Effective Health Care Program

Comparative Effectiveness Review
Number 114

Local Therapies for Unresectable Primary Hepatocellular Carcinoma

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Local Therapies for Unresectable Primary Hepatocellular Carcinoma

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

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

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

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

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

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

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 with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

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 with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers 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 with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Local Therapies for Unresectable Primary Hepatocellular Carcinoma

Structured Abstract

Objectives. To characterize the comparative effectiveness and harms of various local hepatic therapies for patients with unresectable primary hepatocellular carcinoma (HCC) who are not candidates for surgical resection or liver transplantation. Local hepatic therapies include those related to ablation, embolization, and radiotherapy.

Data sources. We searched MEDLINE® and Embase® from January 2000 to July 2012. We also searched for gray literature in databases with regulatory information, clinical trial registries, abstracts and conference papers, as well as information from manufacturers.

Review methods. We sought studies reporting two final health outcomes—overall survival and quality of life—and various adverse events related to the different interventions. Data were dually abstracted by a team of four 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 1,707 articles through the literature search, excluded 1,665 at various stages of screening, and included 42 articles. To these we added 6 hand-searched articles for a total of 48 articles included in this review. Our searches of gray literature sources did not yield any additional published studies. The included literature was comprised of 6 randomized controlled trials (RCTs), 4 nonrandomized comparative studies, 35 case series, and 3 case reports. One RCT was rated as good, three were rated as fair, and two were rated as poor quality. We included 13 local hepatic therapies in this review; however, there was sufficient comparative evidence (three RCTs) to assess only one direct comparison: radiofrequency ablation (RFA) versus percutaneous ethanol injection (PEI)/percutaneous acetic acid injection (PAI). Three-year survival when treated with RFA was superior to that for PEI/PAI for unresectable HCC, with a moderate grade of evidence. Time to progression (TTP) and local recurrence were better for RFA than PEI/PAI, but length of stay (LOS) was longer after RFA than PEI/PAI. Strength of evidence for all other comparisons was rated insufficient. There was a low level of evidence to support longer overall survival following RFA than PEI/PAI for the subgroup of patients with larger lesion size.

Conclusions. Of the 13 interventions included in this report, only 1 comparison had sufficient evidence to receive a rating above insufficient. There was moderate strength of evidence demonstrating better overall survival at 3 years, a low level of evidence supporting improved overall survival for patients with larger lesion sizes, and low strength of evidence for improved TTP and local control for RFA than PEI/PAI for the treatment of unresectable HCC. A low level of evidence also supports a longer LOS following RFA than PEI/PAI. For all other outcomes and comparisons, there is insufficient evidence to permit conclusions on the comparative effectiveness of local hepatic therapies for unresectable HCC. Additional RCTs are necessary for all comparisons. Focusing on comparisons with RFA may allow for the greatest integration of new data with the current body of evidence.

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Introduction

Background

This comparative effectiveness review evaluates local hepatic therapies for patients with unresectable primary hepatocellular carcinoma (HCC) who are not candidates for surgical resection or liver transplantation. Here we describe the epidemiology and staging of HCC, as well as currently available treatment strategies. We also discuss the current practice guidelines and the impetus for this review.

Condition

Hepatocellular carcinoma is the most common primary liver tumor. It is the fifth most common cancer and the third leading cause of cancer death worldwide.[1]Overall 5-year survival rates for HCC are less than 10 percent in Europe and the United States.[1] The main etiology of HCC is chronic infection with the hepatitis B and hepatitis C viruses. Approximately 4 million individuals in the United States are chronically infected with hepatitis C virus, and the annual incidence rate of HCC among patients with hepatitis C–related cirrhosis is estimated to be between 2 and 8 percent. Unlike the case with most solid tumors, the incidence of and mortality rate due to HCC are projected to increase worldwide in the next 20 years, primarily due to the dissemination of hepatitis C virus infection.[2]Other causes include cirrhosis due to any cause (e.g., alcohol), hereditary hemochromatosis and iron overload syndromes, nonalcoholic fatty liver disease, obesity, diabetes, and environmental toxins (e.g., aflatoxin, chewing of betel quid, and contaminated water).[3]

While there are several causes of HCC, etiology is not an independent prognostic factor for HCC;[4,5] rather, the underlying cirrhosis impacts prognosis and treatment decisions. In the United States, most cases of HCC occur in patients with cirrhosis.[1]A small proportion, approximately 5 percent, of all HCC cases in Western countries occur in patients without cirrhosis.[6] For patients with early-stage HCC without underlying cirrhosis, surgical resection is the preferred treatment and offers a high probability of a cure. The Barcelona Clinic Liver Cancer (BCLC) guidelines recommend hepatectomy for patients with a single lesion less than 5 cm in size and mild or no underlying cirrhosis.[7] In contrast, patients with severe cirrhosis are not considered resectable and receive supportive care instead.[7]

This report focuses on the approximately 80 percent of patients who are not surgical candidates due to advanced-stage disease at diagnosis, inadequate hepatic reserve to tolerate resection, tumors in unresectable locations, or medical comorbidities that result in a high surgical risk.[1]

Classification/Staging of Hepatocellular Carcinoma

Both tumor stage and underlying liver function are key considerations in diagnosis, treatment selection, and prognosis of HCC. The 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] This system considers factors related to tumor stage, liver function, performance status, and cancer-related symptoms. HCC is staged from 0 to D.

Other staging systems are used regionally, such as Okuda staging, developed in Japan; 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).8-10 The set of prognostic factors considered in each of these systems varies and includes various measures and combinations of hepatic function, performance status, and tumor characteristics. Given the wide array of prognostic factors across the staging systems, a direct translation from one system to another is inexact.

Classification of Underlying Liver Function

The Child-Pugh classification is a commonly used method to assess the prognosis of patients with underlying liver disease. The system employs five clinical factors: total bilirubin, serum albumin, international normalized ratio (INR; measure of clotting tendency of the blood), ascites (accumulation of fluid in the abdomen), and hepatic encephalopathy (declining brain function caused by toxin accumulation in the brain). Each is scored on a scale of 1–3, from lowest to highest severity. Patients are classified as class A, B, or C based on the total score. HCC patients with class A hepatic impairment have the best prognosis and would be candidates for surgical resection, although many would require local hepatic therapies such as ablative, transarterial, or radiotherapies. HCC patients with class B are not candidates for resection and are typically offered transarterial therapy, ablative therapy, radiotherapy, or systemic therapy. Class C patients are not candidates for local hepatic therapies, with rare exceptions, and usually receive supportive care. Transplantation can be offered to patients of all Child-Pugh classifications if they meet the listing criteria.[11]

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

Treatment Strategies

Over the past few decades, several local, minimally invasive hepatic therapies have been developed to prolong survival and palliate symptoms in patients with unresectable HCC. This report aims to compare the effectiveness and harms of local hepatic therapies for this specific patient population. Therefore, comparisons of ablation versus surgery or systemic chemotherapy versus local hepatic therapy are outside the scope of this report.

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 evaluated for their comparative effectiveness in this review:

- Ablation
  - Radiofrequency ablation (RFA)
  - Percutaneous ethanol injection (PEI)
  - Percutaneous acetic acid injection (PAI)
  - Cryosurgical ablation (cryoablation)
  - Microwave ablation (MWA)
- Embolization

- Transarterial embolization (TAE) or transarterial ethanol ablation (TEA)
- Transarterial chemoembolization (TACE)
- Radioembolization (RE) or selective internal radiation therapy (SIRT)
- Drug-eluting beads (DEB)

- Radiotherapy
  - External-beam three-dimensional conformal radiation therapy (3D-CRT)
  - External-beam intensity-modulated radiation therapy (IMRT)
  - Stereotactic body radiation therapy (SBRT)
  - Hypofractionated proton beam therapy
  - Intraluminal brachytherapy

Several patient and institutional factors may dictate the choice of local hepatic therapy. Patient factors such as vascular anatomy, proportion of liver parenchyma involvement in the tumor, presence of intrahepatic arteriovenous shunts, and performance status may influence the decision to use certain local hepatic therapies.

Ablative therapies such as RFA and external-beam radiation strategies are typically used in patients with unifocal or limited multifocal disease, whereas transarterial strategies such as TACE and RE are typically offered to patients with more advanced, multifocal disease.[7,11] TACE, RE, and RFA are performed by an interventional radiologist experienced in these techniques, although RFA can also be performed by surgeons. External-beam radiation is widely available at most centers;[13] however, it may not be the best treatment option for some patients, such as those who are possible candidates for other modalities (e.g., RE).

The National Comprehensive Cancer Network guidelines state that local hepatic therapies should not be used in place of liver resection or transplantation for patients who meet surgical criteria.[14] The National Institutes of Health consensus recommendation suggests the use of locoregional therapies for selected patients with HCC confined to the liver whose disease is not amenable to resection or transplantation.[15] The existing guidelines do not provide specific guidance on the comparative effectiveness of the therapies. Providers and patients faced with treatment decisions need comparative evidence on which to base these decisions.

Scope and Key Questions

The objective of this systematic review is to examine the comparative effectiveness and harms of various local hepatic therapies for unresectable primary HCC in patients who meet all of the following criteria:

- 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

The analytic framework is available in Figure 1 of the full report.

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. Children are also excluded from this review, as their disease presentation and prognosis are quite different from those of adults.

Nonsurgical candidates eligible for local hepatic therapies are a heterogeneous group. Patient selection criteria are critical for attaining optimal outcomes with the most appropriate local hepatic therapy, and patient selection for these procedures depends on the definition of "medically or technically inoperable patients." We reviewed studies with any length of followup and in both inpatient and outpatient settings. Table A lists the relevant populations, interventions, comparators, outcomes, timeframes of assessment, and settings (PICOTS). The following are the Key Questions (KQs) addressed in this review.

KQ1. 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?

KQ2. 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?

KQ3. 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?

Table A. PICOTS for the Key Questions

PICOTS	KQ1	KQ2	KQ3
Population	Adults with HCC who are candidates for liver-directed therapies, but not for surgical resection or transplantation, who meet the following criteria: • No extrahepatic spread • No portal invasion • Child-Pugh class A or B disease • ECOG status ≤1 *and/or* • BCLC stage A or B, or equivalent This includes: • 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	Same as KQ1	Subgroups of patients in KQ1 stratified by age, sex, disease etiology, and Child-Pugh class

Table A. PICOTS for the Key Questions (continued)

PICOTS	KQ1	KQ2	KQ3
Intervention	**Ablation** • Radiofrequency ablation (RFA) • Percutaneous ethanol injection (PEI)/percutaneous acetic acid injection (PAI) • Cryoablation • Microwave ablation (MWA) **Embolization** • Transarterial embolization (TAE) or transarterial ethanol ablation (TEA) • Transarterial chemoembolization (TACE) • Radioembolization (RE) or selective internal radiation therapy (SIRT) • Drug-eluting beads (DEB) **Radiotherapy** • External-beam 3-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT) • Stereotactic body radiation therapy (SBRT) • Hypofractionated proton beam therapy • Intraluminal brachytherapy Combinations of these interventions were also included in the review (e.g., TACE plus RFA).	Same as KQ1	Same as KQ1
Comparator	Therapies were compared with other liver-directed therapies within the following categories of intervention: 1. Ablative therapies compared with other ablative therapies 2. Transarterial therapies compared with other transarterial therapies 3. Radiotherapies compared with other radiotherapies 4. Combinations of liver-directed therapies including but not limited to TACE plus cryoablation and TAE plus RFA	Same as KQ1	Same as KQ1
Outcome	• ***Final health outcomes:*** Survival, quality of life • ***Intermediate outcomes:*** Time to progression, local recurrence, length of stay, days of missed work	• ***Adverse outcomes:*** hepatic abscess, hepatic hemorrhage, biloma, steatohepatitis, injury to adjacent organ(s), liver failure, infection, increased alkaline phosphatase, increased bilirubin, increased transaminases, and rare adverse events	Same as KQ1
Timing	The relevant periods occur from the time of treatment through followup over months or years	Same as KQ1	Same as KQ1
Setting	Inpatient and outpatient	Same as KQ1	Same as KQ1

Abbreviations: BCLC = Barcelona Clinic Liver Cancer staging classification; ECOG = Eastern Cooperative Oncology Group; HCC = hepatocellular carcinoma; KQ = Key Question; PICOTS = population, intervention, comparator, outcome, timing, and setting.

Methods

Topic Refinement and Review Protocol

The topic for this report was nominated in a public process. With input from Key Informants, the Evidence-based Practice Center (EPC) team drafted the initial KQs and posted them to a Web site for public comment for 4 weeks. Changes to the KQs and the PICOTS framework were made based on the public commentary and discussion with the Technical Expert Panel (TEP). However, the initial stratification of KQs and interventions by intent of treatment (palliative or curative) was deemed inappropriate and confusing. Interventions could not be clearly classified as either curative or palliative. Also, the term "palliative" is often associated with end-of-life care, and applying that term to this population, who may have early-stage disease, would cause confusion.

The inability to translate disease stage from one classification system to another made it difficult to differentiate between patients with BCLC stage A and B liver disease across publications. Therefore, two KQs refer to effectiveness and harms of liver-directed therapy for patients with unresectable disease without portal invasion or extrahepatic spread, with preserved liver function, and with an ECOG status ≤1 *or* BCLC stage A or B, or equivalent. A third KQ was added to address potential differences in effectiveness by patient and tumor characteristics. SBRT was added to the list of interventions. Increased alkaline phosphatase, increased bilirubin, increased transaminases, liver failure, and rare adverse events were added to the list of harms.

After reviewing the public commentary and TEP recommendations, the EPC drafted final KQs and submitted them to AHRQ for approval.

Data Sources and Selection

MEDLINE® and Embase® were searched for randomized, nonrandomized comparative, and case-series studies published between January 1, 2000, and July 27, 2012. Date restrictions were applied to ensure applicability of the interventions. In 1999 the BCLC staging system was published, which links the stage of disease to specific treatment strategies. In addition to the new staging system, some interventions were in their infancy before 2000 and, based on current standards, used outdated regimens.[16-18] Thermal therapies were not used significantly until the late 1990s, and major changes in proton beam and stereotactic therapy occurred during that same period.[19] Chemoembolization drugs and embolic mixtures have also changed a great deal in the last 10 years and are more standard now. For these reasons, with strong support from the TEP, we excluded studies in which patient treatment preceded the year 2000, as significant changes have been made in interventional approaches to local hepatic therapies since 2000. The searches were limited to English-language studies.[20] The TEP noted that most of the pivotal studies are published in English-language journals, and therefore the exclusion of non–English-language articles from this review would not impact the conclusions. See Table B for inclusion and exclusion criteria. Gray literature was also searched, including regulatory databases, clinical trial registries, abstracts and conference papers, and information from manufacturers.

Titles and abstracts were screened in duplicate. Disagreements in the title screening were resolved by abstract screening by two independent reviewers. A third reviewer was consulted when necessary. Full-text review was performed when it was unclear if the abstract met study selection criteria.

Data Extraction

Data were directly extracted into tables created in DistillerSR.® All team members extracted a training set of five articles to ensure uniform extraction procedures. All data extraction was performed in duplicate, with discrepancies resolved by consensus. The full research team met regularly during data extraction to discuss any issues. Extracted data included patient and treatment characteristics, outcomes related to intervention effectiveness, and data on harms.

Table B. Inclusion and exclusion criteria

Category	Criteria
Study population	Adults with HCC who are candidates for local hepatic 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 Specifically, patients who meet all of the following criteria: • No extrahepatic spread • No portal invasion • Child-Pugh class A or B disease • ECOG status ≤1 *and/or* • BCLC stage A or B, or equivalent
Time period	Studies in which patients received treatment since 2000
Publication languages	English only
Admissible evidence (study design and other criteria)	***Admissible designs:*** • All study designs will be considered. • Case reports will be considered only if they report on a rare adverse event. ***Other criteria:*** • Studies must involve 1 or more of the interventions listed in the PICOTS. • Studies must include at least 1 outcome measure listed in the PICOTS. • Relevant outcomes must be extractable from data presented in the articles. • To allow for the inclusion of all potentially relevant evidence, studies that deviated from our inclusion criteria by less than 10% were included (e.g., 5% of patients had HCC or 9% of patients had documented extrahepatic disease).

Abbreviations: BCLC = Barcelona Clinic Liver Cancer staging classification; ECOG = Eastern Cooperative Oncology Group; HCC = hepatocellular carcinoma; PICOTS = population, intervention, comparator, outcome, timing, and setting.

Risk-of-Bias Assessment of Individual Studies

In the assessment of risk of bias in individual studies, we followed the Agency for Healthcare Research and Quality (AHRQ) "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (Methods Guide).[21] Quality assessment of each study was conducted by two independent reviewers, with discrepancies adjudicated by consensus. The United States Preventive Services Task Force (USPSTF) tool for randomized controlled trials (RCTs) and nonrandomized comparative studies[22]and a set of study characteristics proposed by Carey and Boden for studies with a single-arm design[23] were used to assess individual study quality. The USPSTF tool is designed for the assessment of studies with experimental designs and randomized participants. Fundamental domains include assembly and maintenance of comparable groups; loss to followup; equal, reliable, and valid measurements; clear definitions of interventions; consideration of all important outcomes; and analysis that adjusts for potential

confounders and intention-to-treat analysis. It has the following thresholds for good, fair, and poor quality,[22] which were applied to the RCTs and nonrandomized comparative studies:

- *Good:* Studies graded "good" meet all criteria; comparable groups are assembled initially and maintained throughout the study (patient followup at least 80 percent); 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, for RCTs, intention-to-treat analysis is used.
- *Fair:* Studies are graded as "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 question remains as to whether some (although not major) differences occurred with followup; measurement instruments are acceptable (although not the best) and 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 is done for RCTs.
- *Poor:* Studies are graded as "poor" if any of the following fatal flaws exist: groups assembled initially are not close to being comparable or maintained throughout the study; measurement instruments used are unreliable or invalid, or are not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention-to-treat analysis is lacking.

The criteria by Carey and Boden[23] for assessing single-arm studies evaluate whether there are clearly defined study questions, well-described study population, well-described intervention, use of validated outcome measures, appropriate statistical analyses, well-described results, and discussion and conclusion supported by data. These criteria do not produce an overall quality ranking; therefore, we created the following thresholds to convert these ratings into the AHRQ standard quality ratings (good, fair, and poor). A study was ranked as good quality if each of the Carey and Boden[23] criteria listed above was met, a fair quality rating was given if one of the criteria was not met, and a poor quality rating was given to studies with more than one unmet criteria.

The classification of studies into categories of good, fair, and poor was used for differentiation within the group of studies of a specific study design, and not for the overall body of evidence described below. Each study design was evaluated according to its own strengths and weaknesses. These quality ranking forms and their conversion thresholds can be found in Appendix C of the full report.

Data Synthesis

Pooling of treatment effects was considered for each treatment comparison according to AHRQ guidance.[21] Three or more clinically and methodologically similar studies (i.e., studies designed to ask similar questions about treatments in similar populations and to report similarly defined outcomes) were required for pooling. Only trials that reported variance estimates (standard error, standard deviation, or 95 percent confidence interval [CI]) for group-level treatment effects could be pooled. The pooling method involved inverse variance weighting and a random-effects model. For any meta-analysis performed, we assessed statistical heterogeneity by using Cochran's Q statistic (chi-squared test) and the I^2 statistic. A p value of 0.10 was used to determine statistical significance of Cochran's Q statistic. Thresholds for the interpretation of

I^2 were: 0 percent to 40 percent, may not be important; 30 percent to 60 percent, may represent moderate heterogeneity; 50 percent to 90 percent, may represent substantial heterogeneity; 75 percent to 100 percent, represents considerable heterogeneity.

Strength of the Body of Evidence

Two independent reviewers graded the strength of evidence, resolving disagreements by consensus 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,[24] which is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[25] This system explicitly addresses the following domains: risk of bias, consistency, directness, and precision. The strength of evidence was graded as high, moderate, low, or insufficient for each outcome of interest in this report. Rules for the starting strength of evidence and factors that would raise or lower the strength are described in Table C.

Table C. Strength of evidence categories and rules

Strength of Evidence and Rules	Criteria
High SOE	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate SOE	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 SOE	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 SOE	Evidence is either unavailable or does not permit estimation of an effect.
Starting level of strength of RCT evidence	High
Starting level of strength of observational evidence	Low, but a single observational study of good quality without confirmation by at least 1 other study of good or fair quality supports an SOE rating of insufficient.
Raise strength	Among observational studies, raise strength by 1 level if a large effect size is observed, a dose-response association is present, or a plausible confounder could decrease the observed effect. A very large effect size could raise strength by 2 levels.
Reduce strength	Reduce strength by 1 level if there is serious concern in an area such as high risk of bias, inconsistent findings, consistency unknown, indirect evidence, imprecise results, or presence of publication bias. Very serious concern in any of these areas could reduce strength by 2 levels.

Abbreviations: RCT = randomized controlled trial; SOE = strength of evidence.

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.

Peer Review and Public Commentary

This report received external peer review. Peer Reviewers were charged with commenting on the content, structure, and format of the evidence report; providing additional relevant citations; and pointing out issues related to how we conceptualized the topic and analyzed the evidence. Our Peer Reviewers (listed in the front matter) gave us permission to acknowledge their review

of the draft. In addition, the draft report was placed on AHRQ's Effective Health Care Web site (www.effectivehealthcare.ahrq.gov) for public review.

No public comments were received. We compiled all peer review comments and addressed each one individually, revising the text as appropriate. Based on peer review, structure was added to the results section to clarify that all comparisons were made within each category of intervention. Additional language was added to the comparator in the PICOTS to restrict comparisons to the same intervention type. AHRQ staff and an associate editor provided reviews. A disposition of comments from public commentary and peer review will be posted on the Effective Health Care Web site (www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/) 3 months after the final report is posted.

Results

Results are organized by KQ and then by type of local hepatic therapy, followed by the specific comparison. Summary tables presenting the outcomes reported in each article, evidence tables for each local hepatic therapy comparison, and the forest plot for the meta-analysis of RFA compared with PEI/PAI are presented in the full report.

Results of Literature Search

Of the 1,707 articles identified through the literature search, 1,665 were excluded at various stages of screening and 42 articles were included. Six hand-searched articles were also included, for a total of 48 articles in this systematic review. Our searches of various gray literature sources did not yield any additional published studies meeting our inclusion criteria. Characteristics of these included studies are presented in Tables D and E.

Table D. Number of study arms included in this review, by selected characteristics and intervention: monotherapies

Characteristic	Cryoablation	RFA	MWA	PEI/PAI	TAE	TACE[a]	RE	DEB	3D-CRT	IMRT	SBRT	HPBT	IB	Total Study Arms
Total study arms for intervention	3	9	1	3	3	19	4	5	2	0	3	0	0	52
Study Design														
RCT	0	4	0	3	1	1	0	2	0	0	0	0	0	11
Prospective cohort	0	1	0	0	0	1	0	0	0	0	0	0	0	3
Retrospective cohort	1	1	0	0	0	3	0	0	0	0	0	0	0	5
Prospective case control	0	0	0	0	0	1	0	1	0	0	0	0	0	2
Retrospective case control	0	0	0	0	1	1	0	0	1	0	0	0	0	3
Prospective case series	0	1	1	0	0	4[b]	3[c]	1	1	0	0	0	0	10
Retrospective case series	2	0	0	0	1	5	1	1	0	0	3	0	0	13
Case series, unknown temporal frame	0	1	0	0	0	1	0	0	0	0	0	0	0	2
Case report	0	1	0	0	0	2	0	0	0	0	0	0	0	3
Outcomes Reported														
Overall survival	3	8	1	3	3	14	4	5	2	0	3	0	0	41
Quality of life	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Time to progression	0	5	1	2	2	6	0	4	0	0	3	0	0	23
Length of stay	1	2	0	2	0	4	1	3	0	0	0	0	0	13
Local recurrence	2	7	1	3	1	0	0	1	2	0	1	0	0	18
Adverse events	3	8	0	3	2	15	3	5	2	0	3	0	0	44
Study Population														
United States/Canada	0	1	0	0	0	4	3	1	0	0	1	0	0	10
Europe	0	1	0	1	2	6	0	3	0	0	0	0	0	12
Australia	0	0	0	0	0	0	1	0	0	0	0	0	0	1
Asia	3	7	1	2	1	9	0	1	2	0	2	0	0	28
Africa	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total N participants	238	320	60	299	76	1,876	187	362	55	0	91	0	0	3,564

[a]Transarterial embolization (bland, without any chemotherapeutic agent) was performed every time epirubicin was contraindicated in Pietrosi et al., (Pietrosi G, Miraglia R, Luca A, et al. Arterial chemoembolization/embolization and early complications after hepatocellular carcinoma treatment: a safe standardized protocol in selected patients with Child class A and B cirrhosis. J Vasc Interv Radiol. 2009;20(7):896-902. PMID: 19497762).

[b]Includes 1 RCT abstracted as case series.

[c]Includes 1 prospective cohort study abstracted as case series.

Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy; DEB = drug-eluting beads; HPBT = hypofractionated proton beam therapy; IB = intraluminal brachytherapy; IMRT = intensity-modulated radiation therapy; MWA = microwave ablation; N = number; PAI = percutaneous acetic acid injection; PEI = percutaneous ethanol injection; RCT = randomized controlled trial; RE = radioembolization; RFA = radiofrequency ablation; SBRT = stereotactic body radiotherapy; TACE = transarterial chemoembolization; TAE = transarterial embolization.

Table E. Number of study arms included in this review, by selected characteristics and intervention: combination therapies

Characteristic	RFA With TACE	RFA With TAE	RFA With DEB	TACE With PEI	TACE With Cryoablation	Total Study Arms
Total study arms for intervention	2	1	1	1	1	6
Study Design						
RCT	1	0	0	0	0	1
Prospective cohort	0	0	0	0	0	0
Retrospective cohort	0	0	0	0	1	1
Retrospective case control	0	0	0	0	0	0
Prospective case series	0	1	1	1	0	3
Retrospective case series	1	0	0	0	0	1
Case report	0	0	0	0	0	0
Outcomes Reported						
Overall survival	2	1	0	1	1	5
Quality of life	0	0	0	0	0	0
Time to progression	2	0	0	0	0	2
Length of stay	0	0	1	0	0	1
Local recurrence	1	0	0	0	1	2
Adverse events	1	1	1	1	1	5
Study Population						
United States	0	0	0	0	0	0
Europe	0	0	1	0	0	1
Australia	0	0	0	0	0	0
Asia	2	1	0	1	1	5
Total N participants	141	36	20	63	290	550

Abbreviations: DEB = drug-eluting beads; N = number; PEI = percutaneous ethanol injection; RCT = randomized controlled trial; RFA = radiofrequency ablation; TACE = transarterial chemoembolization; TAE = transarterial embolization.

Key Questions 1 and 2: Effectiveness and Harms of Local Hepatic Therapy

KQs 1 and 2 focus on the comparative effectiveness (KQ1) and harms (KQ2) of various local hepatic therapies in patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and have no evidence of extrahepatic disease.

A total of 48 studies met the inclusion criteria to address KQ1 and KQ2: 6 RCTs, 4 nonrandomized comparative studies, 35 case-series studies, and 3 case reports. Three nonrandomized comparative studies were retrospective and one was prospective. We identified the following seven unique comparisons of local hepatic therapies in the 48 studies: RFA versus PEI/PAI, DEB versus TAE, DEB versus TACE, TACE versus TEA, TACE versus TACE-cryoablation, and cross-category comparisons of RFA versus TACE and RFA versus RFA-TACE. The cross-category comparisons included similar patients who would have been eligible for ablative therapy. The outcomes specified in the PICOTS were assessed for each of these comparisons. PEI and PAI were combined, as they are the same procedure but use different agents. The assessment of individual agents is outside the scope of this review. In addition, a Cochrane review found no differences between the two procedures in terms of overall survival.[26]

Key points regarding KQs 1 and 2 are as follows.

- RFA compared with PEI/PAI: There is moderate strength of evidence to support better overall survival at 3 years for RFA compared with PEI/PAI, with a low risk of bias. Three RCTs compared the ablative treatments RFA and PEI/PAI. No nonrandomized comparative studies examined this comparison. In addition to the comparative evidence, three case series of RFA are included in this report. No observational studies on PEI/PAI met inclusion criteria.
- The body of evidence for RFA compared with PEI/PAI was rated low strength to support increased time to progression (TTP), improved local control, and a longer length of stay (LOS) for RFA compared with PEI/PAI, with a high risk of bias.
- Of the 13 interventions included in this report, only one comparison had sufficient evidence to receive a rating above insufficient. For all other comparisons, the body of evidence on overall survival, quality of life, disease progression, local control, LOS, days of missed work, and adverse events for local hepatic therapy for the treatment of HCC is insufficient to support the effectiveness of one local hepatic therapy over another due to the lack of comparative studies.

Table F summarizes the main findings and related strength of evidence for each outcome of interest.

Table F. Summary GRADE strength of evidence for KQ1 and KQ2

Key Question, Comparison, and Outcome	Strength of Evidence	Conclusion
KQ1. 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?		
RFA to PEI/PAI		
Overall survival	Moderate	One good-quality RCT (n = 139) and 2 fair-quality RCTs (n = 157 and n = 187) assessed 3-year overall survival after treatment with RFA or PEI/PAI. In a meta-analysis, the pooled risk difference of 0.16 (95% CI, 0.03 to 0.28) was statistically significant in favor of RFA. The heterogeneity in this pool of studies was moderate (I^2= 48%).
Quality of life	Insufficient	Quality of life was not reported in any of the comparative studies.
Outcomes related to progression	Low	Two fair-quality RCTs reported outcomes related to progression (n = 157 and n = 187). One study reported cancer-free survival (from time of study treatment to local tumor progression), extrahepatic metastases, additional new HCC recurrence, or death. The 3-year cancer-free survival rate was 37%, 17%, and 20% in the RFA, PEI, and higher dose PEI groups, respectively. The RFA group had a significantly higher cancer-free survival rate than the 2 PEI groups (RFA vs. conventional PEI: risk ratio = 0.38; 95% CI, 0.14 to 0.88; p = 0.019; RFA vs. higher dose PEI: risk ratio = 0.41; 95% CI, 0.22 to 0.89; p = 0.024). In the other RCT, 3-year cancer-free survival was 43%, 21%, and 23% in the RFA, PEI, and PAI groups, respectively (RFA vs. PEI: risk ratio = 0.31; 95% CI, 0.18 to 0.85; p = 0.038; RFA vs. PAI: risk ratio = 0.26; 95% CI, 0.13 to 0.81; p = 0.041).
Local recurrence/local tumor progression	Low	Two fair-quality RCTs (n = 157 and n = 187) reported local tumor progression (defined as the presence of an enhanced tumor on CT corresponding to the initial target tumor). In 1 RCT, the RFA group had a significantly lower rate than the PEI groups (RFA vs. conventional PEI: risk ratio= 0.37; 95% CI, 0.12 to 0.76; p = 0.012; RFA vs. higher dose PEI: risk ratio = 0.49; 95% CI, 0.23 to 0.92; p = 0.037). This study assessed local recurrence in all randomized patients. In the second RCT, the local recurrence rate was significantly lower in the RFA group than the PEI (risk ratio = 0.35; 95% CI, 0.21 to 0.89; p = 0.012) and PAI (risk ratio = 0.41; 95% CI, 0.23 to 0.91; p = 0.017) groups. This study assessed local recurrence only for patients achieving complete tumor necrosis following treatment.

Table F. Summary GRADE strength of evidence for KQ1 and KQ2 (continued)

Key Question, Comparison, and Outcome	Strength of Evidence	Conclusion
Length of stay	Low	LOS was reported in 2 fair-quality RCTs (n = 157 and n = 187). Both studies reported LOS only for a subset of patients who achieved complete tumor necrosis. In the first study, the RFA group had a significantly longer mean LOS than the conventional PEI group (4.4 days ± 1.8 vs. 1.6 days ± 0.3; p<0.01). In the second trial, the RFA group had a significantly longer LOS than either the PEI group or the PAI group (4.2 days ± 1.9, 1.7 days ± 0.4, 2.2 days ± 0.6, respectively; all p<0.01).
Days of missed work	Insufficient	Days of missed work were not reported in any of the comparative studies.
DEB to TAE		
Overall survival	Insufficient	One poor-quality RCT (n = 84), reported that there was no statistically significant difference in 1-year overall survival between the groups (85.3% and 86%, respectively; p-value not reported).
Quality of life	Insufficient	Quality of life was not reported in any of the comparative studies.
Outcomes related to progression	Insufficient	One poor-quality RCT (n = 84) reported TTP, defined as the time from the first treatment until progression, which was either local recurrence, new lesions, or a combination of both (overall recurrence). The mean TTP was longer in the DEB group (10.6 ± 2.4 months) than the TAE group (9.1 ± 2.3 months; p = 0.008).
Local recurrence/local tumor progression	Insufficient	One poor-quality RCT (n = 84), reported local recurrence as the number of patients with local recurrence out of the total number of patients evaluated at 6, 9, and 12 months: 1/41 (2.4%), 6/40 (15%), and 11/35 (31.4%) in the DEB group and 4/43 (9.3%), 19/41 (46.3%), and 21/37 (56.8%) in the TAE group, respectively.
Length of stay	Insufficient	LOS was not reported in any of the comparative studies.
Days of missed work	Insufficient	Days of missed work were not reported in any of the comparative studies.
DEB to TACE		
Overall survival	Insufficient	One fair-quality RCT (n = 67) reported that 2-year overall survival rates were not significantly different between the groups (83.6% in the conventional TACE group and 86.8% in the DEB group; p = 0.96). One poor-quality prospective case-control study (n = 105) reported no significant difference in overall median survival between the groups (11.4 months after enrollment in the TACE group vs. 18.4 months after enrollment in the DEB group).
Quality of life	Insufficient	Quality of life was not reported in any of the comparative studies.

Table F. Summary GRADE strength of evidence for KQ1 and KQ2 (continued)

Key Question, Comparison, and Outcome	Strength of Evidence	Conclusion
Outcomes related to progression	Insufficient	One fair-quality RCT (n = 67) reported time to radiologic progression (defined as the time from study treatment to disease progression). The median time had not been reached, and the mean expected time to radiographic progression was not significantly different between the groups (24.2 months after TACE vs. 15.6 months after DEB; p = 0.64). One poor-quality prospective case control study (n = 105) reported relapse-free survival (defined as the time between the embolization to any relapse and the appearance of a second primary cancer or death). The median relapse-free survival was not significantly different between the groups (8.4 months after TACE vs. 13.1 months after DEB).
Local recurrence/local tumor progression	Insufficient	One fair-quality RCT (n = 67) assessed the median expected time to local recurrence within the initial target lesions and found the difference was nonsignificant (12.8 months after TACE and 8.9 months after DEB; p = 0.46).
Length of stay	Insufficient	One fair-quality RCT (n = 67) reported no significant difference between the conventional TACE and DEB groups in terms of mean LOS (6.8 days vs. 5.9 days; p = 0.26). One poor-quality prospective case-control study reported a significant difference in median LOS between TACE and DEB (2.3 days vs. 4.7 days; p<0.0001).
Days of missed work	Insufficient	Days of missed work were not reported in any of the comparative studies.
RFA to TACE		
Overall survival	Insufficient	One poor-quality retrospective cohort study (n = 91) reported overall survival. Two-year survival for RFA and TACE was 72% and 58%, respectively, which was not found to be statistically different (p = 0.21).
Quality of life	Insufficient	Quality of life was not reported in any of the comparative studies.
Outcomes related to progression	Insufficient	One poor-quality retrospective cohort study (n = 91) reported time to disease progression. This was calculated from the date of disease response to treatment to the date of disease progression. Disease progression occurred in 35 patients (88%) in the TACE group and 36 patients (71%) in the RFA group. The median time to disease progression was 9.5 months (range: 1.0 to 47.3 months) in patients treated with TACE and 10.4 months (range: 1.0 to 42.7 months) in patients treated with RFA (p = 0.95).
Local recurrence/local tumor progression	Insufficient	One poor-quality retrospective cohort study (n = 91) reported a local recurrence rate of 14% (n = 7) in the RFA group. The authors did not report the local recurrence rate in the TACE group.
Length of stay	Insufficient	LOS was not reported in any of the comparative studies.
Days of missed work	Insufficient	Days of missed work were not reported in any of the comparative studies.
TACE to TEA		
Overall survival	Insufficient	One poor-quality retrospective case-control study (n = 60) reported there was a significant difference in the 2-year survival rate (measured from the date of first study treatment): 43.3% and 80% for the TACE and TEA groups, respectively (p = 0.0053).

Table F. Summary GRADE strength of evidence for KQ1 and KQ2 (continued)

Key Question, Comparison, and Outcome	Strength of Evidence	Conclusion
Quality of life	Insufficient	Quality of life was not reported in any of the comparative studies.
Outcomes related to progression	Insufficient	One poor-quality retrospective case-control study (n = 60) assessed progression-free survival, measured from the date of first study treatment to the date of death or last followup, and reported a nonsignificant difference between the TACE and TEA groups (46% at 1 year and 42.5% at 2 years for TACE, and 69.8% at 1 year and 58.8% at 2 years for TEA; p = 0.0588).
Local recurrence/local tumor progression	Insufficient	Local recurrence/local tumor progression was not reported in any of the comparative studies.
Length of stay	Insufficient	LOS was not reported in any of the comparative studies.
Days of missed work	Insufficient	Days of missed work were not reported in any of the comparative studies.
RFA to RFA-TACE		
Overall survival	Insufficient	One low-quality RCT (n = 37) reported no statistically significant difference in the 1-, 2-, and 3-year survival rates between the 2 groups (p = 0.369).
Quality of life	Insufficient	Quality of life was not reported in any of the comparative studies.
Outcomes related to progression	Insufficient	Outcomes related to progression were not reported in any of the comparative studies.
Local recurrence/local tumor progression	Insufficient	One low-quality RCT (n = 37) reported a significant difference in local tumor progression rate (undefined) at the end of 1, 2, and 3 years between the TACE-RFA combination therapy group and the RFA monotherapy group (6% vs. 39% at 3 years; p = 0.012).
Length of stay	Insufficient	LOS was not reported in any of the comparative studies.
Days of missed work	Insufficient	Days of missed work were not reported in any of the comparative studies.
TACE to TACE-Cryoablation		
Overall survival	Insufficient	One poor-quality retrospective cohort study (n = 420) reported that 1- to 3-year survival outcomes were not statistically different between groups. However, in years 4 and 5, the combination therapy group showed a superior survival outcome (p = 0.001).
Quality of life	Insufficient	Quality of life was not reported in any of the comparative studies.
Outcomes related to progression	Insufficient	Outcomes related to progression were not reported in any of the comparative studies.
Local recurrence/local tumor progression	Insufficient	One poor-quality retrospective cohort study (n = 420) reported that the local recurrence rate at the ablated area was 17% for all patients, 23% for the cryoablation group, and 11% for the sequential TACE-cryoablation group (p = 0.001).
Length of stay	Insufficient	LOS was not reported in any of the comparative studies.
Days of missed work	Insufficient	Days of missed work were not reported in any of the comparative studies.

Table F. Summary GRADE strength of evidence for KQ1 and KQ2 (continued)

Key Question, Comparison, and Outcome	Strength of Evidence	Conclusion
KQ2. 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?		
RFA to PEI/PAI	Insufficient	None of the 3 RCTs comparing RFA and PEI/PAI reported the following AEs: hepatic abscess, hepatic hemorrhage, biloma, steatohepatitis, injury to adjacent organs, liver failure, or infection.
DEB to TAE	Insufficient	In 1 poor-quality RCT (n = 84), the authors reported hepatic abscess in 2 (4.8%) and 1 (2.3%) patients in the DEB and TAE groups, respectively, and liver failure in 2 patients in each group. The study authors did not report on the following AEs: hepatic hemorrhage, biloma, steatohepatitis, injury to adjacent organs, infection, increased liver enzymes (transaminases, bilirubin, alkaline phosphatase), or rare AEs.
DEB to TACE	Insufficient	One fair-quality RCT (n = 67) reported liver failure in 1 patient (3%) receiving TACE and none in the DEB group. This RCT also reported significant ($p<0.0001$) increases in ALT and bilirubin levels compared with baseline. Increases in ALT were significantly higher in the TACE group than in the DEB group ($p = 0.007$). Increased bilirubin was not different between groups. The study did not report on the following AEs: hepatic abscess, hepatic hemorrhage, biloma, steatohepatitis, injury to adjacent organs, infection, and rare AEs. One poor-quality prospective case-control study (n = 105) reported no significant difference in mean baseline AST values between the TACE and DEB groups (109 ± 12 IU vs. 116 ± 31 IU). After the procedures, the difference between the mean AST values became statistically significant (805 ± 125 IU for TACE vs. 238 ± 57 IU for DEB; $p<0.05$). Increases in the ALT and LDH levels were observed for 9 days in the TACE group and 4 days for the TACE DEB groups.
RFA to TACE	Insufficient	One poor-quality retrospective cohort study (n = 91) reported that liver failure was observed in 1 (2%) and 2 (5%) patients in the RFA and TACE groups, respectively. The study did not report on the following AEs: hepatic abscess, hepatic hemorrhage, biloma, steatohepatitis, injury to adjacent organs, infection, increased liver enzymes (transaminases, bilirubin, alkaline phosphatase), or rare AEs.
TACE to TEA	Insufficient	One poor-quality retrospective case series (n = 60) did not report adverse events.
RFA to RFA-TACE	Insufficient	One low-quality RCT (n = 37) reported no major complications in the TACE-RFA combination and RFA monotherapy groups.

Table F. Summary GRADE strength of evidence for KQ1 and KQ2 (continued)

Key Question, Comparison, and Outcome	Strength of Evidence	Conclusion
TACE to TACE-Cryoablation	Insufficient	One poor-quality retrospective cohort study (n = 420) reported no observed events of hepatic hemorrhage or liver failure. Hepatic abscess, biloma, steatohepatitis, injury to adjacent organs, infection, increased liver enzymes (transaminases, bilirubin, alkaline phosphatase), and rare AEs were not reported.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate transaminase; CI = confidence interval; CT = computed tomography; DEB = drug-eluting beads; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HCC = hepatocellular carcinoma; KQ = Key Question; LDH = lactate dehydrogenase; LOS = length of stay; PAI = percutaneous acetic acid infusion; PEI = percutaneous ethanol infusion; RCT = randomized controlled trial; RFA = radiofrequency ablation; TACE = transarterial chemoembolization; TAE = transarterial embolization; TEA = transarterial ethanol ablation; TTP = time to progression.

Key Question 3: Patient Subgroups

KQ3 focuses on the assessment of heterogeneity of treatment effects across patient subgroups. Subgroups of interest include age, sex, HCC stage, disease etiology, lesion size, and multifocal disease. All included comparative studies were reviewed for KQ3, but case series and case reports were excluded given the lack of a comparator.

Key points regarding KQ3 are as follows.

- Three RCTs reported subgroup analyses of interest for the comparison of RFA with PEI/PAI. Subgroup analyses in these studies were ad hoc rather than prespecified in the analysis plan, leading to a high risk of bias. Two RCTs by Lin et al.[27,28] found that RFA yielded a significantly greater overall survival than PEI/PAI among patients with larger lesions, defined as 2–3 cm in one study and 3.1–4 cm in another study. In contrast, an RCT by Brunello et al.[29] found no significant difference in overall survival between RFA and PEI among patients with lesions >2 cm in size. There is low strength of evidence with a high risk of bias to support increased overall survival for RFA compared with PEI/PAI in patients with larger lesions. The evidence is insufficient to assess the effects of lesion size on other outcomes of interest in this report and insufficient evidence for other patient subgroups on any outcome of interest in this report.
- In one RCT by Brunello et al.,[29] no difference in overall survival was found between RFA and PEI among the subgroups of patients in Child-Pugh class A and those with multifocal HCC. The evidence was graded as insufficient due to results of unknown consistency and a high risk of bias.
- No studies presented subgroup analyses on age, sex, disease etiology, or HCC stage. Therefore, the evidence is insufficient to assess the effect of these subgroups for any outcomes of interest in this review.

Table G summarizes the main findings and related strength of evidence for each outcome of interest.

Table G. Summary GRADE strength of evidence for KQ3

Key Question, Comparison, and Patient or Tumor Characteristics	Strength of Evidence	Conclusion
KQ3. 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?		
RFA to PEI/PAI: age	Insufficient	None of the 3 RCTs reported subgroup analysis by age.
RFA to PEI/PAI: sex	Insufficient	None of the 3 RCTs reported subgroup analysis by sex.
RFA to PEI/PAI: disease etiology	Insufficient	None of the 3 RCTs reported subgroup analysis by disease etiology (e.g., HBV, HCV).
RFA to PEI/PAI: HCC stage	Insufficient	None of the 3 RCTs reported subgroup analysis by HCC stage (e.g., BCLC stage A or B).
RFA to PEI/PAI: Child-Pugh class (overall survival)	Insufficient	One RCT (n = 139) found a nonsignificant difference in overall survival between the RFA and PEI groups among patients in Child-Pugh class A (hazard ratio = 0.67; 95% CI, 0.25 to 1.80; p = 0.43).
RFA to PEI/PAI: lesion size (overall survival)	Low	One RCT (n = 139) found a nonsignificant difference in overall survival between the RFA and PEI groups among patients with HCC lesions >2 cm in diameter (hazard ratio = 0.62; 95% CI, 0.28 to 1.36; p = 0.23). One RCT (n = 157) found that the overall survival rate was significantly higher in the RFA group than the PEI group (p = 0.032) and in the PAI group (p = 0.027) among patients with HCC lesions 2–3 cm in size. Among patients with smaller HCC lesions (1–2 cm), no significant difference between treatment groups was seen. One RCT (n = 187) found that the overall survival rate was significantly higher in the RFA group than the conventional PEI group (p<0.03) and the higher dose PEI group (p<0.04) among patients with HCC lesions 3.1–4 cm in size. Among patients with smaller HCC lesions (1–2 cm and 2.1–3 cm), no significant difference between treatment groups was seen.
RFA to PEI/PAI: lesion size (cancer-free survival)	Insufficient	One RCT (n = 187) found that the 3-year cancer-free survival of the RFA group was significantly higher than both PEI (p = 0.031) and PAI (p = 0.035) groups when lesion size was between 2 and 3 cm. This difference was not significant with smaller lesion sizes (1–2 cm) or earlier cancer-free survival times.
RFA to PEI/PAI: lesion size (local recurrence rate)	Insufficient	One RCT (n = 187) found that the local recurrence rate was lower in the RFA group than the PEI group (p = 0.009) and PAI group (p = 0.011) among the smaller HCC lesion subgroup but not in the larger HCC lesion subgroup.
RFA to PEI/PAI: multifocal HCC	Insufficient	One RCT (n = 139) reported a nonsignificant difference in overall survival between the RFA and PEI groups among patients with multifocal HCC (hazard ratio = 0.48; 95% CI, 0.16 to 1.43; p = 0.19).

Abbreviations: BCLC = Barcelona Clinic Liver Cancer staging classification; CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; KQ = Key Question; PAI = percutaneous acetic acid infusion; PEI = percutaneous ethanol infusion; RCT = randomized controlled trial; RFA = radiofrequency ablation.

Discussion

Key Findings and Strength of Evidence

This review addressed the comparative effectiveness of local hepatic therapy for the treatment of unresectable HCC in patients who are not otherwise eligible for transplantation and do not have extrahepatic spread. Forty-eight studies met our inclusion criteria: 6 RCTs, 4 nonrandomized comparative studies, 35 observational case series, and 3 case reports.

We assessed the strength of evidence for our primary health outcomes of overall survival and quality of life; the intermediate outcomes of TTP, local recurrence, LOS, and days of work missed for KQ1; and adverse events for KQ2. In addition, we reviewed the effect of patient subgroups on the comparative effectiveness of the included comparisons for our population of interest for KQ3.

For the comparison of RFA with PEI/PAI, three RCTs[27-29] were pooled in a meta-analysis, and risk differences were calculated. The pooled estimate was 0.16 (95% CI, 0.03 to 0.28), a statistically significant result that favored RFA. The wide range of effect across the three trials and a moderate level of statistical heterogeneity in this pool of studies (I^2= 48%) led to the classification of the results as inconsistent. We judged the strength of the body of evidence on overall survival in favor of RFA compared with PEI/PAI as moderate. The strength of the body of evidence was downgraded from high, the starting point when multiple RCTs are available, to moderate for the lack of consistency in the results across studies. In addition to overall survival, two RCTs[27,28] reported on the outcomes of TTP, local recurrence, and LOS. Due to the lack of blinding, the risk of bias was high; however, the results were consistent and precise, and all three are indirect measures of a final health outcome. Based on the high risk of bias and indirect measurement, we judged the strength of evidence on TTP and local recurrence in favor of RFA compared with PEI/PAI to be low. Also based on the high risk of bias due to lack of blinding, the strength of evidence was graded low for longer LOS following treatment with RFA compared with PEI/PAI. All three RCTs performed subgroup analyses to determine if overall survival was superior among specific patient subgroups. There is low strength of evidence with a high risk of bias to support increased overall survival for RFA compared with PEI/PAI in patients with larger lesions (defined variably as >2cm, 2–3cm, and 3.1–4cm). The evidence is insufficient to assess the effects of lesion size on other outcomes of interest in this report or the effect of other patient subgroups on any outcome of interest in this report.

