

## *Comparative Effectiveness Research Review Disposition of Comments Report*

### **Research Review Title:** *Local Therapies for Unresectable Primary Hepatocellular Carcinoma*

Draft review available for public comment from July 26, 2012 to August 23, 2012.

**Research Review Citation:** Belinson S, Yang Y, Chopra R, Shankaran V, Samson D, Aronson N. Local Therapies for Unresectable Primary Hepatocellular Carcinoma. Comparative Effectiveness Review No. 114. (Prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-2007-10058-I.) AHRQ Publication No. 13-EHC069-EF. Rockville, MD: Agency for Healthcare Research and Quality. May 2013.  
[www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm).

### **Comments to Research Review**

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Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator	Section	Comment	Response
Peer Reviewer #1	Clarity and Usability	Yes to all.	Thank you.
Peer Reviewer #2	Clarity and Usability	The report is well structured and organized and main points are clearly presented. With the exception of the RFA/PEI comparison, other conclusions cannot be drawn due to poor quality primary data available on this topic.	Thank you.
Peer Reviewer #3	Clarity and Usability	Several sections are repetitive and it is a difficult to navigate (which I admit is one of the causes of my overdue review.)	We apologize for the repetitive nature of the review. We addressed each section thoroughly, which may cause repetition throughout.
Technical Expert #1	Clarity and Usability	This report further confounds a difficult clinical scenario. Patients with unresectable HCC comprise a diverse, heterogeneous group. They vary by liver function, performance status, and tumor stage. These, and other factors, impact clinical decision-making, treatment options, and life expectancy. While a comparative effectiveness study is welcome, the comparative arms need to be appropriately discerned. It would be reasonable to compare ablative procedures vs. each other (RF ablation, microwave ablation, PEI, cryoablation, IRE), and it would be reasonable to compare percutaneous vs. open/laparoscopic approaches and their outcomes. Alternatively, it would be reasonable to attempt to compare chemoembolization with particle embolization, drug-eluting beads, or radioembolization. It wouldn't, however, make sense to compare RF ablation vs. chemoembolization as was done in this study and then suggested for future comparisons.	We have edited the report to be clear that we are not making nor are we suggesting that research be done making comparisons across distinct patient groups. We have added information to the population and settings section stating, "To maintain clinical relevance, comparisons were only made within category of intervention (e.g. ablative therapy vs. ablative therapy). This 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 because these studies involved patients who were all able to receive ablative therapy. "
Technical Expert #2	Clarity and Usability	This report is well structured and clearly presented. The conclusions cannot be used to inform policy or practice decisions substantively or substantially, for the following reasons: (1) only one narrow conclusion is offered by this report, and it happens to be a conclusion that is not all that relevant clinically (because PAI/PEI is no longer clinically used to any extent);	We disagree with the statements made about the clinical relevance of these treatments. A recent search of PubMed identified clinical data published on this intervention in the last year. While clinical use may be limited the treatments are still being seen in clinical practice and published literature.
Technical Expert #2	Clarity and Usability	(2) no other conclusive comparative effectiveness evidence could be gleaned, which limits policy guidance or best-practice.	We agree on the limitations of existing evidence as you identified.

