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Evidence Summary Focal Ablation 2 ARCHIVED

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

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Report Date: March 31, 2015

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ES Focal Ablation 1: Transarterial chemoembolization 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

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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 x^2 test for heterogeneity and the I^2 percentage. A probability level for the x^2 statistic ≤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.

Author, year (reference), study name, country, funding	Objectives, design	Population, data collection period, follow-up	Intervention, control	Outcomes
TACE vs TEA				
Yu, 2014 [36] **Country**: China **Funding**: *nr*	To compare TEA + LEM with TACE. **Design**: Open-label parallel group.	N=200 pts with unresectable HCC. Terminated early at interim analysis after 98 pts because of no difference in OS. **Age** (mean yrs): 65 **Gender**: 80% men **Period**: July 2007 to May 2011 **Follow-up:** Until Sept 2012	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. **Mean number of treatments**: 2.4	*OS TTP (intralesional, any disease) PFS (intralesional, any disease) CR (local) at 3 mo, 6 mo and 12 mo AE
TACE vs bland embolization				
Llovet, 2002 [3] **Country**: Spain **Funding**: Ministerio de Ciencia y Tecnología. Pharmacia-Upjohn	To compare the survival benefit of bland embolization, TACE, or symptomatic treatment. **Design**: Three group, open-label; sequential design; stopped early for benefit.	N=112 pts with unresectable HCC Child-Pugh A or B, Okuda stage I or II, not suited for curative treatment. **Age** (mean yrs): Embolization: 64; TACE: 63; Control: 66 **Gender**: 79.4% male **Period**: July 1996 to July 2000 (9th sequential inspection) **Follow-up** (mean mo): Embolization: 21.7 TACE: 21.2 Control: 14.5	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) **Mean number of treatments**: 3.8 for embolization and 2.8 for TACE	*OS Objective response AE
Meyer, 2013 [28] **Country**: UK **Funding**: National Institute of Health Research, Experimental Cancer Medicine Centre Network (UK)	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.	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	TAE (N=42) polyvinyl alcohol sTACE (N=44) cisplatin administered 4-6 hrs before embolization). **Mean number of treatments**: *nr*	*OS PFS *AE (Phase II) Response QoL[B]

Author, year (reference), study name, country, funding	Objectives, design	Population, data collection period, follow-up	Intervention, control	Outcomes
TACE vs DEB-TACE				
Golfieri, 2014 [22] PRECISION ITALIA **Country**: Italy **Funding**: *nr*	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] **Country**: Austria, France, Germany and Switzerland PRECISION V **Funding**: Biocompatibles, UK, Ltd	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/m^2 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**: *nr*	AE
Lammer, 2010 [24] **Country**: Austria, Germany, Switzerland, Greece, France PRECISION V **Funding**: Biocompatibles Ltd, UK	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 cTACE: 67.4 **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 m^2 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**: *nr*	*Tumour response at 6 mo Disease control *Treatment-related SAE Systemic side effects of doxorubicin PES AE
Sacco, 2011 [31] **Country**: Italy **Funding**: *nr*	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	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.	*AE *Periprocedural toxicity (based on liver function), and *Tumour response at 1 month.

