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Comparative Effectiveness Review
Number 93

Local Hepatic Therapies for Metastases to the Liver From Unresectable Colorectal Cancer

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Prepared by:
Blue Cross and Blue Shield Association Technology Evaluation Center
Evidence-based Practice Center
Chicago, IL

Investigators:
Suzanne Belinson, M.P.H., Ph.D.
Ryan Chopra, M.P.H.
Yoojung Yang, M.S., Pharm.D.
Veena Shankaran, M.D.
Naomi Aronson, Ph.D.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Supriya Janakiraman, M.D., M.P.H.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

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Key Informants

James Andrews, M.D.
Professor of Radiology
Mayo Clinic
Rochester, MN

Al Benson, M.D.
Professor of Medicine
Northwestern University
Chicago, IL

Virginia Calega, M.D., M.B.A.
Vice President of Medical Management/Policy
Highmark, Inc.
Camp Hill, PA

Suzanne Lindley**,** M.S.W.
Patient Advocate
YES! Beat Liver Tumors
Canton, TX

Mark Sands, M.D.
Vice Chair, Clinical Ops, Quality/Section Head, Interventional Radiology
Cleveland Clinic
Cleveland, OH

Technical Expert Panel

James Andrews, M.D.
Professor of Radiology
Mayo Clinic
Rochester, MN

Afsaneh Barzi, M.D., Ph.D.
Assistant Professor of Clinical Medicine/Hematology and Oncology
University of Southern California Hospital
Los Angeles, CA

Al Benson, M.D.
Professor of Medicine
Northwestern University
Chicago, IL

Virginia Calega, M.D., M.B.A.
Vice President of Medical Management/Policy
Highmark, Inc.
Camp Hill, PA

Nancy Kemeny, M.D.
Medical Oncology
Memorial Sloan-Kettering Cancer Center
New York, NY

David C. Madoff, M.D.
New York Presbyterian Hospital/Weil Cornell Medical Center
New York, NY

Mark Sands, M.D.
Vice Chair, Clinical Ops, Quality/Section Head, Interventional Radiology
Cleveland Clinic
Cleveland, OH

Peer Reviewers

Stephen Alberts, M.D.
Professor of Oncology
Mayo Clinic
Rochester, MN

Cathy Eng, M.D.
Associate Professor, Department of Gastrointestinal Medical Oncology
University of Texas
MD Anderson Cancer Center
Houston, TX

Todd Crocenzi, M.D.
Medical Oncologist
Providence Portland Medical Center
Portland, OR

Michael Soulen, M.D.
Professor of Radiology
The Hospital of the University of Pennsylvania
Philadelphia, PA

Local Hepatic Therapies for Metastases to the Liver From Unresectable Colorectal Cancer

Structured Abstract

Objectives. To characterize the comparative effectiveness and harms of various local hepatic therapies for metastases to the liver from unresectable colorectal cancer (CRC) in two distinct populations: patients with liver-dominant metastases (i.e., majority of disease located in the liver) who are not eligible for continued systemic chemotherapy because their disease is refractory (i.e., they have experienced disease progression while on therapy), and patients who are candidates for local liver therapies as an adjunct to systemic chemotherapy. Local hepatic therapies include ablation, embolization, and radiotherapy approaches.

Data sources. We searched MEDLINE® and Embase® from January 2000 to June 2012. We also searched for gray literature in databases with regulatory information, clinical trial registries, abstracts and conference papers, grants and federally funded research, and information from manufacturers.

Review methods. We sought studies reporting two outcomes—overall survival and quality of life—and various adverse events related to the different interventions for the two populations of interest. Data were dually abstracted by a team of reviewers. A third reviewer resolved conflicts when necessary. We assessed the quality of individual studies and graded the strength of the body of evidence according to prespecified methods.

Results. We identified 937 articles through the literature search and excluded 913 at various stages of screening; 24 articles were included in our review. We also included one hand-searched article from Annals of Oncology, two published articles from scientific information packets, and three articles identified from conference abstracts; the total number of articles was 30. Twenty-three articles addressed Key Questions (KQ) 1 (effectiveness) and 2 (harms) for patients ineligible for systemic chemotherapy, and seven addressed KQ3 (effectiveness) and KQ4 (harms) for patients who are candidates for systemic chemotherapy. One randomized controlled trial (RCT) was included but this was treated as a case-series because the comparator was not relevant to this comparative effectiveness review. All others articles were case series. Fifteen studies were of good quality, 12 studies were of fair quality, and 3 were rated as poor quality. No comparative studies met our inclusion criteria. Evidence was insufficient to determine the comparative effectiveness or harms of these interventions.

Conclusions. In the absence of comparative data, the evidence is insufficient to permit conclusions on the comparative effectiveness of these therapies for unresectable CRC metastases to the liver. Gaps in the research base, even for critical benefits or harms, are extensive, and the quality of studies is generally questionable. Conducting RCTs (ideally head-to-head comparisons) to answer many important questions is desirable, but challenging.

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Executive Summary

Background

This report aims to compare the effectiveness and harms of several local hepatic therapies for unresectable colorectal cancer (CRC) metastases to the liver. In the sections that follow, we describe CRC and its diagnosis and treatment to orient the reader to the disease. This is followed by a discussion of the treatment of CRC liver metastasis.

Condition

CRC is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States.[1] It is a cancer that forms in the tissues of the colon and the rectum. Most colorectal cancers are adenocarcinomas, meaning that they are a cancer of the epithelium originating from glandular tissue. Adenocarcinomas develop from adenomas, which are noncancerous tumors in the epithelial tissue. Over time, adenomas can become cancerous. This progression from adenoma to adenocarcinoma occurs through a sequential process of accumulating genetic changes.[2] Although the most common type of CRC is adenocarcinoma, squamous carcinoma and adenosquamous carcinoma have been reported infrequently.[3]

An elevated risk of CRC has been associated with obesity, low physical activity, high dietary intake of refined sugars, low dietary intake of fiber, consumption of meat, and consumption of more than two alcoholic drinks per day.[4] A reduction in risk has been linked to the intake of dietary calcium and diets high in fiber and potassium.[5, 6]

Diagnosis and Treatment of Colorectal Cancer

The diagnosis of CRC requires pathologic review to characterize and stage the tumor.[7] Approximately 39 percent of new cases are diagnosed in the localized state, (i.e., no metastases or spread to regional lymph nodes); 36 percent present with regional spread to lymph nodes; 20 percent present with distant, metastatic cancer; and 5 percent present with unstaged disease.[8] The 5-year survival rate estimated by the National Cancer Institute Surveillance Epidemiology and End Results program (SEER) data analysis was found to be 74.1 percent for stage I, 64.5 percent for stage IIA, 51.6 percent for stage IIB, 32.3 percent for stage IIC, 74 percent for IIIA, 45 percent for IIIB, 33.4 percent for IIIC, and 6 percent for stage IV.[9] Survival declines with increasing depth of tumor penetration, increasing tumor stage, and patient age. For the 20 percent of patients who are initially diagnosed with distant (i.e., metastatic) disease, the 5-year survival rate is 10 percent or less with treatment. Patients with untreated liver metastases have a 5-year survival rate of less than 3 percent.[10] Survival differs by the extent of liver metastases.

Treatment of Localized Disease

For the 39 percent of patients who are diagnosed with localized disease, the cornerstone of treatment is surgery.[8] Advances in surgical technique, such as total mesorectal excision (dissection of the entire intact vascular, lymphatic, and fatty tissues) rather than blunt dissection, have improved local recurrence rates. Local recurrence rates have decreased from as high as 50 percent to less than 10 percent in some cases.[11] Patients whose disease was entirely removed through surgery may be offered adjuvant (i.e., after surgery) chemotherapy or radiation therapy to lower their risk of cancer recurrence. Patients with stage III colon cancer who received

postsurgical FOLFOX chemotherapy had a 3-year survival rate of 75 percent compared with 25 percent in the pre-adjuvant chemotherapy era.[11]

Treatment of Distant Disease

CRC is the most common malignancy that metastasizes to the liver: 25 percent of colon cancer patients present with primary CRC and synchronous liver metastases (i.e., the primary disease and liver metastases are diagnosed at the same time), and another 50 percent develop metachronous disease (i.e., liver metastases develop after the initial CRC diagnosis).[12] For some proportion of patients, the liver may be the only site of metastasis. Autopsy studies have shown that 38 percent of patients who died of metastatic CRC had liver-only metastasis.[13] Thus, therapies directed at the liver ("local hepatic therapies") have been used with the goal of extending survival in these patients.[14]

Surgical Resection

Although the prognosis for patients with metastatic CRC to the liver has been historically quite poor, advances in surgical technique have improved outcomes for patients with liver-confined metastases. In some situations, treatment of limited liver-only metastases may be curative. For example, in patients with resectable liver-only metastases, several studies have demonstrated durable long-term survival in selected patients, with 5-year survival estimates ranging between 30 percent and 58 percent.[15-21] CRC liver metastases are defined as resectable when it is anticipated that disease can be completely resected with negative margins, two adjacent liver segments can be spared, adequate vascular inflow and outflow and biliary drainage can be preserved, and adequate liver volume (20 to 25 percent) will remain postsurgery.[22-24] Approximately 20 to 30 percent of patients with CRC liver metastases are candidates for this approach. Some patients with lesions not well suited for resection may also receive radiofrequency ablation at the time of surgery.

In cases where patients may not have resectable liver metastases at diagnosis, systemic chemotherapy may be used to shrink the tumor and "convert" it to resectable disease.[25] Similar to patients with initially resectable liver metastases, these patients may also experience promising 5-year survival rates of approximately 30 percent.

Local Nonsurgical Treatment Strategies

Despite improved surgical techniques and systemic chemotherapy options, many patients may remain ineligible for resection because of anatomic constraints (tumor location or extent of metastatic lesions), inadequate hepatic functional reserve, or concurrent medical comorbidities such as poor performance status (functional impairment typically defined by a higher Eastern Cooperative Oncology Group [ECOG] grade or a lower Karnofsky score) and cardiac insufficiency.[26]

For patients with unresectable metastatic disease, local hepatic therapy may be used in an attempt to prolong survival or to palliate symptoms (e.g., pain) in patients for whom a cure is no longer within reach. Local hepatic therapy may be used for the following care scenarios:

1. Patients with unresectable, liver-dominant metastases (i.e., majority of disease located in the liver) who are not eligible for continued systemic chemotherapy because their disease is refractory (i.e., they have experienced disease progression while on therapy).These patients generally have large-volume disease and may be offered treatment to debulk the tumor and palliate symptoms when present.[27] Regardless of the local hepatic therapy,

patients should have liver-only metastases or liver-dominant metastases. In general, it is acceptable to have minimal extrahepatic disease (e.g., a single lung nodule) and remain a treatment candidate.

2. Patients with unresectable liver metastases at diagnosis or with limited unresectable hepatic recurrence after previous resection and who are candidates for local hepatic therapy.[28] In these patients, local hepatic therapies can be used as an adjunct to systemic chemotherapy with curative intent. The volume of disease in these patients is small, either in terms of lesion size or number of lesions.[29] These treatments are only appropriate when the entire tumor can be ablated with clear margins. To be considered a candidate for ablation or radiation therapy, patients treated in this setting should have no extrahepatic spread.

This report aims to compare the effectiveness and harms of local hepatic therapies for the two indications above. Therefore, comparisons of ablation with surgery or systemic chemotherapy with local hepatic therapy are outside the scope of this report.

Treatment Strategies

Several local hepatic therapies have been developed to treat patients with hepatic metastases of CRC. In the continuum of care, use of a local hepatic therapy may occur before or after the use of systemic chemotherapy, but it is administered most often in conjunction with systemic chemotherapy. Local hepatic therapies are divided into three groups: (1) ablation (destruction of tissue through procedures involving heating or cooling); (2) embolization (the selective blockage of blood vessels, often with agents that carry a drug to the occluded site); and (3) radiotherapy (directed radiation to destroy abnormal cells). Table A describes the local hepatic therapies included in this review.

Guidelines from the National Comprehensive Cancer Network for metastatic CRC state that ablative therapy for the metastases can be considered when all measurable metastatic disease can in fact be treated.[30] However, the group provides no guidance on *which* ablative therapy is optimal or on the comparative benefits and harms of the various palliative treatments.[30] A perception of clinical equipoise and limited randomized controlled trial (RCT) data comparing local hepatic therapies[31,32] contribute to uncertainty regarding which techniques, either alone or in combination, may be preferable for certain patient groups.

Table A. Local nonsurgical therapies for CRC liver metastases reviewed in this report

Therapy	Treatment Strategy	Mechanism of Cell Death	Setting	Performed By	Specific Harms
Ablation	Cryosurgical ablation	The mechanism of action is based on the rapid formation of intracellular ice crystals during the freezing process. The procedure uses repetitive freezing and thawing of the tissue to produce necrosis and irreversible tissue damage, which occurs at temperatures between -20 and -40°C.[33,34]	This type of treatment typically does not require a hospital stay if the percutaneous method is used. An open procedure requires an abdominal incision under general anesthesia and results in a longer recovery period.	Interventional Radiologist	Serious complications are uncommon but are possible, and for cryosurgical ablation include cryoshock phenomenon (acute renal failure, acute respiratory distress syndrome, disseminated intravascular coagulation, and liver failure); myoglobinuria leading to renal failure; bile leakage; hepatic abscess; pleural effusion; consumptive coagulopathy; thrombocytopenia; hepatic iceball fracture; organ failure; and biliary fistula.[35,36]
	Radiofrequency ablation (RFA)	RFA is performed by generating an alternating current between at least two electrodes in the radiofrequency range that generates heat without muscle contraction. The procedure generates tissue temperatures of 90 to 100°C, which causes protein denaturation and coagulative necrosis.[22]	The procedure is performed under intravenous narcotics for the percutaneous awake approach and does not require a hospital stay. For laparoscopic or open RFA, the procedure is performed under general anesthesia and results in a longer recovery period.[37] Each RFA takes approximately 10 to 30 minutes, with additional time required if multiple ablations are performed. The entire procedure is usually completed within 1 to 3 hours.[38]	Interventional Radiologist, Surgeon	Possible side effects after RFA therapy include abdominal pain, mild fever, increase in liver enzymes due to damage to the bile ducts, abscess, infection in the liver, skin burns, and bleeding into the chest cavity or abdomen. Serious complications are uncommon but are possible, including hepatic failure, hydrothorax, bile duct leaks, intraperitoneal bleeding, and tumor seeding (spill of tumor cells and subsequent growth in an adjacent site).[35,38]

Table A. Local nonsurgical therapies for CRC liver metastases reviewed in this report (continued)

Therapy	Treatment Strategy	Mechanism of Cell Death	Setting	Performed By	Specific Harms
Ablation (continued)	Microwave ablation (MWA)	MWA uses high-frequency electromagnetic radiation to create heat through the excitation of water molecules.[22] The heat causes thermal damage that leads to coagulation necrosis.	This type of treatment typically does not require a hospital stay if the percutaneous method is used. An open procedure requires an abdominal incision under general anesthesia and results in a longer recovery period.	Interventional Radiologist	Very little has been published about complications associated with MWA.[36] Many patients experience a low-grade fever and pain for a few days following MWA. Major complications include liver abscess, bile duct injury, pleural effusion, intestinal obstruction, infections, bleeding and skin burn, and potential inadvertent injury to adjacent structures.[35,36]
Embolization and Transarterial Therapy	Transarterial embolization (TAE)	TAE uses an embolizing agent for selective catheterization and obstruction of the arterial vessel that supplies blood to the tumor.[39]	Most patients can be discharged several hours after treatment with TAE, but an overnight stay is typically required if postembolization syndrome occurs.	Interventional Radiologist	Side effects differ depending on the type of embolization used. Common complications reported are postembolization syndrome (fever, pain, extreme fatigue, nausea/vomiting); infection in the liver; hepatic abscess; gallbladder inflammation; and blood clots in the main blood vessels of the liver. Serious complications are uncommon but possible. Embolization also reduces some of the blood supply to normal liver tissue. This may be dangerous in patients with underlying diseases such as hepatitis or cirrhosis.[40]

Table A. Local nonsurgical therapies for CRC liver metastases reviewed in this report (continued)

Therapy	Treatment Strategy	Mechanism of Cell Death	Setting	Performed By	Specific Harms
Embolization and Transarterial Therapy (continued)	Transarterial chemoembolization (TACE)	TACE involves administering a chemotherapeutic agent directly to the liver tumor to cause ischemia. A chemotherapeutic solution (frequently doxorubicin or cisplatin) is suspended in lipiodol (an oily contrast medium selectively retained within the tumor) and is injected via a catheter into the hepatic arteries that are directly supplying the tumor. Simultaneously, the feeding hepatic arteries are obstructed with an embolizing agent. Tumor ischemia raises the drug concentration, extends retention of the chemotherapeutic agent, and reduces systemic toxicity.	Most patients can be discharged several hours after treatment with TACE, but an overnight stay is typically required if postembolization syndrome occurs.	Interventional Radiologist	Same as above.

Table A. Local nonsurgical therapies for CRC liver metastases reviewed in this report (continued)

Therapy	Treatment Strategy	Mechanism of Cell Death	Setting	Performed By	Specific Harms
Embolization and Transarterial Therapy (continued)	Hepatic artery infusion (HAI)	HAI uses a pump to deliver higher doses of chemotherapy to the tumor compared with systemic chemotherapy, while maintaining low levels of toxicity in the normal tissue. This is achieved by exploiting the unique blood supply to the liver: normal hepatocytes are perfused by the portal vein, whereas the metastases derive most of their blood supply via the hepatic artery. The first-pass effect (a phenomenon of drug metabolism whereby the concentration of a drug is greatly reduced before it reaches the systemic circulation) of drugs delivered to the liver is high.[12,34]	A surgeon intraoperatively places the hepatic artery pump as an indwelling device. The pump delivers chemotherapeutic agent at a slow, fixed rate over a period of several weeks. The pump drug chamber can be refilled percutaneously. Successful hepatic arterial infusion is dependent on surgeon experience with the procedure.[41]	Interventional Radiologist, Surgeon for placement of pump	Complications related to insertion of the pump are rare;[41] however, hepatic artery thrombosis, catheter displacement, hematomas, infections, and liver perfusion are all reported as pump-related complications. The side effects will differ depending upon the type of embolization used. The most common complications reported are postembolization syndrome (fever, pain, extreme fatigue, nausea/vomiting); infection in the liver; hepatic abscess; chemical hepatitis; biliary sclerosis; peptic ulceration; gallbladder inflammation; and blood clots in the main blood vessels of the liver. Serious complications are uncommon but possible. Embolization also reduces some of the blood supply to normal liver tissue. This may be dangerous in patients with underlying diseases such as hepatitis or cirrhosis.[40]

Table A. Local nonsurgical therapies for CRC liver metastases reviewed in this report (continued)

Therapy	Treatment Strategy	Mechanism of Cell Death	Setting	Performed By	Specific Harms
Embolization and Transarterial Therapy (continued)	Radioembolization or selective internal radiation therapy (SIRT)	SIRT involves loading the radionuclide Yttrium-90 into microspheres, which are then placed within the microvasculature of the liver metastases, thus targeting multiple hepatic metastases in a single procedure.[42] The loaded microspheres deliver high localized doses of β-radiation to the tumor while minimizing radiation exposure to the surrounding tissue.[42-44]	Patients are required to undergo a ^{99m}Tc-macro-aggregated albumin (MAA) scan prior to SIRT to assess eligibility.[45] The SIRT procedure takes approximately 90 minutes, and patients can typically return home 4 to 6 hours following treatment.	Interventional Radiologist	The side effects will differ depending on the type of embolization used. The most common complications reported are postembolization syndrome (fever, pain, extreme fatigue, nausea/vomiting); infection in the liver; hepatic abscess; gallbladder inflammation; and blood clots in the main blood vessels of the liver. Serious complications are uncommon but possible.[40] Acute toxicity events include gastritis, ulceration, or pancreatitis due to microsphere deposition in vessels serving these organs.[45] Radiation-induced liver disease (jaundice, weight gain, painful hepatomegaly, and elevated liver enzymes); thrombocytopenia; encephalopathy; elevated results of liver function tests; ascites; and hypoalbuminemia.
	Drug-eluting beads (DEB)	This transarterial embolization system uses a drug-loaded (typically with doxorubicin or cisplatin), superabsorbent polymer microsphere to release drug gradually into the tumor, allowing longer intratumoral exposure and less systemic exposure to the drug.[46]	Most patients can be discharged several hours after treatment, but an overnight stay is typically required if postembolization syndrome occurs.	Interventional Radiologist	The side effects will differ depending on the type of embolization used. The most common complications reported are postembolization syndrome (fever, pain, extreme fatigue, nausea/vomiting); infection in the liver; hepatic abscess; gallbladder inflammation; and blood clots in the main blood vessels of the liver. Serious complications are uncommon but possible.[40]

Table A. Local nonsurgical therapies for CRC liver metastases reviewed in this report (continued)

Therapy	Treatment Strategy	Mechanism of Cell Death	Setting	Performed By	Specific Harms
Radiotherapy	External-beam three-dimensional conformal radiation therapy (3D-CRT)	This type of radiotherapy uses computer-assisted tomography scans (CT or CAT scans), magnetic resonance imaging scans (MR or MRI scans), or both to create detailed, 3D representations of the tumor and the surrounding organs. The radiation oncologist uses these computer-generated images to shape radiation beams to the exact size and shape of the tumor, which is intended to spare nearby healthy tissues from exposure.	Each treatment lasts only a few minutes, although the setup time usually takes longer. Most often, radiation treatments are given 5 days a week for several weeks. The patient's diagnosis determines the total duration of treatment.[47,48]	Radiation Oncologist, Medical Physicist, Dosimetrist, Radiation Therapist, and Radiation Therapy Nurse	Possible side effects of external radiation therapy include sunburn-like skin problems, nausea, vomiting, and fatigue. These typically subside post-treatment. Radiation might also make the side effects of chemotherapy worse.[40] Radiation-induced liver disease is the major dose-limiting toxicity.[49]
	External-beam intensity-modulated radiotherapy (IMRT)	This approach to radiotherapy allows the radiation oncologist to vary both the intensity of a radiation beam and the angle at which it is delivered to the patient. This is intended to deliver a high dose of radiation to the tumor while significantly reducing the exposure of surrounding normal tissue. IMRT offers more refined radiation dosing compared with traditional 3D-CRT.	Same as 3D-CRT, but IMRT requires slightly longer daily treatment times and additional planning and safety checks before the patient can start the treatment.[50]	Same as 3D-CRT	Same as 3D-CRT.
	Stereotactic body radiation therapy (SBRT)	This type of external-beam radiation therapy delivers a high dose of radiation with high targeting accuracy to an extracranial target within the body, in either a single dose or a small number of fractions.[51]	Before treatment, patients may be asked to undergo placement of a fiducial marker (an object used in concert with imaging to provide precise location information), which is commonly performed as an outpatient procedure. SBRT typically consists of one to five treatment sessions over the course of 1 to 2 weeks, and is usually performed as an outpatient procedure.[52]	Same as 3D-CRT and IMRT	Same as 3D-CRT and IMRT.

Scope and Key Questions

The objective of this systematic review is to characterize the comparative effectiveness and harms of various local hepatic therapies for liver metastases from unresectable CRC in two distinct patient populations:

- Patients with unresectable, liver-dominant (i.e., majority of disease located in the liver) metastases who are not eligible for continued systemic chemotherapy because their disease is refractory (i.e., they have experienced disease progression while on therapy).
- Patients who are candidates for local liver therapies as an adjunct to systemic chemotherapy.

There is extensive uncertainty surrounding the optimal use of the various local hepatic therapies. Because of the prevalence of CRC and the high likelihood of metastases, especially to the liver, this topic is important to health care providers, patients, and policymakers.

We addressed four Key Questions (KQs) for the two patient populations described above:

KQ1. What is the comparative effectiveness of the various liver-directed therapies in patients whose disease is refractory to systemic therapy for unresectable CRC metastases to the liver and who have minimal evidence of extrahepatic disease?

KQ2. What are the comparative harms of the various liver-directed therapies in patients whose disease is refractory to systemic therapy for unresectable CRC metastases to the liver and who have minimal evidence of extrahepatic disease?

KQ3. What is the comparative effectiveness of the various liver-directed therapies in patients who are candidates for local hepatic therapy as an adjunct to systemic therapy for unresectable CRC metastases to the liver and have no evidence of extrahepatic disease?

KQ4. What are the comparative harms of the various liver-directed therapies in patients who are candidates for local hepatic therapy as an adjunct to systemic therapy for unresectable CRC metastases to the liver and have no evidence of extrahepatic disease?

Table B provides the PICOTS (population, intervention, comparator, outcome, timing, and setting) for the KQs.

Table B. PICOTS (patient, intervention, comparator, outcome, timing, and setting) for the KQs

PICOTS	KQs 1 and 2	KQs 3 and 4
Population	Patients with unresectable liver metastases from primary CRC who are refractory to systemic chemotherapy but are candidates for local hepatic therapy. • Patients whose hepatic metastases are unresectable due to medical comorbidities, such as low hepatic reserve, cardiac insufficiency, or poor performance status • Patients whose hepatic metastases are unresectable because of certain characteristics of the metastases • Patients with no or minimal extrahepatic disease	Patients with unresectable liver metastases from primary CRC who receive systemic chemotherapy with local hepatic therapy. • Patients whose hepatic metastases are unresectable because of medical comorbidities, such as low hepatic reserve, cardiac insufficiency, or poor performance status • Patients whose hepatic metastases are unresectable because of certain characteristics of the metastases • Patients who have synchronous hepatic metastases • Patients whose hepatic metastases have recurred after resection • Patients with no extrahepatic disease
Intervention	• Cryosurgical ablation • Radiofrequency ablation (RFA) • Microwave ablation (MWA) • Transarterial embolization (TAE) • Transarterial chemoembolization (TACE) • Hepatic arterial infusion (HAI) • Radioembolization or selective internal radiation therapy (SIRT) • Drug-eluting beads (DEB) • External beam with 3D-CRT or IMRT • Stereotactic body radiation therapy (SBRT)	Same as KQs 1 and 2.
Comparator	All the therapies listed above compared with the intervention in question for patients not eligible for systemic chemotherapy for CRC.	All the therapies listed above compared with the intervention in question for patients receiving systemic chemotherapy for CRC.
Outcome	**KQ1:** Ultimate outcomes: Survival and quality of life Intermediate outcomes: Time to progression, local recurrence, and length of stay **KQ2:** Adverse outcomes: biloma, hepatic abscess, hepatic hemorrhage, elevated alkaline phosphatase, elevated bilirubin, elevated transaminases, injury to adjacent organ(s), liver failure, rare adverse events, and steatohepatitis	**KQ3:** Ultimate outcomes: Same as KQs 1 and 2 Intermediate outcomes: Time to recurrence, local recurrence, and length of stay **KQ4:** Adverse outcomes: Same as KQs 1 and 2
Timing	The relevant periods occur at the time of treatment of CRC hepatic metastases through followup over months or years.	Same as KQs 1 and 2.
Setting	Inpatient and outpatient.	Same as KQs 1 and 2.

3D-CRT = three-dimensional conformal radiotherapy; CRC = colorectal cancer; IMRT = intensity-modulated radiation therapy; KQ = Key Question

Methods

Topic Refinement and Review Protocol

The topic for this report was nominated in a public process. With input from Key Informants, the Evidence-based Practice Center (EPC) drafted the initial KQs and, after approval from AHRQ, posted them to a public Web site for 4 weeks for comment. We modified the KQs and the PICOTS based on these comments and discussion with the Technical Expert Panel (TEP). The initial KQs and interventions were stratified by intent of treatment (palliative or curative). This stratification seemed clinically inappropriate and potentially confusing because some interventions could be applied to palliate symptoms and to eliminate (i.e., cure) the liver metastases. The final KQs are distinguished by the population receiving local hepatic therapy (i.e., liver-directed). To be consistent with clinical practice, we modified KQs 1 and 2 to include patients with minimal rather than no extrahepatic disease. In addition, we categorized the 12 interventions to apply to all KQs, we removed some interventions, and we added SBRT. Finally, we expanded the list of harms to be considered.

Data Sources and Selection

To ensure the applicability of the interventions and outcomes data to current clinical practice, MEDLINE® and Embase® were searched for randomized, nonrandomized comparative and observational studies that treated patients between January 1, 2000, and June 27, 2012. Date restrictions were selected to ensure applicability of the interventions. Prior to 2000, some interventions were in their infancy and based on current standards used outdated regimens.[53,54,55] Thermal therapies were not used significantly until the late 1990s, and major changes in proton beam and stereotactic therapy occurred during that same period.[56] Chemoembolization drugs and embolic mixtures have also changed a great deal in the last 10 years and are more standard now. For these reasons, which the TEP strongly supported, we excluded studies where patient treatment preceded 2000. The searches were also limited to the English language.[57] It was thought that the exclusion of non–English-language articles from this review would not have an impact on the conclusions. The gray literature was also searched, including in databases with regulatory information, clinical trial registries, abstracts and conference papers, grants, federally funded research, and manufacturing information.

