Evidence-based Practice Center Systematic Review Protocol

Project Title: Local Therapies for Unresectable Primary Hepatocellular Carcinoma: Comparative Effectiveness Review

Amendment Date: September 27, 2012
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(Amendments Details–see Section VII)

I. Background and Objectives for the Systematic Review

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver tumor. HCC is a highly lethal disease, and worldwide it is the fifth most common cancer and the third leading cause of cancer death.[1] During 2003-2004 in the United States, the incidence of HCC was 5.1 per 100,000 with a mortality rate of 4.0.[2] Overall 5-year survival rates for HCC are lower than 10 percent in Europe and the United States.[1] The main etiology of HCC is chronic infection with hepatitis B (HBV) and hepatitis C (HCV) viruses. Approximately 4 million individuals in the United States are chronically infected with hepatitis C, and the annual incidence rate of HCC among patients with hepatitis C-related cirrhosis is estimated to be between 2 and 8 percent. Unlike most solid tumors, the future incidence of and mortality rate due to HCC are projected to increase worldwide over the next 20 years, mostly as a result of the dissemination of hepatitis C virus infection.[3] Other causes include cirrhosis due to any cause (e.g. alcohol), hereditary hemochromatosis and iron overload syndromes, nonalcoholic fatty liver disease (NAFLD), obesity, diabetes, and environmental toxins (e.g., aflatoxin, chewing of betel quid, and contaminated water).[4] However, etiology does not appear to be an independent prognostic factor for HCC.[5, 6]

Even though prognosis is not dependent on the etiology of HCC, the underlying presence of cirrhosis impacts prognosis and treatment decisions. In situations where HCC occurs in patients without underlying cirrhosis (e.g., HBV infection, NAFLD), resection is the preferred treatment approach.[7] As an example, the Society of Hepatology in Japan recommends hepatectomy for patients with a single lesion, regardless of its size.[8]

Disease Classification

Both tumor stage and underlying liver function are key considerations in diagnosis, treatment selection, and prognosis of HCC.

Classification/staging of hepatocellular carcinoma

The Barcelona Clinic Liver Cancer (BCLC) classification system takes both tumor stage and underlying liver function into account and is widely used as the basis of treatment algorithms in

Europe and North America.[7] It takes into account factors related to tumor stage, liver function, performance status, and cancer-related symptoms. Disease is staged from 0 to D.

Other staging systems such as Okuda staging, American Joint Committee on Cancer (AJCC) TMN staging, Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire (GETCH), Chinese University Prognostic Index (CUPI), Japan Integrated Staging (JIS), and Cancer of the Liver Italian Program (CLIP) are used regionally.[9-11] The set of prognostic factors considered in each of these systems varies but can include hepatic function, performance status, and tumor characteristics and, therefore, a clear translation of staging from one system to another is precluded.

Classification of underlying liver function

The Child-Pugh classification is one method to assess the prognosis of patients with underlying liver disease. The system employs five clinical domains: total bilirubin, serum albumin, international normalized ratio (INR, a measure of coagulation status), ascites, and hepatic encephalopathy. Each is scored on a scale of 1–3, from lowest to highest severity. Patients with chronic liver disease are classified as Child-Pugh class A, B, or C based upon the total score. Patients with class A cirrhosis and concomitant HCC have the best prognosis and would be candidates for surgery, transplantation, or ablative therapies. Patients with class B or C cirrhosis with concomitant HCC are not surgical candidates and are offered either palliative liver-directed therapies or systemic chemotherapy.