Author, year (reference), study name, country, funding	Objectives, design	Population, data collection period, follow-up	Intervention, control	Outcomes
		Period: January 2006 to March 2009 **Follow-up** (mean ds): 816±361	**Mean number of treatments**: *nr*	Number of repeated chemoembolization cycles. Time to recurrence and local recurrence. Time to radiologic progression. Survival
Maleux, 2010 [abs] [27] **Country**: Belgium **Funding**: *nr*	To assess the safety of doxorubicin-eluting SAP microspheres. **Design**: phase II	N=30 pts with different BCLC stages of HCC **Age** (mean yrs): *nr* **Gender**: % male: *nr* **Period**: *nr* **Follow-up**: *nr*	cTACE (N=15): iodinated poppyseed oil iodinated poppyseed oil + doxorubicin SAP (N=15): Doxorubicin-eluting HepaSpheres. **Mean number of treatments**: *nr*	Doxorubicin concentration Liver function AE
DEB-TACE vs bland embolization				
Malagari, 2010 [26] **Country**: Greece **Funding**: *nr*	To evaluate whether tumour necrosis is caused by the chemotherapeutic or by ischemia alone. **Design**: parallel group	N=84 pts with intermediate unresectable and untreatable with RFA HCC. Child-Pugh A or B. **Age** (mean yrs): DEB-TACE: 70.7; cTACE: 70 **Gender**: 77% male **Period**: *nr* **Follow-up**: 12 mo	DEB-TACE (N=41) Bland embolization (N=43) **Mean number of treatments**: *nr*	*Local response *TTP *Recurrence-free rate Survival rate AE
Brown, 2014 [abs][21] **Country**: USA **Funding**: *nr*	To compare response rate with HAE versus DEB-TACE **Design**: Phase II	N=101 pts with Okuda stage I or II **Age** (mean yrs): 67 **Gender**: 77% male **Period**: December 2007 to March 2012 **Follow-up**: *nr*	HAE: (N=51) vs DEB-TACE (N=50) 150 mg doxorubicin **Mean number of treatments**: 2.2 vs 1.9	*Response rate TTP PFS OS AE
TACE vs hepatectomy				
Yin, 2014 [35] **Country**: China	To compare PH with TACE **Design**: Open-label parallel group	N=173 pts with HCC outside the Milan criteria[A]	PH (N=90): by a clamp crushing method TACE (N=90): 5-fluorouracil (1 g), mitomycin C (20 mg), cisplatin (5 mg), and	*OS AE

Author, year (reference), study name, country, funding	Objectives, design	Population, data collection period, follow-up	Intervention, control	Outcomes
Funding: Government, China		**Age** (mean yrs): PH: 51.6; TACE: 54.0 **Gender**: 93% male **Period**: November 2008 to September 2010 **Follow-up**: (median mo): 33.3	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.	
TACE vs radiotherapy				
Mohnike, 2013 [abs] [29] **Country**: Germany **Funding**: *nr*	To compare BT and TACE **Design**: Parallel group. However, cross-over after the primary end point was reached or in case of technical failure.	N=75 with advanced-stage HCC **Age** (mean yrs): BT: 69.9 TACE: 67.1 **Gender**: % male: *nr* **Period**: *nr* **Follow-up**: *nr*	BT (N=38) TACE (N=37) **Mean number of treatments**: *nr*	*TTUP TTP OS AE
Kolligs, 2013 [abs] [23] SIRTACE **Country**: Germany, Spain **Funding**: *nr*	To compare safety, efficacy and health economics of SIRT with yttrium-90 microspheres and TACE **Design**: Open-label multicentre pilot study	N=28 pts with intermediate-stage HCC **Age** (mean yrs): 65.6 **Gender**: % male: *nr* **Period**: *nr* **Follow-up**: *nr*	TACE (N=15): epirubicin, iodinated poppyseed oil iodinated poppyseed oil and embolizing agent; SIRT (N=13):yttrium-90 resin microspheres; **Mean number of treatments**: TACE: 3.4; SIRT: 1	OR Disease control PFS OS Hospital stay Grade ≥3 AE
TACE vs systemic therapy				
Mabed, 2009 [25] **Country**: Egypt **Funding**: *nr*	To compare TACE with systemic chemotherapy **Design**: Parallel group, open-label	N=100 with primary unresectable HCC, Child-Pugh A or B **Age** (mean yrs): TACE: 52, systemic therapy: 51 **Gender**: 65% male **Period**: September 2005 to June 2005 **Follow-up** (mean): 70 wks	TACE (N=50): cisplatin 50 mg, doxorubicin 40 mg, and iodinated poppyseed oil iodinated poppyseed oil 10 mL mixed with 10 mg doxorubicin) Systemic therapy (N=50):15 mg/m^2 doxorubicin intravenously on days 1, 8 and 15 for a total no greater than 500 mg/m^2. **Mean number of treatments**: *nr*	*Tumour response: PFS OS AE
TACE vs symptomatic treatment				
Lo, 2002 [4] **Country**: China **Funding**: *nr*	To compare TACE with symptomatic treatment, and identify prognostic factors	N=79 pts with un-resectable HCC **Age** (mean yrs): TACE: 62, control: 63 **Gender**: 88.6% male	TACE (N=40): cisplatin to a maximum of 30 mg/mL + iodinated poppyseed oil iodinated poppyseed oil + gelatin-sponge pellets + gentamicin)	*OS Tumour response, Patient tolerance Liver function AE