Titles and abstracts were screened in duplicate for studies that looked at overall survival, adverse events, and quality of life among our populations of interest. To be excluded, a study needed to be independently excluded by two team members. In cases where there was disagreement, a second-level abstract screening was completed by two independent reviewers. A third reviewer was consulted when necessary. Full-text review was performed when it was unclear if the abstract met study selection criteria.

Data Extraction and Quality (Risk of Bias) Assessment

Data extraction was performed directly into tables created in DistillerSR, with elements defined in an accompanying data dictionary. All team members extracted a training set of five articles into evidence tables to ensure uniform extraction procedures and test the utility of the table design. All data extractions were performed in duplicate, with discrepancies identified and resolved by consensus. The full research team met regularly during the period of article extraction to discuss any issues related to the extraction process. Extracted data included patient

and treatment characteristics, outcomes related to intervention effectiveness, and information on harms. Harms included specific negative effects, including the narrower definition of adverse effects. Data extraction forms used during this review are presented in the main report in Appendix C.

Where applicable, we followed the Methods Guide[39] in the assessment of risk of bias in individual studies. Our assessment of risk of bias in the included case-series intervention studies was based on a set of study characteristics proposed by Carey and Boden.[58] The Carey and Boden assessment tool does not conclude with an overall score of the individual study. We created thresholds for converting the Carey and Boden[58] risk assessment tool into AHRQ standard quality ratings (good, fair, and poor) to differentiate case-series studies of varied quality. These distinctions were used for differentiation within the group of case-series studies, but not for the overall body of evidence described below. The classification into these categories (i.e., good, fair, poor) is distinct for a specific study design. For a study to be ranked as good quality, each of the Carey and Boden[58] criteria must have been met. For a fair-quality rank, one criterion was not met, and a rank of poor quality was given to studies with more than one criterion not met. These quality ranking forms can be found in the main report in Appendix D.

Data Synthesis

Evidence tables were completed for all included studies, and data are presented in summary tables. Evidence is also presented in text organized by outcome and intervention. No direct comparisons are made. We considered whether formal data synthesis (e.g., meta-analysis) would be possible from the set of included studies. Because the literature was so heterogeneous in terms of the populations (e.g., prior treatments, reason for unresectability, and number and size of lesions) and interventions (e.g., drugs and dose) studied, we concluded that pooling data would be inappropriate for this review. Thus, all data synthesis is based on qualitative summaries and analyses.

Strength of the Body of Evidence

We graded the strength of evidence using two independent reviewers and resolved disagreements by consensus discussion or adjudication by a third reviewer. The system used for grading the strength of the overall body of evidence is outlined in the Methods Guide,[39,59] which is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[60] This system explicitly addresses the following domains: risk of bias, consistency, directness, and precision. The strength of evidence grade can fall into one of four categories: high, moderate, low, and insufficient. The grade rating was made by independent reviewers, and disagreements were resolved by consensus adjudication.

In this review, consistency of the body of literature was graded as “not applicable.” The direction of effect cannot be assessed in noncomparative studies; therefore, consistency in the direction of effect across case series cannot be discerned. In the absence of a comparator, we do not know if the observed estimate is better or worse; therefore, we concluded that consistency was not applicable. Directness pertains to the whether the evidence links the interventions directly to a health outcome. Due to the absence of direct comparisons precision will be rated imprecise.

Results

Of the 937 records identified through the literature search, we excluded 913 at various stages of screening and included 24 records.[61-84] We included one hand-searched article,[85] two published studies from scientific information packets,[86,87] and three articles from conference abstracts.[88-90] A total of 30 articles were included in this report: 29 case series and one RCT[85] for which a single arm was abstracted as a case series. This RCT compared radiofrequency ablation (RFA) with systemic chemotherapy to systemic chemotherapy alone. The scope of the review was liver-directed therapy versus liver-directed therapy. Systemic chemotherapy alone was not a relevant intervention or comparator for this review. Only the RFA combined with systemic chemotherapy arm was abstracted and included in this report as it is relevant for KQ3 and KQ4 (Table C).

Table C. Characteristics of studies included in this review by intervention

Characteristic	RFA	TACE	HAI	RE	DEB	SBRT	RFA With SC	HAI With SC	RE With SC	Total Arms*
Total	1	2[a]	2	13[a]	3	3	3	2	2	31
Study Design										
Prospective Case Series	0	0	0	6	2	1	2[b]	1	1	13
Retrospective Case Series	1	2	2	7	1	2	1	1	1	18
Outcomes Reported										
Overall Survival	1	2	2	13	3	3	3	2	2	31
Quality of Life	0	0	0	1	1	0	1	0	0	3
Time to Recurrence	0	0	0	0	0	0	0	0	0	0
Length of Stay	0	1	0	0	1	0	0	0	0	2
Local Recurrence	1	0	0	0	0	2	3	0	0	6
Adverse Events	1	2	2	13	3	3	3	2	2	31
Study Population										
United States	0	2	0	7	1	0	0	0	0	10
Europe	1	0	1	4	2	2	1	0	1	12
Australia	0	0	0	1	0	0	1	0	1	3
Asia	0	0	1	1	0	1	1	2	0	6
Total Participants (N)	68	142	67	454	157	43	101	36	159	1,227

DEB = drug-eluting beads; HAI = hepatic arterial infusion; N = number; RE = radioembolization; RFA= radiofrequency ablation; SBRT = stereotactic body radiotherapy; SC = systemic chemotherapy; TACE = transarterial chemoembolization
Note: No studies reporting on cryosurgical ablation, MWA, TAE, 3D-CRT, or IMRT met inclusion criteria for this review.
*The total number of articles included in this review is 30.
[a]Hong et al. reports on both TACE and RE interventions.
[b]The study by Ruers et al. is an RCT that was extracted as a case series.

KQs 1 and 2

KQs 1 and 2 focus on the comparative effectiveness (KQ1) and harms (KQ2) of the patient population that was ineligible for systematic therapy and had no or only minimal evidence of extrahepatic disease. The evidence base comprised 23 case series and 931 patients. No comparative study met inclusion criteria for this review.

Key Points

- The evidence is insufficient to draw conclusions about overall survival, quality of life, or adverse events (Table D). Due to the absence of comparative data, we are limited in drawing conclusions regarding the efficacy and effectiveness of these interventions. Risk of bias is a primary concern in observational studies. Intended effects are likely to be biased by preferential prescribing of the intervention based on the patients' prognosis.
- All studies were case series. Carey and Boden quality rankings were converted into AHRQ "good," "fair," and "poor" ratings. Eleven studies were rated as good quality,[64, 66,67,69,71,73-75,80,88,90] nine studies as fair quality,[61,63,76,81,82,84,86,87,89] and three studies as poor quality.[65,69,72]
- The assessment of applicability of the study findings to clinical practice is limited by the poor characterization of the patient populations (e.g., number and size of metastases, performance status) and variations in the delivery of the interventions (e.g., surgical approach, dose and drugs delivered).

Table D. Strength of evidence for KQ1 and KQ2

Outcome	Intervention	Strength of Evidence	Summary of Included Studies
Overall Survival	TACE with DEB	Insufficient	Three studies reported overall survival for this intervention.[61,69,88] Two studies[73a,90] defined survival starting from the time of study treatment and reported a median survival of 25 and 19 months. One study[65b] did not report the point from which survival time was measured and reported a 1-year survival of 61%.
	TACE	Insufficient	Two studies reported overall survival for this intervention.[61,66] Both studies defined survival time from diagnosis of liver metastases and reported median survival times of 27 and 26.3 months. Albert and colleagues presented overall survival data out to 5 years and reported 6% survival.
	SBRT	Insufficient	Three studies reported overall survival for this intervention and all defined survival from time of study treatment.[69,80,86] Two studies reported median survival of 25 and 17 months.[71,88] One study did not report median survival but recorded a 2-year survival of 58%.[80]
	HAI	Insufficient	Two studies reported overall survival for this intervention and both defined survival from time of study treatment.[81,90] Median survival was 9.7 months and 6.7 months (95% CI, 5 to 8.3 months).
	RE	Insufficient	Eight studies reported survival from time of study treatment. One study did not reach median survival but reported a 3-year survival of 77%.[84] In the other seven studies, median survival ranged from 4 to 15.2 months.[78,70,73,75,86,89,91] Three studies reported overall survival from diagnosis of liver metastases, with median survival ranging from 31 to 34.6 months.[66,68,76] Two studies did not report the point from which survival was defined. One study reported a median survival of 11.8 months.[65] The other study reported a 1-year survival of 20%.[74]
	RFA	Insufficient	Only one study reported data on overall survival. Survival was defined from time of study treatment and 3-year survival was 68%.[67]

Table D. Strength of evidence for KQ1 and KQ2 (continued)

Outcome	Intervention	Strength of Evidence	Summary of Included Studies
Quality of Life	TACE with DEB	Insufficient	The authors report qualitatively that 18 or 20 patients reported improvement in quality of life post-treatment.[65]
	RE	Insufficient	This study reported quality-of-life data for 14 of 50 participants using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire and Hamilton Rating Scale for Depression. No information was given for why only 14 patients underwent the quality of life assessment. Quality of life was not adversely affected after RE and anxiety was significantly reduced from pretreatment levels. No significant difference was observed in depression scores pre- and post-treatment.[64]
Length of Stay	TACE	Insufficient	Mean length of stay ranged from 1.3 to 3 days.[61,65]
Local Recurrence	SBRT	Insufficient	Both studies reported a local recurrence rate of 33.3%.[69,86]
	RFA	Insufficient	One study reported local recurrence of 18%.[69]
Adverse Events	TACE with DEB	Insufficient	Liver failure of 3% was reported in one study of this intervention.[73] Increased bilirubin was reported in 50% of patients in one study. Other adverse events are listed in Table 9 of the full report.
	TACE	Insufficient	One study reported elevated alkaline phosphatase of varying severity in 19% of patients and grade 1 elevated bilirubin in 1% of patients.[4] Other adverse events are reported in Table 9 of the full report.
	SBRT	Insufficient	One study reported no major complications.[69] Other adverse events are reported in Table 9 of the full report.
	HAI	Insufficient	One study reported no major complications.[81] One study reported 1.8% increased bilirubin.[90]
	RE	Insufficient	Two studies reported no major complications.[82,84] Liver failure was reported in 2% and 2.4% of patients in two studies.[63,64] Elevated alkaline phosphatase in 8% of patients was reported in one study.[74] Two studies reported elevated bilirubin in 10% and 13% of patients.[74,89] All other adverse events are listed in Table 9 of the full report.
	RFA	Insufficient	One study reported no major complications.[67]

DEB = drug-eluting beads; HAI = hepatic arterial infusion; RE = radioembolization; SBRT = stereotactic body radiation therapy
TACE = trans-arterial chemoembolization

KQs 3 and 4

KQs 3 and 4 focus on the comparative effectiveness (KQ3) and harms (KQ4) of the various local hepatic therapies in patients who are received local hepatic therapy as an adjunct to systemic therapy for unresectable CRC metastases to the liver and who had no evidence of extrahepatic disease.

The body of evidence (seven studies) comprises case series with the exception of a single RCT[81] that was included as a single-arm study. Two-hundred ninety-six patients were included from these seven studies. No comparative studies were available that met inclusion criteria.

- No conclusions on overall survival, quality of life, length of stay, time to recurrence, local recurrence, or adverse events can be drawn from the body of evidence comparing local hepatic therapies for unresectable CRC metastases to the liver (Table E).
- The literature base for this review is comprised of case series and one RCT85 that was abstracted as a case-series study due to a nonrelevant comparator. Four studies were ranked as good quality[62,70,78,85] and three were ranked as fair quality.[77,79,83]

- The assessment of applicability of the study findings to clinical practice is limited by the poor characterization of the patient populations (e.g., number and size of metastases, performance status) and variations in the delivery of the interventions (e.g., surgical approach, dose and drugs delivered).

Table E. Strength of evidence for KQ3 and KQ4

Outcome	Adjunctive Therapy	No. of Studies	Risk of Bias	Consistency	Directness*	Precision	Overall Grade
Overall Survival	RFA	3[59,64,66]	High	Not applicable	Direct	Imprecise	Insufficient
	RE	2[39,47]	High	Not applicable	Direct	Imprecise	Insufficient
	HAI	2[58,60]	High	Not applicable	Direct	Imprecise	Insufficient
Quality of Life	RFA	1[66]	High	Not applicable	Direct	Imprecise	Insufficient
Length of Stay	NR	0	High	Unknown	Indirect	Imprecise	Insufficient
Time to Recurrence	NR	0	High	Unknown	Indirect	Imprecise	Insufficient
Local Recurrence	RFA	3[39,64,66]	High	Not applicable	Indirect	Imprecise	Insufficient
Adverse Events	RFA	3[59,64,66]	High	Not applicable	Direct	Imprecise	Insufficient
	RE	2[39,47]	High	Not applicable	Direct	Imprecise	Insufficient
	HAI	2[58,60]	High	Not applicable	Direct	Imprecise	Insufficient

HAI = hepatic arterial infusion; RE = radioembolization; RFA = radiofrequency ablation
*Directness: Evidence is indirect for all comparisons because there is no comparative data, but evidence is direct for assessment of some health outcomes.

Key Points

- No conclusions on overall survival, quality of life, or adverse events can be drawn from this body of evidence. The strength of evidence is insufficient.

Discussion

Key Findings and Strength of Evidence

No comparative studies met inclusion criteria for any of the four KQs about local hepatic therapy for the treatment of unresectable colorectal cancer (CRC) metastases to the liver. Thirty-one studies met our inclusion criteria and addressed local hepatic therapy for unresectable CRC metastases to the liver.

We assessed the strength of evidence for our primary health outcomes of overall survival and quality of life and for the intermediate outcomes of length of stay, local recurrence, and adverse events for all KQs. In addition, strength of evidence was assessed for the intermediate outcomes of time to progression (KQs 1 and 2) and time to recurrence (KQs 3 and 4). We judged the strength of evidence to be insufficient to draw conclusions for all outcomes. The body of evidence provided no comparative information about differences in effectiveness by type of intervention.

We are not aware of any published systematic reviews of the comparative effectiveness of local hepatic therapies for CRC metastases to the liver, as the literature base does not contain studies comparing one local hepatic therapy with another. Some systematic reviews of single local hepatic therapies have been published. Earlier reviews conforming to a high quality standard interpreted their findings similar to ours in the present review; that is, evidence was insufficient to permit conclusions.[32,91]

This review sought evidence on the comparative benefits and harms of local hepatic therapies in two patient groups for CRC metastasis to the liver. Although we did not find this evidence the strength of the present review is in the identification of this important evidence gap. Distinct patient groups exist within the population receiving local hepatic therapies, yet data to analyze these differences are limited.

Applicability

It is challenging to comment on the applicability of findings from our CER because we found that the available evidence was insufficient for us to draw conclusions. The degree to which the data presented in this report are applicable to clinical practice hinges on the degree to which the populations in the included studies represent the patient populations receiving clinical care in diverse settings, as well as the availability of the interventions. We comment below on the relevance of included studies for population, intervention, comparator, outcomes, timing, and setting (PICOTS) elements. The PICOTS format provides a practical and useful structure to review applicability in a systematic manner and is employed in the subsections that follow.[88]

The goal of any local hepatic therapy for unresectable CRC metastases to the liver is to prolong life by eliminating the metastases if possible or to palliate symptoms such as pain. This report has reviewed the literature on local hepatic therapies to achieve these goals. Due to the noncomparative nature of the literature base, both clinical and policymakers are limited in their ability to apply the published literature base to decisions on effectiveness and comparative effectiveness of these interventions. Survival estimates from individual studies of local hepatic therapies suggest that local hepatic therapies may provide some benefit in terms of survival and symptom relief for some patients, but without comparative data, it is not possible to choose the therapy that will produce the best outcomes for specific patients.

Population and Settings

The question of which subgroups of patients with CRC metastases to the liver may benefit from any particular local hepatic therapy compared with another remains unanswered. This uncertainty is reflected in the heterogeneity of the patient populations included in the published literature. Patient characteristics were often poorly characterized and not uniformly reported. Patients with varying degrees of resectability, extrahepatic disease, portal vein tumor thrombosis, and size and number of lesions are often grouped together and reported on as one group, even though it is uncertain whether these factors are likely to affect outcomes. Patient heterogeneity, combined with poor reporting of stratified or patient-level data, limited our ability to compare patient groups in any meaningful way. As a result, we are currently unable to determine which patients should be receiving which local hepatic therapies.

The setting in which treatment occurs is a major factor in the outcomes of local hepatic therapy. Expertise of both clinicians and centers varies. Based on the available clinical expertise and technology, the choice of a local hepatic therapy may be limited to one option in many centers. Local hepatic therapies, such as radioembolization[93] and hepatic arterial infusion,[94] often

require high levels of training and familiarity with the procedure. Lack of experience may not only affect patient outcomes but also result in adverse effects; patients treated by less-experienced clinicians and centers will likely experience poorer outcomes.

Detailed analysis of differences in outcomes by center has important implications for the relevance of the findings in the literature. Unfortunately, these data were unavailable as part of our systematic review of the published literature.

Interventions

Even for a single local hepatic therapy, variations in how the procedure is performed may be substantial. For instance, variations may occur in the approach (open vs. percutaneous), the choice of chemotherapy drugs delivered, and the schedule of delivery of chemotherapy and radiation therapy. Given the lack of comparative data, the present review did not allow for a more rigorous and systematic comparison of the relative performance of local hepatic therapies stratified by these factors. How these factors may alter health outcomes remains unclear.

Additional heterogeneity exists for the context in which the intervention was delivered. Patients often receive more than one local hepatic therapy over time or more than one session of the same therapy. This often results in variations of prior therapy at study enrollment. The complex treatment history of each patient can further limit the conclusions that can be drawn about the benefits attributable to any one component of the treatment plan.

Comparators

All studies in this review are observational (including the arm of one RCT that was extracted as a case series); as such, they report on the experience of a particular center with one or more local hepatic therapies. Although case series can be useful for hypothesis generation, this approach cannot provide the comparative data the field needs for evaluating effectiveness. The applicability of any case series to another study group is very limited.

Outcomes

Little controversy exists regarding the most appropriate direct health outcomes to measure in a study of local hepatic therapies for CRC metastases to the liver. Overall survival is the ultimate outcome; it was reported in all of the studies included in this review. Quality of life is also a very important patient-centered outcome, but is not routinely reported in the literature in this review.

The importance of outcomes such as disease-free survival or local progression-free survival can be debated, but few experts would suggest that these outcomes replace the need for data on overall survival.

Studies of a comparative design are needed to measure accurately the differences in overall survival, quality of life, and harms that may be attributed to a local hepatic therapy.

Timing

The timing of followup assessment was appropriate given the natural history of unresectable CRC liver metastases and the primary outcome of overall survival. Median survival was reached in 21of 24 studies. We judged this to be an appropriate length of assessment. In addition, two of the studies that did not reach median survival followed patients for up to 3 years to assess overall survival rates.

Research Gaps

In this section, we first present a set of gaps focused on issues in the body of literature. Then we discuss the use of RCTs and observational studies to address these gaps, followed by an example of how a registry might overcome the drawbacks of single-center case series.

Gaps

This systematic review attempted to compare outcomes of local hepatic therapies for patients treated for unresectable CRC metastases to the liver. The review focused on two patient populations: those patients whose disease is refractory to systemic chemotherapy and patients who are receiving local hepatic therapy as an adjunct to systemic chemotherapy. Evidence on patient outcomes is limited, and the strength of evidence is insufficient for us to draw conclusions on effectiveness or harms for either patient population. As detailed above under applicability, there are specific evidence gaps that, if addressed, could enhance this literature base.

We identified four broad evidence gaps during this review. We present them organized by PICOTS framework. No gaps were identified for timing and setting.

- **Populations:** An objective of comparative effectiveness research is to understand the comparative effects for different population subgroups. To achieve this, we must fully delineate the population subgroups of interest. As detailed in the population and setting section above, these data are limited. Future studies must present data by subgroups of interest so that evidence can be interpreted by these variables. Based on published multivariate analyses, examples of patient or tumor characteristics found to be associated with improved overall survival include: ECOG status (0 vs. ≥1 and in another study 0 or 1 vs. ≥2), performance status (0 or 1 vs. ≥ 2), number of extrahepatic metastases sites (0 or 1 vs. ≥2), number of lines of previous chemotherapy (0–1 vs. ≥ 2), performance status (0 or 1 vs. ≥ 2), carcinoembryonic antigen response (Yes, No), and Response Evaluation Criteria in Solid Tumors (RECIST). These variables should be considered when designing future studies. Because there are so many variables being collated, clinical risk scores may be particularly beneficial as a summary measure.[95]
- **Intervention:** There can be substantial variation in the role of local hepatic therapy in the overall treatment strategy for patient populations with unresectable CRC liver metastases reviewed in this report. A thorough delineation of prior and concurrent treatment is necessary to assess the incremental benefit of local hepatic therapy and the comparative outcomes of these therapies for the reviewed patient populations. All other therapies, systemic and local, should be taken into account when evaluating the effectiveness of the intervention under study, as these therapies may have an effect on patient survival. Previous resections and other local hepatic therapies were often not reported in the studies included in this review.
- **Comparator:** A major limitation of the current evidence review was that there was no comparative evidence at the time of publication of this report comparing the various liver-directed therapies with one another.
- **Outcomes:** Outcomes of interest to patients and their physicians include survival, quality of life, and adverse effects such as radiation-induced liver disease, liver failure, and local recurrence (i.e., treatment failure). Evidence comparing these outcomes of local hepatic therapies in the populations of interest for the review are needed. For survival and other

time-to-event outcomes, it is essential for authors to report the time point from which the event was measured (e.g., time from liver-directed therapy, time from CRC diagnosis, time from diagnosis of metastases).

Collection and reporting of quality-of-life data (e.g., pain) using standard measurement tools was inconsistently reported in the literature included in this review. These data are particularly important for the population of patients in which palliation of symptoms, rather than cure, is the intent of therapy.

Study Designs To Address These Gaps

RCTs are the gold standard of clinical evaluation, and there is an absence of randomized controlled clinical trial evidence on the use of local hepatic therapies for the included indications. Because we were unable to find comparative studies to answer any of our KQs, we conducted additional discussions with members of our Technical Expert Panel (TEP) to elicit ideas that could address the gaps in the literature. TEP members identified common barriers to conducting RCTs that would answer our KQs, including limited sources of research funding to support RCTs, reluctance of physicians to randomize patients, and reluctance of patients to be randomized.

In addition to the resistance to randomize, consensus around the most compelling hypothesis for a comparative RCT is lacking. Clinical investigators have competing hypotheses of which treatment is best suited for which patients, and these hypotheses are often based on their own institution's experience. TEP members agreed that certain broad categories of patients with CRC metastasis to the liver, such as the populations included in this review, may well benefit from local hepatic therapies, but they also recognized that the published literature did not permit analysis of patient subgroups to identify characteristics more favorable to one local hepatic therapy over another. RCTs with well-documented patient and treatment characteristics could address the lack of comparative evidence. Lack of funding sources will continue to be an issue under the current regulatory structure. Under this system, the FDA does not require the same level of evidence for device approval as it does for drug approval. Because device companies can obtain approval without data from RCTs, they have very little incentive to provide funding.[92]

Regardless of the study design, we suggest that studies aiming to address the effectiveness or comparative effectiveness of local hepatic therapies take care to address potential confounders and effect measure modification that could obscure the results. This is particularly important for patient characteristics such as size and number of metastases and performance status, which could serve as both modifiers of the effectiveness and factors that are considered when choosing the best local hepatic therapy.

Although RCTs may not be possible for all comparisons in all centers, multivariate analyses from existing case series can aid in identifying additional factors that should be documented and potentially controlled for in the comparative analysis of these data. Several factors were identified in multivariate analyses in the literature base of this report that impacted overall survival. The following factors should be collected and considered in future studies: number and size of lesions, number of extrahepatic metastases, previous treatment history (i.e., number of lines of previous chemotherapy), CEA, performance status, and tumor response. These analyses can enhance the design of future RCTs or observational studies.

Patient Registries

In the absence of consensus regarding the most salient comparative research question, observational data could be useful in driving the generation and prioritization of hypotheses for future research. One approach is the use of a registry to systematically collect observational data. According to the Agency for Healthcare Research and Quality publication on registries for evaluating patient outcomes, patient registries are often constructed to study patient outcomes, the natural history of disease, and disease management under various treatment scenarios.[97] Registries need to be created with a question in mind, which will then guide the identification of the target patient population, the interventions of interest (e.g., a local hepatic therapy), the outcomes of interest, the number of patients (to be adequately powered for future analysis), and the length of followup.

The KQs from this CER could serve as guide for designing one or more registries focused on this clinical area. The aim would be to establish a prospective registry that tracks the outcomes, quality of life, and adverse events in those who receive local nonsurgical treatment for unresectable metastatic CRC to the liver in order to identify the most effective local hepatic therapy strategies. The effectiveness of any one local hepatic therapy is expected to vary by patient subgroup. Provider experience with the local hepatic therapy is also an important factor in patient outcomes. We have identified a core set of variables or core dataset, defined as the information set needed to address the critical questions the registry is developed to answer. This is presented in Table F, organized by PICOTS.

Table F. Core dataset elements for local hepatic therapy registry by PICOTS

Population	Intervention	Comparators	Outcomes	Timing	Setting
Patient Characteristics Age Sex Race Ethnicity Performance status LDH CEA Clinical risk scores (e.g., Fong)[95] **Tumor Characteristics** Location of tumor Size of lesions Number of lesions Tumor volume Portal vein obstruction Course of disease (stabilization, rapid progression) **Other Treatments** Number, dose, and duration for lines of prior therapy by drug Number, dose, and duration for lines of adjunctive therapy by drug Previous liver-directed therapy	**Type of Local Hepatic Therapy** Cryosurgical ablation RFA MWA TAE TACE HAI RE DEB 3D-CRT IMRT SBRT **Characteristics of Local Hepatic Therapy** Dose Duration Surgical site	Same as Intervention	Overall survival Quality of life Response (e.g., complete, partial, no response) Recovery time Length of stay Adverse effects (Short-term and long-term harms) Treatment holidays*	Ongoing	Hospital type Number of procedures by practitioner Type of practitioner Local hepatic therapy availability Inpatient or outpatient procedure

3D-CRT = three-dimensional conformal radiation therapy; CEA = carcinoembryonic antigen; DEB = drug-eluting bead; HAI = hepatic artery infusion; IMRT = intensity-modulated radiation therapy; LDH = lactate dehydrogenase; RE = radioembolization; RFA = radiofrequency ablation; SBRT = stereotactic body radiation therapy; TACE = transarterial chemoembolization; TAE = transarterial embolization

*Treatment holidays refer to time away from systemic chemotherapy and may vary based on the success of treatment with a local hepatic therapy.

Conclusions

Due to the absence of comparative data, the evidence is insufficient for us to draw conclusions about the comparative effectiveness of local hepatic therapies for unresectable CRC metastases to the liver for the patient populations addressed in this review. Important outcomes of therapy include overall survival, quality of life, and adverse effects (harms). A patient registry is one tool for future research that may generate hypotheses for clinical trials or observational evidence on the comparative effectiveness of local hepatic therapies.

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Introduction

Background

This report aims to compare the effectiveness and harms of several local hepatic therapies for unresectable colorectal cancer (CRC) metastases to the liver. In the sections that follow, we describe CRC and its diagnosis and treatment to orient the reader to the disease. This is followed by a discussion of the treatment of CRC liver metastasis. The local hepatic therapies included in the review are described in detail.