Another scoring system for chronic liver disease is the Model for End-Stage Liver Disease (MELD) score, which derives a score based on the patient's serum bilirubin, serum creatinine, and the INR for prothrombin time. The MELD score ranges from 6 to 40 with higher scores corresponding to higher severity of hepatic dysfunction and serves as a numerical scale for adult liver transplant candidates.[12]

Current Treatments

Although surgical resection is the preferred first-line treatment of HCC, approximately 80 percent of patients are not surgical candidates because of advanced-stage disease at the time of diagnosis, inadequate hepatic reserve to tolerate resection, tumors in unresectable locations, or medical comorbidities that result in a high surgical risk.[1] In the United States, most cases of HCC occur in patients with cirrhosis, a challenging population to manage clinically because they tend to have significant comorbidities. Over the past few decades, several local, minimally invasive, liver-directed therapies have been developed in an attempt to prolong survival and palliate symptoms in patients with unresectable HCC. 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.

Several liver-directed therapies have been developed to treat patients with HCC. In the continuum of care, use of liver-directed therapies has traditionally preceded treatment with systemic chemotherapy. The liver-directed therapies are broken into two groups based on the treatment intent (curative or palliative) and include:

- Ablation

- *Percutaneous ethanol injection* (PEI) involves the injection of a high concentration of ethyl alcohol directly into liver tumors with ultrasound or x-ray guidance. Injections into the tissue or into the blood vessel feeding the tissue leads to cell death by destroying cell membranes, modifying the temperature of cellular enzymes, and blocking the blood vessels.
- In *radiofrequency ablation* (RFA), an alternating current is generated between two or more electrodes in the radiofrequency range to produce heat without causing muscle contractions. The procedure aims to generate tissue temperatures between 90 °C and 100 °C that result in protein denaturation and coagulative necrosis.[13]
- *Microwave ablation* (MWA), unlike RFA, uses high-frequency electromagnetic radiation to create heat by exciting (i.e., energizing) water molecules.[14] The heat causes thermal tissue damage that leads to coagulation necrosis and ablation of the tumor.

- Radiotherapy

  - *Stereotactic body radiation therapy* (SBRT) is a type of external-beam radiation therapy that delivers with high targeting accuracy a high dose of radiation to an extracranial target within the body, using either a single dose or a small number of fractions.[15]
  - *Hypofractionated proton beam therapy* is a form of external-beam radiation therapy that delivers high doses of radiation to the tumor target while simultaneously reducing the amount of photons reaching normal surrounding tissue in fewer sessions of larger fraction than are delivered in standard regimens.[16]
  - *Three-dimensional conformal radiation therapy* (3D-CRT) is a type of external-beam radiotherapy that uses computer-assisted tomography scans and/or magnetic resonance imaging 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.[17]
  - *Intensity-modulated radiotherapy* (IMRT) is a specialized form of 3D-CRT that allows the radiation oncologist to vary both the intensity and the angle at which a radiation beam is delivered to the tumor. 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 3D-CRT.[18]
  - *Intraluminal brachytherapy* involves the placement of a radiation source within the body lumen, allowing the delivery of higher doses of radiation directly to a specific tumor.[19]

- Embolization

  - *Transarterial embolization* (TAE) involves selective catheterization and obstruction of the arterial vessel that supplies blood to a tumor and injection of an embolizing agent into it.[20]
  - *Transarterial chemoembolization* (TACE) is a procedure in which a chemotherapeutic agent is injected directly into a liver tumor along with an embolizing agent to cause ischemia. A chemotherapeutic solution (frequently doxorubicin or cisplatin) is suspended in lipiodol (an oily contrast medium selectively retained within tumors) and injected via a catheter into the hepatic arteries that directly supply the tumor. These arteries are then

injected with an embolizing agent to obstruct blood flow to the tumor. Tumor ischemia raises the drug concentration, prolongs the retention of the chemotherapeutic agent, and reduces systemic toxicity.

