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Number XX

Local Hepatic Therapies for Metastases to the Liver from Unresectable Colorectal Cancer: Effectiveness and Comparative Effectiveness

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

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 are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input 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 e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

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Local Hepatic Therapies for Metastases to the Liver from Unresectable Colorectal Cancer: Effectiveness and Comparative Effectiveness

Objectives: To characterize the comparative effectiveness and harms of various local hepatic therapies for metastases to the liver from unresectable colorectal cancer in two distinct populations: patients with liver metastases (or minimal ones outside the liver) who are not eligible for continued systemic chemotherapy as 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 those related to ablation, embolization, and radiotherapy.

Data Sources: We searched MEDLINE® and EMBASE® from January 2000 to September 2011. 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 ultimate 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 802 articles through the literature search, excluded 779 at various stages of screening and 23 articles were included. To these we 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 29. Twenty-three articles addressed Key Questions: KQ1 (effectiveness) and KQ2 (harms) for patients ineligible for systemic chemotherapy, and six addressed KQ3 (effectiveness) and KQ4 (harms) for patients who are candidates for systemic chemotherapy. Two articles were randomized controlled trials which were extracted as a single-arm study due to a comparator of non-interest. All others articles were case-series. Four studies were of good quality, fifteen studies of fair quality, and 10 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: Evidence is insufficient to permit conclusions on the comparative effectiveness of local hepatic therapies for unresectable colorectal cancer 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 randomized controlled trials (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 colorectal cancer 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 non-cancerous tumors in the epithelial tissue. Overtime adenomas can become cancerous. This progression from adenoma to adenocarcinoma occurs through a sequential process of accumulating genetic changes. [2] While 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 among other things, 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 properly diagnose, characterize and stage the tumor.[7] Approximately one-third of new cases are diagnosed in the localized state, (i.e. no metastases). Five year survival is estimated at 90 percent for stage I and 70 percent for stage II.[1] Survival declines with increasing depth of tumor penetration, increasing tumor stage, and patient age. The remaining two-thirds of patients are initially diagnosed with distant (i.e. metastatic) disease. The five year survival for these patients is 10 percent or less with treatment. Patients with untreated liver metastases have 5-year survival of less than 3 percent.[8] Survival differs by the extent of liver metastases.

Treatment of Localized Disease

For the one-third of patients who are diagnosed with localized disease the cornerstone of their treatment is surgery. Advances in surgical technique, such as total mesorectal excision (dissection of the entire intact vascular, lymphatic, and fatty tissues), compared with 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.[9] 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 the cancer returning. Patients with stage III colon cancer who received post-surgery FOLFOX chemotherapy had a survival of 75 percent at three years compared with 25 percent in the pre-adjuvant chemotherapy era.[9]

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 (i.e. the liver metastases were diagnosed at the same time) liver metastases and another 50 percent developing metachronous (i.e. the liver metastases developed after initial diagnosis) disease.[10] 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 have liver-only metastasis.[11] Thus, therapies directed at the liver ("local hepatic therapies") have been used with the goal of extending survival in these patients.[12]

Surgical Resection

While the prognosis for patients with metastatic colorectal cancer to the liver has historically been 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.[13-19]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 to25%) will remain postsurgery.[20-22] Approximately 20 to 30 percent of patients with CRC liver metastases are candidates for this approach.

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.[23] These patients may, like initially resectable patients, experience promising 5-year survival rates around 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 higher Eastern Cooperative Oncology Group [ECOG] grade or lower Karnofsky score) and cardiac insufficiency.[24]

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 cases where a cure is no longer within reach. Two major indications for local hepatic therapies exist:

1. Patients with unresectable liver dominant (majority of disease located in the liver) metastases who are not eligible for continued systemic chemotherapy as 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.[25] 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 are candidates for local hepatic therapy.[26] 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.[27] 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 indications above. Therefore, comparisons of ablation versus surgery or systemic chemotherapy versus 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 from CRC. In the continuum of care, use of a local hepatic therapy may come before or after the use of systemic chemotherapy, but are most often they are administered 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). The following local hepatic therapies were included in this review:

- Ablation (cryosurgical, radiofrequency, and microwave)
- Embolization (transarterial embolization, transarterial chemoembolization, hepatic artery infusion, radioembolization, drug eluting beads)
- Radiotherapy (external-beam three-dimensional conformal radiation therapy, external-beam intensity-modulated radiotherapy, stereotactic body radiation therapy)

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.[28] However, the group provides no guidance about *which* ablative therapy is optimal or about the comparative benefits and harms of the various palliative treatments.[28] A perception of clinical equipoise and limited randomized trial data comparing local hepatic therapies[29, 30] leaves uncertainty around 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 (majority of disease located in the liver) metastases who are not eligible for continued systemic chemotherapy as 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.

The uncertainty surrounding the optimal use of the various local hepatic therapies is extensive. Because of the prevalence of colorectal cancer 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 (KQ) for the two patient populations described above:

KQ 1. 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?

KQ 2. 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?

KQ 3. 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?

KQ 4. 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 ES-1. PICOTS (Patient, Intervention, Comparator, Outcome, Timing, and Setting) for the Key Questions

PICOTS	KQ 1 & 2	KQ 3 & 4
Population	Patients with unresectable liver metastases from a 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 • No or minimal extrahepatic disease	Patients with unresectable liver metastases from a 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 • No or minimal extrahepatic disease
Intervention	• Cryoablation • Radiofrequency ablation • Microwave ablation • Transarterial embolization • Transarterial chemoembolization • Hepatic arterial infusion • Radioembolization or selective internal radiation therapy • Drug-eluting beads • External beam with 3D-CRT or IMRT • Stereotactic body radiation therapy	Same as KQ 1 & 2
Comparator	All the therapies listed above compared with the intervention in question for patients not eligible for systemic chemotherapy of CRC	Same as KQ 1 & 2
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, Increased alkaline phosphatase, Increased bilirubin, Increased transaminases, Injury to adjacent organ(s), Liver failure, Rare adverse events, Steatohepatitis	**KQ3:** Ultimate outcomes: Same as KQ 1 & 2 Intermediate outcomes: Time to recurrence, and local recurrence, length of stay **KQ4:** Adverse outcomes: Same as KQ 1 & 2
Timing	The relevant periods occur at the time of treatment for the CRC hepatic metastases through followup over months or years.	Same as KQ 1 & 2
Setting	Inpatient and outpatient	Same as KQ 1 & 2

CRC: Colorectal Cancer; KQ: Key Question; 3D-CRT: Three-dimensional conformal radiotherapy; IMRT: Intensity-modulated radiation therapy

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 drafted the initial KQs and, after approval from AHRQ, posted them to a public Web site, for four weeks, for comment. We modified the KQs and the PICOTS 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 both to palliate symptoms and to eliminate (i.e. cure) the liver metastases. The final KQs are now distinguished by the population receiving local hepatic (i.e., liver-directed) therapy. 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 rather than specific ones; we removed some interventions and added stereotactic body radiation therapy. Finally, we expanded this 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 published between January 1, 2000, and September 30, 2011. Date restrictions were to ensure applicability of the interventions. The searches was also limited to the English language.[31] It was thought that 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, and 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 the 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 Abstraction and Quality (Risk of Bias) Assessment

Data extraction was performed directly into tables created in Distiller SR with elements defined in an accompanying data dictionary. All team members extracted a training set of five articles into evidence table 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. Data extracted included patient and treatment characteristics, outcomes related to the interventions effectiveness, and data on harms. Harms included specific negative effects, including the narrower term of adverse effects. Data extraction forms used during this review are presented in Appendix C.

In the assessment of Risk of Bias in individual studies we followed the *Methods Guide*,[32] where applicable. Our assessment of risk of bias in the included single-arm intervention studies

was based on a set of study characteristics proposed by Carey and Boden.[33] 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[33] risk assessment tool into AHRQ standard (good, fair, and poor) quality ratings to differentiate single-arms studies of varied quality. These distinctions are to be used for differentiation within the group of single arm studies, not for the overall body of evidence which is 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 of good quality each of the Carey and Boden[33] criteria above must have been met. For a fair quality assessment one criteria may not be met, and for studies with more than one criteria not met a rank of poor quality is given. 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 and analyzed qualitatively in the text. We considered whether formal data synthesis (e.g., meta-analysis) would be possible from the set of included studies. 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 that 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,*[32, 34] which is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[35] This system explicitly addresses the following domains: risk of bias, consistency, directness, and precision. The strength of evidence grade can be one of four categories: high, moderate, low, and insufficient. The grade rating was made by independent reviewers, and disagreements were resolved by consensus adjudication.

Results

Of the 802 records identified through the literature search, 779 were excluded at various stages of screening and 23 records were included.[29, 36-57] One hand searched article[58] was also included along with 2 published studies were included from scientific information packets,[59, 60] and 3 were identified from conference abstracts.[61-63] A total of 29 articles were included in this report which consisted of 27 were case-series and two randomized controlled trials (RCT)[29, 58] for which a single arm was abstracted as a case series. (Table ES-2)

Table ES-2. 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*
Total	2	2[a]	2	12[a]	3	3	2	2	2	30
Study Design										
Prospective case series	1	0	0	6	2	1	2[c]	1	1	14
Retrospective case series	1	2	2	6[b]	1	2	0	1	1	16
Outcomes Reported										
Overall Survival	2	2	2	12	3	3	2	2	2	30
Quality of Life	0	0	0	1	1	0	1	0	0	3
Time to Recurrence	1	0	0	0	0	0	0	0	0	1
Length of Stay	0	1	0	0	1	0	0	0	0	2
Local Recurrence	2	0	0	0	0	2	2	0	0	6
Adverse Events	2	2	2	12	3	3	2	2	2	30
Study population										
United States	0	2	0	6	1	0	0	0	0	9
Europe	2	0	1	5	2	2	1	0	1	14
Australia	0	0	0	1	0	0	1	0	1	3
Asia	0	0	1	0	0	1	0	2	0	4
Total N participants	190	142	67	416	157	43	73	36	159	1283

RFA: Radiofrequency abalation, TACE: Transarterial chemoembolization, HAI: Hepatic arterial infusion; RE: Radioembolization; DEB: Drug-eluting beads; SBRT: Sterotactic body radiotherapy; SC: Systemic chemotherapy; N: Number
No studies reporting on cryoablation, microwave ablation, transarterial embolization, 3D-CRT, or IMRT met inclusion criteria for this review
*The total number of articles included in this review is 29, but the study by Hong et al., reports on both TACE and RE interventions.
[a] Hong et al., reports on both TACE and RE interventions
[b] Helendiz et al., is an RCT that was extracted as a single-arm case-series
[c]The study by Ruers et al., is an RCT that was extracted as a single-arm case series

Key Questions 1 and 2

KQs 1 and 2 focus on the comparative effectiveness (KQ1) and harms (KQ2) of the patient population ineligible for systematic therapy and no or only minimal evidence of extrahepatic disease. The evidence base comprised 22 case series or case reports and 1 randomized controlled trial (RCT) used only as a single-arm study. 1,015 patients were included from these 23 studies. 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 ES -3)
- All studies were case-series. Carey and Boden quality rankings were converted into AHRQ "good", "fair" and "poor" ratings. Two studies were of good quality, [29, 48], twelve were fair quality,[39, 41, 42, 44, 49-51, 55, 56, 60, 61, 63] and nine were poor quality.[36, 38, 40, 43, 46, 47, 57, 59, 62]

- 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 and dose and drugs delivered)

Table ES -3. Strength of Evidence for KQ1 and KQ2

Outcome	Intervention	No of Studies[§]	Risk of Bias	Consistency	Directness*	Precision	Overall Grade
Overall Survival	TACE with DEB	3[61, 69, 82]	High	Not applicable	Direct	Imprecise	Insufficient
	TACE	2[57, 62]	High	Not applicable	Direct	Imprecise	Insufficient
	SBRT	3[65, 76, 80]	High	Not applicable	Direct	Imprecise	Insufficient
	HAI	2[78, 84]	High	Not applicable	Direct	Imprecise	Insufficient
	RE	14[29, 59, 60, 62-64, 67, 68, 70-72, 81, 83, 86]	High	Not applicable	Direct	Imprecise	Insufficient
	RFA	2[63, 77]	High	Not applicable	Direct	Imprecise	Insufficient
Quality of Life	TACE with DEB	1[61]	High	Not applicable	Direct	Imprecise	Insufficient
	RE	1[60]	High	Not applicable	Direct	Imprecise	Insufficient
Length of Stay	TACE	2[57, 61]	High	Not applicable	Indirect	Imprecise	Insufficient
Time to Progression	None	0	High	Not applicable	Indirect	Imprecise	Insufficient
Local Recurrence	SBRT	2[65, 80]	High	Not applicable	Indirect	Imprecise	Insufficient
	RFA	2[63, 77]	High	Not applicable	Indirect	Imprecise	Insufficient
Adverse Events	TACE with DEB	3[61, 69]	High	Not applicable	Direct	Imprecise	Insufficient
	TACE	2[57, 62]	High	Not applicable	Direct	Imprecise	Insufficient
	SBRT	3[65, 76, 80]	High	Not applicable	Direct	Imprecise	Insufficient
	HAI	2[78, 84]	High	Not applicable	Direct	Imprecise	Insufficient
	RE	14[29, 59, 60, 62-64, 67, 68, 70-72, 81, 83, 86]	High	Not applicable	Direct	Imprecise	Insufficient
	RFA	2[63, 77]	High	Not applicable	Direct	Imprecise	Insufficient

* Directness: evidence is indirect for all comparisons as there is no comparative data but direct for assessment of some health outcomes. [§] the article by Hong, et al., applies to both DEB: Drug-eluting beads; HAI: Hepatic arterial infusion; RE: Radioembolization; SBRT: Stereotactic body radiation therapy TACE: Trans-arterial chemoembolization;

Key Questions 3 and 4.

Key questions 3 and 4 focus on the comparative effectiveness (KQ3) and harms (KQ4) of the 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.