Author, year (reference), study name, country, funding	Objectives, design	Population, data collection period, follow-up	Intervention, control	Outcomes
	Design: Single-centre, parallel group, open-label	**Period**: March 1996 to October 1997 **Follow-up** (mean mo): 55	symptomatic treatment (N=40): treatment for symptoms or complications **Mean number of treatments**: 4.5	
Llovet, 2002 [3] **Country**: Spain **Funding**: Ministerio de Ciencia y Tecnología. Pharmacia-Upjohn	To compare the survival benefit of bland embolization, TACE, or symptomatic treatment. **Design**: Three group, open-label; sequential design; stopped early for benefit.	N=112 pts with unresectable HCC Child-Pugh A or B, Okuda stage I or II, not suited for curative treatment. **Age** (mean yrs): Embolization: 64; TACE: 63; control: 66 **Gender**: 79.4% male **Period**: July 1996 to July 2000 (9th sequential inspection) **Follow-up** (mean mo): Embolization: 21.7 TACE: 21.2 Control: 14.5	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) **Mean number of treatments**: 3.8 for embolization and 2.8 for TACE	*OS Objective response AE

* Primary outcome

[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 only 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

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.

Study	Treatment/ comparison	Primary outcome	Required sample size	Loss to follow-up	Sample size, N	Randomization method described	Allocation concealment	Blinding	ITT analysis	Final analysis	Early termination	Ethical approval
TACE vs transarterial injection												
Yu, 2014 [36]	TEA vs TACE	OS	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=sided α at 5%.	0[A]	98	Yes	Yes	Yes[B]	No[C]	Yes	Yes[D]	Yes
TACE vs bland embolization												
Llovet, 2002 [3]	TACE vs bland embolization vs conservative treatment	OS	Assuming TACE and embolization: 2-yr survival: 65%: control: 40% (reference hazard ratio 0.47, allocation ratio 1), with α=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<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.	3	107	Yes	Yes	No	Yes	Yes	No	Yes
Meyer, 2013 [28]	TACE vs embolization alone	OS (Phase III) Safety (Phase II)	80 (Phase II) 322 (Phase III) pts were required to detect a difference in 2-yr OS from 50% to 63% with 80% power and α=0.05 over 4 years with follow-up of 1 yr	*nr*	86	Yes	Yes	Yes[H]	Yes	Yes	Yes[G]	Yes
TACE vs DEB-TACE												
Golfieri, 2014 [22] PRECISION ITALIA	cTACE vs DEB-TACE	2-yr OS	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.	3	177	Yes	Yes	No	Yes	Yes	Yes[E]	Yes
Lammer, 2010 [24] Vogl, 2011 [33] PRECISION V	cTACE vs DEB-TACE	Tumour response at 6 mo	200 pts were required to obtain a power of 81.3% at a one-sided significance level of α=0.025, assuming objective tumour response rates of 55% (DEB-TACE) and 35% (cTACE).	3	201	Yes	Yes	Yes[H]	No[CI]	Yes	No	Yes

Study	Treatment/ comparison	Primary outcome	Required sample size	Loss to follow-up	Sample size, N	Randomization method described	Allocation concealment	Blinding	ITT analysis	Final analysis	Early termination	Ethical approval
Sacco, 2011 [31]	cTACE vs DEB-TACE	Safety, toxicity, and tumour response at 1 month.	*nr*	0	67	Yes	Yes	No	No	Yes	No	Yes
Maleux, 2010 [abs] [27]	Doxorubicin-eluting HepaSpheres (SAP) vs cTACE	*nr*	*nr*	*nr*	30	*nr*	*nr*	*nr*	*nr*	Yes	No	*nr*
DEB-TACE vs bland embolization												
Malagari, 2010 [26]	DEB-TACE vs bland embolization	Local response TTP Recurrence-free rate	*nr*	3 at 12 months	84	Yes	Yes	No	No	Yes	No	*nr*
Brown, 2014 [abs][21]	DEB-TACE vs HAE	Response rate	*nr*	*nr*	101	*nr*	*nr*	*nr*	Yes	Yes	No	*nr*
TACE vs hepatectomy												
Yin, 2014 [35]	PH vs TACE	OS	59 pts per group were needed to obtain a power of 80%, assuming a type-I error of 5% (α=0.05).	7	173	Yes	Yes	No	Yes	Yes	No	Yes
TACE vs radiotherapy												
Mohnike, 2013 [abs] [29]	BT vs TACE	TTUP	*nr*	*nr*	75	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*
Kolligs, 2013 [abs] [23]	TACE vs SIRT	*nr*	*nr*	*nr*	28	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*

