Evidence Summary Focal Ablation 2: Transarterial embolization for Liver Cancer

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Focal Tumour Ablation: Transarterial Chemoembolization for Hepatocellular Carcinoma

A. Ménard, F.G. Baldassarre, G. Martel, J. Kachura and the Focal Ablation Advisory Committee

Report Date: March 31, 2015

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Evidence Summary Citation:
ES Focal Ablation 1: Transarterial chemoembolization for liver cancer

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QUESTIONS
1. What is the effectiveness of transarterial chemoembolization (TACE) for the treatment of patients with hepatocellular carcinoma (HCC)?
   a. What is the side effect profile and treatment outcome of conventional TACE versus drug-eluting bead TACE (DEB-TACE)?
2. What patient populations are most likely to benefit from TACE?
3. Is there a difference in any important outcomes when performing TACE as an inpatient or an outpatient procedure?

TARGET POPULATION
   Patients with HCC.

INTENDED PURPOSE
   To provide a systematic literature review that will be one of the six components of the Recommendation Report (i.e., demand forecasting, costing analysis, jurisdictional review, literature review, system capacity, and current state) of the Focal Ablation Advisory Committee.

INTENDED USERS
   Interventional radiologists, radiation oncologists, hepatobiliary surgeons, medical oncologists, healthcare professionals caring for patients with HCC or colorectal liver metastases.

INTRODUCTION
   This report summarizes the peer-reviewed evidence regarding the use of TACE in the treatment of HCC.

   The incidence of HCC is increasing, and it is the fifth leading cause of death for men and the seventh for women worldwide [1]. In Canada, incidence and mortality rates have increased substantially since 1980; in men, it tripled from 2.2 to 6.8 per 100,000 from 1980 to 2007, and the five-year relative survival in all stages of disease is currently 18% [1]. In 2014, 2100 new cases of liver cancer were predicted to occur, and Ontario had the highest estimated age-standardized incidence rates for men in Canada [2].
TACE is a minimally invasive procedure performed in interventional radiology. A catheter is usually inserted in the common femoral artery, and chemotherapy agents, as well as embolizing particles are injected selectively into the arteries that supply the tumour(s) in the liver. In this way, the tumour is starved of oxygen and stops its growth, and the chemotherapy agents can be applied directly to the focal site at a much higher dose than if administered systemically. Patients who receive this treatment are typically those with relatively good liver function; no portal vein occlusion/thrombosis, ascites, or bleeding esophageal varices; and relatively normal blood counts. These patients are usually not good candidates for transplant, and most often their tumour(s) are unresectable, and have not metastasized beyond the liver. However, in some cases, this treatment is delivered to patients who are waiting for liver transplant.

Two seminal randomized controlled trials (RCTs) were published in 2002 [3,4], and a systematic review and meta-analysis in 2003 [5], which showed an increased overall survival (OS) for patients treated with TACE compared with bland embolization and symptomatic treatment. These studies used conventional TACE (cTACE). cTACE involves the use of doxorubicin, cisplatin, 5-fluorouracil or mutamycin alone or in combination along with iodinated poppyseed oil and gelatin sponge particles (embolizing agent). Since then, technology has evolved and gelatin sponge particles have been replaced by DEBs loaded with chemotherapy agents. The procedure can be performed both in an inpatient and in an outpatient setting.

Results of previously conducted systematic reviews, of which the Working Group was aware [6-9], have been inconsistent and the efficacy of TACE is still questioned. These inconsistent results can be explained by the different selection criteria used by the authors, and sometimes by inconsistent definitions of TACE.

METHODS

This evidence review was developed using a planned, two-stage method, summarized here and described in more detail below.

1. Search and evaluation of existing systematic reviews: If one or more existing systematic reviews are identified that address the research questions and are of reasonable quality, then those systematic reviews would form the core of the evidence review.

2. Systematic review of the primary literature: This review would focus on those areas not covered by existing reviews if any are located and accepted.

3. The Program in Evidence-Based Care (PEBC) is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ministry.

Search for Systematic Reviews

A search was conducted for existing systematic reviews. Systematic reviews, published as systematic reviews only or as part of practice guidelines were considered eligible for inclusion. The search for systematic reviews was aimed at finding a review that covered the questions of the present review and that could be used, at least in part, as the evidentiary basis for this evidence summary.

A search of guidelines was also conducted, to identify the systematic reviews forming their evidentiary basis. The same selection criteria were used for selecting guidelines and systematic reviews.

The electronic databases MEDLINE and EMBASE from 2006 to July 29, 2014 were searched for guidelines. In addition, the authors’ files were searched, and an environmental
scan was conducted searching the web sites of some of the major guidelines producers worldwide (i.e., European Society of Medical Oncology [ESMO] [http://www.esmo.org/Guidelines], National Guideline Clearinghouse [http://www.guideline.gov/], National Institute for Health and Care Excellence [NICE] [https://www.evidence.nhs.uk/]).

The electronic databases MEDLINE, EMBASE, and the Cochrane Library were searched for systematic reviews from 2006 to September 15, 2014. In addition, the authors’ files and the reference lists of the included systematic reviews were hand searched.

The search terms and the search strategies are reported in Appendix 1.

The following selection criteria were applied:

**Included:**
- Systematic reviews including studies with a population of patients with HCC.
- Systematic reviews with a research question looking at TACE.
- Systematic reviews with search strategy dated 2006 or later.
- Systematic reviews that include RCTs or mixed designs for efficacy questions, and non-RCTs for the inpatient, outpatient question.

**Excluded:**
- Studies that are not systematic reviews (i.e., reviews that do not have a specific question and did not state inclusion/exclusion criteria)
- Systematic reviews in language other than English
- Systematic reviews looking at combination therapies that include TACE.
- Systematic reviews of a population of patients with liver metastases.
- Systematic reviews with a question only tangential to TACE (i.e., reviews that do not have a major focus on TACE)
- Systematic reviews with search cut-off prior to 2006
- Systematic reviews that do not report enough data (i.e., protocols, abstracts of systematic reviews)
- Systematic reviews that do not include a non-TACE arm.

The methodologist (FGB) reviewed the titles and the abstracts of the citations resulting from the searches. The full text of potentially relevant reviews were retrieved reviewed (FGB); documents were selected according to the criteria outlined above. Identified systematic reviews were further evaluated by all Working Group members, based on their clinical content and the similarity of the questions they addressed to the questions and objectives of this evidence summary. Systematic reviews that were found to be directly relevant to this evidence summary, and therefore potential foundations for this document, were assessed using the Assessing the Methodological quality of SisTemAtic Reviews (AMSTAR) tool [10,11]. The results of the assessments were used to determine whether an existing systematic review could be used.

Any identified reviews that did not meet the above criteria, that were not clinically similar to the present review, or that had an AMSTAR assessments indicating important deficiencies in quality, are reported in the reference list, but not further described or discussed.

**Search for Primary Literature**

The search for primary literature was two pronged: a) a search for studies of TACE effectiveness to complete the data gathered from systematic reviews (Questions 1, 1a and 2), and b) a search for studies on the feasibility and safety of outpatient TACE (Question 3).

**Literature Search Strategy**
a) Effectiveness of TACE
A search for RCTs was conducted. The databases MEDLINE, EMBASE, and the Cochrane Library, were searched from 2002 to October 21, 2014. In addition, the authors’ files and the reference lists of included articles were hand searched. The search terms and the full search strategies are reported in Appendix 1.

b) TACE in an outpatient setting
A search for observational trials was conducted for the safety of conducting TACE interventions in an outpatient setting. The databases MEDLINE, EMBASE, and the Cochrane Library were searched from 1997 to October 16, 2014. The search terms and the full search strategies are reported in Appendix 1.

Study Selection Criteria and Protocol
The following selection criteria were applied:

Included:
Questions 1 and 2:
- RCTs published from 2002 onwards
- Studies of patients with HCC
- Studies of TACE (either cTACE or DEB-TACE) compared with any other intervention or best supportive care
- Studies reporting on measures of efficacy (e.g., OS, progression-free survival, disease-free survival, etc.), safety and quality of life outcomes

Question 3
- RCTs and Non-RCTs
- Studies of patients with HCC
- Studies of cTACE or DEB-TACE performed in outpatient versus inpatient settings
- Studies reporting on safety outcomes (e.g., readmission rates, and three-day mortality rate)
- cTACE or DEB-TACE performed in an outpatient or inpatient setting

Excluded:
Questions 1 and 2:
- Articles in languages other than English
- Publications that do not provide enough data or do not report on outcomes of interest (e.g., cost)
- Abstracts of interim analyses
- All designs other than RCT
- Interventions where TACE is used in combination with other strategies

Question 3:
- Case studies
- Narrative reviews
- Studies publications in languages other than English
- Studies that do not report enough data for extraction
- Studies that do not focus on TACE
- Studies that do not focus on ambulatory TACE
- Studies with a population other than HCC patients
The methodologist (FGB) reviewed the titles and abstracts identified by the search and applied the selection criteria listed above. The full publications of studies identified as possibly relevant were retrieved in the library and the methodologist (FGB) applied the selection criteria to them.

Data Extraction and Assessment of Study Quality and Potential for Bias

The methodologist (FGB) extracted data and created evidence tables for general characteristics, quality and study results. Ratios, including hazard ratios (HRs), were expressed with a ratio <1.0 indicating that patients receiving TACE had a higher probability of survival. All extracted data and information were audited by an independent auditor.

Important quality features, such as required sample size and actual sample, loss to follow-up, blinding, randomization method, allocation concealment, early termination, intention-to-treat analysis, and ethical approval for each study were extracted.

Synthesizing the Evidence

When clinically homogenous results from two or more trials were available, it was planned to conduct a meta-analysis using the Review Manager software (RevMan 5.3) provided by the Cochrane Collaboration [12]. For time-to-event outcomes, HRs, rather than the number of events at a certain time point, were the preferred statistic for meta-analysis, and would be used as reported. If the HR and/or its standard error were not reported, it was planned to derive them from other information reported in the study, if possible, using the methods described by Parmar et al [13]. For all outcomes, it was planned to use the generic inverse variance model with random effects, or other appropriate random effects models in RevMan 5.3 [12].

Statistical heterogeneity would be calculated using the $\chi^2$ test for heterogeneity and the $I^2$ percentage. A probability level for the $\chi^2$ statistic $\leq 10\%$ ($p\leq 0.10$) and/or an $I^2 > 50\%$ would be considered indicative of statistical heterogeneity.
RESULTS
The flow charts of this study are presented in Figure 1 (guidelines), Figure 2 (systematic reviews), Figure 3 (randomized trials of effectiveness), and Figure 4 (observational studies of ambulatory TACE), in Appendix 2.

Search for Existing Guidelines and Systematic Reviews
The search for guidelines identified 652 citations: 101 from MEDLINE, 225 from EMBASE, and 326 from the authors’ files. The methodologist (FGB) reviewed the titles and the abstracts against the selection criteria, and identified 30 citations as possibly relevant. The full text of these were retrieved and reviewed by the methodologist (FGB); two [14,15] were selected to be kept as a source of evidence.

The search for systematic reviews identified 529 citations: 93 from MEDLINE, 206 from EMBASE, seven from the Cochrane Library, 223 from the authors’ files, and none from the reference lists of included studies. The methodologist (FGB) reviewed the titles and the abstracts against the selection criteria and identified 46 citations as possibly relevant. Of note, 40 systematic reviews were excluded at the title and abstract level because the publications were not in English language. A list of these publications is provided in Appendix 3A along with the citation of the systematic reviews that were excluded at the full-text level with their reason for exclusion. The full text of the 46 citations considered potentially relevant were retrieved and reviewed by the methodologist (FGB), who selected nine systematic reviews as possible candidates for inclusion [6-9,16-20]. These reviews were evaluated by the Working Group for their clinical content and two were selected for further evaluation with the AMSTAR tool: Huang et al, 2014 [20] and Martin et al, 2012 [16]. The detailed results of these evaluations are presented in Tables 1 and 2, Appendix 4. The review by Martin et al [16] was of lower quality and the review by Huang et al [20] focussed on DEB-TACE. The Working Group decided to proceed to a complete search of the primary literature, and to use the review by Huang et al [20] to integrate the new body of evidence on DEB-TACE (Question 1A).