- *Drug-eluting beads* (DEBs) are a novel transarterial embolization system in which a drug-loaded (typically doxorubicin or cisplatin) superabsorbent polymer microsphere is used to provide a gradual release of the drug into the tumor, allowing longer intratumoral exposure and less systemic exposure to the drug.[20]
- *Radioembolization* (RE) or *selective internal radiation therapy* (SIRT) with microspheres loaded with radionuclide yttrium-90 allows targeting of multiple tumors in a single procedure.[21] The loaded microspheres are inserted into the microvasculature of the tumor where they deliver high, localized doses of β-radiation to the tumor, while minimizing radiation exposure to the surrounding tissue.[15, 21, 22]

Due to the limitations of these different interventions, such as the limited volume of coagulative necrosis by RFA, combination therapies have been proposed. For example, a local ablative therapy, such as RFA, can be used in conjunction with an embolization therapy, such as TACE.[23] Adding TACE to RFA may increase the area of necrosis allowing for clearer margins that completely surround the target tumor. This may in turn lead the way for the complete ablation of larger size tumors.[23]

Direct comparisons have been made for some of the local techniques available to treat primary liver cancer.[24-40] It is still not clear which techniques, either alone or in combination, offer superior patient outcomes.

Existing Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines[13] state that there is a panel consensus that local therapies should not be used in place of liver resection or transplantation for patients who meet surgical criteria. The National Institutes of Health (NIH) consensus recommendation for HCC states that for selected patients with HCC confined to the liver, whose disease is not amenable to resection or transplantation, locoregional therapies can be considered.[24] The existing guidelines do not provide specific guidance on the comparative effectiveness of the therapies (i.e., which therapy offers the best outcomes).

Objectives

The objective of this systematic review is to characterize the comparative effectiveness and harms of various liver-directed therapies for unresectable primary HCC among patients eligible for liver-directed therapies who have all the following:

- No extrahepatic spread
- No portal invasion
- Child-Pugh class A or B disease
- Eastern Cooperative Oncology Group (ECOG) status ≤1

and/or

- BCLC stage A or B or equivalent

Candidates for liver resection or transplant as well as patients with advanced and terminal disease are outside the scope of this review as the treatment options for these patients are vastly different and, therefore, warrant treatment modalities not included in this review. Children are also outside the scope of this review as their disease presentation and prognosis are quite different than for adults.

Summary

The principal uncertainty for these local therapies is effectiveness in terms of overall survival. Although guidelines from NCCN exist and the NIH has consensus recommendations with uniform consensus, these guidelines are not based on high-quality comparative effectiveness reviews that rigorously and systematically address the best use of these techniques. It is not known which patient populations with HCC will benefit the most from these therapies. Additionally, regional therapies are associated with adverse effects, including but not limited to hepatic abscess and hemorrhage. Therefore, there is a need to clarify the optimal use of these techniques.

This comparative effectiveness review can provide stakeholders with a systematic review of the existing evidence to make informed decisions about the comparative benefits and harms of the various liver-directed therapies for treating unresectable HCC.

II. The Key Questions

The Key Questions (KQs) were posted for public comment for 4 weeks. Changes to the KQs and the PICOTS framework were made based on these comments and discussion with the Technical Expert Panel (TEP). When the KQs were first written, the KQs and interventions were stratified by intent of treatment (palliative or curative). Based on the public comments received and input from the TEP, it was felt that this stratification was inappropriate and potentially confusing for two main reasons. First, it is difficult to classify interventions based on curative or palliative intent of the treatment. Second, there was concern that the term “palliative” is often synonymous with end-of-life care and applying that term to this population, who may have early stage disease, would cause confusion.

In addition, the use of various disease classification systems and the inability to translate disease stage from one system to another made it difficult to differentiate between patients with BCLC A and B across publications. Therefore, there are two KQs that refer to effectiveness and harms of liver-directed therapy for patients with unresectable disease without portal invasion or extrahepatic spread and preserved liver function with an ECOG status ≤1 or BCLC A or B or equivalent. Specificity was added to these questions in terms of the specific outcomes to make it clearer. A third KQ was also added to look at potential differences in effectiveness by patient and tumor characteristics. Additionally, SBRT was added to the list of interventions.

Question 1

What is the comparative *effectiveness* of the various liver-directed therapies in patients with HCC who are not otherwise candidates for surgical resection or transplantation with no evidence of extrahepatic disease regarding survival and quality of life?