Study	Treatment/ comparison	Primary outcome	Required sample size	Loss to follow-up	Sample size, N	Randomization method described	Allocation concealment	Blinding	ITT analysis	Final analysis	Early termination	Ethical approval
TACE vs systemic therapy												
Mabed, 2009 [25]	TACE vs systemic therapy	Tumour response	50 pts per arm were required to detect a difference of 30% with α=0.05 and power of 90%	3	100	Yes	Yes	No	Yes	Yes	No	Yes
TACE vs symptomatic treatment												
Lo, 2002 [4]	TACE vs symptomatic treatment	OS	40 pts were required in each group to obtain a power of 80% with α=0.05	2	79	Yes	No[J]	No	Yes	Yes	No	Yes
Llovet, 2002 [3]	TACE vs bland embolization vs conservative treatment	OS	Assuming TACE and embolization: 2-yr survival: 65%: control: 40% (reference hazard ratio 0.47, allocation ratio 1), with α=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<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.	3	107	Yes	Yes	No	Yes	Yes	No	Yes

[A] Four patients in each arm were excluded from analysis
[B] Data collectors, outcome assessors and data analysists.
[C] Modified ITT: patients who did not receive any treatment after randomization were excluded from analysis.
[D] 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.
[E] Stopped early for futility.
[F] Patients were blinded.
[G] Trial terminated early because of low accrual.
[H] Outcome assessors
[I] The authors used the last observation carried forward in order to assess the primary end point for the entire ITT population
[J] 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).

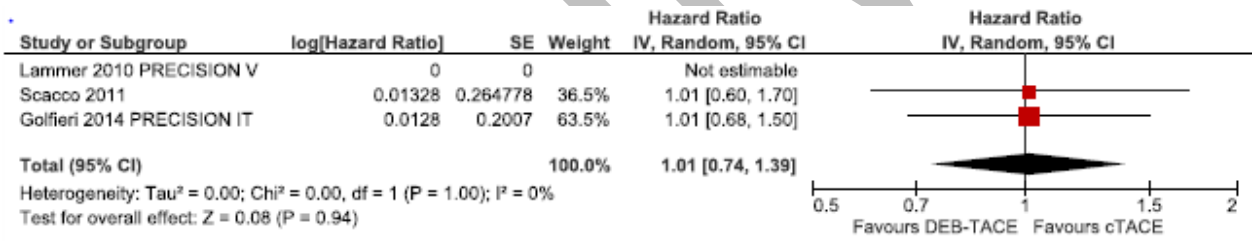

Figure 1. Overall survival: pooled results for the comparison of DEB-TACE with conventional TACE

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 4 – Efficacy of TACE: Outcomes