We judged the strength of evidence to be insufficient to draw conclusions for effectiveness outcomes (overall survival, quality of life, disease progression, local recurrence, LOS, and days of work missed) or for adverse events for patients considered for all other comparisons (Table F). Data were judged to be insufficient due to high risk of bias, imprecision of estimates, and lack of comparative data for some outcomes (i.e., quality of life, days of work missed).

Evaluation of comparative effectiveness requires an intervention and a comparator. Case series do not use comparators. Therefore, comparative effectiveness cannot be assessed using this type of literature. Further, factors that may affect the effectiveness of the interventions within these populations were not controlled for in the included studies. Control may be achieved either through randomized design or statistically though careful adjustment in the analysis. Studies that aim to determine the effectiveness or comparative effectiveness of local treatment for unresectable HCC should use randomized designs. If randomization is not possible, care should be taken to control through regression analysis for covariates such as size and number of hepatic lesions and for performance status.

Findings in Relationship to What Is Already Known

There is a large range of unique comparisons of various local hepatic therapies for HCC. We are not aware of any systematic review that has examined all comparisons. We identified seven previously published comparative systematic reviews, each examining a single comparison of local hepatic therapies. Two systematic reviews compared RFA with PEI;[30,31] three compared TACE-percutaneous ablation (PA), either RFA or PEI, with RFA or TACE monotherapy;[32-34] and one compared PEI with PAI.[26]

Consistent with our findings, the three systematic reviews[30,31,35] comparing the ablative therapies RFA and PEI found that RFA demonstrated a significantly better overall survival rate than PEI. These reviews included the three RCTs that met the inclusion criteria for our evidence review, in addition to one or more trials that were not included in this review due to differences in inclusion criteria. The review by Bouza et al.[30] included three additional trials in which the study intervention was given prior to the year 2000 or the patient sample included those who refused surgical treatment of HCC, both of which are exclusion criteria in our review. The reviews by Cho et al. [31] and Salhab et al.[35] included patients who refused surgery in one and two trials, respectively. The pooled patient population in these two systematic reviews was similar to the population for this comparison in our review—that is, early-stage HCC patients with up to three nodules less than 3 or 4 cm in size.

The three systematic reviews of TACE-PA combination therapy[32-34] included studies of varying patient populations that were collectively broader than the population included in our evidence review. For example, the reviews included studies in patients with more advanced disease or those with unclear Child-Pugh status, as well as studies in which the treatment was given prior to 2000. These reviews included studies that reported comparisons not examined in our review (e.g., TACE-PEI vs. TACE). Given the heterogeneity across studies and the paucity of high-quality comparative data from RCTs, the overall strength of evidence is insufficient to permit conclusions regarding these comparisons. Comparing RFA-TACE combination therapy with RFA monotherapy in a meta-analysis, Yan et al.[34] reported that the combination therapy was associated with higher survival rates. However, the majority of included studies in that review were of low quality with small sample sizes, and therefore Yan et al. judged the overall strength of evidence as low, indicating uncertainties around the pooled estimate of effect. Wang et al.[32] conducted a meta-analysis of TACE-PEI combination therapy versus TACE monotherapy and found an improved overall survival with the combination therapy. The included trials in this review were of generally poor quality, with unclear baseline patient characteristics (e.g., Child-Pugh class and HCC lesion characteristics) and unclear or inadequate blinding and allocated concealment. The authors of the review acknowledged the limited reliability of their conclusion. In another meta-analysis of TACE-PA combination therapy versus PA monotherapy,[33] the combination therapy was shown to improve overall survival compared with the monotherapy. However, in a sensitivity analysis of TACE-RFA versus RFA alone, the authors found that the survival benefit of the combination therapy was not robust, which is in agreement with the inconclusive evidence base identified in our review. This systematic review also included studies in which the treatment was given prior to 2000. The authors noted the limited availability of high-quality data in their pooled analysis; therefore, the findings of this review are limited as well.

A 2009 Cochrane Review[26] compared PEI and PAI, two similar ablative techniques using different chemotherapeutic agents for injection, and found no significant difference with regard

to overall survival. This finding supports our approach of combining the PEI and PAI groups in our meta-analysis of the RFA versus PEI/PAI comparison.

The strength of the present review is that it addresses all local hepatic therapies for the included indications and includes comparisons not previously examined in published systematic reviews. Table 62 in the full report displays the corresponding comparisons between this review and the previously published reviews we identified. In addition, this review also recognizes that distinct patient groups exist within the population receiving local hepatic therapies. Specifically, we addressed a single patient population, those patients who are eligible for local hepatic therapy but are not otherwise eligible for resection or transplantation. Because we focused on a patient group rather than a specific intervention, we were able to present the outcomes for a wide range of local hepatic therapies for the target population.

Implications for Clinical and Policy Decisionmaking

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

For the comparison of RFA with PEI/PAI, our conclusions suggest that treatment with RFA confers a survival benefit at 3 years compared with PEI/PAI. In addition, TTP and local recurrence may be improved in patients treated with RFA compared with PEI/PAI. Patients treated with RFA also seem to have longer lengths of stay after treatment compared with those treated with PEI/PAI. Subgroup analyses on patients with larger size lesions found that patients treated with RFA had superior survival outcomes compared with PEI/PAI. Beyond this, evidence on the comparative effectiveness of these procedures was insufficient. Subsequent comparisons had only one or no comparative studies on a given treatment comparison. For these comparisons, evidence was insufficient for all outcomes; thus there is no comparative evidence base to support decisionmaking. In cases where comparative evidence existed, data were judged to be insufficient due to high risk of bias and/or imprecision of estimates.

Limitations of the Comparative Effectiveness Review Process

Determination of the scope of this review was a lengthy process that began in topic development and continued to be refined even as the review was underway. The topic was initially broader, encompassing other primary tumors metastasizing to the liver and HCC. During the scoping process, this review was narrowed to focus solely on unresectable HCC, and then further narrowed by excluding transplant-eligible patients and those who were treated in an effort to downstage them for resection. Based on the refined scope, the literature search revealed an evidence base with limited comparative data. Nonetheless, the evaluation of the quality of the body of literature to assess our KQs and the identification of research needs are valuable contributions to the field.

Limitations of the Evidence Base

Limitations of the present review are related largely to two factors: (1) the lack of comparative evidence and (2) clinical heterogeneity of patient populations across studies. With the exception of six RCTs, the vast majority of the evidence base included in this review was derived from observational, mostly single-arm, studies. The clinical heterogeneity was most evident in the description of patient and tumor characteristics. For example, the size of lesions being treated with RFA ranged from 4 cm or smaller in the trial by Lin et al.[27] to up to 10 cm in a

study by Minami et al.[36] Often studies failed to report on these patient and tumor characteristics, which potentially could impact treatment-related outcomes. For example, only 17 out of 48 (35.4%) of the included studies reported both the number and size of lesions in the study patient population. Authors varied in how these tumor characteristics were described: mean number and size of tumors, median number and size of tumors, range of number and size of tumors, percent solitary and nonsolitary tumors, interquartile range of size and number, or other categorizations. Full description of the patient population is important, as those with, for example, higher ECOG score (i.e., worse functioning status), higher HCC stage, higher Child-Pugh class, cirrhosis, or multinodular disease generally attain poorer outcomes than those without. For this reason, it would have been ideal to stratify the studies by patient groups (e.g., BCLC stage A vs. BCLC stage B) and to compare studies of equivalent patient populations. However, the poor patient characterization in the studies precluded stratification by patient groups as well as indirect comparison of interventions across studies. To maintain clinical relevance, comparisons were made only within each category of intervention (e.g., ablative therapy vs. ablative therapy). Exceptions to this were two studies of RFA versus TACE and RFA versus TACE + RFA. The patient populations in these studies were patients eligible for ablative therapy.

The comparative data were limited even further in terms of important subgroups, such as those based on age, sex, ECOG score, disease etiology, Child-Pugh class, presence of portal vein thrombosis, HCC stage, lesion size, and multifocal versus single-nodule HCC. Overall survival was examined by subgroup in three RCTs; however, none of these analyses were prespecified, thereby limiting their utility beyond hypothesis generation.

Given the limited number of patients and clinical heterogeneity, we did not systematically review the treatment-specific characteristics such as treatment regimens and techniques used. 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.

None of the studies included in this review used blinded outcome assessment. It can be a challenge to blind participants and outcome assessors in these studies due to the differences in treatment delivery and the appearance of the liver after treatment. This is a particular limitation for the assessment of intermediate outcomes such as disease progression and local recurrence.

In addition to the RCTs meeting our inclusion criteria, this review included four nonrandomized comparative studies. These studies did not use statistical adjustment to reduce confounding; such adjustment for confounding should be consistently used in nonrandomized studies. Regardless of the study design, we suggest that studies examining the effectiveness or comparative effectiveness of local hepatic therapies 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 lesions, Child-Pugh classification, and performance status, which could serve as both modifiers of effectiveness and factors that are considered when choosing the best local hepatic therapy.

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

Applicability

We comment below on the relevance of the included intervention studies (i.e., RCTs and nonrandomized comparative studies) for PICOTS elements. The PICOTS format provides a

practical and useful structure to review applicability in a systematic manner and is employed in the subsections that follow.[37]

Population and Settings

As specified by our inclusion criteria, the study population had unresectable HCC with no extrahepatic spread, no portal invasion, Child-Pugh class A or B disease, ECOG status ≤1 and/or BCLA stage A or B, or equivalent. This patient population comprises the patient group typically considered eligible for the therapies discussed in this review. To maintain clinical relevance, comparisons were made only within a category of intervention (e.g., ablative therapy vs. ablative therapy). This is because patients with different disease characteristics are candidates for different treatments; for example, patients with small accessible tumors are candidates for ablation, whereas those with more extensive disease would undergo embolization therapy. Exceptions to this were two cross-category comparisons of RFA versus TACE and RFA versus TACE + RFA because these studies involved patients who were all able to receive ablative therapy and were thus comparable across arms.

The generalizability of the findings in this review is limited because of the different focused therapies in varied settings across the studies included. The setting in which treatment occurs is a potential factor in the outcomes of local hepatic therapy. Expertise of clinicians and centers varies. In many centers, the choice of a local hepatic therapy may be limited by the available clinical expertise and technology. Local hepatic therapies often require high levels of training and familiarity with the procedure, such as with radioembolization.[38] Lack of experience may not only affect outcomes but also result in adverse effects.

The available studies offered insufficient details to assess operator-dependent factors or the representativeness of these settings compared with those of clinical practice. Detailed analysis of differences in outcomes by center has important implications for the relevance of the findings in the literature.

Interventions/Comparators

For each local hepatic therapy, procedural variation may be substantial. The variation may be in the approach (open vs. percutaneous) or the delivery regimen and schedule of chemotherapeutic drugs 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. The potential impact of these factors on 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 variation in treatment strategies also limits the benefit attributable to any one component of the treatment plan.

Outcomes

Overall survival is the final health outcome in studies of local hepatic therapies for unresectable HCC. It is reported in all of the studies included in this review. There is controversy regarding the utility of outcomes such as disease-free survival or local progression-free survival. 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, but they may agree that these are important intermediate health outcomes. Additional 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 followup assessment was appropriate given the natural history of unresectable HCC and the primary outcome of overall survival. Nearly all studies reported on duration of patient followup, with durations typically lasting until median survival time was reached or beyond.

Research Gaps

There is limited evidence on patient outcomes of local hepatic therapies. Of the 13 interventions included in this report, only one comparison had sufficient evidence to receive a rating above insufficient. There was moderate strength of evidence to support the statement that RFA improved 3-year overall survival compared with PEI/PAI. There was low strength of evidence to support increased TTP, improved local recurrence, and a longer LOS for RFA compared with PEI/PAI. Subgroup analyses on patients with larger size lesions found low strength of evidence that patients treated with RFA had superior survival outcomes compared with PEI/PAI. Strength of evidence was judged to be insufficient for all other comparisons and outcomes.

We identified four broad evidence gaps during this review:

- There is no evidence on quality of life. Quality-of-life outcomes are particularly important for a population of patients in which symptom relief is often the focus of therapy. For all comparisons, collection and reporting of quality-of-life data using standard measurement tools are needed.
- An objective of comparative effectiveness reviews is to understand the comparative effects for different subgroups. RCTs should prespecify subgroup analyses to assess the effects of characteristics such as lesion size, Child-Pugh class, and ECOG score on treatment outcomes. Systematic definitions should be used to delineate the patient subgroups of interest. Further, studies should present data by these subgroups so that evidence can be interpreted accordingly.
- Future studies should employ a standard or uniform set of outcome definitions (e.g., overall survival, local recurrence) as well as patient characteristics in reporting (e.g., BCLC stage, Child-Pugh class, lesion number and size). Such uniformity would allow for a more accurate and level comparison of patient populations across studies that the current evidence base precludes.
- During the peer review process of this Comparative Effectiveness Review, we received the following suggestions for clinically relevant comparisons for future research: (1) RFA versus other ablative therapies (e.g., MWA, cryoablation); (2) RFA versus TACE-RFA combination therapy; (3) RFA versus radiotherapies (e.g., SBRT); and (4) between transarterial therapies (e.g., TACE vs. RE or TACE vs. DEB). Such comparative evidence based on well-designed randomized studies in the patient population included in this review is needed.

Conclusions

This review included 13 local hepatic therapies and their combinations for unresectable HCC. There was moderate strength of evidence demonstrating better overall survival at 3 years, a low level of evidence supporting improved overall survival for patients with larger lesion sizes, and a low strength of evidence for improved TTP and local control for RFA compared with PEI/PAI for the treatment of unresectable HCC. A low level of evidence also supports a longer length of stay following RFA compared with PEI/PAI. For all other outcomes and comparisons, there is insufficient evidence to permit conclusions on the comparative effectiveness of local hepatic therapies for unresectable HCC. Important direct health outcomes of therapy include overall survival, adverse effects, and quality of life. Progression-free survival is an important intermediate health outcome, as progression often marks a change in therapy. Future RCTs comparing RFA with other ablative therapies and comparisons between transarterial therapies (e.g., TACE vs. RE) are needed to close the existing gap in the comparative evidence.

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Introduction

Background

This comparative effectiveness review (CER) evaluates local hepatic therapies for patients with unresectable primary hepatocellular carcinoma (HCC) who are not candidates for surgical resection or liver transplantation. In the following background section, we describe the epidemiology and staging of HCC as well as currently available treatment strategies. We also discuss the current practice guidelines and the impetus for this review. Finally, the specific Key Questions (KQs) and the analytic framework for this review are presented.

Condition

Hepatocellular carcinoma (HCC) is the most common primary liver tumor. It is the fifth most common cancer and the third leading cause of cancer death worldwide.[1]Overall 5-year survival rates for HCC are less than 10 percent in Europe and the United States.[1]The main etiology of HCC is chronic infection with the hepatitis B and hepatitis C viruses. Approximately 4 million individuals in the United States are chronically infected with hepatitis C virus, 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 incidence of and mortality rate due to HCC are projected to increase worldwide in the next 20 years, primarily due to the dissemination of hepatitis C virus infection.[2] Other causes include cirrhosis due to any cause (e.g., alcohol), hereditary hemochromatosis and iron overload syndromes, nonalcoholic fatty liver disease, obesity, diabetes, and environmental toxins (e.g., aflatoxin, chewing of betel quid, and contaminated water).[3]

While there are several causes of HCC, etiology is not an independent prognostic factor for HCC;[4,5] rather, the underlying cirrhosis impacts prognosis and treatment decisions. In the United States, most cases of HCC occur in patients with cirrhosis.[1] A small proportion, approximately 5 percent, of all HCC cases in Western countries occurs in patients without cirrhosis.[6] For patients with early-stage HCC without underlying cirrhosis, surgical resection is the preferred treatment and offers a high probability of a cure. The Barcelona Clinic Liver Cancer (BCLC) guidelines recommend hepatectomy for patients with a single lesion less than 5 cm in size and mild or no underlying cirrhosis.[7] In contrast, patients with severe cirrhosis are not considered resectable and receive supportive care instead.[7]

This report focuses on the approximately 80 percent of patients who are not surgical candidates due to advanced-stage disease at diagnosis, inadequate hepatic reserve to tolerate resection, tumors in unresectable locations, or medical comorbidities that result in a high surgical risk.[1]

Classification/Staging of Hepatocellular Carcinoma

Both tumor stage and underlying liver function are key considerations in diagnosis, treatment selection, and prognosis of HCC. The 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] This system considers factors related to tumor stage, liver function, performance status, and cancer-related symptoms. HCC is staged from 0 to D.

Other staging systems are used regionally, such as Okuda staging developed in Japan, 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).[8-10] The set of prognostic factors considered in each of these systems varies and includes various measures and combinations of hepatic function, performance status, and tumor characteristics. Given the wide array of prognostic factors across the staging systems, a direct translation from one system to another is inexact. For example, though the BCLC staging system and the Okuda staging system both include a measure of tumor size, the numeric parameters of tumor size differ between the systems. Additionally, the BCLC system takes into account performance status and underlying liver function using Child-Pugh classification, whereas the Okuda system does not and instead includes other factors (presence of ascites and serum levels of albumin and bilirubin). Despite the apparent discrepancies, efforts have been made to designate equivalent stages between the two systems, albeit with some overlap (Table 1).[8]

Table 1. Comparison of Barcelona Clinic Liver Cancer (BCLC) and Okuda staging systems*

BCLC Stage	Performance Status	Tumor Number and Size	Liver Function	Equivalent Okuda Stage
Stage 0: very early	0	Single, <2 cm	Child-Pugh A; no portal hypertension and normal bilirubin	I
Stage A: early	NR	NR	NR	NR
A1	0	Single, <5 cm	Child-Pugh A or B; No portal hypertension and normal bilirubin	I
A2	0	Single, <5 cm	Child-Pugh A or B; Portal hypertension and normal bilirubin	I
A3	0	Single, <5 cm	Child-Pugh A or B; Portal hypertension and abnormal bilirubin	I-II
A4	0	3 tumors, <3 cm	Child-Pugh A or B	I-II
Stage B: intermediate	0	Large multinodular	Child-Pugh A or B	I-II
Stage C: advanced	1-2	Vascular invasion or extrahepatic spread	Child-Pugh A or B	I-II
Stage D: terminal	3-4	Any	Child-Pugh C	III

*Adapted from Grieco et al. 2005.[8] NR= not reported

Classification of Underlying Liver Function

The Child-Pugh classification is a commonly used method to assess the prognosis of patients with underlying liver disease. The system employs five clinical factors: total bilirubin, serum albumin, international normalized ratio (INR; measure of clotting tendency of the blood), ascites (accumulation of fluid in the abdomen), and hepatic encephalopathy (declining brain function caused by toxin accumulation in the brain). Each is scored on a scale of 1–3, from lowest to highest severity. Patients are classified as class A, B, or C based on the total score. HCC patients with class A hepatic impairment have the best prognosis and would be candidates for surgical resection, although many would require local hepatic therapies such as ablative, transarterial, and radiotherapies. HCC patients with class B are not candidates for resection and are typically offered transarterial therapy, ablative therapy, radiotherapy, or systemic therapy. Class C patients typically are not candidates for local hepatic therapies, with rare exceptions, and usually receive supportive care. Transplantation can be offered to patients of all Child-Pugh classifications if they meet the listing criteria.[7,11]

Another scoring system for chronic liver disease is the Model for End-Stage Liver Disease (MELD) score, which is based on serum bilirubin, serum creatinine, and INR. The MELD score

ranges from 6 to 40, with a higher score corresponding to a higher severity of hepatic dysfunction. This score serves as a numerical scale for adult liver transplant candidates.[12]

Treatment Strategies

Table 2 through Table 4 present the mechanism of action, treatment setting, personnel involved, and specific harms reported for each of the 13 local hepatic therapies (ablative therapies, transarterial embolization therapies, and radiotherapies) included in this review.

Potential Benefits and Drawbacks of Local Hepatic Therapies

Several patient and institutional factors may dictate the choice of local hepatic therapy for particular patients. Patient factors such as vascular anatomy, proportion of liver parenchyma involved with tumor, presence of shunts (e.g., pulmonary shunting), and performance status may influence the decision to use local hepatic therapies such as radioembolization and chemoembolization. For example, in patients with multifocal disease throughout both hepatic lobes, external-beam radiation may not be optimal due to radiation toxicity.

Ablative therapies such as radiofrequency ablation (RFA) and external beam radiation strategies are typically used in patients with unifocal or limited multifocal disease, whereas transarterial strategies such as chemoembolization (TACE) and radioembolization (RE) are typically offered to patients with more advanced, multifocal disease.[7,11] When examining the comparative efficacy of local hepatic therapies it is important to establish that patient groups are comparable. In general, patients treated with ablative therapies and those treated with transarterial strategies represent two distinct patient populations, and as a result when considering comparisons for this review we compared only ablative therapies to one another, embolization therapies to one another, and external-beam therapies compared to one another. TACE, RE, and RFA are performed by an interventional radiologist experienced in these techniques, though RFA can also be performed by surgeons. External-beam radiation is widely available at most centers;[13] however, it may not be the best treatment option for some patients, such as those who may be candidates for other modalities such as RE.

Discussions in the literature of the potential benefits or harms from any single local hepatic therapy for a given patient group are limited in their usefulness. In this report (KQ3 below), we will review differences in comparative effectiveness of various local hepatic therapies in patients with unresectable HCC for specific patient and tumor characteristics, such as age, sex, disease etiology, and Child-Pugh score.

The National Comprehensive Cancer Network guidelines state that local hepatic therapies should not be used in place of liver resection or transplantation for patients who meet surgical criteria.[14] The National Institutes of Health consensus recommendation suggests the use of locoregional therapies for selected patients with HCC confined to the liver and whose disease is not amenable to resection or transplantation.[15] The existing guidelines do not provide specific guidance on the comparative effectiveness of the therapies. Providers and patients faced with treatment decisions need comparative evidence on which to base these decisions.

Table 2. Local ablative therapies for primary hepatocellular carcinoma reviewed in this report

Treatment Strategy	Mechanism of Cell Death	Setting	Performed By	Specific Harms
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°C–100°C, which produces protein denaturation and coagulative necrosis.[16]	The procedure is performed under intravenous (IV) narcotics for the percutaneous, awake approach and does not require a hospital stay. For laparoscopic or open RFA, the procedure is performed under general anesthesia and results in a longer recovery period.[17] Each radiofrequency ablation takes approximately 10 to 30 minutes, with additional time required if multiple ablations are performed. The entire procedure is usually completed within 1 to 3 hours.[18]	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).[18,19]
Percutaneous ethanol injection (PEI)/ Percutaneous acetic acid injection (PAI)	PEI involves the injection of a high concentration of ethyl alcohol directly into liver tumors with ultrasound guidance.[20] 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. PAI is a variation of PEI where the ethyl alcohol solution is approximately 50% acetic acid. Variations in the drug regimen are outside the scope of this review. Therefore, PEI and PAI will be treated as the same intervention.	PEI is performed as either an inpatient (typical in Japan) or an outpatient (e.g., in European countries) procedure. The patient is given IV sedation and analgesia. Each procedure lasts approximately 20–30 minutes and is repeated twice a week until ethanol seems to be injected throughout the lesion.[20]	Interventional Radiologist	Common adverse effects include pain, fever, and a feeling of alcohol intoxication. Serious complications are rare and include ascites, right pleural effusion, jaundice, intraperitoneal hemorrhage, hepatic infarction, a transient decrease in blood pressure, seeding of malignant cells in the puncture tracks, hepatic vascular and bile duct injury, liver abscess, and liver necrosis.[20]

Table 2. Local ablative therapies for primary hepatocellular carcinoma reviewed in this report (continued)

Treatment Strategy	Mechanism of Cell Death	Setting	Performed By	Specific Harms
Cryosurgical ablation (Cryoablation)	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°C and -40°C.[21,22]	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.[19,23]
Microwave ablation (MWA)	MWA uses high-frequency electromagnetic radiation to create heat through the excitation of water molecules.[16] 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.[23] 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.[19 23]

Table 3. Transarterial embolization therapies for primary hepatocellular carcinoma reviewed in this report

Treatment Strategy	Mechanism of Cell Death	Setting	Performed By	Specific Harms
Transarterial embolization (TAE)	TAE uses selective catheterization and obstruction of the arterial vessel, which supplies blood to the tumor, with an embolizing agent.[24]	Most patients can be discharged several hours after treatment with TAE, but if postembolization syndrome occurs, an overnight stay is typically required.	Interventional Radiologist	Side effects differ depending upon the type of embolization used. Common complications reported are postembolization syndrome (fever, pain, extreme fatigue, nausea/vomiting), infection in the liver, hepatic abscess, gallbladder inflammation, and blood clots in the main blood vessels of the liver. Serious complications are uncommon, but 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.[25]
Transarterial chemo-embolization (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 retained selectively within the tumor) and is injected via a catheter into the hepatic arteries directly supplying the tumor; 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 several hours after treatment with TACE, but if postembolization syndrome occurs, an overnight stay is typically required.	Interventional Radiologist	Same as for TAE.

Table 3. Transarterial embolization therapies for primary hepatocellular carcinoma reviewed in this report (continued)

Treatment Strategy	Mechanism of Cell Death	Setting	Performed By	Specific Harms
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.[26] The loaded microspheres deliver high, localized doses of β-radiation to the tumor while minimizing radiation exposure to the surrounding tissue.[26-28]	Patients are required to undergo a technetium-99m-macro-aggregated albumin (MAA) scan prior to SIRT to assess eligibility.[29] The SIRT procedure takes approximately 90 minutes, and patients can typically return home 4 to 6 hours following treatment.	Interventional Radiologist	The side effects will differ depending upon the type of embolization used. The most common complications reported are postembolization syndrome (fever, pain, extreme fatigue, nausea/vomiting), infection in the liver, hepatic abscess, gallbladder inflammation, and blood clots in the main blood vessels of the liver. Serious complications are uncommon, but they are possible.[25] Acute toxicity events include gastritis, ulceration, and pancreatitis due to microsphere deposition in vessels serving these organs.[29] Radiation-induced liver disease (jaundice, weight gain, painful hepatomegaly, and elevated liver enzymes), thrombocytopenia, encephalopathy, rise in liver function tests, ascites, and 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.[30]	Most patients can be discharged several hours after treatment, but if postembolization 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 postembolization syndrome (fever, pain, extreme fatigue, nausea/vomiting), infection in the liver, hepatic abscess, gallbladder inflammation, and blood clots in the main blood vessels of the liver. Serious complications are uncommon, but they are possible.[25]

Table 4. Local radiotherapies for primary hepatocellular carcinoma reviewed in this report*

Treatment Strategy	Mechanism of Cell Death	Setting	Performed By	Specific Harms
External-beam three-dimensional conformal radiation therapy (3D-CRT)	This type of radiotherapy uses computer-assisted tomography (CT or CAT) and/or magnetic resonance imaging (MR or MRI), 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.	Each treatment lasts only a few minutes, although the setup time usually takes longer. Most often, radiation treatments are given 5 days a week for several weeks. The patient's diagnosis determines the total duration of treatment.[31,32]	Radiation oncologist, medical physicist, dosimetrist, radiation therapist, and radiation therapy nurse	Possible side effects of external radiation therapy include: sunburn-like skin problems, nausea, vomiting, and fatigue. These typically diminish posttreatment. Radiation might also make the side effects of chemotherapy worse.[25] Radiation-induced liver disease is the major dose limiting toxicity.[23]
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 better defined radiation dose over traditional 3D-CRT.	Same as 3D-CRT, but IMRT requires slightly longer daily treatment times and additional planning and safety checks before the patient can start the treatment.[33]	Radiation oncologist, medical physicist, dosimetrist, radiation therapist, and radiation therapy nurse	Same as for 3D-CRT.
Stereotactic body radiation therapy (SBRT)	This type of external-beam radiation therapy delivers a high dose of radiation with high targeting accuracy to an extracranial target within the body in either a single dose or a small number of dose fractions.[34]	SBRT typically consists of one to five treatment sessions over the course of 1 to 2 weeks.[35]	Radiation oncologist, medical physicist, dosimetrist, radiation therapist, and radiation therapy nurse	Same as above for 3D-CRT and IMRT.
Hypofractionated proton beam therapy	This is a type of external-beam radiation therapy that delivers high doses of radiation to the tumor target while simultaneously reducing the number of photons reaching normal surrounding tissue, delivered in fewer sessions of larger dose fractions than are delivered in standard regimens.[34]	Proton beam therapy is performed typically on an outpatient basis. For most tumor sites, the average course of treatment is usually 5 to 7 weeks, with varying length of each treatment depending on the tumor type and stage. The delivery of the proton beam lasts only 1 minute.[35]	Radiation oncologist, radiation physicist, dosimetrist, immobilization specialist, radiation therapy nurse	Same as above for 3D-CRT, IMRT, and SBRT.

Table 4. Local radiotherapies for primary hepatocellular carcinoma reviewed in this report* (continued)

Treatment Strategy	Mechanism of Cell Death	Setting	Performed By	Specific Harms
Intraluminal brachytherapy	This type of radiotherapy places a radiation source within the body, allowing the delivery of higher doses of radiation directly to a specific tumor.[20-22] Brachytherapy can be administered as a permanent or temporary treatment.	In permanent brachytherapy, a radioactive "seed" is permanently implanted in the tumor. Seeds may also be implanted at regular intervals. In temporary brachytherapy, treatments may be delivered at a high dose-rate (HDR) in 10 to 20 minutes per session or at a low dose-rate (LDR) in 20 to 50 hours. HDR brachytherapy is usually an outpatient procedure in which the treatment is repeated two times a day for up to 10 separate treatments in 1 or more weeks. LDR brachytherapy, an inpatient procedure, delivers radiation at a continuous rate in 1 to 2 days. Pulsed dose-rate (PDR) brachytherapy delivers radiation in periodic pulses (usually 1 per hour) rather than continuously.[36]	Radiation oncologist, medical physicist, dosimetrist, radiation therapist, radiation therapy nurse, and in some cases, a surgeon	Brachytherapy typically causes fewer side effects than does external-beam radiation.[37 39]Patients may experience tenderness and swelling in the treatment area and other symptoms depending on the site of brachytherapy and can resume normal activities within days or weeks of brachytherapy.

*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 examine the comparative effectiveness and harms of various local hepatic therapies for unresectable primary HCC in patients who meet all of the following criteria:

- 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. Children are also excluded from this review as their disease presentation and prognosis are quite different from those of adults.

Nonsurgical candidates eligible for local hepatic therapies are a heterogeneous group. Patient selection criteria are critical for attaining optimal outcomes with the most appropriate local hepatic therapy, and patient selection for these procedures depends on how "medically or technically inoperable patients" are defined. We reviewed studies with any length of followup and in both inpatient and outpatient settings.

Table 5 lists the relevant populations, interventions, comparators, outcomes timeframes of assessment, and settings (PICOTS) relevant for this review.

Table 5. PICOTS (population, intervention, comparator, outcome, timing, and setting) for the Key Questions

PICOTS	KQ1	KQ2	KQ3
Population	Adults with HCC who are candidates for local hepatic therapies, but not candidates for surgical resection or transplantation, who meet the following criteria: • No extrahepatic spread • No portal invasion • Child-Pugh class A or B disease • ECOG status ≤1 *and/or* • BCLC stage A or B, or equivalent This includes: • 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	Same as KQ1	Subgroups of patients in KQ1 stratified by age, gender, disease etiology, and Child-Pugh class

Table 5. PICOTS (population, intervention, comparator, outcome, timing, and setting) for the Key Questions (continued)

PICOTS	KQ1	KQ2	KQ3
Intervention	**Ablation** • Radiofrequency ablation (RFA) • Percutaneous ethanol injection (PEI)/Percutaneous acetic acid injection (PAI) • Cryoablation • Microwave ablation (MWA) **Embolization** • Transarterial embolization (TAE) or transarterial ethanol ablation (TEA) • Transarterial chemoembolization (TACE) • Radioembolization (RE) or Selective internal radiation therapy (SIRT) • Drug-eluting beads (DEBs) **Radiotherapy** • External-beam with 3D conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT) • Stereotactic body radiation therapy (SBRT) • Hypofractionated proton beam therapy • Intraluminal brachytherapy Combinations of the interventions listed above were also included in the review, such as TACE plus RFA.	Same as KQ1	Same as KQ1
Comparator	Therapies were compared with other liver directed therapies within the following categories of intervention: 1. Ablative therapies compared with other ablative therapies 2. Transarterial therapies compared with other transarterial therapies 3. Radiotherapies compared with other radiotherapies 4. Combinations of liver directed therapies including but not limited to TACE plus Cryoablation and TAE plus RFA	Same as KQ1	Same as KQ1
Outcome	• Final health outcomes: Survival, quality of life • Intermediate outcomes: Time to progression, local recurrence, length of stay, days of missed work	• Adverse outcomes: hepatic abscess, hepatic hemorrhage, biloma, steatohepatitis, injury to adjacent organ(s), liver failure, infection, increased alkaline phosphatase, increased bilirubin, increased transaminases, and rare adverse events	Same as KQ1
Timing	The relevant periods occur at the time of treatment through followup over months or years.	Same as KQ1	Same as KQ1
Setting	Inpatient and outpatient	Same as KQ1	Same as KQ1

Abbreviations: HCC = hepatocellular carcinoma; KQ = Key Question; ECOG = Eastern Cooperative Oncology Group; BCLC = Barcelona Clinic Liver Cancer.

Key Questions

KQ1. What is the comparative effectiveness of the various local hepatic 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?

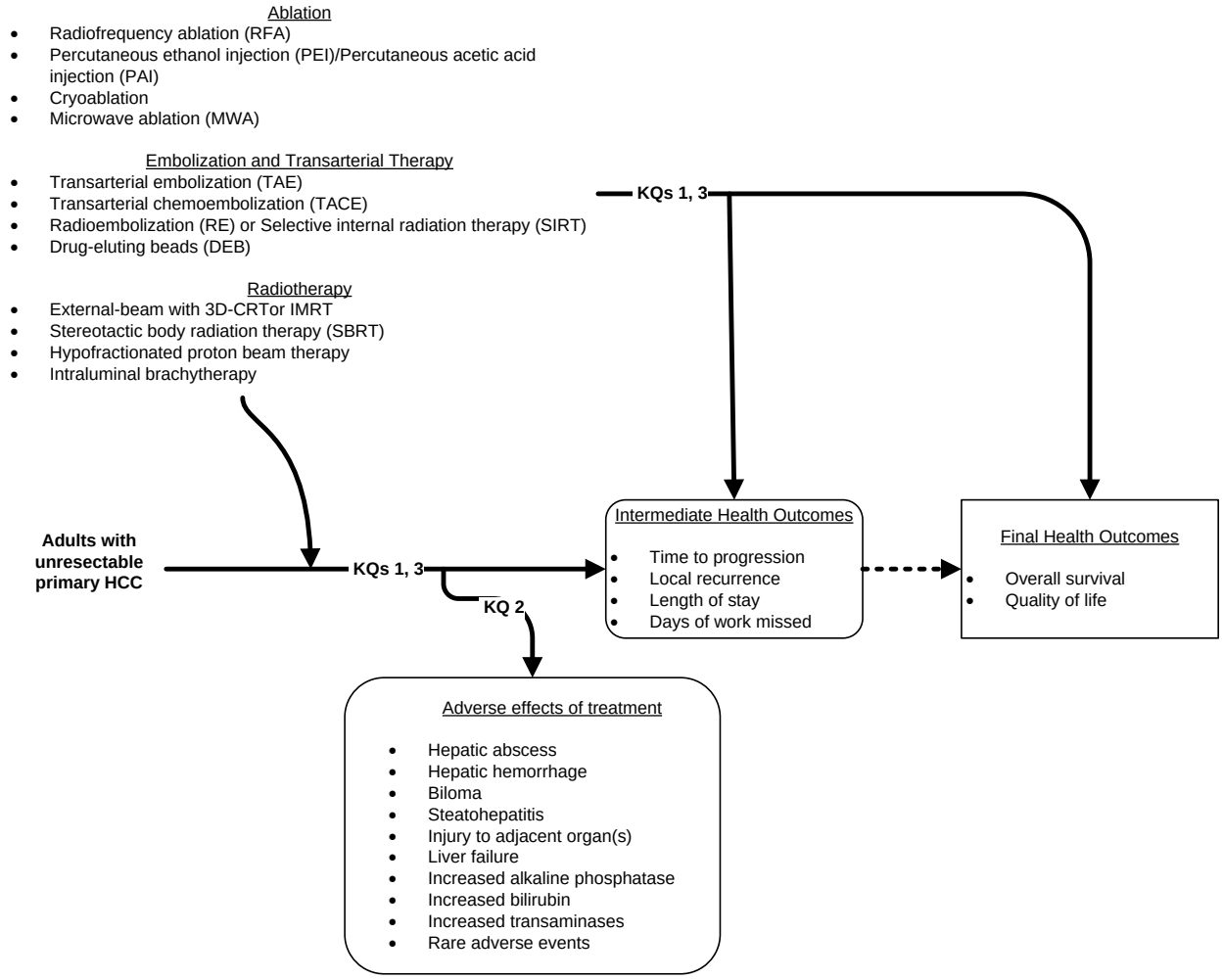
KQ2. What are the comparative harms of the various local hepatic therapies in patients with HCC who are not otherwise candidates for surgical resection or transplantation with no evidence of extrahepatic disease regarding adverse events?

KQ3. Are there differences in comparative effectiveness of various local hepatic 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?

Analytic Framework

We developed the analytic framework shown in Figure 1 based on clinical expertise and refined it with input from our Key Informants and Technical Expert Panel (TEP). The diagram is a revised version 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 not eligible for liver resection or transplantation are using local hepatic therapy. These therapies may affect intermediate health outcomes such as TTP, local recurrence, LOS, and days of work missed as well as final health outcomes of overall survival and quality of life (KQ1 and KQ3). In addition, we attempted to assess the occurrence of adverse effects of local hepatic therapies (KQ2).

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



Abbreviations: HCC = hepatocellular carcinoma; 3D-CRT = External-beam three-dimensional conformal radiation therapy; IMRT = External-beam intensity-modulated radiotherapy.

Organization of This Report

The Methods chapter describes our processes, including our search strategy, inclusion and exclusion criteria, approach to abstract and full text review, methods for extraction of data into evidence tables, and method for 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 KQ, 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 appendices 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 Extraction Forms
- Appendix D: Evidence Tables
- Appendix E: Abbreviations and Acronyms
- Appendix F: Excluded Studies

Uses of This Report

We anticipate this report will be of primary interest to health care providers who care for patients with HCC, particularly those patients who are not candidates for resection or liver transplantation. Treatment is generally provided by medical oncologists or 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 as well as the strength of the body of evidence for each of the KQs. It will be of interest to patients with unresectable HCC—as well as their families—who are concerned about their health and facing treatment choices.

This presentation of the evidence is also of value to researchers who can obtain a concise analysis of the current state of knowledge in the field and where there are gaps in knowledge. This report can help prepare them to conduct research in areas that are needed to advance research methods, understand patient selection, and optimize the effectiveness and safety of treatment for unresectable HCC.

Methods

In this chapter, we document the procedures that our Evidence-based Practice Center (EPC) used to conduct a comparative effectiveness review (CER) on the effectiveness and comparative effectiveness and harms of local hepatic therapies for primary hepatocellular carcinoma (HCC). The methods for this CER follow the methods suggested in the Agency for Healthcare Research and Quality (ARHQ) "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (available at www.effectivehealthcare.ahrq.gov/methodsguide.cfm).

The main sections in this chapter reflect the elements of the protocol established for the CER; certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist.[38] 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 (KQs), our inclusion and exclusion criteria, and the process we used to extract information from the included articles and to 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.

Given the clinical complexity of this topic and the evolution of the scope and KQs, we sought the input 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 (and availability).

Topic Refinement and Review Protocol

The topic for this report was nominated in a public process. With input from Key Informants, the EPC team drafted the initial KQs and posted them to a Web site for public comment for 4 weeks. Changes to the KQs and the PICOTS framework were made based on the public commentary and discussion with the TEP; however, the initial stratification of KQs and interventions by intent of treatment (palliative or curative) was deemed inappropriate and confusing. Interventions could not be clearly classified as either curative or palliative. Also, the term "palliative" is often associated with end-of-life care, and applying that term to this population, who may have early-stage disease, would cause confusion.

The inability to translate disease stage from one classification system to another made it difficult to differentiate between patients with BCLC stage A and B liver disease across publications. Therefore, two KQs refer to effectiveness and harms of liver-directed therapy for patients with unresectable disease without portal invasion or extrahepatic spread, with preserved liver function, and with an ECOG status $\leq$1 *or* BCLC stage A or B, or equivalent. A third KQ was added to address potential differences in effectiveness by patient and tumor characteristics. SBRT was added to the list of interventions. Increased alkaline phosphatase, increased bilirubin, increased transaminases, liver failure, and rare adverse events were added to the list of harms.

After reviewing the public commentary and TEP recommendations, the EPC drafted final KQs and submitted them to AHRQ for approval. Members of the TEP and KI were not involved with the writing, analysis or interpretation of the data. The views represented are solely those of the authors.

Literature Search Strategy

Search Strategy

Our search strategy used the National Library of Medicine's Medical Subject Headings (MeSH) keyword nomenclature developed for MEDLINE® and adapted for use in other databases. The searches were limited to the English language.[39] The TEP noted that most of the pivotal studies are published in English language journals and, therefore, the exclusion of non–English-language articles from this review would not impact the conclusions. The search was further restricted to articles published between January 1, 2000, and July 27, 2012. With input from the TEP, the EPC investigators decided to limit the search to these dates to ensure the applicability of the interventions and outcomes data to current clinical practice. In 1999 the BCLC staging system was published which links the stage of disease to specific treatment strategies. In 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.[40,41,42] Thermal therapies were not used significantly until late 1990s and major changes in proton beam and stereotactic therapy occurred during that same period.[43] Chemoembolization drugs and embolic mixtures have also changed a great deal in the last ten years and are more standard now. For these reasons which were strongly supported by the TEP we excluded studies where patient treatment preceded the year 2000. The texts of the major search strategies are given in Appendix A.

We searched for the following publication types: randomized controlled trials (RCTs), nonrandomized comparative studies, and case series. The TEP was given an opportunity to comment on the list of included articles and were invited to provide additional references if applicable.

Grey literature was sought by searching for clinical trials (www.clinicaltrials.gov, www.controlled-trials.com, apps.who.int/trialsearch), material published on the U.S. Food and Drug Administration Web site (www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm), and relevant conference abstracts (American Society of Clinical Oncology, Gastrointestinal Cancers Symposium, Society of Surgical Oncology, The Radiosurgery Society, American Association for the Study of Liver Diseases) for data pertaining to the interventions used to treat unresectable HCC that are under consideration in this review. Scientific Information Packets from the Scientific Resource Center were reviewed. The original intent was to contact study authors if the EPC staff believed the evidence could meaningfully impact results (i.e., alter Grading of Recommendations Assessment, Development, and Evaluation [GRADE] strength of evidence). However, due to the limited number of studies included in this report, authors were contacted for any article lacking complete information on patient characteristics, interventions, or outcomes. The list of contacted authors is in Appendix B.

Inclusion and Exclusion Criteria

Table 6 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 6. Inclusion and exclusion criteria

Category	Criteria
Study population	Adults with HCC who are candidates for local hepatic 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 Specifically, patients who meet all of the following criteria: • No extrahepatic spread • No portal invasion • Child-Pugh class A or B disease • ECOG status ≤1 *and/or* • BCLC stage A or B, or equivalent
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 • 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. • Relevant outcomes must be extractable from data presented in the articles. • To allow for the inclusion of all potentially relevant evidence studies that deviated from our inclusion criteria by less than 10% were included (e.g., 9% of patients had documented extrahepatic disease)

Abbreviations: HCC = hepatocellular carcinoma; KQ = Key Question; ECOG = Eastern Cooperative Oncology Group; BCLC = Barcelona Clinic Liver Cancer; 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.

A total of four team members participated in the dual data abstractions. Discrepancies were decided by consensus opinion and a third reviewer was consulted when necessary. All four team members were trained using a set of 50 abstracts to ensure uniform application of screening criteria. Full-text review was performed when it was unclear if the abstract met study 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, only the first reason identified was recorded.

Development of Evidence Tables and Data Extraction

The 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 KQs. Evidence table templates were identical for KQ1, KQ2, and KQ3. The format of our evidence tables was based on examples from prior systematic reviews.

Data extraction was performed directly into tables created in DistillerSR with elements defined in an accompanying data dictionary. All team members extracted a training set of five articles into evidence 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. If this was not successful, the project lead arbitrated the dispute. The full research team met regularly during the period of article extraction to discuss any issues related to the extraction process. Extracted data included patient and treatment characteristics, outcomes related to 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.

Risk of Bias Assessment of Individual Studies

In the assessment of risk of bias in individual studies, we followed the Methods Guide.[44] Quality assessment of each study was conducted by two independent reviewers, with discrepancies adjudicated by consensus. The United States Preventive Services Task Force (USPSTF) tool for RCTs and nonrandomized comparative studies[45] and a set of study characteristics proposed by Carey and Boden for studies with a single-arm design [46] were used to assess individual study quality. The USPSTF tool is designed for the assessment of studies with experimental designs and randomized participants. Fundamental domains include assembly and maintenance of comparable groups; loss to followup; equal, reliable and valid measurements; clear definitions of interventions; consideration of all important outcomes; and analysis that adjusts for potential confounders and intention-to-treat analysis. It has thresholds for good, fair, and poor quality as follows,[45] which were applied to the RCTs and nonrandomized comparative studies:

- *Good:* Meets all criteria; comparable groups are assembled initially and maintained throughout the study (follow up at least 80 percent); 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, for RCTs, intention-to-treat analysis is used.
- *Fair:* Studies are graded as "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 question remains as to whether some (although not major) differences occurred with follow up; measurement instruments are acceptable (although not the best) and 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 is done for RCTs.

- *Poor:* Studies are graded as "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 equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention-to-treat analysis is lacking.

The criteria by Carey and Boden[46] for assessing single-arm studies evaluate: 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. These criteria do not produce an overall quality ranking; therefore, we created the following thresholds to convert these ratings into the AHRQ standard quality ratings (good, fair, and poor). A study was ranked as good quality if each of the Carey and Boden[46] criteria listed above was met. A fair quality rating was given if one of the criteria was not met, and a poor quality rating was given to studies with more than one unmet criteria.

The classification of studies into categories of good, fair, and poor was used for differentiation within the group of studies of a specific study design, and not for the overall body of evidence described below. Each study design was evaluated according to its own strengths and weaknesses. These quality ranking forms and their conversion thresholds can be found in Appendix D.

Data Synthesis

Evidence tables were completed for all included studies, and data were presented in summary tables and analyzed qualitatively in the text. We considered whether formal data synthesis (e.g., meta-analysis) would be possible and appropriate from the set of included studies.

Overall Approaches and Meta-Analyses for Direct Comparisons

Pooling of treatment effects was considered for each treatment comparison according to AHRQ guidance.[47] Three or more clinically and methodologically similar studies (i.e., studies designed to ask similar questions about treatments in similar populations and to report similarly defined outcomes) were required for pooling. Only trials that reported variance estimates (standard error, standard deviation, or 95% confidence interval [CI]) for group-level treatment effects could be pooled. The pooling method involved inverse variance weighting and a random-effects model. For any meta-analysis performed, we assessed statistical heterogeneity by using Cochran's Q statistic (chi-squared test) and the I^2 statistic. A p value of 0.10 was used to determine statistical significance of Cochran's Q statistic. Thresholds for the interpretation of I^2 were:

- 0 percent to 40 percent, may not be important
- 30 percent to 60 percent, may represent moderate heterogeneity
- 50 percent to 90 percent, may represent substantial heterogeneity
- 75 percent to 100 percent, represents considerable heterogeneity

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 three KQs. We used the EPC approach developed for the EPC program and

referenced in the Methods Guide,[24,48] which is based on a system developed by the GRADE Working Group.[47] This system explicitly addresses four required domains: risk of bias, consistency, directness, and precision. Table 7 describes criteria for selecting different levels within each of the four required domains. Outcomes with no studies reporting data have a level of unknown for each domain. Each domain is evaluated by outcome of interest in this report.

Table 7. Strength of evidence rating domains

Domain	Level	Criteria
Risk of bias	General	Degree to which studies have high likelihood of protection against bias; derived from assessment of the risk of bias in individual studies; incorporates both study design and conduct. Grading this domain requires assessment of aggregate quality of studies within each major study design and integration into overall risk of bias score. Limitations of design for reducing bias in addressing a key question should be taken into account. If studies differ substantially in risk of bias, may give greater weight to those studies with low risk of bias.
	Low	At least 1 good quality RCT or nonrandomized comparative study.
	Medium	At least 1 fair quality RCT; OR 1 fair quality nonrandomized comparative study; AND 1 additional study of good or fair quality.
	High	Does not meet minimum requirements for low or medium risk of bias.
Consistency	General	Degree to which studies are similar in effect sizes; degree to which studies have same direction of effect (even in presence of statistical heterogeneity).
	Consistent	Effect sizes have same direction. When multiple RCTs were available and the risk of bias was low, the range of effects needed to be narrow.
	Inconsistent	Effect sizes are in different directions.
	Unknown	Single study evidence base.
Directness	General	A single direct link between intervention and health outcome; intervention and comparator(s) compared head-to-head within a study.
	Direct	Direct head-to-head comparison of interventions within a study or assesses a final health outcome.
	Indirect	Not a direct head-to-head comparison of interventions within a study or assesses an intermediate outcome.
Precision	General	Degree of certainty surrounding an effect estimate.
	Precise	Uncertainty around an effect compatible with only one of these: clinically important superiority, inferiority, or noninferiority. In absence of meta-analysis, individual studies consistently report precise and/or statistically significant results.
	Imprecise	Uncertainty around an effect compatible with both clinically important superiority and inferiority. In absence of meta-analysis, individual studies do not consistently report precise and/or statistically significant results.