Commentator	Section	Comment	Response
<b>Technical Expert #3</b>	Clarity and Usability	Yes. The report is most useful and confirms our own anecdotal evidence of HCC patients and RFA. Beautifully done! What a pleasure to read!	Thank you.
<b>Technical Expert #3</b>	Clarity and Usability	I think it would be easier to receive in the mail the actual manuscript to mark up instead of reviewing on line. That is just a suggestion for future reports of this length, where it would be easier to have the report in front of you as you review certain citations (plus avoiding carpal tunnel syndrome because this manuscript takes a lot of wrist maneuverability back and forth amongst the sections). The Technical Advisory Panel should sign NDAs so such a mailing would be without risk to the confidentiality of the manuscript.	Thank you. We will forward your suggestion to AHRQ.
<b>Technical Expert #5</b>	Clarity and Usability	clearly presented	Thank you
<b>Peer Reviewer #4</b>	Conclusions	As for overall survival, reasonable conclusion based on the current evidence, but the study by Llovet et al should be included.	Thank you for the reference. We had included the article in our screening and found that the study includes patients treated from 1996 to 2000. It was excluded in our full text review stage due to the dates of treatment. Because these treatments were new, outcomes from these treatments prior to the year 2000 were deemed not comparable to the outcomes from the interventions after the year 2000."
<b>Peer Reviewer #4</b>	Conclusions	As for the QOL, the study referenced above may need to be factored in.	Thank you for the reference. We had included the article in our screening and found that the study includes patients treated preceding the year 2000. It was excluded in our full text review stage due to the dates of treatment. Because these treatments were new, outcomes from these treatments prior to the year 2000 were deemed not comparable to the outcomes from the interventions after the year 2000
<b>Peer Reviewer #1</b>	Discussion/ conclusion	As quoted - ""Evidence on the comparison of RFA versus PEI/PAI in patients with unresectable HCC was the strongest in this review. This suggests a future research high priority to compare RFA to other therapies, including other monotherapies such as TACE or RE, or combinations of treatment such as RFA-TACE. Outcomes of interest include survival, quality of life, and adverse effects, such as radiation-induced liver disease, liver failure, and local recurrence (i.e., treatment failure). Evidence comparing these outcomes of local hepatic therapies in the populations of interest for the review is needed.""	Thank you. RFA compared to TACE would be outside of the scope of this review generally because the patient populations for these two interventions differ. One study did present data on RFA compared to TACE for patients with lesions that were all amenable to ablation. In this homogenous population the comparison is a valid one and the data from this study is presented in the report.

Commentator	Section	Comment	Response
Peer Reviewer #1	Discussion/ conclusion	Please see general comments. Also I wouldn't waste time and money on combinations therapies when we do not know how well single modality therapies work. Furthermore the ability to generate numbers that allow for logical conclusions will likely never be met (99% likelihood of never happening). And even if it did, the patient population has such advanced disease, the survival benefit will be marginal, notwithstanding QOL issues.	While combination therapies represent a small proportion of the treatments for these patients we felt that it was important to mention them in the FRN section because they were evaluated as interventions of interest in this review.
Peer Reviewer #2	Discussion/ Conclusion	Implications of the major findings are clearly stated. Limitations are adequately described. Limitations of the current data available are clearly emphasized and recommendations for future research are helpful.	Thank you.
Peer Reviewer #2	Discussion/ Conclusion	Recommend the following modifications:  Page 128 line 53: This patient population comprises the group typically considered eligible for the therapies discussed in this review.	The sentence has been edited as suggested.
Peer Reviewer #2	Discussion/ Conclusion	Recommend consideration of the following:  This reviewer would disagree that the RFA vs PEI comparison should be a priority topic of further investigation. Instead, this reviewer recommends an emphasis on high quality comparisons of TACE/RFA versus RFA or radiotherapy (SBRT, external beam) versus RFA, and additionally comparison between catheter based therapies such as TAE, TACE, DEB and RE with appropriate prespecified subgroups. These are areas of intense clinical importance that require further study. The recommendation for standardized quality of life data collection is an excellent recommendation.	Thank you for the recommendations. We have removed the RFA vs. PEI comparison recommendation from the future research needs due to the moderate SOE for this comparison and added the recommended comparisons in research gaps discussion.

Commentator	Section	Comment	Response
<b>Peer Reviewer #3</b>	Discussion/ Conclusion	<p>Page 121 line 4 reports no randomized studies comparing TACE and TAE. Llovet's randomized trial in 2002, Llovet did include a TAE arm and showed no difference in survival between the two groups.</p> <p>J. M. Llovet, M. I. Real, X. Montana, R. Planas, S. Coll, J. Aponte, C. Ayuso, M. Sala, J. Muchart, R. Sola, J. Rodes and J. Bruix. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. <i>Lancet</i> 2002 359(9319): 1734-9. PMID: . R. Lopez, Jr., S. H. Pan, A. L. Hoffman, C. Ramirez, S. E. Rojter, H. Ramos, M. McMonigle an</p>	<p>Thank you for the reference. We had included the article in our screening and found that the study includes patients treated from 1996 to 2000. It was excluded in our full text review stage due to the dates of treatment. Because these treatments were new, outcomes from these treatments prior to the year 2000 were deemed not comparable to the outcomes from the interventions after the year 2000.</p> <p>For the reference by Lopez et al., this paper was also excluded due to a treatment period between 1995 and 2001.</p>
<b>Technical Expert #1</b>	Discussion/ Conclusion	<p>While the conclusion regarding the comparative effectiveness of RF ablation vs. percutaneous ethanol injection is reasonable, there is absolutely no justification to suggest "focusing on comparisons with RFA may allow for the greatest integration of new data with the current body of evidence." It is neither clinically applicable nor useful to compare ablative vs. transcatheter therapies for unresectable HCC because these distinct treatments are offered to entirely different patient populations.</p>	<p>We have revised the research gaps section which now identifies the following comparisons: 1) RFA versus TACE-RFA combination, SBRT or external beam therapy, and 2) between transarterial therapies (e.g., TACE, DEB, RE). The RFA compared with TACE has been removed from this report with the exception of one study. This study had a patient population amenable to ablative therapies and the authors sought to investigate TACE in the setting of smaller and limited number of hepatic tumors.</p> <p>We have also added information to the population and settings, "To maintain clinical relevance, comparisons were only made within category of intervention (e.g. ablative therapy vs. ablative therapy). This 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 because these studies involved patients who were all able to receive ablative therapy.</p> <p>We have also amended the FRN section to reflect the importance of comparing like patient groups.</p>

