Effective Health Care Program

Local Therapies for Unresectable Primary Hepatocellular Carcinoma

Executive Summary

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

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

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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
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 th[erapies
	   – 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

Table A. PICOTS for the Key Questions (continued)			
PICOTS	**KQ1**	**KQ2**	**KQ3**
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

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).

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% 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 I2 statistic. A p value of 0.10 was used to determine statistical significance of Cochran's Q statistic. Thresholds for the interpretation of I2 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.

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

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

Characteristic	Cryoablation	RFA	MWA	PEI/PAI	TAE	TACEª	RE	DEB	3D-CRT	IMRT	SBRT	HPBT	IB	Total Study Arms
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

ªTransarterial 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).
bIncludes 1 RCT abstracted as case series
cIncludes 1 prospective cohort study abstracted as case series.
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

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.

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	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.
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).

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

Key Question, Comparison, and Outcome	Strength of Evidence	Conclusion
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.
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).

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 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).
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).

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

Key Question, Comparison, and Outcome	Strength of Evidence	Conclusion
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.
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.

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

Key Question, Comparison, and Outcome	Strength of Evidence	Conclusion
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.
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.

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).

Table G. Summary GRADE strength of evidence for KQ3 (continued)

Key Question, Comparison, and Patient or Tumor Characteristics	Strength of Evidence	Conclusion
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).

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 (I2 = 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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