HHS Public Access

Author manuscript

J Vasc Interv Radiol. Author manuscript; available in PMC 2015 March 07.

Published in final edited form as:

J Vasc Interv Radiol. 2012 February ; 23(2): 153–163. doi:10.1016/j.jvir.2011.12.003.

Development of a Research Agenda for the Management of Metastatic Colorectal Cancer: Proceedings from a Multidisciplinary Research Consensus Panel

Bertrand Janne d'Othée, MD, MPH, **Constantinos T. Sofocleous, MD, PhD**, **Nader Hanna, MD**, **Robert J. Lewandowski, MD**, **Michael C. Soulen, MD**, **Jean-Nicolas Vauthey, MD**, **Steven J. Cohen, MD**, **Alan P. Venook, MD**, **Matthew S. Johnson, MD**, **Andrew S. Kennedy, MD**, **Ravi Murthy, MD**, **Jean-Francois Geschwind, MD**, and **Stephen T. Kee, MD**

Department of Diagnostic Radiology and Nuclear Medicine, Division of Vascular and Interventional Radiology (B.J.d.O.), and Department of Surgery, Division of Surgical Oncology (N.H.), University of Maryland School of Medicine; Department of Radiology and Radiological Science, Division of Vascular and Interventional Radiology (J.F.G.), Johns Hopkins University School of Medicine, Baltimore, Maryland; Department of Radiology, Division of Interventional Radiology (C.T.S.), Memorial Sloan-Kettering Cancer Center, New York, New York; Department of Radiology (R.J.L.), Northwestern University Feinberg School of Medicine and Northwestern Memorial Hospital, Chicago, Illinois; Department of Radiology (M.C.S.), Hospital of the University of Pennsylvania; Department of Medical Oncology, Division of Gastrointestinal Medical Oncology (S.J.C.), Fox Chase Cancer Center Partners, Philadelphia, Pennsylvania; Department of Diagnostic Radiology (R.M.) and Liver Service (J.N.V.), M. D. Anderson Cancer Center, University of Texas Medical School, Houston; Department of Medicine, Division of Medical Oncology (A.P.V.), University of California, San Francisco, San Francisco; Department of Radiological Sciences, Division of Interventional Radiology (S.T.K.), Ronald Reagan University of California, Los Angeles, Medical Center, Los Angeles, California; Department of Radiology and Imaging Sciences (M.S.J.), Indiana University School of Medicine, Indianapolis, Indiana; and Cancer Centers of North Carolina (A.S.K.), North Carolina State University, Raleigh, North Carolina

INTRODUCTION

Colorectal cancer (CRC), the second leading cause of cancer death in the United States, occurs in an estimated more than 145,000 patients annually, with almost 50,000 deaths each year. Metastatic liver disease is the cause of death in the majority of them (1,2). Liver-only metastases affect up to one half of patients with CRC (1,2), with approximately 15% (range, 8%–26%) presenting synchronously (3,4) and an additional 15% found metachronously during the next 5 years (3). Colorectal liver metastases (CLMs) are resectable in 20%–25%

Address correspondence to B.J.d.O., Department of Diagnostic Radiology and Nuclear Medicine, Division of Vascular and Interventional Radiology, University of Maryland School of Medicine, 22 S. Greene St., N2W74, Baltimore, MD 21201; bjannedothee@umm.edu.

None of the other authors have identified a conflict of interest.

of patients only; some of the remaining 75%–80% may benefit from "downsizing" therapy, which can result in 10%–20% more patients becoming resectable. Overall survival rates in patients with either primarily or secondarily resectable CLMs can be as high as 58% at 5 years and 15% at 10 years (5,6). Current front-line treatments available to improve downsizing and resectability include systemic therapies (chemotherapy with or without bevacizumab or cetuximab) and pre-operative portal vein embolization (PVE). Other approaches include local ablation therapies, regional intraarterial therapies with embolization (transcatheter arterial chemoembolization, or radio-embolization by selective internal radiation therapy with Yttrium 90-loaded microspheres) or infusion (ie, hepatic arterial infusion [HAI] pump chemotherapy), and external beam radiation therapy (RT). The role of these liver-targeted therapies to promote conversion from unresectable to resectable liver disease remains an evaluation in progress. For the majority of patients with unresectable CRC liver metastases, standard of care is first- and second-line triplet chemotherapy, which is associated with a median survival of 18–24 months (7–10). Multiple single-institution retrospective reports suggest the potential for improvement in survival time by the addition of liver-directed therapies such as chemoembolization, HAI, or radioembolization. This has not been prospectively evaluated in controlled trials, but could potentially represent a major development in Interventional Oncology (IO). The Society of Interventional Radiology (SIR) Foundation has identified the management of metastatic CRC (mCRC) as an emerging inter-ventional radiologic research priority and convened a Research Consensus Panel (RCP) Meeting on October 3, 2011 to establish a prioritized research agenda. This article reports the proceedings from this meeting.

METHODS

Panel Membership

In April 2011, the SIR Foundation sent to the SIR membership an invitation to submit applications to lead the RCP Meeting. A lead investigator was selected, who invited, in cooperation with the SIR Foundation, (i) a multidisciplinary group of expert panelists, (ii) representatives from governmental agencies, and (iii) representatives from industries involved in the IO field. The 13 expert panelists included eight interventional radiologists, two medical oncologists, two surgical oncologists, and one radiation oncologist, all with demonstrated relevant experience. Government agencies included the Food and Drug Administration (FDA; four representatives from the Center for Devices and Radiological Health and one from the Center for Drug Evaluation and Research) and the Agency for Healthcare Research and Quality (AHRQ; one representative from the Center for Outcomes and Evidence). Industry representatives came from major companies involved in the production and/or distribution in the United States of products for local or regional liver-directed therapies.

Agenda Methodology

The stated objective of the RCP was to define a prioritized research agenda for the management of mCRC, including topics amenable to basic science/technology research, pilot clinical research, and multicenter clinical trials. The process involved several steps. First, each panelist gave a 10-minute presentation on an assigned topic in their field of

expertise providing an updated review of current knowledge on the outcomes of relevant therapies, using the AHRQ classification of levels of evidence (Table 1) (11). Panelists were also asked to include in their presentations descriptions of gaps in the current knowledge base, and recommendations for basic science and clinical research questions or projects that need further study. Specifically, panelists were asked to (i) define the most important clinical questions that could realistically be answered through pivotal multi-institutional clinical trials or registries, (ii) describe the most promising future directions that merit preclinical or early clinical exploration in the management of mCRC, and (iii) outline the critical alliances that must be developed to advance the prioritized research and how the SIR Foundation can best support these initiatives. A total of 12 presentations were given (11 individual and one joint). Afterwards, a round-robin discussion was held to examine important research questions, potential opportunities for future research studies, and consolidate similar or redundant ideas into succinct titles of research projects that deserved prioritization. Thereafter, invited comments from government and industry representatives were heard. This step resulted in a consolidated list of research projects being voted on anonymously by each expert panelist: panelists were asked to rank from 1 (high priority score) to 5 (low priority) the five top IO priority topics. Government and industry representatives did not vote. Panelists' scores were then added and topics were sorted by order of decreasing priority (increasing score) and further commented on. The top-priority topics (ie, those with the lowest scores) were selected as a basis for further study design. Applications in these areas of research are eligible for consideration for the SIR Foundation Funding Source Development Grant.

Panel Presentations

Natural history of, and National Comprehensive Cancer Network guidelines for, CRC liver metastases—The natural history of liver metastases from CRC differs on the basis of disease distribution, which reflects the presence of three distinct patient populations. Studies from the 1980s (12) demonstrated that, left untreated, patients with a solitary CLM, have survival rates of approximately 70% at 1 year and 45% at 2 years. These patients have better outcomes than those with multiple unilobar CLMs (65% survival at 1 y and 30% at 2 y) and those with multiple bilobar CLMs (40% survival at 1 y and 15% at 2 y). Survival rates decrease to lower than 5% at 3 years in the latter two groups and at 4.5 years in the former. In 2011, almost 30 years later, survival rates have dramatically improved to more than 60% at 2 years and approximately 35% at 5 years.

