Effective Health Care Program

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

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]

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

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An elevated risk of CRC has been associated with obesity, low physical activity, high dietary intake of refined sugars, low dietary intake of fiber,

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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.

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 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]
	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]

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	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]
	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]

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.

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 (continued)	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.

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

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.

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:** <u>Ultimate outcomes</u>: Survival and quality of life <u>Intermediate outcomes</u>: Time to progression, local recurrence, and length of stay **KQ2:** <u>Adverse outcomes</u>: 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:** <u>Ultimate outcomes</u>: Same as KQs 1 and 2 Intermediate outcomes: Time to recurrence, local recurrence, and length of stay **KQ4:** <u>Adverse outcomes</u>: 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

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).

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).

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

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.

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).

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

Outcome	Intervention	Strength of Evidence	Summary of Included Studies
Overall Survival (continued)	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]
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

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 RCT[85] 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).

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

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.

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. $\geq$1 and in another study 0 or 1 vs. $\geq$2), performance status (0 or 1 vs. $\geq$ 2), number of extrahepatic metastases sites (0 or 1 vs. $\geq$2), number of lines of previous chemotherapy (0–1 vs. $\geq$ 2), performance status (0 or 1 vs. $\geq$ 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.

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.

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.

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