Primary Literature Systematic Review

Literature Search Results
Trials of TACE effectiveness
The search for RCTs of TACE effectiveness identified 1115 citations: 123 from the Cochrane library, 432 from EMBASE, 233 from MEDLINE, 327 from authors’ files, and none from the reference lists of included studies. The methodologist (FGB) reviewed the titles and the abstracts against the selection criteria and identified 81 citations as possibly relevant. Of note, 101 citations were excluded at the title and abstract level because they were published in a language other than English. These citations are listed in Appendix 3, along with the citations of the studies that were excluded after full-text review. The full text of two articles that were considered potentially relevant were not available through the library system; all the others were retrieved, and the methodologist reviewed them against the selection criteria. Eighteen publications [3,4,21-36], representing 17 studies were included.

TACE was compared with the following: transarterial injection with no embolization in four studies [30,32,34,36]; bland embolization in two fully published studies [3,28]; DEB-TACE in four studies represented by five full-text articles [22,24,26,31,33] and two abstracts publications [21,27]; hepatic resection in one study [35]; brachytherapy in two abstract publications [23,29]; systemic therapy in one study [25]; and symptomatic treatment in one study [4]. Table 1 presents the general characteristics of the included studies, grouped by comparison.
### Table 1. Effectiveness of TACE. General characteristics of included RCTs.

<table>
<thead>
<tr>
<th>Author, year (reference), study name, country, funding</th>
<th>Objectives, design</th>
<th>Population, data collection period, follow-up</th>
<th>Intervention, control</th>
<th>Outcomes</th>
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<tr>
<td><strong>TACE vs TEA</strong></td>
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<tr>
<td>Yu, 2014 [36]</td>
<td>To compare TEA + LEM with TACE. Design: Open-label parallel group.</td>
<td>N=200 pts with unresectable HCC. Terminated early at interim analysis after 98 pts because of no difference in OS.</td>
<td>TEA+LEM: (N=49) ethiodized oil-ethanol mixture (2:1 ratio by volume up to 60 mL) TACE: (N=49) cisplatin-ethiodized oil emulsion (0.5 mg cisplatin per milliliter up to 30 mg), and 1 mm gelatin-sponge pellets.</td>
<td>&quot;OS PFS (intralesional, any disease) CR (local) at 3 mo, 6 mo and 12 mo AE&quot;</td>
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<tr>
<td>Country: China</td>
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<td>Funding: nr</td>
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<tr>
<td><strong>TACE vs bland embolization</strong></td>
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<td>Llovet, 2002 [3]</td>
<td>To compare the survival benefit of bland embolization, TACE, or symptomatic treatment. Design: Three group, open-label; sequential design; stopped early for benefit.</td>
<td>N=112 pts with unresectable HCC Child-Pugh A or B, Okuda stage I or II, not suited for curative treatment.</td>
<td>TAE (N=25): gelfoam TACE (N=21): gelfoam + doxorubicin + iodinated poppyseed oil iodinated poppyseed oil Symptomatic treatment (control) (n = 25: treatment as in nononcologic pts)</td>
<td>&quot;OS Objective response AE&quot;</td>
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<tr>
<td>Country: Spain</td>
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<tr>
<td>Funding: Ministerio de Ciencia y Tecnologia. Pharmacia-Upjohn</td>
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<td>Meyer, 2013 [28]</td>
<td>Phase II: To test the safety of sTACE with cisplatin compared with TAE. Phase III: To test the effectiveness of sequential TACE compared with TAE. Design: Phase II/III (terminated early) and meta-analysis of previous studies.</td>
<td>N= 86 pts with unresectable HCC Age (mean yrs): TAE: 62; sTACE: 63.2 Gender: 86% male Period: April 2009 to February 2010 Follow-up (median mo): 24.0</td>
<td>TAE (N=42) polyvinyl alcohol sTACE (N=44) cisplatin administered 4-6 hrs before embolization.</td>
<td>&quot;OS PFS AE (Phase II) Response QoL&quot;</td>
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<tr>
<td>Country: UK</td>
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<tr>
<td>Funding: National Institute of Health Research, Experimental Cancer Medicine Centre Network (UK)</td>
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### EVIDENCE SUMMARY FA2

<table>
<thead>
<tr>
<th>Author, year (reference), study name, country, funding</th>
<th>Objectives, design</th>
<th>Population, data collection period, follow-up</th>
<th>Intervention, control</th>
<th>Outcomes</th>
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<tr>
<td><strong>TACE vs DEB-TACE</strong></td>
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</table>
| Govieri, 2014 [22]                                    | To determine whether DEB-TACE is superior to cTACE  
**Design:** Multicentre, parallel-group, open-label | N=177 pts with cirrhosis and HCC in a palliative setting; Child-Pugh class A or B  
**Age** (mean yrs): 68.6  
**Gender:** 76.3% male  
**Period:** March 2008 to December 2012  
**Follow-up:** 2 yrs | cTACE (N=88): mixture of 50 mg dry epirubicin manually emulsified with 10 mL iodized oil followed by embolization with absorbable gelatin sponge particles vs DEB-TACE (N=87): 100 300 µm in diameter DC-Beads with 50 mg of a doxorubicin solution.  
**Mean number of treatments:** 2.2 in each arm | *2-yr OS; TTP  
Local CR (lesion) at 1 month  
Overall CR (pt) at 1 month  
OR  
PR  
DC  
Length of hospital stay  
AE |
| Vogl, 2011 [33]                                       | To conduct further analysis of the PRECISION V dataset to evaluate safety gastrointestinal, liver, and cardiac toxicity with DEB-TACE (doxorubicin) vs cTACE  
**Design:** Multicentre single blind | N=212 with intermediate, unresectable HCC  
**Age** (mean yrs): DEB-TACE: 67.0, cTACE: 67.3  
**Gender:** 87.3% male  
**Period:** November 2005 to June 2007  
**Follow-up:** 6 mo | DEB-TACE: (N=110) pts and 235 procedures; 4 mL of DEBs (doxorubicin 150 mL) mixed with a nonionic contrast medium and no iodinated poppyseed oil iodinated poppyseed oil) vs cTACE: (N=112) pts and 261 procedures; doxorubicin 50-75 mg/m² to a max of 150 mL mixed with iodinated poppyseed oil iodinated poppyseed oil. Embolic agent and particle size were chosen according to the anatomy of the vessels. Investigator’s preference.  
**Mean number of treatments:** 2.2 in each arm | AE |
| Lammer, 2010 [24]                                     | To evaluate safety and efficacy of cTACE and DEB-TACE  
**Design:** Parallel trial, multicenter, single-blind, phase II, superiority trial | N=212 pts with intermediate HCC and Child-Pugh A or B cirrhosis  
**Age** (mean yrs): DEB-TACE: 67.3  
**Gender:** 87% male  
**Period:** November 2005 to June 2007  
**Follow-up:** 6 mo | DEB-TACE: (N=102) 4 mL DC Bead + doxorubicin [150 mg] + nonionic contrast medium; mean total doxorubicin dose: 295 mg vs cTACE (N=110) with doxorubicin (doxorubicin emulsion [50-75 mg/m² up to 150 mg], adjusted for bilirubin concentration and body surface area) + iodinated poppyseed oil iodinated poppyseed oil + particle embolization with an embolic agent; mean total doxorubicin dose: 223 mg.  
**Mean number of treatments:** 2.2 in each arm | *Tumour response at 6 mo  
Disease control  
*Treatment-related SAE  
Systemic side effects of doxorubicin  
PES  
AE |
| Sacco, 2011 [31]                                       | To evaluate short- and long-term technical and clinical results of cTACE and DEB-TACE  
**Design:** Parallel group, open-label | N=67 pts with unresectable HCC (<5 nodules) and cirrhosis, Child-Pugh class A and B.  
**Age** (mean yrs): 70  
**Gender:** 67% male  
**Period:** January 2006 to March 2009 | cTACE (N=34); (iodized oil + doxorubicin hydrochloride + selective arterial embolization with grated gelatin sponge particles) vs DEB-TACE (N=33) (superselective injection of 2.4 mL of DC Bead + doxorubicin - mean 55 mg -and non-ionic contrast medium.  
**Mean number of treatments:** 2.2 in each arm | *AE  
*Periprocedural toxicity (based on liver function), and  
*Tumour response at 1 month.  
Number of repeated chemoembolization cycles. |
<table>
<thead>
<tr>
<th>Author, year (reference), study name, country, funding</th>
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</tr>
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<tbody>
<tr>
<td>Maleux, 2010 [abs] [27]</td>
<td>To assess the safety of doxorubicin-eluting SAP microspheres.</td>
<td>N=30 pts with different BCLC stages of HCC</td>
<td>cTACE (N=15): iodinated poppyseed oil iodinated poppyseed oil + doxorubicin SAP (N=15): Doxorubicin-eluting HepaSpheres. Mean number of treatments: nr</td>
<td>Time to recurrence and local recurrence. Time to radiologic progression. Survival Doxorubicin concentration Liver function AE</td>
</tr>
<tr>
<td>Maleux, 2010 [abs] [27]</td>
<td>Design: phase II</td>
<td>Age (mean yrs): nr</td>
<td></td>
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<tr>
<td>Country: Belgium</td>
<td>Funding: nr</td>
<td>Gender: % male: nr</td>
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<tr>
<td>Follow-up (mean ds): 816±361</td>
<td>Period: nr</td>
<td>Follow-up: nr</td>
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**DEB-TACE vs bland embolization**

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<tr>
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<tr>
<td>Malagari, 2010 [26]</td>
<td>To evaluate whether tumour necrosis is caused by the chemotherapeutic or by ischemia alone.</td>
<td>N=84 pts with intermediate unresectable and unre treatable with RFA HCC. Child-Pugh A or B.</td>
<td>DEB-TACE (N=41 ) Bland embolization (N=43) Mean number of treatments: nr</td>
<td>*Local response *TTP *Recurrence-free rate *Survival rate AE</td>
</tr>
<tr>
<td>Country: Greece</td>
<td>Design: parallel group</td>
<td>Age (mean yrs): DEB-TACE: 70.7; cTACE: 70</td>
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<tr>
<td>Funding: nr</td>
<td>Gender: 77% male</td>
<td>Period: nr</td>
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<tr>
<td>Period: nr</td>
<td>Follow-up: 12 mo</td>
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<tr>
<td>Brown, 2014 [abs][21]</td>
<td>To compare response rate with HAE versus DEB-TACE</td>
<td>N=101 pts with Okuda stage I or II</td>
<td>HAE: (N=51) vs DEB-TACE (N=50) 150 mg doxorubicin</td>
<td>*Response rate TTP PFS OS AE</td>
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<tr>
<td>Country: USA</td>
<td>Design: Phase II</td>
<td>Age (mean yrs): 67</td>
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<tr>
<td>Funding: nr</td>
<td>Gender: 77% male</td>
<td>Period: 77% male</td>
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<tr>
<td>Period: December 2007 to March 2012</td>
<td>Follow-up: nr</td>
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**TACE vs hepatectomy**

