Evidence-based Practice Center Systematic Review Protocol

Project Title: Local Therapies for Unresectable Colorectal Cancer Metastases to the Liver: A Comparative Effectiveness Review

Amendment Date: September 27, 2012

(Amendments Details–see Section VII)

I. Background and Objectives for the Systematic Review

Introduction

The liver is the most common location for solid organ metastases and up to 40 percent of patients who die of any type of cancer die with hepatic metastases.[1] Colorectal cancer is the most common malignancy that metastasizes to the liver, with 25 percent of colon cancer patients presenting with synchronous liver metastases and another 50 percent developing metachronous disease.[1] Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States.

Surgical resection is the treatment of choice in resectable colorectal metastases. However, only 10 to 25 percent of patients with metastases isolated to the liver are eligible 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 and cardiac insufficiency.[3]

Hepatic metastasis from colorectal cancer is 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 will remain postsurgery.[4, 5] For unresectable metastatic disease, local 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.

Treatment Indications

Two major indications for liver-directed therapies exist:

1. Patients who at diagnosis have limited liver metastases and are not candidates for surgical resection or with recurrence in the liver after resection and who cannot be re-resected are candidates for local therapy using ablative techniques[6] and radiation therapy. In these patients liver-directed therapies are used as an adjunct to systemic chemotherapy with the goal of achieving a cure. The volume of disease in these patients is small, either in terms of lesion size or number of lesions.[7] 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.

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2. Patients whose treatment has failed or whose disease progressed while receiving systemic chemotherapy. These patients generally have large–volume, diffuse disease and are not candidates for ablation but can be offered embolization or radiotherapy to debulk the tumor and palliate symptoms when present.[8] Regardless of the liver-directed therapy, patients should have liver-only metastases or liver-dominant metastases. In general, it is acceptable to have a single lung nodule and remain a treatment candidate.

This report aims to compare the effectiveness and harms of liver-directed therapies for the indications outlined above. Therefore, comparisons of ablation versus surgery or systemic chemotherapy versus liver-directed therapy are outside the scope of this report.

Current Treatments

Several liver-directed therapies have been developed to treat patients with CRC hepatic metastases. In the continuum of care, the use of a liver-directed therapy may come before or after the use of systemic chemotherapy but are most often administered in conjunction. Liver-directed therapies are divided into three groups—ablation, embolization, and radiotherapy—and include:

- **Ablation**
  - Cryosurgical ablation—has a mechanism of action 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 between -20 to -40 °C.[9, 10]
  - Radiofrequency ablation—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.[4]
  - Microwave ablation—unlike radiofrequency ablation, uses high-frequency electromagnetic radiation to create heat through the excitation of water molecules.[4] The heat causes thermal damage that leads to coagulation necrosis and ablation of the tumor.

- **Embolization**
  - Transarterial embolization—uses selective catheterization and obstruction of the arterial vessel, which supplies blood to the tumor, with an embolizing agent.[11]
  - Transarterial chemoembolization—is aimed at causing 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), is injected via a catheter into the feeding hepatic arteries directly supplying the tumor, and 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.

- Hepatic artery infusion—allows the delivery of higher doses of chemotherapy to the tumor, as compared to systemic chemotherapy, while maintaining low levels of toxicity in the normal tissue. This is achieved through the unique blood supply to the liver in which normal hepatocytes are perfused by the portal vein while the metastases derive most of their blood supply via the hepatic artery and the high first-passage 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.[12, 13]
- Radioembolization or selective internal radiation therapy (SIRT)—involves loading radionuclide yttrium-90 into microspheres and placing them within the microvasculature of the metastases, thus targeting multiple hepatic metastases in a single procedure.[14] The loaded microspheres deliver high, localized doses of β-radiation to the tumor while minimizing radiation exposure to the surrounding tissue.[15-17]
- Drug-eluting beads—a novel transarterial embolization system that uses a drug-loaded (typically doxorubicin or cisplatin) superabsorbent polymer microsphere to gradually release of doxorubicin into the tumor, allowing a longer intratumoral exposure and less systemic exposure to the drug.[18]

- **Radiotherapy**

  The radiotherapy being reviewed will focus on focal treatment of the lesion or lesions and not whole liver irradiation.