Condition

CRC is the third most frequently diagnosed cancer and the second leading cause of cancer death in the United States.[1] It is a cancer that forms in the tissues of the colon and the rectum. Most colorectal cancers are adenocarcinomas, meaning that they are a cancer of the epithelium originating from glandular tissue. Adenocarcinomas develop from adenomas, which are noncancerous tumors in the epithelial tissue. Over time, adenomas can become cancerous. This progression from adenoma to adenocarcinoma occurs through a sequential process of accumulating genetic changes.[2] Although the most common type of CRC is adenocarcinoma, squamous carcinoma and adenosquamous carcinoma have been reported infrequently.[3]

An elevated risk of CRC has been associated with obesity, low physical activity, high dietary intake of refined sugars, low dietary intake of fiber, consumption of meat, and consumption of more than two alcoholic drinks per day.[4] A reduction in risk has been linked to the intake of dietary calcium and diets high in fiber and potassium.[5,6]

Diagnosis and Treatment of Colorectal Cancer

The diagnosis of CRC requires pathologic review to characterize and stage the tumor. The Tumor, Node, and Metastases (TNM) staging system is recommended for the staging of CRC, but other staging systems, such as Dukes and Astler-Coller, are widely used.[7]

Approximately 39 percent of new cases are diagnosed in the localized state, (i.e., no metastases or spread to regional lymph nodes); 36 percent present with regional spread to lymph nodes; 20 percent present with distant, metastatic cancer; and 5 percent present with unstaged disease.[8] The 5-year survival rate estimated by the National Cancer Institute Surveillance Epidemiology and End Results program (SEER) data analysis was found to be 74.1 percent for stage I, 64.5 percent for stage IIA, 51.6 percent for stage IIB, 32.3 percent for stage IIC, 74 percent for IIIA, 45 percent for IIIB, 33.4 percent for IIIC, and 6 percent for stage IV.[9] Survival declines with increasing depth of tumor penetration, increasing tumor stage, and patient age. For the 20 percent of patients who are initially diagnosed with distant (i.e., metastatic) disease, the 5-year survival rate is 10 percent or less with treatment. Patients with untreated liver metastases have 5-year survival rate of less than 3 percent.[10] Survival differs by the extent of liver metastases. Patients with a solitary metastasis have a median survival of 21 months; those with multiple metastases confined to one lobe have median survival of 15 months; and those with widespread bilobar disease have a median survival of less than 12 months.[10]

Treatment of Localized Disease

For the 39 percent of patients who are diagnosed with localized disease, the cornerstone of treatment is surgery.[8] Advances in surgical technique, such as total mesorectal excision

(dissection of the entire intact vascular, lymphatic, and fatty tissues) rather than blunt dissection, have improved local recurrence rates. Local recurrence rates have decreased from as high as 50 percent to less than 10 percent in some cases.[11] Patients whose disease was entirely removed through surgery may be offered adjuvant (i.e., after surgery) chemotherapy or radiation therapy to lower their risk of cancer recurrence. In the past 20 years, adjuvant therapy has evolved from experimental treatment to standard of care. For example, patients with stage III colon cancer who received postsurgical FOLFOX chemotherapy had a 3-year survival rate of 75 percent compared with 25 percent in the pre-adjuvant chemotherapy era.[11] Trials are currently being undertaken to determine if adjuvant treatment also improves overall survival compared with surgery alone.

Treatment of Distant Disease

CRC is the most common malignancy that metastasizes to the liver: 25 percent of colon cancer patients present with primary CRC and synchronous liver metastases (i.e., the primary disease and liver metastases are diagnosed at the same time), and another 50 percent develop metachronous disease (i.e., liver metastases develop after the initial diagnosis).[12] For some proportion of patients, the liver may be the only site of metastasis. Autopsy studies have shown that 38 percent of patients who died of metastatic CRC had liver-only metastasis.[13] Thus, therapies directed at the liver ("local hepatic therapies") have been used with the goal of extending survival in these patients.[14]

Surgical Resection

Although the prognosis for patients with metastatic CRC to the liver has been historically quite poor, advances in surgical technique have improved outcomes for patients with liver-confined metastases. In some situations, treatment of limited liver-only metastases may be curative. For example, in patients with resectable liver-only metastases, several studies have demonstrated durable long-term survival in selected patients, with 5-year survival estimates ranging between 30 percent and 58 percent.[15-21] CRC liver metastases are defined as resectable when it is anticipated that disease can be completely resected with negative margins, two adjacent liver segments can be spared, adequate vascular inflow and outflow and biliary drainage can be preserved, and adequate liver volume (20 to 25 percent) will remain postsurgery.[22, 23] Approximately 20 to 30 percent of patients with CRC liver metastases are candidates for this approach. Some patients with lesions not well suited for resection may also receive radiofrequency ablation at the time of surgery.

In cases where patients may not have resectable liver metastases at diagnosis, systemic chemotherapy may be used to shrink the tumor and "convert" it to resectable disease.[24] Similar to patients with initially resectable liver metastases, these patients may also experience promising 5-year survival rates or approximately 30 percent. Hepatotoxicity from preoperative chemotherapy (e.g., steatohepatitis, sinusoidal injury) is an important concern in these patients.

Local Nonsurgical Treatment Strategies

Despite improved surgical techniques and systemic chemotherapy options, many patients may remain ineligible for resection because of anatomic constraints (tumor location or extent of metastatic lesions), inadequate hepatic functional reserve, or concurrent medical comorbidities such as poor performance status (functional impairment typically defined by a higher Eastern Cooperative Oncology Group [ECOG] grade or a lower Karnofsky score) and cardiac insufficiency.[25]

For patients with unresectable metastatic disease, local hepatic therapy may be used in an attempt to prolong survival or to palliate symptoms (e.g., pain) in patients for whom a cure is no longer within reach. Local hepatic therapy may be used for the following care scenarios:

1. Patients with unresectable, liver-dominant metastases (i.e., majority of disease located in the liver) who are not eligible for continued systemic chemotherapy because their disease is refractory (i.e., they have experienced disease progression while on therapy). These patients generally have large-volume disease and may be offered treatment to debulk the tumor and palliate symptoms when present.[26] Regardless of the local hepatic therapy, patients should have liver-only metastases or liver-dominant metastases. In general, it is acceptable to have minimal extrahepatic disease (e.g., a single lung nodule) and remain a treatment candidate.
2. Patients with unresectable liver metastases at diagnosis or with limited unresectable hepatic recurrence after previous resection and who are candidates for local hepatic therapy.[27] In these patients, local hepatic therapies can be used as an adjunct to systemic chemotherapy with curative intent. The volume of disease in these patients is small, either in terms of lesion size or number of lesions.[28] These treatments are only appropriate when the entire tumor can be ablated with clear margins. To be considered a candidate for ablation or radiation therapy, patients treated in this setting should have no extrahepatic spread.

Several local hepatic therapies have been developed to treat patients with hepatic metastases of CRC. In the continuum of care, use of a local hepatic therapy may occur before or after the use of systemic chemotherapy, but it is administered most often in conjunction with systemic chemotherapy. Local hepatic therapies are divided into three groups: (1) ablation (destruction of tissue through procedures involving heating or cooling); (2) embolization (the selective blockage of blood vessels, often with agents that carry a drug to the occluded site); and (3) radiotherapy (directed radiation to destroy abnormal cells). Table 1 presents a list of the 12 interventions and their mechanisms of action, the setting in which treatment is performed, who performs the intervention, and the specific harms reported for each. The table presents these interventions grouped by type of ablation, embolization, and radiotherapy approach.

In patients with unresectable hepatic metastases, local hepatic therapy represents an opportunity to treat the major site of disease without exposing patients to the side effects of chronic systemic chemotherapy. Similarly, patients who have exhausted all palliative chemotherapeutic options may benefit from local hepatic therapy as a means of delaying disease progression and, in turn, delaying or preventing liver function deterioration and liver failure. Although nonsurgical local hepatic therapies are not generally considered to be curative options, selected patients may experience effective symptom palliation and, in some cases, long-term disease control.

Guidelines from the National Comprehensive Cancer Network for metastatic CRC state that ablative therapy for the metastases can be considered when all measurable metastatic disease can in fact be treated.[29] However, the group provides no guidance on which ablative therapy is optimal or on the comparative benefits and harms of the various palliative treatments.[29] A perception of clinical equipoise and limited RCT data comparing local hepatic therapies[30,31] contribute to uncertainty regarding which techniques, either alone or in combination, may be preferable for certain patient groups.

Table 1. Local nonsurgical therapies for CRC liver metastases reviewed in this report

Therapy	Treatment Strategy	Mechanism of Cell Death	Setting	Performed By	Specific Harms
Ablation	Cryosurgical ablation	The mechanism of action is based on the rapid formation of intracellular ice crystals during the freezing process. The procedure uses repetitive freezing and thawing of the tissue to produce necrosis and irreversible tissue damage, which occurs at temperatures between -20 and -40°C.[32,33]	This type of treatment typically does not require a hospital stay if the percutaneous method is used. An open procedure requires an abdominal incision under general anesthesia and results in a longer recovery period.	Interventional Radiologist	Serious complications are uncommon but are possible, and for cryosurgical ablation include cryoshock phenomenon (acute renal failure, acute respiratory distress syndrome, disseminated intravascular coagulation, and liver failure); myoglobinuria leading to renal failure; bile leakage; hepatic abscess; pleural effusion; consumptive coagulopathy; thrombocytopenia; hepatic iceball fracture; organ failure; and biliary fistula.[34,35]
	Radiofrequency ablation (RFA)	RFA is performed by generating an alternating current between at least two electrodes in the radiofrequency range that generates heat without muscle contraction. The procedure generates tissue temperatures of 90 to 100°C, which causes protein denaturation and coagulative necrosis.[23]	The procedure is performed under intravenous narcotics for the percutaneous awake approach and does not require a hospital stay. For laparoscopic or open RFA, the procedure is performed under general anesthesia and results in a longer recovery period.[36] Each RFA takes approximately 10 to 30 minutes, with additional time required if multiple ablations are performed. The entire procedure is usually completed within 1 to 3 hours.[37]	Interventional Radiologist, Surgeon	Possible side effects after RFA therapy include abdominal pain, mild fever, increase in liver enzymes due to damage to the bile ducts, abscess, infection in the liver, skin burns, and bleeding into the chest cavity or abdomen. Serious complications are uncommon but are possible, including hepatic failure, hydrothorax, bile duct leaks, intraperitoneal bleeding, and tumor seeding (spill of tumor cells and subsequent growth in an adjacent site).[34,37]
	Microwave ablation (MWA)	MWA uses high-frequency electromagnetic radiation to create heat through the excitation of water molecules.[23] The heat causes thermal damage that leads to coagulation necrosis.	This type of treatment typically does not require a hospital stay if the percutaneous method is used. An open procedure requires an abdominal incision under general anesthesia and results in a longer recovery period.	Interventional Radiologist	Very little has been published about complications associated with MWA.[35] Many patients experience a low-grade fever and pain for a few days following MWA. Major complications include liver abscess, bile duct injury, pleural effusion, intestinal obstruction, infections, bleeding and skin burn, and potential inadvertent injury to adjacent structures.[34,35]

Table 1. Local nonsurgical therapies for CRC liver metastases reviewed in this report (continued)

Therapy	Treatment Strategy	Mechanism of Cell Death	Setting	Performed By	Specific Harms
Embolization and Transarterial Therapy	Transarterial embolization (TAE)	TAE uses an embolizing agent for selective catheterization and obstruction of the arterial vessel that supplies blood to the tumor.[38]	Most patients can be discharged several hours after treatment with TAE, but an overnight stay is typically required if postembolization syndrome occurs.	Interventional Radiologist	Side effects differ depending on the type of embolization used. Common complications reported are postembolization syndrome (fever, pain, extreme fatigue, nausea/vomiting); infection in the liver; hepatic abscess; gallbladder inflammation; and blood clots in the main blood vessels of the liver. Serious complications are uncommon but possible. Embolization also reduces some of the blood supply to normal liver tissue. This may be dangerous in patients with underlying diseases such as hepatitis or cirrhosis.[39]
	Transarterial chemoembolization (TACE)	TACE involves administering a chemotherapeutic agent directly to the liver tumor to cause ischemia. A chemotherapeutic solution (frequently doxorubicin or cisplatin) is suspended in lipiodol (an oily contrast medium selectively retained within the tumor) and is injected via a catheter into the hepatic arteries that are directly supplying the tumor. Simultaneously, the feeding hepatic arteries are obstructed with an embolizing agent. Tumor ischemia raises the drug concentration, extends retention of the chemotherapeutic agent, and reduces systemic toxicity.	Most patients can be discharged several hours after treatment with TACE, but an overnight stay is typically required if postembolization syndrome occurs.	Interventional Radiologist	Same as above.

Table 1. Local nonsurgical therapies for CRC liver metastases reviewed in this report (continued)

Therapy	Treatment Strategy	Mechanism of Cell Death	Setting	Performed By	Specific Harms
Embolization and Transarterial Therapy (continued)	Hepatic artery infusion (HAI)	HAI uses a pump to deliver higher doses of chemotherapy to the tumor compared with systemic chemotherapy, while maintaining low levels of toxicity in the normal tissue. This is achieved by exploiting the unique blood supply to the liver: normal hepatocytes are perfused by the portal vein, whereas the metastases derive most of their blood supply via the hepatic artery. The first-pass effect (a phenomenon of drug metabolism whereby the concentration of a drug is greatly reduced before it reaches the systemic circulation) of drugs delivered to the liver is high.[12,34]	A surgeon intraoperatively places the hepatic artery pump as an indwelling device. The pump delivers chemotherapeutic agent at a slow, fixed rate over a period of several weeks. The pump drug chamber can be refilled percutaneously. Successful hepatic arterial infusion is dependent on surgeon experience with the procedure.[40]	Interventional Radiologist, Surgeon for placement of pump	Complications related to insertion of the pump are rare;[40] however, hepatic artery thrombosis, catheter displacement, hematomas, infections, and liver perfusion are all reported as pump-related complications. The side effects will differ depending upon the type of embolization used. The most common complications reported are postembolization syndrome (fever, pain, extreme fatigue, nausea/vomiting); infection in the liver; hepatic abscess; chemical hepatitis; biliary sclerosis; peptic ulceration; gallbladder inflammation; and blood clots in the main blood vessels of the liver. Serious complications are uncommon but possible. Embolization also reduces some of the blood supply to normal liver tissue. This may be dangerous in patients with underlying diseases such as hepatitis or cirrhosis.[39]

Table 1. Local nonsurgical therapies for CRC liver metastases reviewed in this report (continued)

Therapy	Treatment Strategy	Mechanism of Cell Death	Setting	Performed By	Specific Harms
Embolization and Transarterial Therapy (continued)	Radioembolization or selective internal radiation therapy (SIRT)	SIRT involves loading the radionuclide Yttrium-90 into microspheres, which are then placed within the microvasculature of the liver metastases, thus targeting multiple hepatic metastases in a single procedure.[41] The loaded microspheres deliver high localized doses of β-radiation to the tumor while minimizing radiation exposure to the surrounding tissue.[41-43]	Patients are required to undergo a ^{99m}Tc-macro-aggregated albumin (MAA) scan prior to SIRT to assess eligibility.[44] The SIRT procedure takes approximately 90 minutes, and patients can typically return home 4 to 6 hours following treatment.	Interventional Radiologist	The side effects will differ depending on the type of embolization used. The most common complications reported are postembolization syndrome (fever, pain, extreme fatigue, nausea/vomiting); infection in the liver; hepatic abscess; gallbladder inflammation; and blood clots in the main blood vessels of the liver. Serious complications are uncommon but possible.[39] Acute toxicity events include gastritis, ulceration, or pancreatitis due to microsphere deposition in vessels serving these organs.[44] Radiation-induced liver disease (jaundice, weight gain, painful hepatomegaly and elevated liver enzymes); thrombocytopenia; encephalopathy; elevated results of liver function tests; ascites; and hypoalbuminemia.
	Drug-eluting beads (DEB)	This transarterial embolization system uses a drug-loaded (typically with doxorubicin or cisplatin), superabsorbent polymer microsphere to release drug gradually into the tumor, allowing longer intratumoral exposure and less systemic exposure to the drug.[45]	Most patients can be discharged several hours after treatment, but an overnight stay is typically required if postembolization syndrome occurs.	Interventional Radiologist	The side effects will differ depending on the type of embolization used. The most common complications reported are postembolization syndrome (fever, pain, extreme fatigue, nausea/vomiting); infection in the liver; hepatic abscess; gallbladder inflammation; and blood clots in the main blood vessels of the liver. Serious complications are uncommon but possible.[39]

Table 1. Local nonsurgical therapies for CRC liver metastases reviewed in this report (continued)

Therapy	Treatment Strategy	Mechanism of Cell Death	Setting	Performed By	Specific Harms
Radiotherapy	External-beam three-dimensional conformal radiation therapy (3D-CRT)	This type of radiotherapy uses computer-assisted tomography scans (CT or CAT scans), magnetic resonance imaging scans (MR or MRI scans), or both to create detailed, 3D representations of the tumor and the surrounding organs. The radiation oncologist uses these computer-generated images to shape radiation beams to the exact size and shape of the tumor, which is intended to spare nearby healthy tissues from exposure.	Each treatment lasts only a few minutes, although the setup time usually takes longer. Most often, radiation treatments are given 5 days a week for several weeks. The patient's diagnosis determines the total duration of treatment.[46,47]	Radiation Oncologist, Medical Physicist, Dosimetrist, Radiation Therapist, and Radiation Therapy Nurse	Possible side effects of external radiation therapy include sunburn-like skin problems, nausea, vomiting, and fatigue. These typically subside post-treatment. Radiation might also make the side effects of chemotherapy worse.[39] Radiation-induced liver disease is the major dose-limiting toxicity.[48]
	External-beam intensity-modulated radiotherapy (IMRT)	This approach to radiotherapy allows the radiation oncologist to vary both the intensity of a radiation beam and the angle at which it is delivered to the patient. This is intended to deliver a high dose of radiation to the tumor while significantly reducing the exposure of surrounding normal tissue. IMRT offers more refined radiation dosing compared with traditional 3D-CRT.	Same as 3D-CRT, but IMRT requires slightly longer daily treatment times and additional planning and safety checks before the patient can start the treatment.[49]	Same as 3D-CRT	Same as 3D-CRT
	Stereotactic body radiation therapy (SBRT)	This type of external-beam radiation therapy delivers a high dose of radiation with high targeting accuracy to an extracranial target within the body, in either a single dose or a small number of fractions.[50]	Before treatment, patients may be asked to undergo placement of a fiducial marker (an object used in concert with imaging to provide precise location information), which is commonly performed as an outpatient procedure. SBRT typically consists of one to five treatment sessions over the course of 1 to 2 weeks, and is usually performed as an outpatient procedure.[51]	Same as above	Same as above

Scope and Key Questions

Scope of the Review

The objective of this systematic review is to characterize the comparative effectiveness and harms of various local hepatic therapies for liver metastases from unresectable CRC in two distinct patient populations:

- Patients with unresectable, liver-dominant (i.e., majority of disease located in the liver) metastases who are not eligible for continued systemic chemotherapy because their disease is refractory (i.e., they have experienced disease progression while on therapy).
- Patients who are candidates for local liver therapies as an adjunct to systemic chemotherapy.

Patients whose liver metastases are resectable, who have unresectable liver metastases treated with first-line chemotherapy in combination with local hepatic therapy for downstaging of disease, or who are treated with a first-line local hepatic therapy alone are outside the scope of this review.

Patients with unresectable liver metastasis are a heterogeneous group, in which careful patient selection may offer opportunities for successful treatment. Patient selection criteria are a key issue; the definition of medically or technically inoperable patients is crucial.[52] All patients in the studies included in this review have been classified as having unresectable disease based on either the extent of the tumor or patient characteristics (e.g., poor surgical candidate). As noted, we focus on two distinct patient populations that have different underlying prognoses; thus, we make treatment comparisons within, rather than across, these populations. We considered studies with any length of followup and performed in all inpatient and outpatient settings. Table 2 lists the relevant populations, interventions, comparators, outcomes, timing of assessment, and settings (PICOTS) relevant for this review.

Table 2. PICOTS (Population, Intervention, Comparator, Outcome, Timing, and Setting) for the Key Questions

PICOTS	KQs 1 and 2	KQs 3 and 4
Population	Patients with unresectable liver metastases from primary CRC who are refractory to systemic chemotherapy but are candidates for local hepatic therapy. • Patients whose hepatic metastases are unresectable due to medical comorbidities, such as low hepatic reserve, cardiac insufficiency, or poor performance status • Patients whose hepatic metastases are unresectable because of certain characteristics of the metastases • Patients with no or minimal extrahepatic disease	Patients with unresectable liver metastases from primary CRC who receive systemic chemotherapy with local hepatic therapy. • Patients whose hepatic metastases are unresectable because of medical comorbidities, such as low hepatic reserve, cardiac insufficiency, or poor performance status • Patients whose hepatic metastases are unresectable because of certain characteristics of the metastases • Patients who have synchronous hepatic metastases • Patients whose hepatic metastases have recurred after resection • Patients with no extrahepatic disease
Intervention	• Cryosurgical ablation • Radiofrequency ablation (RFA) • Microwave ablation (MWA) • Transarterial embolization (TAE) • Transarterial chemoembolization (TACE) • Hepatic arterial infusion (HAI) • Radioembolization or selective internal radiation therapy (SIRT) • Drug-eluting beads (DEB) • External beam with 3D-CRT or IMRT • Stereotactic body radiation therapy (SBRT)	Same as KQs 1 and 2.
Comparator	All the therapies listed above compared with the intervention in question for patients not eligible for systemic chemotherapy for CRC	All the therapies listed above compared with the intervention in question for patients receive systemic chemotherapy for CRC.
Outcome	**KQ1:** Ultimate outcomes: Survival and quality of life Intermediate outcomes: Time to progression, and local recurrence, length of stay **KQ2:** Adverse outcomes: biloma, hepatic abscess, hepatic hemorrhage, elevated alkaline phosphatase, elevated bilirubin, elevated transaminases, injury to adjacent organ(s), liver failure, rare adverse events, and steatohepatitis.	**KQ3:** Ultimate outcomes: Same as KQs 1 and 2 Intermediate outcomes: Time to recurrence, and local recurrence, length of stay **KQ4:** Adverse outcomes: Same as KQs 1 and 2
Timing	The relevant periods occur at the time of treatment of CRC hepatic metastases through followup over months or years.	Same as KQs 1 and 2.
Setting	Inpatient and outpatient.	Same as KQs 1 and 2.

3D-CRT = three-dimensional conformal radiotherapy; CRC = colorectal cancer; IMRT = intensity-modulated radiation therapy; KQ = Key Question

Key Questions

KQ1. What is the comparative effectiveness of the various liver-directed therapies in patients whose disease is refractory to systemic therapy for unresectable CRC metastases to the liver and who have minimal evidence of extrahepatic disease?

KQ2. What are the comparative harms of the various liver-directed therapies in patients whose disease is refractory to systemic therapy for unresectable CRC metastases to the liver and who have minimal evidence of extrahepatic disease?

KQ3. What is the comparative effectiveness of the various liver-directed therapies in patients who are candidates for liver-directed therapy as an adjunct to systemic therapy for unresectable CRC metastases to the liver and have no evidence of extrahepatic disease?

KQ4. What are the comparative harms of the various liver-directed therapies in patients who are candidates for liver-directed therapy as an adjunct to systemic therapy for unresectable CRC metastases to the liver and have no evidence of extrahepatic disease?

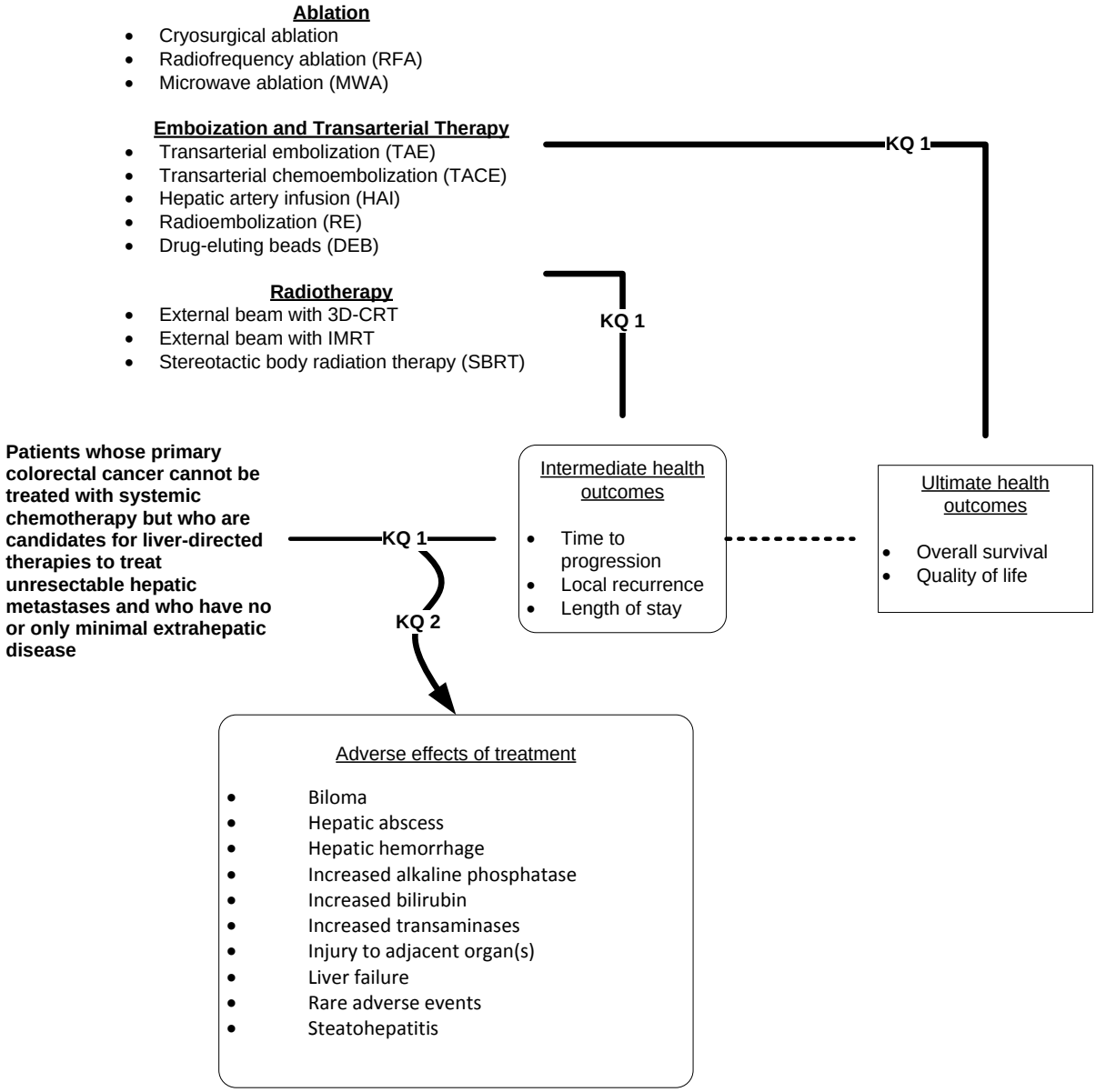
Analytic Frameworks

We developed the analytic frameworks (Figure 1 and Figure 2) based on clinical expertise and refined it with input from our key informants and technical expert panel (TEP). These diagrams are revised versions of those posted with the review protocol; the revisions are intended to make the core elements of our final analyses clearer, given the actual literature available for the review.

Figure 1 outlines potential areas in which patients who are unable to receive systemic chemotherapy are using local hepatic therapy. These therapies may affect intermediate health outcomes such as time to progression, local recurrence, and length of stay, as well as the ultimate outcomes of quality of life and overall survival (KQ1).

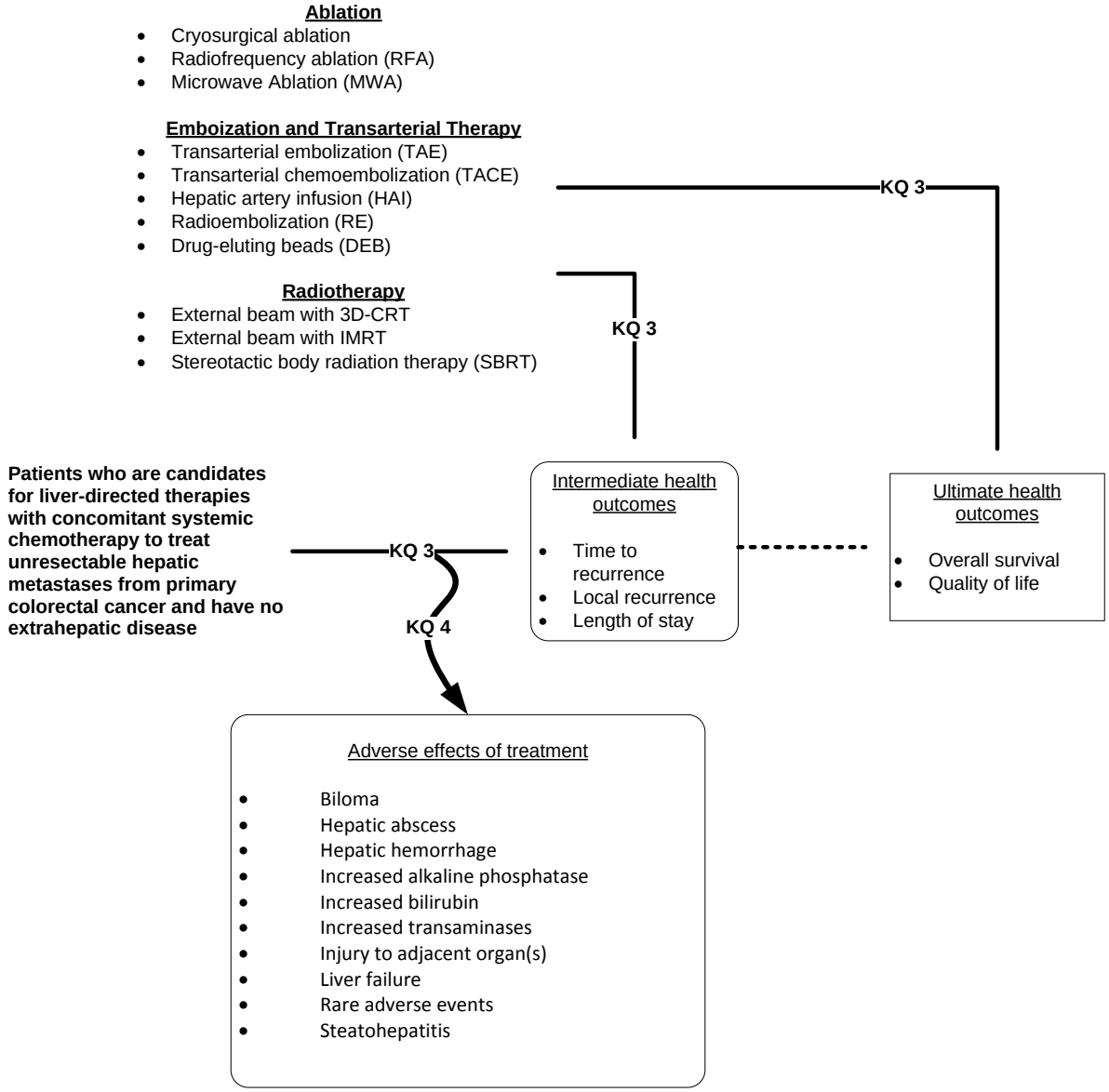
Figure 2 outlines potential areas in which patients receive local hepatic therapy and concomitant systemic chemotherapy. These therapies may affect intermediate health outcomes such as time to recurrence, local recurrence, and length of stay, as well as ultimate outcomes of quality of life and overall survival (KQ3). In both frameworks, we attempted to assess the occurrence of adverse effects due to local hepatic therapies (KQ2 and KQ4).