The body of evidence (six studies) is case series with the exception of a single RCT[58] which was used as a single-arm study. 268 patients were included from these 6 studies. No comparative studies were available and 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. There were no comparative studies that met inclusion criteria for this review (Table ES-4)

- The literature base is comprised of case series and one RCT[58] that was abstracted as single-arm study due to a non-relevant comparator for this review. Two studies were ranked as good quality,[53, 58] three as fair,[37, 45, 52] and one as poor.[54]
- 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 and dose and drugs delivered)

Table ES-4. Strength of Evidence for KQ3 and KQ4

Outcome	Adjunctive therapy	No of Studies[§]	Risk of Bias	Consistency	Directness*	Precision	Overall Grade
Overall Survival	RFA	2[74, 79]	High	Not applicable	Direct	Imprecise	Insufficient
	RE	2[58, 66]	High	Not applicable	Direct	Imprecise	Insufficient
	HAI	2[73, 75]	High	Not applicable	Direct	Imprecise	Insufficient
Quality of Life	RFA	1[74, 79 74]	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	2[58, 79]	High	Not applicable	Indirect	Imprecise	Insufficient
Adverse Events	RFA	2[74, 79]	High	Not applicable	Direct	Imprecise	Insufficient
	RE	2[58, 66]	High	Not applicable	Direct	Imprecise	Insufficient
	HAI	2[73, 75]	High	Not applicable	Direct	Imprecise	Insufficient

* Directness: evidence is indirect for all comparisons as there is no comparative data but direct for assessment of some health outcomes.RE: Radioembolization; HAI: Hepatic arterial infusion; RFA: Radiofrequency ablation

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 key questions (KQs) about local hepatic therapy for the treatment of unresectable colorectal cancer (CRC) metastases to the liver. Twenty-nine studies met our inclusion criteria and addressed local hepatic therapy for unresectable CRC metastases to the liver.

We assessed the Strength of Evidence (SOE) for: our primary health outcomes of overall survival and quality of life; for the intermediate outcomes of length of stay, local recurrence, and adverse events for all Key Questions (KQs). In addition SOE was assessed for the intermediate outcomes of time to progression (KQ 1&2) and time to recurrence (KQ 3&4). We judged the

strength of evidence to be insufficient to draw conclusions for all outcomes. The body of evidence contained no comparative studies and thus provided no direct evidence about differences 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 to another. Some systematic reviews of single local hepatic therapies have been published. Earlier reviews conforming to a high quality standard reach conclusions similar to the present review: evidence is insufficient to permit conclusions.[30, 64]

The strength of this present review is that it addresses all local hepatic therapies for the included indications. In addition, it also recognizes that distinct patient groups exist within the population receiving local hepatic therapies.

Applicability

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 represents the patient population 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.[65]

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 non-comparative nature of the literature base both clinical and policy makers are limited in their ability to apply the published literature base to decisions on effectiveness and comparative effectiveness of these interventions. Studies of local hepatic therapies suggest that for selected patient groups local hepatic therapies may provide some benefit in terms of survival and symptom relief, but without comparative data choosing which therapy will produce the best outcomes for which patients is not possible.

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 whether these factors are likely to affect outcomes is uncertain. 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. In many centers, the choice of a local hepatic therapy may be limited to one option, based on the available clinical expertise and the technology. Local hepatic therapies often require high levels of training and familiarity with the procedure, as with radioembolization[66] and hepatic arterial infusion.[67] Lack of experience may affect not only outcomes but also 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 through the published literature.

Interventions

Even for a single local hepatic therapy, variation in how the procedure is performed may be substantial. For instance, the variation may be in the approach (open versus percutaneous); it may be in the choice of chemotherapy drugs delivered and the schedule of delivery of chemotherapy and radiation therapy. Given the limited evidence base, 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. The complex treatment history of each patient can further limit the conclusions that can be drawn about the benefit attributable to any one component of the treatment plan.

Comparators

All studies in this review are observational (including the single-arm trial); 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. The applicability of any case series to another group is very limited.

Outcomes

Little controversy exists as to 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 is reported in all of the studies included in this review. The utility 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 that may be attributed to a local hepatic therapy.

Timing

The timing of follow-up assessment was appropriate given the natural history of unresectable CRC liver metastases and the primary outcome of overall survival.

Research Gaps

In this section on research gaps, we first present a set of gaps focused on issues in the body of literature. Then we discuss the use of randomized clinical trials 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; strength of evidence is insufficient to permit us to draw conclusions on outcomes for either patient population.

We identified four broad evidence gaps during this review:

- There is a dearth evidence collected and reported in the included literature on quality of life. These data are particularly important for the population of patients where palliation of symptoms, rather than cure, is the intent of therapy.
- 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.
- An objective of comparative effectiveness research is to understand the comparative effects for different population subgroups. First we must fully delineate the population subgroups of interest. To accomplish this systematic definition of patient subgroups is required. Further studies must present data by these subgroups so that evidence can be interpreted by these variables. Examples of relevant variables are number and size of hepatic lesions, and performance status. With so many variables being collated clinical risk scores may be particularly beneficial as a summary measure. [68]
- 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, as these therapies may have an effect on the survival of the patient, should be taken into account when evaluating the effectiveness of the intervention under study. Previous resections and other local hepatic therapies were often not reported in the studies included in this review.

Study Designs to Address these Gaps

RCT's are the gold standard of clinical evaluation and there is an absence of randomized clinical evidence on the use of these therapies for the included indications. Unable to find evidence to answer any of our key questions, we conducted additional discussions with members of our Technical Expert Panel (TEP) to elicit ideas addressing the gaps in the literature. TEP members identified common barriers to conducting randomized controlled trials (RCTs) for

these questions. Among these are challenges common to many research areas including: limited sources of adequate research dollars to support RCTs, reluctance of physicians to randomize patients, and the reluctance of patients to be randomized.

More important than the resistance to randomize is the lack of willing funding sources and the presentation of a fundable research question. 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 that are often based on their own institutional experience. In discussions with TEP members they agreed that certain broad categories of patients with CRC metastasis to the liver, such as the population included in this review, may well benefit from local hepatic therapies, and that the published literature did not permit parsing patient subgroups to identify characteristics more favorable to one local hepatic therapy over another. RCT's with well documented patient and treatment characteristics could address the lack of well described comparative evidence.

Regardless of the study design we suggest that studies aiming to address the effectiveness or comparative effectiveness 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 a modifier of the effectiveness and a factor used to choose the local hepatic therapy.

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

Patient Registries

In the absence of consensus around the most salient comparative research question observational data could be useful in driving the generation and prioritization of hypotheses for future research. One approach to this is the use of a registry to systematically collect observational data for future research. 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 and disease natural history and management under varied treatment scenarios.[69] Registries need to be created with a question in mind, which will then guide the identification of the target patient population, the exposures 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 comparative effectiveness review could serve as guide for one or more registries focused on this clinical area. The aim would be to establish a prospective registry that tracks 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. Although not a key question for this review, TEP members also indicated that the experience of the one provider of the local hepatic therapy would also be important for 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 ES-3, organized by PICOTS.

Table ES-31. Core dataset elements for local hepatic therapy registry by PICOTS

Population	Intervention	Comparators	Outcomes	Timing	Setting
Patient Characteristics	**Type of local hepatic therapy**	Same as Intervention	Overall survival	Ongoing	Hospital type
Age	Cryosurgical ablation		Quality of life		Number of procedures by practitioner
Sex	RFA		Response (e.g. complete, partial, no response)		Type of practitioner
Race	Microwave ablation				Local hepatic therapy availability
Ethnicity	TAE		Recovery time		Inpatient or outpatient procedure
Performance status	TACE		Length of Stay		
LDH	HAI		Adverse effects (Short-term and long-term harms		
CEA	RE		Treatment holidays*		
Clinical risk scores (e.g., Fong)[68]	DEB				
Tumor characteristics	3D-CRT				
Location of tumor	IMRT				
Size of lesions	SBRT				
Number of lesions	**Characteristics of local hepatic therapy**				
Tumor volume	Dose				
Portal vein obstruction	Duration				
Course of disease(stabilization, rapid progression)	Surgical site				
Other treatments					
Number, dose, duration, for lines of prior therapy by drug					
Number, dose, duration for lines of adjunctive therapy by drug					
Previous liver-directed therapy					

* Treatment holidays refer to time away from systemic chemotherapy and may result from successful treatment with a local hepatic therapy. of LDH: lactate dehydrogenase; CEA: carcinoembryonic antigen: RFA: Radiofrequency ablation; TAE: Transarterial embolization; TACE: transarterial chemoembolization; HAI: Hepatic artery infusion; RE: Radioembolization; DEB: Drug-eluting bead; 3D-CRT: three dimensional conformal radiation therapy; IMRT: Intensity-modulated radiation therapy; SBRT: Serotactic body radiation therap

Conclusions

Evidence is insufficient to permit us to draw conclusions about the comparative effectiveness of local hepatic therapies for unresectable CRC metastases to the liver for the populations addressed in this review. Important outcomes of therapy include overall survival and improved quality of life; as well as 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 colorectal cancer 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 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 non-cancerous tumors in the epithelial tissue. Overtime adenomas can become cancerous. This progression from adenoma to adenocarcinoma occurs through a sequential process of accumulating genetic changes.[2] While 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 among other things, 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 properly diagnose, 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 one-third of new cases are diagnosed in the localized state, (i.e. no metastases). Five year survival is estimated at 90 percent for stage I and 70 percent for stage II.[1] Survival declines with increasing depth of tumor penetration, increasing tumor stage, and patient age. The remaining two-thirds of patients are initially diagnosed with distant (i.e. metastatic) disease. The five-year survival for these patients is 10 percent or less with treatment. Patients with untreated liver metastases have five-year survival of less than 3 percent.[8] 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.[8]

Treatment of Localized Disease

For the one-third of patients who are diagnosed with localized disease the cornerstone of their treatment is surgery. Advances in surgical technique, such as total mesorectal excision (dissection of the entire intact vascular, lymphatic, and fatty tissues), compared with 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.[9] 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 the cancer returning. Adjunctive therapy has evolved from

experimental treatment to standard of care over the past 20 years. For example, patients with stage III colon cancer who received post-surgery FOLFOX chemotherapy had a survival of 75 percent at three years compared with 25 percent in the pre-adjuvant chemotherapy era.[9] Trials are currently being undertaken to determine if adjunctive 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 (i.e. the liver metastases were diagnosed at the same time) liver metastases and another 50 percent developing metachronous (i.e. the liver metastases developed after initial diagnosis) disease.[10] 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 have liver-only metastasis.[11] Thus, therapies directed at the liver ("local hepatic therapies") have been used with the goal of extending survival in these patients.[12]

Surgical Resection

While the prognosis for patients with metastatic colorectal cancer to the liver has historically been 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.[13-19] 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%) will remain postsurgery.[20-22] Approximately 20 to 30 percent of patients with CRC liver metastases are candidates for this approach.

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.[23] These patients may, like initially resectable patients, experience promising 5-year survival rates around 30 percent. Hepatotoxicity from preoperative chemotherapy (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 higher Eastern Cooperative Oncology Group [ECOG] grade or lower Karnofsky score) and cardiac insufficiency.[24]

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 cases where a cure is no longer within reach. Two major indications for local hepatic therapies exist:

1. Patients with unresectable liver dominant (majority of disease located in the liver) metastases who are not eligible for continued systemic chemotherapy as 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.[25] 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 are candidates for local hepatic therapy.[26] 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.[27] 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 from CRC. In the continuum of care, use of a local hepatic therapy may occur before or after the use of systemic chemotherapy, but most often it is administered 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 including the mechanism of action of the intervention, the setting where 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.

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 ultimate liver failure. While non-surgical 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.[28] However, the group provides no guidance about which ablative therapy is optimal or about the comparative benefits and harms of the various palliative treatments.[28] A perception of clinical equipoise and limited randomized trial data comparing local hepatic therapies[29, 30] leaves uncertainty around which techniques, either alone or in combination, may be preferable for certain patient groups.

Table 2. Local nonsurgical therapies for CRC liver metastases reviewed in this report

	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 to -40°C[31, 32]	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.[33, 34]
	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 aims to generate tissue temperatures of 90 to 100°C, which produces protein denaturation and coagulative necrosis.[21]	The procedure is performed under intravenous narcotics for the percutaneous, awake, approach and does not require a hospital stay. For laproscopic or open RFA the procedure is performed under general anesthesia and results in a longer recovery period.[35] Each RFA takes about 10 to 30 minutes, with additional time required if multiple ablations are performed. The entire procedure is usually completed within one to three hours.[36]	Interventional Radiologist	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).[33, 36]
	Microwave ablation (MWA)	MWA uses high-frequency electromagnetic radiation to create heat through the excitation of water molecules.[21] 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 the complications associated with MWA. [34] 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 [33, 34]
Embolization and Transarterial Therapy	Transarterial embolization (TAE)	TAE uses selective catheterization and obstruction of the arterial vessel, which supplies blood to the tumor, with an embolizing agent.[37]	Most patients can be discharged a several hours after treatment with TAE, but if post embolization syndrome occurs an overnight stay is typically required.	Interventional Radiologist	Side effects differ depending upon the type of embolization used. Common complications reported are post-embolization syndrome (fever, pain, extreme fatigue, nausea/vomiting),

Treatment strategy	Mechanism of cell death	Setting	Performed by	Specific Harms
				infection in the liver, hepatic abscess, gallbladder inflammation, and blood clots in the main blood vessels of the liver. Serious complications are uncommon, but they are possible. Embolization also reduces some of the blood supply to the normal liver tissue. This may be dangerous in patients with underlying hepatitis or cirrhosis. patients with diseases such as hepatitis or cirrhosis.[38]
Transarterial chemoembolization (TACE)	TACE aims to cause ischemia and involves administering a chemotherapeutic agent directly to the liver tumor. 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 feeding hepatic arteries directly supplying the tumor, and simultaneously the feeding hepatic arteries are obstructed with an embolizing agent. Tumor ischemia raises the drug concentration, extends the retention of the chemotherapeutic agent, and reduces systemic toxicity.	Most patients can be discharged a several hours after treatment with TACE, but if post embolization syndrome occurs an overnight stay is typically required.	Interventional Radiologist	Same as above
Hepatic artery infusion (HAI)	HAI uses a pump to deliver higher doses of chemotherapy to the tumor, as compared with systemic chemotherapy, but it maintains 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 while 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 slowly delivers chemotherapeutic agent at a slow, fixed rate over a period of weeks. The pump drug chamber can be refilled percutaneously. Successful hepatic arterial infusion is dependent on surgeon experience with the procedure.[39]	Interventional Radiologist, surgeon for placement of pump	Complications related to insertion of the pump are rare.[39] 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 post-embolization 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