This improvement is attributed to the availability of numerous new chemotherapeutics and biologic agents and improved imaging and surgical techniques. The indications for surgery have changed as more impact is anticipated from these other treatments, resulting in an increase in the number of patients deemed potentially curable.

Accordingly, current Guidelines from the National Comprehensive Cancer Network (NCCN) (1,2) emphasize chemotherapeutic agents and put less emphasis on interventional technologies. Mainstream systemic therapies include systemic folinic acid/5-fluorouracil/oxaliplatin, folinic acid/5-fluorouracil/irinotecan (FOLFIRI), capecitabine plus oxaliplatin, and other regimens, and multiple combinations with the antivascular endothelial growth

factor receptor agent bevacizumab or, in *KRAS* wild-type patients, one of the epidermal growth factor receptor inhibitors cetuximab or panitumumab. Few IO therapies are recommended in the NCCN Guidelines and, when mentioned, they are supported by level 3 evidence only (ie, based on any level of evidence, there is major NCCN disagreement that the intervention is appropriate). They include (i) PVE before surgical resection; (ii) local ablation therapies, alone or in conjunction with surgical resection, when all disease foci appear treatable; and (iii) intraarterial hepatic embolization in chemotherapy-resistant or chemotherapy-refractory patients with liver only or liver-dominant disease.

Intraarterial hepatic infusion chemotherapy with or without systemic chemotherapy is also an available option in a few experienced centers (level 2B evidence), and is included mostly in footnotes of the NCCN Guidelines. Radioembolization is not included in these Guidelines. These gaps reflect an absence of well-done randomized studies with IO treatments as well as the belief that CRC, is for the most part, a systemic disease. Although it will be difficult to change this paradigm, well-done randomized studies testing the utility of locoregional therapies need to be conducted to establish the relevance of interventional therapies.

Surgical resectability and role of PVE—The major risk factor of perioperative morbidity, liver insufficiency, and mortality from partial hepatectomy is insufficient volume/function of the liver remnant. The current definition of resectability is based on the volume of the future liver remnant (FLR), which can ensure adequate liver function after major resection (13). Postoperative liver function is better evaluated by determining the volume of the FLR than the use of refined biochemical tests, liver biopsy, or the indocyanine green clearance test (14). In patients who are candidates for major resection, PVE is used to increase the size of the FLR by redirecting the portal venous flow to cause hypertrophy of the nonembolized parenchyma (typically the left hepatic lobe), thereby increasing the number of potential resection candidates. The liver remnant after partial hepatectomy should be at least 20% of the total liver volume in normal livers (15–17), 30% in cases of previous chemotherapy (18–21), and 40% in cases of diffuse liver disease or cirrhosis (19,22). Long-term survival rates of CLM have been shown to be equivalent regardless of whether PVE had been performed (5-y survival rates of 34%–44% with PVE vs 37%–53% without) (16,19,23). Although PVE is supported only by level II-2 evidence, its adoption is increasing worldwide and the literature on this topic is growing accordingly. To standardize computed tomographic (CT) volumetry, a standardized FLR volume has been introduced (14), which is the ratio of the FLR to the total estimated liver volume (calculated based on body weight and body surface area). This ratio allows uniform comparison of FLR volume before resection with or without PVE. Variability in the technical performance of PVE remains large, with no proven superiority of any embolic agent.

Modern surgical approaches to increase resectability include the two-stage hepatectomy and the reverse approach, whereby the liver secondary tumors are resected before the colorectal primary tumor. Two-stage hepatectomy is a sequential approach dedicated to patients with multiple, bilobar CLMs that cannot be resected in a single procedure. It generally combines limited resection of lesions located in the FLR during the first stage followed 2–3 months

later by second-stage major hepatic resection (usually right or extended right hepatectomy). A PVE may be included in this strategy, and it is performed between the two stages.

The classical approach to synchronous CLM includes resection of the primary bowel tumor followed by resection of the CLM at a second operation. The main concern with this approach is the delay in treatment of the CLM. A second strategy combines the resection of the CLM and the primary tumor at the same operation, avoiding delayed treatment of CLM. This combined approach can only be offered in selected patients with synchronous CLM (24) as the risk of postoperative complications increases when associated with major liver resection (25). An alternate option in patients without an obstructive primary CRC is the reverse approach, with resection of the liver first followed by resection of the primary tumor during a second procedure (26).

Prediction of outcomes after surgical resection—Until recently a risk score based on clinical criteria (carcinoembryonic antigen level, lymph node status of primary tumor, disease-free interval between resection of primary tumor and metastasis, tumor size, number of metastases) was used to predict outcome after hepatic metastasectomy (27). Pathologic response, defined as the ratio of viable tumor cells to the total tumor surface area, is a novel alternate predictor of survival after resection of CLM (28). Response evaluation criteria in solid tumors (RECIST) do not accurately predict pathologic response or survival following resection of CLM (29). In as many as 50% of patients receiving combined chemotherapy (irinotecan and oxaliplatin) and bevacizumab, CLMs undergo morphologic changes and show a cyst-like appearance with a sharp tumor/liver interface and complete resolution of peripheral rim enhancement, if initially present. This optimal morphologic radiologic response correlates with pathologic response and is predictive of survival in medical and surgical patients with CLM (29).

Surgical outcomes of CRC hepatic metastasectomy—Surgical resection of all metastases remains the only option that enables prolonged survival, with 5-year survival rates up to 50% or greater (30), whether used alone or in conjunction with local ablation and/or PVE. In patients with resectable CLM, only one randomized study that used modern chemotherapy (oxaliplatin) suggested a benefit from preoperative chemotherapy (25% reduction in recurrence rate at 3 y) (31,32). A variety of chemotherapeutic regimens allows conversion to resectability and resections with tumor-free margins (ie, R0) in 15%–33% of patients, with 5-year survival rates of 30%–35%. As a result of its associated worsened prognosis, the presence of peritoneal carcinomatosis is a contraindication to hepatic metastasectomy, regardless of whether CLMs are resectable. In case of resectable CLMs, the presence of particular extrahepatic disease (eg, lung metastases or portal lymphadenopathy) does not in itself contraindicate surgical resection. In unresectable CLM, however, only patients with liver-only disease may eventually qualify for surgery. In patients with bilateral CLMs, a single-center review (33) from a prospectively maintained database of patients undergoing hepatic resection over an 11-year period (440 patients) showed the use of more parenchymal-sparing surgery (eg, wedge resections and fewer segments resected) instead of major, large hepatectomies is associated with improved mortality, shorter hospital stay and decreased blood loss without change in oncologic outcome (33).

An international registry of patients who underwent operative treatment for CLM (34) has shown overall survival is 42% at 5 years and 26% at 10 years after resection (medial survival: 46 mo) (34). After first hepatectomy for CLMs, the 60-day operative mortality rate is less than 3%. Variables independently associated with poor prognosis include the presence of more than three metastases, bilobar metastases, and largest metastasis size greater than 5 cm. Preoperative systemic chemotherapy does not benefit patients with solitary CLM (32), but is associated with improved survival in patients with greater than five metastases (5-y overall survival rates, 22% vs 12% without chemotherapy) (34). Although neoadjuvant chemotherapy may be mandated in patients presenting with unresectable disease, it may be avoided in many resectable patients. These data confirm the prognostic importance of intrahepatic tumor burden, and indicate that the ability of preoperative chemotherapy to improve survival is limited to patients with multiple (ie, more than five) metastases (34).