Figure 1. Analytic framework for comparative effectiveness of local hepatic therapies for unresectable CRC metastases to the liver in patients whose metastatic disease is refractory to systemic chemotherapy and who have no or minimal extrahepatic disease



3D-CRT = three-dimensional conformal radiotherapy; KQ = Key Question; IMRT = intensity-modulated radiation therapy

Figure 2. Analytic framework for comparative effectiveness of local hepatic therapies for unresectable colorectal cancer metastases to the liver in patients receiving local hepatic therapy as an adjunct to systemic chemotherapy and who have no extrahepatic disease



3D-CRT = Three-dimensional conformal radiotherapy; IMRT = Intensity-modulated radiation therapy; KQ = Key Question

Organization of This Evidence Report

The Methods chapter describes our processes, including our search strategy, inclusion and exclusion criteria, approach to abstract and full text review, and methods for extraction of data into evidence tables and then compiling evidence. In addition, we describe the procedures for evaluating bias in individual studies and describing the strength of the body of evidence.

The Results chapter presents the findings of the literature search and the review of the evidence by key question, synthesizing the findings by strategies.

The Discussion chapter presents the key findings and discusses their relationship to other published findings and the applicability of the findings of this report. We also outline challenges for future research in the field.

The report includes a number of appendixes to provide further details about our methods and the studies assessed. The appendixes are as follows:

- Appendix A: Search Strategy
- Appendix B: Contacted Authors
- Appendix C: DistillerSR Screening and Abstraction Forms
- Appendix D: Evidence Tables
- Appendix E: Abbreviations and Acronyms
- Appendix F: Excluded Studies

Uses of This Evidence Report

We anticipate that this report will be of primary value and interest to health care providers who treat patients with CRC and CRC metastases to the liver. Treatment is generally provided by medical oncologists, radiation oncologists, interventional radiologists, and surgeons. This report can bring providers up to date on the current state of the evidence, and it provides a quality assessment of the risk of bias in individual studies that report the outcomes of treatment for unresectable CRC metastases to the liver. It will also be of interest to patients with unresectable CRC liver metastases and their families who are concerned about their health and are facing treatment choices.

Finally, this presentation of the evidence will be of value to researchers, who can obtain a concise analysis of the current state of knowledge in the field and information about gaps in knowledge. The report will help prepare them to conduct research in areas that are needed to advance research methods, understand patient selection, and optimize the effectiveness and safety of treatment for unresectable CRC metastases to the liver.

Methods

In this chapter, we document the procedures that the Blue Cross and Blue Shield EPC used to produce a CER on the effectiveness and comparative effectiveness of local hepatic therapies for CRC metastases to the liver. The methods for this CER follow the methods suggested in the ARHQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (available at www.effectivehealthcare.ahrq.gov/methodsguide.cfm).

The main sections in this chapter reflect the elements of the protocol established for the CER; certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist.[53] We first describe the topic refinement process and the construction of the review protocol. We then present our strategy for identifying articles relevant to our KQs, our inclusion and exclusion criteria, and the process we used to extract information from the included articles and generate our evidence tables. In addition, we discuss our method for grading the quality of individual articles, rating the strength of the evidence, and assessing the applicability of individual studies and the body of evidence for each KQ. Finally, we describe the peer review process. All methods and analyses were determined a priori and documented in a research protocol that was publically posted by AHRQ for comments.

Given the clinical complexity of this topic and the evolution of the scope and the KQs, we sought input from the TEP throughout the process. In some cases, this was done through joint teleconferences; in other cases, we contacted TEP members individually to draw on each member's particular expertise.

Topic Refinement and Review Protocol

The topic for this report was nominated in a public process. With input from technical experts, the EPC drafted the initial KQs and, after approval from AHRQ, posted them to a public Web site. The KQs were posted for 4 weeks for public comment. We modified the KQs and the key elements of PICOTS based on these comments and discussion with the TEP.

When the KQs were first written, both the questions and the interventions were stratified by intent of treatment (palliative or curative). However, this stratification seemed clinically inappropriate and potentially confusing because some interventions could be applied to palliate symptoms and to eliminate (i.e., cure) the liver metastases. Thus, the final KQs are distinguished by the population receiving local hepatic therapy. KQs 1 and 2 apply to patients whose CRC is refractory to systemic chemotherapy (i.e., their disease had progressed), and KQs 3 and 4 apply to patients who are receiving local hepatic therapy and systemic chemotherapy. To be consistent with clinical practice, we modified KQs 1 and 2 to include patients with minimal extrahepatic disease. In addition, we categorized the 12 interventions to apply to all KQs, we removed some interventions, and we added SBRT. Finally, we expanded the list of harms to be considered to include elevated alkaline phosphatase, elevated bilirubin, elevated transaminases, liver failure, and rare adverse events that had not been considered originally.

Literature Search Strategy

Search Strategy

We searched MEDLINE and Embase and the Cochrane Library. Our search strategy used the National Library of Medicine's Medical Subject Heading (MeSH®) keyword nomenclature developed for MEDLINE and adapted for use in other databases. We limited the searches to the

English language[54] but did not limit the search by geographic location of the study. Evidence suggests that language restrictions do not change the results of systematic reviews for conventional medical interventions.[55] We also restricted the searches to articles that treated patients between January 1, 2000, and June 27, 2012, primarily to ensure the applicability of the interventions and outcomes data to current clinical practice. Prior to 2000 some interventions were in their infancy and based on current standards used outdated regimens.[56-58] Thermal therapies were not used significantly until late 1990s and major changes in proton beam and stereotactic therapy occurred during the same period.[59] Chemoembolization drugs and embolic mixtures have also changed a great deal in the last ten years and are more standard now. For these reasons which were strongly supported by the TEP we excluded studies where patient treatment preceded 2000.

We searched for the following publication types: RCTs, nonrandomized comparative studies, and case series. We used the following search terms for the diseases in question: CRC, metastases, and unresectable liver tumors. Appendix A gives the major search strings, including all the terms used for the interventions of interest.

We searched the gray literature for clinical trials, material published on the U.S. Food and Drug Administration Web site, and relevant conference abstracts identified by TEP members (from the American Society of Clinical Oncology, American Society of Clinical Oncology Gastrointestinal Cancers, Surgical Society of Oncology, and Radiosurgery Society). We also reviewed scientific information packets that the Scientific Resource Center had requested and obtained from relevant pharmaceutical or device firms.

Originally, we had intended to contact study authors only if the EPC staff believed that the evidence could meaningfully affect results (i.e., alter eventual grades of the strength of evidence). However, because of the limited number of studies included in this report, we elected to contact authors for any article lacking complete information on patient characteristics, interventions, or outcomes. A listing of the contacted authors is included in Appendix B.

Inclusion and Exclusion Criteria

Table 3 lists the inclusion/exclusion criteria we selected based on our understanding of the literature, key informant and public comments gathered during the topic refinement phase, input from the TEP, and established principles of systematic review methods.

Table 3. Inclusion and exclusion criteria

Category	Criteria
Study population	Patients with primary CRC and unresectable liver metastases due to lesion characteristics or underlying comorbidity • For KQ1 and KQ2, patients refractory to systemic chemotherapy • For KQ3 and KQ4, patients receiving local hepatic therapy as an adjunct to systemic chemotherapy
Time period	Studies with treatment dates after 2000 to represent current interventional approaches to local hepatic therapies
Publication languages	English only
Admissible evidence	Study designs • All study designs • Case reports that report on a rare adverse event Other criteria • Extrahepatic disease permitted only if it is liver dominant • Studies must involve one or more of the interventions listed in the PICOTS • Studies must include at least one outcome measure listed in the PICOTS and the outcome must be extractable from data presented in the articles • To allow for the inclusion of all potentially relevant evidence, studies that deviated from our inclusion criteria by less than 10% were included (e.g., 5% of patients were HCC, or 9% of patients had documented extrahepatic disease)

CRC = colorectal cancer; KQ = Key Question; PICOTS = population, intervention, comparator, outcome, timing, setting

Study Selection

Search results were transferred to EndNote® and subsequently into DistillerSR (Evidence Partners Inc., Ottawa, Canada) for selection. Using the study selection criteria for screening titles and abstracts, each citation was marked as: (1) eligible for review as full-text articles or (2) ineligible for full-text review. Reasons for article exclusions at this level were not noted. The first-level title-only screening was performed in duplicate. To be excluded, a study needed to be independently excluded by both team members. In cases where there was disagreement, second-level abstract screening was completed by two independent reviewers.

Discrepancies were decided by consensus opinion and a third reviewer was consulted when necessary. All team members were trained using a set of 50 abstracts to ensure uniform application of screening criteria. Full-text review was performed if it was unclear whether the abstract met article-selection criteria.

Full-text articles were reviewed in the same fashion to determine their inclusion in the systematic review. Records of the reason for exclusion for each paper retrieved in full-text, but excluded from the review, were maintained in the DistillerSR database. Although an article may have been excluded for multiple reasons, only the first reason identified was recorded.

Development of Evidence Tables and Data Extraction

Evidence tables were constructed by clinical content experts and staff at the EPC. Tables were designed to provide sufficient information and enable readers to understand the studies and determine their quality. Emphasis was given to data elements essential to our KQs. Evidence table templates were identical for KQ1 and KQ3 and KQ2 and KQ4. The format of our evidence tables was based on examples from prior systematic reviews.

Data extraction was performed directly into tables created in DistillerSR, with elements defined in an accompanying data dictionary. All team members extracted a training set of five articles into evidence tables to ensure uniform extraction procedures and test the utility of the table design. All data extractions were performed in duplicate, with discrepancies resolved by

consensus. The full research team met regularly during the period of article extraction to discuss any issues related to the extraction process. Extracted data included patient and treatment characteristics, outcomes related to intervention effectiveness, and information on harms. Harms included specific negative effects, including the narrower definition of adverse effects. Data extraction forms used during this review are presented in Appendix C.

The final evidence tables are presented in their entirety in Appendix D. Studies are presented in the evidence tables by study design, then year of publication alphabetically by the last name of the first author. Abbreviations and acronyms used in the tables are listed as table notes and are presented in Appendix E.

Risk of Bias Assessment of Individual Studies

For the assessment of risk of bias in individual studies, we followed the Methods Guide[38] where applicable. Our assessment of risk of bias in the included case-series intervention studies was based on a set of study characteristics proposed by Carey and Boden.[60] These characteristics include: clearly defined study questions, well-described study population, well-described intervention, use of validated outcome measures, appropriate statistical analyses, well-described results, discussion and conclusion supported by data, and acknowledgement of the funding source. The Carey and Boden assessment tool does not conclude with an overall score of the individual study. We created thresholds for converting the Carey and Boden[60] risk assessment tool into AHRQ standard quality ratings (good, fair, and poor) to differentiate case-series studies of varied quality. These distinctions are to be used for differentiation within the group of case-series studies, but not for the overall body of evidence described below. The classification into these categories (i.e., good, fair, poor) is distinct for a specific study design. Other study designs are evaluated according to their own strengths and weaknesses.

For a study to be ranked as good quality, each of the Carey and Boden[60] criteria must have been met. For a fair quality rank, one criterion was not met, and a rank of poor quality was given to studies with more than one criterion not met. These quality ranking forms can be found in Appendix D.

Data Synthesis

Evidence tables were completed for all included studies, and data are presented in summary tables. Evidence is also presented in text organized by outcome and intervention. No direct comparisons are made. We considered whether formal data synthesis (e.g., meta-analysis) would be possible from the set of included studies. Because the literature was so heterogeneous in terms of the populations (e.g., prior treatments, reason for unresectability and number and size of lesions) and interventions (e.g., drugs and dose) studied, we concluded that pooling data would be inappropriate for this review. Thus, all data synthesis is based on qualitative summaries and analyses.

Strength of the Body of Evidence

We graded the strength of the overall body of evidence for overall survival, quality of life, and harms for the four KQs. We used the EPC approach (developed for the EPC program and referenced in the Methods Guide[38,61]), which is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[62] This

system explicitly addresses four required domains: risk of bias, consistency, directness, and precision.

The overall strength of evidence could be graded as “high” (indicating high confidence that the evidence reflects the true effect, and that further research is very unlikely to change our confidence in the estimate of effect); “moderate” (indicating moderate confidence that the evidence reflects the true effect, and that further research may change our confidence in the estimate of effect and may change the estimate); “low” (indicating low confidence that the evidence reflects the true effect, and that further research is likely to change our confidence in the estimate of effect and is likely to change the estimate); or “insufficient” (indicating that evidence is either unavailable or does not permit estimation of an effect).

Two independent reviewers rated all studies on domain scores and resolved disagreements by consensus discussion; the same reviewers also used the domain scores to assign an overall strength of evidence grade. When evidence was available but the effects could not be estimated from the body of evidence, the overall strength of evidence was rated as “insufficient.” If we could estimate comparative effects, we graded the evidence as “low,” indicating our low level of confidence in the estimates. This decision was based in large part on the biases inherent in a literature base comprising case-series studies. In this review, consistency of the body of literature was graded as “not applicable.” The direction of effect cannot be assessed in noncomparative studies; therefore, consistency in the direction of effect across case series cannot be discerned. In the absence of a comparator, we do not know if the observed estimate is better or worse; therefore, we concluded that consistency was not applicable. Directness pertains to the whether the evidence links the interventions directly to a health outcome. Due to the absence of direct comparisons precision will be rated imprecise.

Assessing Applicability

Applicability of the results presented in this review was assessed in a systematic manner using the PICOTS framework. Assessment included both the design and execution of the studies, as well as their relevance to the target populations, interventions, and outcomes of interest.

Results

In this chapter, we present the results of our systematic review of the literature and synthesis of the extracted data on outcomes on the effectiveness and comparative effectiveness of local hepatic therapy for unresectable CRC metastases to the liver. The Key Questions (KQs) for this review are: KQ1 (effectiveness) and KQ2 (harms) of local hepatic therapy for unresectable CRC metastases to the liver in patients whose disease is refractory to systemic chemotherapy and who have no or minimal extrahepatic disease; and KQ3 (effectiveness) and KQ4 (harms) of local hepatic therapy for unresectable CRC metastases to the liver in patients who are also receiving systemic chemotherapy and have no extrahepatic disease.

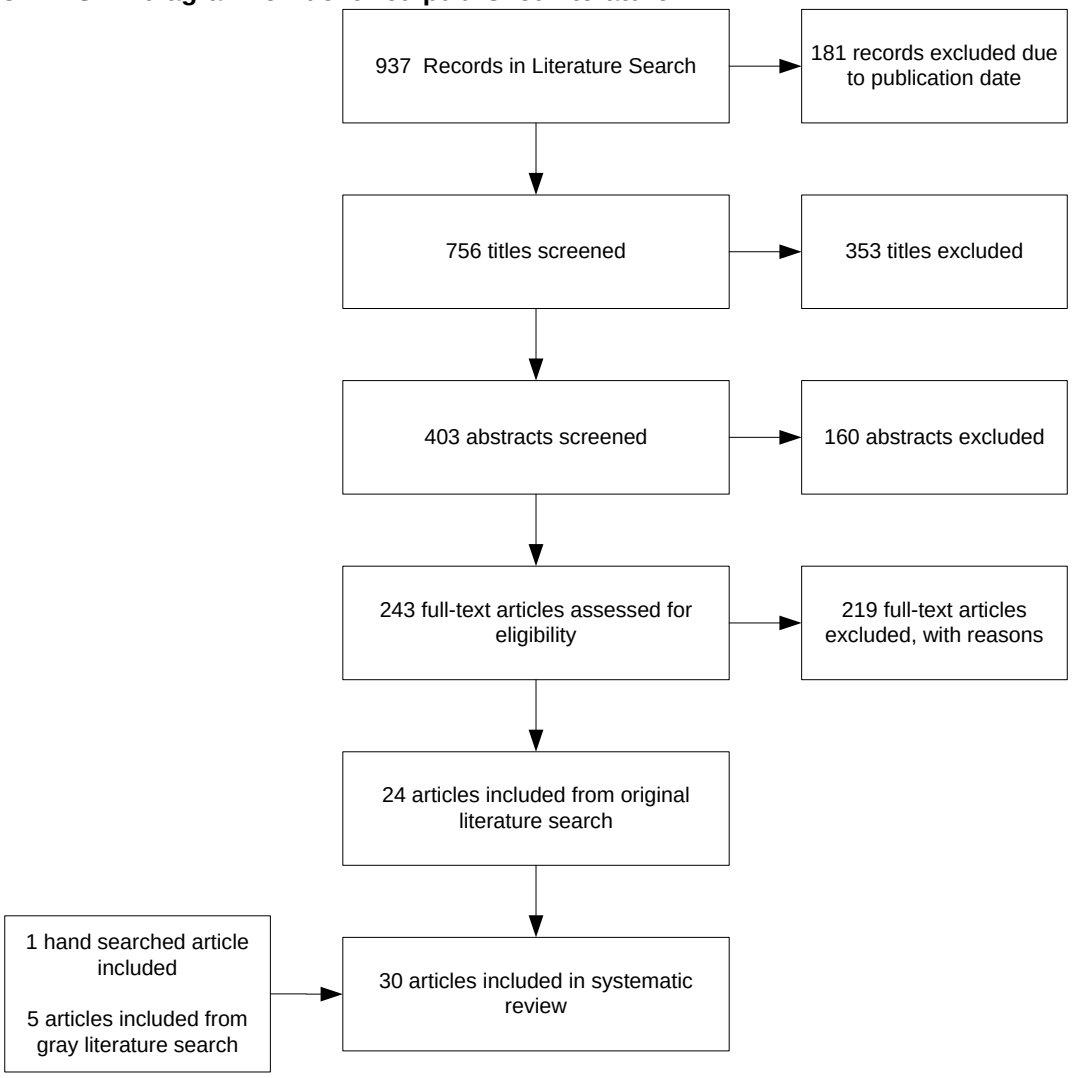
We first describe the results of our literature searches and then present the results for KQ1 and KQ2, which include a list of key points, an overview of the included literature, and a detailed synthesis of the data. This is followed by the same for KQ3 and KQ4. We identified 937 nonduplicate titles or abstracts with potential relevance, and of these, 189 proceeded to full-text review (Figure 3). Thirty-one articles were included in the review, including one hand-searched article and five articles from gray literature identified through other sources (the American Society of Clinical Oncology, American Society of Clinical Oncology Gastrointestinal Cancers, Surgical Society of Oncology, and Radiosurgical Society). The 31 arms represent 30 distinct studies: 1 RCT, 12 prospective case series, and 17 retrospective case series. Twenty-three studies pertain to KQ1, 23 studies to KQ2, 7 studies to KQ3, and 7 studies to KQ4.

Results of Literature Searches

Of the 937 records identified through the literature search, we excluded 913 at various stages of screening and included 24 records.[63-86] We included one hand-searched article,[87] two published studies from scientific information packets,[88,89] and three articles from conference abstracts.[90-92] A total of 30 articles were included in this report: 29 case-series and one RCT[87] for which a single arm was abstracted as a case series. This RCT compared RFA with systemic chemotherapy to systemic chemotherapy alone. The scope of the review was liver-directed therapy versus liver-directed therapy. Systemic chemotherapy alone was not a relevant intervention or comparator for this review. Only the RFA combined with systemic chemotherapy arm was abstracted and included in this report as it is relevant for KQ3 and KQ4.

The PRISMA diagram (Figure 3) depicts the flow of search screening and study selection.[53] A list of full-text studies with reason for exclusion is presented in Appendix F.

Figure 3. PRISMA diagram for identified published literature



Our searches of various gray literature sources yielded five published studies that we added to the articles identified in the search of publications databases and that were included in the analyses presented in this evidence review.[88-92]

We evaluated the results of the gray literature search as follows:

- **Regulatory information:** The search yielded six results, but no new studies were identified from this source.
- **Clinical trial registries (**ClinicalTrials.gov**):** The search yielded 259 clinical trials; we excluded 219 trials during the title and abstract screen. Twenty-five of the remaining 40 trials were excluded. Among the 15 trials remaining, 2 contained too little information to make a conclusion about their relevance to the KQs of this report. Of the remaining 13 studies, three had been terminated, seven were ongoing or recruiting, and three had been completed. We found no publications for the three completed trials. All terminated studies cited low recruitment as the reason for study termination.
- **Abstracts and conference papers:** The search yielded 174 citations, and we excluded 132 during the title and abstract screen. Of the remaining 42 items, two were duplicates

and 37 did not meet inclusion criteria after full-text review. The three remaining references met all inclusion criteria and were included in this report.[90-92]

- **Manufacturer database:** Scientific information packets were received from Accuray (manufacturers of the CyberKnife® SBRT system) and SIRTEX (manufacturers of the Yttrium-90–infused SIR-Spheres microspheres). The submissions consisted of 55 published references, listings of clinical trials, or conference abstracts. Of the 55 references, we excluded 53 during the abstract and title screen. The remaining two references met the inclusion criterion and were included in this report.[88,89]

Overview of the Literature

Thirty-one arms within 30 studies met our inclusion criteria and addressed local hepatic therapy for unresectable CRC metastases to the liver. Nine studies were conducted in the United States, four in Italy, four in Germany, three in Australia, three in Japan, two in the United Kingdom, two in Korea, and one study each in France, the Netherlands, and Turkey (Table 4). The number of patients in each study ranged from 6 to 140.

Table 4. Characteristics of studies included in this review by intervention

Characteristic	RFA	TACE	HAI	RE	DEB	SBRT	RFA With SC	HAI With SC	RE With SC	Total Arms*
Total	1	2[a]	2	13[a]	3	3	3	2	2	31
Study Design										
Prospective Case Series	0	0	0	6	2	1	2[b]	1	1	13
Retrospective Case Series	1	2	2	7	1	2	1	1	1	18
Outcomes Reported										
Overall Survival	1	2	2	13	3	3	3	2	2	31
Quality of Life	0	0	0	1	1	0	1	0	0	3
Time to Recurrence	0	0	0	0	0	0	0	0	0	0
Length of Stay	0	1	0	0	1	0	0	0	0	2
Local Recurrence	1	0	0	0	0	2	3	0	0	6
Adverse Events	1	2	2	13	3	3	3	2	2	31
Study Population										
United States	0	2	0	7	1	0	0	0	0	10
Europe	1	0	1	4	2	2	1	0	1	12
Australia	0	0	0	1	0	0	1	0	1	3
Asia	0	0	1	1	0	1	1	2	0	6
Total Participants (N)	68	142	67	454	157	43	101	36	159	1,227

DEB = drug-eluting beads; HAI = hepatic arterial infusion; RE = radioembolization; N = number; RFA = radiofrequency ablation, SBRT = stereotactic body radiotherapy; SC = systemic chemotherapy; TACE = transarterial chemoembolization
Note: No studies reporting on cryosurgical ablation, MWA, TAE, 3D-CRT, or IMRT met inclusion criteria for this review.
*The total number of articles included in this review is 30.
[a]Hong et al. reports on both TACE and RE interventions.
[b]The study by Ruers et al. is an RCT that was extracted as a case series.

All 30 studies had clearly defined questions and well-described interventions, used validated outcome measures, and had conclusions that were supported by the data. Studies varied on how well they described the study population, how well they described their results, and

acknowledgement of sponsorship and funding. Fifteen studies did not have well-described patient populations,[63,65,67,70,74,78,79,81,83-86,88,89,91] and three studies lacked well-described results.[67,70,74]

Fifteen studies were rated as good quality,[64,66,68,69,71-73,75-77,80,82,87,90,92] 12 studies as fair quality,[57,63,65,78,79,81,84-86,88,89,91]and three as poor quality.[67,70,74]

Key Questions 1 and 2: Effectiveness and Harms of Therapies in Patients Refractory to Systemic Chemotherapy

KQs 1 and 2 focus on the comparative effectiveness (KQ1) and harms (KQ2) of the various local hepatic therapies in patients with unresectable colorectal cancer (CRC) metastases to the liver and who have minimal evidence of extrahepatic disease and whose disease is refractory to systemic therapy (i.e., are not eligible to receive systemic chemotherapy).

Key Points

- The evidence is insufficient to draw conclusions about overall survival, quality of life, or adverse events. Due to the absence of comparative data, we are limited in drawing conclusions regarding the efficacy and effectiveness of these interventions. Risk of bias is a primary concern in observational studies. Intended effects are likely to be biased by preferential prescribing of the intervention based on the patients' prognosis.
- All studies were case series. Carey and Boden quality rankings were converted into AHRQ "good," "fair," and "poor" ratings. Eleven studies were rated as good quality,[66,68,69,71,73,75-77,82,90,92] nine studies as fair quality,[63,65,78,83,84,86,88,89,91] and three as poor quality.[67,70,74]
- The assessment of applicability of the study findings to clinical practice is limited by the poor characterization of the patient populations (e.g., number and size of metastases, performance status) and variability in the delivery of the interventions (e.g., surgical approach, dose and drugs delivered).

Description of Included Studies

Twenty-three case series[63,65-71,73-78,82-84,86,88-92] met inclusion criteria to address KQ1 and KQ2. Of the 23 case series, nine were prospective[66,67,70,73-76,78,88]and 14 were retrospective.[63,65,68,69,71,77,82-84,86,89-92] The total number of patients for whom data were abstracted from the 23 studies was 932. Three studies included patients treated with TACE with DEB;[67,75,90] and two articles reported on TACE alone;[63,68] three on SBRT;[71,82,88] thirteen on RE;[65,66,68,70,73,76-78,84,86,89,91,93] two on HAI,[83,92] and one on RFA.[69] All studies initiated treatment in patients after January 1, 2000, except for the study by Albert and colleagues[21] on TACE. We included this study because it reported on relatively large numbers of patients treated, and analyses showed no differences in outcomes before and after 2000. Table 5 shows the summary of the study and patient characteristics, including number of patients enrolled, study design, intervention period, and intervention, and patient demographics.

Patients ranged in age from 30 to 91 years, but they were generally in their late 50s or early 60s. Thirteen studies reported rates of previous resection that ranged from 2.6 to 83.5 percent.[63,64,66,68-70,75,82,84,88,89,91,92] Five studies reported median ECOG scores of 0-1, with a range of 0-3.[66,67,73,75,77] In all but two studies,[72,81] patients had been treated with prior lines of systemic

chemotherapy, and 11 studies reported patient experience with prior local hepatic therapy.[63,68-70,75,78,82,84,88,89,91] Lines of previous systemic chemotherapy are presented in Appendix D.

The included evidence is clinically diverse with respect to the number of patients undergoing previous resection and local hepatic therapy. Variations are also present in the treatments—in terms of the drugs or dosage—within a given intervention.

Data on tumor characteristics were inconsistently reported across studies and are detailed in Table 6. Synchronous or metachronous disease status was reported in eight studies and synchronous disease ranged from 17 to 73 percent.[66,68,71,75,83,91,92,94] Bilobar or unilobar disease was reported in six studies and bilobar disease ranged from 66.7 to 95.1 percent.[65,66,68,73,76,86] Eight studies reported liver involvement, but used nonuniform measurements.[65,67,70,73,75-77,90] Four studies reported mean or median number of hepatic lesions.[69,71,75,82] Six studies reported the mean size of hepatic lesions, which ranged from 2.9 to 12cm.[66,68,69,82,90,94] Presence of extrahepatic metastases were reported by five studies and ranged from 33 to 81 percent of patients.[63,66,68,91,92] Although extrahepatic disease was reported by these studies, the patients were all described as having liver-dominant disease (i.e., majority of the disease is confined to the liver).