The grade of evidence strength is classified into four categories as shown in Table 8. Rules for the starting strength of evidence and factors that would raise or lower the strength are also described in the table

Table 8. Strength of evidence categories and rules

Strength of Evidence/Rules	Criteria
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.
Starting level of strength of RCT evidence	High.
Starting level of strength, observational evidence	Low, but a single observational study of good quality without confirmation by at least one other study of good or fair quality supports a SOE rating of insufficient.
Raise strength	Among observational studies, raise strength by one level if a large effect size is observed, a dose-response association is present or there is no plausible confounding that would decrease the observed effect. A very large effect size could raise strength by two levels.
Reduce strength	Reduce strength by one level if there is serious concern in an area such as: high risk of bias; inconsistent findings; consistency unknown; indirect evidence; imprecise results; or presence of publication bias. Very serious concern in an area would reduce strength by two levels.

Abbreviation: SOE = strength of evidence.

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 for the body of evidence for each outcome of interest.

Applicability

Applicability of the results presented in this review was assessed in a systematic manner using the PICOT framework (Population, Intervention, Comparison, Outcome, Timing). Assessment included both the design and execution of the studies and their relevance with regard to target populations, interventions, and outcomes of interest.

Peer Review and Public Commentary

This report received external peer review. Peer Reviewers were charged with commenting on the content, structure, and format of the evidence report, providing additional relevant citations, and pointing out issues related to how we conceptualized the topic and analyzed the evidence.

Our Peer Reviewers (listed in the front matter) gave us permission to acknowledge their review of the draft. In addition, the Eisenberg Center placed the draft report on the AHRQ Web site (www.effectivehealthcare.ahrq.gov) for public review.

No public comments were received. We compiled all peer review comments and addressed each one individually, revising the text as appropriate. Based on peer review, structure was added to the results section to distinguish that all comparisons were made within each category of intervention. Additional language was added to the Comparator in the PICOTS to restrict comparisons to the same intervention type. AHRQ staff and an associate editor provided reviews. A disposition of comments from public commentary and peer review will be posted on the AHRQ Effective Healthcare Web site (www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports) 3 months after the final report is posted.

Results

Introduction

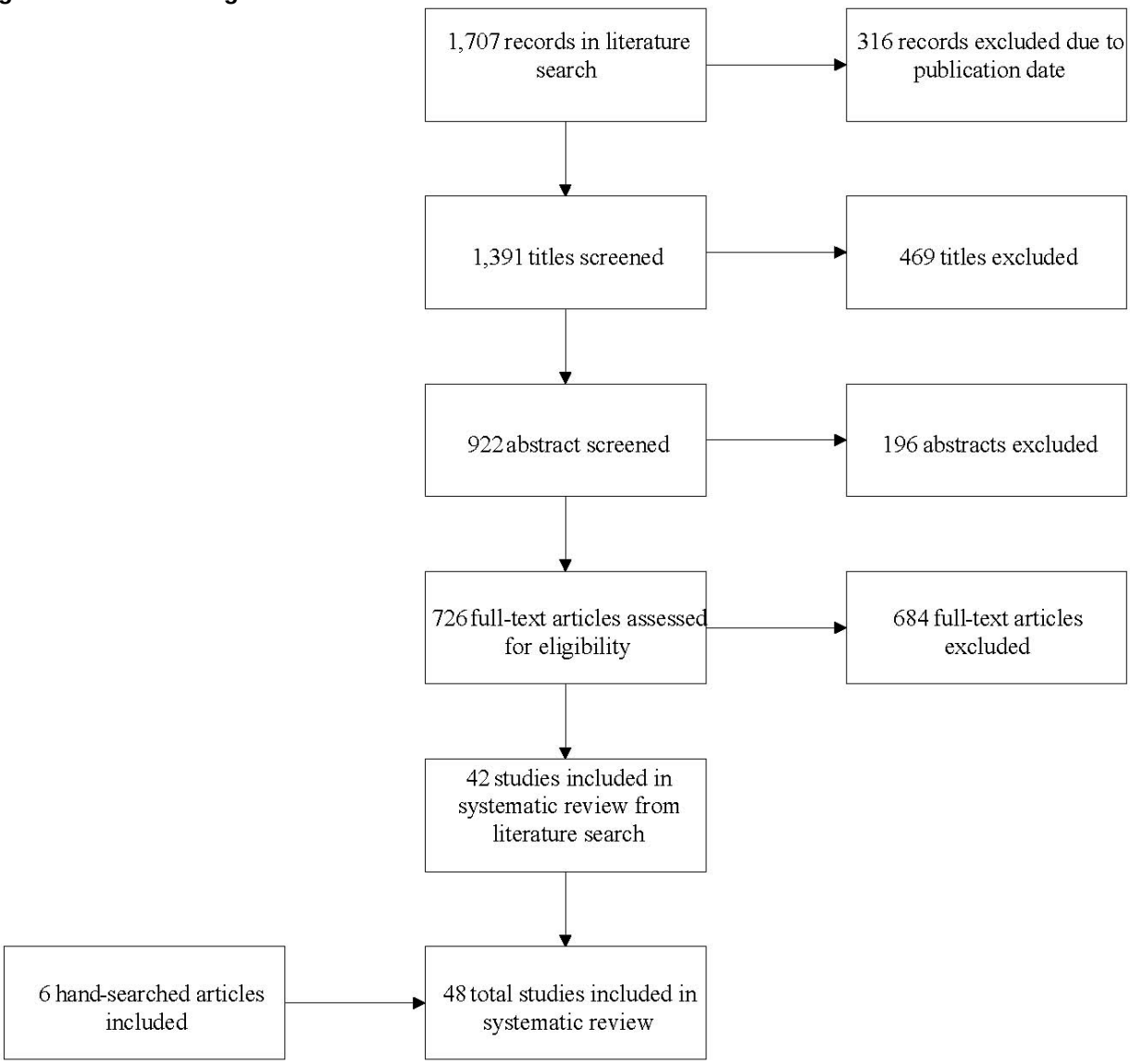
In this chapter, we present the results of our systematic review of the literature and synthesis of the extracted data on outcomes on the effectiveness and comparative effectiveness of local hepatic therapies for unresectable HCC. The Key Questions for this review are: effectiveness (KQ1) and harms (KQ2) of local hepatic therapies in patients with HCC who are not otherwise candidates for surgical resection or transplantation; and comparative effectiveness of local hepatic therapies in subgroups of patients with HCC who are not otherwise candidates for surgical resection or transplantation, stratified by specific patient and tumor characteristics, such as age, sex, disease etiology, and Child-Pugh score (KQ3).

We first describe the results of our literature searches, followed by results for KQ1 and KQ2, which include a list of key points, an overview of the included literature and detailed synthesis of the data. Results for KQ3 are presented in a similar fashion. We identified 1,713 nonduplicate titles or abstracts with potential relevance, with 732 proceeding to full-text review (Figure 2). Forty-eight articles were included in the review, including six hand-searched articles, representing 48 distinct studies: six randomized controlled trials (RCTs), one prospective cohort study, four retrospective cohort studies, one prospective case control study, one retrospective case control study, 14 prospective case series, 16 retrospective case series, two case series of unknown temporal frame, and three case reports. All 48 studies pertain to KQ1 and KQ2, and three studies pertain to KQ3.

Results of Literature Search

Of the 1,707 articles identified through the literature search, 1,665 were excluded at various stages of screening and 42 articles were included. Six hand-searched articles were also included for a total of 48 articles in this systematic review. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram (Figure 2) depicts the flow of search screening and study selection.

Figure 2. PRISMA diagram for identified studies



Our searches of various grey literature sources did not yield any additional published studies meeting our inclusion criteria.

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

- **Regulatory information:** The search yielded 33 results but no new studies were identified from this source.
- **Clinical trial registries** (ClinicalTrials.gov, controlled-trials.com, who.int): The search yielded 207 clinical trials; we excluded 136 trials during the title and abstract screen. All 71 remaining trials were excluded. Of these 71 trials, three had been terminated, 42 were ongoing or recruiting, 23 were of unknown status, and three had been completed. We found no publications for the three completed trials (NCT00867750, NCT00739167, and ISRCTN54481540). There were no ongoing or completed trials that were relevant to this systematic review.

- **Abstracts and conference papers** (American Society of Clinical Oncology, Gastrointestinal Cancers Symposium, Society of Surgical Oncology, The Radiosurgery Society, American Association for the Study of Liver Diseases): The search yielded 134 citations, and we excluded all 134 during the title and abstract screen.
- **Manufacturer database:** Scientific information packets (SIPs) were received from Accuray (manufacturers of the CyberKnife® stereotactic body radiation therapy [SBRT] system), Biocompatibles (DC Bead®), SIRTEX (manufacturers of the yttrium-90–infused SIR-Spheres microspheres), and Nordion (manufacturers of TheraSphere®). There were 150 published studies in the submission, and all 150 were excluded during full-text screen.

Description of Included Studies

Forty-eight studies met our inclusion criteria and addressed local hepatic therapies for unresectable HCC (Table 9 and Table 10). Eleven studies were conducted in China, seven in Italy, nine in Japan, seven in the United States, three in Taiwan, three in South Korea, two in Canada, and one each in France, Egypt, Greece, Austria, Thailand, and Australia. The number of participants ranged from 10 to 320 patients (not including case reports).

Table 9. Characteristics of studies included in this review by intervention: monotherapies

Characteristic	Cryoablation	RFA	MWA	PEI/PAI	TAE	TACE*	RE	DEB	3D-CRT	IMRT	SBRT	HPBT	Intraluminal brachytherapy	Total †
Total	3	9	1	3	3	19	4	5	2	0	3	0	0	52
Study Design														
RCT	0	4	0	3	1	1	0	2	0	0	0	0	0	11
Prospective Cohort	0	1	0	0	0	1	0	0	0	0	0	0	0	3
Retrospective Cohort	1	1	0	0	0	3	0	0	0	0	0	0	0	5
Prospective Case Control	0	0	0	0	0	1	0	1	0	0	0	0	0	2
Retrospective Case Control	0	0	0	0	1	1	0	0	1	0	0	0	0	3
Prospective Case Series	0	1	1	0	0	4‡	3§	1	1	0	0	0	0	10
Retrospective Case Series	2	0	0	0	1	5	1	1	0	0	3	0	0	13
Case Series – Unknown Temporal Frame	0	1	0	0	0	1	0	0	0	0	0	0	0	2
Case Report	0	1	0	0	0	2	0	0	0	0	0	0	0	3
Outcomes Reported														
Overall Survival	3	8	1	3	3	14	4	5	2	0	3	0	0	41
Quality of Life	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Time to Progression	0	5	1	2	2	6	0	4	0	0	3	0	0	23
Length of Stay	1	2	0	2	0	4	1	3	0	0	0	0	0	13
Local Recurrence	2	7	1	3	1	0	0	1	2	0	1	0	0	18
Adverse Events	3	8	0	3	2	15	3	5	2	0	3	0	0	44
Study population														
United States/Canada	0	1	0	0	0	4	3	1	0	0	1	0	0	10
Europe	0	1	0	1	2	6	0	3	0	0	0	0	0	12
Australia	0	0	0	0	0	0	1	0	0	0	0	0	0	1
Asia	3	7	1	2	1	9	0	1	2	0	2	0	0	28
Africa	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total N participants	238	320	60	299	76	1,876	187	362	55	0	91	0	0	3,564

*Transarterial embolization (bland, without any chemotherapeutic agent) was performed every time epirubicin was contraindicated in Pietrosi et al. 2009.[49]

†This number reflects the total number of study arms.

‡Includes one RCT extracted as case series.

§Includes one prospective cohort study extracted as case series.

Abbreviations: 3D-CRT = Three dimensional conformal radiotherapy; DEB = Drug-eluting beads; HPBT = Hypofractionated proton beam therapy; IMRT = Intensity modulated radiation therapy; MWA = Microwave ablation; N = Number; PAI = Percutaneous acetic acid injection; PEI = Percutaneous ethanol injection; RCT = Randomized controlled trial; RE = Radioembolization; RFA = Radiofrequency ablation; SBRT = Stereotactic body radiotherapy; TACE = Transarterial chemoembolization; TAE = Transarterial embolization; N = number.

Table 10. Characteristics of studies included in this review by intervention: combination therapies

Characteristic	RFA With TACE	RFA With TAE	RFA With DEB	TACE With PEI	TACE With Cryoablation	Total
Total	2	1	1	1	1	6
Study Design						
RCT	1	0	0	0	0	1
Prospective Cohort	0	0	0	0	0	0
Retrospective Cohort	0	0	0	0	1	1
Retrospective Case Control	0	0	0	0	0	0
Prospective Case Series	0	1	1	1	0	3
Retrospective Case Series	1	0	0	0	0	1
Case Report	0	0	0	0	0	0
Outcomes Reported						
Overall Survival	2	1	0	1	1	5
Quality of Life	0	0	0	0	0	0
Time to Progression	2	0	0	0	0	2
Length of Stay	0	0	1	0	0	1
Local Recurrence	1	0	0	0	1	2
Adverse Events	1	1	1	1	1	5
Study population						
United States	0	0	0	0	0	0
Europe	0	0	1	0	0	1
Australia	0	0	0	0	0	0
Asia	2	1	0	1	1	5
Total N participants	141	36	20	63	290	550

Abbreviations: DEB = Drug-eluting beads; N = Number; PEI = Percutaneous ethanol injection; RCT = Randomized controlled trial; RFA = Radiofrequency ablation; TACE = Transarterial chemoembolization; TAE = Transarterial embolization.

Appendix D presents the quality ratings for all 48 articles included in this evidence review.

All six RCTs assembled and maintained comparable groups, had minimal loss to followup, clearly defined the interventions, and included important outcomes of interest. The outcome measurements were not equal, valid, and reliable in all six studies, largely due to the lack of blinding of the outcomes assessor. All but two studies performed an intent-to-treat analysis, and three studies acknowledged the funding source. Overall, one study was rated as good quality, three studies were of fair quality, and two were rated as poor quality according to The United States Preventive Services Task Force rating.[45]

Using the same rating system as for the RCTs, the four nonrandomized comparative studies were rated as poor. The studies did not report blinding and did not use appropriate statistical analysis. They had representative samples; valid, reliable, and equal measurements; and adequate length of followup; however, none attempted to balance groups by design, allocate participants to treatment groups to minimize bias, or adjust for confounders in statistical analysis. One study did not report followup loss.

All 35 case series studies had clearly defined questions and well-described interventions, used validated outcome measures, and had conclusions that were supported by the data. Studies varied on how well they described the study population and their results. Twenty studies did not have well-described patient populations and five lacked well-described results. Twelve studies were of good quality, 20 studies of fair quality, and three were rated as poor quality. Quality rating was not applied to the single case report in this review.

Key Questions 1 and 2. Effectiveness and Harms of Local Hepatic Therapy

Key questions 1 and 2 focus on the comparative effectiveness (KQ1) and harms (KQ2) of the various local hepatic therapies in patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and have no evidence of extrahepatic disease.

Data for ablative, transarterial, radiotherapy, and combinations of local therapies are presented in four separate sections.

Key Points

- RFA compared with PEI/PAI: There is moderate strength of evidence to support better overall survival at 3 years for RFA compared with PEI/PAI, with a low risk of bias.
  - Three RCTs compared the ablative treatments RFA and PEI/PAI. No nonrandomized comparative studies examined this comparison. In addition to the comparative evidence, three case series of RFA are included in this report. There are no observational studies on PEI/PAI that met inclusion criteria.
- The body of evidence for RFA compared with PEI/PAI was rated low strength to support increased TTP, improved local control and a longer LOS for RFA compared with PEI/PAI, with a high risk of bias.
- Of the 13 interventions included in this report, only one comparison had sufficient evidence to receive a rating above insufficient. For all other comparisons, the body of evidence on overall survival, quality of life, disease progression, local control, LOS, days of missed work, and adverse events for local hepatic therapy for the treatment of HCC is insufficient to support the effectiveness of one local hepatic therapy over another, due to the lack of comparative studies.

Ablative Therapies

Description of Included Studies

A total of 11 studies met the inclusion criteria to address KQ1 and KQ2 for ablative therapies, including three RCTs,[50-52] one nonrandomized comparative study,[53] six series studies,[54-59] and one case report.[60] The nonrandomized comparative study was retrospective.[53] Of the six case series studies, two were retrospective[54,59] and three were prospective.[55-57] The prospective or retrospective nature of one study could not be determined.[58] The total number of patients for whom data were extracted from the 11 studies was 809. There were 483 patients from RCTs, 91 from nonrandomized comparative studies, 234 from case series, and one from a case report. All 11 studies had patient samples that were restricted to unresectable HCC patients (i.e., not including patients with liver tumors of other primary origins). All studies initiated treatment in patients after January 1, 2000.

One RCT compared RFA to PEI alone,[50] one RCT compared RFA to conventional and high-dose PEI,[51] and the third RCT compared RFA to PEI and PAI.[52] Table 11 and Table 12 present a summary of study and patient characteristics from the RCTs, including the number of patients enrolled, intervention period, intervention, and baseline characteristics. Patients ranged in age from 59 to 70.3 years with the majority in their sixties and seventies. The patients' baseline Child-Pugh liver cirrhosis classes were A or B, and there were no patients in class C cirrhosis. ECOG scores were 0 to 1 in all studies. No study reported BCLC stage. No RCTs reported prior treatment history or presence of portal vein thrombosis. Studies varied in terms of proportions of patients with hepatitis B virus (HBV) and hepatitis C virus (HCV) infection.

Table 11. Summary of ablative therapy study characteristics: RCTs

Study N Rating	Intervention	Intervention Period	Mean Age (Range)	CP A%; B%	BCLC A%; B%	Previous LDT %
Brunello et al. 2008[50] 139 Good	RFA under US guidance with either cool tip or multitined electrodes for 12 min or 15–25 min, respectively	01/2001 - 09/2004	69.0 (NR)	A: 55.7; B: 44.3	NR	NR
	PEI with sterile ethanol (95%, 2–20 mL) injected into each lesion with a single needle (1–4 sessions)	01/2001 - 09/2004	70.3 (NR)	A: 56.5; B: 43.5	NR	NR
Lin et al. 2004[51] 157 Fair	Percutaneous RFA with 15-gauge electrode under US guidance repeated 2 weeks later for up to 2 courses per tumor	04/2000 - 04/2002	62 (NR)	A: 79; B: 21	NR	NR
	PEI with 99.5% ethanol (volume per session mean: 4.5 mL, SD: 1.6 mL, range: 2–10 mL) using a single transhepatic cholangiography needle twice weekly for up to 6 sessions per tumor per course and 12 sessions of the maximal treatment per tumor	04/2000 - 04/2002	59 (NR)	A: 75; B: 25	NR	NR
	PEI with 99.5% ethanol (volume per session mean: 8.5 mL, SD: 2.8 mL, range: 6–18 mL) using two transhepatic cholangiography needles and a third needle if needed twice weekly for up to 3 sessions per tumor per course and 6 sessions of the maximal treatment per tumor	04/2000 - 04/2002	61 (NR)	A: 74; B: 26	NR	NR
Lin et al. 2005[52] 187 Fair	Percutaneous RFA with 15-gauge electrode under US guidance repeated 2 weeks later for up to 2 courses per tumor	04/2000 - 06/2002	61 (NR)	A: 74.2; B: 25.8	NR	NR
	PEI with 99.5% ethanol (volume per session mean: 4.8 mL, SD: 1.4 mL, range: 2–10.4 mL) twice weekly for up to 6 sessions per tumor per course and 12 sessions of the maximal treatment per tumor	04/2000 - 06/2002	60 (NR)	A: 75.8; B: 24.2	NR	NR
	PAI with 50% acetic acid (volume per session mean: 2.2 mL, SD: 1.1 mL, range: 1–3.5 mL) twice weekly for up to 6 sessions per tumor per course and 12 sessions of the maximal treatment per tumor	04/2000 - 06/2002	63 (NR)	A: 71.4; B: 28.6	NR	NR

Abbreviations: BCLC = Barcelona Clinic Liver Center hepatocellular carcinoma stage; CP = Child-Pugh liver cirrhosis class; LDT = liver-directed therapy; N = number of patients; NR = not reported; PAI = percutaneous acetic acid injection; PEI = percutaneous ethanol injection; RFA = radiofrequency ablation; SD = standard deviation; US = ultrasound.

Table 12. Summary of ablative therapy underlying liver disease characteristics: RCTs

Study Rating	Group N	Cirrhosis%	HBV%	HCV%	Alcohol%
Brunello et al. 2008[50] Good	RFA 70	NR	8.6	62.9	15.7
	PEI 69	NR	0	68.1	11.6
Lin et al. 2004[51] Fair	RFA 52	NR	67	31	NR
	Conventional PEI 52	NR	71	27	NR
	High dose PEI 53	NR	69	30	NR
Lin et al. 2005[52] Fair	RFA 62	NR	66.1	32.3	NR
	PEI 62	NR	67.7	30.6	NR
	PAI 63	NR	65.1	33.3	NR

Abbreviations: HBV = hepatitis B virus; HCV = hepatitis C virus; N = number of patients; NR = not reported; PAI = percutaneous acetic acid injection; PEI = percutaneous ethanol injection; RFA = radiofrequency ablation.

As displayed in Table 13, the three RCTs were similar in which tumor characteristics were reported and how these characteristics were reported. None of these studies reported lesion size, or bilobar disease status. The majority of patients presented with solitary tumors which ranged from 73 to 79 percent.

Table 13. Summary of ablative therapy tumor characteristics: RCTs

Study Rating	Group N	Bilobar %	Number of Lesions	Lesion Size Range (cm)	Other Lesion Characteristics
Brunello et al. 2008[50] Good	RFA 70	NR	Mean:1.3 Solitary: 77.1	NR	NR
	PEI 69	NR	Mean:1.3 Solitary: 78.7	NR	NR
Lin et al. 2004[51] Fair	RFA 52	NR	1: 73%, 2: 21%, 3: 6%	NR	NR
	ConventionalPEI 52	NR	1: 77%, 2: 17%, 3: 6%	NR	NR
	High-dose PEI 53	NR	1: 77%, 2: 19%, 3: 4%	NR	NR
Lin et al. 2005[52] Fair	RFA 62	NR	Solitary: 79.0%	NR	NR
	PEI 62	NR	Solitary: 79.0%	NR	NR
	PAI 63	NR	Solitary: 76.2%	NR	NR

Abbreviations: N = number; NR = not reported; PAI = percutaneous acetic acid injection; PEI = percutaneous ethanol injection; RFA = radiofrequency ablation.

Of the eight observational studies (1 nonrandomized comparative study, 6 case series studies, and 1 case report), one study included patients treated with TACE,[53] five studies included patients treated with RFA,[53,56-58,60] two studies treated patients with cryoablation,[54,59] and one study treated patients with MWA.[55] The nonrandomized comparative study treated patients with RFA or TACE and was included in this section because all patients were eligible for ablative therapy due to a small tumor size.[53] Table 14 and Table 15 present a summary of study and patient characteristics from the nonrandomized comparative studies and case series, including number of patients enrolled, intervention period, intervention, and baseline characteristics. Median age ranged from 46 to 67.7 years. The patients' baseline Child-Pugh liver cirrhosis classes were largely A or B, with a very small minority (≤10 percent) in class C. ECOG scores were reported in only one study with all patients having 0 to 1.[55] One study reported BCLC stage A (early) or B (intermediate) of the enrolled patients with all patients classified in the intermediate category.[59] One study reported that no patients had PVT.[55] No studies reported previous liver directed therapies. Two studies reported on the proportion of patients with cirrhosis, ranging from 84.6 percent to 100 percent.[54,58] Studies varied in terms of proportions of patients with HBV and HCV infection.[50-55,57,60] Overall, studies were inconsistent in reporting—and often did not report— these patient and tumor characteristics at baseline (e.g., ECOG score, Child-Pugh class, PVT, HCC stage) which are important prognostic factors to consider when comparing patient populations across studies.

Table 16 and Table 17 present data on underlying liver disease characteristics from the nonrandomized comparative studies and case series. Table 18 presents data on the nonrandomized comparative study tumor characteristics. In Table 19, the seven observational studies varied in which tumor characteristics were reported and how these characteristics were

reported. The proportion of patients with a bilobar disease was reported by three studies and ranged from 25 to 69.2 percent.[54,57,60] The number of lesions was reported in four studies[55,57,58,60] and lesion size was reported in five studies.[55,57-60]

Table 14. Summary of ablative therapy study and patient characteristics: nonrandomized comparative studies

Study N Rating	Study Design	Intervention Period	Intervention	Age, Mean or Median (Range)	ECOG Score	CP A%; B%; C%	BCLC A%; B%	Previous LDT %
Chok et al. 2006[53] 91 Poor	Retrospective cohort	02/2001 - 03/2004	TACE with cisplatin (1 mg/mL), lipiodol (volume ration 1:1), gelatin sponge mixed with gentamicin sulfate (40 mg) via superselective arteries repeated 8 to 12 weeks	Median: 66 (47–85)	NR	A: 78; B: 20; C: 2	NR	NR
		02/2001 - 03/2004	Percutaneous (45%), laparoscopic (2%) or open (53%) RFA with cool-tip electrodes	Median: 62 (42–77)	NR	A: 76; B: 22; C: 2	NR	NR

Abbreviations: BCLC = Barcelona Clinic Liver Center hepatocellular carcinoma stage; CP = Child-Pugh liver cirrhosis class; ECOG = Eastern Cooperative Oncology Group; LDT = liver-directed therapy; N = number of patients; NR = not reported; RFA = radiofrequency ablation.

Table 15. Summary of ablative therapy study and patient characteristics: case series studies

Study N Rating	Study Design	Intervention Period	Intervention	Age, Mean or Median (Range)	ECOG Score	CP A%; B%; C%	BCLC A%; B%	Previous LDT %
Chen et al. 2011[54] 40 Fair	Retrospective case series	01/2006 - 06/2009	US-guided percutaneous cryotherapy	Mean: 59.3 (NR)	NR	A: 30; B: 60; C: 10	NR	NR
Chen et al. 2011[54] 26 Fair	Retrospective case series	01/2006 - 06/2009	US-guided percutaneous cryotherapy	Mean: 57.4 (NR)	NR	A: 23.1; B: 69.2; C: 7.7	NR	NR
Itoh et al. 2011[55] 60 Good	Prospective case series	05/2003 - 12/2010	Surgical microwave therapy administered for 60 s at a power setting of 65 W per pulse using a microwave electrode 1.6mm in diameter and 25cm in length	Mean: 67.7 (47–83)	≤1: 100	A: 68.3; B: 31.6; C: 0	NR	NR
Minami et al. 2007[56] 30 Poor	Prospective case series	05/2000 - 09/2003	Open RFA with cooled-tip needle guided by intraoperative sonography	Mean: 63 (44–76)	NR	NR	NR	NR
Shen et al. 2005[57] 16 Poor	Prospective cohort*	09/2001 - 06/2004	Percutaneous RFA with retractable curved electrodes (90W peak power) under US guidance	Median: 56.1 (36–75)	NR	A: 37.5; B: 62.5; C: 0	NR	NR
Singh et al. 2011[60] 1 Poor	Case report		RFA under US guidance using cool-tip RFA probe	46	NR	A	NR	NR
Tanaka et al. 2009[58] 20 Poor	Case series (uncertain if prospective or retrospective)	07/2000 - 12/2002	Open RFA via laparotomy (17) or thoracotomy (3)	Median: 66 (NR)	NR	A: 50.0; B: 45.0; C: 5.0	NR	NR
Zhou et al. 2009[59] 42 Fair	Retrospective case series	12/2003 - 12/2006	Surgical cryoablation with argon (drop to -140°C for 15–20 min) and helium (raise to 20°C-40°C for 3–5 min) for 2–3 freezing-thawing cycles	Median: 55.8 (NR)	NR	A: 66.7; B: 33.3; C: 0	A: 0; B: 100	NR

*Only a single arm of the two comparative arms was included in this evidence review.

Abbreviations: BCLC = Barcelona Clinic Liver Center hepatocellular carcinoma stage; CP = Child-Pugh liver cirrhosis class; ECOG = Eastern Cooperative Oncology Group; LDT = liver directed therapy; N = number of patients; NR = not reported; RFA = radiofrequency ablation; US = ultrasound.

Table 16. Summary of ablative therapy underlying liver disease characteristics: nonrandomized comparative studies

Study Rating	Group N	Cirrhosis%	HBV%	HCV%	NAFLD%	Alcohol%
Chok et al. 2006[53] Poor	TACE 40	NR	78	NR	NR	NR
	RFA 51	NR	82	NR	NR	NR

Abbreviations: HBV = hepatitis B virus; HCV = hepatitis C virus; N = number of patients; NAFLD = nonalcoholic fatty liver disease; NR = not reported; RFA = radiofrequency ablation; TACE = transarterial chemoembolization

Table 17. Summary of ablative therapy underlying liver disease characteristics: case series studies

Study Rating	Group N	Cirrhosis%	HBV%	HCV%	NAFLD%	Alcohol%
Chen et al. 2011[54] Fair	Cryotherapy 40	85	95	5	NR	NR
Chen et al. 2011[54] Fair	Cryotherapy (recurrent HCC) 26	84.6	96.2	3.8	NR	NR
Itoh et al. 2011[55] Good	MWA 60	NR	13.3	78.3	NR	NR
Minami et al. 2007[56] Poor	RFA 30	NR	NR	NR	NR	NR
Shen et al. 2005[57] Poor	RFA 16	NR	56.2	NR	NR	NR
Singh et al. 2011[60] Poor	RFA 1	NR	100	NR	NR	100
Tanaka et al. 2009[58] Poor	RFA 20	100	NR	NR	NR	NR
Zhou et al. 2009[59] Fair	Cryoablation 42	NR	NR	NR	NR	NR

Abbreviations: HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; MWA = microwave ablation; N = number of patients; NAFLD = nonalcoholic fatty liver disease; NR = not reported; RFA = radiofrequency ablation; RFTA = radiofrequency thermal ablation.

Table 18. Summary of ablative therapy tumor characteristics: nonrandomized comparative studies

Study Rating	Group N	Bilobar %	Number of Lesions	Lesion Size (cm)	Other Lesion Characteristics
Chok - 2006[53] Poor	TACE 40	28	NR	NR	NR
	RFA 51	12	NR	NR	NR

Abbreviations: N = number of patients; NR = not reported; RFA = radiofrequency ablation; TACE = transarterial chemoembolization.

Table 19. Summary of ablative therapy tumor characteristics: case series studies

Study Rating	Group N	Bilobar %	Number of Lesions	Lesion Size (cm)	Other Lesion Characteristics
Chen et al. 2011[54] Fair	Cryotherapy 40	25	NR	NR	NR
Chen et al. 2011[54] Fair	Cryotherapy (Recurrent HCC) 26	69.2	NR	NR	NR
Itoh et al. 2011[55] Good	MWA 60	NR	Median: 2 Range: 1–9 Solitary: 45%	Median: 2.0 Range: 0.8–3.3	NR
Minami et al. 2007[56] Poor	RFA 30	NR	NR	Range: 1.0–10	NR
Shen et al. 2005[57] Poor	RFA 16	37.5	Solitary: 18.8%	Range: 2.3–12.3	NR
Singh et al. 2011[60] Poor	RFA 1	100	2	1.5	NR
Tanaka et al. 2009[58] Poor	RFA 20	NR	Median: 2 IQR: 1-3	IQR: 1.5-2.8	NR
Zhou et al. 2009[59] Fair	Cryoablation 42	NR	NR	Median: 6.2	NR

Abbreviations: HCC = hepatocellular carcinoma; IQR = interquartile range; N = number of patients; NR = not reported; RFA = radiofrequency ablation; SBRT = stereotactic body radiation therapy.

Detailed Synthesis

Table 20 displays the outcomes reported in the three RCTs. All RCTs reported overall survival and survival by year.[50-52] Outcomes related to progression were reported in two trials.[51,52] All RCTs reported local recurrence or local tumor progression as a measure of treatment failure.[50-52] Studies varied in the use of terms and definitions of those outcomes related to disease progression and local recurrence, and we describe them in this report as they are reported in the studies. LOS was reported in two trials.[51,52] Quality of life was not reported in any of the RCTs. All three trials reported adverse events.[50-52]

Study outcomes data were synthesized by intervention comparisons found in the 11 included articles.

Table 20. Ablative therapy outcomes reported for Key Questions 1 and 2: RCTs

Study N Rating	OS	Survival by Year	Outcomes Related to Progression	LR/Local Tumor Progression	LOS	QOL	AE
Brunello et al. 2008[50] 139 Good	●	●	NR	●	NR	NR	●
Lin et al. 2004[51] 157 Fair	●	●	●	●	●	NR	●
Lin et al. 2005[52] 187 Fair	●	●	●	●	●	NR	●

"●" Indicates that this outcome was reported in the article.
Abbreviations: AE = adverse events; LOS = length of stay; LR = local recurrence; N = number of patients; NR = not reported; OS = overall survival; QOL = quality of life.

Table 21 displays the outcomes reported in the nonrandomized comparative study. Overall survival, survival by year, outcomes related to progression, and adverse events were reported. Recurrence was reported only for the RFA group.[53]

Table 21. Ablative therapy outcomes reported for Key Questions 1 and 2: nonrandomized comparative studies

Study N Rating	OS	Survival by Year	Outcomes Related to Progression	LR/Local Tumor Progression	LOS	QOL	AE
Chok et al. 2006[53] 91 Poor	●	●	●	●*	NR	NR	●

Chok et al. 2006 reported local recurrence in the RFA group only.
Abbreviations: AE = adverse events; LOS = length of stay; LR = local recurrence; N = number of patients; NR = not reported; OS = overall survival; QOL = quality of life.

Table 22 displays the outcomes reported in the seven case series and case report studies. All studies, with the exception of the case report,[60] reported overall survival or survival by year. Survival by year presents the duration of survival for the included patients and reporting ranges from 1 to 5 years for the case series. Outcomes related to progression were reported in two studies.[55,58] Local recurrence or local tumor progression were reported in four studies.[54,55,57,58] LOS was reported by one study.[54] Adverse events were reported in all but one study,[55] and no observational studies reported on quality of life.

Table 22. Outcomes reported for Key Questions 1 and 2: case series studies

Study N Rating	OS	Survival by Year	Outcomes Related to Progression	LR/Local Tumor Progression	LOS	QOL	AE
Chen et al. 2011[54] 66 Fair	●	●	NR	●	●*	NR	●
Itoh et al. 2011[55] 60 Good	●	●	●	●	NR	NR	NR
Shen et al. 2005[57] 16 Poor	●	●	NR	●	NR	NR	●
Singh et al. 2011[60] 1 Poor	NR	NR	NR	NR	NR	NR	●
Tanaka et al. 2009[58] 20 Poor	●	●	●	●	NR	NR	●
Zhou et al. 2009[59] 42 Fair	●	●	NR	NR	NR	NR	●

*LOS reported for unresectable HCC group only (not reported for recurrent unresectable HCC group).
"●" Indicates that this outcome was reported in the article.
Abbreviations: AE = adverse events; HCC = hepatocellular carcinoma; LOS = length of stay; LR = local recurrence; N = number of patients; NR = not reported; OS = overall survival; QOL = quality of life.

RFA Compared With PEI/PAI

Three RCTs compared the ablative treatments RFA and PEI/PAI.[50-52] Brunello et al.[50] compared RFA and PEI. Lin et al. compared RFA, conventional PEI, and higher-dose PEI in one study[51] and RFA, PEI, and PAI in another study.[52] Quantitative pooling (meta-analysis) of these results was conducted for the outcome of overall survival at 3 years. As described earlier, PEI and PAI are the same intervention with different drug regimens. Since comparison across regimen is outside the scope of the review, PEI and PAI were treated as one intervention.

No nonrandomized comparative studies examined this comparison. In addition to the comparative evidence, three case series of RFA[56-58] and one case report [60] are included in this report. There are no observational studies on PEI/PAI that met inclusion criteria.

Tables 23–27 give information on RFA compared with PEI/PAI.

Overall Survival

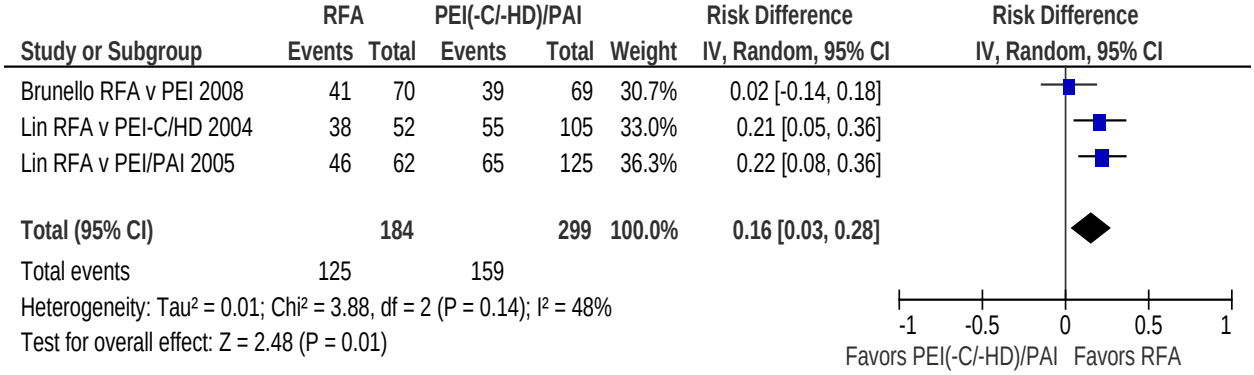
Outcomes related to overall survival are summarized in Table 24.

In comparing RFA and PEI by intent-to-treat analysis, Brunello et al.[50] reported a 3-year overall survival from the time of study treatment of 58.9 percent and 56.7 percent, respectively. No significant difference was observed between groups (adjusted hazard ratio=0.88; 95% CI, 0.50 to 1.53). In a study by Lin et al.,[51] the 3-year overall survival rates were 74 percent, 50 percent, and 55 percent in the RFA, conventional PEI, and higher-dose PEI groups, respectively. The RFA group had a significantly higher overall survival rate from the time of study treatment compared with the two PEI groups (RFA vs. conventional PEI: risk ratio=0.34; 95% CI, 0.11 to 0.79, p=0.014; RFA vs. higher-dose PEI: risk ratio, 0.39; 95% CI, 0.21 to 0.85, p=0.023). Another study by the same investigators,[52] the 3-year overall survival rates were 74 percent, 51 percent, and 53 percent in the RFA, PEI, and PAI groups, respectively. The RFA group achieved

a significantly higher overall survival than PEI and PAI groups (RFA vs. PEI: RR=0.42; 95% CI, 0.21 to 0.98, p=0.031; RFA vs. PAI: RR=0.45; 95% CI, 0.06 to 0.58, p=0.038).

These trials[50-52] were pooled in a meta-analysis (Figure 3). Risk differences were calculated for the three studies. The pooled estimate was 0.16 (95% CI, 0.03 to 0.28), a statistically significant result that favored RFA and was consistent with the direction of effect reported by the individual trials. The degree of statistical heterogeneity in this pool of studies was moderate (I^2=48 percent).

Figure 3. RFA compared with PEI/PAI: meta-analysis of three trials for the outcome of overall survival



Abbreviations: -C = Conventional; -HD = High-dose; CI: Confidence interval; IV = Independent variable; PAI = Percutaneous acetic acid injection; PEI = Percutaneous ethanol injection; RFA = Radiofrequency ablation.

Three case-series[56-58] reported overall survival after treatment with RFA and are summarized in Table 25. The 3-year survival following RFA was 20.4 percent and 90 percent in the studies by Shen et al.[57] and Tanaka et al.,[58] respectively. Minami et al.[56]did not report 3-year survival. Lack of a direct comparison in these studies limits the application of these data to inform conclusions on overall survival. There were no case series on PEI/PAI included in this report.

Strength of Evidence

There is moderate strength of evidence that overall survival is better for RFA compared with PEI/PAI for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease. The three trials[50-52] all lacked blinding and were rated good[50] or fair.[51,52] While the lack of blinding is particularly worrisome, it does not affect the measurement of overall survival. Therefore, the risk of bias for the assessment of overall survival was graded as low. Overall survival is a direct health outcome and the meta-analysis produced a precise estimate. The direction of effect was consistent across the three studies, but there was a very large range of effect (.02 to .22). Combined with the moderate heterogeneity (I^2=48 percent), we considered these results inconsistent. Based on this inconsistency, the strength of evidence was graded as moderate.

Quality of Life

Quality of life was not reported in any of the included studies.

Strength of Evidence

No studies addressed this outcome. Therefore, the strength of evidence to evaluate quality of life for RFA compared with PEI/PAI for the treatment of patients with unresectable HCC who

are not otherwise candidates for surgical resection or transplantation with no evidence of extrahepatic disease was judged to be insufficient due to the lack of evidence.

Outcomes Related to Progression

In a 2004 study, Lin et al.[51] reported cancer-free survival, defined as the time from study treatment to local tumor progression, extrahepatic metastasis, additional new HCC recurrence, or death. Followup occurred every 2 months and included a computed tomography (CT) scan. The 3-year cancer-free survival rate was 37 percent, 17 percent, and 20 percent in the RFA, conventional PEI, and higher-dose PEI groups, respectively. The RFA group had a significantly higher rate than in the two PEI groups (RF vs. conventional PEI: risk ratio=0.38; 95% CI, 0.14 to 0.88, p=0.019; RF vs. higher-dose PEI: risk ratio=0.41; 95% CI, 0.22 to 0.89, p=0.024). In another study by the same investigators,[52] the 3-year cancer-free survival rate was 43 percent, 21 percent, and 23 percent in the RFA, PEI, and PAI groups, respectively. Similar to the previous study, the RFA group achieved a significantly higher cancer-free survival than the PEI group (risk ratio=0.31; 95% CI, 0.18 to 0.85, p=0.038) and the PAI group (risk ratio=0.26, 95% CI, 0.13 to 0.81, p=0.041).

One case series[56] reported a 2-year disease-free survival rate of 39 percent following open RFA. In another study of open RFA by Tanaka et al.,[58] the median disease-free survival was not reached.

Strength of Evidence

There is a low strength of evidence to evaluate TTP for RFA compared with PEI/PAI for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease. Both trials[51,52] lacked blinding and were rated as fair quality studies. Lack of blinding can lead to detection bias. This is particularly true when outcomes are based on interpretation. (i.e., not a hard outcome, like death) Therefore, the risk of bias for the assessment of outcomes related to progression was graded as high. In addition, the results of the two trials were consistent, and progression outcomes are indirect health outcomes. The estimates were precise.

Local Recurrence/Local Tumor Progression

In a 2004 study, Lin et al.[51] reported local tumor progression, defined as the presence of an enhanced tumor on CT, corresponding to the initial target tumor. The cumulative local tumor progression rate at the end of 3 years was 18 percent, 45 percent, and 33 percent in the RFA, conventional PEI, and higher dose PEI groups, respectively. The RFA group had a significantly lower rate than in the PEI groups (RFA vs. conventional PEI: risk ratio=0.37; 95% CI, 0.12 to 0.76, p=0.012; RFA vs. higher-dose PEI: risk ratio=0.49; 95% CI, 0.23 to 0.92, p=0.037). In another study by the same investigators,[52] the cumulative local recurrence rate at the end of 3 years was 14 percent, 34 percent, and 31 percent in the RFA, PEI, and PAI groups, respectively. The local recurrence rate was significantly lower in the RFA group compared with the PEI (risk ratio=0.35; 95% CI, 0.21 to 0.89, p=0.012) and PAI (risk ratio=0.41; 95% CI, 0.23 to 0.91, p=0.017) groups. In the latter study, the authors assessed local recurrence only among the subset of patients achieving complete tumor necrosis following treatment, whereas they assessed it in all randomized patients in the former study.

Local recurrence was reported in two case series on RFA.[57,58]In a study by Tanaka et al.,[58] local recurrence (recurrence within the liver) was observed in one of 20 patients (5 percent)

following open RFA. Shen et al.[57] reported local recurrence (tumor recurrence within or at the periphery of the ablated lesion in the subsequent CT scans after complete ablation) in 5 (31.3 percent) patients following percutaneous RFA.

Strength of Evidence

There is a low strength of evidence to evaluate local recurrence for RFA compared with PEI/PAI for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease. Both trials[51,52] lacked blinding and were rated as fair quality studies. Lack of blinding can lead to detection bias. This is particularly true when outcomes are based on interpretation, (i.e., not a hard outcome like death), which local recurrence is. Therefore, the risk of bias for the assessment of local recurrence was graded as high. In addition, the results of the two trials were consistent. Local recurrence is an indirect health outcome, and the comparison in Lin 2004[51] was direct. Finally, the estimates are precise.

Length of Stay

In a 2004 study by Lin et al.,[51] LOS was reported among the subset of those patients that achieved complete tumor necrosis (50 out of 52, 46 out of 52, and 50 out of 53 in RFA, conventional PEI, and higher dose PEI groups, respectively). The RFA group had a significantly longer mean LOS than in the conventional PEI group (4.4 days ± 1.8 vs. 1.6 days ± 0.3, $p<0.01$). Similarly, in another study by the same investigators,[52] the RFA group had a significantly longer LOS than either the PEI group or the PAI group (4.2 days ± 1.9, 1.7 days ± 0.4, 2.2 days ± 0.6, respectively, all $p<0.01$). Likewise, the LOS data were assessed only for the subset of those patients achieving complete tumor necrosis.

None of the single-arm studies of RFA reported LOS.

Strength of Evidence

There is a low strength of evidence to evaluate LOS for RFA compared with PEI/PAI for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease. Both trials[51,52] lacked blinding and were rated as fair quality studies. Lack of blinding can lead to detection bias. This is particularly true when outcomes are based on interpretation (i.e., not a hard outcome like death). LOS may be determined by the physician and is subject to bias based on knowledge of the treatment received. In addition, both studies assessed LOS for only a subset of patients. Therefore, the risk of bias for the assessment of LOS was graded as high. In addition, the results of the two trials were consistent. Finally, the estimates are precise.

Days of Missed Work

Days of missed work was not reported in any of the included studies.

Strength of Evidence

No studies addressed this outcome. Due to the lack of data for this outcome, the strength of evidence to evaluate days of work missed for RFA compared with PEI/PAI for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Adverse Events

None of the 3 RCTs comparing RFA and PEI/PAI reported the following AEs: hepatic abscess, hepatic hemorrhage, biloma, steatohepatitis, injury to adjacent organs, liver failure, and infection.

Table 26 presents a summary of AEs reported in the 3 RCTs comparing RFA and PEI/PAI. Lin et al.[51] observed transient increases transaminases in most patients regardless of treatment but no occurrences of sustained levels of clinical concern.

Of the single-arm studies of RFA Shen et al.[57] reported one (6.3 percent) case of right pleural effusion after treatment. One case report[60] reported a rare AE of iatrogenic diaphragmatic hernia following RFA treated by urgent laparoscopic repair. No other adverse events of interest were reported in the single-arm studies (Table 27).[57]

Strength of Evidence

The three RCTs[50-52] reported very limited adverse events. The adverse event of elevated transaminases reported in the RCT is not subject to interpretation (i.e., objective outcome based on liver function test results); therefore, the risk of bias for the assessment of adverse events was rated as low. The consistency is unknown, and adverse events are direct health outcomes, but the estimates are imprecise. Due to the limited amount of data, the strength of evidence is insufficient to evaluate adverse events for RFA compared with PEI/PAI for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation with no evidence of extrahepatic disease (Table 23).

Overall GRADE for RFA Compared With PEI/PAI

The strength of evidence ratings for studies comparing RFA to PEI/PAI are displayed in Table 23.

Table 23. Strength of evidence for studies comparing RFA to PEI/PAI

Outcome	No of Studies Type of Study	Risk of Bias	Consistency	Directness	Precision	Overall Grade
Overall Survival	3; Brunello et al. 2008[50] RCT; Lin et al. 2004[51] RCT; Lin et al. 2005[52] RCT	Low	Inconsistent	Direct	Precise	Moderate
Quality of Life	0	Unknown	Unknown	Unknown	Unknown	Insufficient
Time to Progression	2; Lin et al. 2004[51] RCT; Lin et al. 2005[52] RCT	High	Consistent	Indirect	Precise	Low
Local Recurrence	2; Lin et al. 2004[51] RCT; Lin et al. 2005[52] RCT	High	Consistent	Indirect	Precise	Low
Length of Stay	2;Lin et al. 2004[51] RCT; Lin et al. 2005[52] RCT	High	Consistent	Indirect	Precise	Low
Days of Work Missed	0	Unknown	Unknown	Unknown	Unknown	Insufficient
Gastric bleeding	1 Lin et al. 2005[52] RCT	Low	Unknown	Direct	Imprecise	Insufficient
Hemoperitoneum	1 Brunello et al. 2008[50] RCT	Low	Unknown	Direct	Imprecise	Insufficient
Hemothorax	2 Brunello et al. 2008[50] RCT; Lin et al. 2005[52] RCT	Low	Unknown	Direct	Imprecise	Insufficient
Thrombosis	1 Brunello et al. 2008[50] RCT	Low	Unknown	Direct	Imprecise	Insufficient

Abbreviation: RCT = randomized controlled trial.