Outcomes of percutaneous ablative therapies for liver metastases of CRC— The safety and effectiveness of local thermal ablation techniques has been demonstrated in several clinical series since the late 1990s, mostly single-institution retrospective studies of radiofrequency (RF) ablation including selected nonsurgical cases in patients with limited disease volume (Tables 2, 3) (35–49). Despite the inclusion of nonsurgical cases and a relatively lower level of local control, outcomes after percutaneous ablation compared favorably to those after surgical resection (5-y overall survival in the 17%–37% range; AHRQ level II-2 evidence) (35–49). Although difficult to implement, there is a definite need for randomized controlled trials comparing percutaneous ablation versus surgery in selected patients with small size and number of CLMs that can be ablated with appropriate margins. Key factors contributing to CLM ablation success include small size (< 3 cm), location away from major vessels, and achieving clear margins (ie, A0) during local ablation (similar to the goal of reaching R0 tumor-free margins during surgical metastasectomy), with most reported rates of local recurrence in the 12%–39% range for CLMs smaller than 3 cm (50–52).

Significant improvements in our understanding of local ablation techniques and effects have been made since the late 1990s. Examination of tissue collected from the ablation electrodes can identify viable tumor cells that highly predict local failure and shorter progression free survival (53). These studies set the grounds for further investigations to improve ablation technique, which translates into better oncologic outcomes. Also, intravenous injection of liposomal doxorubicin is known to enhance the ablation zone and needs further attention (54,55). Finally, the effects of local ablation on the immune system and the development of tumor specific immunity are being studied, opening a whole different field of application of local ablation in the treatment of patients with advanced metastatic disease (56–58). Further studies are warranted to better understand the effect of ablation on the immune system and potential benefits of this interaction specifically for mCRC patients.

Role of HAI chemotherapy for CLMs—HAI improves oncologic outcomes as a second line treatment for CLMs and as an adjuvant therapy after partial hepatectomy. It is typically combined with systemic intravenous chemotherapy rather than given alone. Different

regimens are used for HAI chemotherapy, with response rates in the 64%–85% range and 1-year survival rates between 82% and 87% (in contrast to systemic chemotherapy alone, which has response rates in the 11%–35% range and 1-y survival rates in the 40%–55% range). The regimen with the highest response rate (85%) and highest 1-year survival rate (87%) combines fluorodeoxyuridine and dexamethasone HAI with intravenous systemic chemotherapy using oxaliplatin and irinotecan (CPT-11). HAI with combined systemic therapy has better outcomes in chemotherapy-naive patients, in terms of response rates (100% vs 85% in patients who had previous systemic chemotherapy), subsequent surgical resection rates (57% vs 38%), and median survival time (50 mo vs 35 mo) (59). Four comparisons between HAI and systemic chemotherapy combined versus chemotherapy alone have all shown improved survival at 2 and 5 years (58–62). Disease-free survival and hepatic disease-free survival were both superior with HAI and systemic chemotherapy combined in three of these four comparisons. When HAI is used after resection, a large series (612 patients) also showed significantly improved survival (median: 82 mo vs 41 mo in the non-HAI group) (5). This conclusion is confirmed by two other studies (63,64). The addition of bevacizumab has added biliary toxicity without any clinical benefit (65). Despite these good results, the use of HAI remains limited to very few centers in the United States (66,67).

Outcomes of chemoembolization of liver metastases of CRC—As metastasectomy (with or without preoperative chemotherapy) is the first-line treatment for resectable metastases, the role of locoregional IO therapies is focused on unresectable CLMs in liver-dominant disease and when performance status and laboratory values are acceptable. When CLMs are not liver-dominant or if embolization is contraindicated, systemic chemotherapy is chosen, which may in successful cases, make CLMs again candidates for locoregional IO therapies. CLM smaller than 3 cm qualify for local ablation, whereas those between 3 and 6 cm may be treated by combined ablation and embolization; lesions larger than 6 cm are approached by combined embolization and systemic therapy. Techniques of intraarterial embolization therapy are not standardized, including bland embolization and chemoembolization (with one or several drugs), and various embolic agents and sizes.

Unresectable CLMs have 1- and 2-year survival rates of 55% and 33%, respectively, with current systemic therapies. With conventional chemoembolization, four major trials (68–71) showed disease control (ie, partial response and stable disease) rates of approximately 63% in three of these four studies (Table 4). Median survival time was 24–38 months after CLM onset, or 9–14 months from first chemoembolization. Although mitomycin C is often included in the drug regimen for conventional chemoembolization, little difference in outcomes is seen when adding other drugs (71).

A novel platform for chemoembolization uses drug-eluting beads loaded with irinotecan (DEBIRI). Complete drug loading on the microspheres can be achieved in 60–120 minutes. Limited clinical outcome data are available so far. An international registry (72) reported collective experience in 55 patients (86% lobar infusions; 30% with concurrent systemic chemotherapy) with response rates of 66% at 6 months and 75% at 12 months, median overall survival time of 19 months, and median progression-free survival time of 11 months. An Italian randomized trial of chemotherapy-refractory, liver-only mCRCs compared

DEBIRI against systemic FOLFIRI; overall and progression-free survival rates were significantly better in the DEBIRI arm, but both arms included additional systemic chemotherapies (73). In conclusion, intraarterial therapies provide disease control in the majority of patients with liver-dominant mCRC, and, retrospectively, survival exceeds expectations for systemic therapy alone. A major hurdle in evaluating the merits of any intraarterial therapy stems from the routine integration of multiple therapeutic modalities (eg, embolization, systemic chemotherapy, RF ablation, ^{90}Y) in the same patients (ie, customized care), making standardization for trials difficult. Another hurdle is the difficulty enrolling patients who are at the early stage of first- or second-line chemotherapy, as this standard of care is routinely provided in the community in the outpatient setting before referral to a cancer center. Although the prospective evaluation of integration strategies is difficult, it is critical to better understand outcomes.

Outcomes of radioembolization of liver metastases of CRC—The safety/efficacy of radioembolization with ^{90}Y selective internal RT in the salvage setting for unresectable mCRC (Table 5) has been established in multiple series of between 27 and 208 patients, with median survival duration between 7.9 and 14.5 months (levels II-1 and II-2 evidence) (74–79). These trials show clear benefits from ^{90}Y combined with systemic chemotherapy compared with systemic therapy alone (improved survival and time to progression [TTP]) (80) or HAI alone (improved TTP) (81). Toxicity includes constitutional (15%–71%) and gastrointestinal disturbances (1%–7%), and radiation induced liver disease (RILD; 0%–2%).

As many chemotherapeutic agents are radiation-sensitizers, they may have a synergistic effect when combined with local delivery of high-dose radiation. Similar to existing chemoradiation protocols, the role of radioembolization as part of first or second line treatment for unresectable mCRC is supported by studies discerning the potential of combining chemotherapy with radioembolization within a short time frame (Table 6) in series of 19–74 patients (levels I, II-1 and II-2 evidence) (77,80–86). Compared with systemic therapy alone, these trials show benefit from radioembolization, although improvements are seen along variable dimensions across studies: some trials showed improvement in TTP and time to local progression (82), others in progression-free survival and overall survival (85).

There may be potential indications for a combined PVE and radioembolization strategy including adjuvant therapy (after PVE; survival benefit in unresectable patients), neoadjuvant therapy (before PVE; increased number of candidates for PVE), and salvage therapy (after PVE; no other options). Potential issues in studies include the variability in subjects enrolled (eg, which therapies they have undergone already), in CT volumetry technique, and in PVE technique.

Outcomes of external beam RI of unresectable CLM—RILD, initially mislabeled as "radiation hepatitis" (87), is caused by central vein occlusion, not an inflammatory response, leading to the loss of a lobule (88). Classic RILD could be observed in patients 2 weeks to 90 days after whole-liver radiation to 30 Gy or more in 2 weeks. Landmark studies at the University of Michigan Radiation Oncology department showed that the significant volume effect of the liver's parallel architecture (ie, lobules) could be exploited by using dose–

volume histograms and partial liver radiation treatment (89,90), eventually allowing delivery of fractionated doses to tumors of at least 90 Gy.