	Treatment strategy	Mechanism of cell death	Setting	Performed by	Specific Harms
					complications are uncommon, but they are possible. Embolization also reduces some of the blood supply to the normal liver tissue. This may be dangerous in patients with underlying hepatitis or cirrhosis. patients with diseases such as hepatitis or cirrhosis. [38]
	Radioembolization or selective internal radiation therapy (SIRT)	SIRT involves loading radionuclide yttrium-90 into microspheres and placing them within the microvasculature of the liver metastases, thus targeting multiple hepatic metastases in a single procedure.[40] The loaded microspheres deliver high, localized doses of β-radiation to the tumor while minimizing radiation exposure to the surrounding tissue.[40-42]	Patients are required to undergo ^{99m}Tc-macro-aggregated albumin (MAA) scan prior to SIRT to assess eligibility.[43] The SIRT procedure takes about 90 minutes, and patients can typically return home four to six hours following treatment.	Interventional Radiologist	The side effects will differ depending upon the type of embolization used. The most common complications reported are post-embolization 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 they are possible.[38] Acute toxicity events include gastritis, ulceration, or pancreatitis due to microsphere deposition in vessels serving these organs.[43] Radiation induced liver disease (jaundice, weight gain, painful hepatomegaly and elevated liver enzymes), thrombocytopenia, encephalopathy, rise in liver function tests, ascites, hypoalbuminemia,
	Drug-eluting beads (DEB)	This novel transarterial embolization system uses a drug-loaded (typically doxorubicin or cisplatin) superabsorbent polymer microsphere to release doxorubicin gradually into the tumor, allowing a longer intratumoral exposure and less systemic exposure to the drug.[44]	Most patients can be discharged a several hours after treatment, but if post embolization syndrome occurs an overnight stay is typically required.	Interventional Radiologist	The side effects will differ depending upon the type of embolization used. The most common complications reported are post-embolization 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 they are possible.[38]
Radiotherapy	External-beam three-dimensional conformal radiation therapy (3D-CRT)	This type of radiotherapy that uses computer-assisted tomography scans (CT or CAT scans) and/or magnetic resonance imaging scans (MR or MRI	Each treatment lasts only a few minutes, although the setup time usually takes longer. Most often, radiation treatments are given 5	Radiation oncologist, medical physicist, dosimetrist,	Possible side effects of external radiation therapy include: sunburn-like skin problems, nausea, vomiting, and fatigue. These typically go away post-

	Treatment strategy	Mechanism of cell death	Setting	Performed by	Specific Harms
		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.	days a week for several weeks. The patient's diagnosis determines the total duration of treatment.[45, 46]	radiation therapist, and radiation therapy nurse	treatment. Radiation might also make the side effects of chemotherapy worse.[38] Radiation induced liver disease is the major dose limiting toxicity.[47]
	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 a tumor while significantly reducing the dose to surrounding normal tissue. IMRT offers a further defined radiation dose over traditional CD-CRT.	Same as above, but IMRT does require slightly longer daily treatment times and additional planning and safety checks before the patient can start the treatment than conventional radiotherapy.[48]	Same as above	Same as above
	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.[49]	Before you begin treatment, you may be asked to have a fiducial marker (an object used in concert with imaging to provide precise location information) commonly as an outpatient procedure. SBRT typically consists of one to five treatment sessions over the course of one to two weeks usually as an outpatient procedure.[50]	Same as above	Same as above

*The radiotherapy presented in this report is focused on focal treatment of the lesion or lesions and not whole liver irradiation.

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 (majority of disease located in the liver) metastases who are not eligible for continued systemic chemotherapy as 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, those who have unresectable liver metastases treated with first-line chemotherapy in combination with local hepatic therapy for downstaging of disease, and those 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.[51] All patients in the studies included in this review will have been classified as having unresectable disease because of either the extent of the tumor or patient characteristics (poor surgical candidate). As noted, we focus on two distinct patient populations, which have different underlying prognoses; thus, we will make treatment comparisons within, rather than across, these populations. We will consider studies with any length of followup and all inpatient and outpatient settings. Table 2 lists the relevant populations, interventions, comparators, outcomes timeframes of assessment, and settings (PICOTS) relevant for this review.

Table 3. PICOTS (Patient, Intervention, Comparator, Outcome, Timing, and Setting) for the Key Questions

PICOTS	KQ 1 & 2	KQ 3 & 4
Population	Patients with unresectable liver metastases from a 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 • No or minimal extrahepatic disease	Patients with unresectable liver metastases from a 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 • No or minimal extrahepatic disease
Intervention	• Cryoablation • Radiofrequency ablation • Microwave ablation • Transarterial embolization • Transarterial chemoembolization • Hepatic arterial infusion • Radioembolization or selective internal radiation therapy • Drug-eluting beads • External beam with 3D-CRT or IMRT • Stereotactic body radiation therapy	Same as KQ 1 & 2
Comparator	All the therapies listed above compared with the intervention in question for patients not eligible for systemic chemotherapy of CRC	Same as KQ 1 & 2
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, Increased alkaline phosphatase, Increased bilirubin, Increased transaminases, Injury to adjacent organ(s), Liver failure, Rare adverse events, Steatohepatitis	**KQ3:** Ultimate outcomes: Same as KQ 1 & 2 Intermediate outcomes: Time to recurrence, and local recurrence, length of stay **KQ4:** Adverse outcomes: Same as KQ 1 & 2
Timing	The relevant periods occur at the time of treatment for the CRC hepatic metastases through followup over months or years.	Same as KQ 1 & 2
Setting	Inpatient and outpatient	Same as KQ 1 & 2

CRC: Colorectal Cancer; KQ: Key Question; 3D-CRT: Three-dimensional conformal radiotherapy; IMRT: Intensity-modulated radiation therapy

Key Questions

KQ 1. 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?

KQ 2. 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?

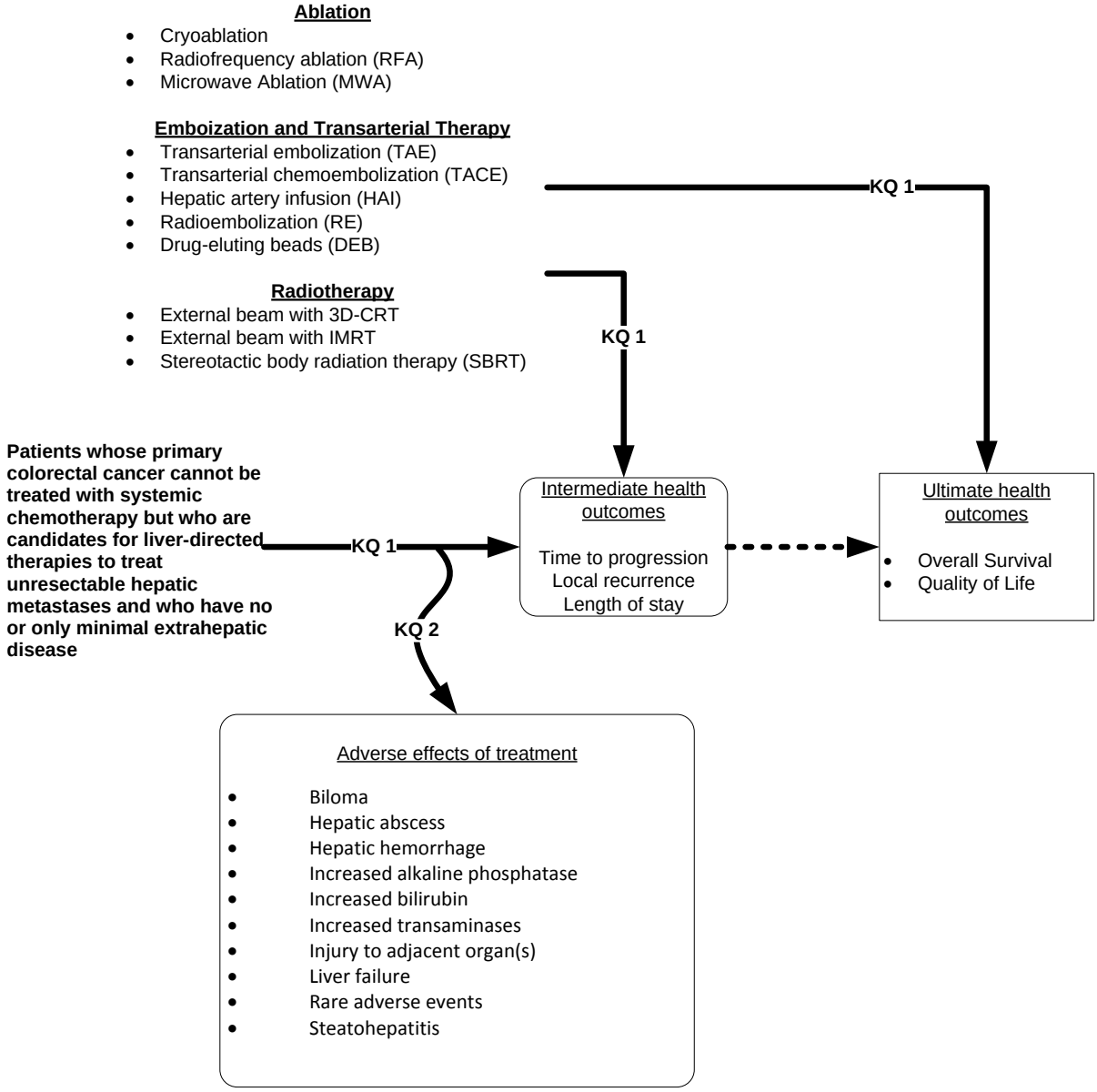
KQ 3. What is the comparative effectiveness of the various liver-directed therapies in patients who are candidates for liver-directed therapy as an adjunct to systemic therapy for unresectable CRC metastases to the liver and have no evidence of extrahepatic disease?

KQ 4. 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

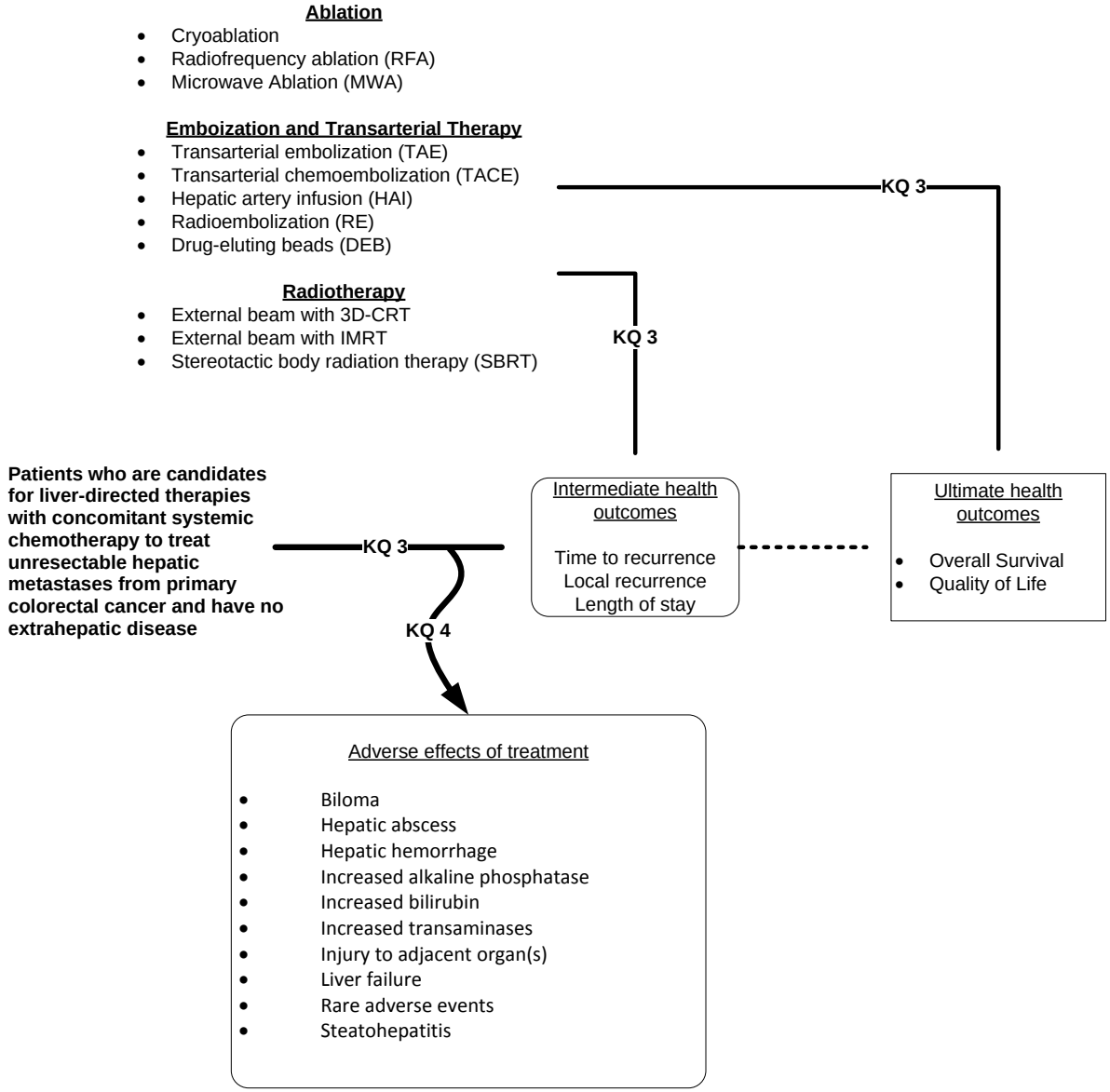
We developed the analytic frameworks (Figure 1 and Figure 2) based on clinical expertise and refined it with input from our key informants and technical expert panel. These diagrams are revised versions of those posted with the review protocol; the revisions are intended to make the core elements of our final analyses clearer, given the actual literature available for the review. Figure 1 outlines potential areas where 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 ultimate outcomes of quality of life and overall survival (KQ1). Figure 2 outlines potential areas where 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 local hepatic therapies for unresectable colorectal cancer metastases to the liver in patients whose metastatic disease is refractory to systemic chemotherapy and who have minimal evidence of extrahepatic disease



Abbreviations: CRC = colorectal cancer; KQ = key question; 3D-CRT: Three-dimensional conformal radiotherapy; 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 evidence of extrahepatic disease



Abbreviations: CRC = colorectal cancer; KQ = key question; 3D-CRT: Three-dimensional conformal radiotherapy; IMRT: Intensity-modulated radiation therapy

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 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 detail on our methods and the studies assessed. The appendixes are as follows:

- Appendix A: Search Strategies
- Appendix B: Contacted Authors
- Appendix C: DistillerSR Screening and Abstraction Forms
- Appendix D: Evidence Tables
- Appendix E: List of abbreviations and acronyms
- Appendix F: List of Excluded Studies

Uses of This Evidence Report

We anticipate 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, and interventional radiologists. 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 aim to determine the outcomes of treatment for unresectable CRC metastases to the liver. It will be of interest to patients with unresectable CRC liver metastases and their families who are concerned about their health and facing treatment choices.