Table 24. Survival outcomes: RFA compared with PEI or PAI

Study Rating Design	Treatment Group N	Intervention	Survival Time From	Median OS	% Survival Year 1	% Survival Year 2	% Survival Year 3	Statistical Comparison
Brunello et al. 2008[50] Good RCT	RFA 70	RFA under US guidance with either cool tip or multitined electrodes for 12 min or 15–25 min, respectively	Study Treatment	40*	NR	NR	58.9	NS, Adjusted hazard ratio=0.88, 95% CI, 0.50 to1.53
	PEI 69	PEI with sterile ethanol (95%, 2–20 mL) injected into each lesions with a single needle (1–4 sessions)	Study Treatment	37*	NR	NR	56.7	
Lin et al. 2004[51] Fair RCT	RFA 52	Percutaneous RFA with 15-gauge electrode under US guidance repeated 2 weeks later for up to 2 courses per tumor	Study Treatment	Not reached*	90	82	74	-
	PEI-conventional 52	PEI with 99.5% ethanol (volume per session mean: 4.5 mL, SD: 1.6mL, range: 2–10 mL) using a single transhepatic cholangiography needle twice weekly for up to 6 sessions per tumor per course and 12 sessions of the maximal treatment per tumor	Study Treatment	36†	85	61	50	RFA vs. conventional PEI: risk ratio=0.34, 95% CI, 0.11 to 0.79, p=0.014
	PEI-higher dose 53	PEI with 99.5% ethanol (volume per session mean: 8.5 mL, SD: 2.8 mL, range: 6–18 mL) using two transhepatic cholangiography needles and a third needle if needed twice weekly for up to 3 sessions per tumor per course and 6 sessions of the maximal treatment per tumor	Study Treatment	41*	88	63	55	RFA vs. higher-dose PEI: risk ratio, 0.39, 95% CI, 0.21 to 0.85, p=0.023
Lin et al. 2005[52] Fair RCT	RFA 62	Percutaneous RFTA with 15-gauge electrode under US guidance repeated 2 weeks later for up to 2 courses per tumor	Not reported	Not reached*	93	81	74	-
	PEI 62	PEI with 99.5% ethanol (volume per session mean: 4.8 mL, SD: 1.4 mL, range: 2–10.4 mL) twice weekly for up to 6 sessions per tumor per course and 12 sessions of the maximal treatment per tumor	Not reported	32*	88	66	51	RFA vs. PEI: risk ratio=0.42, 95% CI, 0.21 to 0.98, p=0.031
	PAI 63	PAI with 50% acetic acid (volume per session mean: 2.2 mL, SD: 1.1 mL, range: 1–3.5 mL) twice weekly for up to 6 sessions per tumor per course and 12 sessions of the maximal treatment per tumor	Not reported	37*	90	67	53	RFA vs. PAI: risk ratio=0.45, 95% CI, 0.06 to 0.58, p=0.038

*Extrapolated from Kaplan-Meier graphs.

Abbreviations: CI = confidence interval; N = number of patients; NS = nonsignificant; NR = not reported; OS = overall survival; PAI = percutaneous acetic acid injection; PEI = percutaneous ethanol injection; RCT = randomized controlled trial; RFA = radiofrequency ablation; RFTA = radiofrequency thermal ablation; SD = standard deviation; US = ultrasound.

Table 25. Survival outcomes: RFA compared with PEI/PAI, case series studies

Study Rating	Group N	Intervention	Survival Time From	Median OS (95% CI)	% Survival Year 1	% Survival Year 2	% Survival Year 3	% Survival Year 4	% Survival Year 5
Minami et al. 2007[56] Poor	RFA 30	Open RFA with cooled-tip needle guided by intraoperative sonography	Study Treatment	Not yet reached	NR	NR	NR	NR	NR
Shen et al. 2005[57] Poor	RFA 16	Percutaneous RFA with retractable curved electrodes (90W peak power) under US guidance	Study Treatment	16*	52.2	NR	20.4	NR	NR
Singh et al. 2011 Poor	RFA 1	RFA under US-guidance using cool-tip RFA probe	NR	NR	NR	NR	NR	NR	NR
Tanaka et al. 2009[58] Poor	RFA 20	Open RFA via laparotomy (17) or thoracotomy (3)	Study Treatment	Not yet reached	100	90†	90†	NR	NR

*Extrapolated from Kaplan-Meier graphs.
Abbreviations: CI = confidence interval; N = number of patients; NR = not reported; OS = overall survival; RFA = radiofrequency ablation; US = ultrasound.

Table 26. Adverse events associated with local hepatic therapies: RFA compared with PEI/PAI

Study Rating Design	Treatment Group N	Intervention	Liver Failure %	Hepatic Hemorrhage %	Hepatic Abscess %	Rare AE, N (%)
Brunello et al. 2008[50] Good RCT	RFA 70	RFA under US guidance with either cool tip or multitined electrodes for 12 min or 15–25 min, respectively	NR	NR	NR	1 (1.4) hemoperitoneum and 1 (1.4) hemothorax that needed urgent thoracotomy
	PEI 69	PEI with sterile ethanol (95%, 2–20 mL) injected into each lesions with a single needle (1–4 sessions)	NR	NR	NR	1 (1.4) hemoperitoneum and 1 (1.4) death from thrombosis and possible bowel infarction 10 days after PEI
Lin et al. 2004[51] Fair RCT	RFA* 52	Percutaneous RFA with 15-gauge electrode under US guidance repeated 2 weeks later for up to 2 courses per tumor	NR	NR	NR	NR
	PEI-conventional* 52	PEI with 99.5% ethanol (volume per session mean: 4.5 mL, SD: 1.6 mL, range: 2–10 mL) using a single transhepatic cholangiography needle twice weekly for up to 6 sessions per tumor per course and 12 sessions of the maximal treatment per tumor	NR	NR	NR	NR
	PEI-higher dose* 53	PEI with 99.5% ethanol (volume per session mean: 8.5 mL, SD: 2.8 mL, range: 6–18 mL) using two transhepatic cholangiography needles and a third needle if needed twice weekly for up to 3 sessions per tumor per course and 6 sessions of the maximal treatment per tumor	NR	NR	NR	NR
Lin et al. 2005[52] Fair RCT	RFA 62	Percutaneous RFTA with 15-gauge electrode under US guidance repeated 2 weeks later for up to 2 courses per tumor	NR	NR	NR	2 (3.2) had hemothorax requiring chest tube drainage and 1 (1.6) had gastric bleeding and perforation and underwent gastric repair during operation.
	PEI* 62	PEI with 99.5% ethanol (volume per session mean: 4.8 mL, SD: 1.4 mL, range: 2–10.4 mL) twice weekly for up to 6 sessions per tumor per course and 12 sessions of the maximal treatment per tumor	NR	NR	NR	NR
	PAI* 63	PAI with 50% acetic acid (volume per session mean: 2.2 mL, SD: 1.1 mL, range: 1–3.5 mL) twice weekly for up to 6 sessions per tumor per course and 12 sessions of the maximal treatment per tumor	NR	NR	NR	NR

*No grade 3 or 4 adverse events of interest were observed for these treatment groups.

Abbreviations: AE = adverse event; N = number of patients; NR = not reported; PAI = percutaneous acetic acid injection; PEI = percutaneous ethanol injection; RCT = randomized controlled trial; RFA = radiofrequency ablation; RFTA = radiofrequency thermal ablation; SD = standard deviation; US = ultrasound.

Table 27. Adverse events associated with local hepatic therapies: RFA compared with PEI/PAI, case series studies

Study Rating	Group N	Liver Failure %	Hepatic Hemorrhage %	Hepatic Abscess %	Rare AE, N (%)
Minami et al. 2007[56] Poor	RFA 30	NR	NR	0	1 operative death due to GI bleeding after surgery.
Shen et al. 2005[57] Poor	RFA 16	0	NR	NR	The only complication was 1 (6.3%) case of right pleural effusion.
Singh et al 2011[60] Poor	RFA 1	NR	NR	NR	Iatrogenic diaphragmatic hernia following RFA treated by urgent laparoscopic repair. There were no postoperative complications and the patient was discharged 6 days after the procedure.
Tanaka et al. 2009[58] Poor	RFA* 20	NR	NR	NR	NR

*No grade 3 or 4 adverse events of interest were observed for these treatment groups.

Abbreviations: AE = adverse events; GI = gastrointestinal; N = number of patients; NR = not reported; RFA = radiofrequency ablation.

RFA Compared With TACE

No RCT examined this comparison. One retrospective cohort study by Chok et al.[53] compared ablative treatment with RFA to TACE. Patients included in this study were all eligible to receive ablative therapy.

Tables 28-30 give information on RFA compared with TACE.

Overall Survival

Outcomes related to overall survival are summarized in Table 29. Two-year survival for RFA compared with TACE was 72 percent and 58 percent, respectively, which was not found to be statistically different (p=0.21) when analyzed with Cox proportional hazards model.

Strength of Evidence

The strength of evidence to evaluate overall survival for RFA compared to TACE for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation with no evidence of extrahepatic disease is rated insufficient. Evidence to evaluate this outcome comes from one poor quality study. Chok et al.[53] is a retrospective cohort study which began with a low strength of evidence due to the nature of the study design (e.g., lack of blinding and no randomization) and was further reduced to insufficient SOE due to a high risk of bias. For an observational study to overcome the limitations of a non-randomized design adequate control of confounders must be considered in the analysis. The authors did not attempt to adjust for confounders in their analysis. Therefore, the risk of bias for the assessment of overall survival was graded as high. There is unknown consistency as there is only one trial, overall survival is a direct health outcome, and the estimate is imprecise.

Quality of Life

Quality of life was not reported in any of the included studies.

Strength of Evidence

No studies addressed this outcome. Due to the lack of data for this outcome, the strength of evidence to evaluate quality of life for RFA compared with TACE for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Outcomes Related to Progression

In the study by Chok et al.,[53] time to disease progression was calculated from the date of disease response to treatment to the date of disease progression. Disease progression occurred in 35 patients (88 percent) in the TACE group and 36 patients (71 percent) in the RFA group. The median time to disease progression was 9.5 months (range: 1.0 to 47.3 months) in patients treated with TACE and 10.4 months (range: 1.0 to 42.7 months) in patients treated with RFA (p=0.95).

Strength of Evidence

The strength of evidence to evaluate outcomes related to progression for RFA compared to TACE for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation with no evidence of extrahepatic disease is rated insufficient.

Evidence to evaluate this outcome comes from one poor quality study. Chok et al.[53] is a retrospective cohort study which began with a low strength of evidence due to the nature of the study design (e.g., lack of blinding and no randomization) and was further reduced to insufficient SOE due to a serious risk of bias. For an observational study to overcome the limitations of a non-randomized design adequate control of confounders must be considered in the analysis. The authors did not attempt to adjust for confounders in their analysis. Lack of blinding can lead to detection bias. Even though blinding would be difficult, not doing so remains a major threat to validity. This is particularly true when outcomes are based on interpretation (i.e., not a hard outcome like death). Therefore, the risk of bias for the assessment of outcomes related to progression was graded as high. In addition, with only one study, consistency is unknown, progression is an indirect measure of a health outcome, and the estimates are imprecise.

Local Recurrence/Local Tumor Progression

In the study by Chok et al.,[53] during a median followup period of 19 months, the local recurrence rate was 14 percent (n=7) in the RFA group. The authors did not report local recurrence rate in the TACE group.

Strength of Evidence

The strength of evidence to local recurrence or local tumor progression for RFA compared to TACE for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation with no evidence of extrahepatic disease is rated insufficient. Evidence to evaluate this outcome comes from one poor quality study. Chok et al.[53] is a retrospective cohort study which began with a low strength of evidence due to the nature of the study design (e.g., lack of blinding and no randomization) and was further reduced to insufficient SOE due to a serious risk of bias. For an observational study to overcome the limitations of a non-randomized design adequate control of confounders must be considered in the analysis. The authors did not attempt to adjust for confounders in their analysis. This is particularly true when outcomes are based on interpretation (i.e., not a hard outcome like death). Therefore, the risk of bias for the assessment of outcomes related to local recurrence as high. In addition, with only one study, consistency is unknown, progression is an indirect measure of a health outcome, and the estimates are imprecise.

Length of Stay

LOS was not a reported outcome in the study by Chok et al.[53]

Strength of Evidence

No studies addressed this outcome. Due to the lack of data for this outcome, the strength of evidence to evaluate LOS for RFA compared with TACE for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Days of Missed Work

Days of missed work was not reported in any of the included studies.

Strength of Evidence

No studies addressed this outcome. Due to the lack of data for this outcome, the strength of evidence to evaluate days of work missed for RFA compared with TACE for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient (Table 28).

Adverse Events

Table 30 presents a summary of AEs reported in the study comparing RFA to TACE. In the study by Chok et al.,[53] liver failure was observed in 1 (2 percent) and 2 (5 percent) patients in the RFA and TACE groups, respectively. The study did not report on the following AEs: hepatic abscess, hepatic hemorrhage, biloma, steatohepatitis, injury to adjacent organs, infection, increased liver enzymes (transaminases, bilirubin, alkaline phosphatase), and rare adverse events.

Strength of Evidence

The strength of evidence to evaluate adverse events for RFA compared with TACE is rated as insufficient because only a single poor quality study assessed this outcome. The lack of blinding affected the risk of bias in the assessment of adverse events. The majority of adverse events of interest, such as hepatic hemorrhage, leave little room for interpretation, but other adverse events, such as liver failure, involve some interpretation; therefore, the risk of bias for the assessment of adverse events was rated as high. The consistency is unknown, adverse events are direct health outcomes, but the estimates are imprecise.

Overall GRADE for RFA Compared With TACE

The strength of evidence ratings for studies comparing RFA to TACE are displayed in Table 28.

Table 28. Strength of evidence for studies comparing RFA to TACE

Outcome	No. of Studies Type of Study	Risk of Bias	Consistency	Directness	Precision	Overall Grade
Overall Survival	1; Chok et al. 2006[53] Retrospective cohort	High	Unknown	Direct	Imprecise	Insufficient
Quality of Life	0	Unknown	Unknown	Unknown	Unknown	Insufficient
Time to Progression	1; Chok et al. 2006[53] Retrospective cohort	High	Unknown	Indirect	Imprecise	Insufficient
Local Control	1; Chok et al. 2006[53] Retrospective cohort	High	Unknown	Indirect	Imprecise	Insufficient
Length of Stay	0	Unknown	Unknown	Unknown	Unknown	Insufficient
Days of Work Missed	0	Unknown	Unknown	Unknown	Unknown	Insufficient
Adverse Events	1; Chok et al. 2006[53] Retrospective cohort	High	Unknown	Direct	Imprecise	Insufficient

Table 29. Survival outcomes: RFA compared with TACE

Study Rating Design	Treatment Group N	Intervention	Survival Time From	Median OS (95% CI)	% Survival Year 1	% Survival Year 2	% Survival Year 3	% Survival Year 4	% Survival Year 5	Statistical Comparison
Chok et al. 2006[53] Poor Retrospective cohort	RFA 51	Percutaneous (45%), laparoscopic (2%) or open (53%) RFA with cool-tip electrodes	Study Treatment	Not yet reached	82	72	NR	NR	NR	2 year survival: NS, p=0.21
	TACE 40	TACE with cisplatin (1 mg/mL), lipiodol (volume ration 1:1), gelatin sponge mixed with gentamicin sulfate (40 mg) via superselective arteries repeated 8 to 12 weeks	Study Treatment	25*	80	58	NR	NR	NR	

*Extrapolated from Kaplan-Meier graphs.
Abbreviations: CI = confidence interval; N = number of patients; NR = not reported; NS = nonsignificant; OS = overall survival; RFA = radiofrequency ablation; TACE = transarterial chemoembolization.

Table 30. Adverse events associated with local hepatic therapies: RFA compared with TACE

Study Rating Design	Treatment Group N	Intervention	Liver Failure %	Hepatic Hemorrhage %	Hepatic Abscess %	Rare AE, N (%)
Chok et al. 2006[53] Poor Retrospective cohort	RFA 51	Percutaneous (45%), laparoscopic (2%) or open (53%) RFA with cool-tip electrodes	NR	NR	0	1 operative death due to GI bleeding after surgery.
	TACE 40	TACE with cisplatin (1 mg/mL), lipiodol (volume ratio 1:1), gelatin sponge mixed with gentamicin sulfate (40 mg) via superselective arteries repeated 8 to 12 weeks	NR	NR	NR	1 case (1%) of bowel perforation (grade 5), 2 cases (1%) of severe sepsis without leucopenia (grade 5)

Abbreviations: AE = adverse event; GI = gastrointestinal; N = number of patients; NR = not reported; RFA = radiofrequency ablation; TACE = transarterial chemoembolization.

Interventions With No Comparative Evidence

Three case series were included in this report for which no comparative evidence exists. Two focused on cryotherapy and one on microwave ablation.[54,55,59]

Strength of Evidence

No comparative studies met inclusion criteria for this review. Therefore strength of evidence is insufficient to evaluate all outcomes of interest: overall survival, quality of life, TTP, local recurrence, LOS, days of work missed, and adverse events for all interventions without comparative studies for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease.

Overall Survival

A case series study by Chen et al.[54]on cryoablation reported a 1-year survival of 81.4 percent in the nonrecurrent HCC group and 70.2 percent in the recurrent HCC group. Zhou et al.[59] reported a 1-year survival of 61.9 percent following cryoablation. One study of MWA reported a 3-year survival of approximately 54 percent.[55] Survival outcomes for the combination treatments are summarized in Table 31. Lack of a direct comparison in these studies limits the application of these data to inform conclusions on overall survival.

Quality of Life

Quality of life was not reported in any of the included studies.

Outcomes Related to Progression

Itoh et al. reported a median progression-free survival of approximately 12 months in patients treated with MWA.[55]

Local Recurrence/Local Tumor Progression

One cryoablation study,[54] local tumor progression (recurrence of the treated tumor) was observed in 12 (30 percent) of the unresectable HCC patients and 6 (23 percent) of the recurrent HCC patients. In the study by Itoh et al., local recurrence was observed in 11.7% of the patients treated with MWA.[55]

Length of Stay

LOS was not reported in any of the included studies.

Days of Missed Work

Days of missed work was not reported in any of the included studies.

Adverse Events

For the studies lacking comparative data, no liver failure or hepatic abscess was reported. An incidence of hepatic hemorrhage of 3.8 percent was reported by Chen et al. in the recurrent HCC arm.[54] Other rare adverse events are listed in Table 32, including fatal and nonfatal events.

Table 31. Outcomes related to overall survival, studies with no comparative data

Study Rating	Group N	Intervention	Survival Time From	Median OS (95% CI)	% Survival Year 1	% Survival Year 2	% Survival Year 3	% Survival Year 4	% Survival Year 5
Chen et al. 2011[54] Fair	Cryoablation 40	US-guided percutaneous cryotherapy	Study Treatment	Not yet reached	81.4	NR	60.3	NR	NR
Chen et al. 2011[54] Fair	Cryotherapy, Recurrent HCC 26	US-guided percutaneous cryotherapy	Study Treatment	24*	70.2	NR	28.8	NR	NR
Itoh et al. 2011[55] Good	MWA 60	Surgical microwave therapy administered for 60 s at a power setting of 65 W per pulse using a microwave electrode 1.6 mm in diameter and 25 cm in length	Study Treatment	42*	93.9	NR	53.8	NR	43.1
Zhou et al. 2009[59] Fair	Cryoablation 42	Surgical cryoablation with argon (drop to -140C for 15-20 min) and helium (raise to 20-40C for 3-5 min) for 2-3 freezing-thawing cycles	Study Treatment	17.4*	61.9	22.9	5.7	NR	NR

*Extrapolated from Kaplan-Meier graphs.
Abbreviations: CI = confidence interval; CP = Child-Pugh liver cirrhosis class; MWA = microwave ablation; N = number of patients; NS = nonsignificant; NR = not reported; OS = overall survival; US = ultrasound.

Table 32. Adverse events associated with local hepatic therapies: studies with no comparative data

Study Rating	Group N	Liver Failure %	Hepatic Hemorrhage %	Hepatic Abscess %	Rare AE, N (%)
Chen et al. 2011[54] Fair	Cryoablation 40	0	0	NR	Infection, 1 (2.5%)
Chen et al. 2011[54] Fair	Cryotherapy, Recurrent HCC 26	0	3.8	NR	Post-operative hemorrhage, 1 (3.8%); Infection, 1 (3.8%)
Zhou et al. 2009[59] Fair	Cryoablation 42	NR	NR	0	Abdominal Infection, 2 (4.8%); Wound Infection, 2 (4.8%)
Itoh et al. 2011[55] Good	MWA 60	NR	NR	NR	NR

*No grade 3 or 4 adverse events of interest were observed for these treatment groups.
Abbreviations: AE = adverse event; CP = Child-Pugh liver cirrhosis class; MWA = microwave ablation; N = number of patients.

Embolization Therapies

Description of Included Studies

A total of 26 studies met the inclusion criteria to address KQ1 and KQ2, including two RCTs,[61,62] two nonrandomized comparative studies,[31,63] 20 case series studies,[49,64-82] and two case reports.[83,84] Two nonrandomized comparative studies were included, one retrospective[63] and one prospective.[31] Of the 19 case series studies,10 were retrospective[65,68-70,72,74,76,79-81] and eight were prospective.[64,66,67,71,73,77,78,82] The prospective or retrospective nature of one study could not be determined.[49] One RCT was abstracted as a case-series because the comparator was not of interest for this report.[75] The total number of patients for whom data were extracted from the 26 studies was 2,461. There were 151 patients from RCTs, 165 from nonrandomized comparative studies, 2,142 from case series, and three from case reports. All studies had patient samples that were restricted to unresectable HCC patients (i.e., not including patients with liver tumors of other primary origins). All studies initiated treatment in patients after January 1, 2000.

One RCT compared DEB to TACE,[62] and another compared DEB to TAE.[61]

Table 33 and Table 34 present a summary of study and patient characteristics from the RCTs, including the number of patients enrolled, intervention period, intervention, and baseline characteristics. Patients ranged in mean age from 68.7 to 71.3 years. The patients' baseline Child-Pugh liver cirrhosis classes were A or B, and there were no patients in class C cirrhosis. ECOG scores were 0 to 1 in all studies. One study reported BCLC HCC stage A (early) or B (intermediate) of the enrolled patients.[62] No RCTs reported prior treatment history or presence of PVT. One study reported that 100 percent of the patients were cirrhotic.[61] One RCT reported the proportion of patients with HBV and HCV infection.[62]

Table 33. Summary of embolization treatment study characteristics: RCTs

Study N Rating	Intervention	Intervention Period	Mean Age (Range)	CP A%; B%	BCLC A%; B%	Previous LDT %
Malagari et al. 2010[61] 84 Poor	Transarterial DEB with DC beads® loaded with doxorubicin (37.5 mg/mL of bead suspension) every 2 months with a maximum of 3 procedures	2005	70.7 (NR)	A: 56.1; B: 43.9	NR	NR
	Bland embolization with nonloaded particles of the same diameter and mechanics as DEB (BeadBlock) every 2 months with a maximum of 3 procedures	2005	70.0 (NR)	A: 60.5; B: 39.5	NR	NR
Sacco et al. 2011[62] 67 Fair	TACE with iodized oil (mean: 16.6 mL, range: 10–25 mL), doxorubicin (mean: 57.0 mg, range: 50–75 mg) and gelatin sponge particles via hepatic arteries	01/2006 - 03/2009	68.7 (NR)	A: 73.5; B: 26.5	A: 64.7; B: 35.3	NR
	DEB chemoembolization with DC Bead® (2-4 mL, 100–300 µm) loaded with doxorubicin (50 mg/vial, mean: 55 mg, range: 25–150 mg) mixed with nonionic contrast medium at a 1:3 ratio via superselective injection	01/2006 - 03/2009	71.3 (NR)	A: 87.9; B: 12.1	A: 66.7; B: 33.3	NR

Abbreviations: BCLC = Barcelona Clinic Liver Center hepatocellular carcinoma stage; CP = Child-Pugh liver cirrhosis class; DEB = drug-eluting bead; LDT = liver-directed therapy; N = number of patients; NR = not reported; TACE = transarterial chemoembolization.

Table 34. Summary of embolization treatment underlying liver disease characteristics: RCTs

Study Rating	Group N	Cirrhosis%	HBV%	HCV%	Alcohol%
Malagari et al. 2010[61] Poor	DEB 41	100	NR	NR	NR
	TAE 43	100	NR	NR	NR
Sacco et al. 2011[62] Fair	TACE 34	NR	11.8	73.5	NR
	DEB 33	NR	12.1	66.7	NR

Abbreviations: DEB = drug-eluting bead; HBV = hepatitis B virus; HCV = hepatitis C virus; N = number of patients; NR = not reported; TACE = transarterial chemoembolization; TAE = transarterial embolization.

As displayed in Table 35, the two RCTs varied in which tumor characteristics were reported and how these characteristics were reported. The proportion of patients with a bilobar disease was reported in one study and consisted of 17.6 percent in the TACE group and 24.2 percent in the DEB group.[62] The mean number of lesions ranged from 1 (solitary tumor) to 1.5. Only one study reported the lesion size, which ranged from 1.0 cm to 13.0 cm.[62] Malagari et al. reported the sum of tumor diameters, which had a mean value of 8.35 cm in the DEB group and 8.1 cm in the TAE group.[61]

Table 35. Summary of embolization treatment tumor characteristics: RCTs

Study Rating	Group N	Bilobar %	Number of Lesions	Lesion Size Range (cm)	Other Lesion Characteristics
Malagari et al. 2010[61] Poor	DEB 41	NR	1: 29.2%, >1: 26.8%,	Sum of tumor diameters, mean (SD): 8.35 (2.75)	Multinodular: 43.9%
	TAE 43	NR	1: 34.9%, >1: 32.6%;	Sum of tumor diameters, mean (SD): 8.1 (2.8)	Multinodular: 32.6%
Sacco et al. 2011[62] Fair	TACE 34	17.6	Mean:1.5 Range: 1–3	Range: 1.3–8.8	NR
	DEB 33	24.2	Mean:1.3	Range: 1.0–13.0	NR

Abbreviations: DEB = drug-eluting bead; N = number; NR = not reported; SD = standard deviation; TACE = transarterial chemoembolization; TAE = transarterial embolization.

Of the observational studies (two nonrandomized comparative studies, 20 case series studies, and two case reports), 16 studies included patients treated with TACE,[49,64,65,68-70,72,73,75,76,78,80-82,84] four studies included patients treated with RE,[66,67,71,74] one study included patients treated with TAE,[79] and one study included patients treated with DEB.[31,77] One article reported on either TACE or TAE but did not report outcomes separately for each procedure.[49] Table 36 and Table 37 present a summary of study and patient characteristics from the nonrandomized comparative studies and case series, including number of patients enrolled, intervention period, intervention, and baseline characteristics. Median age ranged from 48 to 73 years. The patients' baseline Child-Pugh liver cirrhosis classes were largely A or B, with a very small minority (≤10 percent) in class C. Similarly, the ECOG scores were 0 to 1 in the vast majority of patients, with few scoring 2. Two studies reported BCLC HCC stage A (early) or B (intermediate) of the enrolled patients; in one study, most patients (88.1 percent) were in stage A and 0 in stage B.[64] In one study, 100 percent of the patients were in stage B.[82] Eight studies reported the HCC stage using the Okuda staging system, and the vast majority of the patients were in Okuda stage I or II, which are equivalent to BCLC stages A and B, respectively.[31,66,74-77,79,81] Liu et al.[74] included patients in Okuda stage III that exceeded 10 percent of the sample (36 percent); because the study reported Okuda stage II patients separately, we extracted data for this subset of patients only. Six studies reported the proportion of patients with PVT,[63,66,67,70,72,81] which ranged from 0 to 28 percent. Eleven studies described patients' prior treatment history, including local hepatic therapies such as resection.[70,74,78,80,81,83] Twelve studies reported on the proportion of patients

with cirrhosis, ranging from 45 percent to 100 percent.[49,66,67,69-71,74-77,79,81] Studies varied in terms of proportions of patients with HBV and HCV infection.[49,64-67,69-72,74-82] Overall, studies were inconsistent in reporting—and often did not report— these patient and tumor characteristics at baseline (e.g., ECOG score, Child-Pugh class, PVT, HCC stage) which are important prognostic factors to consider when comparing patient populations across studies.

Table 38 and Table 39 present data on underlying liver disease characteristics from the nonrandomized comparative studies and case series. As displayed in Table 40, the two nonrandomized comparative studies varied in which tumor characteristics were reported and how these characteristics were reported. No nonrandomized comparative study reported the proportion of patients with a bilobar disease. The number of lesions and lesion size was reported by one study.[31] As displayed in Table 41, the 22 observational studies varied in which tumor characteristics were reported and how these characteristics were reported. The proportion of patients with a bilobar disease was reported by five studies and ranged from 17.9 to 58 percent.[64,66,67,78,81] The number of lesions was reported in 12 studies[64,65,67,70-72,76-78,80,82,84] and lesion size was reported in 10 studies.[64,68-72,77,80-82]

Table 36. Summary of embolization treatment study and patient characteristics: nonrandomized comparative studies

Study N Rating	Study Design	Intervention Period	Intervention	Age, Mean or Median (Range)	ECOG Score	CP A%; B%; C%	BCLC A%; B%	Previous LDT %
Recchia et al. 2012[31] 105 Poor	Prospective case control	01/2008 – 01/2010	DEB with DC beads® loaded with doxorubicin (50 mg/m^2). For tumors >5 cm the size was between 500 and 700 µm, for tumors between 5 and 3 cm, the size was 300-500 µm, while for tumors <3 cm the size was 300 µm.	Median: 72 (53–80)	≤1: 100	A: 34; B: 66; C: 0	NR	NR
			TACE	Median: 70 (47–80)	≤1: 100	A: 40; B: 60; C: 0	NR	NR
Yu et al. 2009[63] 60 Poor	Retrospective case control	03/2002 - 12/2002	TEA with lipiodol-ethanol mixture (mean: 14.5 mL, SD: 17.6 mL) via tumor feeder vessel(s) for a median of 2 treatments	Mean: 64.4 (NR)	≤1: 100; 2: 0	A: 93.3; B: 6.7; C: 0	NR	NR
		01/2005 - 12/2005	TACE with lipiodol (20 mL) - cisplatin (10 mg) emulsion and gelatin sponge particle embolization via hepatic artery for a median of 3 treatments	Mean: 62.7 (NR)	≤1:96.7; 2: 3.3	A: 93.3; B: 6.7; C: 0	NR	NR

Abbreviations: BCLC = Barcelona Clinic Liver Center hepatocellular carcinoma stage; CP = Child-Pugh liver cirrhosis class; DEB = drug-eluting bead; ECOG = Eastern Cooperative Oncology Group; LDT = liver-directed therapy; N = number of patients; NR = not reported; SD = standard deviation; TACE = transarterial chemoembolization; TEA = transarterial ethanol ablation.

Table 37. Summary of embolization treatment study and patient characteristics: case series studies

Study N Rating	Study Design	Intervention Period	Intervention	Age, Mean or Median (Range)	ECOG Score	CP A%; B%; C%	BCLC A%; B%	Previous LDT %
Bargellini et al. 2011[64] 67 Fair	Prospective case series	01/2006 - 03/2009	TACE with lipiodol (mean: 16.1 mL, range: 10–25 mL), epirubicin hydrochloride (mean: 57 mg, range: 40–75 mg), and gelatin sponge particles via hepatic artery	Mean: 70 (NR)	NR	A: 79.1; B: 20.9; C: 0	0: 13.6; A: 88.1; B: 0	NR
Buijs et al. 2008[65] 190 Fair	Retrospective case series	01/2002 - 01/2007	TACE with cisplatin (100 mg), doxorubicin (50 mg), mitomycin C (10 mg) in a 1:1 mixture with iodized oil, and either polyvinyl alcohol particles or gelatin-coated trisacryl microspheres via femoral artery	Mean: 65 (18–84)	NR	A: 66; B: 34; C: 0	NR	NR
Carr et al. 2004[66] 65 Poor	Prospective case series	08/2000 - 08/2003	RE with Y90 (dose delivered mean: 145.7 Gy, median: 134.3 Gy, range: 61.1–280.9Gy) via hepatic artery	Median: 69 (NR)	NR	NR	NR	NR
Carr et al. 2010[67] 99 Fair	Prospective cohort*	2000 - 2005	RE with Y90 (deliver 135–150 Gy) via hepatic artery over 1–5 min	NR	NR	NR	NR	NR
Giannini et al. 2010[68] 128 Poor	Retrospective cohort*	2003 - 2006	TACE with an emulsion of lipiodol and chemotherapeutic agent (doxorubicin, epirubicin, mitoxantrone)	Median: 66 (NR)	NR	A: 64.8; B: 35.2; C: 0	NR	NR
Guiu et al. 2009[69] 43 Fair	Retrospective case series	09/2000 - 12/2006	TACE with pirarubicin (50 mg) diluted in 5% glucose (20 mL), lipiodol (20 mL), particles of gelatin sponge (2- to 3-mm diameter), and amiodarone (150 mg) via femoral artery once every 6–8 weeks	Median: 64.9 (47–86)	NR	A: 85; B: 12.5; C: 2.5	NR	NR
Imai et al. 2011[70] 122 Poor	Retrospective case series	12/2007 - 12/2010	TACE with miriplatin (median 80 mg, range 20–120 mg) and lipiodol (median 3 mL, range 1–6 mL) via hepatic artery	Median: 72 (48–87)	NR	A: 75.4; B: 24.6; C: 0	NR	TACE: 80
Kanhere et al. 2008[71] 12 Poor	Prospective case series	08/2000 - 02/2005	RE with radiolabelled lipiodol (average dose 1.7GBq (1.4–2.2 GBq) diluted in unlabeled lipiodol (2–10 mL) via hepatic artery	Mean: 63.4 (34–83)	NR	A: 75; B: 25; C: 0	NR	NR

Table 37. Summary of embolization treatment study and patient characteristics: case series studies (continued)

Study N Rating	Study Design	Intervention Period	Intervention	Age, Mean or Median (Range)	ECOG Score	CP A%; B%; C%	BCLC A%; B%	Previous LDT %
Kawaoka et al. 2009[72] 107 Poor	Retrospective case series	06/2000 - 12/2007	TACE with lipiodol and cisplatin (total per case median: 60 mg, range 10–390 mg) with or without embolization via femoral artery	Median: 73 (42–92)	NR	A: 72.1; B: 27.9; C: 2.8	NR	NR
Kim et al. 2012[83] 2 Poor	Case Report		TACE for 6 sessions in one case, unknown schedule in the other case	NR	NR	NR	NR	TACE: 50[†]
Leelawat et al. 2008[73] 15 Poor	Prospective cohort	01/2007 - 12/2007	TACE with doxorubicin (25–50 mg) plus mitomycin C (5–10 mg) in a mixture of ionized oil contrast medium and Ivalon particles	Median: 59 (37–65)	NR	NR	NR	NR
Leelawat et al. 2008[73] 15 Poor	Prospective cohort	01/2007 - 12/2007	TACE with mitomycin C (5–10 mg) in a mixture of ionized oil contrast medium and Ivalon particles	Median: 52 (40–65)	NR	NR	NR	NR
Liu et al. 2004[74] 11 Fair	Retrospective case series	01/2002 - 08/2003	RE with Y90 TheraSphere (prescribed dose 100–150 Gy) via hepatic artery	Median: 67 (51–73)	NR	NR	NR	TACE: 36, TACE and resection: 18, TACE and RFA: 9, RFA 9
Mabed et al. 2009[75] 50 Fair	RCT*	09/2003 - 06/2005	TACE using lipiodol (10 mg), doxorubicin (50 mg) and cisplatin (50 mg) via hepatic artery every 4 weeks as long as the condition permits and total dose of 500 mg/m^2 not exceeded	Median: 52 (36–60)	0:26; 1-2:74	A: 68; B: 32; C: 0	NR	NR
Maeda et al. 2008[76] 33 Fair	Retrospective case series	01/2000 - 03/2006	TACE with iodized oil, epirubicin (accumulated dose average 16.1 mg, range 0–72.5 mg) and gelatin sponge via hepatic artery for an average of 2.3 sessions (range 1–7 sessions)	Mean: 69.6 (38–85)	NR	A: 79; B: 21; C: 0	NR	NR
Martin et al. 2011[77] 118 Poor	Prospective case series	01/2007 - 10/2009	DEB with doxorubicin (75 mg per 2 mL, minimum recommended volume of 10 mL) in 2 bead vials via hepatic artery every 3–8 weeks for 2–4 treatment cycles	Median: 68 (35–88)	0 or 1: 91	A: 72; B: 28; C: 0	NR	NR

Table 37. Summary of embolization treatment study and patient characteristics: case series studies (continued)

Study N Rating	Study Design	Intervention Period	Intervention	Age, Mean or Median (Range)	ECOG Score	CP A%; B%; C%	BCLC A%; B%	Previous LDT %
Molinari et al.[78] 2006 47 Poor	Prospective case series	11/2001 - 05/2004	TACE with doxorubicin (75 mg/m^2) with lipiodol (10 mL) followed in some patients with polyvinyl alcohol particles via hepatic artery or superselectively in some cases	Mean: 63.4 (NR)	NR	NR	NR	RFA: 4.3
Pietrosi et al. 2009[49] 320 Poor	Case series (uncertain if prospective or retrospective)	01/2000 - 12/2004	TACE with epirubicin (50 mg/m^2) with or without iodized oil and/or Gelfoam via hepatic artery or transarterial embolization with iodized oil and/or Gelfoam via superselective artery supplying a single lesion or hepatic artery	Median: 63 (35–81)	NR	A: 61.9; B: 30.6; C: 2.8	NR	NR
Rand et al. 2005[79] 46 Good	Retrospective case series	01/2000 - 09/2002	TAE with tirsacryl gelatin microspheres (size 100–700 µ) followed by cyanoacrylate (0.3–1 mL) and lipiodol via hepatic arteries	NR	NR	A: 45.7; B: 23.9; C: 8.7	NR	NR
Reso et al. 2009[84] 1 Poor	Case report		TACE with cisplatin (50 mg), adriamycin (50 mg) and lipidol (20 mL)	NR	NR	NR	NR	NR
Seki et al. 2011[80] 135 Poor	Retrospective case series	05/2007 - 06/2009	TACE with epirubicin-loaded (25–30 mg) superabsorbent polymer microspheres via hepatic artery	Mean: 72 (31–87)	NR	A: 60.0; B: 39.3; C: 0.7	NR	Interventional radiology: 86.7; TACE: 48.2
Wu et al. 2010[81] 110 Poor	Retrospective cohort	04/2008 - 04/2009	TACE with I-metuximab-131 (median 1720 MBq, 95% CI, 1654–1804 MBq), epirubicin, lipiodol, and/or gelfoam sponge via transhepatic artery for 5–10 min	Median: 48 (25–84)	0:100	A: 69; B: 31; C: 0	NR	None: 72; RFA: 16
Wu et al. 2010[81] 132 Poor	Retrospective cohort	06/2008 - 12/2008	TACE with epirubicin and lipiodol and/or gelfoam sponge	Median: 52 (24–89)	0:100	A: NR; B: 35; C: NR	NR	NR

Table 37. Summary of embolization treatment study and patient characteristics: case series studies (continued)

Study N Rating	Study Design	Intervention Period	Intervention	Age, Mean or Median (Range)	ECOG Score	CP A%; B%; C%	BCLC A%; B%	Previous LDT %
Zhang et al. 2011[82] 277 Good	Prospective case series	12/2003 - 11/2005	TACE with 5-fluorouracil (1 g), cis-dichlorodiamine platinum (80 mg), mitomycin (10 mg) mixed with lipiodol (5–30 mL) and, for some patients, gelatin sponge, via hepatic artery repeated every 8–12 weeks until stabilization of the tumor	Median: 54 (12–85)	NR	A: 89.2; B: 10.8; C: 0	A: 0; B: 100	NR

*Only a single arm of the two comparative arms was included in this evidence review.
Abbreviations: BCLC = Barcelona Clinic Liver Center hepatocellular carcinoma stage; CI = confidence interval; CT = computed tomography; CP = Child-Pugh liver cirrhosis class; DEB = drug-eluting bead; ECOG = Eastern Cooperative Oncology Group; GBq = gigabecquerel; Gy = Gray; LDT = liver directed therapy; N = number of patients; NR = not reported; RCT = randomized controlled trial; RE = radioembolization; SD = standard deviation; TACE = transarterial chemoembolization; TAE = transarterial embolization; US = ultrasound; Y90 = yittrium-90.

Table 38. Summary of embolization treatment underlying liver disease characteristics: nonrandomized comparative studies

Study Rating	Group N	Cirrhosis%	HBV%	HCV%	NAFLD%	Alcohol%
Recchia et al. 2012[31] Poor	DEB 35	NR	NR	NR	NR	NR
	TACE 70	NR	NR	NR	NR	NR
Yu et al. 2009[63] Poor	TEA 30	NR	NR	NR	NR	NR
	TACE 30	NR	NR	NR	NR	NR

Abbreviations: DEB = drug-eluting bead; HBV = hepatitis B virus; HCV = hepatitis C virus; N = number of patients; NAFLD = nonalcoholic fatty liver disease; NR = not reported; TACE = transarterial chemoembolization; TEA = transarterial ethanol ablation.

Table 39. Summary of embolization treatment underlying liver disease characteristics: case series studies

Study Rating	Group N	Cirrhosis%	HBV%	HCV%	NAFLD%	Alcohol%
Bargellini et al. 2011[64] Fair	TACE 67	NR	11.9	74.6	NR	NR
Buijs et al. 2008[65] Fair	TACE 190	NR	21	40	NR	NR
Carr et al. 2004[66] Poor	RE 65	75.0	26.8	45.0	NR	47.5
Carr et al. 2010[67] Fair	RE 99	80	9	30	NR	NR
Giannini et al. 2010[69] 128 Poor	TACE 128	NR	NR	NR	NR	NR
Guiu et al. 2009[69] Fair	TACE 43	93	5	10	7.5	67.5
Imai et al. 2011[70] Poor	TACE 122	100	9.0	84.4	NR	NR
Kanhere et al. 2008[71] Poor	RE 12	66.7	25.0	16.7	0	8.3
Kawaoka et al. 2009[72] Poor	TACE 107	NR	6.7	78.8	NR	NR
Kim et al. 2012[83] Poor	TACE 2	NR	NR	NR	NR	NR
Leelawat et al. 2008[73] Poor	TACE-Doxorubicin 15	NR	NR	NR	NR	NR
Leelawat et al. 2008[73] Poor	TACE 15	NR	NR	NR	NR	NR
Liu et al. 2004[74] Fair	RE 11	45	18	45	NR	NR
Mabed et al. 2009[75] Fair	TACE 50	90	12	74	NR	NR
Maeda et al. 2008[76] Fair	TACE 33	100	24	58	NR	3
Martin et al. 2011[77] Poor	DEB 118	100	12	16	NR	5
Molinari et al.[78] 2006 Poor	TACE 47	NR	49	28	NR	15
Pietrosi et al. 2009[49] Poor	TACE or TAE 320	95.3	13.1	77.8	NR	0.9

Table 39. Summary of embolization treatment underlying liver disease characteristics: case series studies (continued)

Study Rating	Group N	Cirrhosis%	HBV%	HCV%	NAFLD%	Alcohol%
Rand et al. 2005[79] Good	TAE 46	78.3	NR	17.4	NR	NR
Reso et al. 2009[84] Poor	TACE 1	NR	NR	NR	NR	NR
Seki et al. 2011[80] Poor	DEB 135	NR	7.4	81.4	NR	NR
Wu et al. 2010[81] Poor	TACE with iodine 131-metuximab 110	98	95	3	NR	NR
Wu et al. 2010[81] Poor	Conventional TACE 132	97	95	NR	NR	NR
Zhang et al. 2011[82] Good	TACE 277	NR	86.7	1.1	NR	NR
Zhou et al. 2009[59] Fair	Cryoablation 42	NR	NR	NR	NR	NR

Abbreviations: DEB = drug-eluting bead; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; N = number of patients; NAFLD = nonalcoholic fatty liver disease; NR = not reported; TACE = transarterial chemoembolization; TAE = transarterial embolization; RE = radioembolization.

Table 40. Summary of embolization treatment tumor characteristics: nonrandomized comparative studies.

Study Rating	Group N	Bilobar %	Number of lesions	Lesion size (cm)	Other lesion characteristics
Recchia et al. 2012[31] Poor	DEB 35	NR	Range: 1–3	Median: 4.12 Range:1–9	NR
	TACE 70	NR	Range: 1–3	Median: 5.3 Range: 2–9	NR
Yu et al. 2009[63] Poor	TEA 30	NR	NR	NR	NR
	TACE 30	NR	NR	NR	NR

Abbreviations: DEB = drug-eluting bead; N = number of patients; NR = not reported; TACE = transarterial chemoembolization; TEA = transarterial ethanol ablation.

Table 41. Summary of embolization treatment tumor characteristics: case series studies

Study Rating	Group N	Bilobar %	Number of Lesions	Lesion Size (cm)	Other Lesion Characteristics
Bargellini et al. 2011[64] Fair	TACE 67	17.9	Mean:1.5 Range: 1–3 1: 62.7%, 2: 28.5%, 3: 8.9 %	Range: 1.0–6.5	NR
Buijs et al. 2008[65] Fair	TACE 190	NR	1: 26%; multiple lesions: 74%	NR	NR
Carr et al. 2004[66] Poor	RE 65	50.8	NR	NR	Liver involvement >50 percent: 15.4%
Carr et al. 2010[67] Fair	RE 99	43	≥5: 26%	NR	NR
Giannini et al. 2010[68] Poor	TACE 128	NR	NR	Median: 3 95% CI: 3.0–3.5	NR
Guiu et al. 2009[69] Fair	TACE 43	NR	NR	Range: 1–20	Unifocal: 14%, multifocal: 53%, diffuse: 33%
Imai et al. 2011[70] Poor	TACE 122	NR	Mean:4 Range: 1–100 Solitary: 18%;	Range: 1.0–10.0	Portal vein invasion: 2% (also noted in PVT)
Kanhere et al. 2008[71] Poor	RE 12	NR	Solitary: 50%	Range: 5.0–18.5	NR
Kawaoka et al. 2009[72] Poor	TACE 107	NR	1: 40%, 2–3: 33%, >3: 27%	Range: 0.6–13.0	NR
Kim et al. 2012[83] Poor	TACE 2	NR	NR	NR	NR
Leelawat et al. 2008[73] Poor	TACE-Doxorubicin 15	NR	NR	NR	NR
Leelawat et al. 2008[73] Poor	TACE 15	NR	NR	NR	NR
Liu et al. 2004[74] Fair	RE 11	NR	NR	NR	NR
Mabed et al. 2009[75] Fair	TACE 50	NR	NR	NR	NR

Table 41. Summary of embolization treatment tumor characteristics: case series studies (continued)

Study Rating	Group N	Bilobar %	Number of Lesions	Lesion Size (cm)	Other Lesion Characteristics
Maeda et al. 2008[76] Fair	TACE 33	NR	Solitary: 21%	NR	NR
Martin et al. 2011[77] Poor	DEB 118	NR	Median: 2 Range: 1–25 Solitary: 45%	Range: 1.0–16.9	NR
Molinari et al.[78] 2006 Poor	TACE 47	53	Solitary: 17%	NR	NR
Pietrosi et al. 2009[49] Poor	TACE or TAE 320	NR	NR	NR	NR
Rand et al. 2005[79] Good	TAE 46	NR	NR	NR	NR
Reso et al. 2009[84] Poor	TACE 1	NR	1	NR	NR
Seki et al. 2011[80] Poor	DEB 135	NR	1: 22.9%, 2–5: 27.4%, 6–10: 12.6%, >10: 37.0%	Range: 1.0–12.0	NR
Wu et al. 2010[81] Poor	TACE with 131 I-metuximab 110	58	NR	≤5 cm: 72%, > 5 cm: 28%	NR
Wu et al. 2010[81] Poor	Conventional TACE 132	58	NR	NR	NR
Zhang et al. 2011[82] Good	TACE 277	NR	Solitary: 60.6%	Range: 1–20 ≤7 cm: 50.5%, >7 cm: 49.5%	NR

Abbreviations: CI = confidence interval; DEB = drug-eluting beads; HCC = hepatocellular carcinoma; IQR = interquartile range; N = number of patients; NR = not reported; PVT = portal vein thrombosis; RE = radioembolization; RFA = radiofrequency ablation; TACE = transarterial chemoembolization; TAE = transarterial embolization.

Detailed Synthesis

Table 42 displays the outcomes reported in the two RCTs. One RCT reported overall survival,[61] and both trials reported survival rate by year.[61,62] Survival by year presents the duration of survival for the included patients and ranges from 1 to 3 years in the RCTs. Outcomes related to progression were reported in both trials.[61,62] One RCT reported local recurrence or local tumor progression as a measure of treatment failure.[61] LOS was reported in one trial.[62] Quality of life was not reported in any of the RCTs. Both trials reported adverse events.

Study outcomes data were synthesized by intervention comparisons found in the 26 included articles.