Commentator	Section	Comment	Response
Technical Expert #2	Discussion/ Conclusion	The limitation of this report is that it only has one non-major finding of moderate-strength evidence (of RFA vs. PEI/PAI), which is by no means the fault of the authors' but is due to paucity of applicable literature; the finding is clearly stated, however, and limitations of the review are described adequately.	Thank you.
Technical Expert #2	Discussion/ Conclusion	Future research needs are relatively well described in Research Gaps section, but it remains to be seen as to how easily they may be translated into new research. One omission of future research opportunity by this report is comparative effectiveness research to address clinical heterogeneity through stratification of patient subgroups, based on factors such as lesion size, for instance, that would render more meaningful clinical comparisons.	Yes, we agree and included in the draft the future research need for subgroup analysis under "Research Gaps" (3 <sup>rd</sup> bullet point).
Technical Expert #3	Discussion/ Conclusion	The manuscript is elegantly and concisely written. The report is of great use to practitioners--as well as the direct patient navigators and patient advocates such as those here at the International Cancer Advocacy Network (ICAN, www.askican.org) who are immersed in the area of HCC--as well as those who are involved with patients undergoing RFA for liver metastasis from other primary tumors.	Thank you.
Technical Expert #5	Discussion/ Conclusion	Implications and limitations discussed clearly	Thank you
Peer Reviewer #1	General Comment	I applaud the authors on there tenacity in completing this manuscript. I can empathise with them. Given the quality of the literature and the population, it is almost impossible to arrive at any meaningful conclusion(s).	Thank you

Commentator	Section	Comment	Response
Peer Reviewer #1	General Comment	Having said that there are certain facts that must be brought to the attention of the authors at the outset. The selection criteria for these procedures is different - the percutaneous ie RFA , PEI, Cryo are different from the trans-arterial approaches - TACE, DEB , Radioembo etc. The principle reason is in the approach to the 'lesions' - if small <3cm and accessible the default procedure is of the percutaneous variety and everything else is shunted to trans-arterial. Therefore comparison between the 2 groups is always going to introduce preferential bias favoring the percutaneous route.	Changed the statement to the following, "Thank you for this comment. Based upon this and other peer reviewer concerns we have restructured the report so that ablation, embolization, radiotherapy, and combination therapies appear in their own sections with no comparisons across these groupings with one exception. RFA and TACE are compared in a single comparative study where patients had similar disease characteristics and were all amenable to ablative therapy.
Peer Reviewer #1	General Comment	Therefore, what is needed is a comparison between percutaneous methods with resection since the selection criteria are highly similar.	Patients eligible for resection as well as transplantation were determined to be outside the scope of this review which focuses on the comparative effectiveness of local hepatic therapies.
Peer Reviewer #1	General Comment	As far as trans-arterial approaches are concerned what is required is a comparison within this modality ie TACE vs Radioembolotherapy since the selection criteria are similar.	In our review, we include comparisons of drug-eluting beads (DEB) vs. TACE and DEB vs. TAE. Our search did not yield a direct comparison between radioembolization and another transarterial therapy.
Peer Reviewer #2	General Comments	The authors have done an excellent job compiling a broad range of studies and analyzing the data effectively. Unfortunately, the primary data on these topics are limited for the majority of comparisons. The report is clinically meaningful although comparative effectiveness research outcomes are limited by lack of high quality data, limiting strong conclusions in this manuscript. The target population and audience are explicitly defined. The key questions are appropriate and explicitly stated.	We agree on the limitations of existing evidence as you identified.
Peer Reviewer #2	General Comments	Additional questions not addressed in this review that would be clinically meaningful include a comparison of ablative strategies and surgical resection (an area of controversy despite NCCN guidelines, outside of the predefined goal but relevant), as well as a comparison of radioembolization and chemo-embolization (TACE).	We excluded <i>a priori</i> surgical interventions (resection, hepatectomy) in our PICOTS and, therefore, did not include comparisons between local therapies and surgical resection.  We agree that a comparison of radioembolization versus TACE is of interest. However, we did not find such comparative data in the literature and have noted this as a research gap in our discussion.
Peer Reviewer #3	General Comments	This is a very detailed CER analysis comparing ablative, embolic and radiation treatments for unresectable hepatocellular carcinoma without PV thrombosis and Childs A or B cirrhosis.	Thank you