This presentation of the evidence is of value to researchers who can obtain a concise analysis of the current state of knowledge in the field and information about where there are gaps in knowledge. They will be prepared 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 Evidence-based Practice Center (EPC) used to produce a comparative effectiveness review (CER) on the effectiveness and comparative effectiveness of local hepatic therapies for colorectal cancer (CRC) metastases to the liver. The methods for this comparative effectiveness review (CER) follow the methods suggested in the Agency for Healthcare Research and Quality (ARHQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (available at http://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.[52] 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 key questions (KQ), 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 KQs, we sought the inputs of the technical expert panel (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 public comment for 4 weeks. We modified the KQs and the key elements of population, intervention, comparators, outcomes, timeframes, and settings (PICOTS) based on these comments and discussion with the TEP.

When the KQs were first written, both the questions and the interventions had been stratified by intent of treatment (palliative or curative). However, this stratification seemed clinically inappropriate and potentially confusing, because some interventions could be applied both to palliate symptoms and to eliminate (i.e. cure) the liver metastases. Thus, the final KQs are now distinguished by the population receiving local hepatic therapy. KQs 1 and 2 apply to patients whose CRC is refractory (i.e. their disease had progressed) to systemic chemotherapy, 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 rather than no extrahepatic disease. In addition we categorized the 12 interventions to apply to all KQs rather than specific ones; we removed some interventions and added stereotactic body radiation therapy (SBRT). Finally, we expanded the list of harms to be considered to include increased alkaline phosphatase, increased bilirubin, increased transaminases, liver failure, and rare adverse events that had not originally been considered.

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[53] but made no limits on the geographic location of the study. We also restricted the searches to articles published between January 1, 2000, and September 30, 2011, primarily to ensure the applicability of the interventions; and outcomes data to current clinical practice.

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

We sought gray literature by searching for clinical trials, material published on the U.S. Food and Drug Administration Web site, and relevant conference abstracts (from American Society of Clinical Oncology, American Society of Clinical Oncology Gastrointestinal, Surgical Society of Oncology, and the Radiosurgery Society) identified by TEP members). 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 comment during the topic refinement phase, input from the TEP, and established principles of systematic review methods.

Table 4. Inclusion and Exclusion Criteria

Category	Criteria
Study population	Patients with primary CRC and unresectable liver metastases due to lesion characteristics or underlying co-morbidity • For KQ 1 and KQ 2, patients are refractory to systemic chemotherapy • For KQ 3 and KQ 4, patients receive local hepatic therapy as an adjunct to systemic chemotherapy
Time period	Studies published after 2000 due to changes in interventional approaches to local hepatic therapies
Publication languages	English only
Admissible evidence (study design and other criteria)	Admissible designs • All study designs will be considered • Case reports will only be considered if they report on a rare adverse event Other Criteria • Extra-hepatic disease is 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 which 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 as 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 assure uniform application of screening criteria. Full-text review was performed when it was unclear if 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. While an article may have been excluded for multiple reasons, the first reason identified was recorded.

Development of Evidence Tables and Data Extraction

Evidence tables were constructed jointly by the EPC staff members and clinical content experts who conducted this review. Tables were designed to provide sufficient information enabling readers to understand the studies and determine their quality. Emphasis was given to data elements essential to our key questions. Evidence table templates were identical for KQ 1 and KQ3 and KQ 2 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 Distiller SR with elements defined in an accompanying data dictionary. All team members extracted a training set of five articles into an evidence table 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. Data extracted included patient and treatment characteristics, outcomes related to the interventions effectiveness, and data on harms. Harms included specific negative effects, including the narrower term 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.

Quality (Risk of Bias) Assessment of Individual Studies

In the assessment of Risk of Bias in individual studies we followed the *Methods Guide*,[37] where applicable. Our assessment of risk of bias in the included single-arm intervention studies was based on a set of study characteristics proposed by Carey and Boden.[54] 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[54] risk assessment tool into AHRQ standard (good, fair, and poor) quality ratings to differentiate single-arms studies of varied quality. These distinctions are to be used for differentiation within the group of single arm studies, not for the overall body of evidence which is described below. The classification into these categories (i.e. good, fair, poor) is distinct for a specific study design. Other study designs would be evaluated according to their own strengths and weaknesses.

For a study to be ranked good quality each of the Carey and Boden[54] criteria above must have been met. For a fair quality assessment one criteria may not be met, and for studies with more than one criteria not met a rank of poor quality is given. 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 and analyzed qualitatively in the text. We considered whether formal data synthesis (e.g., meta-analysis) would be possible from the set of included studies. 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 that 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*[37, 55]) which is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[56] This system explicitly addresses four required domains: risk of bias, consistency, directness, and precision. Four additional domains can also be used if appropriate: dose-response relationship, plausible confounding dose-response relationship, strength of association, and publication bias. The assessment of risk of bias by study design would also be supplemented by the inherent weaknesses of a particular study design.

The overall strength of evidence could be graded as “high” (indicating high confidence that the evidence reflects the true effect and 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 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 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 effects could not be estimated from the body of evidence the overall strength of evidence was rated as “insufficient”. If comparative effects could be estimated the evidence was graded as “low”, indicating our low level of confidence in the estimates due in large part to the biases inherent in a literature base comprised of single-arm studies.

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, and their relevance with regard to 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 colorectal cancer (CRC) metastases to the liver. The Key Questions (KQ) 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 have minimal extrahepatic disease; 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.

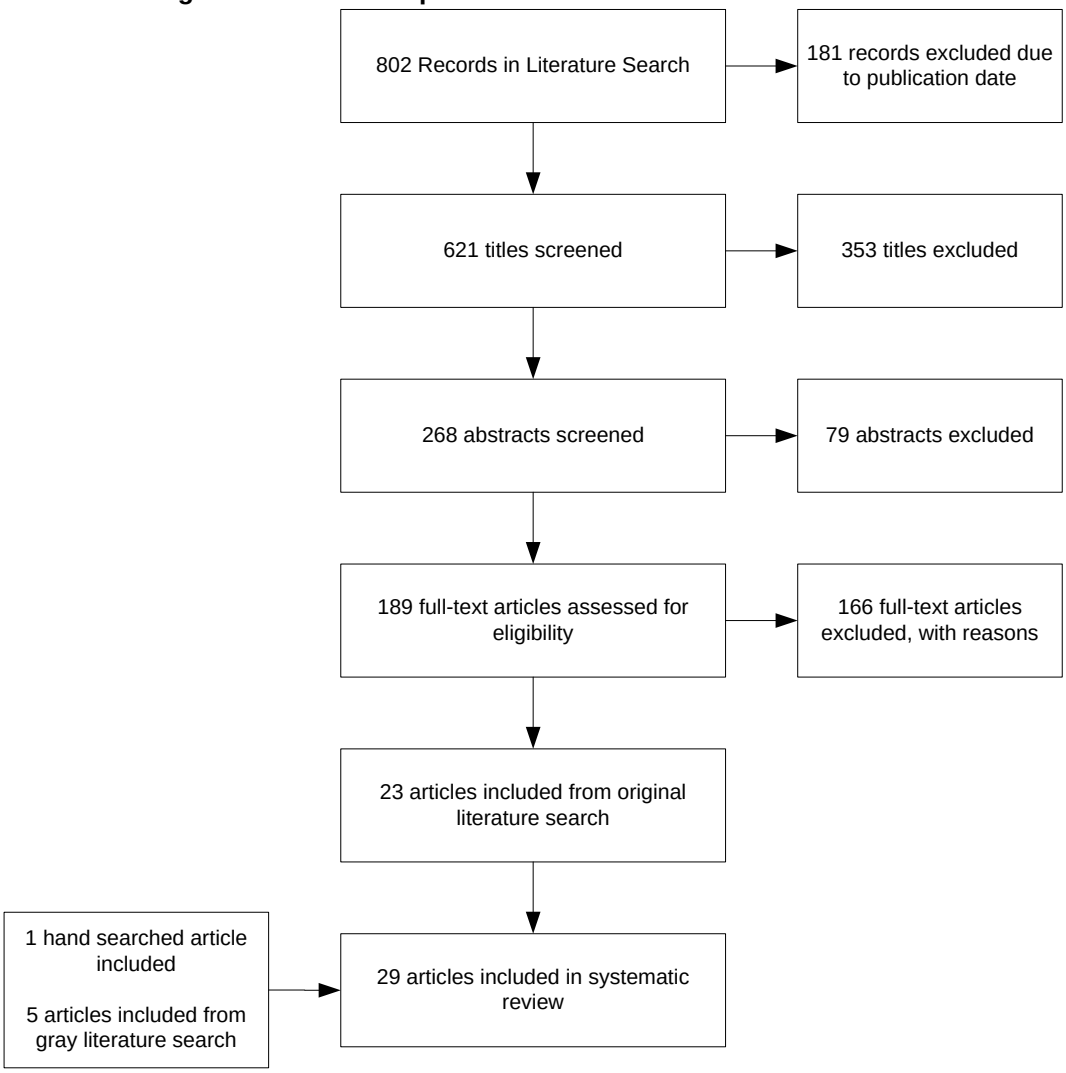
We first describe the results of our literature searches then results are presented for KQ 1 and KQ 2 which includes a list of key points, an overview of the included literature and detailed synthesis of the data. This is followed by the same for KQ 3 and KQ 4. We identified 802 nonduplicate titles or abstracts with potential relevance, with 189 proceeding to full text review (Figure 3). Twenty-nine were included in the review, including one hand searched and five articles identified through other sources (American Society of Clinical Oncology, American Society of Clinical Oncology Gastrointestinal, Surgical Society of Oncology, and the Radiosurgical Society) from gray literature, representing 29 distinct studies: 2 randomized controlled trials (RCT), 13 prospective case series, and 14 retrospective case series. 23 studies pertain to KQ1, 23 studies to KQ2, 6 studies to KQ3, and 6 studies to KQ4.

Results of Literature Searches

Of the 802 records identified through the literature search, we excluded 779 at various stages of screening and included 23 records.[29, 57-78] We included one hand-searched article,[79] two published studies from scientific information packets,[80, 81] and three articles from conference abstracts.[82-84] A total of 29 articles were included in this report which consisted of 27 were case-series and two were randomized controlled trials (RCT)[29, 79] for which a single arm was abstracted as a case series.

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram (Figure 3) depicts the flow of search screening and study selection.[52] 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 included in the analyses presented in this evidence review.[80-84]

We evaluated the results of the gray literature search

- **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 key questions of this report. Of these 13 studies, 3 had been terminated, 7 were ongoing or recruiting, and 3 had been completed. We found no publications for the three completed trials.
- **Abstracts and conference papers:** The search yielded 174 citations, and we excluded 132 during the title and abstract screen. Of these 42 items, 2 were duplicates, and 37 did

not meet inclusion criteria after full-text review. The three remaining references met all inclusion criteria and we added them to this report.[82-84]

- **Manufacturer database (SIPs):** Scientific information packets (SIPs) 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 abstract and title screen. The remaining two references met the inclusion criterion and we added them to this report.[80, 81]

Overview of the Literature

Twenty-nine studies met our inclusion criteria and addressed local hepatic therapy for unresectable CRC metastases to the liver. Eight studies were conducted in the United States, 5 in Italy, 4 in Germany, 3 in Australia, 3 in Japan, 2 in the United Kingdom, and one study each in Belgium, France, Korea and the Netherlands. The number of participants ranged from 6 to 140 patients.

Table 5. 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*
Total	2	2[a]	2	12[a]	3	3	2	2	2	30
Study Design										
Prospective case series	1	0	0	6	2	1	2[c]	1	1	14
Retrospective case series	1	2	2	6[b]	1	2	0	1	1	16
Outcomes Reported										
Overall Survival	2	2	2	12	3	3	2	2	2	30
Quality of Life	0	0	0	1	1	0	1	0	0	3
Time to Recurrence	1	0	0	0	0	0	0	0	0	1
Length of Stay	0	1	0	0	1	0	0	0	0	2
Local Recurrence	2	0	0	0	0	2	2	0	0	6
Adverse Events	2	2	2	12	3	3	2	2	2	30
Study population										
United States	0	2	0	6	1	0	0	0	0	9
Europe	2	0	1	5	2	2	1	0	1	14
Australia	0	0	0	1	0	0	1	0	1	3
Asia	0	0	1	0	0	1	0	2	0	4
Total N participants	190	142	67	416	157	43	73	36	159	1283

RFA: Radiofrequency abalation, TACE: Transarterial chemoembolization, HAI: Hepatic arterial infusion; RE: Radioembolization; DEB: Drug-eluting beads; SBRT: Sterotactic body radiotherapy; SC: Systemic chemotherapy; N: Number
No studies reporting on cryoablation, microwave ablation, transarterial embolization, 3D-CRT, or IMRT met inclusion criteria for this review
*The total number of articles included in this review is 29, but the study by Hong, et al. reports on both TACE and RE interventions.
[a] Hong, et al. reports on both TACE and RE interventions
[b] Helendiz, et al. is an RCT that was extracted as a single-arm case series
[c]The study by Ruers, et al. is an RCT that was extracted as a single-arm case series

All 29 studies had clearly defined questions, 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. Twelve studies did not have well-described patient populations,[57, 59, 61, 64, 68, 72, 73, 75, 78, 80, 81, 83] and 3 lacked well-described results,[61, 64, 68, 85] and 23 studies did not report on sponsorship or funding.[57-68, 70, 71, 73, 75-78, 80, 82-84]

Four studies were of good quality,[29, 69, 74, 79] fifteen studies of fair quality,[60, 62, 65, 70-72, 76, 77, 81-8458, 66, 73] and 10 were rated as poor quality.[57, 59, 61, 64, 67, 68, 75, 78, 80, 83]

Key Questions 1 and 2: Effectiveness and Harms of Therapies in Patients Not Able to Receive Systemic Chemotherapy

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

Key Points

- The evidence is insufficient to draw conclusions about overall survival, quality of life, or adverse events.
- All studies were case series. Carey and Boden quality rankings were converted into AHRQ “good”, “fair” and “poor” ratings. Two studies were of good quality,[29, 69], twelve were fair quality,[60, 62, 63, 65, 70-72, 76, 77, 81, 82, 84] and nine were poor quality.[57, 59, 61, 64, 67, 68, 78, 80, 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 and dose and drugs delivered)

Description of Included Studies

Twenty-two case series[57, 59-65, 67-72, 75-78, 80-84] and one RCT,[29] for a total of 23 studies met inclusion criteria to address KQ 1 and KQ 2. Of the 22 case series, 10 were prospective[60, 61, 64, 67-70, 72, 75, 77, 80] and 12 were retrospective.[57, 59, 62, 63, 65, 71, 76, 78, 81-84] The total number of patients for whom data were abstracted from the 23 studies was 1,015. Three studies included patients treated with transarterial chemoembolization (TACE) with drug-eluting beads (DEB);[61, 69, 82] two articles reported on TACE alone;[57, 62] three on stereotactic body radiation (SBRT);[65, 76, 80] ten reported results after radioembolization (RE);[59, 60, 62, 64, 67, 70-72, 81, 83, 86] two treated patients with hepatic artery infusion (HAI),[78, 84] and two reported on patients treated with radiofrequency ablation (RFA).[63, 77] All studies initiated treatment in patients after January 1, 2000, save the studies by Albert and colleagues,[21] who reported on TACE, and by Veltri, et al.[77] who reported on RFA. We included these studies because the papers reported on relatively large numbers of patients treated, and the papers presented analyses showing no differences in outcomes between treated before 2000 and after 2000. Table 5 shows the summary study and patient characteristics, including number of patients enrolled, design, intervention period, intervention, and patient demographics.