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<tr>
<td>Yin, 2014 [35]</td>
<td>To compare PH with TACE</td>
<td>N=173 pts with HCC outside the Milan criteria*</td>
<td>PH (N=90): by a clamp crushing method TACE (N=90): 5-fluorouracil (1 g), mitomycin C (20 mg), cisplatin (5 mg), and iodinated poppyseed oil iodinated poppyseed oil 10 to 30 mL (1 to 2 mL/cm diameter of the tumour). Mean number of treatments: 3.3 TACE sessions.</td>
<td>*OS AE</td>
</tr>
<tr>
<td>Country: China</td>
<td>Design: Open-label parallel group</td>
<td>Age (mean yrs): PH: 51.6; TACE: 54.0</td>
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<tr>
<td>Funding: Government, China</td>
<td>Gender: 93% male</td>
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## EVIDENCE SUMMARY FA2

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<tr>
<td><strong>TACE vs radiotherapy</strong></td>
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<tr>
<td>Mohnike, 2013 [abs] [29]</td>
<td>To compare BT and TACE</td>
<td>N=75 with advanced-stage HCC</td>
<td>BT (N=38) TACE (N=37)</td>
<td><strong>TTUP</strong></td>
</tr>
<tr>
<td>Country: Germany</td>
<td>Design: Parallel group. However, cross-over after the primary end point was reached or in case of technical failure.</td>
<td>Age (mean yrs): BT: 69.9 TACE: 67.1</td>
<td>Mean number of treatments: nr</td>
<td></td>
</tr>
<tr>
<td>Funding: nr</td>
<td>Gender: % male: nr</td>
<td>Period: nr</td>
<td></td>
<td><strong>OS</strong></td>
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<tr>
<td></td>
<td>Follow-up: nr</td>
<td></td>
<td></td>
<td><strong>AE</strong></td>
</tr>
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</tr>
<tr>
<td>Kolligs, 2013 [abs] [23]</td>
<td>To compare safety, efficacy and health economics of SIRT with yttrium-90 microspheres and TACE</td>
<td>N=28 pts with intermediate-stage HCC</td>
<td>TACE (N=15): epirubicin, iodinated poppyseed oil and embolizing agent; SIRT (N=13): yttrium-90 resin microspheres;</td>
<td><strong>Disease control</strong></td>
</tr>
<tr>
<td>SIRTACE</td>
<td>Design: Open-label multicentre pilot study</td>
<td>Age (mean yrs): 65.6</td>
<td>Mean number of treatments: TACE: 3.4; SIRT: 1</td>
<td></td>
</tr>
<tr>
<td>Country: Germany, Spain</td>
<td>Gender: % male: nr</td>
<td>Period: nr</td>
<td></td>
<td><strong>PFS</strong></td>
</tr>
<tr>
<td>Funding: nr</td>
<td>Follow-up: nr</td>
<td></td>
<td></td>
<td><strong>OS</strong></td>
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<tr>
<td></td>
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<td></td>
<td><strong>Hospital stay</strong></td>
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<td></td>
<td></td>
<td>Grade ≥3 <strong>AE</strong></td>
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<tr>
<td><strong>TACE vs systemic therapy</strong></td>
<td></td>
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<tr>
<td>Mabed, 2009 [25]</td>
<td>To compare TACE with systemic chemotherapy</td>
<td>N=100 with primary unresectable HCC, Child-Pugh A or B</td>
<td>TACE (N=50): cisplatin 50 mg, doxorubicin 40 mg, and iodinated poppyseed oil iodinated poppyseed oil 10 mL mixed with 10 mg doxorubicin)</td>
<td><strong>Tumour response:</strong></td>
</tr>
<tr>
<td>Country: Egypt</td>
<td>Design: Parallel group, open-label</td>
<td>Age (mean yrs): TACE: 52, systemic therapy: 51</td>
<td>Systemic therapy (N=50): 15 mg/m² doxorubicin intravenously on days 1, 8 and 15 for a total no greater than 500 mg/m².</td>
<td><strong>PFS</strong></td>
</tr>
<tr>
<td>Funding: nr</td>
<td>Gender: 65% male</td>
<td>Period: September 2005 to June 2005</td>
<td>Mean number of treatments: nr</td>
<td><strong>OS</strong></td>
</tr>
<tr>
<td></td>
<td>Follow-up (mean): 70 wks</td>
<td></td>
<td></td>
<td><strong>AE</strong></td>
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<tr>
<td><strong>TACE vs symptomatic treatment</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Lo, 2002 [4]</td>
<td>To compare TACE with symptomatic treatment, and identify prognostic factors</td>
<td>N=79 pts with un-resectable HCC</td>
<td>TACE (N=40): cisplatin to a maximum of 30 mg/mL + iodinated poppyseed oil iodinated poppyseed oil 10 mL mixed with 10 mg doxorubicin)</td>
<td><strong>OS</strong></td>
</tr>
<tr>
<td>Funding: nr</td>
<td>Gender: 88.6% male</td>
<td>Period: March 1996 to October 1997</td>
<td>Mean number of treatments: 4.5</td>
<td><strong>Patient tolerance</strong></td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td></td>
<td></td>
<td><strong>Liver function</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>AE</strong></td>
</tr>
<tr>
<td>Author, year (reference), study name, country, funding</td>
<td>Objectives, design</td>
<td>Population, data collection period, follow-up</td>
<td>Intervention, control</td>
<td>Outcomes</td>
</tr>
<tr>
<td>---------------------------------------------------------</td>
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</tbody>
</table>

^a Primary outcome
^b Milan criteria: a solitary tumour up to 5 cm or multiple tumours up to 3 in number and up to 3 cm for each tumour.
^c Quality of life was measured with the EORTC QLQ-C30 questionnaire and the EORTC QLQ-HCC 18 (data available only on 33 pts.
^d Response rate: patients with therapeutic effect (TE) IV and III/III all patients
^e The authors used LOCF in the analysis of the 6 months follow-up.
^f Only measurable pts

Abs = abstract; AE = adverse events, toxicity; BCLC = Barcelona Clinic Liver Cancer; BT = brachytherapy; CR = complete response; cTACE = conventional TACE; DC = Disease control; DEB = drug eluting beads; ds = days; EASL = European Association for the Study of the Liver; EORTC = European Organisation for Research and Treatment of Cancer; HAE = hepatic artery embolization; HCC = hepatocellular carcinoma; Hrs = hours; LEM = iodinated poppyseed oil-ethanol mixture; LOCF = last observation carried forward; mo = months; N = number of patients; n = number of procedures; Nr = not reported; OR = overall response; OS = overall survival; PES = postembolization syndrome; PFS = progression-free survival; PH = partial hepatectomy; PR = partial response; PRECISION = Prospective Randomized Study of Doxorubicin in the Treatment of Hepatocellular Carcinoma by Drug-Eluting Bead Embolization; Pts = patients; QoL = quality of life; RFA = radiofrequency ablation; SAE = serious AE; SAP = superabsorbent polymer; SIRT = selective internal radioembolization; sTACE = sequential TACE; TACE = transarterial chemoembolization; TAE = bland embolization; TE = therapeutic effect; TEA = transarterial ethanol ablation; TTP = time to progression; TTUP = time to untreatable progression; vs = versus; wk= week; yrs=years
Quality of Included Studies

Table 2 summarizes the quality of included studies. The studies are presented grouped according to type of comparison in the following text.

TACE versus transarterial injection

One study [36] examined TACE versus transarterial injection without embolization. The sample size was n=98. The study was stopped early because no difference was shown in overall survival; it was blinded and excluded from analysis those patients who had not received any treatment after randomization.

TACE versus bland embolization

Two fully published studies [3,28] compared TACE with bland embolization. Sample sizes were n=107 [3] and n=86 [28] patients. One of the studies was stopped early because of low accrual [28]; the other had a sequential design, and was stopped at the ninth sequential inspection, after 45 deaths, when TACE was shown to have benefits over conservative treatment. One of the studies blinded outcome assessors [28] while the other was not blinded. Both studies did an intention-to-treat analysis.

TACE versus DEB-TACE

Three fully published studies represented by four publications [22,24,31,33] and an abstract publication [27] compared cTACE with doxorubicin-eluting beads TACE. The sample size varied from n=30 to n=201. One of the studies was stopped early for futility [22]. One study blinded outcome assessors [24], while the others were unblinded [22,31] or did not report on blinding [27]. One study provided an intention-to-treat analysis, [22], while three did not [24,31] or did not report it [27].

DEB-TACE versus bland embolization

One fully published study [26] and a conference abstract [21] compared DEB-TACE with bland embolization. Sample sizes were n=84 in the fully published study [26] and n=101 in the abstract publication [21]. The fully published study used a centralized randomization procedure; however, it was not blinded and did not perform an intention-to-treat analysis [26]. Not enough information was available to evaluate the quality of the abstract publication [21]. This body of evidence presents risk of bias. The evidence base is made of one fully published study, which had a relatively small sample size, was not blinded and did not conduct an intention-to-treat analysis, and of one abstract publication, which did not report enough data to judge the quality of the evidence.

TACE versus hepatectomy

One fully published, unblinded, study provided evidence for this comparison [35].

TACE versus radiotherapy

Two abstract publications [23,29] compared TACE with brachytherapy or selective internal radioembolization. Not enough information was reported to decide on the quality of this body of evidence.

TACE versus systemic therapy

One fully published, unblinded study compared TACE with systemic therapy [25].
TACE versus symptomatic treatment

One fully published study [4] reported on this comparison; the study was unblinded, and it was not clear whether allocation was concealed. Another fully published, unblinded study [3] had a sequential design, and was stopped early at the ninth sequential inspection, after 45 deaths, when TACE was shown to have benefits over conservative treatment. Both studies conducted an intention-to-treat analysis.
Table 2. Quality assessment of included RCTs of TACE effectiveness.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment/comparison</th>
<th>Primary outcome</th>
<th>Required sample size</th>
<th>Loss to follow-up</th>
<th>Sample size, N</th>
<th>Randomization method described</th>
<th>Allocation concealment</th>
<th>Blinding</th>
<th>ITT analysis</th>
<th>Final analysis</th>
<th>Early termination</th>
<th>Ethical approval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TACE vs transarterial injection</td>
<td>OS (Phase III)</td>
<td>178 events were required to detect a hazard ratio of 1.53 (equivalent to a 15% difference at 1 yr) with 80% power and a two-tailed ( \alpha ) at 5%.</td>
<td>0(^a)</td>
<td>98</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes(^b)</td>
<td>No(^c)</td>
<td>Yes</td>
<td>Yes(^d)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>TACE vs bland embolization vs conservative treatment</td>
<td>OS</td>
<td>Assuming TACE and embolization: 2-yr survival: 65%: control: 40% (reference hazard ratio 0.47, allocation ratio 1), with ( \alpha = 0.05 ) and power of 80%, to detect an increase in survival. The maximum and mean numbers of events expected were 85 and 29, respectively, for comparisons between each treatment group and the control group. A positive ( z ) value indicates that treatment was better than control, and a negative value that treatment was worse. The slope of the upper boundary of the triangle was 0.26 (treatment significantly better than control, ( p &lt; 0.05 )) and that of the lower boundary was 0.79 (treatment worse than or equal to control). The study would be stopped when the plot line obtained crossed any boundary of the triangle.</td>
<td>3</td>
<td>107</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td></td>
<td>TACE vs DEB-TACE</td>
<td>2-yr OS</td>
<td>214 patients, 107 per treatment arm, were required to detect a 20% improvement from a 40% survival rate in the cTACE arm to obtain 80% power at 5% significance level.</td>
<td>3</td>
<td>177</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes(^e)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>TACE vs DEB-TACE</td>
<td>Tumour response at 6 mo</td>
<td>200 pts were required to obtain a power of 81.3% at a one-sided significance level of ( \alpha = 0.025 ), assuming objective tumour response rates of 55% (DEB-TACE) and 35% (cTACE).</td>
<td>3</td>
<td>201</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes(^f)</td>
<td>No(^g)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Study</td>
<td>Treatment/comparison</td>
<td>Primary outcome</td>
<td>Required sample size</td>
<td>Loss to follow-up</td>
<td>Sample size, N</td>
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<td>Allocation concealment</td>
<td>Blinding</td>
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</tr>
<tr>
<td>Sacco, 2011 [31]</td>
<td>cTACE vs DEB-TACE</td>
<td>Safety, toxicity, and tumour response at 1 month.</td>
<td>nr</td>
<td>0</td>
<td>67</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Maleux, 2010 [abs][27]</td>
<td>Doxorubicin-eluting HepaSpheres (SAP) vs cTACE</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>30</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>Yes</td>
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<td>nr</td>
</tr>
<tr>
<td>Malagari, 2010 [26]</td>
<td>DEB-TACE vs bland embolization</td>
<td>Local response TTP Recurrence-free rate</td>
<td>nr</td>
<td>3 at 12 months</td>
<td>84</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>nr</td>
</tr>
<tr>
<td>Brown, 2014 [abs][21]</td>
<td>DEB-TACE vs HAE</td>
<td>Response rate</td>
<td>nr</td>
<td>nr</td>
<td>101</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yin, 2014 [35]</td>
<td>PH vs TACE</td>
<td>OS</td>
<td>59 pts per group were needed to obtain a power of 80%, assuming a type-I error of 5% (α=0.05).</td>
<td>7</td>
<td>173</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Mohnike, 2013 [abs][29]</td>
<td>BT vs TACE</td>
<td>TTUP</td>
<td>nr</td>
<td>nr</td>
<td>75</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
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<tr>
<td>Kolligs, 2013 [abs][23]</td>
<td>TACE vs SIRT</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>28</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
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<tr>
<td>Study</td>
<td>Treatment/comparison</td>
<td>Primary outcome</td>
<td>Required sample size</td>
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<td>Sample size, N</td>
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<tr>
<td>TACE vs systemic therapy</td>
<td></td>
<td>TACE vs systemic therapy</td>
<td>Tumour response</td>
<td>3</td>
<td>100</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Mabed, 2009 [25]</td>
<td>TACE vs systemic therapy</td>
<td>Tumour response</td>
<td>50 pts per arm were required to detect a difference of 30% with ( \alpha=0.05 ) and power of 90%</td>
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<th>Study</th>
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<th>Required sample size</th>
<th>Loss to follow-up</th>
<th>Sample size, N</th>
<th>Randomization method described</th>
<th>Allocation concealment</th>
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<th>ITT analysis</th>
<th>Final analysis</th>
<th>Early termination</th>
<th>Ethical approval</th>
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<tbody>
<tr>
<td>Lo, 2002 [4]</td>
<td>TACE vs symptomatic treatment</td>
<td>OS</td>
<td>40 pts were required in each group to obtain a power of 80% with ( \alpha=0.05 )</td>
<td>2</td>
<td>79</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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</table>