Before the availability of CT scans and three-dimensional (3D) radiation treatment planning, conventional whole-liver external-beam RT was used to palliate pain from expanding liver tumors, typically at the end of a patient's life, with pain relief in 80% of patients (complete in 54%) and 30% pain-free at 6 months. In 49% of responders, liver function test results improved (91).

Conformal (ie, 3D) RT allows greater targeting precision, visualization of tumors, and protection of normal tissues with immobilization techniques and CT scans providing 3D data-sets. To further decrease the incidence of RILD, Robertson et al used hepatic artery fluorodeoxyuridine for radiosensitization in primary and metastatic liver tumors. A total of 22 patients with mCRC were treated with a 50% objective response rate and 50% stable disease rate; a median survival time of 20 months, and no RILD (92). A larger phase II trial based on this protocol reported significantly improved overall survival and progression-free survival in 47 patients with mCRC (128 patients total) when the tumor dose was 60 Gy or higher (92). Dawson et al, also using the same protocol, treated 43 patients, most with mCRC, and reported a 68% response rate, with survival rates of 62% at 1 year and 14% at 2 years (89). Intensity-modulated RT, a more sophisticated form of 3D RT, has as yet not been successfully adapted to liver RT for several reasons, most notably abdominal organ motion (93).

Stereotactic body RT allows highly conformable radiation fields, but delivers one to five total fractions of external-beam RT over a period of 1–2 weeks by using specialized immobilization techniques, respiratory gating, limited respiratory motion via abdominal compression, and implanted fiducial markers in the liver to enhance targeting and imaging during treatment. Three recent reports of stereotactic body RT, including its use in CLM, show promising results for tumor control and low risk of toxicity when the lesions are small and number three or fewer per patient. The phase I/II study of Herfarth et al in 37 patients (60 tumors, of which 30 patients had mCRC) showed a local control rate of 81% at 18 months (94). Rusthoven et al reported a six-institution phase I/II study of 47 patients with liver metastases (15 with mCRC) and showed a local control rate of 92% at 2 years and no RILD (95). Lee et al reported a single-institution phase I study with a local control rate of 71% at 1 year in 40 patients with mCRC (68 patients total) (96).

Ongoing trials for patients with CRC liver metastases—As of the date of the RCP Meeting, there were 528 trials on mCRC listed on www.ClinicalTrials.gov, 28% of which were currently open. More than 80% evaluated or compared systemic chemotherapy regimens. Trials studying liver-targeted IO treatments and including specifically mCRC patients consisted of 29 studies on RF ablation (one randomized), six on irinotecan-eluting beads (two randomized), 18 on SIR Spheres (SirTex, Lane Cove, Australia) radioembolization (two randomized), and 29 on Thera-Sphere (Nordion, Ottawa, Ontario, Canada) radioembolization (none randomized). Most of these studies focus on unresectable metastases and are industry-sponsored. All the randomized trials compare IO therapies with a systemic chemotherapy regimen, but none of them compare different IO treatments. There

remain many opportunities for important trials to be done to define the role of IO therapies, as there are no prospective randomized clinical trials (i) comparing radioembolization to chemoembolization, or radioembolization or chemoembolization to HAI chemotherapy, (ii) comparing RF ablation to surgical resection or RF ablation to systemic chemotherapy, or (iii) studying the potential synergy between local ablative therapies and regional intraarterial treatments.

Panel Discussion/Prioritization

After the round-robin discussion, the panelists voted to produce a ranking list of priority research topics as described earlier; members from governmental agencies and from industry did not vote. The final top three research topics (Table 7) are: (i) studies to evaluate the benefit of combining new imaging criteria with fine-needle aspiration or biopsy, (ii) studies to establish new or modified disease status criteria (replacing RECIST), and (iii) studies enrolling selected subsets of patients (eg, those with *KRAS* mutations) to undergo radioembolization, RF ablation, or both. The top two were consolidated into one topic after further discussion. The RCP panelists or SIR members not attending the RCP may apply to assist with the development of a research protocol and/or grant application on any of these two top priority topics so that they may pursue federal and/or industry funding for the trial.

DISCUSSION

Systemic chemotherapy remains the first-line treatment given to patients with unresectable mCRC. Bevacizumab and cetuximab add only modest additional benefit to systemic chemotherapy. However, available alternatives have high success rates, including external-beam RT, intraarterial hepatic chemotherapy, and radioembolization. The use of these alternatives has remained limited to the palliative setting. There are, however, selected subsets of patients in whom results of systemic therapy are poor: for example, those with *KRAS* mutations (who represent 35%–40% of all CRC patients) do not show a benefit from cetuximab or panitumumab and show a low response to second-line FOLFIRI alone (4%). In such subsets, IO treatments may have a role to play. BRAF genomic tumor profiling may also be an important parameter that needs additional evaluation. In the NCCN Guidelines, testing tumor *KRAS* gene status is recommended in any mCRC patient at the time of diagnosis of metastatic disease (1). While awaiting the results of ongoing investigations, the current approach of using systemic therapy as first-line treatment to assess tumor biology and responsiveness remains the standard approach to unresectable mCRC (1,2,34). Similarly, an "ablate and wait" approach has been suggested (42). Finally, not only liver but also other metastases (eg, lung) may benefit from locoregional therapies.

There remain several important hurdles to the implementation of meaningful randomized controlled trials evaluating or comparing IO therapies for mCRC. First, the criteria for unresectability of liver metastases need to be refined as they vary widely based on a number of factors, some of which do not appear fully understood yet. Creating a platform to gather opinions from surgeons on whether a given patient is a candidate for resection is suggested, although its practical implementation may be difficult.

Second, better assessment tools of nonsurvival end-points need to be developed, and their predictive value on survival will need to be evaluated. The creation of a clinical prognostic risk score to predict survival outcomes (or pathologic response) before any IO treatment is a much desired tool. There is indeed very poor correlation between survival and imaging outcomes. Potentially useful predictors of survival after locoregional therapies deserve further investigation (similar to the use of the FLR before potential hepatectomy). Also, imaging alone after locoregional therapies, even with combined positron emission tomography-CT, seems unreliable and often underestimates residual disease, as seen intraoperatively. Searching for improved imaging criteria to assess disease status and response to treatment seemed a crucial initial step to the panel members. In addition, they also favored combining such criteria with more frequent tissue sampling before and after treatment, which can help answer multiple questions and guide treatment. There are multiple potential merits to this combined imaging/tissue diagnosis approach: (i) immunohistochemical analyses of cells adherent to RF ablation probes at the end of ablation procedures can help predict local tumor progression (53); (ii) post-RF ablation fine needle aspirations (53) have also been shown to improve detection of local recurrences with no added morbidity or mortality; (iii) biopsy of the normal parenchyma helps in assessing the degree of liver damage induced by previous systemic chemotherapy. Several panel members expressed concern that many patients become candidates for radioembolization only after having been treated with multiple lines of chemotherapy, which have caused an indeterminate amount of liver damage that cannot be quantified without obtaining pre-radioembolization biopsies; (iv) postradioembolization biopsies may also be helpful to better assess liver parenchymal damage; (v) biopsies of CLMs can also help establish the biologic profile of tumors before and after locoregional therapies. Analyses of deoxyribonucleic acid from biopsy specimens of CLM show that tumoral mutations before and after treatment are an important predictor of outcomes.

In conclusion, the top research priorities identified by this process clearly stress the need to develop better response evaluation tool(s) tailored to IO therapies before moving forward with future comparative trials that may help distinguish which treatments work best in which patient populations. The ability of such tool(s) to predict survival would be a major asset. Therapeutic studies should focus on unresectable CLM, and trials enrolling selected patients subsets, such as those with *KRAS* mutations, were also identified as another important topic for future research.

Acknowledgments

The RCP meeting was sponsored by the SIR Foundation.