Question 2

What are the comparative *harms* of the various liver-directed therapies in patients with HCC who are not otherwise candidates for surgical resection or transplantation with no evidence of extrahepatic disease regarding adverse events?

Question 3

Are there differences in comparative effectiveness of various liver-directed therapies in patients with HCC who are not otherwise candidates for surgical resection or transplantation for specific patient and tumor characteristics, such as age, gender, disease etiology, and Child-Pugh score?

PICOTS Framework

- **Population(s)**

  KQs 1–3:

  Adults with HCC who are candidates for liver-directed therapies, but not candidates for surgical resection or transplantation, without evidence of extrahepatic disease, including:

  - Patients whose disease is unresectable due to medical comorbidities, such as low hepatic reserve, cardiac insufficiency, or poor performance status
  - Patients whose disease is unresectable due to tumor characteristics
  - Patients whose disease has recurred after resection

- **Interventions**

  KQs 1–3:

  - Radiofrequency ablation (RFA)
  - Microwave ablation (MWA)
  - Percutaneous ethanol injection (PEI)
  - Stereotactic body radiation therapy (SBRT)
  - External beam with 3D conformal or intensity-modulated radiotherapy (IMRT)
  - Intraluminal brachytherapy
  - Hypofractionated proton beam therapy
  - Transarterial embolization (TAE)
  - Transarterial chemoembolization (TACE)
  - Radioembolization (RE)
  - Drug-eluting beads (DEBs)

Combinations of the interventions listed above were also included in the review, such as TACE plus RFA.

- **Comparators**

  KQs 1–3:
  All the therapies will be compared to each other as treatment of patients with HCC. This comparison includes any combination of therapies used to treat these patients such as, but not limited to, TACE plus RFA, TACE plus cryoablation, and TAE plus RFA.

- **Outcomes**

  KQs 1 & 3 (effectiveness):

  - Final outcomes: Survival, quality of life
  - Intermediate outcomes: Time-to progression, local recurrence, length of stay, days of missed work, pain

  KQ 2 (harms):

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

- **Timing**

The relevant periods occur at the time of treatment through follow-up over months or years.

- **Settings**

  Inpatient and outpatient

III. Analytic Framework

Figure 1. Analytic framework for comparative effectiveness of local therapies for treatment of unresectable primary hepatocellular carcinoma