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<thead>
<tr>
<th>Study</th>
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<th>Loss to follow-up</th>
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<th>Randomization method described</th>
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<th>Blinding</th>
<th>ITT analysis</th>
<th>Final analysis</th>
<th>Early termination</th>
<th>Ethical approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Llovet, 2002 [3]</td>
<td>TACE vs bland embolization vs conservative treatment</td>
<td>OS</td>
<td>Assuming TACE and embolization: 2-yr survival: 65%; control: 40% (reference hazard ratio 0.47, allocation ratio 1), with ( \alpha=0.05 ) and power of 80%. To detect an increase in survival, the maximum and mean numbers of events expected were 85 and 29, respectively, for comparisons between each treatment group and the control group. A positive ( z ) value indicates that treatment was better than control, and a negative value that treatment was worse. The slope of the upper boundary of the triangle was 0.26 (treatment significantly better than control, ( p&lt;0.05 )) and that of the lower boundary was 0.79 (treatment worse than or equal to control). The study would be stopped when the plot line obtained crossed any boundary of the triangle.</td>
<td>3</td>
<td>107</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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* Four patients in each arm were excluded from analysis
* Data collectors, outcome assessor and data analysists.
* Modified ITT: patients who did not receive any treatment after randomization were excluded from analysis.
* Trial stopped at the first interim analysis after 98 patients because no difference in the primary outcome was detected, and no difference was expected with continued enrollment.
* Stopped early for futility.
* Patients were blinded.
* Trial terminated early because of low accrual.
* Outcome assessors.
* The authors used the last observation carried forward in order to assess the primary end point for the entire ITT population
* The authors used sealed envelopes, but they did not described them as opaques.

BT = brachytherapy; c-TACE = conventional transarterial embolization; DEB-TACE = drug-eluting (doxorubicin) beads associated with TACE; HAE = hepatic artery embolization; ITT = intention-to-treat; nr = not reported; OS = overall survival; PH = partial hepatectomy; Pts = patients; SAP = superabsorbent polymer; SIRT = selective internal radioembolization; TACE = transarterial chemoembolization; chemotherapy; TEA = transarterial ethanol ablation; TTP = time to progression; TTUP = time to untreatable progression; vs = versus; Yr = years
Questions 1 and 1a: Efficacy of TACE.

Outcomes

The results of the included studies are summarized below and in Table 4; results of TACE versus transarterial injection, TACE versus hepatectomy, TACE versus systemic therapy, and TACE versus symptomatic treatment are presented on Table 4.

**TACE versus DEB-TACE**

For this comparison, the Huang et al meta-analysis [20] included six studies: two RCTs (the PRECISION V [24,33] and the Sacco et al study [31]), and four prospective or retrospective cohort studies. Our review identified three fully published RCTs [22,24,31] and an abstract publication [27] for this comparison. The results were statistically pooled for OS in a meta-analysis. Not enough data were available for the other outcomes; therefore, pooling in a meta-analysis was not considered.

**Overall Survival**

The Huang et al meta-analysis [20] did not present results for OS separately for RCTs and non-RCTs. The Sacco et al study [31], included in the Huang et al meta-analysis, and identified by our search, found a statistically nonsignificant between-group difference in OS (p=0.96). Our systematic review identified a more recent study by Golfieri et al [22], which had not been included by Huang et al [20]. We statistically pooled the results of the studies by Golfieri et al [22] and Sacco et al [31] and we found no statistically significant between-group difference (HR, 1.01; 95% confidence interval [CI], 0.74 to 1.39; p=0.94) (Figure 1).

**Progression-Free Survival**

None of the included studies reported on this outcome.

**Time to Progression**

Sacco et al [31] reported a statistically nonsignificant between-group difference time to progression (DEB-TACE, 82.5% versus cTACE, 80.1%; p=0.64).

**Response**

When Huang et al [20] statistically pooled the results for overall response from the two RCTs [24,31], they included in a subgroup analysis; the odds ratio was 1.55 (95% CI, 0.95 to 2.53, p=0.08). The additional study [22] found by our search reported no significant differences for all measures of response.

**Quality of Life**

None of the included studies reported on QoL.

**Length of hospital stay**
Golfieri et al [22] and Lammer et al [24,33] reported on length of hospital stay and did not find any statistically significant between-group difference (median three days [range one to 34 days] for DEB-TACE versus four days for TACE [range one to 26 days]); in Lammer et al (24,33), the mean length of hospital stay was 12 ± 9 days in both arms, respectively.

**DEB-TACE versus bland embolization**

A fully published RCT [26] and an abstract publication [21] compared hepatic artery embolization with DEB-TACE. The results were not pooled in a meta-analysis because not enough data were available for comparison. Results of this comparison are in Table 4.

**TACE versus radiotherapy**

Two conference abstracts [23,29] reported on this comparison. The results were not pooled in a meta-analysis because not enough data were available for comparison, and because the interventions in the two studies were different. The available data are presented in Table 4.

**Other comparisons**

Shi et al [32] reported a statistically significant advantage of the three-drug TACE versus the one-drug (epirubicin) TACE.
<table>
<thead>
<tr>
<th>Table 4 - Efficacy of TACE: Outcomes</th>
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</thead>
<tbody>
<tr>
<td><strong>Author, year (ref)</strong></td>
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<tr>
<td>-------------------------</td>
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<tr>
<td><strong>TACE vs transarterial injection</strong></td>
</tr>
<tr>
<td>Yu, 2014 [36]</td>
</tr>
<tr>
<td><strong>TACE vs Bland embolization</strong></td>
</tr>
<tr>
<td>Llovet, 2002 [3]</td>
</tr>
<tr>
<td>Meyer, 2013 [28]</td>
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<tr>
<td><strong>TACE vs DEB-TACE</strong></td>
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<tr>
<td>Golfieri, 2014 [22]</td>
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<tr>
<td>Lammer, 2010 [24] Vogl [33] PRECISION V</td>
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<tr>
<td>Sacco, 2011</td>
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<tr>
<td>Author, year (ref)</td>
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<tr>
<td>Maleux, 2010 [abs 27]</td>
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<td>Malagari, 2010 [26]</td>
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<td>Brown, 2014 [abs] [21]</td>
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<td>Yin, 2014 [35]</td>
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<td>Mohnike, BT vs TACE</td>
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<td>Author, year (ref)</td>
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<tr>
<td>2013 [abs] [29]</td>
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<td>Kolligs, 2013 [abs] [23]</td>
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<tr>
<td>TACE vs systemic therapy</td>
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<td>Mamed, 2009 [25]</td>
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<tr>
<td>TACE vs symptomatic treatment</td>
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<td>Lo, 2002 [4]</td>
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<tr>
<td>Llovet, 2002 [3]</td>
</tr>
</tbody>
</table>

A Milan criteria: a solitary tumour up to 5 cm or multiple tumours up to 3 in number and up to 3 cm for each tumour.

B Quality of life was measured with the EORTC QLQ-C30 questionnaire and the EORTC QLQ-HCC 18 (data available on 33 pts.

C Response rate: patients with therapeutic effect (TE) IV and III/all patients

D The authors used LOCF in the analysis of the 6 months follow-up.

E Only measurable pts
This study reports on doxorubicin peak concentrations.

Measured with EORTC QLQ-C30 questionnaire on 33 assessable patients.

Abs = abstract; BT = brachytherapy; CI = confidence interval; CR = complete response; cTACE = conventional TACE; DC = disease control; DEB = drug eluting beads; ds = days; EASL = European Association for the Study of the Liver; EORTC = European Organisation for Research and Treatment of Cancer; HR = hazard ratio; LEM = iodinated poppyseed oil-ethanol mixture; LOCF = last observation carried forward; mo = months; N = number of patients; n = number of procedures; NS = nonsignificant; OS = overall survival; PFS = progression-free survival; PH = partial hepatectomy; PR = partial response; PRECISION = Prospective Randomized Study of Doxorubicin in the Treatment of Hepatocellular Carcinoma by Drug-Eluting Bead Embolization; QoL = quality of life; SAP = superabsorbent polymer; SIRT = selective internal radioembolization; TACE = transarterial chemoembolization; TE= therapeutic effect; TEA = transarterial ethanol ablation; TTP = time to progression; TTUP = time to untreatable progression; vs = versus; wk= week; yrs=years
Adverse Events
Table 5 summarizes data on adverse events of all grades reported in the included studies. Grade ≥3 adverse events are reported in the following text.

**TACE versus bland embolization**
Meyer et al [28] reported a significantly better toxicity profile for bland embolization than for sequential TACE with cisplatin 50 mg administered four to six hours before embolization (63.5% versus 83.7%; p=0.019). Llovet et al [3] reported that 10% of patients in the TACE versus 3% in the bland embolization group discontinued treatment because of adverse events, and the difference was not statistically significant.