Table 5. Local hepatic therapies for CRC metastases to the liver: Summary of study characteristics KQ1 and KQ2

Study N[O] (% CRC) Rating	Study Design	Intervention Period	Intervention	Median Age (Range)	Previous Resection %	Median ECOG Score (Range)	Previous Local Hepatic Therapy %
Martin et al., 2012[86,a] 24 (100) Fair	Retrospective case series	02/2005–02/2009	RE with Y90 via hepatic artery catheter infusion	63 (35–83)	NR	NR	NR
Kucuk et al., 2011[84] 78 (44.9) Fair	Retrospective case series	06/2006–10/2010	SIRT with Y90 via hepatic artery catheter under intermittent fluoroscopic visualization	Mean: 62.4	2.6	NR	RFA: 7.7 Chemoembolization: 2.6
Aliberti et al., 2011[90] 82 (100) Good	Retrospective case series	12/2005–09/2011	TACE with irinotecan (100–2000 mg) in DC Beads (2–4 ml of beads)	61.8 (46–82)	NR	1 (0–2)	NR
Martin et al., 2011[75] 55 (100) Good	Prospective case series	10/2006–08/2008	Intervention: TACE with DEB; Drug: irinotecan; Dose: median 185 mg, range 150–650 mg; Site: femoral or axillary artery	60 (34–82)	20	1 (0–2)	Ablation: 9.1
Vautravers-Dewas et al., 2011[82] 42 (66.7) Good	Retrospective case series	07/2007–04/2009	Intervention: SBRT; Radiation dose: 40 Gy and 45 Gy; Site: noninvasive	(23–82)	51.1	NR	RFA: 7
Albert et al., 2011[63] 121 (100) Fair	Retrospective case series	03/1992–07/2008	Intervention: TACE; Drug: mitomycin C, doxorubicin, cisplatin; Site: femoral artery	Mean: 61.9	17	0 (0 -)	RFA: 17
Nace et al., 2011[89] 51 (100) Fair	Retrospective case series	08/2002–05/2008	RE with Y90 (delivery dose 50 Gy) via hepatic artery	64 (37–83)	23.5	NR (0–1)	RFA: 21.6; HAI 9.8
Stintzing et al., 2010[88] 6 (100) Fair	Prospective case series	NR	Radiosurgery (24 Gy) for a single session	66.5 (51–76)	83.5	NR	RFA: 17.6

Table 5. Local hepatic therapies for CRC metastases to the liver: Summary of study characteristics KQ1 and KQ2 (continued)

Study N$^{\odot}$ (% CRC) Rating	Study Design	Intervention Period	Intervention	Median Age (Range)	Previous Resection %	Median ECOG Score (Range)	Previous Local Hepatic Therapy %
Nishiofuku et al., 2010[92] 55 (100) Good	Retrospective case series	04/2005–03/2008	HAI of 5-FU (1000 mg/m^2) via continuous 5-hour infusion once a week; Catheter inserted from left subclavian artery or right femoral artery	62 (30–78)	22	1 (0–3)	NR
Nishiofuku et al., 2010[92] 55 (100) Good	Retrospective case series	04/2005–03/2008	HAI of 5-FU (1000 mg/m2) via continuous 5-hour infusion once a week; Catheter inserted from left subclavian artery or right femoral artery	62 (30–78)	22	1 (0–3)	NR
Cosimelli et al., 2010[66] 50 (100) Good	Prospective case series	05/2005–08/2007	Intervention: RE; Drug: Y90; Site: hepatic artery	67 (34–85)	24	0 (0–3)	NR
Kim et al., 2009[71] 9 (100) Good	Retrospective case series	06/2004–12/2006	Intervention: SBRT; Radiation dose: median 42 Gy, range 36–51 Gy; Site: noninvasive	57 (35–74)	NR	NR (1–2)	NR
Cianni et al., 2009[65] 41 (100) Fair	Retrospective case series	02/2005–01/2008	Intervention: RE; Y90 dose: mean 1.82 GBq; Site: hepatic artery	NR (33–77)	NR	0.7 (0 -)	TACE: 4.8; RFA or cryosurgical ablation: 19.5
Mulcahy et al., 2009[76] 72 (100) Good	Prospective case series	2003–2007	Intervention: RE; Y90 dose: median 118 Gy; Site: hepatic artery	61 (54–86)	NR	0 (0–2)	NR
Jakobs et al., 2008[91] 41 (100) Fair	Retrospective case series	10/2003–04/2007	Intervention: RE; Y90 dose: mean 1.9 GBq (range 0.7–2.8 GBq).	NR	NR	NR	NR
Sato et al., 2008[78] 137 (37.2) Fair	Prospective case series	2002–2006	Intervention: RE; Y90 dose: median 1.83 GBq, range 0.7–6.9 GBq, median 112.8 Gy, range 27–180 Gy; Site: hepatic artery	NR	NR	0 (0–3)	Local hepatic therapy (unspecified): 16

Table 5. Local hepatic therapies for CRC metastases to the liver: Summary of study characteristics KQ1 and KQ2 (continued)

Study N$^{\odot}$ (% CRC) Rating	Study Design	Intervention Period	Intervention	Median Age (Range)	Previous Resection %	Median ECOG Score (Range)	Previous Local Hepatic Therapy %
Vogl et al., 2008[83] 55 (21.8) Fair	Retrospective case series	2002–2006	Intervention: HAI; Drug: mitomycin C, gemcitabine; Site: femoral artery	63.5 (54–80)	NR	NR	NR
Hong et al., 2009[68] 21 (100) Good	Retrospective case series	01/2001–03/2006	Intervention: TACE; Drug: cisplatin, doxorubicin, mitomycin C; Site: femoral artery	67 (32–88)	23	NR	Cryosurgical ablation: 4.8, Radiation: 4.8, RFA: 9.5
			Intervention: RE; Y90 dose: median 112.9 Gy/tx, median 113.0 Gy/pt; Site: femoral artery	67 (51–80)	20	NR	RFA: 6.7, TACE: 13.3
Rowe et al., 2007[77] 24 (29.2) Good	Retrospective case series	07/2004–11/2005	Intervention: RE; Y90 dose: median 103 Gy, range 41–145 Gy, median 1.8 GBq, range 1.5–2.0 GBq; Site: hepatic artery	57 (53 – 68)	NR	1 (0–2)	NR
Jiao et al., 2007[70] 21 (47.6) Poor	Prospective case series	06/2004 – NR	Intervention: RE; Y90 dose: mean 1.9 GBq, range 1.2–2.5 GBq; Site: femoral catheter or hepatic artery port	NR (40–75)	31	NR	RFA: 48
Fiorentini et al., 2007[67] 20 (100) Poor	Prospective case series	11/2005 – ongoing (06/2007)	Intervention: TACE with DEB; Drug: irinotecan; Site: hepatic artery	NR	NR	1 (0–2)	NR
Jakobs et al., 2006[69] 68 (100) Good	Retrospective case series	01/2000–06/2004	Intervention: RFA; Site: percutaneous	(38–87)	16	NR	HAI: 3, TACE: 3

Table 5. Local hepatic therapies for CRC metastases to the liver: Summary of study characteristics KQ1 and KQ2 (continued)

Study N$^{\Theta}$ (% CRC) Rating	Study Design	Intervention Period	Intervention	Median Age (Range)	Previous Resection %	Median ECOG Score (Range)	Previous Local Hepatic Therapy %
Lewandowski et al., 2005[73] 27 (100) Good	Prospective case series	06/2001–12/2003	Intervention: RE; Y90 dose: range 135–150 Gy; Site: lobar	68 (54–86)	NR	0 (0–2)	NR
Lim et al., 2005[74] 30 (100) Poor	Prospective case series	01/2002–03/2004	Intervention: RE; Drug: Y90	61.7 (36 – 77)	NR	0 (0 – 2)	NR

CRC = colorectal cancer; DEB = drug-eluting bead; ECOG = Eastern Cooperative Oncology Group; GBq = Gigabecquerel; Gy = Gray; HAI = hepatic arterial infusion; Mets = Metastases; NR = not reported; RE = radioembolization; RFA = radiofrequency ablation; SBRT = stereotactic body radiation therapy; SIRT = selective internal radiotherapy; TACE = transarterial chemoembolization; tx = treatment; pt = patient; Y90 = Yttrium-90

[a]Data on patient characteristics from this case series include patients with extrahepatic disease; information on outcomes is for patients with non-extrahepatic disease.

$^{\Theta}$This N reflects the total number of patients enrolled in the study from any primary site. The percentage of CRC patients included in this report is presented in parentheses.

Table 6. Local hepatic therapies for CRC metastases to the liver: Summary of tumor characteristics KQ1 and KQ2

Study N[Θ] (% CRC) Rating	Synchronous (%)	Bilobar (%)	Median Liver Involvement (%) (Range)	Mean and Median Number of Hepatic Lesions (Range)	Mean Size of Hepatic Lesion(s) (cm) (Range)	Other Liver Involvement %
Martin et al., 2012[86,d] 24 (100) Fair	NR	67	NR	NR	NR	Extrahepatic metastasis 45.8
Kucuk et al., 2011[84] 78 (44.9) Fair	NR	NR	NR	NR	NR	NR
Aliberti et al., 2011[90] 82 (100) Good	NR	NR	33 (25–50)	NR	12 (6.5–32)	NR
Martin et al., 2011[75] 55 (100) Good	30.9	NR	NR	Median: 4 (1–20)	NR	50 Percent liver involvement : 30.9
Vautravers-Dewas et al., 2011[82] 42 (66.7) Good	NR	NR	NR	Mean: 1.4 (1–4)	3.4 (.7–10)	WHO 0: 94.4; WHO 1: 11.1; WHO 2: 2.2; WHO 3: 2.2
Albert et al., 2011[63] 121 (100) Fair	49	NR	NR	NR	NR	Extrahepatic metastasis 46
Nace et al., 2011[89] 51 (100) Fair	NR	NR	NR	NR	NR	NR
Stintzing et al., 2010[88] 6 (100) Fair	NR	NR	NR	NR	NR	NR

Table 6. Local hepatic therapies for CRC metastases to the liver: Summary of tumor characteristics KQ1 and KQ2 (continued)

Study N[Θ] (% CRC) Rating	Synchronous (%)	Bilobar (%)	Median Liver Involvement (%) (Range)	Mean and Median Number of Hepatic Lesions (Range)	Mean Size of Hepatic Lesion(s) (cm) (Range)	Other Liver Involvement %
Nishiofuku et al., 2010[92] 55 (100) Good	65.5	NR	NR	NR	NR	limited extrahepatic disease 81.8
Cosimelli et al., 2010[66] 50 (100) Good	72	70	NR	NR	(5–.8)	≤4 hepatic mets: 42; >4 hepatic mets: 58
Kim et al., 2009[71,a] 9 (100) Good	55.6	NR	NR	Mean: 1.4 Median: 1 (1–2)	NR	NR
Cianni et al., 2009[65,b] 41 (100) Fair	NR	95.1	NR	NR	NR	50 Percent liver involvement : 24.3
Mulcahy et al., 2009[76] 72 (100) Good	NR	83	NR	NR	NR	Liver replacement ≤25 percent: 78; Liver replacement 26–50 percent: 19; Liver replacement ≥50 percent: 3
Jakobs et al., 2008[91] 41 (100) Fair	73	NR	NR	NR	NR	Limited extrahepatic disease 17
Sato et al., 2008[78] 137 (37.2) Fair	NR	NR	NR	NR	NR	Tumor burden 0–25 percent: 80; Tumor burden 26–50 percent: 15; Tumor burden 51–75 percent: 5
Vogl et al., 2008[83,c] 55 (21.8) Fair	17	NR	NR	NR	NR	Tumor burden 50–75 percent: 16.7
Hong et al., 2009[68] 21 (100) Good	66.7	66.7	NR	NR	9.3 (5–16)	Extrahepatic spread: 43
	53.3	86.7	NR	NR	8.2 (2–19)	Extrahepatic spread: 33

Table 6. Local hepatic therapies for CRC metastases to the liver: Summary of tumor characteristics KQ1 and KQ2 (continued)

Study N[Θ] (% CRC) Rating	Synchronous (%)	Bilobar (%)	Median Liver Involvement (%) (Range)	Mean and Median Number of Hepatic Lesions (Range)	Mean Size of Hepatic Lesion(s) (cm) (Range)	Other Liver Involvement %
Rowe et al., 2007[77] 24 (29.2) Good	NR	NR	25 (3–49)	NR	NR	NR
Jiao et al., 2007[70] 21 (47.6) Poor	NR	NR	NR	NR	NR	Tumor Volume <25 percent:14, Tumor Volume 25-50 percent:81, Tumor Volume >51 percent:5
Fiorentini et al., 2007[67] 20 (100) Poor	NR	NR	40 (20–70)	NR	NR	NR
Jakobs et al., 2006[69] 68 (100) Good	NR	NR	NR	Mean: 2.7 (1–5)	2.3 (.5–5)	NR
Lewandowski et al., 2005[73] 27 (100) Good	NR	78	NR	NR	NR	Liver replacement by tumor ≤25 percent: 78; 26–50 percent: 19; >50 percent: 3
Lim et al., 2005[74] 30 (100) Poor	NR	NR	NR	NR	NR	NR

CRC = colorectal cancer; Mets = metastases; NR = not reported; WHO = World Health Organization

[Θ]This N reflects the total number of patients enrolled in the study from any primary site. The percentage of CRC patients included in this report is presented in parentheses.

[a]Total liver tumor volume: median, 72.8 ml (range 3.4–271.1 ml).

[b]All patients had multiple lesions and four patients (9.7%) had other metastatic involvement (pathologic lymph nodes and bone metastases).

[c]Median tumor volume: 79.2 ml (range 6.6–1,384.4 ml).

[d]Data on patient characteristics from this case series include patients with extrahepatic disease; information on outcomes is for patients with non-extrahepatic disease.

Detailed Synthesis

Table 7 displays the outcomes reported. All studies reported overall survival. All studies reported on adverse events, but four studies aggregated these events by multiple primary cancer sites, which did not permit us to extract CRC-specific adverse events.[69,70,77,78] Eight studies also reported progression-free survival.[63,65,66,71,75,90,92,93] Three studies reported on both liver-specific progression-free survival and overall progression-free survival;[63, 75, 92] no studies reported on liver-specific progression-free survival alone; and the remaining five studies reported overall progression-free survival alone.[65,66,71,74,90] Jakobs et al. (2006)[69] attempted to calculate the time to recurrence statistic but were unable to do so because of the low rate of recurrence (18%). Two studies reported on length of stay,[63,67] and two studies reported on quality of life.[66,67] We report data on individual outcomes, except for results on overall progression-free survival and liver-specific progression-free survival, which are located in Appendix D.

Table 7. Outcomes reported for Key Questions 1 and 2

Study N$^{\Theta}$ (% CRC) Rating	OS	QOL	TTR	LOS	LR	AE
Albert et al., 2011[63] 121 (100) Fair	●	NR	NR	●	NR	●
Aliberti et al., 2011[90] 82 (100) Good	●	NR	NR	NR	NR	●
Cianni et al., 2009[65] 41 (100) Fair	●	NR	NR	NR	NR	●
Cosimelli et al., 2010[66] 50 (100) Good	●	●	NR	NR	NR	●
Fiorentini et al., 2007[67] 20 (100) Poor	●	●	NR	●	NR	●
Hong et al., 2009[68] 21 (100) Good	●	NR	NR	NR	NR	●
Jakobs et al., 2006[69] 68 (100) Good	●	NR	●[a]	NR	●	●[a]
Jakobs et al., 2008[91] 41 (100) Fair	●	NR	NR	NR	NR	●
Jiao et al., 2007[70] 21 (47.6) Poor	●	NR	NR	NR	NR	●[a]
Kim et al., 2009[71] 9 (100) Good	●	NR	NR	NR	●	●
Kucuk et al., 2011[84] 78 (44.9) Fair	●	NR	NR	NR	NR	●
Lewandowski et al., 2005[73] 27 (100) Good	●	NR	NR	NR	NR	●

Table 7. Outcomes reported for Key Questions 1 and (continued)

Study N[Θ] (% CRC) Rating	OS	QOL	TTR	LOS	LR	AE
Lim et al., 2005[74] 30 (100) Poor	●	NR	NR	NR	NR	●
Martin et al., 2011[75] 55 (100) Good	●	NR	NR	NR	NR	●
Martin et al., 2012[86] 24 (100) Fair	●	NR	NR	NR	NR	●
Mulcahy et al., 2009[76] 72 (100) Good	●	NR	NR	NR	NR	●
Nace et al., 2011[89] 51 (100) Fair	●	NR	NR	NR	NR	●
Nishiofuku et al., 2010[92] 55 (100) Good	●	NR	NR	NR	NR	●
Rowe et al., 2007[77] 24 (29.2) Good	●	NR	NR	NR	NR	●
Sato et al., 2008[78] 137 (37.2) Fair	●	NR	NR	NR	NR	●[a]
Stintzing et al., 2010[88] 6 (100) Fair	●	NR	NR	NR	●	●
Vautravers-Dewas et al., 2011[82] 42 (66.7) Good	●	NR	NR	NR	NR	●
Vogl et al., 2008[83] 55 (21.8) Fair	●	NR	NR	NR	NR	●

AE = adverse events; CRC = colorectal cancer; LOS = length of stay; LR = local recurrence; NR = not reported; OS = overall survival; QOL = quality of life; TTR = time to recurrence

[Θ]This N reflects the total number of patients enrolled in the study from any primary site. The percentage of CRC patients included in this report is presented in parentheses.

"●"indicates that this outcome was reported in the article.

[a]Paper reported an outcome of interest but these were grouped with multiple primary presentation sites, which did not permit us to identify CRC-specific data.

Overall Survival

All studies reported on outcomes related to overall survival (Table 8, which is organized by intervention). One RFA study by Jakobs et al. (2006)[69] did not report mean or median survival measures, but did report 1-, 2-, and 3-year survival rates of 96 percent, 71 percent, and 68 percent, respectively, from the time of study treatment. Three studies in our report used TACE with DEB. Median survival was reported by two[75,90] studies and ranged from 19 to 25 months from study treatment. Florentini et al. (2007) reported only a 1-year survival rate of 61 percent.[67] Two studies reported on TACE alone.[63,68] Both studies reported median survival from time of diagnosis of liver metastases, which ranged from 26.3 to 27 months. Thirteen studies of RE with Yttrium-90 were included in this review.[65,66,6 8,70,73,74,76-78,84,86,89,91] One of these studies involved

systemic chemotherapy in addition to RE and is therefore not presented in this summary of results.[30] Eight studies reported survival from study treatment; median survival ranged from 4 to 15.2 months.[70,73,77,78,84,86,89,91] One of these studies[84] did not reach median survival at a follow up of 3 years. Three studies reported survival starting from diagnosis of liver metastases, which ranged from 31 to 34.6 months.[66,68,76] Two studies did not indicate the time point from which survival was measured.[65,74] HAI was used in two studies in our review,[83,92] and reported median survival from the start of study treatment as 6.7 and 9.7 months.[83,92] Three studies reported SBRT in this review and all defined survival from time of study treatment.[71,82,88] Median survival values reported in two studies were 17 and 25 months.[71,88] The third SBRT study only reported 1- and 2-year survival rates of 95 percent and 58 percent, respectively.[82]

Direct comparisons of overall survival cannot be made from the published data because there are no comparative studies and the studies measured survival from different starting points (i.e., time of diagnosis or time of treatment).

Quality of Life

Two studies reported on quality of life.[66,67] Cosimelli and colleagues used a battery of questionnaires to assess both cancer and disease-specific quality of life (The European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire [QLQ] C30, EORTC QLQ C38, and EORTC QLQ LMC-21).[66] They also assessed anxiety and depression (Hamilton Rating Scale for Depression [HAM-D]) and patient satisfaction (EORTC QLQ SAT-32). They reported quality of life measures on 14 of 50 enrolled subjects. The study authors provided no insight as to why only 14 of the participants had available data on quality of life. Six weeks after treatment, the quality of life of 14 patients treated with RE was not adversely affected, and patients' anxiety levels were significantly reduced from pretreatment levels. No significant difference was observed in depression score pre- and post-treatment. In a study of chemoembolization with irinotecan-eluting beads, Fiorentini and colleagues stated that 18 of 20 patients reported improvement in quality of life post-treatment.[41] They used the Edmonton Symptom Assessment System in this study, but only reported qualitatively that these patients had improved without providing any metrics.

Length of Stay

Mean length of stay was reported by two studies[63,67] of TACE and ranged from 1.3 to 3 days. No direct comparisons can be made based on the published studies.

Time to Progression

Time to progression was not reported in any of the included studies.

Local Recurrence

Outcomes related to local recurrence are summarized in Table 9. In this report, local recurrence is defined as recurrence of the liver metastases in the area previously treated. This constitutes a treatment failure or failure to treat the entire lesion and is considered an adverse event. One RFA study reported a local recurrence rate of 18 percent.[69] Local recurrence was also reported in two studies of SBRT, both of which reported a rate of 33.3 percent.[71,88]

Adverse Events

Twenty-four studies reported on adverse events with varying levels of detail and are presented in Table 9 by intervention. One TACE study reported a patient who developed a hepatic abscess.[67] Liver failure was reported in three studies, two on RE[65,66] and one[75] on TACE with DEB intervention. Two studies—one on TACE[63] and one on RE[76]—reported elevated alkaline phosphatase levels. Elevated bilirubin was reported in five studies, one on TACE with DEB[90], one on TACE[63], two on RE[76,91], and one on HAI[92]. Elevated transaminase levels were reported in one RE article,[76] which also reported elevated bilirubin and alkaline phosphatase. Although these results from liver function tests could point to disease progression, in the time period following a local hepatic therapy they are more likely to reflect an adverse effect of the treatment. Only Aliberti et al. reported liver function test results immediately after treatment.[90] Other liver function tests were evaluated as acute or late toxicity[76,91] or were not reported[63,92] at the time adverse events were evaluated. Two authors indicated that liver function toxicity was likely a result of progressive disease or biliary obstruction.[76,91] One TACE with DEB study reported one death from myocardial infarction[75] and one TACE study reported a 30-day morality rate of 3.6 percent.[63] A description of rare adverse events is included in Table 9. No study reported on injury to adjacent organs, hepatic hemorrhage, or steatohepatitis.

Table 8. Local hepatic therapies for CRC metastases to the liver: Outcomes related to overall survival KQ1 and KQ2

Intervention	Survival Time From	Mean or Median Overall Survival (95% CI)	1-Year Survival (%)	2-Year Survival (%)	3-Year Survival (%)	5-Year Survival (%)	Study N[Θ] (% CRC) Rating
RFA	Study Treatment	NR	96	71	68	NR	Jakobs et al., 2006[69,f] 68 (100) Good
Intervention: TACE with DEB; Drug: irinotecan	Study Treatment	Median: 25	~78[g]	~52[g]	~21[g]	NR	Aliberti et al., 2011[90] 82 (100) Good
	Study Treatment	Median: 19	75	NR	NR	NR	Martin et al., 2011[75,a] 55 (100) Good
	NR	NR	61*	NR	NR	NR	Fiorentini et al., 2007[67,b] 20 (100) Poor
Intervention: TACE; Drug: mitomycin C, doxorubicin, cisplatin	Diagnosis of Liver Mets	Median: 27	85	55	NR	6	Albert et al., 2011[63,a] 121 (100) Fair
Intervention: TACE; Drug: cisplatin, doxorubicin, mitomycin C; Site: femoral artery	Diagnosis of Liver Mets	Median: 26.3	NR	NR	NR	NR	Hong et al., 2009[68] 21 (100) Good
Intervention: RE; Drug: Y90	Study Treatment	Median: 11.9 (4.1 to 25.7)	NR	NR	NR	NR	Martin et al., 2012[86,h] 24 (100) Fair
	Study Treatment	Median not reached	~88[g]	~77[g]	~77[g]	NR	Kucuk et al., 2011[84] 78 (44.9) Fair
	Study Treatment	Mean: 14.4 Median: 10.2 (7.5 to 13.0)	NR	NR	NR	NR	Nace et al., 2011[89] 51 (100) Fair
	Diagnosis of Liver Mets	Median: 31 (29 to 34)	50.4	19.6	NR	NR	Cosimelli et al., 2010[66,b] 50 (100) Good
	NR	Median: 11.8	NR	NR	NR	NR	Cianni et al., 2009[65,b] 41 (100) Fair
	Diagnosis of Liver Mets	Median: 34.6 (24.4 to 41.8)	NR	NR	NR	17.7	Mulcahy et al., 2009[76] 72 (100) Good
	Study Treatment	Mean: 13.9 Median: 15.2	53.7	26.7	NR	NR	Sato et al., 2008[78,b] 137 (37.2) Fair

Table 8. Local hepatic therapies for CRC metastases to the liver: Outcomes related to overall survival KQ1 and KQ2 (continued)

Intervention	Survival Time From	Mean or Median Overall Survival (95% CI)	1-Year Survival (%)	2-Year Survival (%)	3-Year Survival (%)	5-Year Survival (%)	Study N[Θ] (% CRC) Rating
Intervention: RE; Drug: Y90 (continued)	Diagnosis of Liver Mets	Median: 32.8	NR	NR	NR	NR	Hong et al., 2009[68,a] 15 (100) Good
	Study Treatment	Median: 10.5	~40[g]	~27[g]	~16[g]	NR	Jakobs et al., 2008[91] 41 (100) Fair
	Study Treatment	Median: ~4[g]	~23[g]	14.3	NR	NR	Jiao et al., 2007[70,d] 21 (47.6) Poor
	Study Treatment	Mean: 11.1 Median: 9	~27[g]	~20[g]	NR	NR	Rowe et al., 2007[77,b] 24 (29.2) Good
	NR	NR	~20[g]	NR	NR	NR	Lim et al., 2005[74] 30 (100) Poor
	Study Treatment	Median: 9.4 (7.3 to 13.5)	NR	NR	NR	NR	Lewandowski et al., 2005[73,c] 27 (100) Good
Intervention: HAI; Drug: mitomycin C, gemcitabine	Study Treatment	Median: 9.7	~48[g]	~30[g]	NR	NR	Vogl et al., 2008[83,a] 55 (21.8) Fair
Intervention: HAI; Drug: 5-FU 1000 mg/m^2	Study Treatment	Median: 6.7 (5 to 8.3)	~18[g]	~5[g]	NR	NR	Nishiofuku et al., 2010[92] 55 (100) Good

Table 8. Local hepatic therapies for CRC metastases to the liver: Outcomes related to overall survival KQ1 and KQ2 (continued)

Intervention	Survival Time From	Mean or Median Overall Survival (95% CI)	1-Year Survival (%)	2-Year Survival (%)	3-Year Survival (%)	5-Year Survival (%)	Study N[Θ] (% CRC) Rating
Intervention: SBRT; Radiation dose: 40 Gy and 45 Gy; Site: noninvasive	Study Treatment	NR	~95[g]	58	NR	NR	Vautravers-Dewas et al., 2011[82] 42 (66.7) Good
	Study Treatment	Median: 25	53	40	40	NR	Kim et al., 2009[71] 9 (100) Good
Intervention: SBRT; Radiation dose: 24 Gy to the 70% isodose; Site: noninvasive	Study Treatment	Mean: 18.3 Median: 17.0	NR	NR	NR	NR	Stintzing et al., 2010[88] 6 (100) Fair

CI = confidence interval; CRC = colorectal cancer; Gy = Gray; HAI = hepatic arterial infusion; Mets = metastases; NR = not reported; RE = radioembolization; SBRT = stereotactic body radiation therapy; TACE = transarterial chemoembolization

[Θ]This N reflects the total number of patients enrolled in the study from any primary site. The percentage of CRC patients included in this report is presented in parentheses.

[a]Treatment through the femoral or axillary artery.

[b]Treatment through the hepatic artery.

[c]Lobar treatment site.

[d]Femoral catheter or hepatic artery port.

[e]Site: percutaneous and intraoperatively.

[f]Site: percutaneous.

[g]Survival estimates were extracted by the EPC from survival curves presented in the article.

[h]Data on this outcome are for patients with non-extrahepatic disease (n=11).