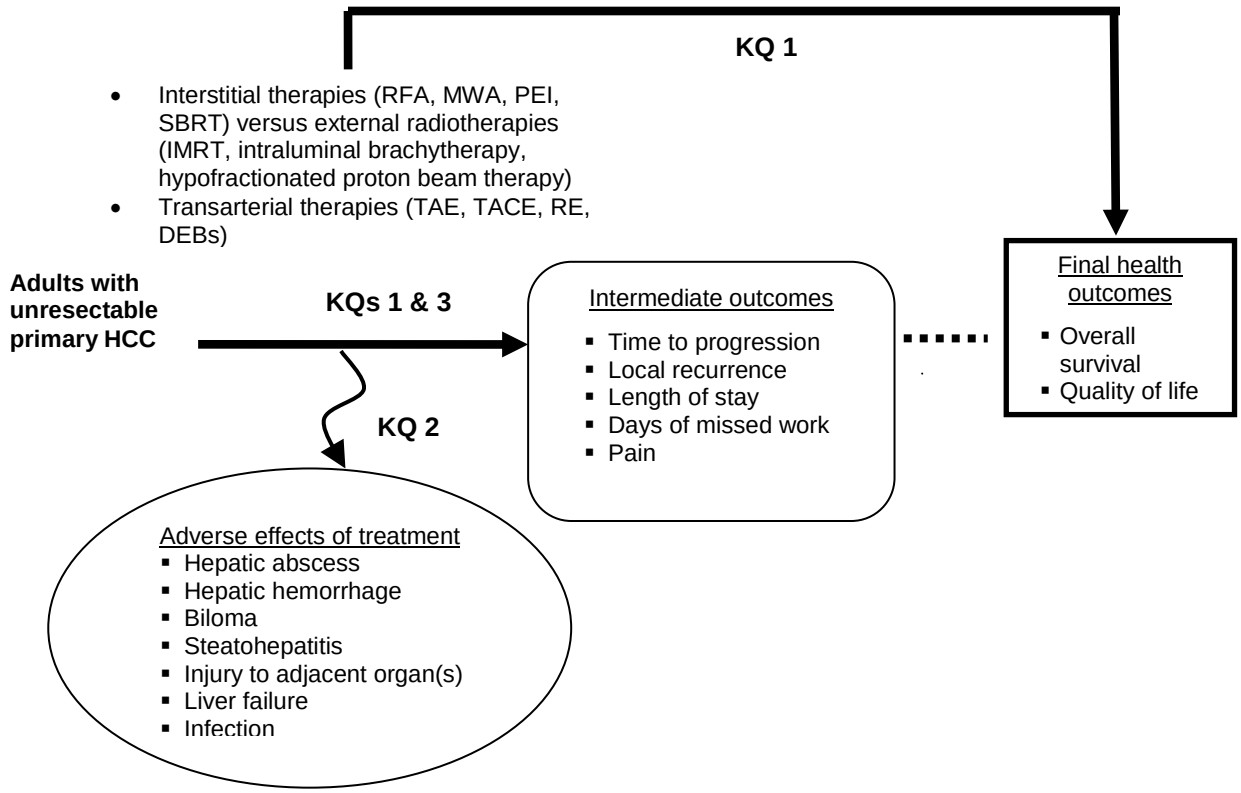


Figure 1. This figure depicts the potential impact of using liver-directed therapies on both intermediate outcomes and final health outcomes. Direct evidence of the impact of the various therapies on health outcomes, including adverse effects, is shown by solid lines. Intermediate outcomes—such as time-to progression and pain—may have an association with the final health outcomes (dotted line).

Abbreviations: DEBs = drug-eluting beads; HCC = hepatocellular carcinoma; MWA = microwave ablation; PEI = percutaneous ethanol injection; RE = radioembolization; RFA = radiofrequency ablation; SBRT = stereotactic body radiation therapy; TAE = transarterial ablation; TACE = transarterial chemoembolization

IV. Methods

Methodological practices to be followed in this review will be derived from the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*[11] (hereafter *Methods Guide*) and its subsequent updates.

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

We will include English-language 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 and harms in populations not well represented in RCTs. To classify observational study designs, we will use the system developed by Briss and colleagues.[41]

Studies will be included for KQs 1–3 if they meet the following criteria:

- Report on an outcome of interest specifically among adult patients with unresectable primary HCC who have no evidence of extrahepatic spread or portal invasion, have Child-Pugh class A or B disease, and an ECOG status ≤1
- Involve an intervention of interest and
- Does not contain more than 10 percent of patients who are outside our patient population of interest.

Studies will be excluded for KQs 1–3 if they:

- Are non-English language
- Are case reports that do not report on a severe adverse event
- Are editorials or literature reviews
- Have treatment dates prior to January 1, 2000
- Have outcome measures including patients outside the scope of the review

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) decided to limit the search to these dates to ensure the applicability of the interventions and outcome data to current clinical practice. The clinical rationale supported by the TEP was that due to changes in clinical practice and treatment regimens, outcomes for patients treated before the year 2000 were not predictive of present-day outcomes and therefore should not be considered in this report. The search will be limited to English-language references.[42] The TEP input suggested that the exclusion of non–English-language articles from this review would not impact the conclusions, as it is anticipated that the vast majority of the evidence base will be published in English.

- 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. (See Appendix A.)