Patients ranged in age from 30 to 91 years, but they were generally in their late fifties or early sixties. Twelve studies reported rates of previous resection that ranged from 16 to 83.5 percent.[57, 58, 60, 62-64, 69, 76, 77, 80, 81, 83, 84] Six studies reported median Eastern Cooperative Oncology Group (ECOG) scores of 0-1 with a total score range of 0-3.[29, 60, 61, 67, 69, 71] In all but two studies,[66, 75] all patients had been treated with prior lines of systemic chemotherapy, and 11 studies reported patient experience with prior local hepatic therapy.[57, 62-64, 69, 72, 76, 77, 80, 81, 83]

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

One randomized controlled trial (RCT) by Hendlisz, et al.[29] was included. Hendlisz, et al. treated patients who were refractory to systemic chemotherapy with local hepatic therapy and systemic chemotherapy. While the intervention addresses KQ 3 and KQ 4, the patient population (i.e. refractory) applies to KQ 1 and KQ 2. Data were abstracted for KQ 1 and KQ 2.

Table 6. Local hepatic therapies for colorectal cancer metastases to the liver: summary of study characteristics

Study N$^{\Theta}$ (% CRC) Rating	Study Design	Intervention Period	Intervention	Median Age (Range)	Previous Resection	ECOG Score Median (Range)	Previous Local Hepatic Therapy
Aliberti, et al. 2011[82] 82 (100) Fair	Retrospective case series	12/2005 - 09/2011	TACE with irinotecan (100-2000 mg) in DC Beads (2-4ml of beads)	61.8 (46 – 82)	NR	NR (0 – 2)	NR
Martin, et al. 2011[69] 55 (100) Good	Prospective case series	10/2006 - 08/2008	TACE with DEB: Intervention: TACE with DEB; Drug: irinotecan; Dose: median 185mg, range 150-650mg; Site: femoral or axillary artery	60 (34 – 82)	20	1 (0 – 2)	Ablation: 9.1
Vautravers-Dewas, et al. 2011[76] 42 (66.7) Fair	Retrospective case series	07/2007 - 04/2009	SBRT: Intervention: SBRT; Drug: radiation; Dose: 40 Gy and 45 Gy; Site: noninvasive	(23 – 82)	51.1	NR	RFA: 7
Albert, et al. 2011[57] 121 (100) Poor	Retrospective case series	03/1992 - 07/2008	TACE: Intervention: TACE; Drug: mitomycin C, doxorubicin, cisplatin; Site: femoral artery	NR	17	NR	RFA: 17
Nace , et al. 2011[81] 51 (100) Fair	Retrospective case series	08/2002-05/2008	RE with Y90 (delivery dose 50Gy) via hepatic artery	64 (37 – 83)	23.5	NR	RFA: 21.6; HAI 9.8
Stintzing, et al. 2010[80] 6 (100) Poor	Prospective case series	NR	Radiosurgery (24 Gy) for a single session	66.5 (51 – 76)	83.5	NR	RFA: 17.6
Nishiofuku, et al. 2010[84] 55 (100) Fair	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	NR	NR
Cosimelli, et al.2010[60] 50 (100) Fair	Prospective case series	05/2005 - 08/2007	RE: Intervention: RE; Drug: Y90; Site: hepatic artery	67 (34 – 85)	24	0 (0 – 3)	NR

Study N[Θ] (% CRC) Rating	Study Design	Intervention Period	Intervention	Median Age (Range)	Previous Resection	ECOG Score Median (Range)	Previous Local Hepatic Therapy
Hendlisz, et al. 2010[29] 21 (100) Good	RCT[a]	12/2004 - 12/2007	RE with Systemic Chemotherapy: Intervention: RE, Chemotherapy; Drug: Y90, FU; Dose: median 1.79 GBq, range 1.32-2.15 GBq; Site: hepatic artery, IV	62 (46 – 91)	NR	1 (0 – 2)	NR
Kim, et al. 2009[65] 9 (100) Fair	Retrospective case series	06/2004 - 12/2006	SBRT: Intervention: SBRT; Drug: radiation; Dose: median 42 Gy, range 36-51 Gy; Site: noninvasive	57 (35 – 74)	NR	NR (1 – 2)	NR
Cianni, et al. 2009[59] 41 (100) Poor	Retrospective case series	02/2005 - 01/2008	RE: Intervention: RE; Drug: Y90; Dose: mean 1.82 GBq; Site: hepatic artery	NR (33 – 77)	NR	NR	TACE: 4.8; RFA or Cryoablation: 19.5
Mulcahy, et al.2009[70] 72 (100) Fair	Prospective case series	2003 - 2007	RE: Intervention: RE; Drug: Y90; Dose: median 118 Gy; Site: hepatic artery	61 (54 – 86)	NR	NR	NR
Jakobs, et al. 2008[83] 41 (100) Poor	Retrospective case series	10/2003 – 04/2007	RE with Yttrium 90, mean activity delivered was 1.9 GBq (range 0.7-2.8 GBq).	NR	NR	NR	NR
Sato, et al. 2008[72] 137 (37.2) Fair	Prospective case series	2002 - 2006	RE: Intervention: RE; Drug: 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	NR	Local hepatic therapy (unspecified): 16
Veltri, et al. 2008[77] 122 (100) Fair	Prospective case series	03/1996 - 01/2005	RFA: Intervention: RFA; Site: percutaneous and intraoperatively	66.7 (30 – 90)	48.4	NR	RFA: 4.1
Vogl, et al. 2008[78] 55 (21.8) Poor	Retrospective case series	2002 - 2006	HAI: Intervention: HAI; Drug: mitomycin C, gemcitabine; Site: femoral artery	63.5 (54 – 80)	NR	NR	NR
Hong, et al. 2009[62] 21 (100) Fair	Retrospective case series	01/2001 - 03/2006	TACE: Intervention: TACE; Drug: cisplatin, doxorubicin, mitomycin C; Site: femoral artery	67 (32 – 88)	23	NR	Cryoablation:4.8, Radiation:4.8, RFA:9.5
			RE: Intervention: RE; Drug: 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[71] 24 (29.2) Fair	Retrospective case series	07/2004 - 11/2005	SIRT: Intervention: RE; Drug: 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[64] 21 (47.6) Poor	Prospective case series	06/2004 – NR	SIRT: Intervention: RE; Drug: 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

Study N[Θ] (% CRC) Rating	Study Design	Intervention Period	Intervention	Median Age (Range)	Previous Resection	ECOG Score Median (Range)	Previous Local Hepatic Therapy
Fiorentini, et al.2007[61] 20 (100) Poor	Prospective case series	11/2005 - ongoing (06/2007)	TACE with DEB: Intervention: TACE with DEB; Drug: irinotecan; Site: hepatic artery	NR	NR	1 (0 – 2)	NR
Jakobs, et al.2006[63] 68 (100) Fair	Retrospective case series	01/2000 - 06/2004	RFA: Intervention: RFA; Site: percutaneous	(38 – 87)	16	NR	HAI:3, TACE:3
Lewandowski, et al. 2005[67] 27 (100) Poor	Prospective case series	06/2001 - 12/2003	RE: Intervention: RE; Drug: Y90; Dose: range 135-150 Gy; Site: lobar	68 (54 – 86)	NR	0 (0 – 2)	NR
Lim, et al. 2005[68] 30 (100) Poor	Prospective case series	01/2002 - 03/2004	SIRT: Intervention: RE; Drug: Y90	61.7 (36 – 77)	NR	NR	NR

[a] Data from this RCT was abstracted and treated as case series data for the purposes of this review, as the comparator in the RCT was outside the scope.
[Θ] This N reflects the total number of patients enrolled in the study from any primary site. The percentage of colorectal cancer patients included in this report is presented in parentheses.
CRC, colorectal cancer; DEB: Drug-eluting bead; ECOG: Eastern Cooperative Oncology Group; GBq: Gigabecquerel; Gy, Gray RE: Radioembolization; RFA: Radiofrequency ablation; HAI: Hepatic arterial infusion; Mets, Metastases RE, Radioembolization NR: not reported. SBRT: Stereotactic body radiation therapy; SIRT: Selective internal radiotherapy; TACE: Trans-arterial chemoembolization; tx: treatment; Y90: Yttrium 90

Data on tumor characteristics were inconsistently reported across studies and are reported in Table 6. Synchronous or metachronous disease status was reported in nine studies and ranged from 17 to 73 percent synchronous disease.[60, 62, 65, 69, 77, 78, 83, 84] Bilobar or unilobar disease was reported in five studies and ranged from 66.7 percent bilobar disease to 95.1 percent. [59, 60, 62, 67, 70] Nine studies reported liver involvement but with non-uniform measurements.[29, 59, 61, 64, 67, 69-71, 82] Four studies reported mean or median number of hepatic lesions.[63, 65, 69, 76] Six studies reported the mean size of hepatic lesions which ranged from a mean hepatic lesion size of 2.9 to 12cm.[60, 62, 63, 76, 77, 82] Presence of extrahepatic metastases, were reported by six studies and ranged from 33 to 81 percent.[29, 57, 60, 62, 83, 84] While extra hepatic 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 7. Local hepatic therapies for colorectal cancer metastases to the liver: summary of tumor characteristics

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 in cm)	Other Liver Involvement
Aliberti, et al. 2011[82] 82 (100) Fair	NR	NR	33 (25 – 50)	NR	12 (6.5 – 32)	NR
Martin 2011[69] 55 (100) Good	30.9	NR	NR	Median: 4 (1 – 20)	NR	Liver Involvement 50:30.9
Vautravers-Dewas, et al. 2011[76] 42 (66.7) Fair	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[57] 121 (100) Poor	49	NR	NR	NR	NR	Extrahepatic metastasis 56 (46%)
Nace, et al. 2011[81] 51 (100) Fair	NR	NR	NR	NR	NR	NR
Stintzing, et al. 2010[80] 6 (100) Poor	NR	NR	NR	NR	NR	NR
Nishiofuku, et al. 2010[84] 55 (100) Fair	65.5	NR	NR	NR	NR	45 (81.8%) had limited extrahepatic disease
Cosimelli, et al. 2010[60] 50 (100) Fair	72	70	NR	NR	(5 - .8)	≤4 hepatic metastases 21 (42%); >4 hepatic mets. 29 (58%) Liver involvement

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 in cm)	Other Liver Involvement
Hendlisz, et al. 2010[29] 21 (100) Good	NR	NR	100	0	NR	No of liver mets: 1 lesion: 10%, 2 -4 lesions: 48%, ≥5 lesions 38%, not measured 5%.
Kim, et al. 2009[65 a] 9 (100) Fair	55.6	NR	NR	Mean: 1.4 Median: 1 (1 – 2)	NR	NR
Cianni, et al. 2009[59 b] 41 (100) Poor	NR	95.1	NR	NR	NR	Liver involvement 50%: 10 (24.3%)
Mulcahy, et al. 2009[70] 72 (100) Fair	NR	83	NR	NR	NR	Liver replacement ≤25%:78%, Liver replacement 26-50%:19%, Liver replacement ≥50%:3%
Jakobs, et al. 2008[83] 41 (100) Poor	73	NR	NR	NR	NR	17% of patients harbored limited extrahepatic disease
Sato, et al. 2008[72] 137 (37.2) Fair	NR	NR	NR	NR	NR	Tumor burden 0-25%:80%, Tumor burden 26-50%:15%, Tumor burden 51-75:5%
Veltri, et al. 2008[77] 122 (100) Fair	46.7	NR	NR	NR	2.9 (0.5 – 8)	NR
Vogl, et al. 2008[78 c] 55 (21.8) Poor	17	NR	NR	NR	NR	tumor burden 50-75:16.7
Hong, et al. 2009[62] 21 (100) Fair	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
Rowe, et al. 2007[71] 24 (29.2) Fair	NR	NR	25 (3 - 49)	NR	NR	NR
Jiao, et al. 2007[64] 21 (47.6) Poor	NR	NR	NR	NR	NR	Tumor Volume 51%:5
Fiorentini, et al. 2007[61] 20 (100) Poor	NR	NR	40 (20 - 70)	NR	NR	NR
Jakobs, et al. 2006[63] 68 (100) Fair	NR	NR	NR	Mean: 2.7 (1-5)	2.3 (.5 – 5)	NR
Lewandowski, et al. 2005[67] 27 (100)	NR	78	NR	NR	NR	Liver replacement by tumor % ≤25: 78%, 26-50: 19%, >50: 3%

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 in cm)	Other Liver Involvement
Poor						
Lim, et al. 2005[68] 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 colorectal cancer patients included in this report is presented in parentheses.