Table 42. Embolization treatment outcomes reported for Key Questions 1 and 2: RCTs

Study N Rating	OS	Survival by Year	Outcomes Related to Progression	LR/Local Tumor Progression	LOS	QOL	AE
Malagari et al. 2010[61] 84 Poor	NR	●	●	●	NR	NR	●
Sacco et al. 2011[62] 67 Fair	●	●	●	NR	●	NR	●

"●" Indicates that this outcome was reported in the article.
Abbreviations: AE = adverse events; LOS = length of stay; LR = local recurrence; N = number of patients; NR = not reported; OS = overall survival; QOL = quality of life.

Table 43 displays the outcomes reported in the two nonrandomized comparative studies. Both studies reported overall survival or survival by year.[31,63] Survival by year presents the duration of survival for the included patients and reporting ranges from 1 to 5 years for the nonrandomized comparative studies. Outcomes related to progression were reported by two studies.[31,63] Local recurrence or local tumor progression and adverse events were not reported by these studies. None of the studies reported on LOS or quality of life outcomes. Adverse events were reported by one nonrandomized comparative study.[31]

Table 43. Embolization treatment outcomes reported for Key Questions 1 and 2: nonrandomized comparative studies

Study N Rating	OS	Survival by Year	Outcomes Related to Progression	LR/Local Tumor Progression	LOS	QOL	AE
Recchia et al. 2012[31] 105 Poor	●	NR	●	NR	●	NR	●
Yu et al. 2009[63] 60 Poor	NR	●	●	NR	NR	NR	NR

Abbreviations: AE = adverse events; LOS = length of stay; LR = local recurrence; N = number of patients; NR = not reported; OS = overall survival; QOL = quality of life.

Table 44 displays the outcomes reported in the 22 case series and case report studies. All but four studies reported overall survival or survival by year.[49,70,83,84] Survival by year presents the duration of survival for the included patients and reporting ranges from 1 to 5 years for the case series. Outcomes related to progression were reported in four studies.[64,69,75,77] Local recurrence or

local tumor progression were reported in one study.[64] LOS was reported by four studies.[64,71,77,78] Adverse events were reported in all but three studies,[67,68,73] and no observational studies reported on quality of life.

Table 44. Embolization treatment outcomes reported for Key Questions 1 and 2: case series studies

Study N Rating	OS	Survival by Year	Outcomes Related to Progression	LR/Local Tumor Progression	LOS	QOL	AE
Bargellini et al. 2011[64] 67 Fair	●	●	●	●	●	NR	●
Buijs et al. 2008[65] 190 Fair	●	●	NR	NR	NR	NR	●
Carr et al. 2004[66] 65 Poor	●	NR	NR	NR	NR	NR	●
Carr et al. 2010[67] 99 Fair	●	NR	NR	NR	NR	NR	NR
Giannini et al. 2010[68] 128 Poor	●	NR	NR	NR	NR	NR	NR
Guiu et al. 2009[69] 43 Fair	●	●	●	NR	NR	NR	●
Imai et al. 2011[70] 122 Poor	NR	NR	NR	NR	NR	NR	●
Kanhere et al. 2008[71] 12 Poor	●	●	NR	NR	●	NR	●
Kawaoka et al. 2009[72] 107 Poor	●	●	NR	NR	NR	NR	●
Kim et al. 2012[83] 2 Poor	NR	NR	NR	NR	NR	NR	●
Leelawat et al. 2008[73] 30 Poor	●	●	NR	NR	NR	NR	NR
Liu et al. 2004[74] 11 Fair	●†	NR	NR	NR	NR	NR	●
Mabed et al. 2009[75] 50 Fair	●	NR	●	NR	NR	NR	●
Maeda et al. 2008[76] 33 Fair	●	●	NR	NR	NR	NR	●
Martin et al. 2011[77] 118 Poor	●	●	●	NR	●	NR	●
Molinari et al. 2006[78] 47 Poor	●	●	NR	NR	●	NR	●

Table 44. Embolization treatment outcomes reported for Key Questions 1 and 2: case series studies (continued)

Study N Rating	OS	Survival by Year	Outcomes Related to Progression	LR/Local Tumor Progression	LOS	QOL	AE
Pietrosi et al. 2009[49] 320 Poor	NR	●	NR	NR	NR	NR	●
Rand et al. 2005[79] 46 Good	●	●	NR	NR	NR	NR	●
Reso et al. 2009[84] 1 Poor	NR	NR	NR	NR	NR	NR	●
Seki et al. 2011[80] 135 Poor	●	●	NR	NR	NR	NR	●
Wu et al. 2010[81] 242 Poor	●	●*	NR	NR	NR	NR	●
Zhang et al. 2011[82] 277 Good	●	●	NR	NR	NR	NR	●

*Survival by year only reported for the TACE with 131I-metuximab arm only (not reported for the conventional TACE arm).
"●" Indicates that this outcome was reported in the article.
Abbreviations: AE = adverse events; HCC = hepatocellular carcinoma; LOS = length of stay; LR = local recurrence; N = number of patients; NR = not reported; OS = overall survival; QOL = quality of life.

DEB Compared With TAE

One RCT by Malagari et al. compared DEB with doxorubicin-loaded beads and TAE with nonleaded particles.[61] Two case series[80,85] reported relevant outcomes for treatment with DEB and one[79] reported outcomes after TAE. No nonrandomized comparative studies examined this comparison, and there were two included case series on DEB[80,85] and one for TAE.[79]

Tables 45-49 give information on DEB compared with TAE.

Overall Survival

Outcomes related to overall survival are summarized in Table 46. Malagari et al.[61] reported that there was no statistically significant difference in 1-year overall survival between the groups (85.3 percent and 86 percent, respectively, p-value not reported). The authors stated that the reported survival is affected by the introduction of further treatment after the three planned procedures and for those with recurrence or disease progression.

The case series reported that 1-year survival following DEB was 75 percent in the Martin[85] study and 73.7 percent in the Seki study.[80] The study by Rand et al.[79] reported a 1-year survival of 70.7 percent. Lack of a direct comparison in these studies limits the application of these data to inform conclusions on overall survival.

Strength of Evidence

The strength of evidence to evaluate overall survival for DEB compared with TAE is rated insufficient for patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease. Evidence to evaluate this outcome comes from one poor quality study. Malagari et al. [61] is an RCT and was rated as a poor quality due to the lack of blinding, participant drop out, and lack of appropriate, controlled

analysis. While the lack of blinding is particularly worrisome, it does not affect the measurement of overall survival. Therefore, the risk of bias for the assessment of overall survival was graded as medium. There is unknown consistency as there is only one trial, overall survival is a direct health outcome, and the estimate is imprecise (Table 45).

Quality of Life

Quality of life was not reported in any of the included studies.

Strength of Evidence

No studies addressed this outcome. Due to the lack of data for this outcome, the strength of evidence to evaluate quality of life for DEB compared with TAE for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Outcomes Related to Progression

Malagari et al.[61] reported time-to-progression (TTP), defined as the time from the first treatment until progression which consisted of as local recurrence, new lesions, or a combination of both (overall recurrence). Progression was assessed at the followup visits 1 month after each procedure and then at 9 and 12 months with CT or magnetic resonance imaging (MRI).

The mean TTP was longer in the DEB group (10.6 ± 2.4 months) than the TAE group (9.1 ± 2.3 months; p=0.008).

One case series by Martin et al.[85] reported a median progression-free survival of 13 months (range: 6 to 32 months) following DEB.

Strength of Evidence

The strength of evidence to evaluate outcomes related to progression for DEB compared with TAE is rated insufficient for patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease. Evidence to evaluate this outcome comes from one study of poor quality. Malagari et al.[61] is an RCT and was rated as poor quality due to the lack of blinding and participant drop out. Lack of blinding can lead to detection bias. This is particularly true when the outcomes are based on interpretation (i.e., not a hard outcome like death). Therefore, the risk of bias for the assessment of outcomes related to progression was graded as high. In addition, with only one study consistency is unknown, progression is an indirect measure of a health outcome, and the estimates are precise.

Local Recurrence/Local Tumor Progression

Malagari et al.[61] reported local recurrence as the number of patients with local recurrence out of the total number of patients evaluated at 6, 9, and 12 months. In the DEB and TAE groups local recurrence at 6 months was observed in 1/41 patients and 4/43 patients (2.4 percent and 9.3 percent, p=0.17), at 9 months in 6/40 and 19/41 (15 percent and 46.3 percent, p=0.002), and at 12 months in 11/35 and 19/41 patients (31.4 percent and 56.8 percent, p=0.03) respectively.

Local recurrence was not reported in case series on DEB[80,85] or TAE.[79]

Strength of Evidence

The strength of evidence to evaluate local recurrence or local tumor progression for DEB compared with TAE is rated insufficient for patients with unresectable HCC who are not

otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease. Evidence to evaluate this outcome comes from one study of poor quality. Malagari et al.[61] is an RCT and was rated as poor quality due to the lack of blinding and participant drop out. Lack of blinding can lead to detection bias. This is particularly true when the outcomes are based on interpretation (i.e., not a hard outcome like death). Therefore, the risk of bias for the assessment of local recurrence was graded as high. In addition, with only one study consistency is unknown, local recurrence is an indirect measure of a health outcome, and the estimates are precise at six and twelve months. The authors calculated local recurrence out of those who returned for followup, which decreased over time.

Length of Stay

LOS was not a reported outcome in the study by Malagari et al.[61]

Strength of Evidence

No studies addressed this outcome. Due to the lack of data for this outcome, the strength of evidence to evaluate LOS for DEB compared with TAE for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Days of Missed Work

Days of missed work was not reported in any of the included studies.

Strength of Evidence

No studies addressed this outcome. Due to the lack of data for this outcome, the strength of evidence to evaluate days of work missed for DEB compared with TAE for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Adverse Events

Table 48 presents a summary of AEs reported in the RCT comparing DEB and TAE. Malagari et al[61] reported hepatic abscess in 2 (4.8 percent) and 1 (2.3 percent) patients in the DEB and TAE groups, respectively, and liver failure in 2 patients in each group. The study authors did not report on the following AEs: hepatic hemorrhage, biloma, steatohepatitis, injury to adjacent organs, infection, increased liver enzymes (transaminases, bilirubin, alkaline phosphatase), and rare adverse events.

In the case series, Seki et al. reported none of 135 patients experienced liver failure, hepatic abscess, or biloma after DEB (Table 49).[80] One patient (0.7 percent) had a grade 3 hematologic toxicity (anemia). In a study by Rand et al.,[79] approximately 2 percent of 46 patients who underwent treatment with TAE experienced liver failure while another 2 percent developed hepatic abscess.

Strength of Evidence

The strength of evidence to evaluate adverse events for DEB compared with TAE is rated as insufficient. Evidence to evaluate this outcome comes from a single poor quality RCT and three observational studies. Malagari et al.[61] is an RCT and was rated as poor quality due to the lack of blinding and participant drop out. The lack of blinding in the trial affected the risk of bias in the

assessment of adverse events. The majority of adverse events of interest leave little room for interpretation, such as hepatic hemorrhage, but some such as liver failure involve some interpretation; therefore, the risk of bias for the assessment of adverse events was rated as medium. The consistency is unknown, and adverse events are direct health outcomes, but the estimates are imprecise.

Overall GRADE for DEB Compared With TAE

The strength of evidence ratings for studies comparing DEB to TAE are displayed in Table 45.

Table 45. Strength of evidence for studies comparing DEB to TAE

Outcome	No. of Studies Type of Study	Risk of Bias	Consistency	Directness	Precision	Overall Grade
Overall Survival	1; Malagari et al. 2010[61] RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Quality of Life	0	Unknown	Unknown	Unknown	Unknown	Insufficient
Time to Progression	1; Malagari et al. 2010[61] RCT	High	Unknown	Indirect	Precise	Insufficient
Local Control	1; Malagari et al. 2010[61] RCT	High	Unknown	Indirect	Imprecise	Insufficient
Length of Stay	0	Unknown	Unknown	Unknown	Unknown	Insufficient
Days of Work Missed	0	Unknown	Unknown	Unknown	Unknown	Insufficient
Adverse Events	1; Malagari et al. 2010[61] RCT	Medium	Unknown	Direct	Precise	Insufficient

Abbreviation: RCT = randomized controlled trial.

Table 46. Survival outcomes: DEB compared with TAE

Study Rating Design	Treatment Group N	Intervention	Survival Time From	Median OS	% Survival Year 1	% Survival Year 2	% Survival Year 3	Statistical Comparison
Malagari et al. 2010[61] Poor RCT	DEB 41	Transarterial DEB with DC beads® loaded with doxorubicin (37.5 mg/mL) of bead suspension every 2 months with a maximum of 3 procedures	Study treatment	NR	85.3	NR	NR	NS, No statistical test of significance reported
	TAE 43	Bland embolization with nonloaded particles of the same diameter and mechanics as DEB (BeadBlock) every 2 months with a maximum of 3 procedures	Study treatment	NR	86.0	NR	NR	

Abbreviations: DEB = drug-eluting bead; N = number of patients; NR = not reported; NS = nonsignificant; OS = overall survival; RCT = randomized controlled trial; TAE = transarterial embolization.

Table 47. Survival outcomes: DEB compared with TAE, case series studies

Study Rating	Group N	Intervention	Survival Time From	Median OS (95% CI)	% Survival Year 1	% Survival Year 2	% Survival Year 3	% Survival Year 4	% Survival Year 5
Martin et al. 2011[85] Poor	DEB 118	DEB with doxorubicin (75 mg per 2 mL, minimum recommended volume of 10 mL) in 2 bead vials via hepatic artery every 3–8 weeks for 2–4 treatment cycles	Not reported	14.2	75	NR	NR	NR	NR
Seki et al. 2011[80] Poor	DEB 135	TACE with epirubicin-loaded (25–30 mg) superabsorbent polymer microspheres via hepatic artery	Study treatment	26	73.7	59.0	NR	NR	NR
Rand et al. 2005[79] Good	TAE 46	TAE with tirsacryl gelatin microspheres (size 100–700 µ) followed by cyanoacrylate (0.3–1 mL) and lipiodol via hepatic arteries	HCC diagnosis	22.2	70.7	NR	NR	NR	NR

Abbreviations: CI = confidence interval; DEB = drug-eluting beads; HCC = hepatocellular carcinoma; N = number of patients; NR = not reported; NS = nonsignificant; OS = overall survival; TACE = transarterial chemoembolization; TAE = transarterial alcohol embolization.

Table 48. Adverse events associated with local hepatic therapies: DEB compared with TAE

Study Rating Design	Treatment Group N	Intervention	Liver Failure %	Hepatic Hemorrhage %	Hepatic Abscess %	Rare AE, N (%)
Malagari et al. 2010[61] Poor RCT	DEB 41	Transarterial DEB with DC beads® loaded with doxorubicin (37.5 mg/mL) of bead suspension every 2 months with a maximum of 3 procedures	4.8	NR	4.8	NR
	TAE 43	Bland embolization with nonloaded particles of the same diameter and mechanics as DEB (BeadBlock) every 2 months with a maximum of 3 procedures	4.6	NR	2.3	NR

Abbreviations: AE = adverse event; N = number of patients; NR = not reported; DEB = drug-eluting bead; TAE = transarterial embolization; RCT = randomized controlled trial.

Table 49. Adverse events associated with local hepatic therapies: DEB compared with TAE, case series studies

Study Rating	Group N	Liver Failure %	Hepatic Hemorrhage %	Hepatic Abscess %	Rare AE, N (%)
Martin et al. 2011[85] Poor	DEB 118	NR	NR	NR	Grade 3+ AE: Bleeding 4 (9%), hematological 2 (5%), pancreatitis 1 (2%), liver dysfunction/failure 2 (5%), hypertension 1 (2%)
Seki et al. 2011[80] Poor	DEB 135	0	NR	0	1 (0.7%) patient with grade 3 hematologic toxicity (anemia)
Rand et al. 2005[79] Good	TAE 46	2.2	NR	2.2	NR

Abbreviations: AE = adverse events; DEB = drug-eluting beads; N = number of patients; NR = not reported; TAE = transarterial alcohol embolization.

DEB Compared With TACE

One RCT by Sacco et al. compared DEB with doxorubicin-loaded beads and conventional TACE with doxorubicin.[62] One prospective case control study also investigated this comparison.[31] There were 14 studies with 16 extracted single-treatment arms for TACE.[64,65,68-70,72,73,75,76,78,81-84] Two of these studies were cohort studies that were extracted as two single arms with varied TACE regimens. As mentioned previously, there were two included case series on DEB.[80,85]

Tables 50-54 give information on DEB compared with TACE.

Overall Survival

Outcomes related to overall survival are summarized in Table 51. In the trial by Sacco et al.[62] the 2-year overall survival rates were not significantly different between the groups (83.6 percent in the conventional TACE group and 86.8 percent in the DEB group, p=0.96).

In the study by Recchia et al.[31] the reported median overall survival was 18.4 months and 11.4 months in the DEB and TACE groups, respectively, with no statistically significant difference.

Two case series report 1-year survival following DEB: 75 percent in the Martin study[85] and 73.7 percent in the Seki study.[80] Following TACE, 1-year survival is reported in 8 case series studies[64,65,69,72,76,78,81,82] and ranged from 52.1 percent to 90.9 percent (Table 52). Lack of a direct comparison in these studies limits the application of these data to inform conclusions on overall survival.

Strength of Evidence

The strength of evidence to evaluate overall survival for DEB compared with TACE is rated as insufficient for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease based on evidence from one poor and one fair quality study. Sacco et al.[62] is an RCT and was rated as fair quality due to the lack of blinding. Recchia et al.[31] is a prospective cohort study which was rated as poor quality study due to the lack of control for relevant confounders during statistical analyses. The overall strength of evidence began with a moderate strength of evidence and was further reduced to insufficient SOE due to a serious risk of bias in the study by Recchia et al. and imprecision in the estimates. For an observational study to overcome the limitation of a non-randomized design, adequate control of confounders must be considered in the analysis. The authors did not control for these confounders and in addition do not discuss loss to follow up, have non-equal measurements between groups and poorly defined interventions. The lack of blinding in the study by Sacco et al is particularly worrisome, however it does not affect the measurement of overall survival. Therefore, the risk of bias for the assessment of overall survival was graded as medium. There is consistency between the RCT and prospective cohort study, overall survival is a direct health outcome, the comparison was direct, and the estimate is imprecise (Table 50).

Quality of Life

Quality of life was not reported in any of the included studies.

Strength of Evidence

No studies addressed this outcome. Due to the lack of data for this outcome, the strength of evidence to evaluate quality of life for DEB compared with TACE for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Outcomes Related to Progression

Sacco et al.[62] reported time-to-radiologic-progression, defined as the time from study treatment to disease progression identified at followup 1 month after chemoembolization and every 3 months thereafter with CT or MRI. Radiologic progression was observed in 12 patients (17.9 percent), who then subsequently received repeated DEB or TACE. While the median time to progression had not been reached, the mean expected time-to-radiographic-progression was not significantly different between the groups (24.2 months after TACE vs. 15.6 months after DEB, p=0.64).

Recchia et al.[31] reported relapse-free survival (RFS) defined as the time between the study treatment to any relapse and the appearance of a second primary cancer or death. The median RFS was 13.1 months and 8.4 months in the DEB and TACE groups, respectively (not statistically significant). One case series by Martin et al.[85] reported a median progression-free survival of 13 months (range: 6 to 32 months) following DEB. Three case series studies on TACE reported on disease progression-related outcomes.[64,69,75] Bargellini et al.[64] reported a radiological disease progression following TACE in 12 patients (17.9 percent). Guiu et al.[69] reported a median progression-free survival of 15 months (95% CI, 11.5 to 20.8) following TACE. In the study by Mabed et al.,[75] the authors reported the median progression-free survival of 8 months (range: 4 to 17.5) among the subset of patients with partial response and stable disease following TACE (29 out of 50).

Strength of Evidence

The strength of evidence to evaluate outcomes related to progression for DEB compared with TACE is rated as insufficient for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease. Evidence to evaluate this outcome comes from two studies; one fair quality RCT and one poor quality observational study. Sacco et al.[62] is an RCT and was rated as fair quality due to the lack of blinding. Recchia et al.[31] is a prospective cohort study which was rated as poor quality study due to the lack of control for relevant confounders during statistical analyses. Lack of blinding can lead to detection bias. This is particularly true when outcomes are based on interpretation (i.e., not a hard outcome like death). Therefore, the risk of bias for the assessment of outcomes related to progression was graded as high. Evidence is consistent, and progression is an indirect measure of a health outcome. The estimates are imprecise.

Local Recurrence/Local Tumor Progression

Sacco et al.[62] assessed the median expected time to local recurrence within the initial target lesions and found the difference is nonsignificant (12.8 months after TACE and 8.9 months after DEB, p=0.46). Recchia et al. did not report local recurrence.[31]

Local recurrence was not reported in case series on DEB.[80,85] Of the 15 extracted single-treatment arms for TACE,[64,65,68-70,72,73,75,76,78,81,82,84] local recurrence was only reported in one

study by Bargellini et al.[64] The authors reported no local recurrence or 100 percent technical success of treatment with TACE.

Strength of Evidence

The strength of evidence to evaluate local control for DEB compared with TACE is rated as insufficient for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease. Evidence to evaluate this outcome comes from one fair quality study. Sacco et al.[62] is an RCT and was rated as fair quality due to the lack of blinding. Lack of blinding can lead to detection bias. This is particularly true when outcomes are based on interpretation (i.e., not a hard outcome like death). Therefore, the risk of bias for the assessment of local recurrence was graded as high. In addition, with only one study, consistency is unknown, local recurrence is an indirect measure of a health outcome, and the estimates are imprecise. Based on the high risk of bias, unknown consistency, and lack of precision, the strength of evidence is insufficient to evaluate local control for DEB compared with TACE for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease.

Length of Stay

Sacco et al.[62] reported no significant difference between the conventional TACE and DEB groups in terms of mean LOS (6.8 days vs. 5.9 days, p=0.26).

In the study by Recchia et al., the mean LOS was 4.7 and 2.3 days in the DEB and TACE groups, respectively ($p<0.0001$).[31]

Strength of Evidence

The strength of evidence to evaluate length of stay for DEB compared with TACE is rated as insufficient for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease. Evidence to evaluate this outcome comes from two studies; one fair quality RCT and one poor quality observational study. Sacco et al.[62] is an RCT and was rated as fair quality due to the lack of blinding. Recchia et al. is a prospective cohort study which was rated as poor quality study due to the lack of control for relevant confounders during statistical analyses.[31] Lack of blinding can lead to assessment bias. This is particularly true when outcomes are based on interpretation, (i.e., not a hard outcome like death). LOS may be determined by the physician and is subject to bias based on knowledge of the treatment received. Therefore, the risk of bias for the assessment of LOS was graded as high. The studies are inconsistent regarding the superiority of one treatment over another for the outcome length of stay, and LOS is an indirect health outcome. Finally, the estimates are imprecise.

Days of Missed Work

Days of missed work was not reported in any of the included studies.

Strength of Evidence

No studies addressed this outcome. Therefore, the strength of evidence to evaluate days of work missed for DEB compared with TACE for the treatment of patients with unresectable HCC

who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Adverse Events

Table 53 presents a summary of AEs reported in the RCT comparing DEB and TACE. Sacco et al.[62] reported liver failure in 1 patient (3 percent) receiving TACE and none in the DEB group. Sacco et al.[62] reported significant ($p<0.0001$) increases in ALT and bilirubin levels compared with baseline. Increase of ALT was significantly higher in the TACE group than in the DEB group ($p=0.007$). Increased bilirubin was not different between groups. Transaminases are intermediate outcomes. Implications are therefore unclear with respect to morbidity, mortality or more terminal health outcomes. The study did not report on the following AEs: hepatic abscess, hepatic hemorrhage, biloma, steatohepatitis, injury to adjacent organs, infection, and rare adverse events.

The study by Recchia et al. did not report any AEs.[31]

In the case series, Seki et al. reported none of 135 patients experienced liver failure, hepatic abscess, or biloma after DEB.[80] One patient (0.7 percent) had a grade 3 hematologic toxicity (anemia). No adverse events of interest were reported in the other DEB study.[85] There were instances of liver failure reported in six single arms, ranging from 0.4 [82] to 22 [75] percent, and two studies reported the incidence of hepatic abscess as 0.5 percent [65] and 2 percent.[75] In a case report by Reso et al,[84] a rare AE of tumor rupture resulting in intraperitoneal bleeding was reported in a patient treated with TACE. In another case report, Kim reported a rare AE of reactivated tuberculosis in two patients treated with TACE.[83] Other rare adverse events are listed in Table 54 and include fatal and nonfatal events.

Strength of Evidence

The strength of evidence to evaluate local control for DEB compared with TACE is rated as insufficient for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease. Evidence to evaluate this outcome comes from one fair quality study. Sacco et al.[62] is an RCT and was rated as fair quality due to the lack of blinding. The lack of blinding in the trial affected the risk of bias in the assessment of adverse events. The majority of adverse events of interest, such as hepatic hemorrhage, leave little room for interpretation, but some, such as liver failure, involve some interpretation; therefore, the risk of bias for the assessment of adverse events was rated as medium. The consistency is unknown, and adverse events are direct health outcomes but the estimates are imprecise.

Overall GRADE for DEB Compared With TACE

The strength of evidence ratings for studies comparing DEB to TACE are displayed in Table 50.

Table 50. Strength of evidence for studies comparing DEB to TACE

Outcome	No. of Studies Type of Study	Risk of Bias	Consistency	Directness	Precision	Overall Grade
Overall Survival	2; Sacco et al. 2011[62] 67 RCT; Recchia et al. 2012[31] 105 Prospective Case Control	Medium	Consistent	Direct	Imprecise	Insufficient
Quality of Life	0	Unknown	Unknown	Unknown	Unknown	Insufficient
Time to Progression	2; Sacco et al. 2011[62] 67 RCT Recchia et al. 2012[31] 105 Prospective Case Control	High	Consistent	Indirect	Imprecise	Insufficient
Local Control	1; Sacco et al. 2011[62] 67 RCT	High	Unknown	Indirect	Imprecise	Insufficient
Length of Stay	2; Sacco et al. 2011[62] 67 RCT Recchia et al. 2012[31] 105 Prospective Case Control	High	Inconsistent	Indirect	Imprecise	Insufficient
Days of Work Missed	0	Unknown	Unknown	Unknown	Unknown	Insufficient
Adverse Events	1; Sacco et al. 2011[62] 67 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

Abbreviation: RCT = randomized controlled trial.

Table 51. Survival outcomes: DEB compared with TACE

Study Rating Design	Treatment Group N	Intervention	Survival Time From	Median OS	% Survival Year 1	% Survival Year 2	% Survival Year 3	Statistical Comparison
Sacco et al. 2011[62] 67 Fair RCT	DEB 33	DEB with DC Bead® (2–4 mL, 100–300 µm) loaded with doxorubicin (50 mg/vial, mean: 55mg, range: 25–150 mg) mixed with nonionic contrast medium at a 1:3 ratio via superselective injection	Study treatment	Not reached	NR	86.8	NR	NS, p=0.96
	TACE 34	TACE with iodized oil (mean: 16.6 mL, range: 10–25 mL), doxorubicin (mean: 57.0, range: 50–75 mg) and gelatin sponge particles via hepatic arteries	Study treatment	Not reached	NR	83.6	NR	
Recchia et al. 2012[31] 105 Poor	DEB 35	DEB with DC beads® loaded with doxorubicin (50mg/m2). For tumors >5 cm the size was between 500 and 700 µm, for tumors between 5 and 3 cm, the size was 300-500 µm, while for tumors <3 cm the size was 300 µm.	Study enrollment	18.4	NR	NR	NR	NS
Prospective Case Control	TACE 70	TACE	Study enrollment	11.4	NR	NR	NR	

Abbreviations: DEB = drug-eluting bead; N = number of patients; NR = not reported; NS = nonsignificant; OS = overall survival; RCT = randomized controlled trial; TACE = transarterial chemoembolization.

Table 52. Survival outcomes: DEB compared with TACE, case series studies

Study Rating	Group N	Intervention	Survival Time From	Median OS (95% CI)	% Survival Year 1	% Survival Year 2	% Survival Year 3	% Survival Year 4	% Survival Year 5
Martin et al. 2011[85] Poor	DEB 118	DEB with doxorubicin (75 mg per 2 mL, minimum recommended volume of 10 mL) in 2 bead vials via hepatic artery every 3–8 weeks for 2–4 treatment cycles	Not reported	14.2	75	NR	NR	NR	NR
Seki et al. 2011[80] Poor	DEB 135	TACE with epirubicin-loaded (25–30 mg) superabsorbent polymer microspheres via hepatic artery	Study Treatment	26	73.7	59.0	NR	NR	NR
Bargellini et al. 2011[64] Fair	TACE 67	TACE with lipiodol (mean: 16.1 mL, range: 10–25 mL), epirubicin hydrochloride (mean:57mg, range: 40–75 mg), and gelatin sponge particles via hepatic artery	Study Treatment	Not reached	90.9	86.1	80.5	NR	NR
Buijs et al. 2008[65] Fair	TACE 190	TACE with cisplatin (100 mg), doxorubicin (50 mg), mitomycin C (10 mg) in a 1:1 mixture with iodized oil, and either polyvinyl alcohol particles or gelatin-coated trisacryl microspheres via femoral artery	From time of HCC diagnosis	16	58	39	29	NR	NR

Table 52. Survival outcomes: DEB compared with TACE, case series studies (continued)

Study Rating	Group N	Intervention	Survival Time From	Median OS (95% CI)	% Survival Year 1	% Survival Year 2	% Survival Year 3	% Survival Year 4	% Survival Year 5
Giannini et al. 2010[68] Poor	TACE 128	TACE with an emulsion of lipiodol and chemotherapeutic agent (doxorubicin, epirubicin, mitoxantrone)	From time of HCC diagnosis	38*	NR	NR	NR	NR	NR
Guiu et al. 2009[69] Fair	TACE 43	TACE with pirarubicin (50 mg) diluted in 5% glucose (20 mL), lipiodol (20 mL), particles of gelatin sponge (2–3mm diameter), and amiodarone (150mg) via femoral artery once every 6–8 weeks	HCC diagnosis	29 (13.8 to 45)	68	55	47	27	NR
Imai et al. 2011[70] Poor	TACE 122	TACE with miriplatin (median 80 mg, range 20–120mg) and lipiodol (median 3 mL, range 1–6 mL) via hepatic artery	NR	NR	NR	NR	NR	NR	NR
Kawaoka et al. 2009[72] Poor	TACE 107	TACE with lipiodol and cisplatin (total per case median: 60 mg, range 10–390 mg) with or without embolization via femoral artery	Study treatment	25*	86	NR	40	NR	20
Kim et al. 2012[83] Poor	TACE 1	TACE for 6 sessions in one case, unknown schedule in the other case	NR	NR	NR	NR	NR	NR	NR
Leelawat et al. 2008[73] Poor	TACE 15	TACE with mitomycin C (5–10 mg) in a mixture of ionized oil contrast medium and Ivalon particles	Study treatment	15*	NR	40	NR	NR	NR
Mabed et al. 2009[75] Fair	TACE 50	TACE using lipiodol (10 mg), doxorubicin (50 mg) and cisplatin (50 mg) via hepatic artery every 4 weeks as long as the condition permits and total dose of 500 mg/m^2 not exceeded	Study treatment	9.5	NR	NR	NR	NR	NR
Maeda et al. 2008[76] Fair	TACE 33	TACE with iodized oil, epirubicin (accumulated dose average 16.1 mg, range 0–72.5mg), and gelatin sponge via hepatic artery for an average of 2.3 sessions (range 1–7)	Study treatment	Not yet reached	93.5	85.2	77.4	NR	NR
Molinari et al.[78] 2006 Poor	TACE 47	TACE with doxorubicin (75 mg/m^2) with lipiodol (10 mL) followed in some patients with polyvinyl alcohol particles via hepatic artery or superselectively in some cases	Study treatment	Not yet reached	76.6	55.5	50.0	NR	NR
Reso et al. 2009[49] Poor	TACE 1	TACE with cisplatin (50 mg), adriamycin (50 mg) and lipidol (20 mL)	NR	NR	NR	NR	NR	NR	NR
Wu et al. 2010[81] Poor	TACE 110	TACE with epirubicin and lipiodol and/or gelfoam sponge	Study treatment	17.7 (14.6 to 19.4)	NR	NR	NR	NR	NR

Table 52. Survival outcomes: DEB compared with TACE, case series studies (continued)

Study Rating	Group N	Intervention	Survival Time From	Median OS (95% CI)	% Survival Year 1	% Survival Year 2	% Survival Year 3	% Survival Year 4	% Survival Year 5
Zhang et al. 2011[82] Good	TACE 277	TACE with 5-fluorouracil (1 g), cis-dichlorodiamine platinum (80 mg), mitomycin (10 mg) mixed with lipiodol (5–30 mL) and, for some patients, gelatin sponge, via hepatic artery repeated every 8–12 weeks until stabilization of the tumor	Study treatment	16.7	52.1	31.8	20.2	NR	11.3
Wu et al. 2010[81] Poor	TACE with 131-I–metuximab 132	TACE with 131-I–metuximab (median 1720 MBq, 95% CI, 1654 to1804 MBq), epirubicin, lipiodol and/or gelfoam sponge via transhepatic artery for 5–10 min	Study treatment	21.2 (18.6 to 23.4)	79.1	NR	NR	NR	NR
Leelawat et al. 2008[73] Poor	TACE-Doxorubicin 15	TACE with doxorubicin (25–50 mg) plus mitomycin C (5–10 mg) in a mixture of ionized oil contrast medium and Ivalon particles	Study treatment	25*	NR	38	NR	NR	NR

*Extrapolated from Kaplan-Meier graphs.

Abbreviations: CI = confidence interval; DEB = drug-eluting beads; HCC = hepatocellular carcinoma; N = number of patients; NR = not reported; OS = overall survival; TACE = transarterial chemoembolization.

Table 53. Adverse events associated with local hepatic therapies: DEB compared with TACE

Study Rating Design	Treatment Group N	Intervention	Liver Failure %	Hepatic Hemorrhage %	Hepatic Abscess %	Rare AE, N (%)
Sacco et al. 2011[62] Fair RCT	DEB 33	DEB with DC Bead® (2–4 mL, 100–300 µm) loaded with doxorubicin (50mg/vial, mean: 55 mg, range: 25–150 mg) mixed with nonionic contrast medium at a 1:3 ratio via superselective injection	0	NR	NR	NR
	TACE 34	TACE with iodized oil (mean: 16.6 mL, range: 10–25 mL), doxorubicin (mean: 57.0, range: 50–75mg) and gelatin sponge particles via hepatic arteries	3.0	NR	NR	NR
Recchia et al. 2012[31] 105 Poor Prospective Case Control	DEB 35	DEB with DC beads® loaded with doxorubicin (50mg/m2). For tumors >5 cm the size was between 500 and 700 µm, for tumors between 5 and 3 cm, the size was 300-500 µm, while for tumors <3 cm the size was 300 µm.	NR	NR	NR	NR
	TACE 70	TACE	NR	NR	NR	NR

Abbreviations: AE = adverse event; DEB = drug-eluting bead; N = number of patients; NR = not reported; TACE = transarterial chemoembolization; RCT = randomized controlled trial.

Table 54. Adverse events associated with local hepatic therapies: DEB compared with TACE, case series studies

Study Rating	Group N	Liver Failure %	Hepatic Hemorrhage %	Hepatic Abscess %	Rare AE, N (%)
Martin et al. 2011[85] Poor	DEB 118	NR	NR	NR	Grade 3+ AE: bleeding 4 (9%), hematological 2 (5%), pancreatitis 1 (2%), liver dysfunction/failure 2 (5%), hypertension 1 (2%)
Seki et al. 2011[80] Poor	DEB 135	0	NR	0	1 (0.7%) patient with grade 3 hematologic toxicity (anemia)
Bargellini et al. 2011[64] Fair	TACE 67	3	NR	NR	1 patient died from liver failure
Buijs et al. 2008[65] Fair	TACE 190	2.6	NR	0.5	Fatal variceal bleeding in 1 patient 4 weeks after TACE; MI in 1 patient 2 days after TACE
Giannini et al. 2010[68] Poor	TACE 128	NR	NR	NR	NR
Guiu et al. 2009[69] Fair	TACE 43	NR	NR	NR	1 case (1%) of bowel perforation (grade 5), 2 cases (1%) of severe sepsis without leucopenia (grade 5), ischemic cholecystitis 2 (1%), gastric ulcer 1 (1%), 2 (1%) cardiac toxicity, 2 (1%), 3 (7%) treatment related deaths
Imai et al. 2011[70] Poor	TACE 122	NR	NR	NR	Grade 4 decrease in neutrophil count 1 (1%), increased AST 4 (3%), increase ALT 1 (1%), all resolved in two weeks
Kawaoka et al. 2009[72] Poor	TACE* 107	NR	NR	0	NR
Kim et al. 2012[83] Poor	TACE 2	NR	NR	NR	Reactivated tuberculosis in both cases
Leelawat et al. 2008[73] Poor	TACE 15	NR	NR	NR	NR
Mabed et al. 2009[75] Fair	TACE 50	22	NR	2	Puncture site bleeding and subsequent hematoma occurred in 3 patients (6%). Hypotension and bradycardia in 1 patient (2%). Two patients (4%) suffered GI bleeds due to ruptured esophageal varices. 1 (2%) patient developed cholecystitis.
Maeda et al. 2008[76] Fair	TACE 33	NR	NR	NR	Grade 3 hepatic arterial disease (15%)
Molinari et al. 2006[78] Poor	TACE 40	NR	NR	NR	Major adverse events: partial PVT 3 (3.7%), upper GI bleeding 3 (3.7%), dehydration and cachexia requiring readmission 3 (3.7%), flare of hepatitis B virus hepatitis 1 (1.2%), neutropenic fever requiring parenteral antibiotics 1 (1.2%), femoral artery pseudo aneurysm 1 (1.2%), paraduodenal chemotherapy extravasation 1 (1.2%), Psoas muscle abscess 1 (1.2%) Mortality within 30 days posttreatment: Myocardial infarction at 3 weeks 1 (1.2%), neutropenic pneumonia complicated by sepsis 1 (1.2%)

Table 54. Adverse events associated with local hepatic therapies: DEB compared with TACE, case series studies (continued)

Study Rating	Group N	Liver Failure %	Hepatic Hemorrhage %	Hepatic Abscess %	Rare AE, N (%)
Reso et al. 2009[84] Poor	TACE 1	NR	NR	NR	Tumor rupture resulting in intraperitoneal bleeding 1 (100%); developed post-embolization syndrome 1 (100%); patient died of respiratory failure 16 days following TACE.
Wu et al. 2010[81] Poor	TACE 110	NR	NR	NR	Grade 3 or 4: bilirubin toxicity 18 (13.6%), alanine aminotransferase toxicity 17 (12.8%), aspartate aminotransferase toxicity 25 (18.9%), white blood cell toxicity 3 (2.3%), platelet toxicity 1 (0.8%) Death possibly related to treatment, arm not reported 1 (0.75%)
Zhang et al. 2011[82] Good	TACE 277	0.4	NR	NR	Tumor rupture in 1 (0.4%), GI bleeding in 2 (0.7%), refractory ascites 1 (0.7%), 1 patient died of liver failure 1 month post treatment
Wu et al. 2010[81] Poor	TACE with 131 I-metuximab 132	NR	NR	NR	Grade 3 or 4: bilirubin toxicity 13 (11.8%), alanine aminotransferase toxicity 17 (15.5%), aspartate aminotransferase toxicity 22 (20%), white blood cell toxicity 6 (5.5%), platelet toxicity 8 (7.2%) Death possibly related to treatment, arm not reported 1 (0.75%)
Leelawat et al. 2008[73] Poor	TACE-Doxorubicin 15	NR	NR	NR	NR

*No grade 3 or 4 adverse events of interest were observed for these treatment groups.

Abbreviations: AE = adverse events; ALT = alanine aminotransferase; AST = aspartate transaminase; DEB = drug-eluting beads; GI = gastrointestinal; HCC = hepatocellular carcinoma; IV = intravenous; MI = myocardial infarction; N = number of patients; NR = not reported; PVT = portal vein thrombosis; TACE = transarterial chemoembolization.

TACE Compared With TEA (TAE)

No RCT examined this comparison. One retrospective case control study by Yu et al.[63] compared TACE to transarterial ethanol ablation (TEA), a type of TAE. In addition to the comparative evidence, there were two[49,79] single-arm studies reporting outcomes after TAE, and 14 studies with 16 extracted single-treatment arms for TACE [64,65,68-70,72,73,75,76,78,81-84] that met inclusion criteria. Two cohort studies[73,81] were extracted as two single arms with varied TACE regimens, and the study by Pietrosi et al.[49] treated patients with both TAE and TACE but did not specify how many patients were treated with each.

Tables 55–59 give information on TACE compared with TEA (TAE).

Overall Survival

Outcomes related to overall survival are summarized in Table 56. There was a significant difference in the 2-year survival rates (measured from the date of first study treatment) of 43.3 percent and 80 percent between the TACE and TEA groups, respectively (p=0.0053). The authors did not report the median overall survival.

Following TACE, 1-year survival is reported in eight case series studies[64,65,69,72,76,78,81,82] and ranged from 52.1 percent to 90.9 percent (Table 57). Following TAE, 1-year survival was 73.8 percent in the Pietrosi study[49] and 70.7 percent in the Rand study.[79] Lack of a direct comparison in these studies limits the application of these data to inform conclusions on overall survival.

Strength of Evidence

The strength of evidence to evaluate overall survival for TACE compared with TEA is rated as insufficient for patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease. Evidence to evaluate this outcome comes from one poor quality study. Yu et al.[63] is a retrospective cohort study which began with a low strength of evidence due to the nature of the study design (e.g., lack of blinding and no randomization) and was further reduced to insufficient due to a serious risk of bias. For an observational study to overcome the limitation of a non-randomized design, adequate control of confounders must be considered in the analysis. The authors did not attempt to adjust for confounders in their analysis. Therefore, the risk of bias for the assessment of outcomes related to progression was graded as high. There is only one study so consistency is unknown. Overall survival is a direct health outcome and the estimate is precise (Table 55).

Quality of Life

Quality of life was not reported in any of the included studies.

Strength of Evidence

No studies addressed this outcome. Due to the lack of data for this outcome, the strength of evidence to evaluate quality of life for TACE compared with TEA (TAE) for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Outcomes Related to Progression

Yu et al.[63] assessed progression-free survival, measured from the date of first study treatment to the date of death or last followup, and reported a nonsignificant difference between the TACE

and TEA groups (46 percent at 1 year and 42.5 percent at 2 years for TACE and 69.8 percent at 1 year and 58.8 percent at 2 years for TEA, p=0.0588).

Three case series studies on TACE reported on disease progression-related outcomes.[64,69,75] Bargellini et al.[64] reported a radiological disease progression following TACE in 12 patients (17.9 percent). Guiu et al.[69] reported a median progression-free survival of 15 months (95% CI, 11.5 to 20.8) following TACE. In the study by Mabed et al.,[75] the authors reported the median progression-free survival of 8 months (range: 4 to 17.5) among the subset of patients with partial response and stable disease following TACE (29 out of 50).

Two case series on TAE did not report on outcomes related to progression.[49,79]

Strength of Evidence

The strength of evidence to evaluate outcomes related to progression for TACE compared with TEA is rated as insufficient for patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease. Evidence to evaluate this outcome comes from one poor quality study. Yu et al.[63] is a retrospective cohort study which began with a low strength of evidence due to the nature of the study design (e.g., lack of blinding and no randomization) and was further reduced to insufficient quality due to a serious risk of bias. . For an observational study to overcome the limitation of a non-randomized design, adequate control of confounders must be considered in the analysis. The authors did not attempt to adjust for confounders in their analysis. Lack of blinding can lead to assessment bias. This is particularly true when outcomes are based on interpretation, (i.e., not a hard outcome like death). This is particularly true when outcomes are based on interpretation (i.e., not a hard outcome like death). Therefore, the risk of bias for the assessment of outcomes related to progression was graded as high. In addition, with only one study, consistency is unknown, progression is an indirect measure of a health outcome, and the estimates are precise.

Local Recurrence/Local Tumor Progression

Local recurrence/local tumor progression was not a reported outcome in the study by Yu et al.[63]

Of the 16 extracted single-treatment arms for TACE, including the study by Pietrosi et al.,[49] local recurrence was only reported in one study by Bargellini et al.[64] The authors reported no local recurrence, or 100 percent technical success of treatment with TACE.

Local recurrence was not reported in the case series of TAE.[49,79]

Strength of Evidence

No comparative studies addressed this outcome. Due to the lack of data for this outcome, the strength of evidence to evaluate local recurrence for TACE compared with TEA (TAE) for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Length of Stay

LOS was not a reported outcome in the study by Yu et al.[63]

Strength of Evidence

No comparative studies addressed this outcome. Due to the lack of data for this outcome, the strength of evidence to evaluate LOS for TACE compared with TEA (TAE) for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Days of Missed Work

Days of missed work was not reported in any of the included studies.

Strength of Evidence

No comparative studies addressed this outcome. Due to the lack of data for this outcome, the strength of evidence to evaluate days of work missed for TACE compared with TEA (TAE) for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Adverse Events

Yu et al.[63] did not report any adverse events (Table 58).

In the case series, there were instances in liver failure reported in six single arms ranging from 0.4[82] to 22[75] percent and two studies reported incidences of hepatic abscess of 0.5 percent[65] and 2 percent.[75] Rand et al.[79] reported 2 percent of 46 patients who underwent treatment with TAE experienced liver failure while another 2 percent developed hepatic abscess.

In a case report by Reso et al.,[84] a rare AE of tumor rupture resulting in intraperitoneal bleeding was reported in a patient treated with TACE. In another case report, Kim et al.[83] reported a rare AE of reactivated tuberculosis in two patients treated with TACE. Other rare adverse events including fatal and nonfatal events are listed in Table 59.

Strength of Evidence

No comparative studies addressed this outcome. Due to the lack of data for this outcome, the strength of evidence to evaluate adverse events for TACE compared with TEA (TAE) for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Overall GRADE for TACE Compared With TEA

The strength of evidence ratings for studies comparing TACE to TEA are displayed in Table 23.

Table 55. Strength of evidence for studies: TACE compared with TEA

Outcome	No of Studies Type of Study	Risk of Bias	Consistency	Directness	Precision	Overall Grade
Overall Survival	1; Yu et al. 2009[63] Retrospective case control	High	Unknown	Direct	Precise	Insufficient
Quality of Life	0	Unknown	Unknown	Unknown	Unknown	Insufficient
Time to Progression	1; Yu et al. 2009[63] Retrospective case control	High	Unknown	Indirect	Precise	Insufficient
Local Control	0	Unknown	Unknown	Unknown	Unknown	Insufficient
Length of Stay	0	Unknown	Unknown	Unknown	Unknown	Insufficient
Days of Work Missed	0	Unknown	Unknown	Unknown	Unknown	Insufficient
Adverse Events	0	Unknown	Unknown	Unknown	Unknown	Insufficient

Table 56. Survival outcomes: TACE compared with TEA (TAE)

Study Rating Design	Treatment Group N	Intervention	Survival Time From	Median OS (95% CI)	% Survival Year 1	% Survival Year 2	% Survival Year 3	% Survival Year 4	% Survival Year 5	Statistical Comparison
Yu et al. 2009[63] Poor Retrospective case control	TACE 30	TACE with lipiodol (20 mL) - cisplatin (10 mg) emulsion and gelatin sponge particle embolization via hepatic artery for a median of 3 treatments	Study treatment	NR	73.3	43.3	NR	NR	NR	2 year survival: p=0.053
	TEA 30	Transarterial ethanol ablation with lipiodol-ethanol mixture (mean: 14.5 mL, SD: 17.6 mL) via tumor feeder vessel(s) for a median of 2 treatments	Study treatment	NR	93.3	80.0	NR	NR	NR	

Abbreviations: CI = confidence interval; N = number of patients; NR = not reported; OS = overall survival; SD = standard deviation; TACE = transarterial chemoembolization; TEA = transarterial ethanol ablation.