Grey literature will be sought by searching a clinical trials registry, the U.S. Food and Drug Administration (FDA) Web site, and relevant conference abstracts (conferences identified by TEP members) for data pertaining to the interventions under consideration used to treat primary HCC. We will review Scientific Information Packets from the Scientific Resource Center. Study authors will be contacted for unpublished results if the primary authors concur that if obtained, evidence could impact results meaningfully (i.e., alter evidence GRADE).

C. Data Abstraction and Data Management

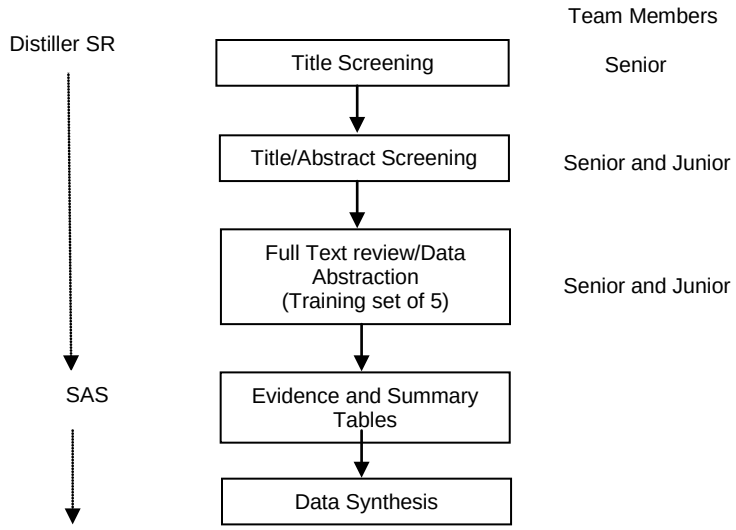
Search results will be transferred to EndNote® (Thomson Reuters, New York, NY) and subsequently into DistillerSR (Evidence Partners Inc., Manotick, ON, Canada) for selection. Using the study-selection criteria for screening titles and abstracts, each citation will be marked as: 1) eligible for review as full-text articles; 2) ineligible for full-text review. Reasons for exclusion will not be noted. The first-level title screening will be performed first by two senior team members. To be excluded, a study must be independently excluded by both team members. In the case where they disagree, Distiller SR, by default, will include the reference and forward it on to abstract screening. Senior and junior team members will conduct the second-level title and abstract screening according to defined 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 references will be examined initially by two team members to assure uniform application of screening criteria. Full-text review will be performed when it is unclear whether the selection criteria have been satisfied.

Full-text articles will be reviewed simultaneously by two reviewers; a third reviewer will handle discrepancies between the two reviewers if necessary to determine whether the studies should be included in the systematic review. Records of the reason for excluding each paper retrieved in full text, but excluded from the review, will be kept in the DistillerSR database.

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

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

Figure 1. Schematic for data management and abstraction



Data Elements

The following data elements from the intervention studies will be abstracted or recorded as not reported. The data elements to be abstracted were defined in consultation with the TEP and 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 but not limited to:
        - Age
        - Sex
        - Race/ethnicity
        - Stage of HCC (e.g., number, size, and location of nodules)
        - Disease duration
        - Etiology of HCC (HBV infection, HCV infection, NAFLD)
        - Presence of cirrhosis

        - Presence of portal vein thrombosis
        - Setting
            - Outpatient
            - Inpatient

    - Treatment characteristics, including:

        - Type of liver-directed therapy(ies)
        - Duration of observation

- Outcome Assessment

    - Identified primary outcome
    - Identified secondary outcomes
    - Follow-up frequency and duration
    - Data analysis details, 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,*[43] the general approach to grading individual comparative studies will be performed by following a method used by the U.S. Preventive Services Task Force.[44] The quality of the abstracted studies and the body of evidence 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; and 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[45] to inform the U.S. Preventive Services Task Force approach[44] 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,[46] 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. Because the goal of any pooling is to estimate unconditional effects,[47] random-effects models will be used. The magnitude of statistical heterogeneity will be examined by using I^2, while acknowledging potential limitations,[48] and when heterogeneity is present (e.g., exceeding 25%), explored in meta-regressions.[49] Indirect quantitative comparisons may be used where indicated.