Author, year (ref)	Intervention/control	OS	TTP	PFS	Response	QoL	Length of hospital stay
TACE vs transarterial injection							
Yu, 2014 [36]	TEA+LEM vs TACE	OS: TEA: 24.3 mo (95% CI, 12.8 to 32.7); TACE: 20.1 mo (95% CI, 9.3 to 31.2), p=0.513	TTP (intralesional): TEA: 34.6 mo (95% CI, 28.2 to 41); TACE: 26.5 mo (95% CI, 18.7 to 33.3), p=0.028 TTP (any disease): TEA: 8.4 mo (95% CI, 5.3 to 11.4) TACE: 4.4 mo (95% CI, 1.8 to 7.1); p=0.128	PFS (intralesional): TEA: 14.8 mo (95% CI, 10.2 to 19.5); TACE 9.3 mo (95% CI, 7.1 to 11.5), p=0.029 PFS (any disease): TEA: 6.5 mo (95% CI, 3.8 to 9.2); TACE: 4.4 mo (95% CI, 1.6 to 7.2), p=0.16	CR: at 3 mo: TEA: 73%; TACE 51%, p=0.012; at 6 mo: TEA: 73% TACE: 54%, p=0.012; at 12 mo: TAE: 75%, TACE: 59%, p=0.031	*nr*	*nr*
TACE vs Bland embolization							
Llovet, 2002 [3]	TAE vs TACE vs Conservative treatment (control)	OS at 1 and 2 yrs: TAE: 75% and 50% TACE: 82% and 63% Control: 63% and 27%	*nr*	*nr*	CR or PR: n=16 after embolization; n=14 after TACE	*nr*	*nr*
Meyer, 2013 [28]	TAE polyvinyl alcohol vs sTACE (cisplatin administered 4-6 hrs before embolization).	OS: median 17.3 vs 16.3 mo, HR, 0.91; 95% CI, 0.51 to 1.62, p=NS	*nr*	PFS: median 7.2 vs 7.5 mo, HR, 0.87; 95% CI, 0.52 to 1.45, p=NS	(CR+PR) 13.2% vs 32.6%, p=0.04	QoL[G]: p=NS	*nr*
TACE vs DEB-TACE							
Golfieri, 2014 [22]	cTACE vs DEB-TACE	OS = median mo: DEB-TACE: 29 vs cTACE: 28, p=NS	p=NS	*nr*	Local CR (lesion level) at 1 mo: cTACE 63.5% vs DEB-TACE 68.7%, NS Overall CR (patient level) : no significant differences P>0.05 in all cases OR: NS PR: NS DC: NS	*nr*	3 ds vs 4 ds p=NS
Lammer, 2010 [24] Vogl [33] PRECISION V	cTACE vs DEB-TACE	*nr*	Disease control: DEB-TACE: 63.4% vs cTACE: 51.9%, p=0.11	*nr*	CR: DEB-TACE: 26.9% vs cTACE: 22.2% PR: DEB-TACE: 24.7% vs cTACE: 21.3% Stable disease: DEB-TACE: 11.8% vs cTACE: 98.3% Progressive disease: DEB-TACE: 32.3% vs cTACE: 40.7% Objective response: DEB-TACE: 51.6% vs cTACE: 43.5%, P=0.11	*nr*	12±9 ds in both groups

Author, year (ref)	Intervention/control	OS	TTP	PFS	Response	QoL	Length of hospital stay
Sacco, 2011 [31]	cTACE vs DEB-TACE	Survival at 24 mo: cTACE: 83.6%; DEB-TACE: 86.8%, p=NS.	Time to radiologic progression (mean expected mo): cTACE: 24.2 vs DEB-TACE 15.6, p=NS.	Time to recurrence: P = NS	Tumour response at 1 mo: CR: cTACE: 70.6%; DEB-TACE: 51.5%; PR: cTACE: 29.4%; DEB-TACE 48.5%, p=NS Number of repeated chemoembolizations: p=NS	*nr*	*nr*
Maleux, 2010 [abs] [27]	cTACE vs Doxorubicin-eluting HepaSpheres (SAP)[F].	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*
DEB-TACE vs bland embolization							
Malagari, 2010 [26]	DEB-TACE vs TAE	Survival: DEB-TACE: 100% (at 6 mo), 97.5% (at 9 mo), and 85.3 % (at 12 mo); bland embolization: 100% (at 6 mo), 95.3% (41/43) (at 9 mo), and 86% (at 12 mo); p=NS	TTP: DEB-TACE vs bland embolization: 42.4±9.5 vs 36.2±9.0 weeks 42.4, p=0.008. Recurrence rate: DEB-TACE: 7.3% (at 6 mo), 30% (at 9 mo), 45.7% (at 12 mo); bland embolization: 20.9% (at 6 mo), 46.3% (at 9 mo), 78.3% (at 12 mo); p<0.0001	*nr*	Local response (EASL criteria): CR: DEB-TACE: (at 6 mo) 26.8%, (at 9 mo) 22.5%, (at 12 mo) 20%; bland embolization: (at 6 mo) 14%, (at 9 mo) 14.6%, (at 12 mo) 16.2%; p=NS for all time points OR: DEB-TACE: DEB-TACE | TAE | P 6 mo | 73.2% | 55.8% | 0.11 9 mo | 55%, | 31.7% | 0.04 12 mo | 25.7% | 18.9% | 0.58	*nr*	*nr*
Brown, 2014 [abs] [21]	HAE vs DEB-TACE	p=NS	Not reached	6.8 months vs 8.9 months (p=0.59).	p=NS	*nr*	*nr*
TACE vs hepatectomy							
Yin, 2014 [35]	PH vs TACE	OS at 14 months PH | TACE 1 yr | 76.1% | 51.8% 2 yrs | 63.5% | 34.8% 3 yrs | 51.5% | 18.1% p<0.001	*nr*	*nr*	*nr*	*nr*	*nr*
TACE vs radiotherapy							