A.P.V. has research funded by Nordion (Ottawa, Ontario, Canada). J.F.G. has research funded by Bayer (Robinson Township, Pennsylvania), Biocompatibles (Farnham, UK), Nordion, Genentech (South San Francisco, California), Phillips Medical (Andover, Massachusetts), Context Vision, CeloNova (Newnan, Georgia), the National Institutes of Health (NIH/NCI RO1 CA160771-01), and the Radiological Society of North America. J.F.G. is a consultant for Bayer, Bio-compatibles, Guerbet (Roissy, France), Nordion, Genentch, and Abbott (North Chicago, Illinois), and is the CEO and Founder of PreScience Labs (Potomac, Maryland). M.S.J. is a speaker and teacher for Angiotech (Vancouver, British Columbia, Canada), Bayer, Boston Scientific (Natick, Massachusetts), CeloNova, Nordion, and SirTex (Lane Cove, Australia). M.S.J. is a consultant for Cook and receives grant support from Nordion. R.J.L. is a consultant for Nordion and PhaseRX (Seattle, Washington) and is on the advisory committee of SureFire Medical (Westminster, Colorado). R.M. received an unrestricted research grant from SirTex and Nordion and is on the advisory co®mmittee and a review panel member of Astra Zeneca (Wilmington, Delaware). A.S.K. is a consultant,

speaker, and teacher for, and received a grant from, SirTex. M.C.S. is a consultant for Guerbet, Biocompatibles/BTG, and Biosphere/Merit (South Jordan, Utah). S.J.C. is an advisory committee and review panel member for Nordion and receives grant support from SirTex. C.T.S. receives grant support from SirTex and the NIH (Award 1 R21 CA131763-01A1) and is a consultant for SirTex.

ABBREVIATIONS

AHRQ	Agency for Healthcare Research and Quality
CLM	colorectal liver metastases
CRC	colorectal cancer
DEBIRI	drug-eluting beads loaded with irinotecan
FLR	future liver remnant
FOLFIRI	folinic acid/5-fluorouracil/irinotecan [systemic chemotherapy regimen]
FOLFOX	folinic acid, fluorouracil, and oxaliplatin [systemic chemotherapy regimen]
HAI	hepatic arterial infusion
IO	interventional oncology
mCRC	metastatic colorectal cancer
NCCN	National Comprehensive Cancer Network
PVE	portal vein embolization
RCP	Research Consensus Panel
RECIST	response evaluation criteria in solid tumors
RF	radiofrequency
RILD	radiation-induced liver disease
RT	radiation therapy
3D	three-dimensional
TTP	time to progression
VEGF	anti-vascular endothelial growth factor

References

1. Engstrom PF, Arnoletti JP, Benson AB III, et al. NCCN Clinical Practice Guidelines in Oncology: colon cancer. J Natl Compr Canc Netw. 2009; 7:778–831. [PubMed: 19755046]
2. Engstrom PF, Arnoletti JP, Benson AB III, et al. NCCN Clinical Practice Guidelines in Oncology: rectal cancer. J Natl Compr Canc Netw. 2009; 7:838–881. [PubMed: 19755047]
3. Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. Epidemiology and management of liver metastases from colorectal cancer. Ann Surg. 2006; 244:254–259. [PubMed: 16858188]
4. Vogt P, Raab R, Ringe B, Pichlmayr R. Resection of synchronous liver metastases from colorectal cancer. World J Surg. 1991; 15:62–67. [PubMed: 1994607]
5. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol. 2007; 25:4575–4580. [PubMed: 17925551]

6. Adam R. The importance of visceral metastasectomy in colorectal cancer. Ann Oncol. 2000; 11(suppl 3):29–36. [PubMed: 11079115]
7. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet. 2000; 355:1041–1047. [PubMed: 10744089]
8. Giacchetti S, Perpoint B, Zidani R, et al. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. J Clin Oncol. 2000; 18:136–147. [PubMed: 10623704]
9. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004; 350:2335–2342. [PubMed: 15175435]
10. Cascinu S, Berardi R, Salvagni S, et al. A combination of gefitinib and FOLFOX-4 as first-line treatment in advanced colorectal cancer patients. A GISCAD multicentre phase II study including a biological analysis of EGFR overexpression, amplification and NF-kB activation. Br J Cancer. 2008; 98:71–76. [PubMed: 18059397]
11. Owens, DK.; Lohr, KN.; Atkins, D., et al. Grading the strength of a body of evidence when comparing medical interventions. Rockville, MD: Agency for Healthcare Research and Quality; 2009.
12. Wagner JS, Adson MA, Van Heerden JA, Adson MH, Ilstrup DM. The natural history of hepatic metastases from colorectal cancer. A comparison with resective treatment. Ann Surg. 1984; 199:502–508. [PubMed: 6721600]
13. 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; 127:512–519. [PubMed: 10819059]
14. Vauthey JN, Abdalla EK, Doherty DA, et al. Body surface area and body weight predict total liver volume in Western adults. Liver Transpl. 2002; 8:233–240. [PubMed: 11910568]
15. 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; 250:540–548. [PubMed: 19730239]
16. Abdalla EK, Barnett CC, Doherty D, Curley SA, Vauthey JN. Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. Arch Surg. 2002; 137:675–680. [PubMed: 12049538]
17. Vauthey JN, Pawlik TM, Abdalla EK, et al. Is extended hepatectomy for hepatobiliary malignancy justified? Ann Surg. 2004; 239:722–730. [PubMed: 15082977]
18. 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; 240:644–657. [PubMed: 15383792]
19. Azoulay D, Castaing D, Krissat J, et al. Percutaneous portal vein embolization increases the feasibility and safety of major liver resection for hepatocellular carcinoma in injured liver. Ann Surg. 2000; 232:665–672. [PubMed: 11066138]
20. 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; 24:2065–2072. [PubMed: 16648507]
21. Zorzi D, Chun YS, Madoff DC, Abdalla EK, Vauthey JN. Chemotherapy with bevacizumab does not affect liver regeneration after portal vein embolization in the treatment of colorectal liver metastases. Ann Surg Oncol. 2008; 15:2765–2772. [PubMed: 18636296]
22. Kubota K, Makuuchi M, Kusaka K, et al. Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. Hepatology. 1997; 26:1176–1181. [PubMed: 9362359]
23. Elias D, Ouellet JF, De Baere T, Lasser P, Roche A. Preoperative selective portal vein embolization before hepatectomy for liver metastases: long-term results and impact on survival. Surgery. 2002; 131:294–299. [PubMed: 11894034]
24. Capussotti L, Ferrero A, Vigano L, Ribero D, Lo Tesoriere R, Polastri R. Major liver resections synchronous with colorectal surgery. Ann Surg Oncol. 2007; 14:195–201. [PubMed: 17080238]