F. Grading the Evidence for Each Key Question

Determination of the strength of the body of evidence will be based on the EPC approach, which is outlined in the *Methods Guide*[43] and is based on a system developed by the GRADE Working Group.[50] 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.

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, and Timestamp).[51] The objective of this review is to provide an evidence-based approach to treating hepatocellular cancer. Hence, the population of interest is patients with unresectable hepatocellular cancer. The body of evidence, however, often includes a few patients who are candidates for surgical resection, or patients with advanced disease. To limit their affect on the conclusions in this report these patients have been excluded from the review. However, we have allowed for 10 percent contamination of a study population for this review. Such evidence will require extrapolation to the population of interest.

Other examples of anticipated limitations in interpretation of the evidence include differences in the dosages of chemotherapy and other treatment specifics that may or may not be reported that render comparisons difficult. Since pediatric patients were excluded from this review because of differences in presentation and prognosis when compared with adults, these findings may not be applicable to the pediatric patient populations.

V. References

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VI. Definition of Terms

None

VII. Summary of Protocol Amendments

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. In 1999 the BCLC staging system was published which links the stage of disease to specific treatment strategies. On addition to the new staging system 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 also changed a great deal prior to 2000 and are now more

				standard. For these reasons, strongly supported by the TEP, we excluded studies where patient treatment preceded the year 2000.
11/28/12	PICOTS Framework	All the therapies will be compared to each other as treatment of patients with HCC. This comparison includes any combination of therapies used to treat these patients such as, but not limited to, TACE plus RFA, TACE plus cryoablation, and TAE plus RFA.	When considering comparisons for this review we compared within category of intervention only, rather than across category. Ablative therapies to one another, transarterial therapies to one another, and external-beam therapies compared to one another. Combinations of therapies were also presented together in a section separate from the within category comparisons.	Patients treated with ablative and transarterial or radiation therapy strategies represent two distinct patient populations. Comparing across these treatment categories assumes patients were eligible for both treatments. This is not the case. We have organized the report by treatment category for this reason and have amended the protocol.

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

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.

Appendix A: Search Strings

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

"Carcinoma, Hepatocellular"[Mesh] OR (hepatocellular AND (neoplasm* OR cancer OR cancers OR carcinoma)) 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 "microwave ablation" OR (microwave AND ablation) OR ((percutaneous OR intralesional) AND (ethanol OR acetic acid)) OR embolization OR embolisation OR embolize* OR embolise* OR "transarterial chemoembolization" OR "transarterial chemoembolisation" OR TACE OR "transarterial embolization" OR "transarterial embolisation" OR TAE OR radioembolization OR radioembolisation OR radiotherapy OR radiation OR "external beam" OR "3D conformal" OR "3-D Conformal" OR "intensity modulated radiotherapy" OR IMRT OR "intraluminal brachytherapy" OR "liver-directed chemotherapy" OR 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:

hepatocellular AND (neoplasm* OR cancer OR cancers OR carcinoma) AND (unresectable OR nonresectable OR inoperable OR irresectable) AND (radiofrequency AND ablation) OR RFA OR "microwave ablation" OR (microwave AND ablation) OR ((percutaneous OR intralesional) AND (ethanol OR acetic acid)) OR embolization OR embolisation OR embolize* OR embolise* OR "transarterial chemoembolization" OR "transarterial chemoembolisation" OR TACE OR "transarterial embolization" OR "transarterial embolisation" OR TAE OR radioembolization OR radioembolisation OR radiotherapy OR radiation OR "external beam" OR "3D conformal" OR "3-D Conformal" OR "intensity modulated radiotherapy" OR IMRT OR "intraluminal brachytherapy" OR "liver-directed chemotherapy" OR " OR chemotherapy OR "drug-eluting beads"