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

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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%

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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.

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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

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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).

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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.