[A] Total liver tumor volume: median, 72.8ml (3.4-271.1 ml);

[B] All pts 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 (6.6-1,384.4 ml);

Detailed Synthesis

Table 5 displays the outcomes reported. All studies reported overall survival (OS). All studies reported on adverse events, but four aggregated these events by multiple primary cancer sites which did not permit extraction of CRC-specific adverse events.[63, 64, 71, 72] Nine studies also reported progression-free survival.[29, 57, 59, 60, 65, 69, 82, 84, 86] Four studies reported on both liver progression-free survival and overall progression-free survival;[29, 57, 69, 84] no studies reported on liver progression-free survival alone; and the remaining five studies report overall progression-free survival alone.[59, 60, 65, 68, 82] Median time to recurrence was reported in one study;[77] Jakobs et al. (2006)[63] attempted to calculate this statistic but were unable to do so because of the low rate of recurrence (18 %). Two studies reported on length of stay,[57, 61] and two studies also reported on quality of life.[60, 61] Data on the individual outcomes follows save data on liver and overall progression- free survival which is located in Appendix D.

Table 8. Outcomes reported for Key Questions 1 and 2

Study N[Θ] (% CRC) Rating	OS	QOL	TTR	LOS	LR	AE
Albert, et al. 2011[57] 121 (100) Poor	●	NR	NR	●	NR	●
Aliberti, et al. 2011[82] 82 (100) Fair	●	NR	NR	NR	NR	●
Cianni, et al. 2009[59] 41 (100) Poor	●	NR	NR	NR	NR	●
Cosimelli, et al. 2010[60] 50 (100) Fair	●	●	NR	NR	NR	●
Fiorentini, et al. 2007[61] 20 (100) Poor	●	●	NR	●	NR	●
Hendlisz, et al. 2010[29] 21 (100) Good	●	NR	NR	NR	NR	●
Hong, et al. 2009[62] 21 (100) Fair	●	NR	NR	NR	NR	●
Jakobs, et al. 2006[63] 68 (100) Fair	●	NR	●[b]	NR	●	●[b]
Jakobs, et al. 2008[83] 41 (100) Poor	●	NR	NR	NR	NR	●
Jiao, et al. 2007[64] 21 (47.6) Poor	●	NR	NR	NR	NR	●[b]
Kim, et al. 2009[65] 9 (100) Fair	●	NR	NR	NR	●	●
Lewandowski, et al. 2005[67] 27 (100) Poor	●	NR	NR	NR	NR	●

Study N[Θ] (% CRC) Rating	OS	QOL	TTR	LOS	LR	AE
Lim, et al. 2005[68] 30 (100) Poor	●	NR	NR	NR	NR	●
Martin, et al. 2011[69] 55 (100) Good	●	NR	NR	NR	NR	●
Mulcahy, et al. 2009[70] 72 (100) Fair	●	NR	NR	NR	NR	●
Nace, et al. 2011[81] 51 (100) Fair	●	NR	NR	NR	NR	●
Nishiofuku, et al. 2010[84] 55 (100) Fair	●	NR	NR	NR	NR	●
Rowe, et al. 2007[71] 24 (29.2) Fair	●	NR	NR	NR	NR	●
Sato, et al. 2008[72] 137 (37.2) Fair	●	NR	NR	NR	NR	●[b]
Stintzing, et al. 2010[80] 6 (100) Poor	●	NR	NR	NR	●	●
Vautravers-Dewas, et al. 2011[76] 42 (66.7) Fair	●	NR	NR	NR	NR	●
Veltri, et al. 2008[77] 122 (100) Fair	●	NR	●	NR	●	●
Vogl, et al. 2008[78] 55 (21.8) Poor	●	NR	NR	NR	NR	●

[Θ] This N reflects the total number of patients enrolled in the study from any primary site. The percentage of colorectal cancer patients included in this report is presented in parentheses.
[a] Data from this RCT were abstracted and treated as case series data for the purposes of this review, as the comparator in the RCT was outside the scope. [b]Paper reported an outcome of interest but these were grouped with multiple primary presentation sites which could not permit disentangling of CRC specific data;. "●" Indicates that this outcome was reported in the article.
OS: Overall Survival; QOL: Quality of life; TTR: Time to recurrence; LOS: Length of stay; LR: Local recurrence; AE: Adverse events; CRC: colorectal carcinoma; NR: not reported

Overall Survival

All studies reported on outcomes related to overall survival (Table 8, which is organized by intervention). Two studies used RFA as a local hepatic therapy for CRC liver metastases and reported survival from different time points. Veltri, et al. (2008)[77] found a mean survival of 48.3 months with a median of 38.3 months and measured survival from diagnosis of liver metastases. Jakobs, et al. (2006)[63] did not report mean or median survival measures but reported 1, 2 and 3 years survival of 96 percent, 71 percent and 68 percent respectively from time of study treatment. Three studies in our report used TACE with drug-eluting beads. Median survival was

reported by two[69, 82] studies and ranged from 19 to 25 months from study treatment. Florentini, et al. (2007) reported only 1 year survival of 61 percent.[61] Two studies in our report reported on TACE alone.[57, 62] Both studies reported median survival from time of liver metastases diagnosis which ranged from 26.3 to 27 months. Twelve studies of radioembolization with yttrium 90 were included in this review.[29, 59, 60, 62, 64, 67, 68, 70-72, 81, 83] One of these studies involved systemic chemotherapy in addition to radioembolization and is not presented in this summation of results.[29] Six studies reported survival from study treatment and had a median survival that ranged from 4 to 15.2 months.[64, 67, 71, 72, 81, 83] Three studies reported survival from diagnosis of liver metastases and ranged from a median of 31 to 34.6 months.[60, 62, 70] Two studies lacked an explanation of from what time survival was measured.[59, 68] HAI was used in two studies in our review [78, 84] both reported median survival from study treatment with a range of 6.7 to 9.7 months.[78, 84] Three studies reported SBRT in this review and all defined survival from time of study treatment.[65, 76, 80] Median values were reported in two studies and ranged from 17 to 25 months[65, 80] The other study only reported 1 and 2 year survival of 95 percent and 58 percent respectively.[76]

Direct comparisons of overall survival cannot be made from the published data as there are no comparative studies.

Quality of Life

Two studies reported on quality of life.[60, 61] 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, EORTC QLQ LMC-21);[60] 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 into 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 radioembolization 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 whether this was the quality of life assessment tool is not clear.

Length of Stay

Mean length of stay was reported by two studies[57, 61] both of TACE and ranged from 1.3 to 3 days. No direct comparisons can be made based on the published evidence as there are no comparative 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. Two RFA studies reported local recurrence and gave rates of 18 and 26.3 percent.[63, 77] Local recurrence was also reported in two studies of SBRT both of which reported a rate or 33.3 percent.[65, 80]

Adverse Events

Twenty-three 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.[61] Liver failure was reported in three studies, two RE[59, 60] and one[69] TACE with DEB intervention. Biloma was reported in one RFA study[77]. Two studies -- one TACE[57] intervention and one RE[70] -- reported increased alkaline phosphatase levels. Increased bilirubin was reported in 5 studies, one TACE with DEB[82], one TACE[57], two RE[70, 83], and one HAI[84] intervention. Increased transaminase levels were reported in one RE article[70] that also reported on increased bilirubin and alkaline phosphatase levels. While increased liver functions tests could point to disease progression, in the time period following a local hepatic therapy they are more likely to reflect adverse effect of the treatment. Only Aliberti, et al. reported liver function test results immediately after treatment.[82] Other liver function tests were evaluated as acute or late toxicity[70, 83] or did not report[57, 84] when the adverse events were evaluated. Two authors indicated that liver function toxicity was likely a result of progressive disease or biliary obstruction.[70, 83] A TACE with DEB study reported 1 death from myocardial infarction[69] and a TACE study reported a thirty day morality of 3.6 percent.[57] A description of rare adverse events is located in Table 9. No study reported on injury to adjacent organs, hepatic hemorrhage, or steatohepatitis.

Table 9. Local hepatic therapies for colorectal cancer metastases to the liver: outcomes related to overall survival

Intervention	Survival Time from	Mean Overall Survival Median Overall Survival (95% CI)	% Survival Year 1	% Survival Year 2	% Survival Year 3	% Survival Year 5	Study N[Θ] (% CRC) Rating
RFA	Diagnosis of liver Mets	Mean: 48.3 Median: 38.3 (32.7 to 54.7)	91	71	54	33	Veltri, et al. 2008[77e] 122 (100) Fair
	Study Treatment	NR	96	71	68	NR	Jakobs, et al. 2006[63f] 68 (100) Fair
TACE with DEB: Intervention: TACE with DEB; Drug: irinotecan	Study Treatment	Median: 25	~78	~52	~21	NR	Aliberti, et al. 2011[82] 82 (100) Fair
	Study Treatment	Median: 19	75	NR	NR	NR	Martin, et al. 2011[69a] 55 (100) Good
	NR	NR	61*	NR	NR	NR	Fiorentini, et al. 2007[61b] 20 (100) Poor
TACE: Intervention: TACE; Drug: mitomycin C, doxorubicin, cisplatin	Diagnosis of liver Mets	Median: 27	85	55	NR	6	Albert, et al. 2011[57 a] 121 (100) Poor
TACE: 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[62] 21 (100) Fair
RE: Intervention: RE; Drug: Y90	Study Treatment	Mean: 14.4 Median: 10.2 (7.5 to 13.0)	NR	NR	NR	NR	Nace, et al. 2011[81] 51 (100) Fair
	Diagnosis of liver Mets	Median: 31 (29 to 34)	50.4	19.6	NR	NR	Cosimelli, et al. 2010[60 b] 50 (100) Fair
	NR	Median: 11.8	NR	NR	NR	NR	Cianni, et al. 2009[59 b] 41 (100) Poor
	Diagnosis of liver Mets	Median: 34.6 (24.4 to 41.8)	NR	NR	NR	17.7	Mulcahy, et al. 2009[70] 72 (100) Fair
	Study Treatment	Mean: 13.9 Median: 15.2	53.7	26.7	NR	NR	Sato, et al. 2008[72 b] 137 (37.2) Fair
	Diagnosis of liver Mets	Median: 32.8	NR	NR	NR	NR	Hong, et al. -2009[62 a] 15 (100) Fair
	Study Treatment	Median: 10.5	~40	~27	~16	NR	Jakobs, et al. 2008[83] 41 (100) Poor

Intervention	Survival Time from	Mean Overall Survival Median Overall Survival (95% CI)	% Survival Year 1	% Survival Year 2	% Survival Year 3	% Survival Year 5	Study N[Θ] (% CRC) Rating
	Study Treatment	Median: ~4[g]	~23[g]	14.3	NR	NR	Jiao, et al. 2007[64] [d] 21 (47.6) Poor
	Study Treatment	Mean: 11.1 Median: 9	~27[g]	~20[g]	NR	NR	Rowe, et al. 2007[71] [b] 24 (29.2) Fair
	NR	NR	~20[g]	NR	NR	NR	Lim, et al. 2005[68] 30 (100) Poor
	Study Treatment	Median: 9.4 (7.3 to 13.5)	NR	NR	NR	NR	Lewandowski, et al. 2005[67] [c] 27 (100) Poor
RE with Systemic Chemotherapy: Intervention: RE, Chemotherapy; Drug: Y90	Randomization	Median: 10	NR	NR	NR	NR	Hendlisz, et al. 2010[29] [b] 21 (100) Good
HAI: Intervention: HAI; Drug: mitomycin C, gemcitabine;	Study Treatment	Median: 9.7	~48[g]	~30[g]	NR	NR	Vogl, et al. 2008[78] [a] 55 (21.8) Poor
HAI of 5-FU 1000mg/m^2	Study Treatment	Median: 6.7 (5 to 8.3)	~18	~5	NR	NR	Nishiofuku, et al. 2010[84] 55 (100) Fair
SBRT: Intervention: SBRT; Drug: radiation; Dose: 40 Gy and 45 Gy; Site: noninvasive	Study Treatment	NR	~95[g]	58	NR	NR	Vautravers-Dewas, et al. 2011[76] 42 (66.7) Fair
	Study Treatment	Median: 25	53	40	40	NR	Kim, et al. 2009[65] 9 (100) Fair
SBRT: Intervention: SBRT; Drug: 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[80] 6 (100) Poor

CI: Confidence interval; CRC, colorectal cancer; Gy, Gray RE: Radioembolization; HAI: Hepatic arterial infusion; Mets, Metastases RE, Radioembolization NR, not reported. SBRT: Stereotactic body radiation therapy; TACE: Trans-arterial chemoembolization

[Θ] This N reflects the total number of patients enrolled in the study from any primary site. The percentage of colorectal cancer 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 because.