Commentator	Section	Comment	Response
<b>Technical Expert #1</b>	General comments	This report is not clinically meaningful because the authors have gone against the advice/consultation of their key informants and Technical Expert Panel (pages 15-16 of the document). Certainly, this is a heterogeneous patient population with many factors impacting clinical treatment decisions and overall survival. These include (but are not limited to) underlying liver disease, patient performance status, and tumor burden. Patients are only offered locoregional therapy for unresectable hepatocellular carcinoma (HCC) if they have preserved liver function and performance status. If they meet these criteria, they are triaged to the appropriate therapy based on tumor burden. Patients with low tumor burden (typically < 3 tumors all less than 3 cm) are offered percutaneous/operative ablation (radiofrequency or microwave ablation). If they have more advanced disease (intermediate-staged HCC) with multifocal tumors or large tumors (> 3 cm), they are typically offered transcatheter intra-arterial therapies (i.e., chemoembolization with or without drug-eluting beads, arterial embolization, radioembolization). It is inappropriate and clinically insignificant to compare the outcomes from ablative therapies (which have curative intent) versus the transcatheter therapies (which have a palliative intent).	<p>We appreciate the comment and struggles with this issue during the review. Due to the limited data reported by study authors it was not possible for us to judge if the included participants in any one paper were triaged appropriately by their physician. What we were able to do is present the available data accompanied by the demographic data that would help readers just the appropriateness of treatment for themselves.</p> <p>We did not do any comparisons across treatment modalities, other than a comparison of RFA to TACE, but all patients in this study were all eligible for RFA as they were patients with early stage disease.</p> <p>To add clarity to our report we have done the following: Reconfigured the PICOTS to group local hepatic therapies into the following three comparison groups: 1) ablative therapies 2) transarterial therapies 3) Radiotherapies like SBRT, 3DRT, and external beam radiation and 4) combination therapies . Details were added to our explanation of discussions with the TEP regarding the PICOTS and KQs to make it clear why we chose the path we did for the report Detail the deficiencies in the current literature on local therapies for HCC (inconsistent patient criteria, insufficient reporting of baseline characteristics, lack of high quality randomized comparative trials, etc) making a more clinically relevant classification based on patient characteristics impossible, and Expand the Future research needs section to emphasize some comparisons of interest that were mentioned to us during the public comment period.</p>
<b>Technical Expert #2</b>	General comments	Clinical relevance is limited by the narrow conclusion that this report can draw. It is clinically meaningful only in that it highlights the lack of available comparative effectiveness evidence for the objective selection of local therapy for unresectable hepatocellular carcinoma, and which is currently predominantly dictated by institutional bias and preferences (training) of interventional radiologists. The target population is explicitly defined. The key questions are appropriate and explicitly stated.	Thank you.
<b>Technical Expert #3</b>	General Comments	The report is clinically meaningful. The target population and audience are carefully and meticulously defined. The key questions are stated with clarity.	Thank you.