**DEB-TACE versus TACE**
The PRECISION V study [24,33] reported a 50% smaller postprocedural increase in ALT and a 41% smaller increase of aspartate aminotransferase (AST) in the doxorubicin-eluting beads TACE (DEB-TACE) group compared with cTACE (95% CI, 39% to 65%; p<0.001 and 95% CI, 46% to 76%; p<0.001, respectively). However, at six months follow-up, this difference in ALT and AST was no longer significant. Similarly, Sacco et al [31] reported a greater increase of postprocedural ALT in the cTACE (p=0.007), and Maleux et al [27] reported better liver function in the doxorubicin-eluting beads group than in the cTACE group (p=0.027). Golfieri et al [22] reported that DEB-TACE caused postprocedural pain in significantly fewer patients than cTACE (24.7% versus 71.6%, p=0.001). Alopecia was also found to be less severe in the DEB-TACE group compared with the cTACE group [24,33], although p values were not reported. No statistically significant between-group difference was found for postembolization syndrome [24,31,33] and, generally, other toxicities. These results are consistent with those of Huang et al [20], who included also non-RCTs in their meta-analysis.

**DEB-TACE versus TAE**
When comparing DEB-TACE with bland embolization, Malagari et al [26] and Brown et al [21] did not report any statistically significant difference in postembolization syndrome. Malagari et al [26] reported a statistically nonsignificant between-group difference for liver function derangements, respiratory failure, and all adverse events in general.

**TACE versus hepatectomy**
Yin et al [35] compared TACE with partial hepatectomy. Adverse events were different and, therefore, not comparable. No statistically significant between-group difference in treatment-related deaths was detected.

**TACE versus radiotherapy**
The abstract by Mohnike et al [29] did not report on adverse events of brachytherapy compared with TACE. The abstract by Kolligs et al [23] reported an overall statistically nonsignificant difference between TACE and selective internal radioembolization for all adverse events.
TACE versus systemic therapy
Mamed et al [25] compared TACE with systemic chemotherapy. Treatment-related mortality was 4% in the TACE arm and 0% in the chemotherapy arm. The other adverse events were of a different nature in the two treatment arms.

TACE versus symptomatic treatment
Table 5. Adverse events (all grades)

<table>
<thead>
<tr>
<th>Author, year (reference)</th>
<th>Intervention/control</th>
<th>Postembolization syndrome</th>
<th>Liver function derangements</th>
<th>Hematological</th>
<th>Cardiac impairment</th>
<th>Respiratory failure</th>
<th>Renal failure</th>
<th>Other</th>
<th>All adverse events</th>
<th>Treatment-related deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TACE vs transarterial ethanol injection</strong></td>
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<tr>
<td>Yu, 2014 [36]</td>
<td>TEA+LEM vs TACE       </td>
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<tr>
<td>Llovet, 2002 [3]</td>
<td>TAE vs TACE vs Control</td>
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<tr>
<td>Meyer, 2013 [28]</td>
<td>TAE vs sTACE</td>
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<tr>
<td><strong>DEB-TACE vs TACE</strong></td>
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<tr>
<td>Golfieri, 2014 [22]</td>
<td>DEB-TACE vs cTACE</td>
<td>      </td>
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<tr>
<td>Vogl, 2011 [33] PRECISION V</td>
<td>DEB-TACE (doxorubicin) vs cTACE</td>
<td>      </td>
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<tr>
<td>Author, year (reference)</td>
<td>Intervention/control</td>
<td>Post-embolization syndrome</td>
<td>Liver function derangements</td>
<td>Hematological</td>
<td>Cardiac impairment</td>
<td>Respiratory failure</td>
<td>Renal failure</td>
<td>Other</td>
<td>All adverse events</td>
<td>Treatment-related deaths</td>
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<tr>
<td>Sacco, 2011 [31]</td>
<td>cTACE and DEB-TACE</td>
<td>cTACE: 55.9%; DEB-TACE: 63.6%, p=0.51 (NS)</td>
<td>Greater increase of ALT 24 hrs after the procedure in the cTACE vs DEB-TACE, P=0.007. Bilirubin: p=NS</td>
<td>Prothrombin: p=NS</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>2 major complications, one in each arm.</td>
<td>nr</td>
</tr>
<tr>
<td>Maleux, 2010 [27]</td>
<td>cTACE vs Doxorubicin-eluting HepaSpheres (SAP).</td>
<td>nr</td>
<td>Better liver function in the SAP vs cTACE group (P=0.027)</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
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</tr>
</tbody>
</table>

**DEB-TACE vs bland embolization (TAE)**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Intervention/control</th>
<th>Postembolization syndrome HAE: 84.3%, vs LCB 83.7% P=NS</th>
<th>Liver failure: 4.8% vs 4.6%, p=NS cholecystitis: 4.8% vs 0%, p=NS</th>
<th>nr</th>
<th>nr</th>
<th>Pleural effusion: 4% vs 4%, p=NS</th>
<th>nr</th>
<th>p=NS for all; and skin erythema: 2.4% vs 0%</th>
<th>nr</th>
<th>nr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown, 2014 [21]</td>
<td>HAE vs DEB-TACE</td>
<td>nr</td>
<td></td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>Overall Gr3, Gr4, or Gr5 toxicity occurred in 45.7% of HAE and 54.3% of DEB-TACE patients</td>
</tr>
</tbody>
</table>

**TACE vs hepatectomy**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Intervention/control</th>
<th>Postembolization syndrome</th>
<th>Liver failure: 1%</th>
<th>Bleed leak: 5%</th>
<th>nr</th>
<th>nr</th>
<th>nr</th>
<th>nr</th>
<th>Bleeding: 2%</th>
<th>Infection:</th>
<th>nr</th>
<th>at 30-d and 90-d: 1 vs nr, p=NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yin, 2014 [35]</td>
<td>PH vs</td>
<td>NA</td>
<td>Liver failure: 1%</td>
<td>Bile leak: 5%</td>
<td>NA</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>at 30-d and 90-d: 1 vs nr, p=NS</td>
</tr>
</tbody>
</table>
## EVIDENCE SUMMARY FA2

<table>
<thead>
<tr>
<th>Author, year (reference)</th>
<th>Intervention/control</th>
<th>Post-embolization syndrome</th>
<th>Liver function derangements</th>
<th>Hematological</th>
<th>Cardiac impairment</th>
<th>Respiratory failure</th>
<th>Renal failure</th>
<th>Other</th>
<th>All adverse events</th>
<th>Treatment-related deaths</th>
</tr>
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<tbody>
<tr>
<td><strong>TACE</strong></td>
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<td>Nausea/Vomiting: 98% Pain: 56%</td>
<td>Increase in ALT/AST: 66% Increase in GGT: 40% Decrease in albumin: 29% Increase in bilirubin: 53%</td>
<td>Leukopenia: 39%</td>
<td>nr</td>
<td>nr</td>
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<tr>
<td><strong>TACE vs radiotherapy</strong></td>
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<tr>
<td>Mohnike, 2013 [abs] [29]</td>
<td>BT vs TACE</td>
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<td>nr</td>
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<tr>
<td>Kolligs, 2013 [abs] [23]</td>
<td>SIRT with yttrium-90 microspheres vs TACE</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>6 vs 4, P =0.433</td>
<td>nr</td>
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<tr>
<td><strong>TACE vs systemic therapy</strong></td>
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<tr>
<td>Mabed, 2009 [25]</td>
<td>TACE vs Systemic chemotherapy</td>
<td>92%</td>
<td>Gr 1 increase of liver enzymes: 64% Deterioration of liver function: 36% Liver failure 22% Liver abscess: 2%</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>Puncture site bleeding: 6% Esophageal varices rupture: 4% Cholecystitis: 2%</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>nr</td>
<td>Hematological toxicity: 38%</td>
<td>Gr2 cardiotoxicity: 4%</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>GI toxicity: 28%</td>
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<tr>
<td><strong>TACE vs symptomatic treatment</strong></td>
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<tr>
<td>Lo, 2002 [4]</td>
<td>TACE vs symptomatic</td>
<td>Fever: 32% Pain: 26% Vomiting: 16.7%</td>
<td>Liver abscess: 0.5%</td>
<td>Bradycardia: 0.5% Hypotension: 0.5%</td>
<td>nr</td>
<td>Pleural effusion: 1%</td>
<td>Hematuria: 0.5%</td>
<td>Ascites: 5.2% GI bleeding: 4.2%</td>
<td>1%</td>
<td>nr</td>
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</tbody>
</table>

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## EVIDENCE SUMMARY FA2

<table>
<thead>
<tr>
<th>Author, year (reference)</th>
<th>Intervention/control</th>
<th>Post-embolization syndrome</th>
<th>Liver function derangements</th>
<th>Hematological</th>
<th>Cardiac impairment</th>
<th>Respiratory failure</th>
<th>Renal failure</th>
<th>Other</th>
<th>All adverse events</th>
<th>Treatment-related deaths</th>
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<tbody>
<tr>
<td>treatment</td>
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<tr>
<td>Llovet, 2002 [3]</td>
<td>TAE vs TACE vs Control</td>
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<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>4% vs 10% vs 0%</td>
</tr>
</tbody>
</table>

*Grade 1 and 2; *All grades;

Abs = abstract; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BT = brachytherapy; CI = confidence interval; cTACE = conventional TACE; DEB = drug-eluting beads; GGT = gamma-glutamyl transpeptidase; GI = gastrointestinal; Gr = grade; LCB = LC bead; HAE = hepatic artery embolization; LEM = iodinated poppyseed oil-ethanol mixture; NA = not applicable; Nr = not reported; NS = not significant; PRECISION = Prospective Randomized Study of Doxorubicin in the Treatment of Hepatocellular Carcinoma by Drug-Eluting Bead Embolization; Pts = patients; SAP = superabsorbent polymer; SIRT = selective internal radioembolization; sTACE = sequential transarterial chemoembolization; TACE = transarterial chemoembolization; TAE = transarterial embolisation; TEA = transarterial ethanol ablation; vs = versus; wk = week; yrs = years
QUESTION 2 - SUBGROUPS

Four studies [22,24,32,36] reported subgroup analyses. Table 6 presents the results of these analyses.

Golfieri et al [22] and Lammer et al [24] used the same interventions. Lammer et al [24], in their pre-planned analysis, found that patients with more advanced disease (ECOG-1 and Child-Pugh B) had a better overall response, complete response, and disease control with DEB-TACE than with TACE (p=0.038, p=0.091, and p=0.026, respectively). In a post hoc analysis, Golfieri et al. [22] found that complete response was better after conventional TACE than after DEB-TACE for patients with less advanced disease. Yu et al. [36] did not detect any statistically significant difference in any subgroups. However, these authors found a better intrahepatic and intralesional time to progression and progression-free survival for transarterial ethanol ablation than with TACE (see Table 6 for results).

Table 6. Results of subgroups analyses.