Table 10. Local hepatic therapies for unresectable colorectal cancer metastases to the liver: adverse events

Intervention	Local Recurrence N (%)	Biloma %	Liver failure %	Increased Alkaline Phosphatase N (%)	Increased Bilirubin N (%)	Rare Adverse Events	Study N$^{\Theta}$ (% CRC) Rating
RFA	(26.3)	0.8	NR	NR	NR	1 (.8%) segmental biliary dilation followed by cholangitis and subsequent biliobronchial fistula	Veltri, et al. 2008[77] 122 (100) Fair
	(18)	NR	NR	NR	NR	No major complications	Jakobs, et al. 2006[63] 68 (100) Fair
TACE with DEB: Intervention: TACE with DEB; Drug: irinotecan;	NR	NR	NR	NR	41 (50)	NR	Aliberti, et al. 2011[82] 82 (100) Fair
	NR	NR	3	NR	NR	All AE are from the number of DEB treatments (99) not from the total 55 pts. 3% of patients had severe liver dysfunction with 1 patient dead. 1% had cholecystitis, 1% had gastritis, and 1% had myocardial infarction which was a cause of death in 1 patient.	Martin, et al. 2011[69] 55 (100) Good
	NR	NR	NR	NR	NR	liver abscess: 5% (1 pt)	Fiorentini, et al. 2007[61] 20 (100) Poor
TACE: 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 4, hematoma at the site of catheterization 3, infection 3, acute edema 2, myocardial infarction 2, pulmonary embolism 1, transient ischemic attack 1, hypoxia, 1, abnormal heart rhythm 1. Thirty day mortality was 3.6%	Albert, et al. 2011[57] 121 (100) Poor
TACE: 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[62] 21 (100) Fair
RE: Intervention: RE; Drug: Y90	NR	NR	0	NR	NR	Ventricular tachycardia: 1 (2%)	Nace, et al. 2011[81] 51 (100) Fair
	NR	NR	2	NR	NR	NR	Cosimelli, et al. 2010[60] 50 (100) Fair
	NR	NR	2.4	NR	NR	NR	Cianni, et al. 2009[59] 41 (100) Poor
	NR	NR	NR	6 (8)	9 (13)	GI ulcer	Mulcahy, et al. 2009[70] 72 (100)

Intervention	Local Recurrence N (%)	Biloma %	Liver failure %	Increased Alkaline Phosphatase N (%)	Increased Bilirubin N (%)	Rare Adverse Events	Study N[Θ] (% CRC) Rating
							Fair
	NR	Non-specific to CRC	NR	NR	Non-specific to CRC	Sato, et al. 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, 1 hepatic abscess.	Sato, et al. 2008[72b] 137 (37.2) Fair
	NR	NR	NR	NR	NR	1 (2.7%) pulmonary embolism	Hong, et al. 2009[62] 15 (100) Fair
	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[83] 41 (100) Poor
	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[86] 30 (100) Poor
	NR	NR	NR	NR	NR	Jiao, et al. included non-CRC patients in this article and did not report specific adverse events for CRC mets. to the liver. 4 rare adverse events occurred post SIRT: 1 pt. developed 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[64b] 21 (47.6) Poor
	NR	NR	NR	NR	NR	Toxicity data was only available for 14 of 24 patients and not reported specifically for CRC mets. to the liver. 1 patient had a symptomatic gastric ulcer post surgery and 1 patient had a femoral artery plaque rupture with thromboembolism in the lower extremity.	Rowe, et al. 2007[71 b] 24 (29.2) Fair
	NR	NR	NR	NR	NR	1 case of radiation-induced ulceration caused by technical error.1 case of right plural effusion 1 month. after treatment.	Lewandowski, et al. 2005[67] 27 (100) Poor
RE with Systemic Chemotherapy: Intervention: RE, Chemotherapy; Drug: Y90,	NR	NR	NR	NR	NR	1 pt. with grade 3 hand-foot syndrome	Hendlisz, et al. 2010[29] 21 (100) Good
HAI: Intervention: HAI; Drug: mitomycin C,	NR	NR	NR	NR	NR	No common toxicity criteria grade III, IV or V adverse events were observed.	Vogl, et al. 2008[78 a] 55 (21.8)

Intervention	Local Recurrence N (%)	Biloma %	Liver failure %	Increased Alkaline Phosphatase N (%)	Increased Bilirubin N (%)	Rare Adverse Events	Study N[Θ] (% CRC) Rating
gemcitabine;							Poor
HAI of 5-FU 1000mg/m^2	NR	NR	NR	NR	1 (1.8)	NR	Nishiofuku, et al. 2010[84] 55 (100) Fair
SBRT: Intervention	2 (33.3%)	NR	NR	NR	NR	NR	Stintzing, et al. 2010[80] 6 (100) Poor
	NR	NR	NR	NR	NR	1 pt. had cirrhotic failure at 5 months. 1 patient had gastic ulceration. 1 patient had esophagitis. 1 patient had grade 3 epidermitis. No grade 4 toxicity was observed.	Vautravers-Dewas, et al. 2011[76] 42 (66.7) Fair
	3 (33.3%)	NR	NR	NR	NR	No grade 3 or 4 acute complications	Kim, et al. 2009[65] 9 (100) Fair

[Θ] This N reflects the total number of patients enrolled in the study from any primary site. The percentage of colorectal cancer patients included in this report is presented in parentheses.
CE: Chemoembolization; DEB: Drug-eluting beads; HAI: Hepatic arterial infusion; NR, not reported; RE: Radioembolization; SBRT: Stereotactic body radiation therapy TACE: Trans-arterial chemoembolization;
[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;

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 seven case series[57, 67, 70, 72, 77, 83, 84] 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 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), RECIST (Response Evaluation Criteria in Solid Tumors).

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 that met inclusion criteria for this review.
- The literature base is comprised of case series and one RCT[79] that was abstracted as single-arm study due to a non-relevant comparator for this review. Two studies were ranked as good quality,[74, 79] three as fair,[58, 66, 73] and one as poor.[75]
- 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 and dose and drugs delivered)

Description of Included Studies

Table 10, Table 11 and Table 12 show the study and patient characteristics including 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. Six studies were included, [58, 66, 73-75, 79] five of which were case series. One randomized, controlled trial[79] was included in the review but was abstracted as a single-arm study as the comparator, systemic chemotherapy, was an intervention outside the scope of this review. Of the five case series three were prospective[58, 74, 75] and two were retrospective.[66, 73] The total number of patients for which data was abstracted from the five studies was 268. Two studies included patients treated with RE with concurrent systemic chemotherapy;[58, 66] two articles reported on RFA with chemotherapy;[74, 79] and two reported on patients treated with HAI and systemic chemotherapy.[73, 75] All studies treated patients after January 1, 2000.

Patients ranged in age from 31-84 years, but were generally in their sixties. One study reported ECOG score with a median value of 0 and a range of 0 to 2.[58] Two studies reported rates of resection for previous CRC liver metastases of 15 and 27 percent,[58, 79] and three[58, 66, 74] reported the proportion of patients who had received prior systemic chemotherapy which ranged from 0 to 94 percent. One study[58] 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 two studies[66, 79], bilobar or unilobar disease reported in one study[58], degree liver involvement was reported by three studies,[58, 66, 73] number of hepatic lesions was reported by two studies[74, 79] and one study also reported lesion size.[74] The details of these characteristics are presented in Table 12).

Table 11. Local hepatic therapies adjunctive to systemic chemotherapy for colorectal cancer metastases to the liver: summary of study characteristics

Study N[Θ] (% CRC) Rating	Study Design	Intervention Period	Intervention
Ruers, et al. 2012[79] 60 (100) Good	RCT[a]	04/2002-06/2007	RFA and systemic treatment with 5-FU/L/oxaliplatin with bevacizumab added post 10/2005
Kosmider, et al. 2011[66] 19 (100) Fair	Retrospective case series	01/2002 - 10/2008	RE with concurrent Systemic Chemotherapy: Intervention: RE, systemic chemotherapy; Drug: Y90, FOLFOX or 5-FU; Dose: median 1.96 GBq, mean 2.08 GBq, range 1.60-2.60 GBq; Site: hepatic artery
Sgouros, et al. 2011 [74] 13 (100) Good	Prospective case series	09/2000 - 08/2004	RFA and chemotherapy: Intervention: RFA, systemic chemotherapy; Drug: FOLFIRI; Site: percutaneous
Chua, et al. 2011[58] 140 (100) Fair	Prospective case series	03/2006 - 05/2009	RE with systemic chemotherapy: Intervention: RE; Drug: Y90; Dose: mean 1.8 GBq, median 1.8 GBq, range 0.4-2.6 GBq; Site: femoral or brachial artery
Seki 2009[73] 20 (100) Fair	Retrospective case series	07/2004 - 01/2008	HAI followed by systemic chemotherapy: Intervention: HAI, systemic chemotherapy; Drug: 5-FU, FOLFOX4 or FOLFOX6; Site: hepatic artery, IV
Tsutsumi, et al. 2008 [75] 16 (100) Poor	Prospective case series	08/2003 - 09/2006	HAI with concurrent systemic chemotherapy: Intervention: HAI, systemic chemotherapy; Drug: 5-FU and l-leucovorin, UFT and UZEL; Site: femoral artery, oral

[Θ] This N reflects the total number of patients enrolled in the study from any primary site. The percentage of colorectal cancer patients included in this report is presented in parentheses.
[a] Data from this RCT were abstracted and treated as case series data for the purposes of this review, as the comparator in the RCT was outside the scope.
RE: Radioembolization; RFA: Radiofrequency ablation; HAI: Hepatic arterial infusion; 5-FU: 5-florouracil; UFT: tegafur-uracil ; UZEL: UFT and leucovorin

Table 12. Local hepatic therapies adjunctive to systemic chemotherapy for colorectal cancer metastases to the liver: summary of patient characteristics

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[79] 60 (100) Good	RCT[a]	64 (31 – 79)	15	NR	NR	NR
Kosmider, et al. 2011[66] 19 (100) Fair	Retrospective case series	62 (44 – 75)	NR	NR	0	NR
Sgouros, et al. 2011[74] 13 (100) Good	Prospective case series	77 (47 – 84)	NR	NR	76.9	NR
Chua, et al. 2011[58] 140 (100) Fair	Prospective case series	64 (37 – 85)	27	0 (0-2)	94	SIRT: 66%, Ablation 6%
Seki 2009[73] 20 (100) Fair	Retrospective case series	49	NR	NR	NR	NR
Tsutsumi, et al. 2008[75] 16 (100) Poor	Prospective case series	62 (43 – 74)	NR	NR	NR	NR

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

Table 13. Local hepatic therapies adjunctive to systemic chemotherapy for colorectal cancer metastases to the liver: summary of tumor characteristics

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[79] 60 (100) Good	38.3	NR	NR	4 (1 – 9)	NR	NR	NR
Kosmider, et al. 2011[66] 19 (100) Fair	95	NR	40 (25 - 65)	NR	NR	NR	NR
Sgouros, et al. 2011[74] 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[58] 140 (100) Fair	NR	90	NR	NR	NR	NR	%liver involvement 0-25% (55%); 26-50 (36%); 51-75 (9%)
Seki, et al. 2009[73] 20 (100) Fair	NR	NR	NR	NR	NR	NR	Liver involvement ≤60%:85, Liver involvement >60%:15
Tsutsumi, et al. 2008 [75] 16 (100) Poor	NR	NR	NR	NR	NR	NR	NR

[Θ] This N reflects the total number of patients enrolled in the study from any primary site. The percentage of colorectal cancer patients included in this report is presented in parentheses.
CRC: Colorectal cancer; NR: not reported

Detailed Synthesis

Table 13 displays the outcomes reported by study for KQ 3 and 4. All studies reported overall survival (OS) and adverse events. Four studies reported on overall progression free survival.[66, 73, 74, 79] Local recurrence was reported in two studies.[58, 79] One study reported on quality of life.[60, 61, 79] Data on the individual outcomes follows save data on overall progression-free survival which is located in Appendix D. No study reported on median time to recurrence, length of stay, or liver progression free survival.

Table 14. Outcomes reported for Key Questions 3 and 4

Study N[Θ] (% CRC) Rating	OS	QOL	LOS	TTR	LR	AE
Ruers, et al. 2012[79] 60 (100) Good	●	●	NR	NR	●	●
Kosmider, et al. 2011[66] 19 (100) Fair	●	NR	NR	NR	NR	●
Sgouros, et al. 2011[74] 13 (100) Good	●	NR	NR	NR	NR	●
Chua, et al. 2011[58] 140 (100) Fair	●	NR	NR	NR	●	●
Seki 2009[73] 20 (100) Fair	●	NR	NR	NR	NR	●
Tsutsumi, et al. 2008[75] 16 (100) Poor	●	NR	NR	NR	NR	●

[Θ] This N reflects the total number of patients enrolled in the study from any primary site. The percentage of colorectal cancer patients included in this report is presented in parentheses.
OS: Overall Survival; QOL: Quality of life; LOS: Length of stay; TTR: Time to recurrence; LR: Local recurrence; AE: Adverse events
"●" 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 as there are no comparative studies.

RFA was performed in two studies as an adjunct to systemic chemotherapy for unresectable CRC liver metastases.[74, 79] Ruers, et al. (2012) reported median survival of 45.3 months from time of randomization and Sgouros, et al. (2011) reported a median survival of 24 months of 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.[58, 66] HAI as an adjunct to systemic chemotherapy was reported on in two studies. In both studies the authors did not report from when survival time was measured.[73, 75] Survival ranged from 22 to 30.1 months.

Quality of Life

One study by Ruers and colleagues[79] 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 six 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 as there are no comparative studies.

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. Two RFA studies reported local recurrence between 45 and 81.3 percent.[58, 79]

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.[66, 74] Increased bilirubin was reported in two studies[66, 79] and elevated alkaline phosphatase and transaminases in one.[66] Kosmider, et al. [29] reported elevated liver function test levels within 60 days post treatment not related to progressive disease which normalized shortly thereafter, and Ruers, et al.[42] did not report when the patients had hepatic dysfunction due to elevated bilirubin levels. Local recurrence was reported by two studies.[58, 79] A single post-operative death was reported by both RFA studies.[74, 79] No direct comparisons can be made based on the published evidence as there are no comparative studies.