Commentator	Section	Comment	Response
<b>Technical Expert #4</b>	General Comments	<p>I want to make sure that readers of this article will understand that intraarterial therapies play a major role in the treatment of patients with HCC and that the published data is robust enough to justify inclusion of those therapies in recommendations and guidelines as the AASLD, NCCN and others have done.</p> <p>Those procedures cannot be compared with ablative therapies because they do not deal with the same patient population at all. Ablative therapies are limited to patients with very to early stage disease and are never used for tumors greater than 4 cm in size. The opposite is true for intraarterial therapies.</p>	<p>We have edited the report to be clear that we did not make comparisons across therapies. A comparison of RFA vs. TACE was found in the literature however both arms contained early stage patients amenable to ablation. We have also added language to make clear that stratification by type of therapy does not address the heterogeneity of patients within treatment type. We have presented all the data in the hopes of being transparent.</p> <p>More details on the specific edits to the report can be found in the response to question 12.</p>
<b>Technical Expert #5</b>	General Comments	the report is clinically meaningful and the target population and audience are explicitly defined	Thank you
<b>Peer Reviewer #4</b>	General Comments:	Well written.	Thank you
<b>Peer Reviewer #4</b>	Introduction	Well written.	Thank you
<b>Peer Reviewer #1</b>	Introduction	The incidence of non-cirrhosis related HCC of 5% in the western population is far lower than what is seen in clinical practice. ES-1 line 35	While variation in clinical practice is expected, our reference, Bruix et al., 2011, indicates 5% overall in western populations.
<b>Peer Reviewer #1</b>	Introduction	ES-3, 19 - Extremely important point. Since these therapies require technical hands on expertise, qualified MDs may not be available at a given site and therefore the default procedure may be different than what may seem ' best option' in order to expedite care. This seems justifiable in the absence of level 1 evidence.	Yes, we agree. Thank you.

Commentator	Section	Comment	Response
Peer Reviewer #2	Introduction	<p>The introduction is well written but this reviewer strongly recommends consideration of the following modifications:</p> <p>ES-2 line 19: HCC patients with class A hepatic impairment have the best prognosis and a subset would be candidates for surgical resection, although many require therapy with ablative interventions, transarterial therapy, radiotherapy or systemic therapy. HCC patients with class B are not surgical candidates and are typically offered transarterial therapy, ablative therapy, radiotherapy or systemic therapy. Childs C patients typically are not candidates for cancer directed therapies with rare exception. Transplantation can be offered to patients of all Child's Pugh Classifications.</p>	<p>The paragraph on ES-2 and in the main report Pg. 2 has been edited to reflect reviewer's corrections. Thank you.</p>
Peer Reviewer #2	Introduction	<p>ES3 line 18: Recommend insertion of the following: Catheter directed strategies such as chemoembolization (TACE), transarterial embolization (TAE) and radioembolization (RE/SIRT) offer the benefit of treating disease when tumor multifocality extends beyond three detectible lesions, while ablative and external beam radiation strategies are more commonly used in cases or unifocal or limited multifocal disease.</p>	<p>Thank you. We have incorporated the suggested addition.</p>
Peer Reviewer #2	Introduction	<p>ES-15 line 14: TAE not TEA</p>	<p>One study specifically used the term transarterial ethanol ablation (TEA) and, therefore, we honored the exact terminology in our report.</p>
Peer Reviewer #2	Introduction	<p>ES-21 line 55: The reviewer disagrees with this statement. A more accurate statement might be "This patient population most accurately reflects the patient population considered eligible for local therapies discussed in this review who present to a clinician's practice."</p>	<p>Thank you. Sentence has been revised as suggested.</p>