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Subgroups</th>
<th>Results</th>
</tr>
</thead>
</table>
| Lammer, 2010 [24] | Patients with more advanced disease<sup>a</sup> | OR: higher in the DEB-TACE vs cTACE: p=0.038  
Disease control: higher in the DEB-TACE vs cTACE; p=0.026;  
CR: higher in the DEB-TACE vs cTACE; p=0.091 |
| Golfieri, 2014 [22] | Patients with less advanced disease<sup>b</sup> | CR at 30 ds was better after cTACE than after DEB-TACE (p=0.014 for pts in ECOG-0 [n=67 vs n=64] and p=0.027 in BCLC A [n=41 vs n=41]) |
| Yu, 2014 [36] | Any subgroups | TTP and PFS for any disease progression: NS difference  
Subclasses of TTP and PFS: Intrahepatic, intralesional progression:  
TTP: TEA: 34.6 mo (95% CI, 28.2 to 41.0) vs TACE: 26.05 mo (95% CI, 18.7 to 33.3), p=0.028  
PFS:TEA: 14.8 mo (95% CI, 10.2 to 19.5) vs TACE: 9.3 mo (95% CI, 7.1 to 11.5), p=0.029 |

<sup>a</sup>Child Pugh class B, ECOG-1, bilobar or recurrent disease; <sup>b</sup>patients in ECOG-0 and BCLC A

BCLC=Barcelona Clinic Liver Cancer liver cancer stage - patients in stage B (intermediate) have a large, multifocal tumour, patients in stage C (advanced) have tumours that invaded the blood vessels or that spread to other sites; CI = confidence interval; CR = complete response; cTACE = conventional TACE; DEB = drug-eluting beads; ECOG-0 = Eastern Cooperative Oncology Group performance status grade 0 (fully active, able to carry on all pre-disease performance without restriction); ECOG 1 = patients in grade 1 are restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; mo = months; NS = non significant; OR = overall response; PFS = progression-free survival; pts = patients; TACE = transarterial chemoembolization; TAE= bland embolization; TEA = transarterial ethanol ablation; TTP = time to progression; vs = versus; yrs = years

Ongoing, Unpublished, or Incomplete Studies

An abstract publication was an interim analysis [37]. Table 7 shows the ongoing trials that have been identified through clinicaltrials.gov.
<table>
<thead>
<tr>
<th>Interventions</th>
<th>Official title</th>
<th>Status</th>
<th>Protocol ID</th>
<th>Completion Date</th>
<th>Last updated</th>
</tr>
</thead>
<tbody>
<tr>
<td>TACE vs TARE</td>
<td>A Randomized, Multi-center, Open Label, Phase 3 Trial Comparing Conventional TACE and Transarterial Radioembolization in Patients With Unilobar Advanced Hepatocellular Carcinoma</td>
<td>Recruiting</td>
<td>NCT02004210</td>
<td>April 2018</td>
<td>November 26, 2014</td>
</tr>
<tr>
<td>TACE vs HR</td>
<td>Hepatic Resection Versus Transcatheter Arterial Chemoembolization for Hepatocellular Carcinoma Complicated by Portal Vein Tumor Thrombosis. A Prospective and Randomized Clinical Trial</td>
<td>Unknown</td>
<td>NCT01350206</td>
<td>May 2013</td>
<td>Not available</td>
</tr>
<tr>
<td>TACE vs non-TACE</td>
<td>The Efficacy and Safety of Retreatment With Transarterial Chemoembolization (TACE) for Patients Who Showed TACE-resistant: A Randomized Controlled Trial</td>
<td>Recruiting</td>
<td>NCT02220088</td>
<td>January 2016</td>
<td>August 18, 2014</td>
</tr>
<tr>
<td>Chemoembolization and Response-Dependent Resection vs Immediate Resection</td>
<td>Hepatic Resection Versus Transarterial Chemoembolization as the Initial Treatment for Resectable Hepatocellular Carcinoma Beyond Milan Criteria</td>
<td>Recruiting</td>
<td>NCT02138981</td>
<td>August 2018</td>
<td>May 14, 2014</td>
</tr>
<tr>
<td>TACE vs radiotherapy</td>
<td>Adjuvant Radiotherapy Comparing Transarterial Chemoembolization for Curative Hepatocellular Carcinoma: a Randomized Controlled Trials</td>
<td>Recruiting</td>
<td>NCT02125396</td>
<td>June 2016</td>
<td>Not applicable</td>
</tr>
<tr>
<td>DEB-TACE vs 90Y-RE</td>
<td>Transarterial Radioembolization Versus ChemoEmbolization for the Treatment of HCC: A Multicenter Randomized Controlled Trial (TRACE Trial)</td>
<td>Recruiting</td>
<td>NCT01381211</td>
<td>December 2014</td>
<td>December 2014</td>
</tr>
<tr>
<td>TACE vs CT-guided brachytherapy</td>
<td>Phase-III Study to Evaluate the Efficacy of CT-guided Brachytherapy Versus Transarterial Chemoembolization in Patients With Unresectable Hepatocellular Carcinoma</td>
<td>Recruiting</td>
<td>NCT00807300</td>
<td>December 2015</td>
<td>January 2015</td>
</tr>
<tr>
<td>TACE vs Sorafenib</td>
<td>An Open Label, Phase 2 Trial Comparing Sorafenib And TACE in Advanced Hepatocellular Carcinoma With Portal Vein Invasion</td>
<td>Recruiting</td>
<td>NCT01480817</td>
<td>December 2014</td>
<td>November 26, 2014</td>
</tr>
<tr>
<td>SBRT after incomplete TAE vs TACE vs Exclusive TAE or TACE</td>
<td>A Randomised Phase III Trial on Stereotactic Body Radiotherapy (SBRT) After Incomplete Transcatheter Arterial Embolization (TAE) or Chemoembolization (TACE) Versus Exclusive TAE or TACE for Inoperable Hepatocellular Carcinoma (HCC)</td>
<td>Recruiting</td>
<td>NCT02323360</td>
<td>May 2018</td>
<td>December 22, 2014</td>
</tr>
<tr>
<td>cTACE vs hepasphere1quadrasphere microspheres</td>
<td>Phase 3 Prospective, Randomized, Blinded, and Controlled Investigation of HepaSphere/QuadraSphere Microspheres for Delivery of Doxorubicin for the Treatment of Hepatocellular Carcinoma</td>
<td>Recruiting</td>
<td>NCT01387932</td>
<td>December 2014</td>
<td>December 2, 2014</td>
</tr>
<tr>
<td>Transarterial embolization vs: Transarterial infusion chemotherapy vs: Transarterial iodinated poppyseed oil iodinated poppyseed oil chemotherapy</td>
<td>Chemoembolization of Unresectable Hepatocellular Carcinoma With or Without iodinated poppyseed oil Chemotherapy: Effectiveness and Safety. A Prospective and Randomized Clinical Trial.</td>
<td>Recruiting</td>
<td>NCT01229839</td>
<td>November 2016</td>
<td>August 3, 2013</td>
</tr>
<tr>
<td>TACE with mitomycin C, doxorubicin hydrochloride, and cisplatin vs 90Y-RE</td>
<td>An Investigator Initiated Multicenter Prospective Randomized Study of Chemoembolization Versus Radioembolization for the Treatment of Hepatocellular Carcinoma (PREMIERE Trial)</td>
<td>Recruiting</td>
<td>NCT00956930</td>
<td>August 2018</td>
<td>November 11, 2014</td>
</tr>
<tr>
<td>TACE+ sorafenib vs sorafenib</td>
<td>A Randomized, Controlled Phase III Trial of Sorafenib With or Without Conventional Transarterial Chemoembolization in Patients With Advanced Hepatocellular Carcinoma (STAH Study)</td>
<td>Recruiting</td>
<td>NCT01829035</td>
<td>October 2016</td>
<td>April 2, 2014</td>
</tr>
</tbody>
</table>
EVIDENCE SUMMARY FA2

\(^{90}\text{Y-RE} = \) Yttrium 90 radioembolization; CT = computed tomography; cTACE = conventional TACE; DEB-TACE = TACE with drug-eluting beads; HR = hepatic resection; SBRT = stereotactic body radiation therapy; TACE = transarterial chemoembolization; TAE = bland embolization; TARE = transarterial radioembolization; vs = versus
QUESTION 3 - Ambulatory versus inpatient TACE

Literature Search Results

Trials of feasibility and safety of ambulatory TACE

The search for observational studies of ambulatory TACE identified 94 citations: 14 from MEDLINE, 77 from EMBASE, none from the Cochrane Library, none from the reference lists of included studies, and three from authors’ files. The methodologist (FGB) reviewed the titles and the abstracts against the selection criteria and identified six citations as possibly relevant. Eleven citations were excluded at the title and abstract level because they were published in a language other than English (see Appendix 3C). The full text of the six articles was retrieved in the library and the methodologist reviewed the full text against the selection criteria outlined above. Five studies were included [38-42]. The general characteristics and summary results of these studies are presented in Table 8.

Quality of included studies

Prapjapati et al [38] was a prospective comparative study. All the other included studies were observational noncomparative studies. Nasser et al [39] was prospective, and Todd et al [41], Goldstein et al [42], and Mitchell et al [40] were retrospective chart reviews. Goldstein et al [42] and Todd et al [41] were abstract publications; the others were fully published articles. We did not evaluate these studies with a specific tool.

Outcomes

Prapjapati et al [38] showed that patients who received outpatient DEB-TACE experienced a shorter recovery time, fewer hospitalization days, and fewer complications. The Nasser et al [39] study was a single-arm, prospective trial of DEB-TACE. The authors reported a high rate of technical success, and a small complication rate, with no readmissions to hospital or deaths at one month. The other studies [40-42] were retrospective chart reviews, which evaluated TACE and bland embolization, and also reported low rates of complications after outpatients procedures (data are reported in Table 8).
Table 8. Ambulatory TACE. General characteristics and results of included observational studies.

<table>
<thead>
<tr>
<th>Author, year (reference)</th>
<th>Objectives, Design</th>
<th>Population, data collection period</th>
<th>Intervention, (control)</th>
<th>Outcomes</th>
<th>Summary results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prajapati, 2012 [38]</td>
<td>To investigate safety and feasibility of same-day discharge after DEB-TACE and to explore prognostic factors for hospital admission</td>
<td>N=76 pts with unresectable HCC receiving 110 procedures Group A: pts treated in an outpts setting Group B: pts admitted to hospital Child-Pugh class: A: 61% B: 37% C: 0.9% Age (mean): 61 years Gender: 78.9% men Follow-up: 4 wks Period: November 2009 to June 2010</td>
<td>Superselective 100-300 µm DEB-TACE</td>
<td>(1) Hospital stay and discharge (2) Median recovery duration (3) Median hospital stay (4) Safety</td>
<td>(1) 84.5% of pts were discharged on the same day; 15.5% of pts were admitted to hospital for overnight stays. In 64.1% of procedures, pts had BCLC stage C HCC; after 84% of procedures in this group pts were discharged safely on the same day. In 29.1% of procedures, pts had partial or complete PVT; In this group after 87.5% of procedures the pts were safely discharged on the same day.</td>
</tr>
<tr>
<td>Nasser, 2014 [39]</td>
<td>To evaluate the safety and feasibility of same-day discharge, and to uncover the prognostic factors for hospital admission</td>
<td>N=154 pts with HCC in a liver transplantation program receiving 266 procedures Child-Pugh class: A: n=142, B: n=111; C: n=13; Downstaging: n=87 Bridging: n=179 Single tumour: 110 Multinodular: 156 Age (mean): 58 yrs Gender: 77% male Follow-up: 4 wks Period: March 2011 to February 2013</td>
<td>DEB-TACE performed with an outpatient protocol before liver transplantation as a bridging or downstaging method</td>
<td>(1) Admission to hospital after the procedure (2) Readmission to hospital within 1 month (3) procedure-related morbidity and mortality (4) Prognostic factors for hospitalization</td>
<td>(1) Technical success rate 99.6%. Post-procedure hospital admission 67.8% Feasibility: 89.5% of procedures were feasible in outpatient setting; 10.5% needed overnight admission. (2) No readmissions or deaths at 1 month. (3) Complication rate: 2.6% including artery dissection during the procedure, puncture site bleeding, hematoma, acute MI. (4) Prognostic factors associated with increased hospitalization: chemoembolization performed for HCC downstaging (p=0.012), increased doxorubicin dose (p=0.004), and the use of more than one vial of embolic agent (p=0.007). Prognostic factors associated with decreased hospitalizations: Preprocedural use of oxycodone (p=0.043)</td>
</tr>
<tr>
<td>Todd, 2014 [abs] [41]</td>
<td>To evaluate the safety of outpatient TACE in pts with intermediate and advanced HCC</td>
<td>n=26 pts in Child-Pugh B and C receiving 69 procedures Age: NR Gender: NR Follow-up: NR</td>
<td>TACE</td>
<td>(1) Readmission to hospital (48 hrs post discharge), (2) ER visit (48 hrs post discharge)</td>
<td>(1) Readmissions: None (2) ER visit: 1 pt with intermediate disease in the outpatients group; 0 in the inpatient group</td>
</tr>
<tr>
<td>Author, year (reference)</td>
<td>Objectives, Design</td>
<td>Population, data collection period</td>
<td>Intervention, (control)</td>
<td>Outcomes</td>
<td>Summary results</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------------</td>
<td>-------------------------------------</td>
<td>-------------------------</td>
<td>----------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Goldstein, 2014 [abs] [42]</td>
<td>To verify if outpatient chemoembolization is safe</td>
<td>N=238 pts in an outpatient setting Period: July 2009 to October 2011 Age: NR Gender: NR Follow-up: 4-6 wks</td>
<td>Chemoembolization</td>
<td>Complications</td>
<td>Complication rate: 0.8%; HCC rupture (n=1) and hepatic abcess (n=1)</td>
</tr>
<tr>
<td>Mitchell, 2009 [40]</td>
<td>To evaluate the safety and feasibility of outpatient TAE and TACE</td>
<td>N=77 pts with lesions larger than 3 cm or with multiple tumours in a liver transplant program who received 133 procedures Child-Pugh class: A: 81% B: 19% Solitary tumour: 64% Multifocal: 36% Age (mean): 60.1 yrs Gender: 73% men Follow-up: 4 wks Period: January 2005 to June 2006</td>
<td>Bland embolization and chemoembolization</td>
<td>Safety</td>
<td>In 2 of 133 procedures (2%) pts were admitted to hospital after the procedure, and in 2 cases of 131 procedures (2%) pts were admitted to hospital after being discharged at home because of complications.</td>
</tr>
</tbody>
</table>