25. Bolton JS, Fuhrman GM. Survival after resection of multiple bilobar hepatic metastases from colorectal carcinoma. Ann Surg. 2000; 231:743–751. [PubMed: 10767796]
26. Brouquet A, Mortenson MM, Vauthey JN, et al. Surgical strategies for synchronous colorectal liver metastases in 156 consecutive patients: classic, combined or reverse strategy? J Am Coll Surg. 2010; 210:934–941. [PubMed: 20510802]
27. Fong Y. Surgical therapy of hepatic colorectal metastasis. CA Cancer J Clin. 1999; 49:231–255. [PubMed: 11198884]
28. Blazer DG III, Kishi Y, Maru DM, et al. Pathologic response to preoperative chemotherapy: a new outcome end point after resection of hepatic colorectal metastases. J Clin Oncol. 2008; 26:5344–5351. [PubMed: 18936472]
29. Chun YS, Vauthey JN, Boonsirikamchai P, et al. Association of computed tomography morphologic criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases. JAMA. 2009; 302:2338–2344. [PubMed: 19952320]
30. Kopetz S, Chang GJ, Overman MJ, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol. 2009; 27:3677–3683. [PubMed: 19470929]
31. 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; 371:1007–1016. [PubMed: 18358928]
32. Adam R, Bhangui P, Poston G, et al. Is perioperative chemotherapy useful for solitary, metachronous, colorectal liver metastases? Ann Surg. 2010; 252:774–787. [PubMed: 21037433]
33. Gold JS, Are C, Kornprat P, et al. Increased use of parenchymal-sparing surgery for bilateral liver metastases from colorectal cancer is associated with improved mortality without change in oncologic outcome: trends in treatment over time in 440 patients. Ann Surg. 2008; 247:109–117. [PubMed: 18156930]
34. Adam R, Aloia T, Figueras J, et al. LiverMetSurvey: analysis of clinicopathologic factors associated with the efficacy of preoperative chemotherapy in 2,122 patients with colorectal liver metastases. J Clin Oncol. 2006; 24(18 suppl):151s. Abstract 3521.
35. Elias D, De Baere T, Smayra T, Ouellet JF, Roche A, Lasser P. Percutaneous radiofrequency thermoablation as an alternative to surgery for treatment of liver tumour recurrence after hepatectomy. Br J Surg. 2002; 89:752–756. [PubMed: 12027986]
36. Vogl TJ, Straub R, Eichler K, Sollner O, Mack MG. Colorectal carcinoma metastases in liver: laser-induced interstitial thermotherapy–local tumor control rate and survival data. Radiology. 2004; 230:450–458. [PubMed: 14688400]
37. Hur H, Ko YT, Min BS, et al. Comparative study of resection and radiofrequency ablation in the treatment of solitary colorectal liver me-tastases. Am J Surg. 2009; 197:728–736. [PubMed: 18789428]
38. Adam R, Hagopian EJ, Linhares M, et al. A comparison of percutaneous cryosurgery and percutaneous radiofrequency for unresectable hepatic malignancies. Arch Surg. 2002; 137:1332–1339. [PubMed: 12470093]
39. Gillams AR, Lees WR. Five-year survival following radiofrequency ablation of small, solitary, hepatic colorectal metastases. J Vasc Interv Radiol. 2008; 19:712–717. [PubMed: 18440460]
40. Helmberger T, Holzknecht N, Schopf U, et al. Radiofrequency ablation of liver metastases. Technique and initial results. Radiologe. 2001; 41:69–76. [PubMed: 11220100]
41. Lencioni R, Goletti O, Armillotta N, et al. Radio-frequency thermal ablation of liver metastases with a cooled-tip electrode needle: results of a pilot clinical trial. Eur Radiol. 1998; 8:1205–1211. [PubMed: 9724440]
42. Livraghi T, Solbiati L, Meloni F, Ierace T, Goldberg SN, Gazelle GS. Percutaneous radiofrequency ablation of liver metastases in potential candidates for resection: the "test-of-time approach". Cancer. 2003; 97:3027–3035. [PubMed: 12784338]
43. Sofocleous CT, Petre EN, Gonen M, et al. CT-guided radiofrequency ablation as a salvage treatment of colorectal cancer hepatic metastases developing after hepatectomy. J Vasc Interv Radiol. 2011; 22:755–761. [PubMed: 21514841]

44. Solbiati L, Livraghi T, Goldberg SN, et al. Percutaneous radiofrequency ablation of hepatic metastases from colorectal cancer: long-term results in 117 patients. Radiology. 2001; 221:159–166. [PubMed: 11568334]
45. 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; 11:256–263. [PubMed: 17458595]
46. Gillams AR, Lees WR. Five-year survival in 309 patients with colorectal liver metastases treated with radiofrequency ablation. Eur Radiol. 2009; 19:1206–1213. [PubMed: 19137310]
47. Machi J, Oishi AJ, Sumida K, et al. Long-term outcome of radiofrequency ablation for unresectable liver metastases from colorectal cancer: evaluation of prognostic factors and effectiveness in first- and second-line management. Cancer J. 2006; 12:318–326. [PubMed: 16925977]
48. Oshowo A, Gillams A, Harrison E, Lees WR, Taylor I. Comparison of resection and radiofrequency ablation for treatment of solitary colorectal liver metastases. Br J Surg. 2003; 90:1240–1243. [PubMed: 14515293]
49. Sørensen SM, Mortensen FV, Nielsen DT. Radiofrequency ablation of colorectal liver metastases: long-term survival. Acta Radiol. 2007; 48:253–258. [PubMed: 17453491]
50. Lu DS, Yu NC, Raman SS, et al. Radiofrequency ablation of hepatocellular carcinoma: treatment success as defined by histologic examination of the explanted liver. Radiology. 2005; 234:954–960. [PubMed: 15681691]
51. Mulier S, Ni Y, Jamart J, Michel L, Marchal G, Ruers T. Radiofrequency ablation versus resection for resectable colorectal liver metastases: time for a randomized trial? Ann Surg Oncol. 2008; 15:144–157. [PubMed: 17906898]
52. Poon RT, Ng KK, Lam CM, et al. Learning curve for radiofrequency ablation of liver tumors: prospective analysis of initial 100 patients in a tertiary institution. Ann Surg. 2004; 239:441–449. [PubMed: 15024304]
53. Sofocleous CT, Nascimento RG, Petrovic LM, et al. Histopathologic and immunohistochemical features of tissue adherent to multitined electrodes after RF ablation of liver malignancies can help predict local tumor progression: initial results. Radiology. 2008; 249:364–374. [PubMed: 18796687]
54. Poon RT, Borys N. Lyso-thermosensitive liposomal doxorubicin: an adjuvant to increase the cure rate of radiofrequency ablation in liver cancer. Future Oncol. 2011; 7:937–945. [PubMed: 21823888]
55. Solazzo SA, Ahmed M, Schor-Bardach R, et al. Liposomal doxorubicin increases radiofrequency ablation-induced tumor destruction by increasing cellular oxidative and nitrative stress and accelerating apoptotic pathways. Radiology. 2010; 255:62–74. [PubMed: 20160000]
56. Hansler J, Wissniowski TT, Schuppan D, et al. Activation and dramatically increased cytolytic activity of tumor specific T lymphocytes after radio-frequency ablation in patients with hepatocellular carcinoma and colorectal liver metastases. World J Gastroenterol. 2006; 12:3716–3721. [PubMed: 16773688]
57. Ravindranath MH, Wood TF, Soh D, et al. Cryosurgical ablation of liver tumors in colon cancer patients increases the serum total ganglioside level and then selectively augments antiganglioside IgM. Cryobiology. 2002; 45:10–21. [PubMed: 12445546]
58. Zhang Y, Deng J, Feng J, Wu F. Enhancement of antitumor vaccine in ablated hepatocellular carcinoma by high-intensity focused ultrasound. World J Gastroenterol. 2010; 16:3584–3591. [PubMed: 20653069]
59. 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; 27:3465–3471. [PubMed: 19470932]
60. Lorenz M, Muller HH. Randomized, multicenter trial of fluorouracil plus leucovorin administered either via hepatic arterial or intravenous infusion versus fluorodeoxyuridine administered via hepatic arterial infusion in patients with nonresectable liver metastases from colorectal carcinoma. J Clin Oncol. 2000; 18:243–254. [PubMed: 10637236]