Commentator	Section	Comment	Response
Peer Reviewer #2	Introduction	Page 2 introduction line 46-51: HCC patients with class A hepatic impairment have the best prognosis and a subset would be candidates for surgical resection, although many require therapy with ablative interventions, transarterial therapy, radiotherapy or systemic therapy. HCC patients with class B are not surgical candidates and are typically offered transarterial therapy, ablative therapy, radiotherapy or systemic therapy. Childs C patients typically are not candidates for cancer directed therapies with rare exception. Transplantation can be offered to patients of all Child's Pugh Classifications.	The paragraph has been edited to reflect reviewer's corrections. Thank you.
Peer Reviewer #3	Introduction	Good. Page 13 lines 19-22: Most patients who undergo loco-regional therapy for HCC are Childs-Pugh A, occasionally B. Most patients with Childs C cirrhosis are more likely to die of cirrhosis than HCC and rarely is treatment of this population indicated (or tolerated.) In the next 10 years, I foresee the question being whether patients who are Childs A and resectable will instead be better served with loco-regional therapies instead. On page 14, under the scope of the project it is correctly noted that the scope of this CER includes Childs A and B patients (not C.)	Thank you for your comments.
Technical Expert #1	Introduction	The introduction is confounded with unsubstantiated claims. Most hospitals have expertise to perform both transcatheter (especially chemoembolization) and ablative therapies. Radioembolization is less widely available, but there are still many centers that do offer this treatment modality. Further, surgeons perform ablation procedures as do interventional radiologists. The statement that external-beam radiation is less costly is not substantiated. This is not a cost-effectiveness analysis, nor are any references supplied. Lastly, I am not sure that including intraluminal brachytherapy is necessary. This therapy is mostly used for cholangiocarcinoma, not HCC.	<p>Thank you. We have revised this section to reflect the reviewer's correction as follows:  <i>"TACE, RE, and RFA all require an interventional radiologist experienced in these techniques, though RFA can also be performed by surgeons. External-beam radiation is widely available at most centers<sup>13</sup>; 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."</i></p> <p>We have deleted "is less costly" from the sentence describing external beam radiation.</p> <p>Intraluminal brachytherapy was included in the list of local hepatic therapies that the TEP reviewed for this systematic review.</p>

Commentator	Section	Comment	Response
<b>Technical Expert #2</b>	Introduction	The Introduction section is well conceived and written. It lays out the background of hepatocellular carcinoma logically, including basic epidemiology, classification and staging, etc.	Thank you.
<b>Technical Expert #3</b>	Introduction	Well done. My only suggestion for the report is to add a brief section on the breathtaking achievements of the IR area. Even a simple reference to the following website might serve as the appropriate "tip of the hat" to the inventors in this most productive area of radiology:  <a href="http://www.sirweb.org/about-us/historyIR.shtml">http://www.sirweb.org/about-us/historyIR.shtml</a>	We have chosen not to address specific subspecialties and their accomplishments in this document. We aimed only to review the comparative effectiveness of the interventions.
<b>Technical Expert #5</b>	Introduction	On page ES-2 of the Introduction under: Classification of underlying liver function: authors indicate that patients with Child-Pugh B and C are not surgical and therefore receive local therapies. This is not accurate and should be changed to reflect that, in clinical practice, Child-Pugh C patients are candidates for supportive care only if they are not transplant candidates.	This section has been edited and a new citation added.  <a href="http://annonc.oxfordjournals.org/content/21/suppl_5/v59.full">http://annonc.oxfordjournals.org/content/21/suppl_5/v59.full</a>
<b>Peer Reviewer #4</b>	Methods	Well thought out. Extensively studied. End points of Overall survival and Quality of life (QOL) are legitimate.	Thank you
<b>Peer Reviewer #1</b>	Methods	Please see general comments.	Thank you.
<b>Peer Reviewer #2</b>	Methods	Inclusion and exclusion criteria are justifiable, search strategies are explicitly stated and logical. Statistical methods used appear appropriate.	Thank you.
<b>Peer Reviewer #2</b>	Methods	The reviewer is unclear regarding why hand selected papers were not identified in this search methodology.	Although intended to be comprehensive, systematic literature search using search terms can sometimes miss a few relevant articles. To complement this, we conducted manual screening of citations in review articles and identified a few articles for inclusion.
<b>Peer Reviewer #2</b>	Methods	Recommend consideration of the following: Page 17 line 31 correction: do the authors intend "95% of patients had HCC"?	We have revised the sentence to add more clarity. Thank you.
<b>Peer Reviewer #3</b>	Methods	Page 39 line 19 refers only to a few of the loco-regional therapies, to avoid bias should include TAE, PEI, etc.	We were unable to locate this in the draft.
<b>Technical Expert #1</b>	Methods	The inherent flaw of this study is comparing the outcome of ablative vs. transcatheter therapies. These therapies are offered to patients with distinctly different tumor stages.	As is stated above in response to comment 12 we have made it clear that we did not make comparisons across therapies, other than RFA vs. TACE which contained early stage patients amenable to ablation in both arms.