* Multivariate analysis

Abs = abstract; BCLC = Barcelona Clinic Liver Cancer; DEB = drug-eluting beads; ER = emergency department; HCC = hepatocellular carcinoma; Hrs = hours; MI = myocardial infarction; N = number of patients; n = number of procedures; NR = not reported; PES = postembolization syndrome; Pts = patients; PVT = portal vein thrombosis; TACE = transarterial chemoembolization; TAE = bland embolization; wk = week; yrs = years
DISCUSSION

**Question 1 and 1a: Effectiveness of TACE and side effect profile of TACE versus DEB-TACE**

- Some evidence suggests that OS is better with TACE than with no therapy [3,4].
- There is lack of extensive evidence regarding bland embolization versus TACE. The two major RCTs have not demonstrated superiority of TACE over bland embolization [3,28].
- A single RCT [36] demonstrated equivalency of TAE to TACE for OS, with improved CR and PFS for TAE over TACE.
- A single RCT [35] demonstrates superior OS of partial hepatectomy over TACE for patients with resectable HCC with multiple lesions that do not meet the Milan criteria, and are at low surgical risk.
- No statistically significant between-group difference in adverse event profile of TACE versus DEB-TACE was reported. One study [24] reported a greater degree of alopecia in patients who received TACE than in those who received DEB-TACE, but statistical significance values were not reported.

**Question 2: Subgroups of patients that most likely benefit from TACE**

- Some evidence from a preplanned subgroup analysis shows that patients with more advanced disease (ECOG-1 and Child-Pugh B) had a better overall response, complete response, and disease control with DEB-TACE than with conventional TACE [24]. Conversely, a post hoc analysis showed that in patients with less advanced disease (ECOG-0 and Barcelona Cancer Liver Clinic A), complete response was better after conventional TACE than after DEB-TACE [22].
- One study showed, in a preplanned analysis, that for subclasses of PFS and TTP (intrahepatic, intralesional progression) TEA was better than TACE [36].

**Question 3: Ambulatory TACE**

- One observational comparative study [38] showed a shorter recovery time and hospital stay, as well as lower complication rates in the outpatient versus the inpatient group.
- Observational evidence from single-arm studies showed very low complication rates and readmission rates for outpatients [39,40].

**Report Review by the Director of the PEBC**

The purpose of the review by the Director of the PEBC is to ensure the methodological rigour and quality of PEBC evidence summaries. The Working Group is responsible for ensuring the necessary changes are made. If those changes could be made without substantially altering the conclusions, the altered draft would not need to be resubmitted for approval again.

The Director of the PEBC reviewed the document on April 13, 2015. During this review the Director provided feedback.

In response to this feedback, the Working Group made some small editorial changes.

**Report Approval by the Focal Ablation Advisory Committee**

After internal review, the report is presented to the the Focal Ablation Advisory Committee.

The the Focal Ablation Advisory Committee reviewed the document and approved it at on March 6, 2015.
CONFLICT OF INTEREST
In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, the Focal Ablation Advisory Committee members, and internal reviewers were asked to disclose potential conflicts of interest. The conflict of interest statements of the working group and of the Advisory Committee are summarized in Appendix 5.

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- Elizabeth Chan and Kristy Yu for conducting a data audit.
- Sara Miller for copyediting.

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For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca
APPENDIX 1: Search Strategies

Focal ablation effectiveness of TACE: Search strategy for systematic reviews

Database: Ovid MEDLINE(R) without Revisions <1996 to September Week 1 2014>, Ovid MEDLINE(R) Daily Update <September 12, 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <September 12, 2014>

Search Strategy:

1. (systematic adj (review: or overview:)).mp.
2. (meta-analy: or metaanaly:).mp.
3. (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthesis: or quantitative overview:).mp. (4904)
4. (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw. (55540)
5. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab. (92904)
6. (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab. (24279)
7. or/1-6 (183308)
8. (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab. (37586)
9. (stud: adj1 select:).ab. (12233)
10. (8 or 9) and review.pt. (24464)
11. 7 or 10 (185976)
12. (guideline or practice guideline).pt. (20662)
13. exp consensus development conference/ (7612)
14. consensus/ (4682)
15. (guideline: or recommend: or consensus or standards).ti. (80444)
16. 12 or 13 or 14 or 15 (93341)
17. 11 or 16 (273956)
18. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or case report or historical article).pt. (1198757)
19. 17 not 18 (253008)
20. exp Embolization, Therapeutic/ (22117)
21. (((transcatheter or transarterial) and (emboli* or chemoemboli*)) or TAE or TACE).mp. (8568)
22. 20 or 21 (25788)
23. exp Carcinoma, Hepatocellular/ (38653)
24. (Hepatocellular carcinoma* or HCC* or hepatoma*).mp. (54486)
25. 23 or 24 (60797)
26. 22 and 25 (4180)
27. 19 and 26 (172)

***************************
Database: EMBASE <1996 to 2014 Week 37>
Search Strategy:

1 exp artificial embolism/ (47834)
2 (((transcatheter or transarterial) and (emboli* or chemoem- bolit*)) or TAE or TACE).mp. (11535)
3 1 or 2 (51392)
4 exp liver cell carcinoma/ (73609)
5 (hepatocellular carcinoma* or HCC* or hepatoma*).mp. (56895)
6 4 or 5 (91106)
7 3 and 6 (9025)
8 (systematic adj (review: or overview:)).mp. (110590)
9 (meta-analy: or metaanaly:).mp. (122345)
10 (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthesis: or quantitative overview:).mp. (7360)
11 (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw. (53172)
12 (cochrane or embase or psychlit or psycheit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab. (109827)
13 (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab. (28502)
14 (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab. (44125)
15 (stud: adj1 select:).ab. (15033)
16 (14 or 15) and review.pt. (23155)
17 or/8-13 (258090)
18 16 or 17 (261230)
19 consensus development conference/ (8011)
20 practice guideline/ (233302)
21 *consensus development/ or *consensus/ (3420)
22 *standard/ (1525)
23 (guideline: or recommend: or consensus or standards).kw. (29172)
24 (guideline: or recommend: or consensus or standards).ti. (104315)
25 or/19-24 (299721)
26 (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/ (1771864)
27 (18 or 25) not 26 (457097)
28 7 and 27 (496)

Search Strategy:

1 Embolization.mp. [mp=ti, ot, ab, tx, kw, ct] (108)
2 (((transcatheter or transarterial) and (emboli* or chemoemboli*)) or TAE or TACE).mp. (91)
3 (Hepatocellular carcinoma* or HCC* or hepatoma*).mp. (372)
4 1 and 2 (15)
5 3 and 4 (11)

*****************************************************************************
Focal ablation effectiveness of TACE: Search strategy for randomized controlled trials

Database: Ovid MEDLINE(R) without Revisions <2002 to October Week 4 2014>, Ovid MEDLINE(R) Daily Update <October 21, 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <October 21, 2014>

Search Strategy:

1. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
2. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
3. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
4. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
5. or/1-4
6. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
7. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
8. (6 or 7) and random$.tw.
9. (clinic$ adj trial$1).tw.
10. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
11. placebos/
12. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
14. or/9-13
15. 5 or 8 or 14
16. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
17. 15 not 16
18. exp animals/ not humans/
19. 17 not 18
20. exp Embolization, Therapeutic/
21. (((transcatheter or transarterial) and (emboli* or chemoembol*)) or TAE or TACE).mp.
22. 20 or 21
23. exp Carcinoma, Hepatocellular/
24. (Hepatocellular carcinoma* or HCC* or hepatoma*).mp.
25. 23 or 24
26. 22 and 25
27. 19 and 26
Database: EMBASE <2002 to 2014 Week 46>

1. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
2. randomization/ or single blind procedure/ or double blind procedure/
3. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
4. or/1-3
5. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
6. 5 and random$.tw.
7. (clinic$ adj trial$1).tw.
8. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
9. placebo/
10. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
11. (allocated adj2 random).tw.
12. or/7-11
13. 4 or 6 or 12
14. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
15. 13 not 14
16. animal/ not human/
17. 15 not 16
18. exp artificial embolism/
19. (((transcatheter or transarterial) and (emboli* or chemoemboli*)) or TAE or TACE).mp.
20. 18 or 19
21. exp liver cell carcinoma/
22. (Hepatocellular carcinoma* or HCC* or hepatoma*).mp.
23. 21 or 22
24. 20 and 23
25. 17 and 24
Database: EBM Reviews - Cochrane Central Register of Controlled Trials <October 2014>
Search Strategy:
1. exp Embolization, Therapeutic/
2. (((transcatheter, or transarterial) and (emboli or chemoemboli)) or TAE or TACE).mp.
3. 1 or 2
4. exp Carcinoma, Hepatocellular/
5. (Hepatocellular carcinoma* or HCC* or hepatoma*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6. 4 or 5
7. 3 and 6
Focal ablation ambulatory versus inpatient TACE: Search strategy for systematic reviews

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <3rd Quarter 2014>
Search Strategy:
--------------------------------------------------------------------------------
1  chemoembolization.mp. [mp=title, full text, keywords] (50)
2  (((transcatheter, or transarterial) and (emboli or chemoemboli)) or TAE or TACe).mp. (15)
3  1 or 2 (55)
4  (hepatocellular carcinoma or HCC or hepatoma).tw. (231)
5  3 and 4 (45)
6  outpatient.mp. [mp=title, full text, keywords] (269)
7  ambulatory care.mp. [mp=title, full text, keywords] (152)
8  patient discharge.mp. [mp=title, full text, keywords] (80)
9  length of stay.mp. [mp=title, full text, keywords] (749)
10  (same-day adj2 discharge).tw. (12)
11  6 or 7 or 8 or 9 or 10 (1158)
12  5 and 11 (0)
Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to September 2014>
Search Strategy:

1 chemoembolization.mp.
Focal ablation for liver cancer: TACE in ambulatory settings: Search for primary studies

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy: Oct 16, 2014

exp Embolization, Therapeutic/ (30362)
2 (((transcatheter or transarterial) and (emboli* or chemoemboli*)) or TAE or TACE).mp. (10933)
3 1 or 2 (34596)
4 exp Carcinoma, Hepatocellular/ (61356)
5 (Hepatocellular carcinoma* or HCC* or hepatoma*).mp. (80383)
6 4 or 5 (94432)
7 3 and 6 (5434)
8 *ambulatory care/ (15993)
9 "Length of Stay"/ (61066)
10 *patient discharge/ (8918)
11 (outpatient adj4 embolization).mp. (11)
12 (same-day adj2 discharge).tw. (292)
13 8 or 9 or 10 or 11 or 12 (84104)
14 7 and 13 (17)
15 from 14 keep 1-17 (17)

***************
Database: Embase <1996 to 2014 Week 41>
Search Strategy:
--------------------------------------------------------------------------------
1 exp artificial embolism/ (48366)
2 (((transcatheter, or transarterial) and (emboli or chemoemboli)) or TAE or TACe).mp. (7428)
3 1 or 2 (50910)
4 exp liver cell carcinoma/ (74190)
5 (Hepatocellular carcinoma* or HCC* or hepatoma*).mp. (81394)
6 4 or 5 (97080)
7 3 and 6 (9243)
8 *ambulatory care/ (5675)
9 outpatient.mp. or *outpatient/ (145212)
10 (same-day adj2 discharge).tw. (450)
11 *hospital discharge/ (5625)
12 8 or 9 or 10 or 11 (154457)
13 7 and 12 (84)
*******************************************************************************
APPENDIX 2: Study Flow Charts

A). Figure 1: Study flow chart: guidelines.

