID: 12436433 DOI: 10.1002/cncr.10973]

86 **Allen PJ**, D'Angelica M, Hodyl C, Lee J, You YJ, Fong Y. The effects of hepatic cryosurgery on tumor growth in the liver. *J Surg Res* 1998; **77**: 132-136 [PMID: 9733599 DOI: 10.1006/jsre.1998.5365]

87 **Bhardwaj N**, Strickland AD, Ahmad F, Atanesyan L, West K, Lloyd DM. A comparative histological evaluation of the ablations produced by microwave, cryotherapy and radiofrequency in the liver. *Pathology* 2009; **41**: 168-172 [PMID: 19152189 DOI: 10.1080/00313020802579292]

88 **Seifert JK**, Morris DL. World survey on the complications of hepatic and prostate cryotherapy. *World J Surg* 1999; **23**: 109-113; discussion 113-114 [PMID: 9880417 DOI: 10.1007/PL00013173]

89 **Primrose JN**. Treatment of colorectal metastases: surgery, cryotherapy, or radiofrequency ablation. *Gut* 2002; **50**: 1-5 [PMID: 11772955 DOI: 10.1136/gut.50.1.1]

90 **Rocha FG**, D'Angelica M. Treatment of liver colorectal metastases: role of laparoscopy, radiofrequency ablation, and microwave coagulation. *J Surg Oncol* 2010; **102**: 968-974 [PMID: 21166000 DOI: 10.1002/jso.21720]

91 **Hompes D**, Prevoo W, Ruers T. Radiofrequency ablation as a treatment tool for liver metastases of colorectal origin. *Cancer Imaging* 2011; **11**: 23-30 [PMID: 21435988]

92 **Stang A**, Fischbach R, Teichmann W, Bokemeyer C, Braumann D. A systematic review on the clinical benefit and role of radiofrequency ablation as treatment of colorectal liver metastases. *Eur J Cancer* 2009; **45**: 1748-1756 [PMID: 19356924 DOI: 10.1016/j.ejca.2009.03.012]

93 **Wong SL**, Mangu PB, Choti MA, Crocenzi TS, Dodd GD, Dorfman GS, Eng C, Fong Y, Giusti AF, Lu D, Marsland TA, Michelson R, Poston GJ, Schrag D, Seidenfeld J, Benson AB. American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. *J Clin Oncol* 2010; **28**: 493-508 [PMID: 19841322 DOI: 10.1200/JCO.2009.23.4450]

94 **Jiang HC**, Liu LX, Piao DX, Xu J, Zheng M, Zhu AL, Qi SY, Zhang WH, Wu LF. Clinical short-term results of radiofrequency ablation in liver cancers. *World J Gastroenterol* 2002; **8**: 624-630 [PMID: 12174368]

95 **Mulier S**, Mulier P, Ni Y, Miao Y, Dupas B, Marchal G, De Wever I, Michel L. Complications of radiofrequency coagulation of liver tumours. *Br J Surg* 2002; **89**: 1206-1222 [PMID: 12296886 DOI: 10.1046/j.1365-2168.2002.02168.x]
96 **Pathak S**, Jones R, Tang JM, Parmar C, Fenwick S, Malik H, Poston G. Ablative therapies for colorectal liver metastases: a systematic review. *Colorectal Dis* 2011; **13**: e252-e265 [PMID: 21689362 DOI: 10.1111/j.1463-1318.2011.02695.x]
97 **Iannitti DA**, Martin RC, Simon CJ, Hope WW, Newcomb WL, McMasters KM, Dupuy D. Hepatic tumor ablation with clustered microwave antennae: the US Phase II trial. *HPB* (Oxford) 2007; **9**: 120-124 [PMID: 18333126 DOI: 10.1080/13651820701222677]
98 **Martin RC**, Scoggins CR, McMasters KM. Safety and efficacy of microwave ablation of hepatic tumors: a prospective review of a 5-year experience. *Ann Surg Oncol* 2010; **17**: 171-178 [PMID: 19707829 DOI: 10.1245/s10434-009-0686-z]
99 **Wright AS**, Sampson LA, Warner TF, Mahvi DM, Lee FT. Radiofrequency versus microwave ablation in a hepatic porcine model. *Radiology* 2005; **236**: 132-139 [PMID: 15987969 DOI: 10.1148/radiol.2361031249]
100 **Shibata T**, Niinobu T, Ogata N. Comparison of the effects of in-vivo thermal ablation of pig liver by microwave and radiofrequency coagulation. *J Hepatobiliary Pancreat Surg* 2000; **7**: 592-598 [PMID: 11180892 DOI: 10.1007/s005340070009]
101 **Chang DT**, Swaminath A, Kozak M, Weintraub J, Koong AC, Kim J, Dinniwell R, Brierley J, Kavanagh BD, Dawson LA, Schefter TE. Stereotactic body radiotherapy for colorectal liver metastases: a pooled analysis. *Cancer* 2011; **117**: 4060-4069 [PMID: 21432842 DOI: 10.1002/cncr.25997]
102 **Baumann P**, Nyman J, Hoyer M, Wennberg B, Gagliardi G, Lax I, Drugge N, Ekberg L, Friesland S, Johansson KA, Lund JA, Morhed E, Nilsson K, Levin N, Paludan M, Sederholm C, Traberg A, Wittgren L, Lewensohn R. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. *J Clin Oncol* 2009; **27**: 3290-3296 [PMID: 19414667 DOI: 10.1200/JCO.2008.21.5681]
103 **Timmerman R**, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, Fakiris A, Bezjak A, Videtic G, Johnstone D, Fowler J, Gore E, Choy H. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010; **303**: 1070-1076 [PMID: 20233825 DOI: 10.1001/jama.2010.261]
104 **van der Pool AE**, Méndez Romero A, Wunderink W, Heijmen BJ, Levendag PC, Verhoef C, Ijzermans JN. Stereotactic body radiation therapy for colorectal liver metastases. *Br J Surg* 2010; **97**: 377-382 [PMID: 20095016 DOI: 10.1002/bjs.6895]

P- Reviewer: Higuera-de la Tijera MF, Ogura T, Tan CH
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Liu SQ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com