Table 9. Local hepatic therapies for unresectable CRC metastases to the liver: Adverse events KQ1 and KQ2

Intervention	Local Recurrence N (%)	Biloma (%)	Liver Failure (%)	Elevated Alkaline Phosphatase N (%)	Elevated Bilirubin N (%)	Rare Adverse Events	Study N$^{\Theta}$ (% CRC) Rating
RFA	12 (18)	NR	NR	NR	NR	No major complications.	Jakobs et al., 2006[69] 68 (100) Good
Intervention: TACE with DEB; Drug: irinotecan;	NR	NR	NR	NR	41 (50)	NR	Aliberti et al., 2011[90] 82 (100) Good
	NR	NR	3	NR	NR	All AE are from the number of DEB treatments (99) and not from the total 55 patients. 3% of patients had severe liver dysfunction, 1 patient died. 1% had cholecystitis, 1% had gastritis, and 1% had myocardial infarction, which was the cause of death in 1 patient.	Martin et al., 2011[75] 55 (100) Good
	NR	NR	NR	NR	NR	Liver abscess: 5% (1 patient)	Fiorentini et al., 2007[67] 20 (100) Poor
Intervention: TACE; Drug: mitomycin C, doxorubicin, cisplatin	NR	NR	NR	Grade 1:10% Grade 2: 7% Grade 3: 2%	Grade 1: 1%	Prolonged in-hospital visits after major complications occurred in 11% (20) of the 174 treatments. These included hepatic infarction in 4, hematoma at the site of catheterization in 3, infection in 3, acute edema in 2, myocardial infarction in 2, pulmonary embolism in1, transient ischemic attack in 1, hypoxia in 1, and abnormal heart rhythm in 1. Thirty-day mortality was 3.6%.	Albert et al., 2011[63] 121 (100) Fair
Intervention: TACE; Drug: cisplatin, doxorubicin, mitomycin C;	NR	NR	NR	NR	NR	1 (2.7%) pulmonary embolism in the CE group.	Hong et al., 2009[68] 21 (100) Good
Intervention: RE; Drug: Y90	NR	NR	NR	NR	NR	No major complications.	Martin et al., 2012[86] 24 (100) Fair
	NR	NR	NR	NR	NR	No major complications.	Kucuk et al., 2011[84] 78 (44.9) Fair
	NR	NR	0	NR	NR	Ventricular tachycardia: 1 (2%)	Nace et al., 2011[89] 51 (100) Fair

Table 9. Local hepatic therapies for unresectable CRC metastases to the liver: Adverse events KQ1 and KQ2 (continued)

Intervention	Local Recurrence N (%)	Biloma (%)	Liver Failure (%)	Elevated Alkaline Phosphatase N (%)	Elevated Bilirubin N (%)	Rare Adverse Events	Study N$^{\Theta}$ (% CRC) Rating
Intervention: RE; Drug: Y90 (continued)	R	NR	2	NR	NR	NR	Cosimelli et al. ,2010[66] 50 (100) Good
	NR	NR	2.4	NR	NR	NR	Cianniet al., 2009[65] 41 (100) Fair
	NR	NR	NR	6 (8)	9 (13)	GI ulcer	Mulcahy, et al., 2009[76] 72 (100) Good
	NR	Nonspecific to CRC	NR	NR	Nonspecific to CRC	Included non-CRC patients in this article and did not report specific adverse events for CRC mets to the liver Significant toxicity included grade 3 or 4 bilirubin toxicity, 1 GI ulceration, 1 radiation-induced cholecystitis, 2 bilomas, and 1 hepatic abscess.	Sato et al., 2008[78,b] 137 (37.2) Fair
	NR	NR	NR	NR	NR	1 (2.7%) pulmonary embolism	Hong et al., 2009[68] 15 (100) Good
	NR	NR	NR	NR	8 (10)	One patient (2.4%) presented with acute grade 4 cholecystitis 4 weeks after radioembolization and was referred for surgery.	Jakobs et al., 2008[91] 41 (100) Fair
	NR	NR	NR	NR	NR	Gastric/duodenal ulceration: 4 (13%); severe disabling pain, anorexia, and nausea: 1 (3.3%); radiation hepatitis: 1 (3.3%)	Lim et al., 2005[93] 30 (100) Poor
	NR	NR	NR	NR	NR	Included non-CRC patients in this article and did not report specific adverse events for CRC mets to the liver. Four rare adverse events occurred post-SIRT: 1 cholecystitis followed by fibrosis and portal hypertension; 1 peptic ulceration in the lesser curvature of the stomach; and 2 radiation hepatitis.	Jiao et al., 2007[70,c] 21 (47.6) Poor

Table 9. Local hepatic therapies for unresectable CRC metastases to the liver: Adverse events KQ1 and KQ2 (continued)

Intervention	Local Recurrence N (%)	Biloma (%)	Liver Failure (%)	Elevated Alkaline Phosphatase N (%)	Elevated Bilirubin N (%)	Rare Adverse Events	Study N$^{\Theta}$ (% CRC) Rating
Intervention: RE; Drug: Y90 (continued)	NR	NR	NR	NR	NR	Toxicity data were only available for 14 of 24 patients and not reported specifically for CRC mets to the liver. One patient had a symptomatic gastric ulcer postsurgery and 1 patient had a femoral artery plaque rupture with thromboembolism in the lower extremity.	Rowe et al., 2007[77,b] 24 (29.2) Good
	NR	NR	NR	NR	NR	One case of radiation-induced ulceration caused by technical error and 1 case of right plural effusion 1 month after treatment.	Lewandowski et al., 2005[73] 27 (100) Good
Intervention: HA; Drug: mitomycin C, gemcitabine	NR	NR	NR	NR	NR	No common toxicity criteria grade III, IV, or V adverse events were observed.	Vogl et al., 2008[83,a] 55 (21.8) Fair
Intervention: HAI; Drug: 5-FU 1000 mg/m^2	NR	NR	NR	NR	1 (1.8)	NR	Nishiofuku et al., 2010[92] 55 (100) Good
Intervention: SBRT	2 (33.3%)	NR	NR	NR	NR	NR	Stintzing et al., 2010[88] 6 (100) Fair
	NR	NR	NR	NR	NR	One patient had cirrhotic failure at 5 months; 1 patient had gastric ulceration; 1 patient had esophagitis; and 1 patient had grade 3 epidermitis. No grade 4 toxicity was observed.	Vautravers-Dewas et al., 2011[82] 42 (66.7) Good
	3 (33.3%)	NR	NR	NR	NR	No grade 3 or 4 acute complications	Kim et al., 2009[71] 9 (100) Good

CE = chemoembolization; DEB = drug-eluting beads; HAI = hepatic arterial infusion; NR = not reported; RE = radioembolization; SBRT = stereotactic body radiation therapy; TACE = transarterial chemoembolization.

$^{\Theta}$This N reflects the total number of patients enrolled in the study from any primary site. The percentage of CRC patients included in this report is presented in parentheses.

[a]Treatment through the femoral or axillary artery.

[b]Treatment through the hepatic artery.

[c]Femoral catheter or hepatic artery port.

Multivariate Analyses

Univariate or multivariate analyses of prognostic factors for overall survival including, but not limited to, ECOG score, presence of extrahepatic disease, and treatment response, were variously reported in six case series[63,73,76,78,91,92] of local hepatic therapies. All analyses reported on overall survival as the dependent variable.

Among the patient or tumor characteristics found to be associated with improved overall survival were the following: ECOG status (0 vs. ≥1 and in another study 0 or 1 vs. ≥2), performance status (0 or 1 vs. ≥ 2), number of extrahepatic metastases sites (0 or 1 vs. ≥2), number of lines of previous chemotherapy (0–1 vs. ≥ 2), performance status (0 or 1 vs. ≥ 2), carcinoembryonic antigen response (Yes, No), and Response Evaluation Criteria in Solid Tumors (RECIST).

Key Questions 3 and 4

Key Questions 3 and 4 focus on the comparative effectiveness (KQ3) and harms (KQ4) of the various local hepatic therapies in patients who are receiving local hepatic therapy as an adjunct to systemic therapy for unresectable CRC metastases to the liver and who have no evidence of extrahepatic disease.

Key Points

- No conclusions on overall survival, quality of life, length of stay, time to recurrence, local recurrence, or adverse events can be drawn from the body of evidence comparing local hepatic therapies for unresectable CRC metastases to the liver. No comparative studies met the inclusion criteria for this review.
- The literature base for this review is comprised of case series and one RCT[87] that was abstracted as a case-series study due to a nonrelevant comparator. Four studies were ranked as good quality,[64,72,80,87] and three were ranked as fair quality.[79,81,85]
- The assessment of applicability of the study findings to clinical practice is limited by the poor characterization of the patient populations (e.g., number and size of metastases, performance status) and variability in the delivery of the interventions (e.g., surgical approach, dose and drugs delivered)

Description of Included Studies

Table 10, Table 11, and Table 12 show the study, patient, and tumor characteristics, including study design, intervention period, intervention, number of patients enrolled, and patient demographics for studies of local hepatic therapies for patients with unresectable CRC metastases to the liver who are receiving local hepatic therapy as an adjunct to systemic therapy. Table 13 through Table 15 present data on study outcomes. Seven studies were included, [64,72,79-81,85,87] six of which were case series. One RCT[87] was included in the review but was abstracted as a case-series study because the comparator, systemic chemotherapy, was an intervention outside the scope of this review. Of the six case series, three were prospective[64,80,81] and three were retrospective.[72,79,85] The total number of patients for which data were abstracted from the five studies was 296. Two studies included patients treated with RE with concurrent systemic chemotherapy;[64,72] three articles reported on RFA with chemotherapy;[80,85,87] and two reported on

patients treated with HAI and systemic chemotherapy.[79,81] All studies treated patients after January 1, 2000.

Patients ranged in age from 31 to 84 years, but were generally in their 60s. One study reported the ECOG score, with a median value of 0 and a range of 0 to 2.[64] Two studies reported rates of resection for previous CRC liver metastases of 15 and 27 percent,[64,87] and three studies[64,72,80] reported the proportion of patients who had received prior systemic chemotherapy, which ranged from 0 to 94 percent. One study[64] reported patient experience with prior local hepatic therapy, with 66 percent of patients having prior RE and 6 percent having had prior ablation.

Tumor characteristics were inconsistently reported across studies, with synchronous or metachronous disease status reported in three studies[72,85,87]; bilobar or unilobar disease reported in two studies;[64,85] degree of liver involvement reported in three studies;[64,72,79] number of hepatic lesions reported by two studies;[80,87] and lesion size reported in two studies.[80,85] The details of these characteristics are presented in Table 12.

Table 10. Local hepatic therapies adjunctive to systemic chemotherapy for CRC metastases to the liver: Summary of study characteristics KQ3 and KQ4

Study N[Θ] (% CRC) Rating	Study Design	Intervention Period	Intervention
Ruers et al., 2012[87] 60 (100) Good	RCT[a]	04/2002–06/2007	RFA and systemic treatment with 5-FU/L/oxaliplatin, with bevacizumab added post 10/2005.
Lee et al., 2012[85] 28 (100) Fair	Retrospective case series	07/2002–04/2008	Percutaneous RFA performed under real-time sonographic guidance. The radiofrequency current was applied for 12 minutes at 200 W to create a radius of ablation at least 10 mm larger than the largest tumor diameter.
Kosmider et al., 2011[72] 19 (100) Good	Retrospective case series	01/2002–10/2008	Intervention: RE with systemic chemotherapy; Drug: FOLFOX or 5-FU; Y90 dose: median 1.96 GBq, mean 2.08 GBq, range 1.60-2.60 GBq; Site: hepatic artery
Sgouros et al., 2011[80] 13 (100) Good	Prospective case series	09/2000–08/2004	Intervention: RFA with systemic chemotherapy; Drug: FOLFIRI; Site: percutaneous
Chua et al. 2011[64] 140 (100) Good	Prospective case series	03/2006 - 05/2009	Intervention: RE with systemic chemotherapy; Drug: Y90 dose: mean 1.8 GBq, median 1.8 GBq, range 0.4-2.6 GBq; Site: femoral or brachial artery
Seki et al., 2009[79] 20 (100) Fair	Retrospective case series	07/2004 - 01/2008	Intervention: HAI followed by systemic chemotherapy; Drug: 5-FU, FOLFOX4, or FOLFOX6; Site: hepatic artery, IV
Tsutsumi et al., 2008[81] 16 (100) Fair	Prospective case series	08/2003 - 09/2006	Intervention: HAI with concurrent systemic chemotherapy; Drug: 5-FU and l-leucovorin, UFT and UZEL; Site: femoral artery, oral

5-FU = 5-florouracil; CRC = colorectal cancer; HAI = hepatic arterial infusion; RE = radioembolization; RFA = radiofrequency ablation; UFT = tegafur-uracil; UZEL = UFT and leucovorin

[Θ]This N reflects the total number of patients enrolled in the study from any primary site. The percentage of CRC patients included in this report is presented in parentheses.

[a]Data from this RCT were abstracted and treated as case series data because the comparator in the RCT was outside the scope of this review.

Table 11. Local hepatic therapies adjunctive to systemic chemotherapy for CRC metastases to the liver: Summary of patient characteristics
KQ3 and KQ4

Study N[Θ] (% CRC) Rating	Study Design	Median Age (Range)	Previous Resection (%)	ECOG Score Median (Range)	Previous Systemic Chemotherapy (%)	Previous Local Hepatic Therapy (%)
Ruers et al., 2012[87] 60 (100) Good	RCT[a]	64 (31–79)	15	NR	NR	NR
Lee et al., 2012[85] 28 (100) Fair	Retrospective case series	61 (32–82)	NR	NR	NR	NR
Kosmider et al., 2011[72] 19 (100) Good	Retrospective case series	62 (44–75)	NR	0 (0–1)	0	NR
Sgouros et al., 2011[80] 13 (100) Good	Prospective case series	77 (47–84)	NR	NR	76.9	NR
Chua et al., 2011[64] 140 (100) Good	Prospective case series	64 (37–85)	27	0 (0–2)	94	SIRT: 66, Ablation 6
Seki et al., 2009[79] 20 (100) Fair	Retrospective case series	49	NR	NR	NR	NR
Tsutsumi et al., 2008[81] 16 (100) Fair	Prospective case series	62 (43–74)	NR	NR	NR	NR

CRC = colorectal cancer; ECOG = Eastern Cooperative Oncology Group; NR = not reported; SIRT = selective internal radiation therapy
[Θ]This N reflects the total number of patients enrolled in the study from any primary site. The percentage of CRC patients included in this report is presented in parentheses.
[a]Data from this RCT were abstracted and treated as case series data because the comparator in the RCT was outside the scope of this review.

Table 12. Local hepatic therapies adjunctive to systemic chemotherapy for CRC metastases to the liver: Summary of tumor characteristics KQ3 and KQ4

Study N[Θ] (% CRC) Rating	Synchronous (%)	Bilobar (%)	% Median Liver Involvement (Range)	Median Number of Hepatic Lesions (Range)	Mean Size of Hepatic Lesion(s) (cm) (Range)	Median Size of Hepatic Lesion(s) (cm)	Other Liver Involvement
Ruers et al., 2012[87] 60 (100) Good	38.3	NR	NR	4 (1–9)	NR	NR	NR
Lee et al., 2012[85] 28 (100) Fair	50	NR	NR	NR	NR	NR	NR
Kosmider et al., 2011[72] 19 (100) Good	95	NR	40 (25–65)	NR	NR	NR	NR
Sgouros et al., 2011[80] 13 (100) Good	NR	NR	NR	1 (1–3)	3 (1.5–5.5)	NR	Sum of the maximum diameters of liver metastases per patient at inclusion in cm; Mean: 4.1, Range: 2–8
Chua et al., 2011[64] 140 (100) Good	NR	90	NR	NR	NR	NR	% liver involvement 0–25% (55%); 26–50 (36%); 51–75 (9%)
Seki et al., 2009[79] 20 (100) Fair	NR	NR	NR	NR	NR	NR	Liver involvement ≤60%: 85; Liver involvement >60%: 15
Tsutsumi et al., 2008[81] 16 (100) Fair	NR	NR	NR	NR	NR	NR	NR

CRC = Colorectal cancer; NR = not reported

[Θ]This N reflects the total number of patients enrolled in the study from any primary site. The percentage of CRC patients included in this report is presented in parentheses.

Detailed Synthesis

Table 13 displays the outcomes reported by study for KQ3 and KQ4. All studies reported overall survival and adverse events. Four studies reported on overall progression-free survival.[72, 79, 80, 87] Local recurrence was reported in three studies.[64, 85, 87] One study reported on quality of life.[87] We report data on individual outcomes, except for results on overall progression-free survival and liver-specific progression-free survival, which are located in Appendix D. No study reported on median time to recurrence, length of stay, or liver progression-free survival.

Table 13. Outcomes reported for Key Questions 3 and 4

Study N[Θ] (% CRC) Rating	OS	QOL	LOS	TTR	LR	AE
Ruers et al., 2012[87] 60 (100) Good	●	●	NR	NR	●	●
Lee et al., 2012[85] 28 (100) Fair	●	NR	NR	NR	●	●
Kosmider et al., 2011[72] 19 (100) Good	●	NR	NR	NR	NR	●
Sgouros et al., 2011[80] 13 (100) Good	●	NR	NR	NR	NR	●
Chua et al., 2011[64] 140 (100) Good	●	NR	NR	NR	●	●
Seki, et al., 2009[79] 20 (100) Fair	●	NR	NR	NR	NR	●
Tsutsumi et al., 2008[81] 16 (100) Fair	●	NR	NR	NR	NR	●

AE = adverse events; LOS = length of stay; LR = local recurrence; OS = overall survival; QOL = quality of life; TTR = time to recurrence

[Θ]This N reflects the total number of patients enrolled in the study from any primary site. The percentage of CRC patients included in this report is presented in parentheses.

"●"Indicates that this outcome was reported in the article.

Overall Survival

Outcomes related to overall survival are summarized in Table 14, which is organized by intervention. All studies reported median overall survival. No direct comparisons can be made from the published data.

RFA was performed in three studies as an adjunct to systemic chemotherapy for unresectable CRC liver metastases.[80,85,87] Ruers et al. (2012) reported a median survival of 45.3 months from time of randomization; Lee et al. (2012) reported a median survival of 24 months and Sgouros et al. (2011) reported a median survival of 24 months from study enrollment. Radioembolization was given as an adjunct to systemic chemotherapy in two studies, both of which reported survival from time of study treatment with a range of 9 to 37.8 months.[64,72] HAI as an adjunct to systemic chemotherapy was reported in two studies. In both studies, the authors did not report the time point from which survival was measured.[79,81] Survival ranged from 22 to 30.1 months.

Quality of Life

One study by Ruers and colleagues[87] reported on the outcome of quality of life for patients treated with RFA and concurrent systemic chemotherapy. Quality of life was assessed by the EORTC QLQ-C30 questionnaire at baseline, every 6 weeks during study treatment, and during study followup. A 20-point difference is considered a significant change. Of the 60 patients enrolled, it is unclear how many of them were included in the analysis of quality of life. For those with available data, health-related quality of life declined 27 points following RFA. At 4 to 8 weeks post-RFA, prior to the start of systemic chemotherapy, the scores had risen to approximately 10 points below baseline. No other studies reported on quality of life and no direct comparisons can be made based on the published evidence.

Length of Stay

Mean length of stay was not reported by any studies.

Time to Recurrence

Time to recurrence was not reported in any of the included studies.

Local Recurrence

Outcomes related to local recurrence are summarized in Table 15. In this report, local recurrence is defined as recurrence of the liver metastases in the area previously treated. This constitutes a treatment failure or failure to treat the entire lesion and is considered an adverse event. Three RFA studies reported local recurrence rates between 45 and 81.3 percent.[64,85,87]

Adverse Events

Outcomes related to adverse events are summarized in Table 15, which is organized by intervention. One study of RE and one study of RFA reported injury to adjacent organs and liver failure.[72,80] Elevated bilirubin was reported in two studies[72,87] and elevated alkaline phosphatase and transaminases were reported in one study.[72] Kosmider et al.[72] reported elevated liver function test results within 60 days post-treatment that were not related to progressive disease and normalized shortly thereafter; Ruers et al.[87] did not report when the patients had hepatic dysfunction related to elevated bilirubin. Lee et al. reported one patient (3.6 percent) who suffered from a 10-cm subcapsular hematoma.[85] Local recurrence was reported by three studies.[64,85,87] A single postoperative death was reported in two RFA studies.[80,87] No direct comparisons can be made based on the published evidence.

Table 14. Local hepatic therapies for CRC metastases to the liver: Outcomes related to overall survival for patients receiving local hepatic therapy as an adjunct to systemic therapy KQ3 and KQ4

Intervention	Survival Time From	Median OS (95% CI)	1-Year Survival (%)	2-Year Survival (%)	3-Year Survival (%)	Study N[Θ] (% CRC) Rating
Intervention: RE with concurrent systemic chemotherapy; Drug: FOLFOX or 5-FU; Y90 dose: median 1.96 GBq, mean 2.08 GBq, range 1.60-2.60 GBq; Site: hepatic artery	Study Treatment	37.8	~83[a]	~73[a]	~52[a]	Kosmider et al., 2011[72] 19 (100) Good
Intervention: RE with systemic chemotherapy: Drug: Y90 dose: mean 1.8 GBq, median 1.8 GBq, range 0.4-2.6 GBq; Site: femoral or brachial artery	Study Treatment	9 (6.4 to 11.3)	42	22	20	Chua et al., 2010[64] 140 (100) Good
Intervention: RFA and systemic chemotherapy: Drug: FOLFIRI; Site: percutaneous	Study Enrollment	24 (17 to 31.1)	NR	NR	NR	Sgouros et al., 2011[80] 13 (100) Good
Intervention: RFA and systemic chemotherapy; Drug: FOLFIRI or FOLFOX; Site: percutaneous	Study Treatment	24	~88 [a]	~54 [a]	~28 [a]	Lee et al., 2012[85] 28 (100) Fair
RFA followed by systemic treatment with 5-FU/L/oxaliplatin, with bevacizumab added post 10/2005	Randomization	45.3 (33.1 to NA)	88.1	72.8	45.7	Ruers et al., 2012[87] 60 (100) Good
Intervention: HAI followed by systemic chemotherapy; Drug: 5-FU, FOLFOX4 or FOLFOX6; Site: hepatic artery, IV	NR	30.1	~90[a]	~72[a]	~15[a]	Seki et al., 2009[79] 20 (100) Fair
Intervention: HAI with concurrent systemic chemotherapy; Drug: 5-FU and l-leucovorin, UFT and UZEL; Site: femoral artery, oral	NR	22.0 (19.2 to 26.2)	NR	NR	NR	Tsutsumi et al., 2008[81] 16 (100) Fair

CRC = colorectal cancer; GBq = Gigabecquerel; HAI = hepatic arterial infusion; NR = not reported; OS = overall survival; RE = radioembolization; RFA = radiofrequency ablation

[Θ]This N reflects the total number of patients enrolled in the study from any primary site. The percentage of CRC patients included in this report is presented in parentheses.

[a]Survival estimates were approximated by the EPC from survival curves presented in the manuscript.

Table 15. Local hepatic therapies for unresectable CRC metastases to the liver: Adverse events for patients receiving local hepatic therapy as an adjunct to systemic therapy KQ3 and KQ4

Intervention	Local Recurrence N (%)	Injury to Organs (%)	Liver Failure (%)	Elevated Alkaline Phosphatase N (%)	Elevated Bilirubin N (%)	Rare AE	Study N$^{\Theta}$ (% CRC) Rating
Intervention: RE with concurrent systemic chemotherapy; Drug: FOLFOX or 5-FU; Y90 dose: median 1.96 GBq, mean 2.08 GBq, range 1.60-2.60 GBq; Site: hepatic artery	NR	5.3	5.3	5 (26.3)	5 (26.3)	AEs include extrahepatic metastases and 1 (5.3%) treatment-related death from hepatic failure (presumed to be radiation hepatitis). Gastroduodenitis was present in 3 patients (15.8%) and 1 (5.3%) grade 3 anorexia was observed.	Kosmider et al., 2011[72] 19 (100) Good
Intervention: RE with systemic chemotherapy; Y90 dose: mean 1.8 GBq, median 1.8 GBq, range 0.4-2.6 GBq; Site: femoral or brachial artery	NR	1	NR	NR	NR	Three patients (2%) developed radiation-induced liver dysfunction.	Chua et al., 2011[64] 13 (100) Good
Intervention: RFA and systemic chemotherapy; Drug: FOLFIRI; Site: percutaneous	(81.3)	NR	NR	NR	NR	One patient discontinued chemotherapy early after developing bacterial endocarditis that required a prolonged course of antibiotics. Another patient died suddenly during treatment. The cause of death was determined postmortem as acute cardiomyopathy thought to be related to 5-FU toxicity.	Sgouros et al., 2011[80] 140 (100) Good
Intervention: RFA and systemic chemotherapy; Drug: FOLFIRI or FOLFOX; Site: percutaneous	22 (78.6)	NR	NR	NR	NR	One patient (3.6%) suffered from a 10-cm subcapsular hematoma.	Lee et al., 2012[85] 28 (100) Fair
Intervention: RFA with concurrent systemic chemotherapy; Drug: FOLFOX 4; Site: laparoscopic or percutaneous	27 (45)	3.5	1.8	NR	3 (5.3)	Respiratory failure: 1 (1.8%); wound infection: 3 (5.3%); postoperative death: 1 (1.8%); need for reoperation: 3 (5.3%); Tolerance to systemic chemotherapy (Grade 3-4), neutropenia: 14 (27.5%); cardiotoxicity 5 (9.8%); diarrhea: 10 (19.6%); vomiting: 5 (9.8%); nausea: 7 (13.7%); other gastrointestinal toxicity: 4 (7.8%); pulmonary: 3 (5.9); renal 1 (2); neuropathy: 9 (17.6); fatigue: 7 (13.7); hypertension: 2 (3.9)	Ruers et al., 2012[87] 60 (100) Good

Table 15. Local hepatic therapies for unresectable CRC metastases to the liver: Adverse events for patients receiving local hepatic therapy as an adjunct to systemic therapy KQ3 and KQ4 (continued)

Intervention	Local Recurrence N (%)	Injury to Organs (%)	Liver Failure (%)	Elevated Alkaline Phosphatase N (%)	Elevated Bilirubin N (%)	Rare AE	Study N[Θ] (% CRC) Rating
Intervention: HAI followed by systemic chemotherapy; Drug: 5-FU, FOLFOX4 or FOLFOX6; Site: hepatic artery, IV	NR	NR	NR	NR	NR	1 patient resected post HAI, and 1 patient discontinued treatment during HAI therapy due to grade 3 hypersensitivity and sensory neuropathy. No grade 4 toxicity was reported.	Seki et al., 2009[79] 20 (100)
Intervention: HAI with concurrent systemic chemotherapy; Drug: 5-FU and l-leucovorin, UFT and UZEL; Site: femoral artery, oral	NR	NR	NR	NR	NR	Only grade 1 and 2 toxicity was reported. No hematologic toxicity was encountered.	Tsutsumi et al., 2008[81] 16 (100) Fair

CRC = colorectal cancer; GBq = Gigabecquerel; HAI = hepatic arterial infusion; NR = not reported; OS = overall survival; RE = radioembolization; RFA = radiofrequency ablation

[Θ]This N reflects the total number of patients enrolled in the study from any primary site. The percentage of CRC patients included in this report is presented in parentheses.

[a]Survival estimates were approximated by the EPC from survival curves presented in the manuscript.

Multivariate Analyses

Relevant univariate or multivariate analyses of prognostic factors for overall survival including, but not limited to, ECOG score, presence of extra hepatic disease, and treatment response, were reported in one case-series study[52] of RE for unresectable CRC metastasis to the liver among patients who are candidates for local hepatic therapy as an adjunct to systemic therapy (Appendix D). These analyses reported on overall survival as the dependent variable; none evaluated factors associated with frequency of adverse events. Among the patient or tumor characteristics found to be associated with overall survival were extrahepatic disease (no vs. yes) and treatment response (complete vs. partial). Although these analyses may be hypothesis generating, they do not address the comparative benefit of radiotherapy techniques.

Overall Conclusions for Key Questions 1–4

- The body of evidence is insufficient to assess effectiveness or comparative effectiveness based on overall survival, quality of life, length of stay, time to progression, local recurrence, and adverse events for local hepatic therapy for the treatment of unresectable CRC metastases to the liver among patients whose disease is refractory to systemic therapy.
- The body of evidence is insufficient to assess effectiveness or comparative effectiveness based on overall survival, quality of life, length of stay, time to recurrence, local recurrence and adverse events for local hepatic therapy as an adjunct to systemic therapy for the treatment of unresectable CRC metastases to the liver.
- The assessment of applicability of the study findings to clinical practice is limited by the poor characterization of the patient populations (e.g., number and size of metastases, performance status) and variability in the delivery of the interventions (e.g., surgical approach, dose and drugs delivered).

For all Key Questions, we could only find case-series evidence that met inclusion criteria. There were no comparative studies, which limits our ability to draw conclusions for all key questions.

Discussion

Key Findings and Strength of Evidence

No comparative studies met the inclusion criteria for any of the four KQs about local hepatic therapy for the treatment of unresectable CRC metastases to the liver. Thirty-one studies met our inclusion criteria and addressed local hepatic therapy for unresectable CRC metastases to the liver.

We assessed the strength of evidence for all KQs for the primary health outcomes of overall survival and quality of life and for the intermediate outcomes of length of stay, local recurrence, and adverse events. In addition strength of evidence was assessed for the intermediate outcomes of time to progression (KQs 1 and 2) and time to recurrence (KQs 3 and 4). We judged the strength of evidence to be insufficient to draw conclusions for effectiveness outcomes (overall survival, quality of life, length of stay, time to progression, time to recurrence, and local recurrence) and for adverse events for all KQs (Table 16 and Table 17). The body of evidence provided no comparative information about differences in effectiveness by type of intervention. Indirect comparisons were not considered because of the heterogeneity in the patient population, intervention characteristics, and outcome definitions, as well as the biases inherent in observational studies.