  - External-beam three-dimensional conformal radiation therapy (3D-CRT)—a type of radiotherapy that uses computer-assisted tomography scans (CT or CAT scans) and/or magnetic resonance imaging scans (MR or MRI scans) 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, thereby sparing nearby healthy tissues
  - External-beam intensity-modulated radiotherapy (IMRT)—a specialized form of 3D-CRT that 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 permits the delivery of 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.
  - Stereotactic body radiation therapy (SBRT)—a type of external-beam radiation therapy that delivers a high dose of radiation with high targeting accuracy to an extracranial target within the body in either a single dose or in a small number of fractions. [21]

Guidelines from the National Comprehensive Cancer Network for metastatic colorectal cancer state that ablative therapy can be considered when all measurable metastatic disease can be treated. However, there is no guidance about which ablative therapy is optimal or about the comparative benefits and harms of the various palliative treatments. A perception of clinical

equipoise and limited randomized trial data comparing liver-directed therapies[22, 23] leaves uncertainty around which techniques, either alone or in combination, offer superior patient outcomes.

Objectives

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

- Those with extensive liver-predominant hepatic metastases that are refractory to systemic chemotherapy
- Those who are candidates for ablative 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 liver-directed therapy for downstaging of disease, and those treated with a first-line liver-directed therapy alone are outside the scope of this review.

Summary

The standard of care of care for metastatic CRC confined to the liver is surgical resection; however, most patients are not surgical candidates due to patient and tumor characteristics. Liver-directed therapy is an option for many of these patients whose liver metastases are unresectable. There is uncertainty surrounding the optimal use of the various local therapies in these settings. This topic is clinically relevant and one of importance to health care providers, patients, and policymakers.

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, in particular the definition of medically or technically inoperable patients.[24] All patients in our review will have been classified as having unresectable disease, either due to the extent of the tumor or patient characteristics (poor surgical candidate). Our review will include two distinct patient populations: those who are refractory to systemic chemotherapy and those who are candidates for ablative therapies as an adjunct to systemic chemotherapy. The treatment comparisons will be made within rather than across these populations, as the underlying prognoses of these patients are different (see PICOTS below).

Primary clinical outcomes for our review include overall survival, quality of life, and adverse events secondary to the interventions of interest (see PICOTS below). Intermediate outcomes that impact overall survival include time to progression of disease and tumor recurrence.

In addition to comparative effectiveness, the comparative harms of liver-directed therapies will be reviewed. Harms systematically reviewed by strict patient-selection criteria will summarize the available data to evaluate the balance of benefits and harms of these therapies. Harms under review include, but are not limited to, hepatic abscess, hemorrhage, injury to adjacent organs, and liver failure (see PICOTS below).

The data summarized in a comparative effectiveness review can provide stakeholders with evidence they can rely on for informed decisionmaking about the comparative benefits and harms of the various liver-directed therapies for CRC metastases among patients whose disease is refractory to systemic therapy and those receiving liver-directed therapy as an adjunct to systemic chemotherapy.

II. The Key Questions

Question 1

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

Question 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?

Question 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?

Question 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?

The Key Questions (KQs) were posted for public comment for 4 weeks. Changes to the KQs and the PICOTS were made based on these comments and discussion with the Technical Expert Panel (TEP). When the KQs were first written, they and the interventions were stratified by intent of treatment (palliative or curative). The TEP felt that this stratification was inappropriate and potentially confusing, as some interventions could be applied both to palliate symptoms and in hopes of curing disease. The KQs are now stratified by population receiving liver-directed therapy. KQs 1 and 2 apply to those who are refractory to systemic chemotherapy and KQs 3 and 4 to those receiving it as an adjunct to systemic chemotherapy. Interventions were categorized to apply to all KQs rather than specific ones, and some interventions were removed and SBRT was added. Additionally, to be consistent with clinical practice, KQs 1 and 2 were changed to include patients with minimal rather than no extrahepatic disease, and additional harms were added to the PICOTS.