61. Lygidakis NJ, Sgourakis G, Vlachos L, et al. Metastatic liver disease of colorectal origin: the value of locoregional immunochemotherapy combined with systemic chemotherapy following liver resection. Results of a prospective randomized study. Hepatogastroenterology. 2001; 48:1685–1691. [PubMed: 11813601]
62. Boige V, Malka D, Elias D, et al. Hepatic arterial infusion of oxaliplatin and intravenous LV5FU2 in unresectable liver metastases from colorectal cancer after systemic chemotherapy failure. Ann Surg Oncol. 2008; 15:219–226. [PubMed: 17896145]
63. House MG, Kemeny NE, Gönen M, et al. Comparison of adjuvant systemic chemotherapy with or without hepatic arterial infusional chemotherapy after hepatic resection for metastatic colorectal cancer. Ann Surg. 2011; 254:851–856. [PubMed: 21975318]
64. Ito H, Are C, Gönen M, et al. Effect of postoperative morbidity on long-term survival after hepatic resection for metastatic colorectal cancer. Ann Surg. 2008; 247:994–1002. [PubMed: 18520227]
65. Kemeny NE, Jarnagin WR, Capanu M, et al. Randomized phase II trial of adjuvant hepatic arterial infusion and systemic chemotherapy with or without bevacizumab in patients with resected hepatic metastases from colorectal cancer. J Clin Oncol. 2011; 29:884–889. [PubMed: 21189384]
66. Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. N Engl J Med. 1999; 341:2039–2048. [PubMed: 10615075]
67. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. N Engl J Med. 2005; 352:734–735. [PubMed: 15716576]
68. Sanz-Altamira PM, Spence LD, Huberman MS, et al. Selective chemoembolization in the management of hepatic metastases in refractory colorectal carcinoma: a phase II trial. Dis Colon Rectum. 1997; 40:770–775. [PubMed: 9221850]
69. Tellez C, Benson AB III, Lyster MT, et al. Phase II trial of chemoembolization for the treatment of metastatic colorectal carcinoma to the liver and review of the literature. Cancer. 1998; 82:1250–1259. [PubMed: 9529016]
70. Albert M, Kiefer MV, Sun W, et al. Chemoembolization of colorectal liver metastases with cisplatin, doxorubicin, mitomycin C, Ethiodol, and polyvinyl alcohol. Cancer. 2011; 117:343–352. [PubMed: 20830766]
71. Vogl TJ, Gruber T, Balzer JO, Eichler K, Hammerstingl R, Zangos S. Repeated transarterial chemoembolization in the treatment of liver metastases of colorectal cancer: prospective study. Radiology. 2009; 250:281–289. [PubMed: 19092099]
72. Martin RC, Joshi J, Robbins K, et al. Hepatic intra-arterial injection of drug-eluting bead, irinotecan (DEBIRI) in unresectable colorectal liver metastases refractory to systemic chemotherapy: results of multi-institutional study. Ann Surg Oncol. 2011; 18:192–198. [PubMed: 20740319]
73. Fiorentini G, Aliberti C, Tilli M, et al. Evaluation of a phase III clinical trial comparing transarterial chemoembolisation (TACE) using irinotecan-loaded polyvinyl alcohol microspheres (Debiri) vs systemic chemotherapy FOLFIRI (CT) for the treatment of unresectable metastases to the liver (LM) in patients with advanced colorectal cancer (MCRC). Cardiovasc Intervent Radiol. 2011; 34:599. Abstract P-286.
74. Lewandowski RJ, Thurston KG, Goin JE, et al. 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. [PubMed: 16371530]
75. Jakobs TF, Hoffmann RT, Dehm K, et al. Hepatic yttrium-90 radioembolization of chemotherapy-refractory colorectal cancer liver metastases. J Vasc Interv Radiol. 2008; 19:1187–1195. [PubMed: 18656012]
76. 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; 65:412–425. [PubMed: 16690429]
77. Mulcahy MF, Lewandowski RJ, Ibrahim SM, et al. Radioembolization of colorectal hepatic metastases using yttrium-90 microspheres. Cancer. 2009; 115:1849–1858. [PubMed: 19267416]

78. Cianni R, Urigo C, Notarianni E, et al. Radioembolisation using yttrium 90 (Y-90) in patients affected by unresectable hepatic metastases. Radiol Med. 2010; 115:619–633. [PubMed: 20091135]

79. Evans KA, Richardson MG, Pavlakis N, Morris DL, Liauw W, Bester L. Survival outcomes of a salvage patient population after radioembolization of hepatic metastases with yttrium-90 microspheres. J Vasc Interv Radiol. 2010; 21:1521–1526. [PubMed: 20813542]

80. Van Hazel G, Blackwell A, Anderson J, et al. Randomised phase 2 trial of SIR-Spheres plus fluorouracil/leucovorin chemotherapy versus fluorouracil/leucovorin chemotherapy alone in advanced colorectal cancer. J Surg Oncol. 2004; 88:78–85. [PubMed: 15499601]

81. Gray B, Van Hazel G, Hope M, et al. 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. [PubMed: 11843249]

82. Hendlisz A, Van den Eynde M, Peeters M, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. J Clin Oncol. 2010; 28:3687–3694. [PubMed: 20567019]

83. Sharma RA, Van Hazel GA, Morgan B, et al. Radioembolization of liver metastases from colorectal cancer using yttrium-90 microspheres with concomitant systemic oxaliplatin, fluorouracil, and leucovorin chemotherapy. J Clin Oncol. 2007; 25:1099–1106. [PubMed: 17369573]

84. van Hazel GA, Pavlakis N, Goldstein D, et al. Treatment of fluorouracilrefractory patients with liver metastases from colorectal cancer by using yttrium-90 resin microspheres plus concomitant systemic irinotecan chemotherapy. J Clin Oncol. 2009; 27:4089–4095. [PubMed: 19652069]

85. Kosmider S, Tan TH, Yip D, Dowling R, Lichtenstein M, Gibbs P. Radioembolization in combination with systemic chemotherapy as first-line therapy for liver metastases from colorectal cancer. J Vasc Interv Radiol. 2011; 22:780–786. [PubMed: 21515072]

86. Seidensticker R, Denecke T, Kraus P, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. Cardiovasc Intervent Radiol. 2011 Jul 29. Epub ahead of print. 10.1007/s00270-011-0234-7

87. Ingold JA, Reed GB, Kaplan HS, Bagshaw MA. Radiation hepatitis. Am J Roentgenol Radium Ther Nucl Med. 1965; 93:200–208.

88. Reed GB Jr, Cox AJ Jr. The human liver after radiation injury. A form of veno-occlusive disease. Am J Pathol. 1966; 48:597–611. [PubMed: 5327788]

89. Dawson LA, McGinn CJ, Normolle D, et al. Escalated focal liver radiation and concurrent hepatic artery fluorodeoxyuridine for unresectable intrahepatic malignancies. J Clin Oncol. 2000; 18:2210–2218. [PubMed: 10829040]

90. Lawrence TS, Ten Haken RK, Kessler ML, et al. The use of 3-D dose volume analysis to predict radiation hepatitis. Int J Radiat Oncol Biol Phys. 1992; 23:781–788. [PubMed: 1618671]

91. Leibel SA, Pajak TF, Massullo V, et al. A comparison of misonidazole sensitized radiation therapy to radiation therapy alone for the palliation of hepatic metastases: results of a Radiation Therapy Oncology Group randomized prospective trial. Int J Radiat Oncol Biol Phys. 1987; 13:1057–1064. [PubMed: 3597149]

92. Robertson JM, Lawrence TS, Walker S, Kessler ML, Andrews JC, Ensminger WD. The treatment of colorectal liver metastases with conformal radiation therapy and regional chemotherapy. Int J Radiat Oncol Biol Phys. 1995; 32:445–450. [PubMed: 7751185]

93. Cheng JC, Wu JK, Huang CM, et al. Dosimetric analysis and comparison of three-dimensional conformal radiotherapy and intensity-modulated radiation therapy for patients with hepatocellular carcinoma and radiation-induced liver disease. Int J Radiat Oncol Biol Phys. 2003; 56:229–234. [PubMed: 12694843]

94. Herfarth KK, Debus J, Lohr F, et al. Stereotactic single-dose radiation therapy of liver tumors: results of a phase I/II trial. J Clin Oncol. 2001; 19:164–170. [PubMed: 11134209]

95. 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; 27:1572–1578. [PubMed: 19255321]

96. Lee MT, Kim JJ, Dinniwell R, et al. Phase I study of individualized stereotactic body radiotherapy of liver metastases. J Clin Oncol. 2009; 27:1585–1591. [PubMed: 19255313]

Table 1

United States Agency for Healthcare Research and Quality Classification of Levels of Evidence (11)

Level	Description
I	Evidence from randomized controlled trial(s)
II-1	Evidence from controlled trial(s) without randomization
II-2	Evidence from cohort or case-control analytic studies, preferably from more than one center or research group
II-3	Evidence from comparisons between times or places with or without the intervention; dramatic results in uncontrolled experiments could be included here
III	Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees

Note.—Modified from Owens et al (11).