Table 16. Strength of evidence for KQ1 and KQ2

Outcome	Intervention	Strength of Evidence	Conclusion
Overall Survival	TACE with DEB	Insufficient	Three studies reported overall survival for this intervention.[67,75,90] Two studies[75a,86] defined survival from time of study treatment and reached a median survival of 25 and 19 months. One study[67b] did not report the time point from which survival was measured, but reported a 1-year survival rate of 61%.
	TACE	Insufficient	Two studies reported overall survival for this intervention.[63,68] Both studies defined survival time from diagnosis of liver metastases and reported median survival times of 27 and 26.3 months. Albert and colleagues presented overall survival data out to 5 years and reported a 6% survival rate.
	SBRT	Insufficient	Three studies reported overall survival for this intervention and all defined survival from time of study treatment.[71,82,88] Two studies reported median survival of 25 and 17 months.[67,84] One study did not report median survival but recorded a 2-year survival rate of 58%.[82]
	HAI	Insufficient	Two studies reported overall survival for this intervention and both defined survival from time of study treatment.[83,92] Median survival was 9.7 and 6.7 months (95% CI 5 to 8.3 months).
	RE	Insufficient	Eight studies reported survival from time of study treatment. One study did not reach median survival but reported a 3-year survival rate of 77%.[80] In the other seven studies, median survival ranged from 4 to 15.2 months.[70,73,77,78,84,86,89,91]Three studies reported overall survival from diagnosis of liver metastases, with median survival ranging from 31 to 34.6 months.[66,68,76] Two studies did not report the time point from which survival was defined. One reported a median survival of 11.8 months.[61] The other study reported a 1-year survival rate of 20%.[70]
	RFA	Insufficient	Only one RFA study reported data on overall survival. Survival was defined from the time of study treatment and the 3-year survival rate was 68%.[69]

Table 16. Strength of evidence for KQ1 and KQ2 (continued)

Outcome	Intervention	Strength of Evidence	Conclusion
Quality of Life	TACE with DEB	Insufficient	The authors reported qualitatively that 18 or 20 patients reported improvement in quality of life post-treatment.[67]
	RE	Insufficient	This study reported quality of life data for 14 of 50 participants using the EORTC QLQ and HAM-D. No information was given to explain why only 14 patients were given a quality of life assessment was given. Quality of life was not adversely affected after RE and anxiety was significantly reduced from pretreatment levels. No significant difference was observed in depression score pre- and post-treatment.[66]
Length of Stay	TACE	Insufficient	Mean length of stay ranged from 1.3 to 3 days.[63,67]
Local Recurrence	SBRT	Insufficient	Both studies reported a local recurrence rate of 33.3%.[71,88]
	RFA	Insufficient	One RFA study reported local a recurrence rate of 18%.[65]
Adverse Events	TACE with DEB	Insufficient	A 3% liver failure rate was reported in one study of this intervention.[75] Elevated bilirubin was reported in 50% of patients in one study. Other adverse events are listed in Table 9.
	TACE	Insufficient	One study reported elevated alkaline phosphatase of varying severity in 19% of patients and grade 1 elevated bilirubin in 1%.[63] Other adverse events are reported in Table 9.
	SBRT	Insufficient	One study reported no major complications.[71] Other adverse events are reported in Table 9.
	HAI	Insufficient	One HAI study reported no major complications.[83] One study reported elevated bilirubin in 1.8% of patients.[92]
	RE	Insufficient	Two studies reported no major complications.[84,86] Liver failure was reported in 2% and 2.4% of patients in two studies.[65,66] Elevated alkaline phosphatase was reported in 8% of patients in one study.[76] Two studies reported elevated bilirubin in 10% and 13% of patients.[76,91] All other adverse events are listed in Table 9.
	RFA	Insufficient	One RFA study reported no major complications.[69]

DEB = drug-eluting beads; EORTC = European Organization for Research and Treatment of Cancer; HAI = hepatic arterial infusion; HAM-D = Hamilton Rating Scale for Depression; QLQ = quality of life questionnaire; RE = radioembolization; RFA = radiofrequency ablation; SBRT = stereotactic body radiation therapy TACE = transarterial chemoembolization

Table 17. Strength of evidence for KQ3 and KQ4

Outcome	Adjunctive Therapy	Overall Grade	Conclusion
Overall Survival	RFA	Insufficient	One study reported overall survival from study enrollment with a median survival of 24 months.[80] One study reported overall survival from study treatment with a median survival of 24 months.[85] One study reported overall survival from randomization with a median survival of 45.3 months.[87]
	RE	Insufficient	Two studies reported overall survival from study treatment with a median overall survival of 9 and 37.8 months.[64,72]
	HAI	Insufficient	Two HAI studies did not report the point from which overall survival was measured. Median overall survival was 30.1 and 22 months.[79, 81]
Quality of Life	RFA	Insufficient	One study by Ruers et al. reported quality of life based on EORTC QLQ-C30. A 20-point difference is considered a significant change. Of the 60 patients enrolled, it is unclear how many were included in the analysis of quality of life. For those with available data, health-related quality of life declined 27 points following RFA. At 4 to 8 weeks post-RFA, prior to the start of systemic chemotherapy, the scores had risen to approximately 10 points below baseline.
Local Recurrence	RFA	Insufficient	All RFA studies reported local recurrence. Rates of recurrence were 45%,[87] 78.6%,[85] and 81.3%.[80]
Adverse Events	RFA	Insufficient	One study reported injury to organs of 3.5% and liver failure of 1.8%.[87] This study also reported elevated bilirubin in 5.3% of patients.[87] Other adverse events are given in Table 15.
	RE	Insufficient	Two studies reported injury to organs of 1 to 5.3%.[64,72] Liver failure was reported in one study of 5.3%.[72] This study also reported elevated alkaline phosphatase and bilirubin in 26.3% of patients.[72] Other adverse events are given in Table 15.
	HAI	Insufficient	One study reported no major adverse events.[81] Other adverse events are given in Table 15.

EORTC = European Organization for Research and Treatment of Cancer; HAI = hepatic arterial infusion; QLQ = quality of life questionnaire RE = radioembolization; RFA = radiofrequency ablation

Findings in Relationship to What Is Already Known

We are not aware of any published systematic reviews of the comparative effectiveness of local hepatic therapies for CRC metastases to the liver, and the literature base does not contain studies that compare one local hepatic therapy with another. Some systematic reviews of single local hepatic therapies have been published. Although the reviews vary in quality, they generally agree that evidence is insufficient to demonstrate the effectiveness of these modalities, particularly in terms of survival benefit.[95-99] Earlier reviews conforming to a high quality standard interpreted their findings similarly to the present review; that is, evidence was insufficient to permit conclusions.[31,100]

This review sought evidence on the comparative benefits and harms of local hepatic therapies in two patient groups for CRC metastasis to the liver. Although we did not find this evidence the strength of this present review is in the identification of this important evidence gap. While distinct patient groups exist within the population receiving local hepatic therapies, data to analyze these differences are limited. In our review, we addressed two distinct patient populations: those receiving local hepatic therapies as an adjunct to systemic chemotherapy and those whose disease is refractory to systemic treatment. Because we focused on patient groups rather than a specific intervention, we were able to present the outcomes for a wide range of local hepatic therapies for each target population.

Applicability

It is challenging to comment on the applicability of findings from our CER because we that found that the available evidence was insufficient for us to draw conclusions. The degree to which the data presented in this report are applicable to clinical practice hinges on the degree to which the populations in the included studies represent the patient populations receiving clinical care in diverse settings, as well as the availability of the interventions. We comment below on the relevance of included studies for PICOTS elements. The PICOTS format provides a practical and useful structure to review applicability in a systematic manner and is employed in the subsections that follow.[101]

Population and Settings

The question of which subgroups of patients with CRC metastases to the liver may benefit from any particular local hepatic therapy compared with another remains unanswered. This uncertainty is reflected in the heterogeneity of the patient populations included in the published literature. Patient characteristics were often poorly characterized and not uniformly reported. Patients with varying degrees of resectability, extrahepatic disease, portal vein tumor thrombosis, and size and number of lesions are often grouped together and reported on as one group, even though it is uncertain whether these factors are likely to affect outcomes. Patient heterogeneity, combined with poor reporting of stratified or patient-level data, limited our ability to compare patient groups in any meaningful way. As a result, we are currently unable to determine which patients should be receiving which local hepatic therapies.

The setting in which treatment occurs is a major factor in the outcomes of local hepatic therapy. Expertise of both clinicians and centers varies. Based on the available clinical expertise and technology, the choice of a local hepatic therapy may be limited to one option in many centers. Local hepatic therapies, such as radioembolization[102] and hepatic arterial infusion,[103] often require high levels of training and familiarity with the procedure. Lack of experience may not only affect patient outcomes but also result in adverse effects; patients treated by less-experienced clinicians and centers will likely experience poorer outcomes.

Detailed analysis of differences in outcomes by center has important implications for the relevance of the findings in the literature. Unfortunately, these data were unavailable as part of our systematic review of the published literature.

Interventions

Even for a single local hepatic therapy, variations in how the procedure is performed may be substantial. For instance, variations may occur in the approach (open vs. percutaneous), the choice of chemotherapy drugs delivered, and the schedule of delivery of chemotherapy and radiation therapy. Given the lack of comparative data, the present review did not allow for a more rigorous and systematic comparison of the relative performance of local hepatic therapies stratified by these factors. How these factors may alter health outcomes remains unclear.

Additional heterogeneity exists for the context in which the intervention was delivered. Patients often receive more than one local hepatic therapy over time or more than one session of the same therapy. This often results in variations of prior therapy at study enrollment. The complex treatment history of each patient can further limit the conclusions that can be drawn about the benefits attributable to any one component of the treatment plan.

Comparators

All studies in this review are observational (including the arm of one RCT that was extracted as a case-series); as such, they report on the experience of a particular center with one or more local hepatic therapies. Although case series can be useful for hypothesis generation, this approach cannot provide the comparative data the field needs for evaluating effectiveness. The applicability of any case series to another study group is very limited.

Outcomes

Little controversy exists regarding the most appropriate direct health outcomes to measure in a study of local hepatic therapies for CRC metastases to the liver. Overall survival is the ultimate outcome; it was reported in all of the studies included in this review. Quality of life is also a very important patient-centered outcome, but was not routinely reported in the literature in this review.

The importance of outcomes such as disease-free survival or local progression-free survival can be debated. Outcomes such as progression-free survival may not accurately predict changes in overall survival. However, these clinical events may mark changes in therapies and treatment that may be important to patients. Few experts would suggest that these outcomes replace the need for data on overall survival.

Studies of a comparative design are needed to measure accurately the differences in overall survival, quality of life, and harms that may be attributed to a local hepatic therapy.

Timing

The timing of followup assessment was appropriate given the natural history of unresectable CRC liver metastases and the primary outcome of overall survival. Median survival was reached in 21 of 24 studies. We judged this to be an appropriate length of assessment. In addition, two of the studies that did not reach median survival followed patients for up to 3 years to assess overall survival rates.

Implications for Clinical and Policy Decisionmaking

The goal of any local hepatic therapy for unresectable CRC metastases to the liver is to prolong life by eliminating the metastases if possible or to palliate symptoms such as pain. This report has reviewed the literature on local hepatic therapies to achieve these goals.

Due to the noncomparative nature of the literature base, both clinicians and policymakers are limited in their ability to apply the published literature base to decisions on effectiveness and comparative effectiveness of these interventions. Survival estimates from individual studies of local hepatic therapies suggest that local hepatic therapies may provide some benefit in terms of survival and symptom relief for some patients, but without comparative data, it is not possible to choose the therapy that will produce the best outcomes for specific patients. Several ongoing clinical trials pertaining to the interventions and population of interest to this review were identified through clinicaltrials.gov and are presented in Appendix D. None of these trials compares a local hepatic therapy with another local hepatic therapy.

Limitations of the Comparative Effectiveness Review Process

Determination of the scope of this review was a lengthy process that began in topic development but did not end until the CER was well underway. The topic was initially broader, encompassing other primary tumors metastasizing to the liver and hepatocellular carcinoma, a primary liver cancer. Although these liver tumors are all treated with a subset of the local hepatic therapies reviewed here, the evidence of their effectiveness is distinct, as are the clinical circumstances. During the scoping process, the review was narrowed to focus solely on unresectable CRC metastases to the liver. After the scope was set and inclusion and exclusion criteria were refined and reviewed by clinical experts, the literature search revealed an evidence base comprised of case-series studies. The decision was made to complete the report with its limitations. CRC metastases to the liver are a common condition and patients and providers may need to choose from many treatment options. The evaluation of the quality of the body of literature to assess our KQs and the identification of research needs are important contributions to the field.

Limitations of the Evidence Base

Limitations of the present review are related largely to the lack of comparative evidence. Because of the limited number of patients and clinical heterogeneity, we did not systematically review doses, regimens, or treatment-specific characteristics. A very large sample size with uniform data collection of these variables would be required to assess whether specific treatment characteristics were associated with survival differences. We did abstract from the literature information on patient characteristics such as performance status (degree of physical impairment typically assessed by an instrument such as ECOG or Karnofsky scale), number of lesions, and size of lesions. However, because of limitations of these data, the association between these variables and overall survival, quality of life, or adverse effects could not be assessed.

Evaluation of comparative effectiveness requires an intervention and a comparator. Case-series do not use comparators. Therefore, comparative effectiveness cannot be assessed using this type of literature. Further, factors that may affect the effectiveness of the interventions within these populations were not controlled for in the included studies. Control may be achieved either though randomized design or statistically though careful adjustment in the analysis. Studies that aim to determine the effectiveness or comparative effectiveness of local treatment for unresectable CRC metastases to the liver should use randomized designs. If randomization is not possible, care should be taken to control for covariates such as size and number of hepatic lesions, extrahepatic lesion number, CEA, treatment characteristics prior to local hepatic therapy (i.e. number of lines of previous chemotherapy), and performance status through regression analysis as these have been shown to impact survival outcomes.

Research Gaps

In this section, we first present a set of gaps focused on issues in the body of literature. Then we discuss the use of RCTs and observational studies to address these gaps, followed by an example of how a registry might overcome the drawbacks of single-center case series.

Gaps

This systematic review attempted to compare outcomes of local hepatic therapies for patients treated for unresectable CRC metastases to the liver. The review focused on two patient populations: those patients whose disease is refractory to systemic chemotherapy and patients who are receiving local hepatic therapy as an adjunct to systemic chemotherapy. Evidence on patient outcomes is limited, and the strength of evidence is insufficient for us to draw conclusions on effectiveness or harms for either patient population. As detailed above under applicability, there are specific evidence gaps that, if addressed, could enhance this literature base.

We identified four broad evidence gaps during this review organized by PICOTS framework. No gaps were identified for timing and setting.

- **Populations:** An objective of comparative effectiveness research is to understand the comparative effects for different population subgroups. To achieve this, we must fully delineate the population subgroups of interest. As detailed in the population and setting section above, these data are limited. Future studies must present data by subgroups of interest so that evidence can be interpreted by these variables. Based on published multivariate analyses examples of patient or tumor characteristics found to be associated with improved overall survival include: ECOG status (0 vs. ≥1 and in another study 0 or 1 vs. ≥2), performance status (0 or 1 vs. ≥ 2), number of extrahepatic metastases sites (0 or 1 vs. ≥2), number of lines of previous chemotherapy (0–1 vs. ≥ 2), performance status (0 or 1 vs. ≥ 2), carcinoembryonic antigen response (Yes, No), and Response Evaluation Criteria in Solid Tumors (RECIST). These variables should be considered when designing future studies. Because there are so many variables being collated, clinical risk scores may be particularly beneficial as a summary measure.[104]
- **Intervention:** There can be substantial variation in the role of local hepatic therapy in the overall treatment strategy for patient populations with unresectable CRC liver metastases reviewed in this report. A thorough delineation of prior and concurrent treatment is necessary to assess the incremental benefit of local hepatic therapy and the comparative outcomes of these therapies for the reviewed patient populations. All other therapies, systemic and local, should be taken into account when evaluating the effectiveness of the intervention under study, as these therapies may have an effect on patient survival. Previous resections and other local hepatic therapies were often not reported in the studies included in this review.
- **Comparator:** A major limitation of the current evidence review was that there was no comparative evidence at the time of publication of this report comparing the various liver-directed therapies with one another.
- **Outcomes:** Outcomes of interest to patients and their physicians include survival, quality of life, and adverse effects such as radiation-induced liver disease, liver failure, and local recurrence (i.e., treatment failure). Evidence comparing these outcomes of local hepatic therapies in the populations of interest for the review are needed. For survival and other time-to-event outcomes, it is essential for authors to report the time point from which the event was measured (e.g., time from liver-directed therapy, time from CRC diagnosis, time from diagnosis of metastases).

  Collection and reporting of quality-of-life data (e.g., pain) using standard measurement tools was inconsistently reported in the literature included in this review. These data are

particularly important for the population of patients in which palliation of symptoms, rather than cure, is the intent of therapy.

Study Designs To Address These Gaps

RCTs are the gold standard of clinical evaluation and there is an absence of randomized controlled clinical trial evidence on the use of local hepatic therapies for the included indications. Because we were unable to find evidence to answer any of our key questions, we conducted additional discussions with members of our TEP to elicit ideas that could address the gaps in the literature. TEP members identified common barriers to conducting RCTs that would answer our key questions, including limited sources of research funding to support RCTs, reluctance of physicians to randomize patients, and the reluctance of patients to be randomized.

In addition to the resistance to randomize, consensus around the most compelling hypothesis for a comparative RCT is lacking. Clinical investigators have competing hypotheses of which treatment is best suited for which patients, and these hypotheses are often based on their own institution's experience. TEP members agreed that certain broad categories of patients with CRC metastasis to the liver, such as the populations included in this review, may well benefit from local hepatic therapies, but they also recognized that the published literature did not permit analysis of patient subgroups to identify characteristics more favorable to one local hepatic therapy over another. RCTs with well-documented patient and treatment characteristics could address the lack of comparative evidence. Lack of funding sources will continue to be an issue under the current regulatory structure. Under this system, the FDA does not require the same level of evidence for device approval as it does for drug approval. Because device companies can obtain approval without data from RCTs, they have very little incentive to provide funding.[105]

Regardless of the study design, we suggest that studies aiming to address the effectiveness or comparative effectiveness of local hepatic therapies take care to address potential confounders and effect measure modification that could obscure the results. This is particularly important for patient characteristics such as size and number of metastases and performance status, which could serve as both modifiers of the effectiveness and factors that are considered when choosing the best local hepatic therapy.

Although RCTs may not be possible for all comparisons in all centers, well done multivariate analyses from existing case series can aid in identifying additional factors that should be documented and potentially controlled for in the comparative analysis of these data. These analyses can enhance the design of future RCTs or observational studies.

Patient Registries

In the absence of consensus regarding the most salient comparative research question, observational data could be useful in driving the generation and prioritization of hypotheses for future research. One approach is the use of a registry to systematically collect observational data. According to the Agency for Healthcare Research and Quality publication on registries for evaluating patient outcomes, patient registries are often constructed to study patient outcomes, the natural history of disease, and disease management under various treatment scenarios.[106] Registries need to be created with a question in mind, which will then guide the identification of the target patient population, the interventions of interest (e.g., a local hepatic therapy), the outcomes of interest, the number of patients (to be adequately powered for future analysis), and the length of followup.

The KQs from this CER could serve as guide for designing one or more registries focused on this clinical area. The aim would be to establish a prospective registry that tracks the outcomes, quality of life, and adverse events in those who receive local nonsurgical treatment for unresectable metastatic CRC to the liver in order to identify the most effective local hepatic therapy strategies. The effectiveness of any one local hepatic therapy is expected to vary by patient subgroup. TEP members also indicated that the provider experience with the local hepatic therapy is also an important factor in patient outcomes.

We have identified a core set of variables or core dataset, defined as the information set needed to address the critical questions the registry is developed to answer. This is presented in Table 18, organized by PICOTS.

Table 18. Core dataset elements for local hepatic therapy registry by PICOTS

Population	Intervention	Comparators	Outcomes	Timing	Setting
Patient Characteristics Age Sex Race Ethnicity Performance status LDH CEA Clinical risk scores (e.g., Fong)[104] **Tumor Characteristics** Location of tumor Size of lesions Number of lesions Number of extrahepatic metastases Tumor volume Portal vein obstruction Course of disease(stabilization, rapid progression) **Other Treatments** Number, dose, and duration for lines of prior therapy by drug Number, dose, and duration for lines of adjunctive therapy by drug Previous liver-directed therapy	**Type of Local Hepatic Therapy** Cryosurgical ablation RFA MWA TAE TACE HAI RE DEB 3D-CRT IMRT SBRT **Characteristics of Local Hepatic Therapy** Dose Duration Surgical site	Same as Intervention	Overall survival Quality of life Response (e.g., complete, partial, no response) Recovery time Length of stay Adverse effects (Short-term and long-term harms) Treatment holidays*	Ongoing	Hospital type Number of procedures by practitioner Type of practitioner Local hepatic therapy availability Inpatient or outpatient procedure

3D-CRT = three-dimensional conformal radiation therapy; CEA = carcinoembryonic antigen: DEB = drug-eluting bead; HAI = hepatic artery infusion; IMRT = intensity-modulated radiation therapy; LDH = lactate dehydrogenase; RE = radioembolization; RFA = radiofrequency ablation; SBRT = stereotactic body radiation therapy; TACE = transarterial chemoembolization; TAE = transarterial embolization;
*Treatment holidays refer to time away from systemic chemotherapy and may vary based on the success of treatment with a local hepatic therapy.

Conclusions

Due to the absence of published comparative data, the evidence is insufficient for us to draw conclusions about the comparative effectiveness of local hepatic therapies for unresectable CRC metastases to the liver for the patient populations addressed in this review. Important outcomes of therapy include overall survival, quality of life, and adverse effects (harms). A patient registry is one tool for future research that may generate hypotheses for clinical trials or observational evidence on the comparative effectiveness of local hepatic therapies.

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Abbreviations and Acronyms

3D	three-dimensional
AE	adverse events
AHRQ	Agency for Healthcare Research and Quality
CEA	carcinoembryonic antigen
CER	comparative effectiveness review
CRC	colorectal cancer
CRT	conformal radiotherapy
DEB	drug-eluting beads
DEBIRI	drug-eluting bead, irinotecan
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EPC	Evidence-based Practice Center
FU	fluorouracil
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Gy	Gray
HAI	hepatic artery infusion
HAM-D	Hamilton rating scale for depression
IMRT	intensity-modulated radiation therapy
KQ(s)	Key Question(s)
LDH	lactic dehydrogenase
LDT	liver-directed therapy(ies)
MAA	^{99m}Tc-macro-aggregated albumin scan
MWA	microwave ablation
N	number; no.
NA	not available
No	number
PICOTS	Population, Intervention, Comparator, Outcomes, Timing, Setting
PFS	progression-free survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QOL	quality of life
RCT	randomized controlled trial
RE	radioembolization
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	radiofrequency ablation
SBRT	stereotactic body radiation
SIRT	selective internal radiotherapy
TACE	transarterial chemoembolization
TAE	transarterial embolization
TEP	technical expert panel
TTR	time to recurrence

Appendix A. Search Strategy

We searched MEDLINE® for RCTs, nonrandomized comparative studies, and case series by using the following string of search terms:

1. "Liver Neoplasms"[Mesh] OR ((hepatic OR liver) AND (cancer OR cancers OR oncology OR neoplasms))
2. "Colorectal Neoplasms"[Mesh] OR colon OR colorectal OR rectal OR intestinal OR rectum OR intestine*
3. "secondary "[Subheading] OR metastatic OR metastasis OR metastases
4. Unresectable OR nonresectable OR inoperable OR irresectable
5. "Ablation Techniques"[Mesh] OR "Embolization, Therapeutic"[Mesh] OR "Chemoembolization, Therapeutic"[Mesh] OR "Radiotherapy"[Mesh] OR "radiotherapy "[Subheading] OR "drug therapy "[Subheading] OR "Drug Therapy"[Mesh] OR "radiofrequency ablation" OR (radiofrequency AND ablation) OR RFA OR cryoablation OR cryosurgical OR cryosurgery OR "microwave ablation" OR (microwave AND ablation) OR ((percutaneous OR intralesional) AND (ethanol OR acetic acid)) OR embolization OR embolisation OR embolize* OR embolise* OR "transarterial chemoembolization" OR "transarterial chemoembolisation" OR TACE OR "transarterial embolization" OR "transarterial embolisation" OR TAE OR radioembolization OR radioembolisation OR radiotherapy OR radiation OR "external beam" OR "3D conformal" OR "3-D Conformal" OR "intensity modulated radiotherapy" OR IMRT OR "intraluminal brachytherapy" OR "liver-directed chemotherapy" OR "hepatic artery infusion" OR HAI OR chemotherapy OR "drug-eluting beads"

((((1 AND 2) AND 3) AND 4) AND 5)

Limits: Humans, English

We searched Embase® for RCTs, nonrandomized comparative studies, and case series by using the following string of search terms:

1. ((hepatic OR 'liver'/exp) AND ('cancer'/exp OR 'cancers'/exp OR 'oncology'/exp OR 'neoplasms'/exp))
2. ('colorectal neoplasms'/exp OR (('colon'/exp OR colorectal OR 'rectal'/exp OR intestinal OR 'rectum'/exp OR 'intestine'/exp OR 'intestines'/exp) AND ('cancer'/exp OR 'carcinoma'/exp OR primary)))
3. secondary OR metastatic OR 'metastasis'/exp OR 'metastases'/exp
4. unresectable OR nonresectable OR inoperable OR irresectable

5. 'ablation techniques'/exp OR 'therapeutic embolization' OR 'therapeutic chemoembolization' OR 'drug therapy'/exp OR 'radiofrequency ablation'/exp OR ('radiofrequency'/exp AND ablation) OR rfa OR 'cryoablation'/exp OR cryosurgical OR 'cryosurgery'/exp OR 'microwave ablation'/exp OR ('microwave'/exp AND ablation) OR (percutaneous OR 'intralesional'/exp AND ('ethanol'/exp OR acetic) AND 'acid'/exp) OR 'embolization'/exp OR 'embolisation'/exp OR embolize* OR embolise* OR 'transarterial chemoembolization' OR 'transarterial chemoembolisation' OR 'tace'/exp OR 'transarterial embolization' OR 'transarterial embolisation' OR tae OR radioembolization OR radioembolisation OR 'radiotherapy'/exp OR 'radiation'/exp OR 'external beam' OR '3d conformal' OR '3-d conformal' OR 'intensity modulated radiotherapy'/exp OR 'imrt'/exp OR 'intraluminal brachytherapy' OR 'liver-directed chemotherapy' OR 'hepatic artery infusion' OR hai OR 'chemotherapy'/exp OR 'drug-eluting beads'

((((1 AND 2) AND 3) AND 4) AND 5)

Limits: Human, English and not MEDLINE.