PICOTS Framework

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a. Population(s)

KQs 1 & 2: Patients whose disease is refractory to systemic therapy, are candidates for liver-directed therapies to treat unresectable hepatic metastases from primary CRC, and have minimal evidence of extrahepatic disease, including:

- 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

KQs 3 & 4: Patients who are candidates for liver-directed therapies with concomitant systemic chemotherapy to treat unresectable hepatic metastases from primary CRC and have no evidence of extrahepatic disease, including:

- Patients whose hepatic metastases are unresectable due to medical comorbidities, such as low hepatic reserve, cardiac insufficiency, or poor performance status
- Patients whose hepatic metastases are unresectable because of certain characteristics of the metastases
- Patients who have synchronous hepatic metastases
- Patients whose hepatic metastases have recurred after resection

b. Interventions

KQs 1–4:

- Transarterial embolization (TAE)
- Transarterial chemoembolization (TACE)
- Radioembolization (RE)
- External beam with 3D-CRT or IMRT
- Hepatic arterial infusion (HAI)
- Drug-eluting beads
- SBRT
- Cryoablation
- Radiofrequency ablation (RFA)
- Microwave ablation (MWA)

c. Comparators

KQ 1 & 2:

- All the therapies will be compared to each other as treatment of patients whose CRC hepatic metastases are refractory to systemic therapy.

KQs 3 & 4:

- All the therapies will be compared to each other as treatment of patients who are receiving liver-directed therapy as an adjunct to systemic chemotherapy for CRC.

d. Outcomes

KQ 1:

Final outcomes: Survival and quality of life
Intermediate outcomes: Time to progression, local recurrence, and pain

KQ 2:

Adverse outcomes: hepatic abscess, hemorrhage, biloma, steatohepatitis, injury to adjacent organ(s), and liver failure

KQ 3:

Final outcomes: Survival and quality of life
Intermediate outcomes: Length of stay, time to recurrence, and local recurrence

KQ4:

Adverse outcomes: hepatic abscess, hemorrhage, biloma, steatohepatitis, injury to adjacent organ(s), and liver failure

e. Timing

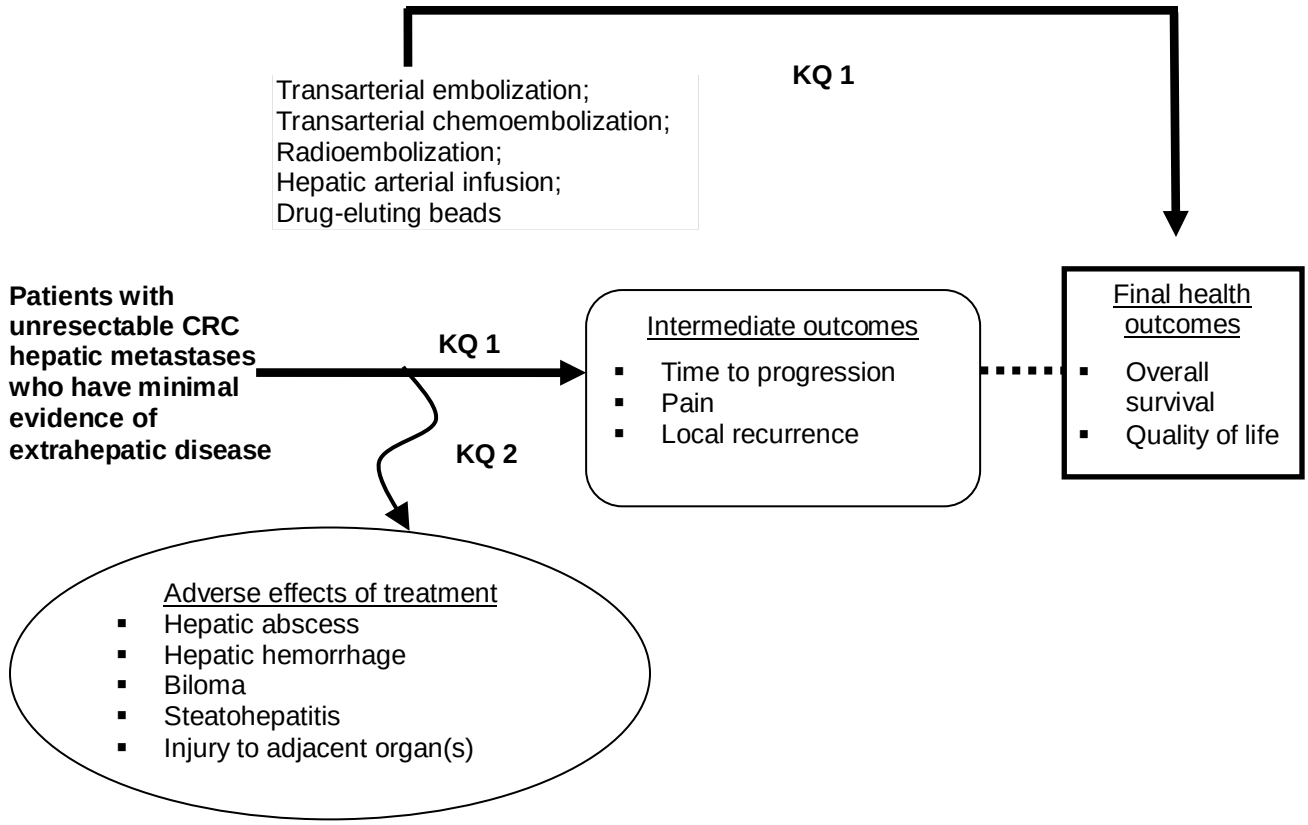
- The relevant periods occur at the time of treatment for the CRC hepatic metastases through followup over months or years.