Table 2

Outcomes after Percutaneous Local Ablation for Liver Metastases of CRC: Survival (35–37,39,43,44,47)

Study, Year	Modality	No. of Pts./Lesions	Level of Evidence	Median OS after Ablation (mo)
Hur et al (37), 2009	RF	25/25	II-2	41*
Solbiati et al (44), 2001	RF (P)	117/179	II-2	36
Gillams and Lees (39), 2009†	RF (P)	309/617	II-2	32‡
Elias et al (35), 2002	RF (P)	29/NA	II-2	> 24§
Oshowo et al (48), 2003†	RF	25/25	II-2	37//
Machi et al (47), 2006	RF	100/507 (42%P)	II-2	28
Vogl et al (36), 2004	LITT (P)	603/1,801	II-2	35
Sorensen et al (49), 2007	RF (P)	100/332	II-2	32
Sofocleous et al (43), 2011	RF (P)	56/71	II-2	31¶

Note.—CRC = colorectal cancer, LITT = laser-induced interstitial thermotherapy, NA = not available, OS = overall survival, P = percutaneous, RF = radiofrequency.

*Series includes 12 percutaneous and 13 intraoperative RF ablation cases; resection arm of this study (42 patients, 42 lesions) showed medial OS duration of 60 mo.

†Partially redundant series.

‡Medial survival time was 36 mo in 123 patients with ≤ 5 colorectal metastases ≤ 5 cm in size.

§Series on RF ablation of postresection local recurrences (47 patients, 65 lesions), including 29 non-CRC cases; summary median survival includes non-CRC cases.

//Resection arm of this study (20 patients, 20 lesions) showed medial OS duration of 41 mo.

¶Salvage RF ablation for colorectal metastases developing after surgical resection.

Table 3

Outcomes after Percutaneous Local Ablation for Liver Metastases of CRC: Local Recurrence (38,40–46)

Study, Year	Lesions	Level of Evidence	Size of Lesions (mm)	Lesions per Patient	Lesion-Based Local Recurrence (%)
Solbiati et al (44), 2001	179	II-2	6–96 (median, 28)	1–4	39
Adam et al (38), 2002	43	II-2	28 (median)	1–4 (median, 1.32)	18 (patient-based, 16)
Gillams and Lees (46), 2009	684	II-2	10–120 (mean, 39)	1–27 (median, 4.1)	14 (patient-based)
Lencioni et al (41), 1998	53	II-2	11–48	NS	12
Helmberger et al (40), 2001	74	II-2	NS	NS	0 (9-mo follow-up)
Livraghi et al (42), 2003	134	II-2	6–40 (mean, 21)	NS	37 (patient-based, 40)
White et al (45), 2007	56	II-2	8–70 (mean, 30)	1.9 (mean)	39
Sofocleous et al (43), 2011	71	II-2	5–57 (median, 19)	1–4 (mean, 1.2)	37.7 (CRS < 2), 75 (CRS > 2)

Note.—CRC = colorectal cancer, CRS = clinical risk score, NS = not specified.

Table 4

Outcomes after Chemoembolization for CLM (66–69)

				Median OS (mo)	
Study, Year	**No. of Pts.**	**Level of Evidence**	**Disease Control (%)**	**After CLM Detection**	**After Chemoembolization**
Sanz-Altamira et al (68), 1997	40	II-1	63	24	10
Tellez et al (69), 1998	30	II-2	63	29	8.6
Albert et al (70), 2011	120	II-2	43	27	9
Vogl et al (71), 2009	463	II-2	63	38	14

Note.—Disease control rates include patients with complete response, partial response or stable disease. CLM = colorectal metastases, OS = overall survival.

Table 5

Outcomes after Yttrium-90 Radioembolization for CLM in Salvage Setting (72–77)

Study, Year	No. of Pts.	Level of Evidence	Response (%)	Median OS after ^{90}Y Treatment (mo)	Toxicity (%)
Lewandowski et al (74), 2005	27	II-1	35 (CT), 88 (PET)	9.3	Constitutional, 48; GI, 4
Kennedy et al (75), 2006	208	II-2	35 (CT), 91 (PET)	10.5*	Constitutional, 2; GI, 5
Jakobs et al (76), 2008	36	II-1	17 (CT)	10.5	Constitutional, 71; GI, 7.4
Mulcahy et al (77), 2009	72	II-1	40 (CT), 77 (PET)	14.5	Constitutional, 61; GI, 1.4
Cianni et al (78), 2009	41	II-1	46 (CT)	11.6	Constitutional, 15; GI, 7; RILD, 2.4
Evans et al (79), 2010	140	II-2	NA	7.9	Constitutional, 31; GI, 6; RILD, 2

Note.—Disease control rates include patients with complete response, partial response or stable disease. CLM = colorectal metastases, GI = gastrointestinal, NA = not available, OS = overall survival, PET = positron emission tomography, RILD = radiation-induced liver disease.

* In responders (vs 4.5 mo in nonresponders).

J Vasc Interv Radiol. Author manuscript; available in PMC 2015 March 07.

Table 6

Outcomes after Combined Yttrium-90 Radioembolization and Systemic Therapy for CLM (78–83)

Study, Year	No. of Pts.	Level of Evidence	Median OS after ^{90}Y Treatment (mo)	Study Arms/Design
Gray et al (81), 2001	74	I	17	Floxuridine HAC with/without ^{90}Y
van Hazel et al (80), 2004	21	II-1	29.4	5-FU/LV with/without ^{90}Y
Sharma et al (83), 2007	20	II-1	NA	FOLFOX plus ^{90}Y, oxaliplatin dose escalation
van Hazel et al (84), 2009	25	II-1	12.2	Irinotecan plus ^{90}Y, irinotecan dose escalation
Hendlisz et al (82), 2010	46	I	10	5-FU with or without ^{90}Y
Kosmider et al (85), 2011	19	II-2	37.8	5-FU/LV or FOLFOX plus ^{90}Y

Note.—CLM = colorectal metastases, 5-FU = 5-fluorouracil, FOLFOX = folinic acid, fluorouracil, and oxaliplatin [systemic chemotherapy regimen], HAC = hepatic arterial chemotherapy, LV = leucovorin, NA = not available, OS = overall survival.

Table 7

Results of Voting Tally

Rank	List of Consolidated Priority Topics	Score
1	Study to evaluate benefit of combining new imaging criteria with FNA	46
2	Studies to establish new/modified disease status criteria (EASL/RECIST)	48
3	Studies enrolling selected subsets of patients (eg, *KRAS* mutants) to radioembolization, RF ablation, or both	50
4	RCT comparing surgical resection vs ablation for small CLM	53
5	Studies investigating correlation between TTP and OS	59
6	RCT comparing systemic chemotherapy with/without chemoembolization	63
7	RCT comparing radioembolization plus HAI chemotherapy (plus IV FOLFOX) vs DEBIRI (plus IV FOLFOX)	65
8	Studies on standardization of portal vein embolization	68
9	RCT comparing DEBIRI chemoembolization vs radioembolization	70
10	Studies investigating dose determination for radioembolization (animal study; dose escalation)	71
11	Building database or voting approach to determine surgical resectability	74
12	RCT comparing DEBIRI chemoembolization vs systemic chemotherapy	75
13	Studies of FLR as surrogate for survival	77

Note.—CLM = colorectal metastases, DEBIRI = drug-eluting beads loaded with irinotecan, EASL = European Association for the Study of the Liver, FLR = future liver remnant, FNA = fine needle aspiration, FOLFOX = folinic acid, fluorouracil, and oxaliplatin [systemic chemotherapy regimen], HAI = hepatic arterial infusion, IV = intravenous, OS = overall survival, RCT = randomized controlled trial, RECIST = Response Evaluation Criteria In Solid Tumors, RF = radiofrequency, TTP = time to progression.