Identification

# of records identified through database searching
N=326

# of additional records identified through other sources
N=326

Screening

# of records screened at the title and abstract level
N=652

# of records excluded
n=617
# of records kept as background
n=6

Eligibility

# of full-text articles assessed for eligibility
N=29

Studies included and kept as a source of evidence
N=2

Full-text articles excluded:
Consensus based on narrative review:
(n=11)
Focus not on TACE (n = 5)
Duplicate (n=1)
Not population of interest (n=2)
Narrative review with no recommendations:
(n=8)
APPENDIX 2B): Figure 2: Study flow chart: systematic reviews.

- # of records identified through database searching: N=306
- # of additional records identified through other sources: N=223
- # of records screened at the title and abstract level: N=529
- # of full-text articles assessed for eligibility: N=46
- # of studies included after full text: N=9
- Studies evaluated with AMSTAR: N=2
- Studies used to integrate the evidence from primary studies: N=1

# of records excluded: (n=477)
- Of these 40 were excluded because not in English language

# of records kept as background: (n=6)

# of full-text articles excluded:
- Search before 2006: (n=3)
- Not English: (n=2)
- Combination therapy: (n=10)
- Not TACE: (n=6)
- Not outcomes of interest: (n=1)
- Not systematic review: (n=15)
APPENDIX 2C: Figure 3: Study flow chart: randomized controlled trials of TACE effectiveness.

- **Identification**
  - # of records identified through database searching N=788
  - # of additional records identified through other sources N=327
  - # of records after duplicates removed N=1115

- **Screening**
  - # of records screened N=1115
  - Excluded n=1031
    - Background n=3

- **Eligibility**
  - # of full-text articles assessed for eligibility N=81
  - Excluded
    - Not population of interest: n=2
    - Abstract of interim analysis: n=1
    - Not intervention of interest: n=40
    - Duplicate publications: n=10
    - Not outcome of interest: n=7
    - Not design of interest: n=2
    - Not English language: n=1

- **Included**
  - # of studies included in qualitative synthesis N=15 represented by 16 publications
APPENDIX 2D): Study flow chart: observational studies (inpatient vs outpatient question).

- # of records identified through database searching N=91
- # of additional records identified through other sources N=3
- # of records after duplicates removed N=94
- # of records screened N=94
- # of full-text articles assessed for eligibility N=6
- # of records excluded n=85
  - Background n=3
- # of full-text articles excluded, with reasons
  - n=1
  - Abstract of interim analysis
- # of studies included in qualitative synthesis N=5
APPENDIX 3: Excluded studies trials by reason for exclusion.

A) Systematic reviews

Systematic reviews excluded at the title and abstract level because published in languages other than English


Systematic reviews excluded at the full-text level.

Studies with a search cut-off prior to 2006


Studies reporting on TACE in combination with other therapies


Studies published in a language other than English

Studies not reporting on the intervention of interest

Studies not reporting on outcomes of interest


B) Randomized controlled trials

Articles that were excluded at the title and abstract level because they were in a language other than English


37. Aube C. [Annotated analysis of the article: chemoembolization combined with radiofrequency ablation for patients with hepatocellular carcinoma larger than 3 cm. A randomized controlled trial]. J Radiol. 2008;89(9 Pt 1):1050-2. Ablation tumorale par radiofrequence des CHC de plus de 3 cm: avec ou sans chimio-embolisation iodinated poppyseed oil iodinated poppyseed oil?


83. Chen DL, Xu XM, Chen MC. Transcatheter arterial chemoembolization combined with intratumoral injection of iodized oil and ethanol for middle-advanced stage


Randomized controlled trials: studies excluded at full text because did not report on the population of interest:


Randomized controlled trials: studies excluded at full text because were abstracts reports of interim analyses:


Randomized controlled trials: studies that were excluded at full text because reported on TACE in combination with other strategies


Randomized controlled trials: studies excluded at full text because were duplicate publications:


Randomized controlled trials: studies excluded at full text because did not report on any outcomes of interest:


Randomized controlled trials: studies excluded at full text because did not report on any intervention of interest:


overall survival increase in inoperable hepatocellular carcinoma (hcc) patients. Hepatology. 2011;54:1388A-9A.


Randomized controlled trials: studies excluded at full text because were not randomized trials:


C) Observational studies of ambulatory TACE. Studies excluded at the title and abstract level because not in English language


APPENDIX 4: AMSTAR ratings of included systematic reviews

Table 1. Systematic reviews of TACE included at full text. Results of the clinical evaluation

<table>
<thead>
<tr>
<th>Citation</th>
<th>Results of Evaluation of clinical content*</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang, 2014 [20]</td>
<td>yes</td>
<td>Answers question 1A</td>
</tr>
<tr>
<td>Han, 2014 [19]</td>
<td>no</td>
<td>Combines in meta rcts and case control studies -</td>
</tr>
<tr>
<td>Cheng, 2014 [18]</td>
<td>no</td>
<td>Some of the trials are post-op (combination therapy)</td>
</tr>
<tr>
<td>Gao, 2013 [7]</td>
<td>no</td>
<td>Includes only deb TACE, and excludes other drugs for the beads other than doxorubicin.</td>
</tr>
<tr>
<td>Zhao, 2013 [17]</td>
<td>no</td>
<td>Includes only non rcts 3 prospective 12 retrospective</td>
</tr>
<tr>
<td>Xue, 2013 [9]</td>
<td>no</td>
<td>Includes only non-RCTs</td>
</tr>
<tr>
<td>Martin, 2012 [16]</td>
<td>yes</td>
<td>Answers question 1A</td>
</tr>
<tr>
<td>Oliveri, 2011 [8]</td>
<td>no</td>
<td>Includes TACE and TAE</td>
</tr>
<tr>
<td>Carter, 2009 [6]</td>
<td>no</td>
<td>Includes 4 studies on HCC, the other studies on metastatic population</td>
</tr>
</tbody>
</table>

* Yes = include, see AMSTAR ratings; No = used as a source of evidence

Table 2. AMSTAR rating of the studies that were considered clinically similar to the present review

<table>
<thead>
<tr>
<th>AMSTAR item</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was an “a priori” design provided?</td>
<td>Y</td>
</tr>
<tr>
<td>2. Was there duplicate study selection and data extraction?</td>
<td>Y</td>
</tr>
<tr>
<td>3. Was a comprehensive literature search performed?</td>
<td>Y</td>
</tr>
<tr>
<td>4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?</td>
<td>Y handsearch</td>
</tr>
<tr>
<td>5. Was a list of studies (included and excluded) provided?</td>
<td>Y included only</td>
</tr>
<tr>
<td>6. Were the characteristics of the included studies provided?</td>
<td>Y</td>
</tr>
<tr>
<td>7. Was the scientific quality of the included studies assessed and documented?</td>
<td>Y</td>
</tr>
<tr>
<td>8. Was the scientific quality of the included studies used appropriately in formulating conclusions?</td>
<td>Y</td>
</tr>
<tr>
<td>9. Were the methods used to combine the findings of studies appropriate?</td>
<td>Y separate analysis for RCT and nRCTs</td>
</tr>
<tr>
<td>10. Was the likelihood of publication bias assessed?</td>
<td>Y</td>
</tr>
<tr>
<td>11. Was the conflict of interest stated?</td>
<td>Y</td>
</tr>
</tbody>
</table>

Y = _yes; N = no; CA = Cannot answer; NA = not applicable
Appendix 5: Conflict of Interest Disclosures: Focal Ablation Committee.

<table>
<thead>
<tr>
<th>Members</th>
<th>Role</th>
<th>Conflict of Interest</th>
</tr>
</thead>
</table>
| John Kachura             | Co-Chair   | Past President of CIRA (Canadian Interventional Radiology Association). The Following parties contribute financially to CIRA: Abbott Vascular, Angiodynamics, Bard, Boston Scientific, Cook Medical, Cardis Endovascular, Covidier, GE Healthcare, Gore, InterV Medical, Medronic and Philips  
Co-applicant for patent regarding an invention for thermal therapy  
Investigator in a sponsored research agreement between University Health Network and Bard regarding thermal therapy invention. |
| Sriharsha Athreya        | Member     | None declared                                                                                                                                                                                                      |
| Mark Baerlocher          | Member     | Temporary consultant to Cook In to help with documents related to PICC lines                                                                                                                                         |
| Robert Beecroft          | Member     | Course director of master class in Interventional Oncology at Toronto General Hospital. Honorarium of $3000 sponsored by Covidien  
Spoke at industry sponsored symposium at CIRA (May 2013) -- Sponsored by Covidien ($400 honorarium)                                                                 |
| Elizabeth David          | Member     | Principle Investigator on Philips HIFU trial for fibroids                                                                                                                                                            |
| Darren Knibutat          | Member     | None declared                                                                                                                                                                                                      |
| Kitchener/Waterloo-Grand  | None declared |
| River Regional           |            |                                                                                                                                                                                                                     |
| George Markose           | Member     | None declared                                                                                                                                                                                                      |
| Alex Menard              | Member     | Unlikely to experience increase in salary greater than $5000/year if Focal Tumour Ablation program were further developed. Volumes would need to increase 10 fold   |
| Mehran Midia             | Member     | None declared                                                                                                                                                                                                      |
| Amol Mujoomdar           | Member     | Speaker honorarium received from Covidien and Cook Medical                                                                                                                                                         |
| Wael Shabana             | Member     | Will be attendee for Ablation Master Class at Toronto General Hospital Advanced Imaging and Education - sponsored by Covidien Company                                                                                  |
| Laura Dawson             | Member     | Bayer Clinical Trials - paid to Institution  
In 2005, published editorial/commentary regarding objects of study                                                                                   |
<p>| Richard Malthaner        | Member     | None declared                                                                                                                                                                                                      |
| Guillaume Martel         | Member     | Part of Fellowship conference travel stipend in 2013 was covered by a bursary from Covidien (&lt;$5000)                                                                                                                |
| Catherine. Wang          | Member     | Managerial responsibility on unrestricted research/education grants from Bard, Medtronic, Covidien, Gore, Boston Scientific, Sorin Medical                                                                         |</p>
<table>
<thead>
<tr>
<th>Members</th>
<th>Role</th>
<th>Conflict of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ania Kielar</td>
<td>Member</td>
<td>GE CHAR grant for MRI post RFA investigation</td>
</tr>
<tr>
<td>Calvin Law</td>
<td>Member</td>
<td>None declared</td>
</tr>
<tr>
<td>David Gast</td>
<td>Patient Family Advisor</td>
<td>None declared</td>
</tr>
<tr>
<td>Brigitta Bokkers</td>
<td>Patient Family Advisor</td>
<td>None declared</td>
</tr>
</tbody>
</table>
References