f. Settings

- Inpatient and outpatient

III. Analytic Framework

Figure 1. Analytic framework for local 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



This figure depicts the potential impact of using liver-directed therapies on both intermediate outcomes and final health outcomes. Direct evidence of the impact of the various therapies on health outcomes, including adverse effects, is shown by solid lines. Intermediate outcomes—such as time to progression and pain—may have an association with the final health outcomes (dotted line).

Abbreviations: CRC = colorectal cancer; KQ = key question

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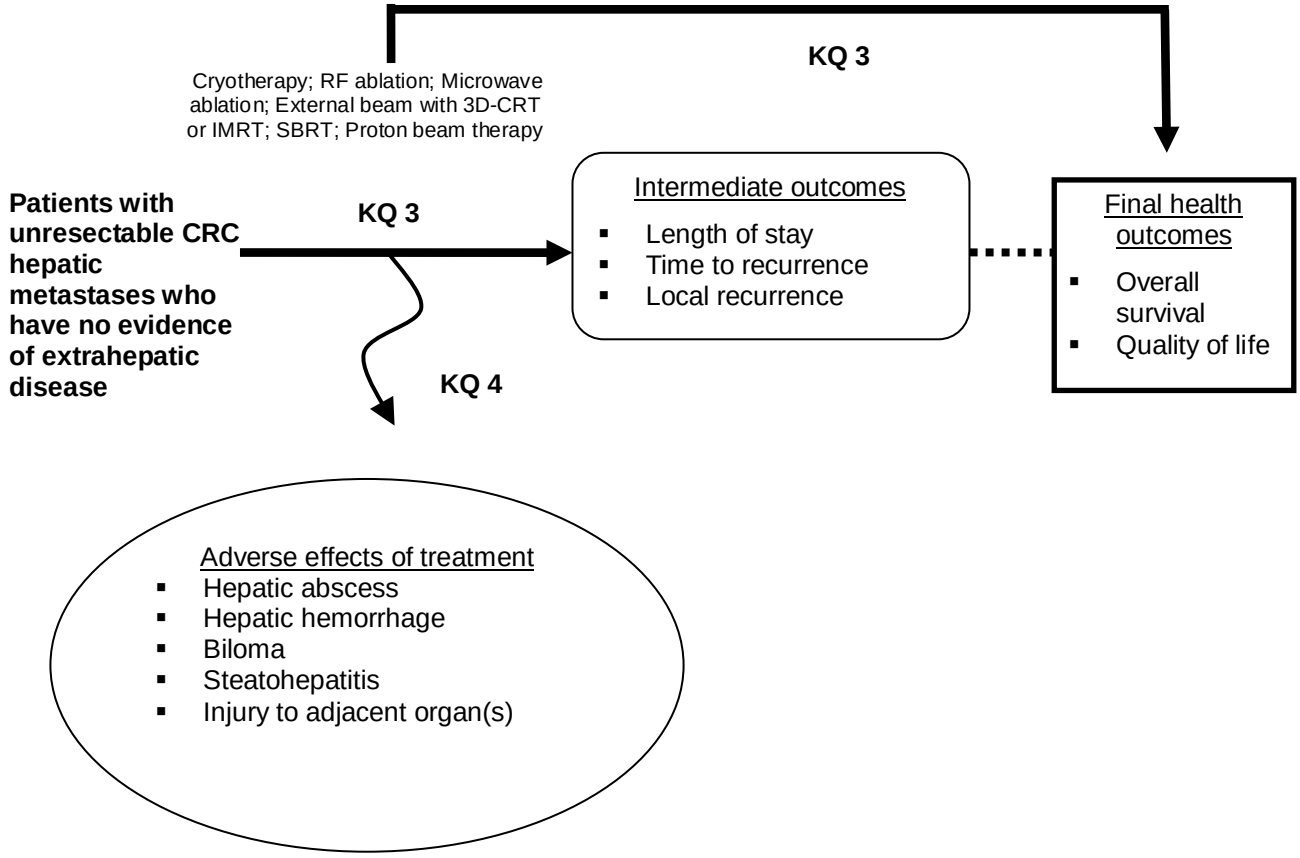
Figure 2. Analytic framework for comparative effectiveness of local therapies for unresectable colorectal cancer metastases to the liver in patients receiving liver-directed therapy as an adjunct to systemic chemotherapy and who have no evidence of extrahepatic disease