Table 57. Survival outcomes: TACE compared with TEA (TAE) case series studies

Study Rating	Group N	Intervention	Survival Time From	Median OS (95% CI)	% Survival Year 1	% Survival Year 2	% Survival Year 3	% Survival Year 4	% Survival Year 5
Bargellini et al. 2011[64] Fair	TACE 67	TACE with lipiodol (mean: 16.1 mL, range: 10–25 mL), epirubicin hydrochloride (mean: 57 mg, range: 40–75 mg), and gelatin sponge particles via hepatic artery	Study treatment	Not reached	90.9	86.1	80.5	NR	NR
Buijs et al. 2008[65] Fair	TACE 190	TACE with cisplatin (100 mg), doxorubicin (50 mg), mitomycin C (10 mg) in a 1:1 mixture with iodized oil, and either polyvinyl alcohol particles or gelatin-coated trisacryl microspheres via femoral artery	HCC diagnosis	16	58	39	29	NR	NR
Giannini et al. 2010[68] Poor	TACE 128	TACE with an emulsion of Lipiodol and chemotherapeutic agent (doxorubicin, epirubicin, mitoxantrone)	HCC diagnosis	38*	NR	NR	NR	NR	NR
Guiu et al. 2009[69] Fair	TACE 43	TACE with pirarubicin (50 mg) diluted in 5% glucose (20 mL), Lipiodol (20 mL), particles of gelatin sponge (2–3 mm diameter), and amiodarone (150 mg) via femoral artery once every 6-8 weeks	HCC diagnosis	29 (13.8 to 45)	68	55	47	27	NR
Imai et al. 2011[70] Poor	TACE 122	TACE with miriplatin (median 80 mg, range 20–120 mg) and lipiodol (median 3 mL, range 1–6 mL) via hepatic artery	NR	NR	NR	NR	NR	NR	NR

Table 57. Survival outcomes: TACE compared with TEA (TAE) case series studies (continued)

Study Rating	Group N	Intervention	Survival Time From	Median OS (95% CI)	% Survival Year 1	% Survival Year 2	% Survival Year 3	% Survival Year 4	% Survival Year 5
Kawaoka et al. 2009[72] Poor	TACE 107	TACE with lipiodol and cisplatin (total per case median: 60 mg, range 10–390 mg) with or without embolization via femoral artery	Study treatment	25*	86	NR	40	NR	20
Kim et al. 2012[83] Poor	TACE 1	TACE for 6 sessions in one case, unknown schedule in the other case	NR	NR	NR	NR	NR	NR	NR
Leelawat et al. 2008[73] Poor	TACE 15	TACE with mitomycin C (5–10 mg) in a mixture of ionized oil contrast medium and Ivalon particles	Study treatment	15*	NR	40	NR	NR	NR
Mabed et al. 2009[75] Fair	TACE 50	TACE using lipiodol (10 mg), doxorubicin (50 mg) and cisplatin (50 mg) via hepatic artery every 4 weeks as long as the condition permits and total dose of 500 mg/m^2 not exceeded	Study treatment	9.5	NR	NR	NR	NR	NR
Maeda et al. 2008[76] Fair	TACE 33	TACE with iodized oil, epirubicin (accumulated dose average 16.1 mg, range 0–72.5 mg) and gelatin sponge via hepatic artery for an average of 2.3 sessions (range 1–7 sessions)	Study treatment	Not yet reached	93.5	85.2	77.4	NR	NR
Molinari et al. 2006[78] Poor	TACE 47	TACE with doxorubicin (75 mg/m^2) with lipiodol (10 mL) followed in some patients with polyvinyl alcohol particles via hepatic artery or superselectively in some cases	Study treatment	Not yet reached	76.6	55.5	50.0	NR	NR
Reso et al. 2009[84] Poor	TACE 1	TACE with cisplatin (50 mg), adriamycin (50 mg) and lipidol (20 mL)	NR	NR	NR	NR	NR	NR	NR
Wu et al. 2010[81] Poor	TACE 110	TACE with epirubicin and lipiodol and/or gelfoam sponge	Study treatment	17.7 (14.6 to 19.4)	NR	NR	NR	NR	NR
Zhang et al. 2011[82] Good	TACE 277	TACE with 5-fluorouracil (1 g), cis-dichlorodiamine platinum (80 mg), mitomycin (10 mg) mixed with lipiodol (5–30 mL) and, for some patients, gelatin sponge, via hepatic artery repeated every 8–12 weeks until stabilization of the tumor	Study treatment	16.7	52.1	31.8	20.2	NR	11.3
Wu et al. 2010[81] Poor	TACE with 131 I-metuximab 132	TACE with I-metuximab131 (median 1720 MBq, 95% CI, 1654 to1804 MBq), epirubicin, lipiodol and/or gelfoam sponge via trans-hepatic artery for 5-10 min	Study treatment	21.2 (18.6 to 23.4)	79.1	NR	NR	NR	NR

Table 57. Survival outcomes: TACE compared with TEA (TAE) case series studies (continued)

Study Rating	Group N	Intervention	Survival Time From	Median OS (95% CI)	% Survival Year 1	% Survival Year 2	% Survival Year 3	% Survival Year 4	% Survival Year 5
Leelawat et al. 2008[73] Poor	TACE-Doxorubicin 15	TACE with doxorubicin (25–50 mg) plus mitomycin C (5–10 mg) in a mixture of ionized oil contrast medium and Ivalon particles	Study treatment	25*	NR	38	NR	NR	NR
Pietrosi et al. 2009[49] Poor	TACE or TAE 320	Transarterial chemoembolization with epirubicin (50 mg/m^2) with or without iodized oil and/or Gelfoam via hepatic artery or transarterial embolization with iodized oil and/or Gelfoam via superselective artery supplying a single lesion or hepatic artery	Study treatment	NR	73.8	53.9	44.7	NR	NR
Rand et al. 2005[79] Good	TAE 46	TAE with tirsacryl gelatin microspheres (size 100–700 µ) followed by cyanoacrylate (0.3–1 mL) and lipiodol via hepatic arteries	HCC diagnosis	22.2	70.7	NR	NR	NR	NR

*Extrapolated from Kaplan-Meier graphs.
Abbreviations: CI = confidence interval; HCC = hepatocellular carcinoma; N = number of patients; NR = not reported; NS = nonsignificant; OS = overall survival; TACE = transarterial chemoembolization; TAE = transarterial embolization.

Table 58. Adverse events associated with local hepatic therapies: TACE compared with TEA (TAE)

Study Rating Design	Treatment Group N	Intervention	Liver Failure %	Hepatic Hemorrhage %	Hepatic Abscess %	Rare AE, N (%)
Yu et al. 2009[63] Poor Retrospective case control	TACE 30	TACE with lipiodol (20mL) - cisplatin (10mg) emulsion and gelatin sponge particle embolization via hepatic artery for a median of 3 treatments	NR	NR	NR	NR
	TEA 30	TEA with lipiodol-ethanol mixture (mean: 14.5mL, SD: 17.6mL) via tumor feeder vessel(s) for a median of 2 treatments	NR	NR	NR	NR

Abbreviations: AE = adverse event; N = number of patients; NR = not reported; SD = standard deviation; TACE = transarterial chemoembolization; TEA = transarterial ethanol ablation.

Table 59. Adverse events associated with local hepatic therapies: TACE compared with TEA (TAE), case series studies

Study Rating	Group N	Liver Failure %	Hepatic Hemorrhage %	Hepatic Abscess %	Rare AE, N (%)
Bargellini et al. 2011[64] Fair	TACE 67	3	NR	NR	NR
Buijs et al. 2008[65] Fair	TACE 190	2.6	NR	0.5	Fatal variceal bleeding in 1 patient 4 weeks after TACE; MI in 1 patient 2 days after TACE;
Giannini et al.2010[68] Poor	TACE 128	NR	NR	NR	NR
Guiu et al. 2009[69] Fair	TACE 43	NR	NR	NR	1 case (1%) of bowel perforation (grade 5), 2 cases (1%) of severe sepsis without leucopenia (grade 5), ischemic cholecystitis 2 (1%), gastric ulcer 1 (1%), 2 (1%) cardiac toxicity, 2 (1%), 3 (7%) treatment related deaths
Imai et al. 2011[70] Poor	TACE 122	NR	NR	NR	Grade 4 decrease in neutrophil count 1 (1%), increased AST 4 (3%), increase ALT 1 (1%), all resolved in two weeks
Kawaoka et al. 2009[72] Poor	TACE* 107	NR	NR	0	NR
Kim et al. 2012[83] Poor	TACE 2	NR	NR	NR	Reactivated tuberculosis in both cases
Leelawat et al. 2008[73] Poor	TACE 15	NR	NR	NR	NR
Mabed et al. 2009[75] Fair	TACE 50	22	NR	2	Puncture site bleeding and subsequent hematoma occurred in 3 patients (6%). Hypotension and bradycardia in 1 patient (2%). Two patients (4%) suffered GI bleeds due to ruptured esophageal varices. 1 (2%) patient developed cholecystitis.
Maeda et al. 2008[76] Fair	TACE 33	NR	NR	NR	Grade 3 hepatic arterial disease (15%)
Molinari et al. 2006[78] Poor	TACE 40	NR	NR	NR	Major adverse events: Partial PVT 3 (3.7%), Upper GI bleeding 3 (3.7%), Dehydration and cachexia requiring readmission 3 (3.7%), Flare of hepatitis B virus hepatitis 1 (1.2%), Neutropenic fever requiring parenteral antibiotics 1 (1.2%), Femoral artery pseudo aneurysm 1 (1.2%), Paraduodenal chemotherapy extravasation 1 (1.2%), Psoas muscle abscess 1 (1.2%) Mortality within 30 days post treatment: Myocardial infarction at 3 weeks 1 (1.2%), Neutropenic pneumonia complicated by sepsis 1 (1.2%)

Table 59. Adverse events associated with local hepatic therapies: TACE compared with TEA (TAE), case series studies (continued)

Study Rating	Group N	Liver Failure %	Hepatic Hemorrhage %	Hepatic Abscess %	Rare AE, N (%)
Reso et al. 2009[84] Poor	TACE 1	NR	NR	NR	Tumor rupture resulting in intraperitoneal bleeding 1 (100%); developed post-embolization syndrome 1 (100%); Patient died of respiratory failure 16 days following TACE.
Wu et al. 2010[81] Poor	TACE 110	NR	NR	NR	Grade 3 or 4: bilirubin toxicity 18 (13.6%), alanine aminotransferase toxicity 17 (12.8%), aspartate aminotransferase toxicity 25 (18.9%), white blood cell toxicity 3 (2.3%), platelet toxicity 1 (0.8%) Death possibly related to treatment, arm not reported 1 (0.75%)
Zhang et al. 2011[82] Good	TACE 277	0.4	NR	NR	Tumor rupture in 1 (0.4%), GI bleeding in 2 (0.7%)
Wu et al. 2010[81] Poor	TACE with 131 I-metuximab 132	NR	NR	NR	Grade 3 or 4: bilirubin toxicity 13 (11.8%), alanine aminotransferase toxicity 17 (15.5%), aspartate aminotransferase toxicity 22 (20%), white blood cell toxicity 6 (5.5%), platelet toxicity 8 (7.2%) Death possibly related to treatment, arm not reported 1 (0.75%)
Leelawat et al. 2008[73] Poor	TACE-Doxorubicin 15	NR	NR	NR	NR
Pietrosi et al. 2009[49] Poor	TACE or TAE 320	0.3	NR	NR	2(1%) ischemic cholecystitis, 1 (1%)gastric ulcer, 1 (1%)bowel perforation, 4 (3%) edemo-ascitic decompensation, 1 (1%) gastrointestinal hemorrhage, 2 (1%) cardiac toxicity, 2 (1%) severe sepsis, 3 (7%) treatment related deaths
Rand et al. 2005[79] Good	TAE 46	2.2	NR	2.2	NR

*No grade 3 or 4 adverse events of interest were observed for these treatment groups.

Abbreviations: AE = adverse events; ALT = alanine aminotransferase; AST = aspartate transaminase; GI = gastrointestinal; HCC = hepatocellular carcinoma; MI = myocardial infarction; N = number of patients; NR = not reported; PVT = portal vein thrombosis; TACE = transarterial chemoembolization; TAE = transarterial alcohol embolization.

Interventions With No Comparative Evidence

Four case series were included in this report for which no comparative evidence exists.[66,67,71,74] All four studies performed radioembolization.[66,67,71,74]

Strength of Evidence

No comparative studies met inclusion criteria for this review. Therefore strength of evidence is insufficient to evaluate all outcomes of interest: overall survival, quality of life, TTP, local recurrence, LOS, days of work missed, and adverse events for all interventions without comparative studies for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease.

Overall Survival

One of four studies on RE reported 1-year survival of 75 percent,[71] while three studies reported a median survival ranging from 11 months[74] to 15 months (Table 60).[71]

Quality of Life

Quality of life was not reported in any of the included studies.

Outcomes Related to Progression

Four RE studies[66,67,71,74] did not report on outcomes related to progression.

Local Recurrence/Local Tumor Progression

Case series on RE,[66,67,71,74] did not report on local recurrence.

Length of Stay

LOS was reported in two studies. One radioembolization study by Kanhere et al.[71] reported a mean LOS of 7 days.

Days of Missed Work

Days of missed work was not reported in any of the included studies.

Adverse Events

For the studies lacking comparative data, no liver failure or hepatic abscess was reported. Other rare adverse events are listed in Table 61, including fatal and nonfatal events.

Table 60. Outcomes related to overall survival, studies with no comparative data

Study Rating	Group N	Intervention	Survival Time From	Median OS (95% CI)	% Survival Year 1	% Survival Year 2	% Survival Year 3	% Survival Year 4	% Survival Year 5
Carr et al. 2004[66] Poor	RE 65	RE with Y90 (dose delivered mean: 145.7 Gy, median: 134.3 Gy, range: 61.1–280.9Gy) via hepatic artery	NR	NR	NR	NR	NR	NR	NR
Carr et al. 2010[67] Fair	RE 99	RE with Y90 (deliver 135–150 Gy) via hepatic artery over 1–5 min	Study treatment	11.5	NR	NR	NR	NR	NR
Kanhere et al. 2008[71] Poor	RE 12	RE with radiolabelled lipiodol (average dose 1.7 GBq (1.4–2.2 GBq) diluted in unlabeled lipiodol (2–10 mL) via hepatic artery	Study treatment	15	75	25	NR	NR	NR
Liu et al. 2004[74] Fair	RE 11	RE with Y90 TheraSphere (prescribed dose 100–150 Gy) via hepatic artery	Study treatment	11	NR	NR	NR	NR	NR

Abbreviations: CI = confidence interval; CT = computed tomography; CP = Child-Pugh liver cirrhosis class; GBq = gigabecquerel; Gy = Gray; N = number of patients; NR = not reported; OS = overall survival; RE = radioembolization; Y90 = yittrium-90.

Table 61. Adverse events associated with local hepatic therapies: studies with no comparative data

Study Rating	Group N	Liver Failure %	Hepatic Hemorrhage %	Hepatic Abscess %	Rare AE, N (%)
Carr et al. 2004[66] Poor	RE 65	NR	NR	NR	Acute cholecystectomy (2%)
Carr et al. 2010[67] Fair	RE 99	NR	NR	NR	NR
Kanhere et al. 2008[71] Poor	RE 12	NR	NR	NR	Severe thrombocytopenia (8.3%); radiation pneumonitis (8.3%); radiation-induced hepatitis with pneumonia (8.3%)
Liu et al. 2004[74] Fair	RE* 11	NR	NR	NR	NR

*No grade 3 or 4 adverse events of interest were observed for these treatment groups.
Abbreviations: AE = adverse event; CP = Child-Pugh liver cirrhosis class; N = number of patients; NR = not reported; RE = radioembolization.

Radiation Therapies

Description of Included Studies

A total of five case series met the inclusion criteria to address KQ1 and KQ2.[86-90] Of these, four case series were retrospective[86,87,89,90] and one was prospective.[88] The total number of patients for whom data were extracted from the five studies was 146. All five studies had patient samples that were restricted to unresectable HCC patients (i.e., not including patients with liver tumors of other primary origins). All studies initiated treatment in patients after January 1, 2000.

Three studies were of SBRT, one reviewed 3D-CRT, and one presented data on real-time tumor tracking radiotherapy. No studies of IMRT, HPBT, or intraluminal brachytherapy met the inclusion criteria for this evidence review.

Table 62 and Table 63 present a summary of study and patient characteristics, including number of patients enrolled, intervention period, intervention, and baseline characteristics. Median age ranged from 57 to 63 years. The patients' baseline Child-Pugh liver cirrhosis classes were A or B. One study reported Eastern Cooperative Oncology Group (ECOG) scores of 0 to 1 in 97.5 present of enrolled patients.[88] No studies reported BCLC HCC stage. One study by Taguchi et al.,[90] reported Okuda stage, and less than 10 percent of the patients were in Okuda stage III (6.5 percent). Two studies described patients' prior treatment history.[88,89] In both studies, 100 percent of the patients had prior treatment with TACE. Three studies reported on the proportion of patients with cirrhosis, ranging from 29 percent to 100 percent.[86,88,89] Studies varied in terms of proportions of patients with HBV and HCV infection. Overall, studies were inconsistent in reporting—and often did not report—these patient and tumor characteristics at baseline (e.g., ECOG score, PVT, HCC stage) which are important prognostic factors to consider when comparing patient populations across studies.

Table 64 presents data on tumor characteristics from the included studies. No studies presented the proportion of patients with a bilobar disease, and one study[86] reported number of lesions, with 94.6 and 5.4 percent having one and two lesion(s), respectively. Lesion size ranged between 1 and 7 cm across three studies.[86,87,90] Oh and colleagues[88] reported a dichotomized range of 45 and 55 percent of patients having lesions of <5 cm and ≥ 5 cm, respectively.

Table 62. Summary of study and patient characteristics: case series studies

Study N Rating	Study Design	Intervention Period	Intervention	Age, Mean or Median (Range)	ECOG Score	CP A%; B%; C%	BCLC A%; B%	Previous LDT %
Andolino et al. 2011[86] 37 Poor	Retrospective case series	2005 - 2009	SBRT with a total dose of 48 Gy in 3 fractions for CP A cirrhosis patients and a total dose of 40 Gy in 5 fractions for CP B cirrhosis patients	Median: 63 (24–85)	NR	A: 64.9; B: 35.1; C: 0	NR	NR
Chan et al. 2011[87] 16 Fair	Retrospective case series	05/2000 - 11/2004	SBRT (4.5 Gy) for 10 daily fractions, 2.5 Gy for 18–20 fractions where planned target volume encompassed hepatic portal area or gallbladder, or 1.8 Gy for 28–30 fractions where planned target volume included the bowel	Mean: 55.2 Median: 57.5 (23–69)	NR	A: 75; B: 25; C: 0	NR	NR
Oh et al. 2010[88] 40 Good	Prospective case series	01/2006 - 02/2007	3D-CRT (median delivered 54 Gy, range 30–54 Gy) in 2.5–5 Gy per fraction	Median: 59.5 (36–92)	0–1: 97.5; 2:2.5	A: 90; B: 10; C: 0	NR	TACE: 100
Seo et al. 2010[89] 38 Fair	Retrospective case series	03/2003 - 04/2008	SBRT with escalating doses(33–57 Gy in 3 or 4fractions)	Median: 61 (37–81)	NR	A: 89.5; B: 10.5; C: 0	NR	TACE: 100
Taguchi et al. 2007[90] 15 Fair	Retrospective case series	2001 - 2004	Real-time tumor-tracking radiotherapy (RTRT) on a hypofractionated schedule (most common dose: 48 Gy in 8 fractions)	Median: 57 (54–73)	NR	A: 80; B: 20; C: 0	NR	NR

Abbreviations: 3D-CRT = Three dimensional conformal radiotherapy; BCLC = Barcelona Clinic Liver Center hepatocellular carcinoma stage; CI = Confidence interval; CP = Child-Pugh liver cirrhosis class; ECOG = Eastern Cooperative Oncology Group; GBq = gigabecquerel; Gy = Gray; LDT = liver directed therapy; N = number of patients; NR = not reported; SBRT = stereotactic body radiotherapy.

Table 63. Summary of underlying liver disease characteristics: case series studies

Study Rating	Group N	Cirrhosis%	HBV%	HCV%	NAFLD%	Alcohol%
Andolino et al. 2011[86] Poor	SBRT 37	100	8.1	43.2	NR	NR
Chan et al. 2011[87] Fair	SBRT 16	NR	81.3	6.3	NR	NR
Oh et al. 2010[88] Good	3D-CRT 40	97.5	NR	NR	NR	NR
Seo et al. 2010[89] Fair	SBRT 38	28.9	NR	NR	NR	NR
Taguchi et al. 2007[90] Fair	3D-CRT with real-time tumor tracking 15	NR	33.3	60.0	NR	6.7

Abbreviations: 3D-CRT = three dimensional conformal radiotherapy; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; N = number of patients; NAFLD = nonalcoholic fatty liver disease; NR = not reported; SBRT = stereotactic body radiotherapy.

Table 64. Summary of tumor characteristics: case series studies

Study Rating	Group N	Bilobar %	Number of Lesions	Lesion Size (cm)	Other Lesion Characteristics
Andolino et al. 2011[86] Poor	SBRT 37	NR	1: 94.6%, 2: 5.4%, 3: 0%; Range: 1–2	Range: 1–6.5	NR
Chan et al. 2011[87] Fair	SBRT 16	NR	NR	Range: 1-7	NR
Oh et al. 2010[88] Good	3D-CRT 40	NR	NR	<5 cm: 45%; ≥5 cm: 55%	NR
Seo et al. 2010[89] Fair	SBRT 38	NR	NR	NR	NR
Taguchi et al. 2007[90] Fair	3D-CRT with real-time target tracking 15	NR	NR	Range:1.5–5.2	NR

Abbreviations: 3D-CRT = three dimensional conformal radiation therapy; HCC = hepatocellular carcinoma; N = number of patients; NR = not reported; PVT = portal vein thrombosis; SBRT = stereotactic body radiation therapy.

Detailed Synthesis

Table 65 displays the outcomes reported in the five case series. All studies reported overall survival and survival by year.[86-90] Survival by year presents the duration of survival for the included patients and reporting ranges from 1 to 3 years. Outcomes related to progression were reported in two studies,[86,89] and local recurrence or local tumor progression were reported in three studies.[86,88,90] Adverse events were reported in all five of the studies. No studies reported on LOS and quality of life.

Table 65. Outcomes reported for Key Questions 1 and 2: case series studies

Study N Rating	OS	Survival by Year	Outcomes Related to Progression	LR/Local Tumor Progression	LOS	QOL	AE
Andolino et al. 2011[86] 37 Poor	●	●	●	●	NR	NR	●
Chan et al. 2011[87] 16 Fair	●	●	NR	NR	NR	NR	●
Oh et al. 2010[88] 40 Good	●	●	NR	●	NR	NR	●
Seo et al. 2010[89] 38 Fair	●	●	●	NR	NR	NR	●
Taguchi et al. 2007[90] 15 Fair	●	●	NR	●	NR	NR	●

"●" Indicates that this outcome was reported in the article.
Abbreviations: AE = adverse events; HCC = hepatocellular carcinoma; LOS = length of stay; LR = local recurrence; N = number of patients; NR = not reported; OS = overall survival; QOL = quality of life.

Radiotherapy Interventions With No Comparative Evidence

Five case series, for which no comparative evidence exists, reported on treatment with radiotherapy and were included in this report. Two studies of 3D-CRT, one of which reported on real-time target tracking[88,90] and three SBRT studies[86,87,89] met inclusion criteria.

Strength of Evidence

No comparative studies of radiotherapy met inclusion criteria for this review. Therefore, strength of evidence is insufficient to evaluate all outcomes of interest: overall survival, quality of life, TTP, local recurrence, LOS, days of work missed, and adverse events for all interventions without comparative studies for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease.

Overall Survival

Two case series on 3D-CRT reported 1-year survival rates of 72 percent[88] and 79 percent (Table 66).[90]

All three SBRT studies reported median survival from study treatment with a range of 23 to 32 months.[86,87,89] Lack of a direct comparison in these studies limits the application of these data to inform conclusions on overall survival.

Quality of Life

Quality of life was not reported in any of the included radiotherapy studies.

Outcomes Related to Progression

The case series on 3D-CRT,[88,90] did not report on outcomes related to progression.

Of the 3 studies on SBRT, two reported on outcomes related to progression.[86,89] In a study by Andolino et al.,[86] the median progression-free survival and 2-year progression-free survival rate following the first treatment with SBRT were 14.1 months and 33 percent, respectively. In another study of SBRT by Seo et al.,[89] the median time to disease progression and 2-year disease progression-free survival rate were 10 months and 37.5 percent, respectively. Chan et al.[87] did not report on outcomes related to progression.

Local Recurrence/Local Tumor Progression

Both 3D-CRT studies reported local recurrence with rates of 13.3 percent (2 out of 15 patients)[90] to 22.5 percent (9 out of 40 patients)[88]. One SBRT study reported a local recurrence rate of 5.4 percent.[91] In another study of SBRT,[86] the local control rate (lack of recurrence within the treated planned target volume) at 2 years was 87 percent.

Length of Stay

LOS was not reported in any of the included radiotherapy studies.

Days of Missed Work

Days of missed work was not reported in any of the included radiotherapy studies.

Adverse Events

There were no instances of liver failure or hepatic abscess was reported in the included radiotherapy studies. Three cases of radiation induced liver disease were reported by Chan et al. 2010,[87] and one was fatal. Other rare adverse events are listed in Table 67, including fatal and nonfatal events.

Table 66. Outcomes related to overall survival, studies with no comparative data

Study Rating	Group N	Intervention	Survival Time From	Median OS (95% CI)	% Survival Year 1	% Survival Year 2	% Survival Year 3	% Survival Year 4	% Survival Year 5
Oh et al. 2010[88] Good	3D-CRT 40	3D-CRT (median delivered 54 Gy, range 30–54 Gy) in 2.5 to 5 Gy per fraction	Study treatment	19	72.0	45.6	NR	NR	NR
Taguchi et al. 2007[90] Fair	3D-CRT with real-time target tracking 15	Real-time tumor-tracking radiotherapy (RTRT) on a hypofractionated schedule (most common dose: 48 Gy in 8 fractions)	Study treatment	21*	79	44	NR	NR	NR
Andolino et al. 2011[86] Poor	SBRT 37	SBRT with a total dose of 48 Gy in 3 fractions for CP A cirrhosis patients and a total dose of 40 Gy in 5 fractions for CP B cirrhosis patients	Study treatment	20.4	NR	47	NR	NR	NR
Chan et al. 2011[87] Fair	SBRT 16	SBRT (4.5 Gy) for 10 daily fractions, 2.5 Gy for 18–-20 fractions where planned target volume encompassed hepatic portal area or gall bladder, or 1.8 Gy for 28–-30 fractions where planned target volume included the bowel	Study treatment	23	62	NR	28	NR	NR
Seo et al. 2010[89] Fair	SBRT 38	SBRT with escalating doses(33–57 Gy in 3 or 4 fractions)	Study treatment	32	68.4	61.4	42.1	NR	NR

*Extrapolated from Kaplan-Meier graphs.

Abbreviations: 3D-CRT = three dimensional conformal radiation therapy; CI = confidence interval; CP = Child-Pugh liver cirrhosis class; Gy = Gray; N = number of patients; NS = nonsignificant; NR = not reported; OS = overall survival; SBRT = stereotactic body radiation therapy.

Table 67. Adverse events associated with local hepatic therapies: studies with no comparative data

Study Rating	Group N	Liver Failure %	Hepatic Hemorrhage %	Hepatic Abscess %	Rare AE, N (%)
Oh et al. 2010[88] Good	3D-CRT 40	NR	NR	NR	NR
Taguchi et al. 2007[90] Fair	3D-CRT with real-time target tracking 15	NR	NR	NR	Grade 3 transient gastric ulcer, 1 (6.6%); Grade 3 increase of amino transaminase, 2 (13.2%)
Andolino et al. 2011[86] Poor	SBRT 37	NR	NR	NR	Grade 3 liver enzymes and/or hyper bilirubinemia, 9 (24%); grade 3 thrombocytopenia, 9 (24%); elevated international normalized ratio of prothrombin, 2 (5.4%); grade 3 hypoalbuminemia, 7 (19%); grade 3 hematologic/hepatic toxicity, 21 (57%); Grade 4 thrombocytopenia and hyperbilirubinemia developed, 1 (2.7%)
Chan et al. 2011[87] Fair	SBRT 16	NR	NR	NR	Radiation-induced liver disease, 2 (12.5%); fatal radiation-induced liver disease, 1 (6.3%)
Seo et al. 2010[89] Fair	SBRT 38	NR	NR	NR	Acute radiation dermatitis leading to Grade 3 soft tissue toxicity,1 (2.6%). No grade 4 toxicity or treatment related death was observed.

Abbreviations: 3D-CRT = three dimensional conformal radiation therapy; AE = adverse event; CP = Child-Pugh liver cirrhosis class; N = number of patients; SBRT = stereotactic body radiation therapy.

Combination Therapies

Key questions 1 and 2 focus on the comparative effectiveness (KQ1) and harms (KQ2) of the various combined local hepatic therapies in patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and have no evidence of extrahepatic disease.

Description of Included Studies

A total of six combination therapy studies met the inclusion criteria to address KQ1 and KQ2, including one RCT,[92] one nonrandomized comparative study,[93] and four series studies[33,91,94-97] The nonrandomized comparative study was retrospective.[93] Of the six case series studies, two were retrospective[33,94] and four were prospective.[91,95-97] The total number of patients for whom data were extracted from the six studies was 698. There were 37 patients from the RCT, 420 from the nonrandomized comparative study, and 241from case series. All six studies had patient samples that were restricted to unresectable HCC patients (i.e., not including patients with liver tumors of other primary origins). All studies initiated treatment in patients after January 1, 2000.

The RCT compared RFA to a combination of TACE-RFA.[92]

Table 68 and Table 69 present a summary of study and patient characteristics from the RCT, including the number of patients enrolled, intervention period, intervention, and baseline characteristics. Patients ranged in age from 48 to 84 years with the mean age per group in the seventies. The patients' baseline Child-Pugh liver cirrhosis classes were A or B, and there were no patients in class C cirrhosis. ECOG scores were 0 to 1. The RCT did not report prior treatment history or presence of PVT. The study reported 89 percent of the patients with HCV infection.

Table 68. Summary of combination therapy study characteristics: RCTs

Study N Rating	Intervention	Intervention Period	Mean Age (Range)	CP A%; B%	BCLC A%; B%	Previous LDT %
Morimoto et al. 2010[92] 37 Poor	TACE with epirubicin (30–50 mg per body surface), lipiodol, and gelatin sponge particles via hepatic artery followed by percutaneous RFA with multitined expandable electrode or internally cooled electrode	08/2005 - 04/2009	70 (57–78)	A: 95; B: 5	NR	NR
	Percutaneous RFA with multitined expandable electrode or internally cooled electrode	08/2005 - 04/2009	73 (48–84)	A: 89; B: 11	NR	NR

Abbreviations: BCLC = Barcelona Clinic Liver Center hepatocellular carcinoma stage; CP = Child-Pugh liver cirrhosis class; LDT = liver-directed therapy; N = number of patients; NR = not reported; RFA = radiofrequency ablation; TACE = transarterial chemoembolization.

Table 69. Summary of combination therapy underlying liver disease characteristics: RCTs

Study Rating	Group N	Cirrhosis%	HBV%	HCV%	Alcohol%
Morimoto et al. 2010[92] Poor	TACE-RFA 19	NR	0	89	11
	RFA 18	NR	0	89	0

Abbreviations: HBV = hepatitis B virus; HCV = hepatitis C virus; N = number of patients; NR = not reported; RFA = radiofrequency ablation; TACE = transarterial chemoembolization.

As displayed in Table 70, the RCT did not report the proportion of patients with a bilobar disease, mean number of lesions, lesion size, or other lesion characteristics.

Table 70. Summary of combination therapy tumor characteristics: RCTs

Study Rating	Group N	Bilobar %	Number of Lesions	Lesion Size Range (cm)	Other Lesion Characteristics
Morimoto et al. 2010[92] Poor	TACE-RFA 19	NR	NR	NR	NR
	RFA 18	NR	NR	NR	NR

Abbreviations: N = number; NR = not reported; RFA = radiofrequency ablation; TACE = transarterial chemoembolization.

Of the five observational studies (one nonrandomized comparative studies and four case series studies), one study included patients treated with each of the following; TACE,[93] TACE and cryoablation,[93] TACE and PEA,[94] RFA and DEB,[91] TAE and RFA,[95] and TACE and RFA.[33] TACE and systemic chemotherapy,[96] and RE and systemic chemotherapy.[97] Table 71 and Table 72 present a summary of study and patient characteristics from the nonrandomized comparative study and case series, including number of patients enrolled, intervention period, intervention, and baseline characteristics. Mean age ranged from 53 to 70 years. The patients' baseline Child-Pugh liver cirrhosis classes were A or B. The ECOG scores and BCLC HCC stage were not reported in the included studies. One study included both intermediate and advanced stage patients.[33] Results were reported separately by stage and extracted for the intermediate stage patients. One study reported the HCC stage using the Okuda staging system, and all the patients were in Okuda stage I or II, which are equivalent to BCLC stages A and B, respectively.[94] One study reported the proportion of patients with PVT, which was 19 percent.[94] One study described patients' prior treatment history, including local hepatic therapies such as PEI and TAE.[95] Two studies reported on the proportion of patients with cirrhosis, which was100 percent for both.[91,95] Studies varied in terms of proportions of patients with HBV and HCV infection.[33,91,94,95] Overall, studies were inconsistent in reporting—and often did not report— these patient and tumor characteristics at baseline (e.g., ECOG score, Child-Pugh class, PVT, HCC stage) which are important prognostic factors to consider when comparing patient populations across studies.

Table 73 and Table 74 present data on underlying liver disease characteristics from the nonrandomized comparative study and case series. As displayed in Table 75, the nonrandomized comparative study reported number of lesions and lesion size per group. The proportion of patients with a bilobar disease was not reported. As displayed in Table 76, the four case series studies varied in which tumor characteristics were reported and how these characteristics were reported. The proportion of patients with a bilobar disease was reported by two studies and ranged from 27 to 28 percent.[94,95] The number of lesions was reported in three studies[33,94,95] and lesion size was reported in two studies.[91,95]

Table 71. Summary of combination therapy study and patient characteristics: nonrandomized comparative studies

Study N Rating	Study Design	Intervention Period	Intervention	Age, Mean or Median (Range)	ECOG Score	CP A%; B%; C%	BCLC A%; B%	Previous LDT %
Xu et al. 2009[93] 420 Poor	Retrospective cohort	03/2001 - 12/2006	TACE with doxorubicin (50 mg), mitomycin (10 mg) and lipiodol (4–15 mL) via arterial branches followed by percutaneous cryoablation via right lateral intercostal access	Median: 46 (NR)	NR	A: 31.4; B: 68.6; C: 0	NR	NR
		03/2001 - 12/2006	Percutaneous cryoablation via right lateral intercostal access	Median: 41 (NR)	NR	A: 32.3; B: 67.7; C: 0	NR	NR

Abbreviations: BCLC = Barcelona Clinic Liver Center hepatocellular carcinoma stage; CP = Child-Pugh liver cirrhosis class; ECOG = Eastern Cooperative Oncology Group; LDT = liver-directed therapy; N = number of patients; NR = not reported; TACE = transarterial chemoembolization.

Table 72. Summary of combination therapy study and patient characteristics: case series studies

Study N Rating	Study design	Intervention Period	Intervention	Age, Mean or Median (Range)	ECOG Score	CP A%; B%; C%	BCLC A%; B%	Previous LDT %
Gao et al. 2011[94] 63 Fair	Retrospective case series	11/2001 - 09/2009	TACE with lipiodol, perarubicin (50 mg/m^2), DDP (80 mg/m^2) via hepatic artery 1–2 times followed by CT-guided percutaneous ethanol ablation with ethanol (99% concentration) mixed with lipiodol (9:1 volume ratio, mean 30.5 mL per patient) via hepatic artery	Mean: 57.2 (NR)	NR	A: 60.3; B: 39.7; C: 0	NR	NR
Lencioni et al. 2008[91] 20 Poor	Prospective case series	09/2005 - 11/2006	Percutaneous, US-guided RFA (target temp 105°C) followed within 24 hours with DEB of doxorubicin (range 50–125 mg; mean 60.2 mg; SD 21.8 mg) via arterial branches feeding the tumor	Mean: 70 (63–83)	NR	NR	NR	NR
Liao et al. 2008[95] 36 Poor	Prospective case series	01/2000 - 12/2005	TAE with lipiodol followed by RFA between the 7th and 14th days after TAE	Mean: 56.4 (43–81)	NR	A: 75; B: 25 C: 0	NR	TAE and/or PEI: 17.1
Zhao et al. 2012[33] 122* Fair	Retrospective case series	01/2000 – 12/2009	TACE with lipiodol (10–30 ml), epirubicin (6–12 mg), mitomycin C (6–12 mg) and normal saline solution (3 ml) via femoral artery using the Seldinger technique followed by RFA 3–4 weeks later with multitined expandable electrodes (01/00-12/03) or monopolar electrode system (01/04-12/09)	Mean: 53 (18–86)	NR	A: 79; B: 21; C: 0	NR	NR

*Patient characteristics are reported for combined intermediate and advanced stage groups (n=122). Results are reported for the intermediate stage group separately (n=72).
Abbreviations: BCLC = Barcelona Clinic Liver Center hepatocellular carcinoma stage; CT = computed tomography; CP = Child-Pugh liver cirrhosis class; DEB = drug-eluting bead; ECOG = Eastern Cooperative Oncology Group; LDT = liver-directed therapy; N = number of patients; NR = not reported; RFA = radiofrequency ablation; SD = standard deviation; TACE = transarterial chemoembolization; TAE = transarterial embolization; US = ultrasound.

Table 73. Summary of combination therapy underlying liver disease characteristics: nonrandomized comparative studies

Study Rating	Group N	Cirrhosis%	HBV%	HCV%	NAFLD%	Alcohol%
Xu et al. 2009[93] Poor	TACE and Cryoablation 290	NR	NR	NR	NR	NR
	Cryoablation 130	NR	NR	NR	NR	NR

Abbreviations: HBV = hepatitis B virus; HCV = hepatitis C virus; N = number of patients; NAFLD = nonalcoholic fatty liver disease; NR = not reported; TACE = transarterial chemoembolization.

Table 74. Summary of combination therapy underlying liver disease characteristics: case series studies

Study Rating	Group N	Cirrhosis%	HBV%	HCV%	NAFLD%	Alcohol%
Gao et al. 2011[94] Fair	TACE+PEA 63	NR	96.8	0	NR	NR
Lencioni et al. 2008[91] Poor	RFA+DEB 20	100	10	55	NR	5
Liao et al. 2008[95] Poor	TAE+RFA 36	100	75.0	16.7	NR	NR
Zhao et al. 2012[33] Fair	TACE+RFA 122*	NR	74	3	NR	NR

*Patient characteristics are reported for combined intermediate and advanced stage groups (n=122). Results are reported for the intermediate stage group separately (n=72).
Abbreviations: DEB = drug-eluting bead; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; N = number of patients; NAFLD = nonalcoholic fatty liver disease; NR = not reported; RFA = radiofrequency ablation; TACE = transarterial chemoembolization; TAE = transarterial embolization.

Table 75. Summary of combination therapy tumor characteristics: nonrandomized comparative studies

Study Rating	Group N	Bilobar %	Number of Lesions	Lesion Size (cm)	Other Lesion Characteristics
Xu - 2009[93] Poor	TACE and Cryoablation 290	NR	1, 45.5%; 2, 28.9%; 3, 11.0%; >3, 14.5%	Range: 4.5–15.0; >10 cm: 23.8%	NR
	Cryoablation 130	NR	1, 57.7%; 2, 25.4%; 3, 10.0%; >3, 6.9%	Range: 3.1–7.0; >10 cm: 0%	mean size difference p=0.04;

Abbreviations: N = number of patients; NR = not reported; TACE = transarterial chemoembolization.

Table 76. Summary of combination therapy tumor characteristics: case series studies

Study Rating	Group N	Bilobar %	Number of Lesions	Lesion Size (cm)	Other Lesion Characteristics
Gao et al. 2011[94] Fair	TACE+PEA 63	27.0	Solitary: 68.3%	NR	NR
Lencioni et al. 2008[91] Poor	RFA+DEB 20	NR	NR	Range: 3.3–7.0	NR
Liao et al. 2008[95] Poor	TAE+RFA 36	28	Mean:1.1 Solitary: 61%	Range: 3.0–12.0	NR
Zhao et al. 2012[33] Fair	TACE+RFA 122*	NR	Solitary: 44%	NR	NR

*Patient characteristics are reported for combined intermediate and advanced stage groups (n=122). Results are reported for the intermediate stage group separately (n=72).
Abbreviations: DEB = drug-eluting beads; HCC = hepatocellular carcinoma; N = number of patients; NR = not reported; PEA = percutaneous ethanol ablation; RFA = radiofrequency ablation; TACE = transarterial chemoembolization; TAE = transarterial embolization.

Detailed Synthesis

Table 77 displays the outcomes reported in the RCT. The RCT reported survival rate by year, local recurrence, and adverse events.[92] Survival by year presents the duration of survival for the included patients and ranges from 1–3 years in the RCT. Studies varied in the use of terms and definitions of those outcomes related to disease progression and local recurrence, and we describe them in this report as they are reported in the studies. Overall survival, outcomes related to progression, LOS, and quality of life were not reported in the RCTs.

Study outcomes data were synthesized by intervention comparisons found in the six included articles.

Table 77. Outcomes reported for Key Questions 1 and 2: RCTs

Study N Rating	OS	Survival by Year	Outcomes Related to Progression	LR/Local Tumor Progression	LOS	QOL	AE
Morimoto et al. 2010[92] 37 Poor	NR	•	NR	•	NR	NR	•

"•" Indicates that this outcome was reported in the article.
Abbreviations: AE = adverse events; LOS = length of stay; LR = local recurrence; N = number of patients; NR = not reported; OS = overall survival; QOL = quality of life.

Table 78 displays the outcomes reported in the nonrandomized comparative studies. The study reported survival by year, local recurrence, and adverse events.[93] Survival by year presents the duration of survival for the included patients and reporting ranges from 1 to 5 years for the nonrandomized comparative study. The study did not report on overall survival, outcomes related to progression, LOS, or quality of life outcomes.

Table 78. Outcomes reported for Key Questions 1 and 2: nonrandomized comparative studies

Study N Rating	OS	Survival by Year	Outcomes Related to Progression	LR/Local Tumor Progression	LOS	QOL	AE
Xu et al. 2009[93] 420 Poor	NR	•	NR	•	NR	NR	•

Abbreviations: AE = adverse events; LOS = length of stay; LR = local recurrence; N = number of patients; NR = not reported; OS = overall survival; QOL = quality of life.

Table 79 displays the outcomes reported in the four case series studies. All but one study reported overall survival or survival by year.[91] Survival by year presents the duration of survival for the included patients and reporting ranges from 1 to 5 years for the case series. Outcomes related to progression were reported in one study.[33] LOS was reported by one study.[91] Adverse events were reported in all but one study,[33] and no observational studies reported on local recurrence or quality of life.

Table 79. Outcomes reported for Key Questions 1 and 2: case series studies

Study N Rating	OS	Survival by Year	Outcomes Related to Progression	LR/Local Tumor Progression	LOS	QOL	AE
Gao et al. 2011[94] 63 Fair	●	●	NR	NR	NR	NR	●
Lencioni et al. 2008[91] 20 Poor	NR	NR	NR	NR	●	NR	●
Liao et al. 2008[95] 36 Poor	●	●	NR	NR	NR	NR	●
Zhao et al. 2012[33] 122* Fair	●	●	●	NR	NR	NR	NR

*Patient characteristics are reported for combined intermediate and advanced stage groups (n=122). Results are reported for the intermediate stage group separately (n=72).
"●" Indicates that this outcome was reported in the article.
Abbreviations: AE = adverse events; HCC = hepatocellular carcinoma; LOS = length of stay; LR = local recurrence; N = number of patients; NR = not reported; OS = overall survival; QOL = quality of life.

RFA Compared With TACE-RFA

One RCT by Morimoto et al.[92] compared RFA monotherapy to TACE-RFA combination therapy. No nonrandomized comparative studies examined this comparison. One case series using TACE-RFA met inclusion criteria.[33]

Tables 80–84 give information on RFA compared with TACE-RFA.

Overall Survival

Outcomes for the RCT related to overall survival are summarized in Table 81. There was no statistically significant difference in the 1-, 2-, and 3-year survival rates between the two groups (p=0.369).

One case series by Zhao et al., reported overall survival after treatment with TACE-RFA combination (Table 82).[33] Zhao et al., reported a 3-year survival of 58 months. Lack of a direct comparison in these studies limits the application of these data to inform conclusions on overall survival.

Strength of Evidence

The strength of evidence to evaluate overall survival for RFA compared with TACE-RFA is rated as insufficient for patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease. Evidence to evaluate this outcome comes one poor quality study. Morimoto et al. is an RCT and was rated as a poor quality study due to the lack of blinding and insufficient power to confirm the superiority of one group to another.[92] The low sample size of 37 is below the calculated 40 participants required to establish the specified 80 percent power calculation provided by the authors. Therefore, the risk of bias for the assessment of overall survival was graded as high. There is unknown consistency as there is only one study, overall survival is a direct health outcome, and the estimate is imprecise (Table 80).

Quality of Life

Quality of life was not reported in any of the included studies.

Strength of Evidence

No comparative studies addressed this outcome. Due to the lack of data for this outcome, the strength of evidence to evaluate quality of life for RFA compared with TACE-RFA for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Outcomes Related to Progression

Outcomes related to progression were not reported in the study by Morimoto et al.[92]

Zhao et al., defined TTP as the interval from the date of treatment to the date of progressive disease (sum of the diameters of the target lesions had increased >20% or any new intrahepatic or extrahepatic lesions), death or the last followup visit.[33] Mean TTP was 8.8 months (range 1.5–69 months).

Strength of Evidence

No comparative studies addressed this outcome. Due to the lack of data for this outcome, the strength of evidence to evaluate TTP for RFA compared with TACE-RFA for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Local Recurrence/Local Tumor Progression

Morimoto et al. reported a significant difference in local tumor progression rate (undefined) at the end of 1, 2, and 3 years between the TACE-RFA combination therapy group and the RFA monotherapy group (6 percent vs. 39 percent, respectively, p=0.012).[92]

Strength of Evidence

The strength of evidence to evaluate local control for RFA compared with TACE-RFA is rated as insufficient for patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease. Evidence to evaluate this outcome comes from one poor quality study Morimoto et al. is an RCT and was rated as poor quality due to the lack of blinding and insufficient power. Lack of blinding can lead to detection bias.[92] This is particularly true when outcomes are based on interpretation (i.e., not a hard outcome like death). Therefore, the risk of bias for the assessment of outcomes related to local recurrence as high. In addition, with only one study consistency is unknown, progression is an indirect measure of a health outcome, and the estimates are precise.

Length of Stay

LOS was not a reported outcome in the study by Morimoto et al.[92]

Strength of Evidence

No comparative studies addressed this outcome. Due to the lack of data for this outcome, the strength of evidence to evaluate LOS for RFA compared with TACE-RFA for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Days of Missed Work

Days of missed work not a reported outcome in the study by Morimoto et al.[92]

Strength of Evidence

No comparative studies addressed this outcome. Due to the lack of data for this outcome, the strength of evidence to evaluate days of work missed for RFA compared with TACE-RFA for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Adverse Events

No major complications were observed in the TACE-RFA combination and RFA monotherapy groups (Table 84).[92] The study did not report on the following AEs: hepatic abscess, hepatic hemorrhage, biloma, steatohepatitis, injury to adjacent organs, liver failure, infection, increased liver enzymes (transaminases, bilirubin, alkaline phosphatase), and rare adverse events (Table 83).

Strength of Evidence

No comparative studies addressed this outcome. Due to the limited amount of data, the strength of evidence is insufficient to evaluate adverse events for RFA compared with TACE-RFA for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease.

Overall GRADE for RFA Compared With TACE-RFA

The strength of evidence ratings for studies comparing RFA to TACE-RFA are displayed in Table 80.

Table 80. Strength of evidence for studies comparing RFA to TACE-RFA

Outcome	No of Studies Type of Study	Risk of Bias	Consistency	Directness	Precision	Overall Grade
Overall Survival	1; Morimoto et al. 2010[92] RCT	High	Unknown	Direct	Imprecise	Insufficient
Quality of Life	0	Unknown	Unknown	Unknown	Unknown	Insufficient
Time to Progression	0	Unknown	Unknown	Unknown	Unknown	Insufficient
Local Control	1; Morimoto et al. 2010[92] RCT	High	Unknown	Indirect	Precise	Insufficient
Length of Stay	0	Unknown	Unknown	Unknown	Unknown	Insufficient
Days of Work Missed	0	Unknown	Unknown	Unknown	Unknown	Insufficient
Adverse Events	0	Unknown	Unknown	Unknown	Unknown	Insufficient

Abbreviation: RCT = randomized controlled trial.

Table 81. Survival outcomes: RFA compared with TACE-RFA, randomized controlled trial

Study Rating Design	Treatment Group N	Intervention	Survival Time From	Median OS (95% CI)	% Survival Year 1	% Survival Year 2	% Survival Year 3	% Survival Year 4	% Survival Year 5	Statistical Comparison
Morimoto et al. 2010[92] 37 Poor RCT	TACE-RFA 19	TACE with epirubicin (30–50 mg per body surface), lipiodol, and gelatin sponge particles via hepatic artery followed by percutaneous RFA with multitined expandable electrode or internally cooled electrode followed	Randomization	NR	100	93	93	NR	NR	NS, p=0.369
	RFA 18	Percutaneous RFA with multitined expandable electrode or internally cooled electrode	Randomization	NR	89	89	80	NR	NR	

Abbreviations: CI = confidence interval; N = number of patients; NR = not reported; NS = nonsignificant; OS = overall survival; RCT = randomized controlled trial; RFA = radiofrequency ablation; TACE = transarterial chemoembolization.