Commentator	Section	Comment	Response
<b>Technical Expert #2</b>	Methods	The inclusion and exclusion criteria are justifiable, and reflects the limited sample sizes of patients as well as clinical heterogeneity. Search strategies are explicitly stated and logical. Definitions for outcome measures are appropriate. Statistical methods are not used in this report. AHRQ's Methods Guide for Effectiveness and Comparative Effectiveness Reviews is referenced.	Thank you.
<b>Technical Expert #3</b>	Methods	Yes to all questions.	Thank you.
<b>Technical Expert #5</b>	Methods	The inclusion and exclusion criteria are justifiable. Methodology is appropriate	Thank you
<b>Peer Reviewer #4</b>	Results	I would include the following RCT, especially for the question of QOL.  Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, Pitton M, Sergent G, Pfammatter T, Terraz S, Benhamou Y, Avajon Y, Gruenberger T, Pomoni M, Langenberger H, Schuchmann M, Dumortier J, Mueller C, Chevallier P, Lencioni R; PRECISION V Investigators. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study, Cardiovasc Intervent Radiol. 2010 Feb;33(1):41-52. Epub 2009 Nov 12.	Thank you. We found this RCT in our search and excluded it per our inclusion/exclusion criteria as the study population included patients who were eligible for and wound up receiving liver transplantation.
<b>Peer Reviewer #4</b>	Results	As for comparisons of different local therapies, patient's liver status, performance status and HCC tumor burden need to be factored in for accurate survival comparisons. Such substratified analysis is not available, and valid conclusion cannot be made based on current body of literatures.	Yes, we agree. Our Key Question #3 intended to review the subgroup comparisons, but was limited by the paucity of subgroup data in the current literature.

Commentator	Section	Comment	Response
<b>Peer Reviewer #4</b>	Results	<p>I would include the following RCT for the overall survival differences between TACE vs. TAE. This study shows evidence that TACE, not TAE, resulted in significantly improved overall survival when compared to supportive care.</p> <p>Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Solà R, Rodés J, Bruix J; Barcelona Liver Cancer Group, Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial, Lancet. 2002 May 18;359(9319):1734-9.</p>	<p>Thank you for the reference. We had included the article in our screening and found that the study includes patients treated treatment preceding the year 2000. It was excluded in our full text review stage due to the dates of treatment. Because these treatments were new, outcomes from these treatments prior to the year 2000 were deemed not comparable to the outcomes from the interventions after the year 2000</p>
<b>Peer Reviewer #1</b>	Results	Appropriate	Thank you
<b>Peer Reviewer #2</b>	Results	The detail provided is appropriate given the goal of the document. Characteristics of the studies are clearly described, although inclusion of patient populations (tumor extent, hepatic function) would add value to the tables.	Patient characteristics are separately reported in tables 13-15 for all included studies.
<b>Peer Reviewer #2</b>	Results	Figures, tables and appendices are adequate and descriptive. However, there are several tables where the second column is too short and require reformatting for improved aesthetics eg. Tables 23, 28, 33 etc.	Thank you. We have adjusted the table formatting for enhanced viewing.
<b>Peer Reviewer #2</b>	Results	I note a large retrospective case control study relevant to the article is not discussed regarding radioembolization versus chemoembolization in a retrospective review of 245 patients (ref Salem et al, Gastroenterology 2011; 140:497-507) which might be beneficial for inclusion in this review for the purpose of completeness, if not already identified in the authors search.	Thank you for the reference. We had included the article in our screening and found that the study includes patients treated preceding the year 2000. It was excluded in our full text review stage due to the dates of treatment. Because these treatments were new, outcomes from these treatments prior to the year 2000 were deemed not comparable to the outcomes from the interventions after the year 2000.