This figure depicts the potential impact of using liver-directed therapies on both intermediate outcomes and final health outcomes. Direct evidence of the impact of the various therapies on health outcomes, including adverse effects, is shown by solid lines. Intermediate outcomes—such as length of stay, time to recurrence, and tumor response—may have an association with final health outcomes (dotted line).

Abbreviations: CRC = colorectal cancer; IMRT = intensity-modulated radiation therapy; KQ = key question; RF = radiofrequency; SBRT = stereotactic body radiation therapy; 3D-CRT = three-dimensional conformal radiation therapy

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IV. Methods

Methodological practices to be followed in this review will be derived from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*[25] (hereafter *Methods Guide*) and its subsequent updates.

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A. Criteria for Inclusion/Exclusion of Studies in the Review

We will include randomized controlled trials (RCTs) and nonrandomized comparative studies (observational, case-control, and cohort studies) of populations, comparisons, interventions, and outcomes that were not adequately studied in the RCTs. We will also use noncomparative observational studies (case series) to assess comparative effectiveness in populations not well represented in RCTs. To classify observational study designs, we will use the system developed by Briss and colleagues.[26]

Studies will be included for KQs 1 and 2 if they:

- Report on an outcome of interest, specifically among adult patients who have unresectable CRC metastasis to the liver with limited extrahepatic spread and whose metastatic disease is refractory to systemic chemotherapy
- Involve an intervention of interest
- Do not contain more than 10 percent of patients who are outside our patient population of interest

Studies will be included for KQs 3 and 4 if they:

- Report on an outcome of interest specifically among adult patients who have unresectable CRC metastasis to the liver with no extrahepatic spread and who are receiving liver-directed therapy as an adjunct to systemic chemotherapyInvolve an intervention of interest
- Do not contain more than 10 percent of patients who are outside our patient population of interest

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

The databases listed below will be searched for citations published between January 1, 2000, and September 30, 2011. With input from the TEP, the Evidence-based Practice Center (EPC) investigators decided to limit the search to these dates to ensure the applicability of the interventions and outcomes data to current clinical practice. The clinical rationale supported by the TEP was that because of changes in clinical practice and because outcomes of treatment regimens used before 2000 are not predictive of present-day outcomes, studies preceding that date should not be considered in this report. The search will also be limited to English-language references.[27] Based on our experience, non–English-language references did not yield enough high-quality information to justify the resources required for translation. The TEP agreed that the exclusion of non–English-language articles from this review would not impact the conclusions.

- MEDLINE®
- EMBASE®
- Cochrane Controlled Trials Register

Our search strategy will use the National Library of Medicine's Medical Subject Headings (MeSH®) keyword nomenclature developed for MEDLINE® and adapted for use in other databases. The searches will be limited to studies of human subjects.