Table 82. Survival outcomes: RFA compared with TACE-RFA, case series studies

Study Rating	Group N	Intervention	Survival Time From	Median OS (95% CI)	% Survival Year 1	% Survival Year 2	% Survival Year 3	% Survival Year 4	% Survival Year 5
Zhao et al. 2012[33] Fair	TACE-RFA 122†	TACE with lipiodol (10–30 ml), epirubicin (6–12 mg), mitomycin C (6–12 mg) and normal saline solution (3 ml) via femoral artery using the Seldinger technique followed by RFA 3–4 weeks later with multitined expandable electrodes (01/00-12/03) or monopolar electrode system (01/04-12/09)	Study Treatment	32*	88.9	NR	58.3	NR	13.9

*Extrapolated from Kaplan-Meier graphs.
†Patient characteristics are reported for combined intermediate and advanced stage groups (n=122). Results are reported for the intermediate stage group separately (n=72).
Abbreviations: CI = confidence interval; N = number of patients; NR = not reported; OS = overall survival; RFA = radiofrequency ablation; TACE = transarterial chemoembolization.

Table 83. Adverse events associated with local hepatic therapies: RFA compared with TACE-RFA

Study Rating Design	Treatment Group N	Intervention	Liver Failure %	Hepatic Hemorrhage %	Hepatic Abscess %	Rare AE, N (%)
Morimoto et al. 2010[92] 37 Poor RCT	TACE-RFA 19	TACE with epirubicin (30–50 mg per body surface), lipiodol, and gelatin sponge particles via hepatic artery followed by percutaneous RFA with multitined expandable electrode or internally cooled electrode followed	NR	NR	NR	NR
	RFA 18	Percutaneous RFA with multitined expandable electrode or internally cooled electrode	NR	NR	NR	NR

Abbreviations: AE = adverse event; N = number of patients; NR = not reported; RCT = randomized controlled trial; RFA = radiofrequency ablation; TACE = transarterial chemoembolization.

Table 84. Adverse events associated with local hepatic therapies: RFA compared with TACE-RFA, case series studies

Study Rating	Group N	Liver Failure %	Hepatic Hemorrhage %	Hepatic Abscess %	Rare AE, N (%)
Zhao et al. 2012[33] Fair	TACE-RFA 122†	NR	NR	NR	NR

†Patient characteristics are reported for combined intermediate and advanced stage groups (n=122). Results are reported for the intermediate stage group separately (n=72).
Abbreviations: AE = adverse events; N = number of patients; NR = not reported; RFA = radiofrequency ablation; TACE = transarterial chemoembolization.

Cryoablation Compared With TACE-Cryoablation

One retrospective cohort study by Xu et al.[93] compared cryoablation to sequential TACE and cryoablation for the treatment of HCC.

Tables 85-87 give information on cryoablation compared with TACE-cryoablation.

Overall Survival

Outcomes related to overall survival for Xu et al.[93] are summarized in Table 86. Survival was measured from the time of cryoablation to the time of death or last followup. One- to 3-year survival outcomes were not statistically different between groups, but were in years 4 and 5 (p=0.001), with the combination therapy showing a superior survival outcome. The authors also noted that 18 patients with HCC lesions larger than 5 cm in diameter survived more than 5 years in the sequential treatment group, whereas no patients with large HCC lesions survived for 5 years after cryoablation alone.

Lack of a direct comparison in these studies limits the application of these data to inform conclusions on overall survival.

Strength of Evidence

The strength of evidence to evaluate overall survival for cryoablation compared with TACE-Cryoablation is rated as insufficient for patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease. Evidence to evaluate this outcome comes from one poor quality study. Xu et al.[93] is a retrospective cohort study which began with a low strength of evidence due to the nature of the study design (e.g., lack of blinding and no randomization) and was further reduced to insufficient quality due to a serious risk of bias. For an observational study to overcome the limitation of a non-randomized design, adequate control of confounders must be considered in the analysis. The authors did not attempt to adjust for confounders in their analysis. Therefore, the risk of bias for the assessment of overall survival was graded as high. There is unknown consistency as there is only one trial, overall survival is a direct health outcome, the comparison was direct, and the estimate is precise (Table 85).

Quality of Life

Quality of life was not reported in any of the included studies.

Strength of Evidence

No comparative studies addressed this outcome. Therefore, the strength of evidence to evaluate quality of life for cryoablation compared with TACE-cryoablation for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Outcomes Related to Progression

Outcomes related to progression were not reported in the study by Xu et al.[93]

Strength of Evidence

No comparative studies addressed this outcome. Therefore, the strength of evidence to evaluate TTP for cryoablation compared with TACE-cryoablation for the treatment of patients

with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Local Recurrence/Local Tumor Progression

Xu et al.[93] assessed local tumor recurrence of the ablated lesions (identified via CT scan) during followup occurring every 2–3 months for 1–2 years. With a mean followup period of 42 ± 17 months (range: 24–70 months), the local recurrence rate at the ablated area was 17 percent for all patients, and 23 percent and 11 percent for the cryoablation and the sequential TACE-cryoablation groups, respectively (p=0.001).

Strength of Evidence

The strength of evidence to evaluate local control for cryoablation compared with TACE-cryoablation is rated as insufficient for patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease. Evidence to evaluate this outcome comes from one poor quality study. Xu et al.[93] is a retrospective cohort study which began with a low strength of evidence due to the nature of the study design (e.g., lack of blinding and no randomization) and was further reduced to insufficient SOE due to a serious risk of bias. For an observational study to overcome the limitation of a non-randomized design, adequate control of confounders must be considered in the analysis. The authors did not attempt to adjust for confounders in their analysis. Therefore, the risk of bias for the assessment of outcomes related to progression was graded as high. In addition, with only one study, consistency is unknown, progression is an indirect measure of a health outcome, and the estimates are precise.

Length of Stay

LOS was not a reported outcome in the study by Xu et al.[93]

Strength of Evidence

No comparative studies addressed this outcome. Therefore, the strength of evidence to evaluate LOS for cryoablation compared with TACE-cryoablation for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Days of Missed Work

Days of missed work was not reported in any of the included studies.

Strength of Evidence

No comparative studies addressed this outcome. Therefore, the strength of evidence to evaluate days of work missed for cryoablation compared with TACE-cryoablation for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Adverse Events

Xu et al.[93] reported no observed events of hepatic hemorrhage or liver failure as reported in Table 87. Hepatic abscess, biloma, steatohepatitis, injury to adjacent organs, infection, increased

liver enzymes (transaminases, bilirubin, alkaline phosphatase), and rare adverse events were not reported.

Strength of Evidence

The strength of evidence to evaluate adverse events for cryoablation compared with TACE-cryoablation is rated as insufficient for patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease. Evidence to evaluate this outcome comes from one poor quality study. The lack of blinding affected the risk of bias in the assessment of adverse events. The majority of adverse events of interest, such as hepatic hemorrhage, leave little room for interpretation, but others, such as liver failure, involve some interpretation; therefore, the risk of bias for the assessment of adverse events was rated as medium. The consistency is unknown, and adverse events are direct health outcomes but the estimates are imprecise.

Overall GRADE for TACE Compared With TACE-Cryoablation

The strength of evidence ratings for studies comparing TACE to TACE-cryoablation are displayed in Table 85.

Table 85. Strength of evidence for studies comparing cryoablation to TACE-cryoablation

Outcome	No of Studies Type of Study	Risk of Bias	Consistency	Directness	Precision	Overall Grade
Overall Survival	1; Xu et al. 2009[93] Retrospective cohort	High	Unknown	Direct	Precise	Insufficient
Quality of Life	0	Unknown	Unknown	Unknown	Unknown	Insufficient
Time to Progression	0	Unknown	Unknown	Unknown	Unknown	Insufficient
Local Control	1; Xu et al. 2009[93] Retrospective cohort	High	Unknown	Indirect	Precise	Insufficient
Length of Stay	0	Unknown	Unknown	Unknown	Unknown	Insufficient
Days of Work Missed	0	Unknown	Unknown	Unknown	Unknown	Insufficient
Adverse Events	1; Xu et al. 2009[93] Retrospective cohort	Medium	Unknown	Direct	Imprecise	Insufficient

Table 86. Survival outcomes: cryoablation compared with TACE with sequential cryoablation

Study Rating Design	Treatment Group N	Intervention	Survival Time From	Median OS (95% CI)	% Survival Year 1	% Survival Year 2	% Survival Year 3	% Survival Year 4	% Survival Year 5	Statistical Comparison
Xu et al. 2009[93] Poor Retrospective cohort	Cryoablation 130	Percutaneous cryoablation via right lateral intercostal access	Study treatment	NR	73	54	42	29	23	1-year: p=0.668 2-year: p=0.147 3-year: p=0.064 4-year: p=0.001 5-year: p=0.001
	TACE and Cryoablation 290	TACE with doxorubicin (50 mg), mitomycin (10 mg) and lipiodol (4–15 mL) via arterial branches followed by percutaneous cryoablation via right lateral intercostal access	Study treatment	NR	71	61	52	49	39	

Abbreviations: CI = confidence interval; N = number of patients; NR = not reported; OS = overall survival; TACE = transarterial chemoembolization.

Table 87. Adverse events associated with local hepatic therapies: cryoablation compared with TACE with sequential cryoablation

Study Rating Design	Treatment Group N	Intervention	Liver Failure %	Hepatic Hemorrhage %	Hepatic Abscess %	Rare AE, N (%)
Xu, et al. 2009[93] Poor Retrospective cohort	Cryoablation 130	Percutaneous cryoablation via right lateral intercostal access	0	0	NR	NR
	TACE and Cryoablation 290	TACE with doxorubicin (50 mg), mitomycin (10 mg) and lipiodol (4–15 mL) via arterial branches followed by percutaneous cryoablation via right lateral intercostal access	4.1	1.7	NR	NR

Abbreviations: AE = adverse event; N = number of patients; NR = not reported; TACE = transarterial chemoembolization.

Combination Therapy Interventions With No Comparative Evidence

Three combination therapy case series were included in this report for which no comparative evidence exists: RFA followed by DEB,[91] TACE followed by PEA,[94] and TAE followed by RFA.[95]

Strength of Evidence

No comparative studies met inclusion criteria for this review. Therefore, strength of evidence is insufficient to evaluate all outcomes of interest: overall survival, quality of life, TTP, local recurrence, LOS, days of work missed, and adverse events for all interventions without comparative studies for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease.

Overall Survival

Survival outcomes for the combination treatments are summarized in Table 88. Lack of a direct comparison in these studies limits the application of these data to inform conclusions on overall survival.

Quality of Life

Quality of life was not reported in any of the included studies.

Outcomes Related to Progression

Outcomes related to progression were not reported in any of the included studies.

Local Recurrence/Local Tumor Progression

Local recurrence or local tumor progression was not reported in any of the included studies.

Length of Stay

A study of RFA followed by DEB reported a mean LOS of 2.7 days with a range of 2 to 4 days.

Days of Missed Work

Days of missed work was not reported in any of the included studies.

Adverse Events

For the studies lacking comparative data, no liver failure or hepatic abscess was reported. Other rare adverse events are listed in Table 89, including fatal and nonfatal events.

Table 88. Outcomes related to overall survival, combination therapy studies with no comparative data

Study Rating	Group N	Intervention	Survival Time From	Median OS (95% CI)	% Survival Year 1	% Survival Year 2	% Survival Year 3	% Survival Year 4	% Survival year 5
Lencioni et al. 2008[91] Poor	RFA and DEB 20	Percutaneous, US-guided RFA (target temp 105°C) followed within 24 hours with DEB of doxorubicin (range 50–125 mg; mean 60.2 mg; SD 21.8 mg) via arterial branches feeding the tumor	NR	NR	NR	NR	NR	NR	NR
Gao et al. 2011[94] Fair	TACE+PEA 63	TACE with lipiodol, perarubicin (50 mg/m^2), DDP (80 mg/m^2) via hepatic artery 1–2 times followed by CT-guided percutaneous ethanol ablation with ethanol (99% concentration) mixed with lipiodol (9:1 volume ratio, mean 30.5 mL per patient) via hepatic artery	Study Treatment	27.7	54.0	NR	31.7	NR	17.5
Liao et al. 2008[95] Poor	TAE+RFA 36	TAE with Lipiodol followed by RFA between the 7th and 14th days after TAE	Not reported	34*	90	57	40	NR	NR

*Extrapolated from Kaplan-Meier graphs.

Abbreviations: CI = confidence interval; CT = computed tomography; CP = Child-Pugh liver cirrhosis class; DEB = drug-eluting beads; GBq = gigabecquerel; Gy = Gray; N = number of patients; NS = nonsignificant; NR = not reported; OS = overall survival; PEA = percutaneous ethanol ablation; RFA = radiofrequency ablation; SD = standard deviation; TACE = transarterial chemoembolization; TAE = transarterial embolization; US = ultrasound.

Table 89. Adverse events associated with local hepatic therapies: combination therapy studies with no comparative data

Study Rating	Group N	Liver Failure %	Hepatic Hemorrhage %	Hepatic Abscess %	Rare AE, N (%)
Lencioni et al. 2008[91] Poor	RFA+DEB* 20	NR	NR	0	NR
Gao et al. 2011[94] Fair	TACE+PEA 63	NR	NR	NR	Fatal variceal bleeding due to increased portal vein pressure caused by deterioration of liver cirrhosis after repeated TACE-PEA, 2 (3.2%)
Liao et al. 2008[95] Poor	TAE+RFA* 36	NR	NR	NR	NR

*No grade 3 or 4 adverse events of interest were observed for these treatment groups.

Abbreviations: AE = adverse event; CP = Child-Pugh liver cirrhosis class; DEB = drug-eluting beads; N = number of patients; PEA = percutaneous ethanol ablation; RFA = radiofrequency ablation; SC = systemic chemotherapy; SD = standard deviation; TACE = transarterial chemoembolization; TAE = transarterial embolization.

Key Question 3. Comparative Effectiveness by Patient Subgroups

Key question 3 focuses on the assessment of heterogeneity of treatment effects across patient subgroups. Subgroups of interest include age, sex, HCC stage, disease etiology, lesion size, and multifocal disease. All included comparative studies were reviewed for KQ3, whereas case series and the case report were excluded as we were only interested in subgroups within the comparison of two interventions.

Description of Included Studies

Three RCTs undertook ad hoc subgroup analyses to assess the impact of various patient and tumor factors on treatment outcomes.[50-52] The results are described below and organized by the treatment comparison followed by patient subgroup of interest.

Key Points

- Three RCTs reported subgroup analyses of interest for the comparison of RFA to PEI/PAI. Subgroup analyses in these studies were ad hoc rather than prespecified in the analysis plan, leading to a high risk of bias. Two RCTs by Lin et al.[51,52] found that RFA yielded a significantly greater overall survival than PEI/PAI among patients with larger lesions, defined as 2–3 cm in one study and 3.1–4 cm in another study. In contrast, an RCT by Brunello et al.[50] found no significant difference in overall survival between RFA and PEI among patients with lesions >2 cm in size. There is a low strength of evidence to support increased overall survival for RFA compared with PEI/PAI in patients with larger lesions with a high risk of bias. The evidence is insufficient to assess the effects lesion size on other outcomes of interest in this report and of other patient subgroups on any outcome of interest in this report.
- In one RCT by Brunello et al.[50] no difference in overall survival was found between RFA and PEI among the subgroups of patients in Child-Pugh class A and those with multifocal HCC. The evidence was graded as insufficient due to results of unknown consistency and a high risk of bias.
- No studies presented subgroup analyses on age, sex, disease etiology, and HCC stage. Therefore, the evidence is insufficient to assess the effect of these subgroups for all outcomes of interest in this review.

Detailed Synthesis

Subgroup analyses were only present in studies comparing RFA to PEI/PAI.

RFA Compared With PEI/PAI

Age

None of the three RCTs reported subgroup analysis by age.

Strength of Evidence

No studies evaluated this subgroup. Due to the lack of data, the strength of evidence to evaluate the effect of age on the comparative effectiveness of RFA and PEI/PAI for the treatment

of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient (Table 90).

Sex

None of the three RCTs reported subgroup analysis by sex.

Strength of Evidence

No studies evaluated this subgroup. Due to the lack of data, the strength of evidence to evaluate the effect of sex on the comparative effectiveness of RFA and PEI/PAI for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Disease Etiology

None of the three RCTs reported subgroup analysis by disease etiology (e.g., HBV, HCV).

Strength of Evidence

No studies evaluated this subgroup. Due to the lack of data, the strength of evidence to evaluate the effect of disease etiology on the comparative effectiveness of RFA and PEI/PAI for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

HCC Stage

None of the three RCTs reported subgroup analysis by HCC stage (e.g., BCLC stage A or B).

Strength of Evidence

No studies evaluated this subgroup. Due to the lack of data, the strength of evidence to evaluate the effect of HCC stage on the comparative effectiveness of RFA and PEI/PAI for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Child-Pugh Class

Brunello et al.[50] found a nonsignificant difference in overall survival between the RFA and PEI groups among patients in Child-Pugh class A (hazard ratio=0.67; 95% CI, 0.25 to 1.80; p=0.43). In multivariate models, Child-Pugh class B had a positive association with risk of death (hazard ratio=2.94; 95% CI, 1.6-5.42; p=0.001).

Strength of Evidence

One RCT presented a post hoc analysis of the impact of Child-Pugh class on overall survival. The risk of bias for this particular analysis is high because it was not a prespecified analysis.. Only one study reported results by Child-Pugh class; therefore, the consistency is unknown, the measurement is direct for a health outcome, and the estimate is imprecise. Thus, the strength of evidence to evaluate the effect of Child-Pugh classification on the comparative effectiveness of RFA and PEI/PAI for the treatment of patients with unresectable HCC who are not otherwise

candidates for surgical resection or transplantation and with no evidence of extrahepatic disease was judged to be insufficient.

Lesion Size

Overall Survival

Brunello et al.[50] reported a nonsignificant difference in overall survival between the RFA and PEI groups among patients HCC lesions >2 cm in diameter (hazard ratio=0.62; 95% CI, 0.28 to 1.36; p=0.23).

In the stratified subgroup analysis by lesion size (1–2 cm and 2–3 cm), Lin et al.[52] found that the overall survival rate was significantly higher in the RFA group compared with the PEI group (p=0.032) and the PAI group (p=0.027) among patients with HCC lesions 2–3 cm in size. Among patients with smaller HCC lesions (1–2 cm), no significant difference between treatment groups was seen.

In a similar study comparing RFA to conventional PEI and higher-dose PEI, Lin et al.[51] conducted a stratified subgroup analysis by lesion size (1–2 cm, 2.1–3 cm, and 3.1–4 cm) and found that the overall survival rate was significantly higher in the RFA group compared with the conventional PEI group (p<0.03) and the higher-dose PEI group (p<0.04) among patients with HCC lesions 3.1–4 cm in size. Among patients with smaller HCC lesions (1–2 cm and 2.1–3 cm), no significant difference between treatment groups was seen.

Strength of Evidence

Three RCTs presented a post hoc analysis of the impact of lesion size on overall survival. While randomization would prevent selection bias, the risk of bias remains high since these subgroup analyses were not prespecified (i.e., the lesion size cutoffs). In addition, there is no rationale given for the lesion size cutoffs in these papers. It is particularly troubling for the two papers by Lin et al., in which different cutoffs were used. Results are directionally consistent, showing better survival for patients with larger lesions treated with RFA compared with PEI/PAI. The strength of evidence is low to evaluate the effect of lesion size on the comparative effectiveness of RFA and PEI/PAI for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease.

Cancer-Free Survival

In addition to overall survival, Lin et al.[48] reported subgroup analyses for cancer-free survival, the RFA group had a significantly higher cumulative survival rate than the PEI group (p=0.031) or PAI group (p=0.035) among patients with 2–3 cm HCC lesions, but not among patients with 1–2 cm HCC lesions.

Strength of Evidence

One RCT presented a post hoc analysis of the impact of lesion size on cancer-free survival. The risk of bias for this particular analysis is high because it was not a prespecified analysis. Only one study reported results by lesion size; therefore, the consistency is unknown, the measurement is direct for a health outcome, and the estimate is precise. Thus, the strength of evidence is insufficient to evaluate the effect of lesion size on the comparative effectiveness of

RFA and PEI/PAI for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease.

Local Recurrence

Lin et al.[48] also reported subgroup analyses for local recurrence rate. Local recurrence rate was lower in the RFA group compared with the PEI group (p=0.009) and PAI group (p=0.011) among the smaller HCC lesion subgroup, but not in the larger HCC lesion subgroup.

Strength of Evidence

One RCT presented a post hoc analysis of the impact of lesion size on local recurrence. The risk of bias for this particular analysis is high because it was not a prespecified analysis. Only one study reported results by lesion size, therefore the consistency is unknown, the measurement is direct for a health outcome, and the estimate is precise. Due to the high risk of bias and unknown consistency the strength of evidence is insufficient to evaluate the effect of multifocal disease classification on the comparative effectiveness of RFA and PEI/PAI for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease.

Multifocal HCC

Brunello et al.[50] reported a nonsignificant difference in overall survival between the RFA and PEI groups among patients with multifocal HCC (hazard ratio=0.48; 95% CI, 0.16 to 1.43; p=0.19).

Strength of Evidence

One RCT presented a post hoc analysis of the impact of multifocal HCC on overall survival. The risk of bias for this particular analysis is high because it was not a prespecified analysis. Only one study reported results by multifocal HCC; therefore, the consistency is unknown, the measurement is direct for a health outcome, and the estimate is imprecise. Thus, the strength of evidence is insufficient to evaluate the effect of multifocal disease classification on the comparative effectiveness of RFA and PEI/PAI for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation and with no evidence of extrahepatic disease.

Table 90. Strength of evidence for studies comparing RFA to PEI/PAI

Patient or tumor characteristic	No. of Studies Type of Study	Risk of Bias	Consistency	Directness	Precision	Overall Grade
Age	0	Unknown	Unknown	Direct	Unknown	Insufficient
Sex	0	Unknown	Unknown	Direct	Unknown	Insufficient
Disease Etiology	0	Unknown	Unknown	Direct	Unknown	Insufficient
HCC Stage	0	Unknown	Unknown	Direct	Unknown	Insufficient
Child-Pugh Class	1; Brunello et al. 2008[50] RCT	High	Unknown	Direct	Imprecise	Insufficient
Lesion Size	3; Brunello et al. 2008[50] RCT; Lin et al. 2004[51] RCT; Lin et al. 2005[52] RCT	High	Consistent	Direct	Imprecise	Low
Multifocal HCC	1; Brunello et al. 2008[50] RCT	High	Unknown	Direct	Precise	Insufficient

Abbreviation: RCT = randomized controlled trial

Overall Conclusions for Key Questions 1–3

- Six RCTs, four nonrandomized comparative studies, 35 case series, and three case reports comprised the body of literature. One RCT was rated as good,[50] three were rated as fair,[51,52,62] and two were rated as poor quality.[61,92]
- The body of evidence for RFA compared with PEI/PAI was rated moderate strength to support better overall survival at 3 years for RFA compared with PEI/PAI with a low risk of bias.
- The body of evidence for RFA compared with PEI/PAI was rated low strength to support increased TTP, improved local control, and a longer LOS for RFA compared with PEI/PAI, with a high risk of bias.
- For all other comparisons, the body of evidence on overall survival, quality of life, disease progression, local control, LOS, days of missed work, and adverse events for local hepatic therapy for the treatment HCC is insufficient to support the effectiveness of one local hepatic therapy over another, due to the lack of comparative studies.
- Studies with subgroup analyses were limited to the three studies[50-52] reporting on the comparison of RFA to PEI/PAI. These analyses reviewed Child-Pugh class, lesion size, and multifocal disease for their effects on overall survival, but were not prespecified. Lesion size was also examined by Lin et al 2004[51] for its effects on cancer-free survival and local recurrence. There is a low strength of evidence to support increased overall survival for RFA compared with PEI/PAI in patients with larger lesions with a high risk of bias. The evidence is insufficient to assess the effects lesion size on other outcomes of interest in this report and of other patient subgroups on any outcome of interest in this report.
- 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).

Discussion

Key Findings and Strength of Evidence

This review addressed the comparative effectiveness of local hepatic therapy for the treatment of unresectable HCC in patients who are not otherwise eligible for transplantation and do not have extrahepatic spread. Forty-eight studies met our inclusion criteria and included six RCTs, four nonrandomized comparative studies, 35 observational case series, and three case reports.

We assessed the strength of evidence for our primary health outcomes of overall survival and quality of life; the intermediate outcomes of TTP, local recurrence, LOS, and days of work missed for KQ1; and adverse events for KQ2 (Table 91). In addition, we reviewed the effect of patient subgroups on the comparative effectiveness of the included comparisons for our population of interest for KQ3.

For the comparison of RFA to PEI/PAI, three RCTs[50-52] were pooled in a meta-analysis (Figure 3), and risk differences were calculated. The pooled estimate was 0.16 (95 percent confidence interval [CI], 0.03 to 0.28), a statistically significant result that favored RFA. The wide range of effect across the three trials and a moderate level of statistical heterogeneity in this pool of studies (I^2=48 percent) led to the classification of the results as inconsistent. We judged the strength of the body of evidence on overall survival in favor of RFA compared with PEI/PAI as moderate. The strength of the body of evidence was downgraded from high, the starting point when multiple RCTs are available, to moderate for the lack of consistency in the results across studies. In addition to overall survival, two RCTs[51,52] reported on the outcomes of TTP, local control, and LOS. Due to the lack of blinding, the risk of bias was high, the results were consistent and precise, and all three are indirect measures of a final health outcome. Based on the high risk of bias and indirect measurement, we judged the strength of evidence on TTP and local control in favor of RFA compared with PEI/PAI to be low. Also based on the high risk of bias due to a lack of blinding, the strength of evidence is graded low for a longer LOS following treatment with RFA compared with PEI/PAI. All three RCTs[50-52] performed subgroup analyses to determine if overall survival was superior among specific patient subgroups. There is a low strength of evidence to support increased overall survival for RFA compared with PEI/PAI in patients with larger lesions (defined variably as >2cm, 2-3cm, and 3.1-4cm) with a high risk of bias. The evidence is insufficient to assess the effects lesion size on other outcomes of interest in this report and of other patient subgroups on any outcome of interest in this report.

We judged the strength of evidence to be insufficient to draw conclusions for effectiveness outcomes (overall survival, quality of life, disease progression, local recurrence, LOS, and days of work missed) and for adverse events for patients considered for all other comparisons.

Data were judged to be insufficient due to high risk of bias, imprecision of estimates, and lack of comparative data for some outcomes (e.g., quality of life, days of work missed).

Table 91. Summary GRADE strength of evidence for KQ1 and KQ2

Key Question	Strength of Evidence	Conclusion
Key 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?		
RFA to PEI/ PAI		
Overall Survival	Moderate	One good-quality RCT (n=139), and two fair quality RCTs (n=157 and n=187) assessed 3-year overall survival after treatment with RFA or PEI/PAI. In a meta-analysis, the pooled risk difference of 0.16 (95% CI 0.03 to 0.28) was statistically significant in favor of RFA. The heterogeneity in this pool of studies was moderate (I^2=48%).
Quality of Life	Insufficient	Quality of life was not reported in any of the comparative studies.
Outcomes Related to Progression	Low	Two fair-quality RCTs reported outcomes related to progression (n=157 and n=187). One study reported cancer-free survival (from time of study treatment to local tumor progression, extrahepatic metastases, additional new HCC recurrence, or death). The 3-year cancer-free survival rate was 37%, 17%, and 20% in the RFA, PEI, and higher-dose PEI groups respectively. The RFA group had a significantly higher rate than the two PEI groups (RFA vs. conventional PEI: risk ratio=0.38; 95%CI, 0.14 to 0.88, p=0.019; RF vs. higher-dose PEI: risk ratio=0.41; 95%CI, 0.22 to 0.89, p=0.024). In the other RCT, 3-year cancer-free survival was 43%, 21%, and 23% in the RFA, PEI and PAI groups respectively (RFA vs. PEI: risk ratio=0.31; 95% CI, 0.18 to 0.85, p=0.038; RFA vs. PAI: risk ratio=0.26, 95% CI, 0.13 to 0.81, p=0.041).
Local Recurrence/Local Tumor Progression	Low	Two fair-quality RCTs (n=157 and n=187) reported local tumor progression (defined as the presence of an enhanced tumor on CT, corresponding to the initial target tumor). In one RCT, the RFA group had a significantly lower rate than in the PEI groups (RFA vs. conventional PEI: risk ratio=0.37; 95% CI, 0.12 to 0.76, p=0.012; RFA vs. higher-dose PEI: risk ratio=0.49; 95% CI, 0.23 to 0.92, p=0.037). This study assessed local recurrence in all randomized patients. In the second RCT, the local recurrence rate was significantly lower in the RFA group compared with the PEI (risk ratio=0.35; 95% CI, 0.21 to 0.89, p=0.012) and PAI (risk ratio=0.41; 95% CI, 0.23 to 0.91, p=0.017) groups. This study assessed local recurrence only for patients achieving complete tumor necrosis following treatment.

Table 91. Summary GRADE strength of evidence for KQ1 and KQ2 (continued)

Key Question	Strength of Evidence	Conclusion
Length of Stay	Low	LOS was reported in two fair-quality RCTs (n=157 and n=187). Both studies reported LOS only for a subset of patients who achieved complete tumor necrosis. In the first study, the RFA group had a significantly longer mean LOS than the conventional PEI group (4.4 days ± 1.8 vs. 1.6 days ± 0.3, p<0.01). In the second trial, the RFA group had a significantly longer LOS than either the PEI group or the PAI group (4.2 days ± 1.9, 1.7 days ± 0.4, 2.2 days ± 0.6, respectively, all p<0.01).
Days of Missed Work	Insufficient	Days of missed work was not reported in any of the comparative studies.
DEB to TAE		
Overall Survival	Insufficient	One poor-quality RCT (n=84) reported that there was no statistically significant difference in 1-year overall survival between the groups (85.3% and 86%, respectively, p-value not reported).
Quality of Life	Insufficient	Quality of life was not reported in any of the comparative studies.
Outcomes Related to Progression	Insufficient	One poor-quality RCT (n=84), reported TTP, defined as the time from the first treatment until progression which consisted of as local recurrence, new lesions, or a combination of both (overall recurrence). The mean TTP was longer in the DEB group (10.6 ± 2.4 months) than the TAE group (9.1 ± 2.3 months; p=0.008).
Local Recurrence/Local Tumor Progression	Insufficient	One poor-quality RCT (n=84), reported local recurrence as the number of patients with local recurrence out of the total number of patients evaluated at 6, 9, and 12 months: 1/41 (2.4%), 6/40 (15%), and 11/35 (31.4%) in the DEB group and 4/43 (9.3%), 19/41 (46.3%), and 21/37 (56.8%) in the TAE group, respectively.
Length of Stay	Insufficient	LOS was not reported in any of the comparative studies.
Days of Missed Work	Insufficient	Days of missed work was not reported in any of the comparative studies.
DEB to TACE		
Overall Survival	Insufficient	One fair-quality RCT (n=67) reported the 2-year overall survival rates were not significantly different between the groups (83.6% in the conventional TACE group and 86.8% in the DEB group, p=0.96). One poor-quality prospective case control study (n=105) reported no significant difference in overall median survival between the groups (11.4 months after enrollment in the TACE group vs. 18.4 months after enrollment in the DEB group).
Quality of Life	Insufficient	Quality of life was not reported in any of the comparative studies.

Table 91. Summary GRADE strength of evidence for KQ1 and KQ2 (continued)

Key Question	Strength of Evidence	Conclusion
Outcomes Related to Progression	Insufficient	One fair-quality RCT (n=67) reported time to radiologic progression (defined as the time from study treatment to disease progression). The median time had not been reached, the mean expected time-to-radiographic-progression was not significantly different between the groups (24.2 months after TACE vs. 15.6 months after DEB, p=0.64). One poor-quality prospective case control study (n=105) reported relapse-free survival (defined as the time between the embolization to any relapse and the appearance of a second primary cancer or death). The median relapse-free survival was not significantly different between the groups (8.4 months after TACE vs. 13.1 months after DEB).
Local Recurrence/Local Tumor Progression	Insufficient	One fair-quality RCT (n=67) assessed the median expected time to local recurrence within the initial target lesions and found the difference is nonsignificant (12.8 months after TACE and 8.9 months after DEB, p=0.46).
Length of Stay	Insufficient	One fair-quality RCT (n=67) reported no significant difference between the conventional TACE and DEB groups in terms of mean LOS (6.8 days vs. 5.9 days, p=0.26). One poor-quality prospective case control study reported a significant difference in median LOS between TACE and DEB (2.3 days vs. 4.7 days, p<0.0001).
Days of Missed Work	Insufficient	Days of missed work was not reported in any of the comparative studies.
RFA to TACE		
Overall Survival	Insufficient	One poor-quality retrospective cohort study (n=91) reported overall survival. Two-year survival for RFA compared with TACE was 72% and 58%, respectively, which was not found to be statistically different (p=0.21).
Quality of Life	Insufficient	Quality of life was not reported in any of the comparative studies.
Outcomes Related to Progression	Insufficient	One poor-quality retrospective cohort study (n=91) reported time to disease progression. This was calculated from the date of disease response to treatment to the date of disease progression. Disease progression occurred in 35 patients (88%) in the TACE group and 36 patients (71%) in the RFA group. The median time to disease progression was 9.5 months (range: 1.0 to 47.3 months) in patients treated with TACE and 10.4 months (range: 1.0 to 42.7 months) in patients treated with RFA (p=0.95).
Local Recurrence/Local Tumor Progression	Insufficient	One poor-quality retrospective cohort study (n=91) reported the local recurrence rate was 14% (n=7) in the RFA group. The authors did not report local recurrence rate in the TACE group.
Length of Stay	Insufficient	LOS was not reported in any of the comparative studies.
Days of Missed Work	Insufficient	Days of missed work was not reported in any of the comparative studies.

Table 91. Summary GRADE strength of evidence for KQ1 and KQ2 (continued)

Key Question	Strength of Evidence	Conclusion
TACE to TEA		
Overall Survival	Insufficient	One poor-quality retrospective case control study (n=60) reported there was a significant difference in the 2-year survival rates (measured from the date of first study treatment) of 43.3% and 80% between the TACE and TEA groups, respectively (p=0.0053).
Quality of Life	Insufficient	Quality of life was not reported in any of the comparative studies.
Outcomes Related to Progression	Insufficient	One poor-quality retrospective case control study (n=60) assessed progression-free survival, measured from the date of first study treatment to the date of death or last followup, and reported a nonsignificant difference between the TACE and TEA groups (46% at 1 year and 42.5% at 2 years for TACE and 69.8% at 1 year and 58.8% at 2 years for TEA, p=0.0588).
Local Recurrence/Local Tumor Progression	Insufficient	Local recurrence/local tumor progression was not reported in any of the comparative studies.
Length of Stay	Insufficient	LOS was not reported in any of the comparative studies.
Days of Missed Work	Insufficient	Days of missed work was not reported in any of the comparative studies.
RFA to RFA-TACE		
Overall Survival	Insufficient	One low-quality RCT (n=37) reported no statistically significant difference in the 1-, 2-, and 3-year survival rates between the two groups (p=0.369).
Quality of Life	Insufficient	Quality of life was not reported in any of the comparative studies.
Outcomes Related to Progression	Insufficient	Outcomes related to progression were not reported in any of the comparative studies.
Local Recurrence/Local Tumor Progression	Insufficient	One low-quality RCT (n=37) reported a significant difference in local tumor progression rate (undefined) at the end of 1, 2, and 3 years between the TACE-RFA combination therapy group and the RFA monotherapy group (6% vs. 39%, respectively, p=0.012).
Length of Stay	Insufficient	LOS was not reported in any of the comparative studies.
Days of Missed Work	Insufficient	Days of missed work was not reported in any of the comparative studies.
TACE to TACE-Cryoablation		
Overall Survival	Insufficient	One poor-quality retrospective cohort study (n=420) reported that 1- to 3-year survival outcomes were not statistically different between groups. However, in years 4 and 5, the combination therapy group showed a superior survival outcome (p=0.001).
Quality of Life	Insufficient	Quality of life was not reported in any of the comparative studies.
Outcomes Related to Progression	Insufficient	Outcomes related to progression were not reported in any of the comparative studies.
Local Recurrence/Local Tumor Progression	Insufficient	One poor-quality retrospective cohort study (n=420) reported the local recurrence rate at the ablated area was 17% for all patients, and 23% and 11% for the cryoablation and the sequential TACE-cryoablation groups, respectively (p=0.001).
Length of Stay	Insufficient	LOS was not reported in any of the comparative studies.
Days of Missed Work	Insufficient	Days of missed work was not reported in any of the comparative studies.

Table 91. Summary GRADE strength of evidence for KQ1 and KQ2 (continued)

Key Question	Strength of Evidence	Conclusion
Key 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?		
RFA to PEI/ PAI	Insufficient	None of the 3 RCTs comparing RFA and PEI/PAI reported the following AEs: hepatic abscess, hepatic hemorrhage, biloma, steatohepatitis, injury to adjacent organs, liver failure, and infection. Due to the limited amount of data, the strength of evidence is insufficient to evaluate adverse events for RFA compared with PEI/PAI for the treatment of patients with unresectable HCC who are not otherwise candidates for surgical resection or transplantation with no evidence of extrahepatic disease
DEB to TAE	Insufficient	In one poor-quality RCT (n=84), the authors reported hepatic abscess in 2 (4.8%) and 1 (2.3%) patients in the DEB and TAE groups, respectively, and liver failure in 2 patients in each group. The study authors did not report on the following AEs: hepatic hemorrhage, biloma, steatohepatitis, injury to adjacent organs, infection, increased liver enzymes (transaminases, bilirubin, alkaline phosphatase), and rare adverse events.
DEB to TACE	Insufficient	One fair-quality RCT (n=67) reported liver failure in 1 patient (3%) receiving TACE and none in the DEB group. This RCT also reported significant ($p<0.0001$) increases in ALT and bilirubin levels compared with baseline. Increase of ALT was significantly higher in the TACE group than in the DEB group ($p=0.007$). Increased bilirubin was not different between groups. The study did not report on the following AEs: hepatic abscess, hepatic hemorrhage, biloma, steatohepatitis, injury to adjacent organs, infection, and rare adverse events. One poor-quality prospective case control study (n=105) reported no significant difference in mean baseline AST values between the TACE and DEB groups (109±12 IU vs. 116±31 IU). After the procedures the difference between the mean AST values became statistically significant (805±125 IU for TACE vs. 238±57 IU for DEB, $p<0.05$). Increases in the ALT and LDH levels were observed for 9 days and at 4 days for the TACE and DEB groups, respectively.
RFA to TACE	Insufficient	One poor-quality retrospective cohort study (n=91) reported that liver failure was observed in 1 (2%) and 2 (5%) patients in the RFA and TACE groups, respectively. The study did not report on the following AEs: hepatic abscess, hepatic hemorrhage, biloma, steatohepatitis, injury to adjacent organs, infection, increased liver enzymes (transaminases, bilirubin, alkaline phosphatase), and rare adverse events.
TACE to TEA	Insufficient	One poor-quality retrospective case series (n=60) did not report adverse events.
RFA to RFA-TACE	Insufficient	No comparative studies reported on adverse events of interest.

Table 91. Summary GRADE strength of evidence for KQ1 and KQ2 (continued)

Key Question	Strength of Evidence	Conclusion
TACE to TACE-Cryoablation	Insufficient	One poor-quality retrospective cohort study (n=420) reported no observed events of hepatic hemorrhage or liver failure. Hepatic abscess, biloma, steatohepatitis, injury to adjacent organs, infection, increased liver enzymes (transaminases, bilirubin, alkaline phosphatase), and rare adverse events were not reported.
Key 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?		
RFA to PEI/ PAI: Age	Insufficient	None of the 3 RCTs reported subgroup analysis by age.
RFA to PEI/ PAI: Sex	Insufficient	None of the 3 RCTs reported subgroup analysis by sex.
RFA to PEI/ PAI: Disease Etiology	Insufficient	None of the 3 RCTs reported subgroup analysis by disease etiology (e.g., HBV, HCV).
RFA to PEI/ PAI: HCC Stage	Insufficient	None of the 3 RCTs reported subgroup analysis by HCC stage (e.g., BCLC stage A or B).
RFA to PEI/ PAI: Child-Pugh Class (Overall Survival)	Insufficient	One RCT (n=139) found a nonsignificant difference in overall survival between the RFA and PEI groups among patients in Child-Pugh class A (hazard ratio=0.67; 95% CI, 0.25 to 1.80; p=0.43).
RFA to PEI/ PAI: Lesion Size (Overall Survival)	Low	One RCT (n=139) found a nonsignificant difference in overall survival between the RFA and PEI groups among patients HCC lesions >2 cm in diameter (hazard ratio=0.62; 95% CI, 0.28 to 1.36; p=0.23). One RCT (n=157) found that the overall survival rate was significantly higher in the RFA group compared with the PEI group (p=0.032) and the PAI group (p=0.027) among patients with HCC lesions 2–3 cm in size. Among patients with smaller HCC lesions (1–2 cm), no significant difference between treatment groups was seen. One RCT (n=187) found that the overall survival rate was significantly higher in the RFA group compared with the conventional PEI group (p<0.03) and the higher-dose PEI group (p<0.04) among patients with HCC lesions 3.1–4 cm in size. Among patients with smaller HCC lesions (1–2 cm and 2.1–3 cm), no significant difference between treatment groups was seen.
RFA to PEI/ PAI: Lesion Size (Cancer-free Survival)	Insufficient	One RCT (n=187) found that the 3-year cancer-free survival of the RFA group was significantly higher than both PEI (p=0.031) and PAI (p=0.035) groups when lesions size was between 2 to 3 cm. This difference was not significant at smaller lesion sizes (1 to 2 cm) or earlier cancer-free survival times.
RFA to PEI/ PAI: Lesion Size (Local Recurrence Rate)	Insufficient	One RCT (n=187) found that local recurrence rate was lower in the RFA group compared with the PEI group (p=0.009) and PAI group (p=0.011) among the smaller HCC lesion subgroup, but not in the larger HCC lesion subgroup.

Table 91. Summary GRADE strength of evidence for KQ1 and KQ2 (continued)

Key Question	Strength of Evidence	Conclusion
RFA to PEI/ PAI: Multifocal HCC	Insufficient	One RCT (n=139) reported a nonsignificant difference in overall survival between the RFA and PEI groups among patients with multifocal HCC (hazard ratio=0.48; 95% CI, 0.16 to 1.43; p=0.19).

Abbreviations: ALT = alanine aminotransferase; BCLC= Barcelona Clinic Liver Cancer staging classification; CI= confidence interval; DEB = drug-eluting beads; HBV= hepatitis B virus; HCC= hepatocellular carcinoma; HCV= hepatitis C virus; LOS= length of stay; PAI = percutaneous acetic acid infusion; PEI = percutaneous ethanol infusion; RCT= randomized controlled trial; RFA = radiofrequency ablation; TAE = transarterial embolization; TACE = transarterial chemoembolization; TEA = transarterial ethanol ablation; TTP = time to progression.

Evaluation of comparative effectiveness requires an intervention and a comparator. Case-series do not use comparators. Therefore, comparative effectiveness cannot be assessed using this type of literature. Further, factors that may affect the effectiveness of the interventions within these populations were not controlled for in the included studies. Control may be achieved either though randomized design or statistically though careful adjustment in the analysis. Studies that aim to determine the effectiveness or comparative effectiveness of local treatment for unresectable HCC 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 through regression analysis.

Findings in Relationship to What Is Already Known

There is a large range of unique comparisons of various local hepatic therapies for HCC. We are not aware of any systematic review that has examined all comparisons. We identified seven previously published comparative systematic reviews, each examining a single comparison of local hepatic therapies. Two systematic reviews compared RFA to PEI,[98,99] three compared TACE-percutaneous ablation (PA; either RFA or PEI) to RFA or TACE monotherapy,[100-102] and one compared PEI to PAI.[103]

Consistent with our findings, the three systematic reviews [98,99,104]comparing the ablative therapies RFA and PEI found that RFA demonstrated a significantly better overall survival rate than PEI. These reviews included the three RCTs that met the inclusion criteria for our evidence review, in addition to one or more trials that were not included in this review due to differences in inclusion criteria. The review by Bouza et al.[98] included three additional trials in which the study intervention was given prior to the year 2000 or the patient sample included those who refused surgical treatment of HCC, both of which are included in our exclusion criteria. The reviews by Cho et al.[99] and Salhab et al.[104] included patients refusing surgery in one and two trials, respectively. The pooled patient population in these two systematic reviews was similar to the population for this comparison in our review, that is, early stage HCC patients with up to three nodules less than 3 or 4 cm in size.

The three systematic reviews of TACE-PA combination therapy [100-102] included studies of varying patient populations that were collectively broader than that included in our evidence review. For example, the reviews included studies in patients with more advanced disease or those with unclear Child-Pugh status, as well as studies in which the treatment was given prior to 2000. As such, these reviews included studies that reported comparisons not examined in our review (e.g., TACE-PEI vs. TACE). However, given the heterogeneity across studies and the paucity of high-quality comparative data from randomized clinical trials, the overall strength of evidence is insufficient to permit conclusions regarding these comparisons. Comparing RFA-

TACE combination therapy to RFA monotherapy in a meta-analysis, Yan et al.[102] reported that the combination therapy was associated with higher survival rates. However, the majority of included studies in that review were of low quality with small sample sizes, and, therefore, Yan et al. judged the overall strength of evidence as low, indicating uncertainties around the pooled estimate of effect. Wang et al.[100] conducted a meta-analysis of TACE-PEI combination therapy versus TACE monotherapy and found an improved overall survival with the combination therapy. The included trials in this review were of generally poor quality, with unclear baseline patient characteristics (e.g., Child-Pugh class and HCC lesion characteristics) and unclear or inadequate blinding and allocated concealment. As such, the authors of the review acknowledged the limited reliability of their conclusion. In another meta-analysis of TACE-PA combination therapy versus PA monotherapy,[101] the combination therapy was shown to improve overall survival compared with the monotherapy. However, in a sensitivity analysis of TACE-RFA versus RFA alone, the authors found that the survival benefit of the combination therapy was not robust, which is in agreement with the inconclusive evidence base identified in our review. This systematic review also included studies in which the treatment was given prior to 2000. The authors noted the limited availability of high-quality data in their pooled analysis; therefore, the findings of this review are limited as well.

A 2009 Cochrane Review[103] compared PEI and PAI, two similar ablative techniques with different chemotherapeutic agents for injection, and found no significant difference with regard to overall survival. This finding supports our approach of combining the PEI and PAI groups in our meta-analysis of the RFA versus PEI/PAI comparison.

The strength of the present review is that it addresses all local hepatic therapies for the included indications and includes comparisons not previously examined in published systematic reviews. Table 92 displays the corresponding comparisons between this review and the previously published reviews we identified. In addition, this report also recognizes that distinct patient groups exist within the population receiving local hepatic therapies. Specifically, we addressed a single patient population, those patients who are eligible for local hepatic therapy but are not otherwise eligible for resection or transplantation. Because we focused on a patient group rather than a specific intervention, we were able to present the outcomes for a wide range of local hepatic therapies for the target population.

Table 92. Comparisons made by current report and identified recent systematic reviews

Author, Year	RFA to PEI/PAI	DEB to TAE	DEB to TACE	RFA to TACE	TACE to TEA	TACE-RFA to RFA	TACE to TACE-Cryoablation	Other
Current Report	X	X	X	X	X	X	X	
Bouza et al. 2009[98]	X							
Cho et al. 2009[99]	X							
Salhab et al.[104]	X							
Yan et al. 2012[102]						X		
Wang et al. 2010[101]								TACE-PA vs. PA alone
Wang, 2011[100]								TACE-PEI vs. TACE alone
Schoppnmeyer, 2009[103]								PEI vs. PAI

Abbreviations: DEB = drug-eluting beads; PA = percutaneous ablation (either RFA or PEI); PAI = percutaneous acetic acid infusion; PEI = percutaneous ethanol infusion; RFA = radiofrequency ablation; TACE = transarterial chemoembolization; TAE = transarterial embolization; TEA = transarterial ethanol ablation.

Applicability

We comment below on the relevance of the included intervention studies (i.e., RCTs and nonrandomized comparative 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.[105]

Population and Settings

As specified by our inclusion criteria the study population had unresectable HCC with no extrahepatic spread, no portal invasion, Child-Pugh class A or B disease, ECOG status ≤1 and/or BCLA stage A or B, or equivalent. This patient population comprises the patient group typically considered eligible for the therapies discussed in this review.

We have no information on which we can assess the generalizability of these results of the studies included in our review. The setting in which treatment occurs is a potential factor in the outcomes of local hepatic therapy. Simple generalizability of included studies could not be easily made because expertise of both clinicians and centers varies. In many centers, the choice of a local hepatic therapy may be limited by the available clinical expertise and technology. Local hepatic therapies often require high levels of training and familiarity with the procedure, as with radioembolization.[106] Lack of experience may not only affect outcomes but also result in adverse effects; patients who are treated by less-experienced clinicians and centers will likely experience poorer outcomes.

The available studies offered insufficient details for us to assess operator-dependent factors or the representativeness of these settings compared with those of clinical practice. Detailed analysis of differences in outcomes by center has important implications for the relevance of the findings in the literature. Unfortunately, the published literature did not provide this information for our systematic review.

Interventions/Comparators

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 vs. percutaneous), or 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 variation in treatment strategies also limits the benefit attributable to any one component of the treatment plan.

Outcomes

Little controversy exists as to the most appropriate direct health outcomes to measure in a study of local hepatic therapies for unresectable HCC. Overall survival is the final health 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, but

they may agree that these are important intermediate health outcomes. Additional 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 followup assessment was appropriate given the natural history of unresectable HCC and the primary outcome of overall survival. Nearly all studies reported on duration of patient followup with durations typically lasting until median survival time was reached or beyond.