Table 15. Local hepatic therapies for colorectal cancer metastases to the liver: outcomes related to overall survival for patients receiving local hepatic therapy as an adjunct to systemic therapy

Intervention	Survival Time from	Median OS (95% CI)	% Survival Year 1	% Survival Year 2	% Survival Year 3	Study N[Θ] (% CRC) Rating
RE with concurrent Systemic Chemotherapy: Intervention: RE, systemic chemotherapy; Drug: Y90, FOLFOX or 5-FU; 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 [66] 19 (100) Fair
RE with systemic chemotherapy: Intervention: RE; 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 [58] 140 (100) Fair
RFA and chemotherapy: Intervention: RFA, systemic chemotherapy; Drug: FOLFIRI; Site: percutaneous	Study Enrollment	24 (17 to 31.1)	NR	NR	NR	Sgouros, et al. 2011 [74] 13 (100) Good
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[79] 60 (100) Good
HAI followed by systemic chemotherapy: Intervention: HAI, 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[73] 20 (100)
HAI with concurrent systemic chemotherapy: Intervention: HAI, 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 [75] 16 (100) Poor

[Θ] This N reflects the total number of patients enrolled in the study from any primary site. The percentage of colorectal cancer patients included in this report is presented in parentheses.
[A] Survival estimates were approximated by the EPC from survival curves presented in the manuscript.
CRC: Colorectal cancer; NR: Not reported; OS: Overall survival; RE: Radioembolization; RFA: Radiofrequency ablation; GBq (gigabecquerel)

Table 16. Local hepatic therapies for unresectable colorectal cancer metastases to the liver: adverse events for patients receiving local hepatic therapy as an adjunct to systemic therapy

Intervention	Local Recurrence N (%)	Injury to organs %	Liver failure %	Increased Alkaline Phosphatase N (%)	Increased Bilirubin N (%)	Rare AE	Study N[Θ] (% CRC) Rating
RE with concurrent Systemic Chemotherapy: Intervention: RE, systemic chemotherapy; Drug: Y90	NR	5.3	5.3	5 (26.3)	5 (26.3)	AE include extra-hepatic metastases. 1 (5.3%) treatment-related death from hepatic failure (presumed to be radiation hepatitis). Gastroduodenitis was present in 3 patients (15.8%). 1 (5.3%) grade 3 anorexia was observed.	Kosmider, et al. 2011 [66] 19 (100) Fair
RE with systemic chemotherapy: Intervention: RE; Drug: 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 [58] 13 (100) Fair
RFA and chemotherapy: Intervention: RFA, systemic chemotherapy; Drug: FOLFIRI; Site: percutaneous	(81.3)	NR	NR	NR	NR	One patient discontinued chemotherapy early as he developed bacterial endocarditis requiring a prolonged course of antibiotics. Another patient died suddenly during treatment. The cause of death was determined post-mortem as acute cardiomyopathy and was thought to be related to 5-fluorouracil toxicity.	Sgouros, et al. 2011 [74] 140 (100)
RFA with concurrent systemic chemotherapy: Intervention: RFA, 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%), Post-operative 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[79] 60 (100) Good
HAI followed by systemic chemotherapy: Intervention: HAI, systemic chemotherapy; Drug: 5-FU, FOLFOX4 or FOLFOX6	NR	NR	NR	NR	NR	1 pt. resected post HAI. 1 pt discontinued treatment during HAI therapy due to grade 3 hypersensitivity and sensory neuropathy. No Grade 4 toxicity.	Seki, et al. 2009 [73] 20 (100)
HAI with concurrent systemic chemotherapy: Intervention: HAI, 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 reported. No hematologic toxicity encounterd.	Tsutsumi, et al. 2008 [75] 16 (100) Poor

[Θ] This N reflects the total number of patients enrolled in the study from any primary site. The percentage of colorectal cancer patients included in this report is presented in parentheses.
AE: Adverse Event; CE: Chemoembolization; DEB: Drug-eluting beads; NR: Not reported; RE: Radioembolization; TACE: Trans-arterial chemoembolization; HAI: Hepatic arterial infusion; SBRT: Stereotactic body radiation therapy

Multivariate Analyses

Relevant univariate or multivariate analyses of prognostic factors for overall survival and including but not limited to ECOG score, presence of extra hepatic disease, treatment response, were reported in one single-arm study[51] 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 extra hepatic disease (no vs. yes) and treatment response (unfavorable vs. favorable). While these analyses may be hypothesis generating they do not address comparative benefit of radiotherapy techniques.

Overall Conclusions for Key Questions 1-4

- The body of evidence 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 and overall survival is insufficient.
- The body of evidence 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 is insufficient.
- 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 and dose and drugs delivered).

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

Discussion

Key Findings and Strength of Evidence

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

We assessed the Strength of Evidence (SOE) for: our primary health outcomes of overall survival and quality of life; for the intermediate outcomes of length of stay, local recurrence, and adverse events for all Key Questions (KQs). In addition SOE was assessed for the intermediate outcomes of time to progression (KQ 1&2) and time to recurrence (KQ 3&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 patients considered for all KQs (Table 16 and Table 17). The body of evidence contained no comparative studies and thus provided no direct evidence about differences by type of intervention.

Table 17. Strength of Evidence for KQ1 and KQ2

Outcome	Intervention	No of Studies[§]	Risk of Bias	Consistency	Directness*	Precision	Overall Grade
Overall Survival	TACE with DEB	3[61, 69, 82]	High	Not applicable	Direct	Imprecise	Insufficient
	TACE	2[57, 62]	High	Not applicable	Direct	Imprecise	Insufficient
	SBRT	3[65, 76, 80]	High	Not applicable	Direct	Imprecise	Insufficient
	HAI	2[78, 84]	High	Not applicable	Direct	Imprecise	Insufficient
	RE	14[29, 59, 60, 62-64, 67, 68, 70-72, 81, 83, 86]	High	Not applicable	Direct	Imprecise	Insufficient
	RFA	2[63, 77]	High	Not applicable	Direct	Imprecise	Insufficient
Quality of Life	TACE with DEB	1[61]	High	Not applicable	Direct	Imprecise	Insufficient
	RE	1[60]	High	Not applicable	Direct	Imprecise	Insufficient
Length of Stay	TACE	2[57, 61]	High	Not applicable	Indirect	Imprecise	Insufficient
Time to Progression	None	0	High	Not applicable	Indirect	Imprecise	Insufficient
Local Recurrence	SBRT	2[65, 80]	High	Not applicable	Indirect	Imprecise	Insufficient
	RFA	2[63, 77]	High	Not applicable	Indirect	Imprecise	Insufficient
Adverse Events	TACE with DEB	3[61, 69]	High	Not applicable	Direct	Imprecise	Insufficient
	TACE	2[57, 62]	High	Not applicable	Direct	Imprecise	Insufficient
	SBRT	3[65, 76, 80]	High	Not applicable	Direct	Imprecise	Insufficient
	HAI	2[78, 84]	High	Not applicable	Direct	Imprecise	Insufficient
	RE	14[29, 59, 60, 62-64, 67, 68, 70-72, 81, 83, 86]	High	Not applicable	Direct	Imprecise	Insufficient
	RFA	2[63, 77]	High	Not applicable	Direct	Imprecise	Insufficient

* Directness: evidence is indirect for all comparisons as there is no comparative data but direct for assessment of some health outcomes. [§] the article by Hong, et al., applies to both DEB: Drug-eluting beads; HAI: Hepatic arterial infusion; RE: Radioembolization; SBRT: Stereotactic body radiation therapy TACE: Trans-arterial chemoembolization;

Table 18. Strength of Evidence for KQ3 and KQ4

Outcome	Adjunctive therapy	No of Studies[§]	Risk of Bias	Consistency	Directness*	Precision	Overall Grade
Overall Survival	RFA	2[74, 79]	High	Not applicable	Direct	Imprecise	Insufficient
	RE	2[58, 66]	High	Not applicable	Direct	Imprecise	Insufficient
	HAI	2[73, 75]	High	Not applicable	Direct	Imprecise	Insufficient
Quality of Life	RFA	1[74, 79 74]	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	2[58, 79]	High	Not applicable	Indirect	Imprecise	Insufficient
Adverse Events	RFA	2[74, 79]	High	Not applicable	Direct	Imprecise	Insufficient
	RE	2[58, 66]	High	Not applicable	Direct	Imprecise	Insufficient
	HAI	2[73, 75]	High	Not applicable	Direct	Imprecise	Insufficient

* Directness: evidence is indirect for all comparisons as there is no comparative data but direct for assessment of some health outcomes.RE: Radioembolization; HAI: Hepatic arterial infusion; 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, as the literature base does not contain studies comparing one local hepatic therapy to 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.[87-91] Earlier reviews conforming to a high quality standard reach conclusions similar to the present review: evidence is insufficient to permit conclusions.[30, 92]

The strength of this present review is that it addresses all local hepatic therapies for the included indications. In addition, it also recognizes that distinct patient groups exist within the population receiving local hepatic therapies. 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

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 represents the patient population 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.[93]

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 is uncertain. 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. In many centers, the choice of a local hepatic therapy may be limited to one option, because of the available clinical expertise and the technology. Local hepatic therapies often require high levels of training and familiarity with the procedure, as with radioembolization[94] and hepatic arterial infusion.[95] Lack of experience may not only affect 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 through the published literature.

Interventions

Even for a single local hepatic therapy, variation in how the procedure is performed may be substantial. For instance, the variation may be in the approach (open versus percutaneous); it may be in the choice of chemotherapy drugs delivered and the schedule of delivery of chemotherapy and radiation therapy. Given the limited evidence base, 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. The complex treatment history of each patient can further limit the conclusions that can be drawn about the benefit attributable to any one component of the treatment plan.

Comparators

All studies in this review are observational (including the single-arm trial); 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. The applicability of any case series to another group is very limited.

Timing

The timing of followup assessment was appropriate given the natural history of unresectable CRC liver metastases and the primary outcome of overall survival.

Outcomes

Little controversy exists as to 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 is reported in all of the studies included in this review. The utility 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 that may be attributed to a local hepatic therapy.

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 non-comparative nature of the literature base both clinicians and policy makers are limited in their ability to apply the published literature base to decisions on effectiveness and comparative effectiveness of these interventions. Studies of local hepatic therapies suggest that for selected patient groups local hepatic therapies may provide some benefit in terms of survival and symptom relief, but without comparative data choosing which therapy will produce the best outcomes for which patients is not possible.

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. While 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 single arm 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 be choosing from many treatment options. The evaluation of the quality of the body of literature to assess our KQ's and the identification of research needs is a contribution 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 lesion. 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.

Due to the single arm design of the included studies, there is a high potential for confounding and effect measure modification to obscure the true effectiveness of the interventions within the population. 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 and performance status.

Research Gaps

In this section on research gaps, we first present a set of gaps focused on issues in the body of literature. Then we discuss the use of randomized clinical trials 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; strength of evidence is insufficient to permit us to draw conclusions on outcomes for either patient population.

We identified four broad evidence gaps during this review:

- There is a dearth evidence collected and reported in the included literature on quality of life. These data are particularly important for the population of patients where palliation of symptoms, rather than cure, is the intent of therapy. Collection and reporting of quality of life data (e.g. pain) using standard measurement tools.
- 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.
- An objective of comparative effectiveness research is to understand the comparative effects for different population subgroups. First we must fully delineate the population subgroups of interest. To accomplish this systematic definition of patient subgroups is required. Further studies must present data by these subgroups so that evidence can be interpreted by these variables. Examples of relevant variables are number and size of hepatic lesions, and performance status. With so many variables being collated clinical risk scores may be particularly beneficial as a summary measure. [96]
- 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, as these therapies may have an effect on the survival of the patient,

should be taken into account when evaluating the effectiveness of the intervention under study. Previous resections and other local hepatic therapies were often not reported in the studies included in this review.

Study Designs to Address these Gaps

RCT's are the gold standard of clinical evaluation and there is an absence of randomized clinical evidence on the use of these therapies for the included indications. Unable to find evidence to answer any of our key questions, we conducted additional discussions with members of our Technical Expert Panel (TEP) to elicit ideas addressing the gaps in the literature. TEP members identified common barriers to conducting randomized controlled trials (RCTs) for these questions. Among these are challenges common to many research areas including: limited sources of adequate research dollars to support RCTs, reluctance of physicians to randomize patients, and the reluctance of patients to be randomized.

More important than the resistance to randomize is the lack of willing funding sources and the presentation of a fundable research question. 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 that are often based on their own institutional experience. In discussions with TEP members they agreed that certain broad categories of patients with CRC metastasis to the liver, such as the population included in this review, may well benefit from local hepatic therapies, and that the published literature did not permit parsing patient subgroups to identify characteristics more favorable to one local hepatic therapy over another. RCT's with well documented patient and treatment characteristics could address the lack of well described comparative evidence.

Regardless of the study design we suggest that studies aiming to address the effectiveness or comparative effectiveness 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 a modifier of the effectiveness and a factor used to choose the local hepatic therapy.

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

Patient Registries

In the absence of consensus around the most salient comparative research question observational data could be useful in driving the generation and prioritization of hypotheses for future research. One approach to this is the use of a registry to systematically collect observational data for future research. 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 and disease natural history and management under varied 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 exposures 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 comparative effectiveness review could serve as guide for one or more registries focused on this clinical area. The aim would be to establish a prospective registry that tracks 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. Although not a key question for this review, TEP members also indicated that the experience of the one provider of the local hepatic therapy would also be important for 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 19. Core dataset elements for local hepatic therapy registry by PICOTS

Population	Intervention	Comparators	Outcomes	Timing	Setting
Patient Characteristics	**Type of local hepatic therapy**	Same as Intervention	Overall survival	Ongoing	Hospital type
Age	Cryosurgical ablation		Quality of life		Number of procedures by practitioner
Sex	RFA		Response (e.g. complete, partial, no response)		Type of practitioner
Race	Microwave ablation		Recovery time		Local hepatic therapy availability
Ethnicity	TAE		Length of Stay		Inpatient or outpatient procedure
Performance status	TACE		Adverse effects (Short-term and long-term harms		
LDH	HAI		Treatment holidays*		
CEA	RE				
Clinical risk scores (e.g., Fong)[96]	DEB				
Tumor characteristics	3D-CRT				
Location of tumor	IMRT				
Size of lesions	SBRT				
Number of lesions	**Characteristics of local hepatic therapy**				
Tumor volume	Dose				
Portal vein obstruction	Duration				
Course of disease(stabilization, rapid progression)	Surgical site				
Other treatments					
Number, dose, duration, for lines of prior therapy by drug					
Number, dose, duration for lines of adjunctive therapy by drug					
Previous liver-directed therapy					

* Treatment holidays refer to time away from systemic chemotherapy and may result from successful treatment with a local hepatic therapy. of LDH: lactate dehydrogenase; CEA: carcinoembryonic antigen: RFA: Radiofrequency ablation; TAE: Transarterial embolization; TACE: transarterial chemoembolization; HAI: Hepatic artery infusion; RE: Radioembolization; DEB: Drug-eluting bead; 3D-CRT: three dimensional conformal radiation therapy; IMRT: Intensity-modulated radiation therapy; SBRT: Serotactic body radiation therapy

Conclusions

Evidence is insufficient to permit us to draw conclusions about the comparative effectiveness of local hepatic therapies for unresectable CRC metastases to the liver for the populations addressed in this review. Important outcomes of therapy include overall survival and improved quality of life; as well as 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 Traetment of Cancer
EPC:	Evidence-based Practice Center
FU:	fluorouracil
GRADE:	Grading of Recommendations Asessment, Developtment 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:	Preffered Reporting Items for Systematic Reviews and Meta-Analyses
QOL:	quality of life
RCT:	randomized, controlled trial
RE:	radioembolization
RECIST:	Response Evalaution 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