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

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

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

> Hepatic OR liver AND cancer OR cancers OR oncology OR neoplasms AND colon OR colorectal OR rectal OR intestinal OR rectum OR intestine AND "secondary " OR metastatic OR metastasis OR metastases AND Unresectable OR nonresectable OR inoperable OR irresectable AND "radiofrequency ablation" OR (radiofrequency AND ablation) OR RFA OR cryoablation OR cryosurgical OR cryosurgery OR "microwave ablation" OR (microwave AND ablation) OR ((percutaneous OR intralesional) AND (ethanol OR acetic acid)) OR embolization OR embolisation OR embolize* OR embolise* OR "transarterial chemoembolization" OR "transarterial chemoembolisation" OR TACE OR "transarterial embolization" OR "transarterial embolisation" OR TAE OR radioembolization OR radioembolisation OR radiotherapy OR radiation OR "external beam" OR "3D conformal" OR "3-D Conformal" OR "intensity modulated radiotherapy" OR IMRT OR SBRT OR stereotactic OR "liver-directed chemotherapy" OR "hepatic artery infusion" OR HAI OR chemotherapy OR "drug-eluting beads"

Grey literature will be sought by searching for clinical trials, material published on the U.S. Food and Drug Administration Web site, and relevant conference abstracts (from conferences identified by TEP members) for data pertaining to the interventions used to treat unresectable CRC hepatic metastases that are under consideration in the review. We will review Scientific

Information Packets from the Scientific Resource Center. Study authors will be contacted for unpublished results including, but not limited to, clarification of patient characteristics or treatment data, if the EPC staff believes that such evidence could impact results meaningfully (i.e., alter evidence GRADE).

C. Data Abstraction and Data Management

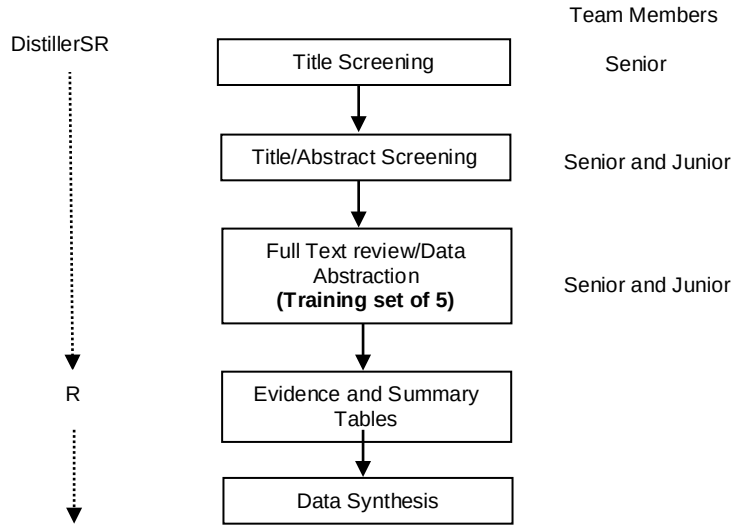
Search results will be transferred to EndNote® and subsequently into DistillerSR (Evidence Partners Inc., Ottawa, Canada) for selection. Using the study-selection criteria for screening titles and abstracts, each citation will be marked as: 1) eligible for review as full-text articles or as 2) ineligible for full-text review. Reasons for study exclusions will not be noted. The first-level title-only screening will be performed by two senior team members. To be excluded, a study must be independently excluded by both team members. In cases where the senior team members disagree, the senior and junior team members will conduct the second-level abstract screening according to predefined criteria in a duplicate manner. Discrepancies will be decided by consensus opinion; a third reviewer will be consulted if necessary. A training set of 25 to 50 will be examined initially by duplicate members to assure uniform application of screening criteria. Full-text review will be performed when it is unclear whether the study-selection criteria have been satisfied.

Full-text articles will be 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, will be kept in the DistillerSR database. While a paper may be excluded for multiple reasons, the first reason identified will be recorded.

Data abstraction will be performed directly into tables created in Distiller SR with elements defined in an accompanying data dictionary. A training set of five articles will be abstracted by all team members. All data abstractions will be performed in duplicate, with discrepancies identified and resolved by consensus.

To provide reproducibility, abstracted data will be transferred from a DistillerSR to a SAS® (SAS Institute Inc., Cary, NC) database. SAS will be used to compile study-level and summary tables in Microsoft® Excel format for inclusion in the report.