Regulatory Information

FDA
Source: www.FDA.gov
Date searched: 4/3/2012
Search strategy: key word “colorectal metastases”
Records: 6

Clinical trial registries

NIH database
Source: http://clinicaltrials.gov/
Date searched: 4/03/2012
Search strategy: Colorectal AND "Liver metastases"
Records: 259

Conference papers and abstracts
Specific conferences and association meetings
Source – number of results returned for search strategy:
Annual meeting of American Society of Clinical Oncology (ASCO) - 98
Annual meeting of American Society of Clinical Oncology Gastrointestinal (ASCO GI) - 56
Annual meeting of Surgery Society of Oncology (SSO) - 14
Annual meeting of Radiosurgical Society - 6
Date searched: 4/04/2012
Search strategy: KW: “liver metastases” in the title
Records: 174

Manufacturer database

Source: Accuray Incorporated
Date posted: 3/19/2012
Date searched:4/05/2012
Search strategy: Not applicable
Records:20

Source: Sirtex SIR-Spheres Pty Limited
Date posted: 3/21/2012
Date searched:4/05/2012
Search strategy: Not applicable
Records:35

Appendix B. Contacted Authors

Table D-1. List of authors contacted with questions during this review and the question resolution

Author	Response from Authors Sufficient for Issue Resolution	Question/Resolution
Chua - 2010[1]	Yes	Time from which survival is measured? / Measured from date of RE to date of death or last FU
Albert – 2011[2]	No	Need to determine number of patients received 0 lines of previous systemic chemotherapy / None
Hendlisz – 2010[3]	Yes	Need to clarify why patients were given further chemotherapy / Chemotherapy given for disease progression. Include study and use time to liver progression statistics.
Meijerink - 2011[4]	No	Uncertain if patients were refractory to chemotherapy. / Study excluded due to small sample size and potential contamination.
Stintzing – 2011[5]	Yes	Did any of the CRC liver mets. Patients refuse treatment? / None of these patients refused treatment
Vautravers-Dewas - 2011[6]	No	Uncertain about extrahepatic metastases in patients. / None
Murthy - 2007[7]	No	Uncertain about treatment dates for this study / None
Ritz – 2007[8]	No	Uncertain if patients are refractory / None
Martin – 2011[9]	No	Do survival statistics correspond to complete responders alone? / No response but study included and assumed that issue resulted from a typographical error in table creation.
Tsutsumi - 2008[10]	No	Article does not give survival starting point / None
Cianni – 2009[11]	Yes	Article does not give survival starting point, potential overlap in study populations / Author clarified that this was from time of treatment and that this was not a duplicated patient population.
Hong - 2009[12]	No	Discrepancy in table statistics / none
Lim - 2005[13]	Yes	Article does not give survival starting point / Author clarified that this was from study treatment.
Fiorentini – 2007[14]	No	Article does not give survival starting point / None

1. Chua TC, Bester L, Akther J, et al. Successful right hepatectomy after four treatments of yttrium-90 microspheres (SIR-Spheres) and concomitant FOLFOX as bridging therapy to resection of colorectal liver metastases. Anticancer Res. 2010 Jul;30(7):3005-7. PMID: 20683046.
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3. 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 Aug 10;28(23):3687-94. PMID: 20567019.
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5. Stintzing S, Hoffmann RT, Heinemann V, et al. Frameless single-session robotic radiosurgery of liver metastases in colorectal cancer patients. Eur J Cancer. 2010 Apr;46(6):1026-32. PMID: 20153959.
6. Vautravers-Dewas C, Dewas S, Bonodeau F, et al. Image-guided robotic stereotactic body radiation therapy for liver metastases: Is there a dose response relationship? Int J Radiat Oncol Biol Phys. 2011 Mar 4PMID: 21377292.
7. Murthy R, Eng C, Krishnan S, et al. Hepatic yttrium-90 radioembolotherapy in metastatic colorectal cancer treated with cetuximab or bevacizumab. J Vasc Interv Radiol. 2007 Dec;18(12):1588-91. PMID: 18057297.
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10. Tsutsumi S, Yamaguchi S, Tsuboi K, et al. Hepatic arterial infusion combined with oral UFT/UZEL systemic chemotherapy for unresectable liver metastasis of colorectal cancer. Hepatogastroenterology. 2008 Jul-Aug;55(85):1419-22. PMID: 18795703.
11. Cianni R, Urigo C, Notarianni E, et al. Selective internal radiation therapy with SIR-spheres for the treatment of unresectable colorectal hepatic metastases. Cardiovasc Intervent Radiol. 2009 Nov;32(6):1179-86. PMID: 19680720.
12. Hong K, McBride JD, Georgiades CS, et al. Salvage therapy for liver-dominant colorectal metastatic adenocarcinoma: comparison between transcatheter arterial chemoembolization versus yttrium-90 radioembolization. J Vasc Interv Radiol. 2009 Mar;20(3):360-7. PMID: 19167245.
13. Lim L, Gibbs P, Yip D, et al. A prospective evaluation of treatment with Selective Internal Radiation Therapy (SIR-spheres) in patients with unresectable liver metastases from colorectal cancer previously treated with 5-FU based chemotherapy. BMC Cancer. 2005;5:132. PMID: 16225697.
14. Fiorentini G, Aliberti C, Turrisi G, et al. Intraarterial hepatic chemoembolization of liver metastases from colorectal cancer adopting irinotecan-eluting beads: Results of a phase II clinical study. In Vivo. 2007;21(6):1085-92.

Appendix C. DistillerSR Screening and Abstraction Forms

Title Screening
Is the article published in English?
Does the article report primary data?
Are the participants in the article human?
Is unresectable colorectal cancer the primary focus of the article?

Abstract Screening
Is the article published in English?
Does the article report primary data?
Are the participants in the article human?
Is unresectable colorectal cancer the primary focus of the article?

CRC Full-text Screening
Is article published in English?
Is treatment date prior to January 1, 2000?
Is the study of relevant design?
Are the study participants human?
Does the article report on the correct patient population?
Did the study employ a relevant intervention?
Did the study report a relevant outcome?

STUDY DESCRIPTION
First Author (Last name):
Year of Publication:
Study design:
What key question(s) does this article address?
Descriptors of Treatment (e.g., drug(s) used, route, etc)
Enrollment Start Date (mm/yyyy)
Enrollment End Date (mm/yyyy)
Number in Group
Outcomes
Setting
Patient population with CRC (%)
Previous Treatment
Previous resection: % yes
Previous systemic chemotherapy: % yes
Previous liver-directed therapy: Therapy: %, Therapy2: ...
Previous LDT: select all that apply
DIAGNOSIS
Adenocarcinoma
Mucinous
Synchronous
Mean Liver
Median Liver
Min Liver
Max Liver
Mean N Hepatic
Median N Hepatic
Min N Hepatic
Max N Hepatic
Other Liver Involvement: Name: %, Name2: ...
PATHOLOGY
Mean Size of Hepatic (cm) Lesion(s)
Median Size of Hepatic (cm) L**esion(s)**

Min Size of Hepatic Lesion(s)
Max Size of Hepatic Lesion(s)
% Unilobar Hepatic Lesion(s)
% Bilobar Hepatic Lesion(s)
Other noted lesion characteristics

PATIENT CHARACTERISITCS
Sex (% Male)
Mean Age
Median Age
Min Age
Max Age
RACE: White (%)
RACE: Black (%)
RACE: Asian (%)
RACE: Hispanic (%)
Child-pugh score: Mean
Child-pugh score: Median
Child-pugh score: Min
Child-pugh score: Max
Child-pugh class (A, B, or C)
ECOG Performance Score: Mean
ECOG Performance Score: Median
ECOG Performance Score: Min
ECOG Performance Score: Max
Karnofsky Score: Mean
Karnofsky Score: Median
Karnofsky score: Min
Karnofsky Score: Max
ABSTRACTOR COMMENTS: If you would like to leave a comment pertaining to the information above indicate your name below:

Outcomes Form

FOLLOW-UP
Follow-up assessed?
Length of Follow-up (weeks)
N Subjects Lost to Follow-up

OUTCOMES
Survival outcome definition:
Median Overall Survival (months)
95% CI: Lower limit
95% CI: Upper limit
Mean Overall Survival (months)
95% CI: Lower limit
95% CI: Upper limit

Survival by Year
% survived at year 1
% survived at year 2
% survived at year 3
% survived at year 4
% survived at year 5

Progression Free Survival
Progression free survival definition:
Liver PFS
Median (months)
95% CI: Lower Limit

95% CI: Upper Limit
Liver PFS
Mean (months)
95% CI: Lower Limit
95% CI: Upper Limit
Overall PFS
Median (months)
95% CI: Lower Limit
95% CI: Upper Limit
Overall PFS
Mean (months)
95% CI: Lower Limit
95% CI: Upper Limit

Outcomes Continued
Local Recurrence N
Local Recurrence %
Pain, Instrument
Mean Pain Score
Min Pain Score
Max Pain Score
Pain Score p-value

QOL, Instrument
Min QOL Score
Max QOL Score
QOL Score p-value
Mean LOS (days)
Min LOS (days)
Max LOS (days)
LOS p-value

Hepatic Abscess (%)
Hepatic Hemorrhage (%)
Biloma (%)
Steatohepatitis (%)
Injury to adjacent organ(s) (%)
Liver failure (%)
Increased alkaline phosphatase (N)
Increased alkaline phosphatase (%)
Increased bilirubin (N)
Increased bilirubin (%)
Increased transaminases (N)
Increased transaminases (%)

Please describe any rare adverse events which do not fit into the categorizations above:

ABSTRACTOR COMMENTS: If you would like to leave a comment pertaining to the information above indicate your name below:

Study Quality
Comparative Studies Quality Assessment (USPSTF)
Initial assembly of comparable groups
Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination)
Avoidance of important differential loss to followup or overall high loss to followup.
Measurements reliable, valid, equal (includes masking of outcome assessment)
Interventions comparable/ clearly defined

All important outcomes considered
Appropriate analysis of results (adjustment for potential confounders and intention-to-treat analysis)
Funding/ sponsorship source acknowledged
Overall Rating

Non-Randomized Comparative-Deeks and colleagues

Prospective sample definition and selection
Clearly described inclusion/exclusion criteria
Representative Sample
Attempt to balance groups by design
Comparable groups as baseline, including clearly described prognostic characteristics
Clearly specified interventions
Participants in treatment groups recruited within the same time period
Attempt to allocate particpants to treatment groups to minimize bias
Concurrent treatment(s) given equally to all treatment groups
Valid, reliable, and equal outcome measures
Blinded outcome assessment
Adequate length of follow-up
Attrition below an overall high level(<20%)
Difference in attrition between treatment groups below a high level (<15%)
Adjusted for confounders in statistical analysis

Carey and Boden case series quality assessment tool
Clearly Defined Question
Well-described study population
Well-described intervention
Use of Validated Outcome Measures
Appropriate Statistical Analysis
Well-Described Results
Discussion/Conclusions Supported by Data
Funding/Sponsorship Source Acknowledged

Appendix D. Evidence Tables

Tables Related to Key Questions 1 and 2

Appendix Table D-1. Local therapies for colorectal cancer metastases to the liver, study quality Carey and Boden Case Series quality Assessment

Reference	Clearly Defined Question	Well-Described Study Population	Well-Described Intervention	Use of Validated Outcome Measures	Appropriate Statistical Analysis	Well-Described Results	Discussion/Conclusions Supported by Data	Rank*
Albert – 2011	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Aliberti – 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Cianni – 2009	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Cosimelli - 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Fiorentini – 2007	Yes	No	Yes	Yes	Yes	No	Yes	Poor
Hong – 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Jakobs – 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Jakobs – 2008	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Jiao – 2007	Yes	No	Yes	Yes	Yes	No	Yes	Poor
Kim – 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Kucuk – 2011	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Lewandowski – 2005	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Lim – 2005	Yes	No	Yes	Yes	Yes	No	Yes	Poor
Martin – 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Martin – 2012	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Mulcahy - 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Nace – 2011	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Nishiofuku - 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Rowe - 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Sato - 2008	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Stintzing – 2010	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Vautravers-Dewas - 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Vogl - 2008	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair

* A rank of good indicates that all Carey and Boden critera are fulfilled, a rank of fair indicates that one criterion was unfulfilled or it was not possible to assess a criterion given the published information, a rank of poor indicates that two or more criteria were unfulfilled or it was not possible to assess two or more criteria given the published information.

Table Appendix Table D-2. Local therapies for unresectable colorectal cancer metastases to the liver—Summary of multivariable analyses in single-arm studies

Author - Year	Independent Variable	Model	Age (<64, ≥64)	Gender	ECOG Status (0,	Primary Site (Colon, Rectum)	Number of Radioembolization Treatments (1,	Extent of liver metastases (0-25%, 26-50%, 51-75%)	Hepatic lobar involvement (unilobar, bilobar)	Prior liver resection (No, Yes)	Prior ablation (No, Yes)	Extrahepatic disease (No, Yes)	Number of lines of chemotherapy (>2)	Radiation dose (<2,	Chemo-SIRT (No, Yes)	Treatment Response (Unfavorable, favorable)	CRC Stage at Liver Metastases Diagnosis (2/3, 4)	Tumor Burden (0%-25%, 26%- 50%, 51%-75%,	Tumor replacement (	Liver Metastases Diameter (>3cm)	ECOG status (0 or 1/≥ 2)	CEA Response (Yes, No)	RECIST Response (PR, SD, PD)
Albert - 2011	Overall Survival Since Time of First Treatment	Log-rank test (univariate)	-	-	<0.001	-	-	-	-	-	-	0.48	0.03	-	-	-	-	-	-	-	-	-	-
		Hazard Ratio (95% CI) (univariate)	-	-	0.466 (0.15 - 0.61)	-	-	-	-	-	-	0.80 (0.52-1.17)	-	-	-	-	-	-	-	-	-	-	-
Nishiofuku – 2010	Overall Survival Since Time of First Treatment	Hazard Ratio (95% CI) p value (univariate)	NS	-	-	-	-	-	-	NS	-	0-1 vs >= 2* 2.6 (1.4 – 4.8) 0.003	-	-	-	-	-	-	-	-	7.9 (3.5 – 18.1) 0.000	-	-
		Hazard Ratio (95% CI) p value (multivariate)	-									8.3 (3.6 – 19) 0.000									2.5 (1.3 – 4.6) 0.00	-	-

Author - Year	Independent Variable	Model	Age (<64, ≥64)	Gender	ECOG Status (0,	Primary Site (Colon, Rectum)	Number of Radioembolization Treatments (1,	Extent of liver metastases (0-25%, 26-50%, 51-75%)	Hepatic lobar involvement (unilobar, bilobar)	Prior liver resection (No, Yes)	Prior ablation (No, Yes)	Extrahepatic disease (No, Yes)	Number of lines of chemotherapy (>2)	Radiation dose (<2,	Chemo-SIRT (No, Yes)	Treatment Response (Unfavorable, favorable)	CRC Stage at Liver Metastases Diagnosis (2/3, 4)	Tumor Burden (0%-25%, 26%- 50%, 51%-75%,	Tumor replacement (	Liver Metastases Diameter (>3cm)	ECOG status (0 or 1/≥ 2)	CEA Response (Yes, No)	RECIST Response (PR, SD, PD)
																					5		
Mulcahy - 2009	Overall Survival Since Time of First Y90 Treatment	Log-rank test (univariate)	-	-	<0.0001	-	-	-	0.0953	-	-	0.0004	-	-	-	<.0001	0.1691	-	<0.0001	-	-	-	-
Jakobs – 2008	Overall Survival Since Time of First Treatment	Log-rank test (univariate)	NS	NS	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	p= 0.0001	p= 0.0001
Sato -2008*	Overall Survival	Log-rank test (univariate)	-	-	<0.001	-	-	-	-	-	-	-	-	-	-	-	-	0.001	-	-	-	-	-
Lewandowski - 2005	Overall Survival Since First Treatment	Log-rank test (univariate)	-	-	0.12	-	-	-	0.11	-	-	-	0.2	-	-	-	-	-	0.002	-	--	-	-

"-" indicates not reported or not analyzed

“NS” indicates a non-significant p value of ≥ 0.05, exact p value not reported

● Indicates a p value ≤ 0.05

◊ indicates a non-significant p value of ≥ 0.05

* Sato et al. report data on a population which contains non-CRC patients. In their multivariate analysis some variables (Age, Gender, Primary Diagnosis, Angiographic vascularity, CT vascularity, and more than four lesions) were aggregated with these non-CRC patients and not presented in this table.

ǂThis study looked ECOG status categories of 0, 1 and 2

ΔThis study looked at previous lines of chemotherapy categories of 0-1, 2 and 3-5

□This study also reported NS for lymphatic metastasis at diagnosis, metachronous vs. synchronous metastasis, history of other metastases at time of treatment, and solitary lesions vs. multiple lesions

Appendix Table D-3. Follow up assessment for KQ 1 and 2

First Author	Study Design	Group	Followup assessed?	Followup Weeks	Lost to followup
Albert - 2011	Retrospective case series	TACE	No	NR	5
Aliberti - 2011	Retrospective case series	TACE w/ DEB	Yes	Median: 166, Range: 28-192	NR
Cianni - 2009	Retrospective case series	RE	No	Last survival outcome documented at ~610 days	NR
Cosimelli - 2010	Prospective case series	RE	Yes	Median: 44, Range: 8-116	NR
Fiorentini - 2007	Prospective case series	TACE with DEB	Yes	Median:28.6, range: 12.9-54.3	NR
Hong - 2008	Retrospective case series	TACE RE	Yes	Mean: 25.2 Mean: 22.8	NR
Jakobs - 2006	Retrospective case series	RFA	Yes	Mean: 85.6, SD: 42.4, Range: 24-152	NR
Jakobs - 2008	Retrospective case series	RE	Yes	Median: 31.6, (5.2-153.2)	2
Jiao - 2007	Prospective case series	SIRT	Yes	Pts. followed every 3 months for 2 years (from OS curve)	NR
Kim - 2009	Retrospective case series	SBRT	Yes	Median: 48, Range: 28 - 196	NR
Kucuk	Retrospective Case Series	RE	No	NR	NR
Kosmider - 2011	Retrospective case series	RE with concurrent Systemic Chemotherapy	Yes	Median: 74.4, Range: 12.8-314 *These are from all pts. inc extra-hepatic mets	NR
Lewandowski - 2005	Prospective case series	RE	Yes	All pts. followed through December 12, 2003	8
Lim - 2005	Prospective case series	SIRT	Yes	Median:18.3	NR
Martin - 2011	Prospective case series	TACE with DEB	Yes	Median: 72, Range: 48-160	NR
Martin – 2012	Retrospective Case Series	RE	No	NR	NR
Mulcahy - 2009	Prospective case series	RE	Yes	Median: 26.2	NR
Nace - 2011	Retrospective case series	RE	Yes	NR	NR
Nishiofuku - 2010	Retrospective case series	HAI	Yes	Median: 21.4, 2-110	NR
Rowe - 2007	Retrospective case series	SIRT	No	NR	NR
Sato - 2008	Prospective case series	RE	Yes	Mean: 41 (all pts.)	NR
Stintzing - 2010	Prospective case series	Radiosurgery	Yes	Median: 15.6, Mean: 15.3, Range: 8-20.7	NR
Vautravers-Dewas - 2011	Retrospective case control	SBRT	Yes	Median: 57.2, Range: 12-92 *all pts.	NR
Vogl - 2008	Retrospective case series	HAI	Yes	108	0

DEB: drug eluting bead; HAI: hepatic arterial infusion; NR: not reported; OS: overall survival; RE: radioembolization; RFA: radiofrequency ablation; SBRT: stereotactic body radiation therapy; SD: standard deviation; SIRT: selective internal radiation therapy; TACE: transarterial chemoembolization

Tables related to Key Question 3 and 4

Appendix Table D-4. Local therapies for colorectal cancer metastases to the liver, study quality Carey and Boden Case Series quality Assessment

Reference	Clearly Defined Question	Well-Described Study Population	Well-Described Intervention	Use of Validated Outcome Measures	Appropriate Statistical Analysis	Well-Described Results	Discussion/Conclusions Supported by Data	Rank*
Chua - 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Kosmider - 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Lee – 2012	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Ruers - 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Seki - 2009	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Sguoros - 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Tsutsumi - 2008	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair

* A rank of good indicates that all Carey and Boden critera are fulfilled, a rank of fair indicates that one criterion was unfulfilled or it was not possible to assess a criterion given the published information, a rank of poor indicates that two or more criteria were unfulfilled or it was not possible to assess two or more criteria given the published information.

Appendix Table D-5. Local therapies for unresectable colorectal cancer metastases to the liver—Summary of multivariable analyses in single-arm studies

Author - Year	Independent Variable	Model	Age (<64,	Gender	ECOG Status (0,	Primary Site (Colon, Rectum)	Number of Radioembolization Treatments (1,	Extent of liver metastases (0-25%, 26-50%, 51-75%)	Hepatic lobar involvement (unilobar, bilobar)	Prior liver resection (No, Yes)	Prior ablation (No, Yes)	Extrahepatic disease (No, Yes)	Number of lines of chemotherapy (>2)	Radiation dose (<2,	Chemo-SIRT (No, Yes)	Treatment Response (Unfavorable, favorable)	CRC Stage at Liver Metastases Diagnosis (2/3, 4)	Tumor Burden (0%-25%, 26%- 50%, 51%-75%,	Tumor replacement (	Liver Metastases Diameter (≤3cm, >3cm)
Chua - 2011	Overall Survival	Log-rank test (univariate)	0.464	0.034	0.144	0.008	0.048	0.005	0.663	0.859	0.321	0.063	0.006	0.965	0.017	<0.001	-	-	-	-
	Overall Survival	Cox regression (multivariate)	-	0.275	-	0.019	0.253	0.512	-	-	-	0.033	0.134	-	0.449	<0.001	-	-	-	-

CRC: colorectal cancer; ECOG: Eastern cooperative oncology group; SIRT: selective internal radiation therapy

Appendix Table D-6. Follow up assessment for KQ 3 and 4

First Author	Study Design	Group	Followup assessed?	Followup Weeks	Lost to followup
Chua - 2010	Prospective case series	RE with systemic chemotherapy	Yes	Median: 36, range: 4-172	NR
Kosmider - 2011	Retrospective case series	RE with concurrent Systemic Chemotherapy	Yes	Median: 74.4, Range: 12.8-314 *These are from all pts. inc extra-hepatic mets	NR
Lee – 2012	Retrospective case series	RFA plus systemic chemotherapy	Yes	Median: 92 (4.8 – 248)	NR
Ruers - 2012	RCT	RFA plus systemic treatment	Yes	211 weeks	2
Seki - 2009	Retrospective case control	HAI followed by systemic chemotherapy	Yes	Mean:111.7, Range:37.3-194.6	NR
Sguoros - 2011	Prospective case series	RFA and chemotherapy	No	NR	NR

KQ: Key Question; HAI: hepatic arterial infusion; NR: not reported; RCT: randomized controlled trial; RE: radioembolization; RFA: radiofrequency abalation

Appendix Table D-7. Progression free survival outcomes for KQ 1 and 2

Author, Year	Intervention	Progression Definition	Liver PFS Median (months) (95% CI)	Overall PFS Median (months) (95% CI)
Albert - 2011	TACE	Study Treatment	5	3
Martin - 2011	TACE with DEB	Study Treatment	15	11
Vautravers-Dewas - 2011	SBRT	NR	NR	NR
Nace - 2011	RE	NR	NR	NR
Aliberti - 2011	TACE w/ DEB	Study Treatment	NR	23
Cosimelli - 2010	RE	Study Treatment	NR	3.7 (2.6 to 4.9)
Stintzing - 2010	SBRT	NR	NR	NR
Nishiofuku - 2010	HAI	Study Treatment	4.6 (2.8 to 6.3)	2.8 (2 to 3.6)
Kim - 2009	SBRT	Study Treatment	NR	10
Cianni - 2009	RE	Study Treatment	NR	9.3
Mulcahy - 2009	RE	NR	NR	NR
Martin – 2012	RE	Study Treatment	5.1 (2.4 to 5.9)	NR
Hong - 2009	TACE	NR	NR	NR
Sato - 2008	RE	NR	NR	NR
Vogl - 2008	HAI	NR	NR	NR
Jakobs - 2008	RE	NR	NR	NR
Rowe - 2007	SIRT	NR	NR	NR
Jiao - 2007	SIRT	NR	NR	NR
Fiorentini - 2007	TACE with DEB	NR	NR	NR
Jakobs - 2006	RFA	NR	NR	NR
Lewandowski - 2005	RE	NR	NR	NR
Lim - 2005	SIRT	Study Treatment	NR	5.3

CI: confidence interval; DEB: drug eluting bead; KQ: Key Question; HAI: hepatic arterial infusion; NR: not reported; pFS: Progression free survival; RE: radioembolization; RFA: radiofrequency abalation; SBRT: stereotactic body radiation therapy; SIRT: selective internal radiation therapy; TACE: transarterial chemoembolization

Appendix Table D-8. Progression free survival outcomes for KQ 3 and 4

Author, Year	Intervention	Progression Definition	Liver PFS Median (months) (95% CI)	Overall PFS Median (months) (95% CI)
Ruers - 2012	RFA plus systemic treatment	Randomization	NR	16.8 (11.7 to 22.1)
Lee – 2012	RFA plus systemic chemotherapy	NR	NR	NR
Kosmider - 2011	RE with concurrent Systemic Chemotherapy	Study Treatment	NR	10.4
Sguoros - 2011	RFA and chemotherapy	Study enrollment	NR	13 (3.1 to 22.9)
Chua - 2010	RE with systemic chemotherapy	NR	NR	NR
Seki - 2009	HAI followed by systemic chemotherapy	NR	NR	5.1
Tsutsumi - 2008	HAI with concurrent systemic chemotherapy	NR	NR	9.2 (7.9 to 10.5)

CI: confidence interval; PFS: progression free survival; RFA: radiofrequency ablation; RE: adioembolization; HAI: hepatic arterial infusion; NR: not reported

Appendix Table D-9. Recently completed (without results posted) or ongoing clinical trials

Trial Name	NCT Number	Status	Sponsor
Postoperative Folfox4 Only Versus Folfox4 Plus Transhepatic Arterial Chemotherapy (TAC) in the Treatment Unresectable Liver Metastasis of Colorectal Cancer	NCT00869271	Completed	Fudan University
Combination Chemotherapy With or Without Chemoembolization in Treating Patients With Colorectal Cancer Metastatic to the Liver	NCT00023868	Completed	American College of Radiology Imaging Network
Hepatic Arterial Infusion With Floxuridine and Dexamethasone Combination With Chemotherapy With/Without Bevacizumab for Hepatic Metastases From Colorectal Cancer	NCT00200200	Ongoing	Memorial Sloan-Kettering Cancer Center
Transhepatic Arterial Chemotherapy (TAC) Versus Transcatheter Arterial Chemoembolization (TACE) Plus Folfox4 as the Treatment of Unresectable Liver Metastasis of Colorectal Cancer	NCT00868569	Recruiting	Fudan University
FOLFOX Plus SIR-SPHERES MICROSPHERES Versus FOLFOX Alone in Patients With Liver Mets From Primary Colorectal Cancer	NCT00724503	Recruiting	Sirtex Medical
A Study of Yttrium-90 Radioactive Resin Microspheres to Treat Colorectal Adenocarcinoma Metastatic to the Liver	NCT01098422	Recruiting	University of California, San Diego
Intra-arterial Y-90 TheraSpheres for Hepatic Metastases From Solid Tumors	NCT01177007	Recruiting	Sidney Kimmel Comprehensive Cancer Center
Efficacy Evaluation of TheraSphere Following Failed First Line Chemotherapy in Metastatic Colorectal Cancer	NCT01483027	Recruiting	Nordion (Canada) Inc.
TheraSphere for the Treatment of Liver Metastases	NCT00511862	Completed	Nordion (Canada) Inc.
Yttrium-90 Radioembolization Using Glass Microspheres (TheraSphere) for Patients With Liver Metastases	NCT01290536	Completed	Nicholas Fidelman

Appendix D-10: Previous lines of chemotherapy KQ 1 and KQ 2

Author	Median lines of previous therapy	Range Lines of Previous Chemotherapy
Albert, et al. 2011[2] 121 (100) Poor	0-1	0 to 5
Aliberti, et al. 2011[15] 82 (100) Fair	NR	2+
Cianni, et al. 2009[11 b] 41 (100) Poor	NR	3+
Cosimelli, et al. 2010[16] 50 (100) Fair	4+	3 to 5
Fiorentini, et al. 2007[14] 20 (100) Poor	2	2
Hong, et al. 2009[12] 21 (100) Fair	NR	1+
Jakobs, et al. 2006[17] 68 (100) Fair	NR	NR
Jakobs, et al. 2008[18] 41 (100) Poor	Mean: 2.8	1 to 5
Jiao, et al. 2007[19] 21 (47.6) Poor	NR	2+
Kim, et al. 2009[20 a] 9 (100) Fair	NR	NR
Kucuk, et al. 2011[21] 78 (44.9) Poor	NR	1+
Lewandowski, et al. 2005[22] 27 (100) Poor	NR	NR
Lim, et al. 2005[13] 30 (100) Poor	1	1 +
Martin 2011[9] 55 (100) Good	2	1 to 3
Martin, et al. 2012[23d] 24 (100) Poor	3	0-7
Mulcahy, et al. 2009[24] 72 (100) Fair	2	0-3
Nace, et al. 2011[25] 51 (100) Fair	2	1 to 4
Nishiofuku, et al. 2010[26] 55 (100) Fair	2	2+
Rowe, et al. 2007[27] 24 (29.2) Fair	NR	1+
Sato, et al. 2008[28] 137 (37.2) Fair	NR	1+
Stintzing, et al. 2010[5] 6 (100)	1	1 to 2

Author	Median lines of previous therapy	Range Lines of Previous Chemotherapy
Poor		
Vautravers-Dewas, et al. 2011[6] 42 (66.7) Fair	NR	0 +
Vogl, et al. 2008[29 c] 55 (21.8) Poor	NR	1+

NR: not reported

Appendix E. Abbreviations and Acronyms

3D	three-dimensional
AE	adverse events
AHRQ	Agency for Healthcare Research and Quality
CEA	carcinoembryonic antigen
CER	comparative effectiveness review
CRC	colorectal cancer
CRT	conformal radiotherapy
DEB	drug-eluting beads
DEBIRI	drug-eluting bead, irinotecan
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EPC	Evidence-based Practice Center
FU	fluorouracil
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Gy	Gray
HAI	hepatic artery infusion
HAM-D	Hamilton rating scale for depression
IMRT	intensity-modulated radiation therapy
KQ(s)	Key Question(s)
LDH	lactic dehydrogenase
LDT	liver-directed therapy(ies)
MAA	^{99m}Tc-macro-aggregated albumin scan
MWA	microwave ablation
N	number; no
NA	not available
No	number
PICOTS	Population, Intervention, Comparator, Outcomes, Timing, Setting
PFS	progression free survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QOL	quality of life
RCT	randomized, controlled trial
RE	radioembolization
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	radiofrequency ablation
SBRT	stereotactic body radiation
SIRT	selective internal radiotherapy
TACE	transcatheter arterial chemoembolization
TAE	transarterial embolization
TEP	Technical Expert Panel
TTR	Time to recurrence

Appendix F. Excluded Studies

Level 1, Form Title Screening, Does the article report primary data? -> Exclude (No)

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