Commentator	Section	Comment	Response
Peer Reviewer #2	Results	Additional comments for consideration include:  Page 76-78 RFA vs. TACE sections: I recommend insertion of a statement under strength of evidence sections noting "lack of direct comparisons and differences in patient populations limit the application of this data." Studies involving catheter based therapies inherently include patients with substantial multifocality, while RFA and ablative strategies can only be used for a few lesions (no more than 3 typically)	The results section of the report has been restructured by type of intervention (e.g. ablative, transarterial) The suggested statement has been added to the strength of evidence paragraph for overall survival in its new location.
Peer Reviewer #2	Results	Page 85-87: same as above	It is our understanding that the patients who would be treated with TACE vs. TEA(TAE) are both patients with multifocal disease. In addition there is a statement that reflects the limitations due to the lack of comparative data. Therefore we did not add any additional language to this section.
Peer Reviewer #3	Results	One of the issues that needs to be clarified in the text, is that a direct comparison between, for example, ablative therapies (RFA, PEI...) and embolization techniques (TACE, TAE, Y90) is not reasonable because in most cases the extent of disease dictates the modality. For example, the authors note there is insufficient evidence to compare outcome between RFA and TACE, but only patients with small, accessible tumors are candidates for RF. Patients with more extensive disease are not candidates, and instead commonly undergo embolization. For example this is seen on Page 30 line 25 "A direct comparison between embolization (at this reference DEB) and ablation (here PEI) is not possible." Direct comparison is therefore comparing apples to oranges. This applies also on page 111 to the statement about no randomized comparisons of RFA vs TACE.	We appreciate the comment and struggled with this issue during the review. Due to the limited data reported by study authors it was not possible for us to judge if the included participates in any one paper were triaged appropriately by their physician. What we were able to do is present the available data accompanied by the demographic data that would help readers just the appropriateness of treatment for themselves.  We did not do any comparisons across treatment modalities, other than a comparison of RFA to TACE, but all patients in this study were all eligible for RFA as they were patients with early stage disease. To add clarity to our report we have done the following: Reconfigured the PICOTS to group local hepatic therapies into the following three comparison groups: 1) ablative therapies 2) transarterial therapies 3) Radiotherapies like SBRT, 3DRT, and external beam radiation and 4) combination therapies . Details were added to our explanation of discussions with the TEP regarding the PICOTS and KQs to make it clear why we chose the path we did for the report Detail the deficiencies in the current literature on local therapies for HCC (inconsistent patient criteria, insufficient reporting of baseline characteristics, lack of high quality randomized comparative trials, etc) making a more clinically relevant classification based on patient characteristics impossible, and expand the future research needs section to emphasize some comparisons of interest that were mentioned to us during the

Commentator	Section	Comment	Response
			<p>public comment period.</p> <p>We have added the following, “To maintain clinical relevance, comparisons were only made within category of intervention (e.g. ablative therapy vs. ablative therapy). This 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.{Chok, 2006 #53} This cross-category comparison was included under the ablative therapies section because Chok <i>et al.</i>, 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.”</p>
<b>Peer Reviewer #3</b>	Results	Page 71 Table 15 should reference M. A. Maluccio, A. M. Covey, L. B. Porat, J. Schubert, L. A. Brody, C. T. Sofocleous, G. I. Getrajdman, W. Jarnagin, R. Dematteo, L. H. Blumgart, Y. Fong and K. T. Brown. Transcatheter arterial embolization with only particles for the treatment of unresectable hepatocellular carcinoma. J Vasc Interv Radiol 2008 19(6): 862-9. PMID. I acknowledge I am a co-author on this paper, but it is the largest case series in the U.S. reporting outcome of TAE and should be included.	Thank you for the reference. We had included the article in our screening and found that the study includes patients treated before the year 2000. It was excluded in our full text review stage due to the dates of treatment. Because these treatments were new, outcomes from these treatments prior to the year 2000 were deemed not comparable to the outcomes from the interventions after the year 2000
<b>Technical Expert #1</b>	Results	While the analysis appears very exhaustive, the Results lack meaning given the limitations regarding the analysis undertaken as described above.	We understand the limitations inherent in this review. We have enhanced the section on limitations of this review to more clearly outline these issues.
<b>Technical Expert #2</b>	Results	The amount of detail presented in the results section is appropriate, but suffers from repetition.	Thank you. We addressed each section thoroughly, which may cause repetition throughout.
<b>Technical Expert #2</b>	Results	The characteristics of the 44 studies included are well described, and key messages are explicit, albeit with only limited applicability with respect to conclusion (i.e. RFA vs. PEI/PAI), and repetitious.	Thank you. We addressed each section thoroughly, which may cause repetition throughout. While some may feel PEI/PAI are outdated a recent literature search show as least some use in clinical centers in the United States and some publications within 2012.



Commentator	Section	Comment	Response
Technical Expert #2	Results	Tables and appendix are well done and easy to follow. I am unaware of any omission of key studies or inclusion of inappropriate studies in this report.	Thank you.
Technical Expert #3	Results	Yes to the first four questions. The investigators do not appear to have overlooked any study of which I am aware.	Thank you.
Technical Expert #5	Results	A little lengthy, but appropriate for the type of readers	Thank you