Figure 3. Schematic for data management and abstraction



Data Elements

The following data elements will be abstracted from the intervention studies or recorded as not reported. The data elements to be abstracted were defined in consultation with the TEP and will include the following:

- Quality Assessment
    - Number of participants and flow of participants through steps of study
    - Treatment-allocation methods (including concealment)
    - Use of blinding
    - Prospective versus retrospective
    - Use of an independent outcome assessor
      Additional elements are described below under Assessment of Methodological Quality of Individual Studies

- Assessment of Applicability and Clinical Diversity
    - Patient characteristics, including:
        - Age
        - Sex
        - Race/ethnicity
        - Liver tumor characteristics (e.g., size, number, location, and extent of liver involvement)
        - Other prognostic characteristics such as but not limited to
            - Medical comorbidities including, but not limited to, cardiac conditions and hepatic reserve

        - Performance status
    - Setting
        - Outpatient
        - Inpatient

- Treatment characteristics, including:

    - Type of liver-directed therapy(ies)
    - Duration of observation
    - Other treatment modalities (e.g., systemic chemotherapy)
    - Number and types of previous lines of treatment

- Outcome Assessment

    - Identified primary outcome
    - Identified secondary outcomes
    - Followup frequency and duration
    - Details of the data analysis, including:

    - Statistical analyses (statistical test/estimation results)
        - Test used
        - Summary measures
        - Sample variability measures
        - Precision of estimate
        - *p* values

    - Regression modeling techniques
        - Model type
        - Candidate predictors and methods for identifying candidates
        - Univariate analysis results
        - Selected predictors and methods for selecting predictors
        - Testing of assumptions
        - Inclusion of interaction terms
        - Multivariable model results
        - Discrimination or validation methods and results
        - Calibration or "goodness-of-fit" results

- The same abstraction tables will be used for comparative and single-arm studies, although some elements may not apply to the latter (e.g., description of the control group).

D. Assessment of Methodological Quality of Individual Studies

Definition of Ratings Based on Criteria

In adherence with the *Methods Guide*,[25] the general approach to grading individual comparative studies will be performed by using a method used by the U.S. Preventive Services Task Force.[28] The quality of the abstracted studies will be assessed by two independent reviewers. Discordant quality assessments will be resolved with input from a third reviewer, if necessary.

- The quality of studies will be assessed on the basis of the following criteria:
  - Initial assembly of comparable groups: adequate randomization, including concealment and whether potential confounders (e.g., other concomitant care) were distributed equally among groups
  - Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination)
  - Important differential loss to followup or overall high loss to followup
  - Measurements: equal, reliable, and valid (includes masking of outcome assessment)
  - Clear definition of interventions
  - All important outcomes considered
  - Analysis: adjustment for potential confounders and intention-to-treat analysis
- The rating of intervention studies encompasses these three quality categories:
  - **Good.** Meets all criteria; comparable groups are assembled initially and maintained throughout the study (followup at least 80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is given to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.
  - **Fair.** Studies are graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: In general, comparable groups are assembled initially, but some questions remain about whether some (although not major) differences occurred with followup; measurement instruments are acceptable (although not the best) and are generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis has been done for RCTs.
  - **Poor.** Studies are graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups; key confounders are given little or no attention; lack of masked outcome assessment; and, for RCTs, intention-to-treat analysis is lacking.
- The quality of included nonrandomized comparative intervention studies will also be assessed based on a selection of items proposed by Deeks and colleagues[29] to inform the U.S. Preventive Services Task Force approach[28] as follows:
  - Was sample definition and selection prospective or retrospective?
  - Were inclusion/exclusion criteria clearly described?

- Were participants selected to be representative?
- Was there an attempt to balance groups by design?
- Were baseline prognostic characteristics clearly described and groups shown to be comparable?
- Were interventions clearly specified?
- Were participants in treatment groups recruited within the same time period?
- Was there an attempt by investigators to allocate participants to treatment groups in an attempt to minimize bias?
- Were concurrent/concomitant treatments clearly specified and given equally to treatment groups?
- Were outcome measures clearly valid, reliable, and equally applied to treatment groups?
- Were outcome assessors blinded?
- Was the length of followup adequate?
- Was attrition below an overall high level (<20%)?
- Was the difference in attrition between treatment groups below a high level (<15%)?
- Did the analysis of outcome data incorporate a method for handling confounders such as statistical adjustment?