Implications for Clinical and Policy Decisionmaking

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

For the comparison of RFA to PEI/PAI, our conclusions suggest that for these patients treatment with RFA confers a survival benefit at 3 years compared with PEI/PAI. In addition, TTP and local recurrence may be improved in patients treated with RFA compared with PEI/PAI. Patients treated with RFA also seem to have longer LOS after treatment compared with those treated with PEI/PAI. Beyond this evidence on the comparative effectiveness of these procedures was insufficient. Subsequent comparisons had only one or no comparative studies on a given treatment comparison. For these comparisons, evidence was insufficient for all outcomes; thus, there is no comparative evidence base to support decisionmaking. In cases where comparative evidence existed, data were judged to be insufficient due to high risk of bias and/or imprecision of estimates.

Limitations of the Comparative Effectiveness Review Process

Determination of the scope of this review was derived from a lengthy process that began in topic development and continued to be refined even as the CER was underway. The topic was initially broader, encompassing other primary tumors metastasizing to the liver and HCC. During the scoping process, this review was narrowed to focus solely on unresectable HCC, and then further by excluding transplant eligible patients and those who were treated in an effort to downstage them for resection. Based on the refined scope, the literature search revealed an evidence base with limited comparative data. When examining the comparative efficacy of local hepatic therapies it is important to establish that patient groups are comparable. In general, patients treated with ablative therapies and those treated with transarterial strategies represent two distinct patient populations, and as a result, when considering comparisons for this review we compared only ablative therapies to one another, embolization therapies to one another, and external-beam therapies to one another. Combinations of therapies were presented together, but none utilized the same interventions and could not be synthesized. Nonetheless, the evaluation of the quality of the body of literature to assess our KQs and the identification of research needs is a valuable contribution to the field.

Limitations of the Evidence Base

Limitations of the present review are related largely to two factors: (1) the lack of comparative evidence and (2) clinical heterogeneity of patient populations across studies. With the exception of six RCTs, the vast majority of the evidence base included in this review derived from observational—mostly single-arm—studies. The clinical heterogeneity was most evident in the description of patient and tumor characteristics. For example, the size of lesions being treated with RFA ranged from 4 cm or smaller in the trial by Lin[51] to up to 10 cm in a study by Minami et al.[56] Often, studies failed to report on these patient and tumor characteristics, which potentially impact treatment-related outcomes. For example, only 17 out of 48 (35.4%) included studies reported both the number and size of lesions in the study patient population. Authors varied in how these tumor characteristics were described including: mean number and size of tumors, median number and size of tumors, range of number and size of tumors, percent solitary and nonsolitary tumor, interquartile range of size and number, or other categorizations. Full descriptions of the patient population is important, as those with—for example—higher ECOG score (i.e., worse functioning status), higher HCC stage, higher Child-Pugh class cirrhosis, or multinodular disease, generally experience poorer outcomes than those without. For this reason, it is ideal to stratify the studies by patient groups (e.g., BCLC stage A versus BCLC stage B) and to compare studies of equivalent patient populations. However, the poor patient characterization in the studies precluded stratification by patient groups as well as indirect comparison of interventions across studies. To maintain clinical relevance, comparisons were only made within category of intervention (e.g., ablative therapy vs. ablative therapy). This stratification is because patients with different disease characteristics are candidates for different treatments (e.g., patients with small accessible tumors are candidates for ablation whereas more extensive disease would undergo embolization therapy). Exceptions to this were two cross category comparisons of RFA and TACE and RFA versus TACE+RFA. The patient populations in these studies were patients eligible for ablative therapy. Chok and colleagues compared RFA to TACE in a patient population with tumor diameters less than 5cm with less than four nodules.[53] This cross-category comparison was included under the ablative therapies section because Chok et al. assessed the performance of TACE in these patients to determine if selection bias (caused by advanced disease and poor liver functional reserve) contributed to the perceived benefit of RFA compared to TACE.

The comparative data were limited even further in terms of important subgroups such as those based on age, sex, ECOG score, disease etiology, Child-Pugh class, presence of PVT, HCC stage, lesion size, and multifocal versus single-nodule HCC. Overall survival was examined by subgroup in three RCTs; however, none of these analyses were prespecified, thereby limiting their utility beyond hypothesis generation.

Given the limited number of patients and clinical heterogeneity, we did not systematically review the treatment-specific characteristics such as treatment regimens and techniques used. 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.

None of the studies included in this review used blinded outcome assessment. It can be a challenge to blind participants and outcome assessors in these studies due to the differences in treatment delivery and the appearance of the liver after treatment. This is a particular limitation for the assessment of intermediate outcomes such as progression and local recurrence.

In addition to the RCTs meeting our inclusion criteria, this review included four nonrandomized comparative studies. These studies did not use statistical adjustment to reduce

confounding; such adjustment for confounding should be consistently used in nonrandomized studies. Regardless of the study design, we suggest that studies examining the effectiveness or comparative effectiveness of local hepatic therapies 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 the lesions, Child-Pugh classification, and performance status, which could serve as both modifiers of the effectiveness and factors that are considered when choosing the best local hepatic therapy.

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

Research Gaps

This systematic review attempted to compare outcomes of local hepatic therapies for patients treated for unresectable HCC without evidence of extrahepatic spread who are not eligible for transplant. Evidence on patient outcomes is limited. There was a moderate strength of evidence to support that RFA improved 3-year overall survival compared with PEI/PAI. There was low strength of evidence to support higher TTP, less local recurrence, and a longer LOS for RFA compared with PEI/PAI. For all other comparisons and outcomes, strength of evidence was judged to be insufficient.

We identified four broad evidence gaps during this review:

- There is no evidence on quality of life. Quality-of-life outcomes are particularly important for a population of patients in which palliation is often the focus of therapy. For all comparisons, collection and reporting of quality-of-life data using standard measurement tools is needed.
- An objective of CER is to understand the comparative effects for different subgroups. RCTs should prespecify subgroup analyses to assess the effects of characteristics such as lesion size, Child-Pugh class, and ECOG score on treatment outcomes. The subgroups of interest must be delineated using systematic definitions of patient subgroups. Further, studies should present data by these subgroups so that evidence can be interpreted accordingly.
- Future studies should employ a standard or uniform set of outcome definitions (e.g., overall survival, local recurrence) as well as patient characteristics to report (e.g., BCLC stage, Child-Pugh class, lesion number and size). Such uniformity would allow for a more accurate and level comparison of patient populations across studies which the current evidence base precludes.
- During the Peer Review process of this CER, we received the following suggested comparisons for future research: (1) RFA versus other ablative therapies (e.g., MWA, cryoablation), (2) RFA versus TACE-RFA combination therapy, (3) RFA versus radiotherapies (e.g., SBRT), and (4) between transarterial therapies (e.g., TACE versus RE or TACE versus DEB). Such comparative evidence, based on well-designed randomized studies in the patient population included in this review, is needed.

Conclusions

This review included 13 local hepatic therapies and their combinations for unresectable HCC. There was a moderate strength of evidence demonstrating better overall survival at 3 years, a low level of evidence supporting improved overall survival for patients with larger lesion sizes, and a low strength of evidence for improved TTP and local control for RFA compared with PEI/PAI for the treatment of unresectable HCC. A low level of evidence also supports a longer LOS following RFA compared with PEI/PAI. For all other outcomes and comparisons, there is insufficient evidence to permit conclusions on the comparative effectiveness of local hepatic therapies for unresectable HCC. Important direct health outcomes of therapy include overall survival, adverse effects, and quality of life. Progression-free survival is an important intermediate health outcome, as progression often marks a change in therapy. Future RCTs comparing RFA with other ablative therapies and comparisons between transarterial therapies (e.g., TACE versus RE) are needed to close the existing gap in the comparative evidence.

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Appendix A. Search Strategy

We searched 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"
Limits: Humans, English

We searched 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"
Limits: Human, English and not MEDLINE.

Regulatory Information

FDA
Source: www.FDA.gov
Date searched: 5/24/2012
Search strategy: key word "TheraSphere," "SIR-Spheres," "EmboSphere," "QuadraSphere," " LC Bead," "CyberKnife," "Cool-tip RF ablation system," " cryoablation," "microwave ablation," "radiofrequency ablation"
Records: 33

Clinical Trial Registries

NIH database

Source: http://clinicaltrials.gov/
Date searched: 5/17/2012
Search strategy: hepatocellular carcinoma (Limits: Adult, senior, received from 01/01/2008 to 05/17/2012)
Records: 164

Controlled-Trials.com
Source: www.controlled-trials.com
Date searched: 5/24/2012
Search strategy: hepatocellular carcinoma
Records: 20

WHO database
Source: http://apps.who.int/trialsearch/
Date searched: 5/24/2012
Search strategy: hepatocellular carcinoma
Records: 37

Conference Papers and Abstracts

Specific conferences and association meetings
Source – number of results returned for search strategy:
Annual meeting of American Society of Clinical Oncology (ASCO) - 11
Annual meeting of American Society of Clinical Oncology Gastrointestinal (ASCO GI) - 83
Annual meeting of Surgery Society of Oncology (SSO) - 21
Annual meeting of Radiosurgical Society - 3
Date searched: 05/12/2012
Search strategy: KW: “hepatocellular”
Records: 118

Manufacturer Database

Source: Accuray Incorporated
Date posted: 5/14/2012
Date searched: 5/30/2012
Search strategy: Not applicable
Records:8

Source: Biocompatibles
Date posted: 5/30/2012
Date searched: 5/30/2012
Search strategy: Not applicable
Records: 108

Source: BioSphere
Date posted: 5/14/2012
Date searched: 5/30/2012
Search strategy: Not applicable

Records: 8

Source: Nordion
Date posted: 5/25/2012
Date searched: 6/7/2012
Search strategy: Not applicable
Records: 26

Appendix B. Contacted Authors

Appendix Table B-1. Contacted authors, issue and response

Study	Issue	Response
T. Kato, T. Yamagami, T. Hirota, T. Matsumoto, R. Yoshimatsu and T. Nishimura. Transpulmonary radiofrequency ablation for hepatocellular carcinoma under real-time computed tomography-fluoroscopic guidance. Hepatogastroenterology 2008 55(85): 1450-3. PMID: .	Need info on extrahep mets, PV invasion, ECOG, Stage, Child Pugh	JK: emailed 3/6 JK: sent followup 3/21 JK: reemailed 3/30, need response by 4/13 No response as of 4/17, excluded
P. Hildebrand, M. Kleemann, U. Roblick, L. Mirow, M. Birth and H. P. Bruch. Laparoscopic radiofrequency ablation of unresectable hepatic malignancies: indication, limitation and results. Hepatogastroenterology 2007 54(79): 2069-72. PMID: .	Individual patients listed in two tables. Table 1 has pt. charac. For 14 patients (needed since only 4 are HCC). Table 2 has outcomes for only 10 patients with no explanation on how they got rid of 4 patients or how those patients match to table 1.	JK: emailed 3/20 Team: if no response, exclude JK: reemailed 3/30, need response by 4/13 No response as of 4/17, excluded
K. C. Xu, L. Z. Niu, W. B. He, Z. Q. Guo, Y. Z. Hu and J. S. Zuo. Percutaneous cryoablation in combination with ethanol injection for unresectable hepatocellular carcinoma. World J Gastroenterol 2003 9(12): 2686-9. PMID	65 patients rec'd cryoablation, but only 36 rec'd PEI following cryoablation. Results not reported separately.	JK: emailed 3/20 Team: if no response, exclude JK: reemailed 3/30, need response by 4/13 Email bounced back 3/30 due to recipient mailbox full No response as of 4/17, excluded
H. C. Jiang, L. X. Liu, D. X. Piao, J. Xu, M. Zheng, A. L. Zhu, S. Y. Qi, W. H. Zhang and L. F. Wu. Clinical short-term results of radiofrequency ablation in liver cancers. World J Gastroenterol 2002 8(4): 624-30. PMID: .	Need HCC-specific results	JK: emailed 3/20 Emails bounced back, tried what I could find. So far, 'liulianxin@medmail.com.cn' hasn't bounced back. I think 'hongchaojiang@yahoo.com.cn' is probably not the same author - I found that on PubMed. JK: re-emailed 3/30, need response by 4/13 No response as of 4/17, exlude
A. Reso, C. G. Ball, F. R. Sutherland, O. Bathe and E. Dixon. Rupture and intra-peritoneal bleeding of a hepatocellular carcinoma after a transarterial chemoembolization procedure: a case report. Cases J 2009 2(1): 68. PMID: .	pt charac - PVT, extrahep mets, CP score, ECOG, BCLC or equivalent	JK: emailed 3/21 JK: reemailed 3/30, need response by 4/13 No response as of 4/17, include and note
N. Miyamoto, K. Tsuji, Y. Sakurai, H. Nishimori, J. H. Kang, S. Mitsui and H. Maguchi. Percutaneous radiofrequency ablation for unresectable large hepatic tumours during hepatic blood flow occlusion in four patients. Clin Radiol 2004 59(9): 812-8. PMID: .	In the paper, you stated that 1 patient was deemed inoperable because he/she refused hepatectomy. We would like to know which patient this is in the list of 4 patients in your paper.	YY: emailed 4/11 No response as of 4/17, exclude

Study	Issue	Response
G. S. Liao, C. Y. Yu, M. L. Shih, D. C. Chan, Y. C. Liu, J. C. Yu, T. W. Chen and C. B. Hsieh. Radiofrequency ablation after transarterial embolization as therapy for patients with unresectable hepatocellular carcinoma. Eur J Surg Oncol 2008 34(1): 61-6. PMID: .	Survival time point	JK: emailed 3/20 Emails bounced back. I tried without '.tw' and that also bounced back. Found the third email through more detective work - so far hasn't bounced back. JK: re-emailed 4/3 with 4/13 deadline No response as of 4/17
B. I. Carr. Hepatic arterial 90Yttrium glass microspheres (Therasphere) for unresectable hepatocellular carcinoma: interim safety and survival data on 65 patients. Liver Transpl 2004 10(2 Suppl 1): S107-10. PMID: .	Survival time point. Did PVT include PVTT?	JK: emailed 3/20 JK: re-emailed 4/3 with 4/13 deadline No response as of 4/17
R. C. Martin, 2nd, L. Rustein, D. P. Enguix, J. Palmero, V. Carvalheiro, J. Urbano, A. Valdata, I. Kralj, P. Bosnjakovic and C. Tatum. Hepatic arterial infusion of Doxorubicin-loaded microsphere for treatment of hepatocellular cancer: a multi-institutional registry. J Am Coll Surg 2011 213(4): 493-500. PMID: .	Survival time point	JK: emailed 3/20 JK: re-emailed 4/3 with 4/13 deadline No response as of 4/17
F. Gao, Y. K. Gu, W. J. Fan, L. Zhang and J. H. Huang. Evaluation of transarterial chemoembolization combined with percutaneous ethanol ablation for large hepatocellular carcinoma. World J Gastroenterol 2011 17(26): 3145-50. PMID:	Survival time point	JK: emailed 4/17 Response: Dear Jenna Khan, I have received your question about 'Evaluation of transarterial chemoembolization combined with percutaneous ethanol ablation for large hepatocellular carcinoma'. The survival time was counted from the first TACE treatment.Thank you for your question! Best wishes. Jinhua Huang
D. Oh, H. Lim do, H. C. Park, S. W. Paik, K. C. Koh, J. H. Lee, M. S. Choi, B. C. Yoo, H. K. Lim, W. J. Lee, H. Rhim, S. W. Shin and K. B. Park. Early three-dimensional conformal radiotherapy for patients with unresectable hepatocellular carcinoma after incomplete transcatheter arterial chemoembolization: a prospective evaluation of efficacy and toxicity. Am J Clin Oncol 2010 33(4): 370-5. PMID: .	discrepency between text and table on recurrence status	JK: emailed 3/28 JK: re-emailed 4/3 with 4/13 deadline Author response: Sorry for late reply. I didn't see your first e-mail. I review my data and the number of newly diagnosed HCC was 22 (55%). Thank you. Sincerely yours, Do Hoon Lim

Study	Issue	Response
K. Yamanaka, E. Hatano, M. Narita, K. Taura, K. Yasuchika, T. Nitta, S. Arizono, H. Isoda, T. Shibata, I. Ikai, T. Sato and S. Uemoto. Comparative study of cisplatin and epirubicin in transcatheter arterial chemoembolization for hepatocellular carcinoma. Hepatol Res 2011 41(4): 303-9. PMID: .	21% in group 1 and 19% in group 2 were also getting RFA or PEIT with TACE, results not separated out.	JK: Emailed 3/21 if no response, exclude JK: reemailed 3/30, need response by 4/13 Response: However, we added a new result in accordance to your suggestion that RFA and PEIT were excluded in this study. RRs of patients with a single tumor were 75.0% (9/12) and 65.3% (21/32) for CDDP-TACE and EPI-TACE and RRs of patients with multiple tumors were 71.4% (10/14) and 37.0% (17/46) for CDDP-TACE and EPI-TACE. For the patients with multiple tumors, the relative risk and the odds ratio were 1.93 (95%CI 1.17-3.19) and 4.53 (95%CI 1.22-16.8). This was consistent with the result that included the patients receiving the simultaneous treatment of RFA and PEIT. We added the following sentences. (P. 10) Of these, we included RFA or PEIT combined with TACE in the eligibility criteria because either of the two treatment options can be exercised after TACE. However, since this factor would affect the RR, we also estimated the RR in patients without RFA or PEIT combined with TACE. (P. 14) When patients receiving RFA or PEIT combined with TACE were excluded, RRs of patients with a single tumor were 75.0% (9/12) and 65.3% (21/32) and those of patients with multiple tumors were 71.4% (10/14) and 37.0% (17/46) for CDDP-TACE and EPI-TACE, respectively. For patients with multiple tumors, the relative risk and the odds ratio were 1.93 (95% CI 1.17-3.19) and 4.53 (95% CI 1.22-16.8), respectively. CDDP-TACE also showed a higher RR than EPI-TACE in this analysis. Etsuro Hatano JK+YY: Exclude

Study	Issue	Response
T. H. Kim, D. Y. Kim, J. W. Park, Y. I. Kim, S. H. Kim, H. S. Park, W. J. Lee, S. J. Park, E. K. Hong and C. M. Kim. Three-dimensional conformal radiotherapy of unresectable hepatocellular carcinoma patients for whom transcatheter arterial chemoembolization was ineffective or unsuitable. Am J Clin Oncol 2006 29(6): 568-75. PMID: .	58.6% had PVT, might be using PVT to describe tumor and bland thrombus, 75.7% AJCC stage T3, which can include invasion, 5.7% T4 which is invasion	JK: emailed 3/20 JK: reemailed 3/30, need response by 4/13 Author Response: In my previous paper, 58.5% was percentage of HCC patients with portal vein tumor thrombosis. Unfortunately, I did not have statistics regarding to incidence of blend thrombosis because the blend thrombosis is not target of radiotherapy. Usually, portal vein tumor thrombosis is enhanced in dynamic CT, typically enhanced in arterial phase and wash out in portal or delayed phase, but blend thrombosis is not enhanced in dynamic CT. Blend thrombosis and tumor thrombosis is different in imaging study and thus, I only count the portal vein tumor thrombosis not blend thrombosis. Anyway, small percent of HCC patients with or without portal vein tumor thrombosis may has blend thrombosis. Best Wishes, Tae Hyun Kim JK: Exclude on study pop

Study	Issue	Response
H. W. Chen, E. C. Lai, Z. J. Zhen, W. Z. Cui, S. Liao and W. Y. Lau. Ultrasound-guided percutaneous cryotherapy of hepatocellular carcinoma. Int J Surg 2011 9(2): 188-91. PMID: .	The two groups of patients include 'unresectable HCC' and 'recurrent HCC'. Just to confirm, the 'recurrent HCC' group has unresectable recurrent HCC, correct? Also, table 1 lists statistics on 'Liver function status at time of partial hepatectomy' for both the unresectable HCC and Recurrent HCC groups. Did the unresectable HCC group also have previous partial hepatectomy? Or is that their liver function status at the time of enrollment whereas the recurrent HCC group has reported status at the time of partial hepatectomy? The two patient groups (unresectable and reccurrent unresectable) have outcomes reported separately. Do they have combined survival stats or even stats comparing the two groups?	JK: emailed 2/1 Dr. Lau responded 2/8: For the 2 questions which you raised in your email to us, the replies are: (1) The two groups of patients included in our study are patients with unresectable HCC, and patients with recurrent HCC. The recurrent HCC group had patients with unresectable recurrent HCC; (2) For both groups of patients, the liver function status indicated was at the time of enrollment of the patients into the study. I hope I have answered what you asked. If there is any query, please do not hesitate to write to us again. With best wishes, W.Y. Lau JK: emailed about combined stats 2/8 JK: sent follow up email 3/21 Author 3/23: Dear Jenna Khan, The survival curves of two different groups were shown in the paper. We have not compared the difference of both groups. Best regards, W.Y. Lau Team: Leave as is in two separate treatment group rows.
R. A. Lencioni, H. P. Allgaier, D. Cioni, M. Olschewski, P. Deibert, L. Crocetti, H. Frings, J. Laubenberger, I. Zuber, H. E. Blum and C. Bartolozzi. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. Radiology 2003 228(1): 235-40. PMID: .	Treatment dates	JK: emailed 2/28

Study	Issue	Response
R. A. Lencioni, H. P. Allgaier, D. Cioni, M. Olschewski, P. Deibert, L. Crocetti, H. Frings, J. Laubenberger, I. Zuber, H. E. Blum and C. Bartolozzi. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. Radiology 2003 228(1): 235-40. PMID: .	YY: The question is what is the date range (month/year – month/year) of the study in which you report the mean follow-up period of 22.9 months in the RF group and 22.4 months in the PEI group? I am particularly interested in whether or not the actual treatment (RF or PEI) was given after year 2000.	YY: emailed 2/27 ***YY: If no response from author, we may be able to exclude on date. Paper was published in 2003 and follow-up was as long as 36 months, so some patients were likely treated before 2003 EXCLUDED based on date it was received by the journal (6/2002) and followup time (mean 22months)
S. M. Lin, C. J. Lin, C. C. Lin, C. W. Hsu and Y. C. Chen. Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma < or =4 cm. Gastroenterology 2004 127(6): 1714-23. PMID: .	Unresectable? Same patient pop as ref 8?	JK: emailed 2/28 about resectable status and if the same patient population (2005 pub had a few more than 2004 pub) JK: email bounced back 3/4
S. M. Lin, C. J. Lin, C. C. Lin, C. W. Hsu and Y. C. Chen. Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. Gut 2005 54(8): 1151-6. PMID: .	Unresectable?	JK: emailed 2/28 about resectable status and if the same patient population (2005 pub had a few more than 2004 pub) Team: We will abstract both since they have a different set of comparators, slightly different # of patients and use different criteria (<3 cm and <=4cm lesions). A note will be made that these may have some of the same pt. population.
T. J. Vogl, N. E. Nour-Eldin, S. Emad-Eldin, N. N. Naguib, J. Trojan, H. Ackermann and O. Abdelaziz. Portal vein thrombosis and arterioportal shunts: effects on tumor response after chemoembolization of hepatocellular carcinoma. World J Gastroenterol 2011 17(10): 1267-75. PMID: .	YY: In the inclusion criteria, the authors stated "tumors of any size associated with PVT, either partial thrombosis of the main portal vein or segmental portal vein branch thrombosis." The question is, does this imply that patients with portal vein tumor thrombus (PVTT), meaning PVT due to tumor invasion, were included in the study? If yes, what % of the entire sample consisted of patients with PVTT?	YY: emailed 2/17 YY: emailed again 3/16. If no response, will send to Veena. Author response 3/20: Dear Dr Yoojung Yang Thanks for your inquiry and sorry for delay in your answer as the email was unintentionally reported as spam email. The sample of the study included all cases with PVT whether due to to tumor invasion or not. We did not subclassify the results into PVT and PVTT. My best regards Dr. med. Nour-Eldin A. Nour-Eldin Mohammed YY+SB: Since 48.7% reported as having PVT and that does include PVTT, Exclude

Study	Issue	Response
B. Caspani, A. M. Ierardi, F. Motta, P. Cecconi, E. Fesce and L. Belli. Small nodular hepatocellular carcinoma treated by laser thermal ablation in high risk locations: preliminary results. Eur Radiol 2010 20(9): 2286-92. PMID: .	States in results that 7 of 32 successfully treated lesions had local recurrence, but in discussion section says 7 of 32 patients. There were 52 lesions among 49 total patients, so emailed to verify that it was 7 of 32 patients.	JK: emailed 3/28 Response 3/28: 7 of the 32 patients. Regards AMI
F. Laspas, E. Sotiropoulou, S. Mylona, A. Manataki, P. Tsagouli, I. Tsangaridou and L. Thanos. Computed tomography-guided radiofrequency ablation of hepatocellular carcinoma: treatment efficacy and complications. J Gastrointestin Liver Dis 2009 18(3): 323-8. PMID: .	patient pop - CP scores, ECOG, BCLC or equiv??	JK: emailed 2/28 JK: sent follow up email 3/21 Team: if no answer then exclude Response: Dear Jenna Khan, I apologize for the delay in my response to you, but I am too busy this period. Unfortunately, I could not find the requested information about the study population. Regards, F. Laspas, MD, MSc Exclude
L. Zhou, Y. P. Yang, Y. Y. Feng, Y. Y. Lu, C. P. Wang, X. Z. Wang, L. J. An, X. Zhang and F. S. Wang. Efficacy of argon-helium cryosurgical ablation on primary hepatocellular carcinoma: a pilot clinical study. Ai Zheng 2009 28(1): 45-8. PMID: .	YY: I am writing with a clarifying question on your 2009 publication entitled, “Efficacy of argon-helium cryosurgical ablation on primary hepatocellular carcinoma: a pilot clinical study.” Your study staged HCC patients based on BCLC as “early,” “middle,” and “advanced.” Do these correspond to A, B, and C? Please kindly confirm.	YY: emailed 2/17 Author: I am so happy to receive your letter. Thanks a lots. You are very interest on our work. In my manuscript entitled “ Efficacy of argon-helium cryosurgical ablation on primary hepatocellular carcinoma: a pilot clinical study”, our patients with HCC staged based on Barcelona Clinic Liver Cancer staging, “early” is correspond to stage A, “middle” as stage B and “ advanced” as stage C. In the near future, my some work was publiction. Please download from attachments. I hope you give me some directions. Best wishes and good Luck. Regards, Yongping Yang
L. M. Kulik, B. I. Carr, M. F. Mulcahy, R. J. Lewandowski, B. Atassi, R. K. Ryu, K. T. Sato, A. Benson, 3rd, A. A. Nemcek, Jr., V. L. Gates, M. Abecassis, R. A. Omary and R. Salem. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. Hepatology 2008 47(1): 71-81. PMID: .	Treatment dates	JK: emailed 2/8 JK: emailed 2/28 again Response from Author 2/29: 2002 to 2004

Study	Issue	Response
R. Miraglia, G. Pietrosi, L. Maruzzelli, I. Petridis, S. Caruso, G. Marrone, G. Mamone, G. Vizzini, A. Luca and B. Gridelli. Predictive factors of tumor response to trans-catheter treatment in cirrhotic patients with hepatocellular carcinoma: a multivariate analysis of pre-treatment findings. World J Gastroenterol 2007 13(45): 6022-6. PMID: .	Treatment dates and survival time point Treatments were TOCE, TACE or TAE. Pt. characteristics and survival reported combined. We need separate stats for the 3 different treatments.	JK: emailed 2/8 Response on 2/8: will be able to address my questions after 2/15, JK will email when back on 2/21 Author response 2/10: Ciao Jenna One of mine co-authors sent me the data you asked me. - the study period is from 1/2000 to 12/2003 - survival was calculated considering the data of the first treatmet. Let me know if you need some other data. Ciao da palermo! Roberto JK: emailed 3/20 to see if we could get TACE, TOCE and TAE results reported separately Response 3/23: Dear Jenna unfortunately it is impossible to give you separate patient survival statistics for TOCE, TACE and TAE. this because in the protocol we use to treat HCC patients the type of treatment is tailored in the basis of the clinical condition of the patient the day of the procedure. so the same patient can be treated with TOCE and the next time only with TAE if bilirubin worsened a little bit for example. The protocol used should be explained in the paper. so it is impossible to give you separate survival according to different treatments, we can just considered the cumulative survival for the protocol used. sorry Roberto Team: Exclude

Study	Issue	Response
R. Miraglia, G. Pietrosi, L. Maruzzelli, I. Petridis, S. Caruso, G. Marrone, G. Mamone, G. Vizzini, A. Luca and B. Gridelli. Predictive factors of tumor response to trans-catheter treatment in cirrhotic patients with hepatocellular carcinoma: a multivariate analysis of pre-treatment findings. World J Gastroenterol 2007 13(45): 6022-6. PMID: .	YY: 1. In Table 1, you report the BCLC stages as follows: BCLC stage (1/2/3/4) 61/115/14/0. Do stages 1, 2, 3, and 4 correspond to BCLC stages A (early), B (intermediate), C (advanced), and D (terminal)? Also, since these numbers do not add up to the entire sample of 200 patients (61+115+14+0=190), I am wondering if this was simply a type error or if the remaining 10 patients were staged BCLC 0 (very early stage). 2. You stated that patients were evaluated for pre-treatment portal vein invasion (lobar, segmental, or subsegmental) per CT imaging. How many patients (n, %) in the sample actually had portal vein invasion?	YY: emailed 2/23 Author: Thanks for your interest in our paper. - BCLC stages 1,2,3,4 correspond to A,B,C,D. - BCLC A are 71 patients and not 61, sorry this was type error. - 15 patients had partial non-tumoral portal vein thrombosis (no enhancement in the thrombus in arterial phase). No patient had macroscopic neoplastic portal vein invasion at the time of diagnosis. Thanks again and let me know if you need more information. Kind regards Roberto Miraglia Author: 1/2000 - 12/2003 is the period considered. Before (we started in 6/1999) we used a different protocol so for this reason we excluded those patients from the analisis. Ciao Roberto
F. S. Chan, K. K. Ng, R. T. Poon, J. Yuen, W. K. Tso and S. T. Fan. Duodenopleural fistula formation after percutaneous radiofrequency ablation for recurrent hepatocellular carcinoma. Asian J Surg 2007 30(4): 278-82. PMID: .	Treatment date Other patient characterisitics: ECOG, stage, Child Pugh	JK: emailed 3/7 - bounced back, tried twice, could not find an alternate email Team: Exclude

Study	Issue	Response
W. Lu, Y. H. Li, Z. J. Yu, X. F. He, Y. Chen, J. B. Zhao and Z. Y. Zhu. A comparative study of damage to liver function after TACE with use of low-dose versus conventional-dose of anticancer drugs in hepatocellular carcinoma. Hepatogastroenterology 2007 54(77): 1499-502. PMID: .	YY: In the paper, you stated there were total 112 patients who were randomized to low-dose group (n=52) and conventional dose (n=60). However, in Table 1, the group sizes are reported as 40 and 42, respectively. Is this an error? Also, does "PV involvement" refer to portal vein invasion? Please kindly explain the statistics reported here: 48/4 for low dose and 55/5 for conventional dose.	YY: emailed 2/23 Author: Dear Dr.Yang: I am very sorry for the misprinting mistakes in my manuscipt. The total number in our groups is 112 cases. There are 52 cases in group A and 60 in group B. "PV involvement" refer to portal vein trunk or main branch invasion, not including small PV branch invasion. 48/4 refer to no PV invasion in 48 cases and PV invasion in 4 cases. Thank you for you kindly attention to my manuscript YY: 3/5 Per the author's response, there were <10% of pts in each arm with portal vein trunk or main branch invasion, not including small PV branch invasion. Our protocol does not define portal vein invasion in such detail (i.e., location of the pv) – so the question is do we exclude this paper given that there may be >10% of pts with any type of portal vein invasion --- OR do we keep it since we do not have the #s for small PV branch invasion? I've emailed the author again with the question about #s of small pv branch invasion. Hopefully he has those numbers, but if not, we may have to exclude the paper given the uncertainties. Team: if no response, send email to Veena YY: follow-up email 3/20 Author response 3/20: Dr. Yang : Thank you very much for your interesting on my paper. I remember that about 8% of the patient had small PV branch invasion in each arm. Thanks . Wei lu YY: Refid 536 author response below. If we add the 8% of small pv branch invasion to the % portal vein trunk or main branch invasion (reported in the paper), the overall PV invasion exceeds 10% in each arm, which would exclude this paper.

Study	Issue	Response
A. Kumar, D. N. Srivastava, T. T. Chau, H. D. Long, C. Bal, P. Chandra, T. Chien le, N. V. Hoa, S. Thulkar, S. Sharma, H. Tam le, T. Q. Xuan, N. X. Canh, G. S. Pant and G. P. Bandopadhyaya. Inoperable hepatocellular carcinoma: transarterial 188Re HDD-labeled iodized oil for treatment--prospective multicenter clinical trial. Radiology 2007 243(2): 509-19. PMID: .	Survival time point	JK: emailed 3/7 Excluded - 38% had PVTT Email bounced back 3/7
I. R. Kamel, D. K. Reyes, E. Liapi, D. A. Bluemke and J. F. Geschwind. Functional MR imaging assessment of tumor response after 90Y microsphere treatment in patients with unresectable hepatocellular carcinoma. J Vasc Interv Radiol 2007 18(1 Pt 1): 49-56. PMID: .	Paper states they allowed extrahepatic mets, PVT and portal invasion, but they only report PVT for pt. dem. In the results. Emailed author about extrahep mets and portal invasion.	JK: emailed 3/9 Author response: I do not recall but portal vein thrombosis is indicative of vascular invasion, and considered by some as proof of extrahepatic disease. Hope this helps. JK: excluded based on study population
K. S. Chok, K. K. Ng, R. T. Poon, C. M. Lam, J. Yuen, W. K. Tso and S. T. Fan. Comparable survival in patients with unresectable hepatocellular carcinoma treated by radiofrequency ablation or transarterial chemoembolization. Arch Surg 2006 141(12): 1231-6. PMID: .	Survival time point	JK: emailed 3/20 Response 3/21: Hi Mr Khan, Thank you for your question. Survival time measurement from the time of treatment. Thank you! Dr Chok
C. S. Georgiades, K. Hong, M. D'Angelo and J. F. Geschwind. Safety and efficacy of transarterial chemoembolization in patients with unresectable hepatocellular carcinoma and portal vein thrombosis. J Vasc Interv Radiol 2005 16(12): 1653-9. PMID: .	Need % with PVTT since it seems they are using PVT to include PVTT and bland thrombus	JK: emailed 3/20 Response 3/20: Sorry but this is so long ago I can't remember but yes it was probably more than 10%. J.F. Geschwind, MD Exclude on patient population
J. L. Raoul, E. Boucher, D. Olivie, A. Guillygomarc'h, K. Boudjema and E. Garin. Association of cisplatin and intra-arterial injection of 131I-lipiodol in treatment of hepatocellular carcinoma: results of phase II trial. Int J Radiat Oncol Biol Phys 2006 64(3): 745-50. PMID: .	Treatment period? Survival time point?	JK: emailed 3/20 - first email bounced back, found alternate Response 3/20: Sorry, I do not remember exactly the period but it was around 2001 -02 Survival time: tà = day of signature of informed consent meaning 2 – 4 weeks before the first injection Best regards Jean-Luc Raoul

Study	Issue	Response
D. A. Bush, D. J. Hillebrand, J. M. Slater and J. D. Slater. High-dose proton beam radiotherapy of hepatocellular carcinoma: preliminary results of a phase II trial. Gastroenterology 2004 127(5 Suppl 1): S189-93. PMID: .	PV invasion?	YY: emailed 2/17 Author: Patients in our study did not have portal vein invasion. I've attached our most recent publication. I included two references from Japan describing good results with proton beam in patients with vascular invasion. D Bush YY: His 2011 paper (update on refid 718 published in 2004) is not in Distiller --- probably didn't get picked up during initial search. BUT we'd exclude it based on the treatment dates between April 1998 and October 2006. The 2004 paper doesn't specify the treatment dates --- do we exclude it assuming the same tx dates given that the earlier report was preliminary results of the same phase II study? Interestingly, the 2004 report has n=34 and 2011 has n=76. The two other attachments (both Japanese studies) do not meet our inclusion criteria as pts exhibited PVTT (also pre-2000 tx dates). YY: Excluded
J. Hansler, M. Frieser, S. Schaber, C. Kutschall, T. Bernatik, W. Muller, D. Becker, E. G. Hahn and D. Strobel. Radiofrequency ablation of hepatocellular carcinoma with a saline solution perfusion device: a pilot study. J Vasc Interv Radiol 2003 14(5): 575-80. PMID: .	Treatment dates	JK: emailed 2/8 - bounced back, tried several times, can't find alternate email JK: followup ranges to 2.9 years and paper received by journal in 2002. Exclude on date.
R. Sacco, I. Bargellini, M. Bertini, E. Bozzi, A. Romano, P. Petruzzi, E. Tumino, B. Ginanni, G. Federici, R. Cioni, S. Metrangolo, M. Bertoni, G. Bresci, G. Parisi, E. Altomare, A. Capria and C. Bartolozzi. Conventional versus Doxorubicin-eluting Bead Transarterial Chemoembolization for Hepatocellular Carcinoma. J Vasc Interv Radiol 2011 (): . PMID: .	Survival time point	JK: emailed 3/20 Response 3/20: time point for survival was the time of treatment (C or DEB TACE) Best regards Rodolfo Sacco, MD, Ph.D.

Study	Issue	Response
I. Bargellini, R. Sacco, E. Bozzi, M. Bertini, B. Ginanni, A. Romano, A. Cicorelli, E. Tumino, G. Federici, R. Cioni, S. Metrangolo, M. Bertoni, G. Bresci, G. Parisi, E. Altomare, A. Capria and C. Bartolozzi. Transarterial chemoembolization in very early and early-stage hepatocellular carcinoma patients excluded from curative treatment: A prospective cohort study. Eur J Radiol 2011 (): PMID: .	YY: Your study included HCC patients in BCLC stage 0 and A "who could not be offered surgical or ablative treatments and underwent TACE." Was the distinction between stage 0 and A purely the tumor size and number – i.e., stage 0 defined as single nodule <2cm and stage A defined as single nodule <5cm or up to 3 nodules ≤3cm? JK: Survival time point	YY: emailed 2/17 Author: Dear dr yang, the distinction between Bclc 0 and A was based on lesion size. thank you for your interest in our paper Best regards Irene Bargellini JK: emailed about survival definition 3/21 Author 3/23: in the paper survival was calculated from study treatment. Feel free to contact me for any need. Best regards, Irene Bargellini
R. G. Gish, S. C. Gordon, D. Nelson, V. Rustgi and I. Rios. A randomized controlled trial of thymalfasin plus transarterial chemoembolization for unresectable hepatocellular carcinoma. Hepatol Int 2009 (): . PMID: .	treatment period	JK: emailed 3/21, Re-emailed 3/27 GishR@sutterhealth.org, bounced back so I emailed all authors since their emails were available Response 3/26: The study period was 2004-2006. Thanks. Israel Rios, MD
F. Sundram, T. C. M. Chau, P. Onkhuudai, P. Bernal and A. K. Padhy. Preliminary results of transarterial rhenium-188 HDD lipiodol in the treatment of inoperable primary hepatocellular carcinoma. European Journal of Nuclear Medicine and Molecular Imaging 2004 31(2): 250-257. PMID:	Treatment dates, PVT?	JK: emailed 2/28, bounced back and can't find alternate email address JK: Excluded - same as 737, so 737 was kept

Appendix C. DistillerSR Screening and Abstraction Forms

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

Abstract Screening
Is the article published in English?
Does the article report primary data?
Are the participants in the article human?
Is primary hepatocellular carcinoma the primary focus of the article?

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

STUDY DESCRIPTION
First Author (Last name):
Year of Publication:
Study design:
What key question(s) does this article address?
Descriptors of Treatment (e.g., drug(s) used, route, etc)
Enrollment Start Date (mm/yyyy)
Enrollment End Date (mm/yyyy)
Number in Group
Outcomes
Setting
Patient population with HCC (%)
Previous Treatment
Previous resection: % yes
Previous systemic chemotherapy: % yes
Previous liver-directed therapy: Therapy: %, Therapy2: ...
Previous LDT: select all that apply
DIAGNOSIS
Adenocarcinoma
Mucinous
Synchronous
Mean Liver

Median Liver
Min Liver
Max Liver
Mean N Hepatic
Median N Hepatic
Min N Hepatic
Max N Hepatic
Other Liver Involvement: Name: %, Name2: ...
AFP mean
AFP median
AFP SD, range or 95% CI
AFP unit
AFP other
PATHOLOGY
Mean Size of Hepatic (cm) Lesion(s)
Median Size of Hepatic (cm) Lesion(s)
Min Size of Hepatic Lesion(s)
Max Size of Hepatic Lesion(s)
% Unilobar Hepatic Lesion(s)
% Bilobar Hepatic Lesion(s)
Other noted lesion characteristics

PATIENT CHARACTERISITCS:
Sex (% Male)
Mean Age
Median Age
Min Age
Max Age
RACE: White (%)
RACE: Black (%)
RACE: Asian (%)
RACE: Hispanic (%)
BCLC Stage (A, B)
Okuda Stage (I, II)
Other staging system: (stage (%))
Etiology of HCC: HBV %
Etiology of HCC: HCV %
Etiology of HCC NAFLD %
Etiology of HCC Alcohol %
Recurrent HCC %
Portal Vein Thrombosis %
Child-pugh score: Mean
Child-pugh score: Median
Child-pugh score: Min
Child-pugh score: Max
Child-pugh class (A, B, or C)

ECOG Performance Score: Mean
ECOG Performance Score: Median
ECOG Performance Score: Min
ECOG Performance Score: Max
Karnofsky Score: Mean
Karnofsky Score: Median
Karnofsky score: Min
Karnofsky Score: Max
ABSTRACTOR COMMENTS: If you would like to leave a comment pertaining to the information above indicate your name below:

Outcomes Form

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

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

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

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

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

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

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

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

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

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

Study Quality
Comparative Studies Quality Assessment (USPSTF)
Initial assembly of comparable groups
Maintenance of comparable groups (includes attrition, crossovers,

adherence, and contamination)
Avoidance of important differential loss to followup or overall high loss to followup.
Measurements reliable, valid, equal (includes masking of outcome assessment)
Interventions comparable/ clearly defined
All important outcomes considered
Appropriate analysis of results (adjustment for potential confounders and intention-to-treat analysis)
Funding/ sponsorship source acknowledged
Overall Rating

Non-Randomized Comparative-Deeks and colleagues

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

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

Appendix D. Evidence Tables

Appendix Table D-1. Study quality ratings: RCTs and non-randomized comparative studies

Study	Study Design	Assembled comparable groups	Maintained comparable groups	Minimal follow up loss	Measurements equal, valid and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Funding acknowledged	Overall rating
Sacco 2011	RCT	Yes*****	Yes	Yes	No*	Yes	Yes	Yes	No	Fair
Malagari 2010	RCT	Yes	Yes	Yes	No*	Yes	Yes	No**	No	Poor
Morimoto 2010	RCT	Yes	Yes	No	No*	Yes	Yes	Yes	Yes	Poor
Brunello 2008	RCT	Yes	Yes	Yes	No****	Yes	Yes	Yes	Yes	Good
Lin 2005	RCT	Yes	Yes	Yes	No*	Yes	Yes	Yes	No	Fair
Lin 2004	RCT	Yes	Yes	Yes	No*	Yes	Yes	Yes	No	Fair
Recchia 2012	NRC	Yes	Yes	No******	No	No	Yes	Yes	No	Poor
Xu 2009	NRC	No	No	Yes	No*	Yes	Yes	Yes	No	Poor
Chok 2006	NRC	Yes	Yes	No******	No*	Yes	Yes	Yes	Yes	Poor
Yu 2009	NRC	Yes	Yes	Yes	No*	Yes	Yes	Yes	No	Poor

*This response reflects that the authors did not describe blinding to outcome(s) of interest.
**This response reflects that the study did not analyze results according to intent-to-treat analysis.
***This response reflects that the study did not report overall survival.
****Outcomes could not be blinded due to different radiological signs produced by the two intervention techniques.
*****Randomization was done in an open fashion but known confounders between groups appear comparable.
******Authors did not discuss follow up loss.
Abbreviations: RCT: Randomized controlled trial; NRC: Non-randomized comparative study

Appendix Table D-2. Study quality ratings: case series studies

Study	Study Design	Clearly Defined Question	Well-described study population	Well-described intervention	Use of Validated Outcome Measures	Appropriate Statistical Analysis	Well-Described Results	Discussion/ Conclusions Supported by Data	Overall Rating
Andolino 2011	Retrospective case series	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Bargellini 2011	Prospective case series	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Buijs 2008	Retrospective case series	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Carr 2004	Prospective case series	Yes	Yes	Yes	Yes	Yes	No	Yes	Fair
Carr 2010	Prospective cohort*	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Chan 2011	Retrospective case series	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Chen 2011	Retrospective case series	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Gao 2011	Retrospective case series	Yes	Yes	Yes	Yes	Yes	No	Yes	Fair
Giannini 2010	Retrospective cohort*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Guiu 2009	Retrospective case series	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Imai 2011	Retrospective case series	Yes	No	Yes	Yes	Yes	No	Yes	Poor
Itoh 2011	Prospective case series	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Kanhere 2008	Prospective case series	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Kawaoka 2009	Retrospective case series	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Leelawat 2008	Prospective cohort*	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Lencioni 2008	Prospective case series	Yes	No	Yes	Yes	Yes	No	Yes	Poor
Liao 2008	Prospective case series	Yes	No	No	Yes	Yes	Yes	Yes	Poor
Liu 2004	Retrospective case series	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good

Study	Study Design	Clearly Defined Question	Well-described study population	Well-described intervention	Use of Validated Outcome Measures	Appropriate Statistical Analysis	Well-Described Results	Discussion/ Conclusions Supported by Data	Overall Rating
Mabed 2009	RCT*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Maeda 2008	Retrospective case series	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Martin 2011	Prospective case series	Yes	Yes	Yes	Yes	Yes	No	Yes	Fair
Minami 2007	Prospective case series	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Molinari 2006	Prospective case series	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Oh 2010	Prospective case series	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Pietrosi 2009	Case series (uncertain if prospective or retrospective)	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Rand 2005	Retrospective case series	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Seki 2011	Retrospective case series	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Seo 2010	Retrospective case series	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Shen 2005	Prospective cohort*	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Taguchi 2007	Retrospective case series	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Tanaka 2009	Case series (uncertain if prospective or retrospective)	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair
Wu 2010	Retrospective cohort*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Zhang 2011	Prospective case series	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Zhao 2012	Retrospective case series	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair

Study	Study Design	Clearly Defined Question	Well-described study population	Well-described intervention	Use of Validated Outcome Measures	Appropriate Statistical Analysis	Well-Described Results	Discussion/ Conclusions Supported by Data	Overall Rating
Zhou 2009	Retrospective case series	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good

*Comparative studies from which only a single comparator arm meeting inclusion criteria in this evidence review

Appendix E. Abbreviations and Acronyms

Acronym	Definition
3D-CRT	Three dimensional conformal radiotherapy
AES	Adverse events
AHRQ	Agency for Healthcare Research and Quality
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
AST	Aspartate transaminase
BCLC	Barcelona Clinic Liver Cancer
CAT	Computed axial tomography
CER	Comparative effectiveness review
CLIP	Cancer of the Liver Italian Program
CRT	Conformal Radiation Therapy
CT	Computed tomography
CP	Child-tucotte-Pugh
CUPI	Chinese University Prognostic Index
DEB	Drug-eluting Beads
ECOG	Eastern Cooperative Oncology Group
EPC	Evidence-based Practice Center
GETCH	Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAI	Hepatic arterial infusion
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C Virus
HDR	High-dose rate
IMRT	Intensity Modulated Radiation Therapy
INR	International normalized ratio
IQR	Inter-quartile range
JIS	Japan Integrated Staging
LDR	Low-dose rate
LDT	Liver directed therapy
LOS	Length of stay
MAA	^{99m}Tc-macro-aggregated albumin
MELD	Model for End-Stage Liver Disease
MRI	Magnetic resonance imaging
MWA	Microwave ablation
NAFLD	Non-alcoholic fatty liver disease
NCCN	National Comprehensive Cancer Network
NIH	National Institutes of Health
PAI	Percutaneous alcohol injection
PDR	Pulsed-dose rate
PEA	Percutaneous ethanol ablation
PEI	Percutaneous ethanol infusion
PFS	Progression-free survival
PICOTS	population, intervention, comparator, outcomes, timing, and setting
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PVT	Portal vein thrombosis
QOL	Quality of life
RCT	Randomized controlled trial
RFA	Radiofrequency ablation
RFTA	Radiofrequency thermal ablation
RTRT	Real-time target tracking

Acronym	Definition
SBRT	Stereotactic body radiation therapy
SCHIP	State Children's Health Insurance Program
SOE	Strength of evidence
SRC	Scientific Resource Center
TACE	Transarterial chemoembolization
TAE	Transarterial embolization
TEA	Transarterial ethanol ablation
TEP	Technical expert panel
TMN	Tumor, Node, Metastases
TTP	Time to progression
US	Ultrasound
Y90	Yittrium-90

Appendix F. Excluded Studies

Level 1, Form Title Screening, Is the article published in English?... -> Exclude

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