- The quality of included single-arm intervention studies will be assessed based on a set of study characteristics proposed by Carey and Boden,[30] as follows:

  - Clearly defined question
  - Well-described study population
  - Well-described intervention
  - Use of validated outcome measures
  - Appropriate statistical analyses
  - Well-described results
  - Discussion and conclusion supported by data
  - Funding source acknowledged

E. Data Synthesis

Whether or not our evidence review will incorporate formal data synthesis (e.g., meta-analysis) will be determined after completing the formal literature search. The decision to pool studies will be based on the following: 1) are the studies addressing a common question and 2) are they fairly homogenous with respect to population, methods, and interventions. If a meta-analysis can be performed, subgroup and sensitivity analyses will be based on assessment of clinical diversity in available studies. Indirect quantitative comparisons may be used where indicated.

F. Grading the Evidence for Each Key Question

Selected studies will be assessed for relevance against target populations, interventions of interest, and outcomes of interest. The system used for rating the strength of the overall body of

evidence is outlined in the *Methods Guide*[25] and is based on a system developed by the GRADE Working Group.[31] This system explicitly addresses the following domains: risk of bias, consistency, directness, and precision. The grade of evidence strength is classified into the following four categories:

- **High.** High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate.** Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- **Low.** Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
- **Insufficient.** Evidence is either unavailable or does not permit estimation of an effect.
- Additional domains—including strength of association, publication bias, coherence, dose-response relationship, and residual confounding—will be addressed if appropriate.

Specific outcomes and comparisons to be rated will depend on the evidence found in the literature review. The grade rating will be made by independent reviewers, and disagreements will be resolved by consensus adjudication.

G. Assessing Applicability

Applicability of findings in this review will be assessed within the EPICOT framework (Evidence, Population, Intervention, Comparison, Outcome, Timestamp).[32] Factors that may limit the applicability of the findings from our review include the following subgroups: patients with liver metastases from primary CRC that are candidates for a surgical resection or liver transplantation, patients with initially unresectable liver metastases from CRC who receive liver-directed therapy(ies) as a preoperative conversion therapy to become eligible for a surgical therapy, and patients with gross extrahepatic disease. Findings may also vary between adult and pediatric patient populations.

V. References

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VI. Definition of Terms

None

VII. Summary of Protocol Amendments

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Date	Section	Original Protocol	Revised Protocol	Rationale
9/25/12	Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions	The databases listed below will be searched for citations published between January 1, 2000, and September 30, 2011. With input from the TEP, the Evidence-based Practice Center (EPC) investigators decided to limit the search to these dates to ensure the applicability of the interventions and outcomes data to current clinical practice. The clinical rationale supported by the TEP was that because of changes in clinical practice and because outcomes of treatment regimens used before 2000 are not predictive of present-day outcomes, studies preceding that date should not be considered in this report	The databases listed below will be searched for citations published between January 1, 2000, and September 30, 2011. With input from the TEP, the Evidence-based Practice Center (EPC) investigators decided to limit the search to these dates to ensure the applicability of the interventions and outcomes data to current clinical practice. The clinical rationale supported by the TEP was that because of changes in clinical practice and because outcomes of treatment regimens used before 2000 are not predictive of present-day outcomes, **studies where patient treatment preceded that date should** not be considered in this report	To improve the clarity of our exclusion criteria we added text to the end of the paragraph. Prior to the year 2000 some interventions were in their infancy and based on current standards used outdated regimens. Thermal therapies were not used significantly until late 1990s and major changes in proton beam therapy and stereotactic therapy occurred during that same period. Chemoembolization drugs and embolic mixtures have also changed a great deal in the last ten years and are more standard now. For these reasons which were strongly supported by the TEP we chose to exclude studies where patient treatment

				preceded the year 2000.

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VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end-users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants, and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

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Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published 3 months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures:

The EPC team members have no conflicts of interest to disclose.

XIII. Role of the Funder:

This project was funded under Contract No. xxx-xxx from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.