Author, year (ref)	Intervention/control	OS	TTP	PFS	Response	QoL	Length of hospital stay
Mohnike, 2013 [abs] [29]	BT vs TACE	OS (median mo): BT: 25.6; TACE: 23.4, p=NS	TTUP (median mo): BT: 25.1; TACE: 12.6 TTP (median mo): BT: 13.0; TACE: 5.7, p<0.05	*nr*	*nr*	*nr*	*nr*
Kolligs, 2013 [abs] [23]	SIRT with yttrium-90 microspheres vs TACE	p=NS	Disease control TACE: 73.3%/67.7%/67.7% vs SIRT: 76.9%/ 84.6%/69.2%	PFS (median mo) (RECIST 1.1): TACE: 5.5 mo (95% CI, 1.6-not reached) vs SIRT: 4.1 mo (95% CI, 2.3 to 9.9), p=NS.	OR: (RECIST 1.0/1.1/mRECIST, best response rates): TACE: 13.3%/20.0%/33.3% vs SIRT: 30.8%/ 30.8%/23.1%	*nr*	Mean ± SD hospital admission ds:TACE 13.8±13.2; SIRT: 11.6±7.3
TACE vs systemic therapy							
Mabed, 2009 [25]	TACE vs systemic chemotherapy	TACE: 38 wks; systemic therapy: 32 wks; p=0.08	*nr*	TACE: 32 wks; systemic therapy: 26 wks; p=0.03	Tumour response: PR: TACE: 32%; systemic therapy: 10%, p=0.007; SD: 26% vs 19%, p=*nr*; PD: 36% vs 44%, p=*nr*	*nr*	*nr*
TACE vs symptomatic treatment							
Lo, 2002 [4]	TACE vs symptomatic treatment	OS: Estimated survival at 1 year, 57%; 2 years, 31%; 3 years, 26% for TACE and 1 year, 32%; 2 years, 11%; 3 years, 3% in the control group, p=0.002	*nr*	*nr*	Tumour response[E]: Objective tumour response: TACE: 39% vs control: 6%, p=0.014 α-fetoprotein response: (72% vs 10%; p=0.001).	*nr*	*nr*
Llovet, 2002 [3]	TAE vs TACE vs conservative treatment (control)	OS at 1 and 2 yrs: TAE: 75% and 50% TACE: 82% and 63% Control: 63% and 27% TACE vs control: p=0.009 HR for death for TACE vs control: 0.47 (95% CI, 0.25 to 0.91), p=0.025 HR for death for embolization vs control, adjusted for bilirubin concentration: 0.57 (95% CI, 0.31 to 1.04), p=0.07	*nr*	*nr*	CR or PR: n=16 after emblization; n=14 after TACE (embolisation vs control, P=0·001; TACE vs control, P=0·004).	*nr*	*nr*

[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 ly 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
[F]This study reports on doxorubicin peak concentrations.
[G]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; 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

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

Mabed 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

Lo et al [4] reported adverse events related to TACE only. Llovet et al [3] reported adverse events related to TACE and bland embolization.

Table 5. Adverse events (all grades)

Author, year (reference)	Intervention/ control	Post-embolization syndrome	Liver function derangements	Hematological	Cardiac impairment	Respiratory failure	Renal failure	Other	All adverse events	Treatment-related deaths
TACE vs transarterial ethanol injection										
Yu, 2014 [36]	TEA+LEM vs TACE	Pain: Gr1: 70% vs 52% p=0.03; Gr2 and Gr3, p=NS; Fever: N=33 vs 22, p=0.017[A] Vomiting: N=6 vs 21, p=0.001[A]	p=NS	*nr*	*nr*	2 vs 0 p=NS	0 vs 2 NS	*nr*	*nr*	0
TACE vs bland embolization										
Llovet, 2002 [3]	TAE vs TACE vs Control	*nr*	Ischemic hepatitis: 3% vs 3% Liver failure: 3% (TAE) Hepatic infarct 3% (TACE), p=NS	Leukopenia 0% vs 3%	*nr*	NS	*nr*	Cholecystitis: 5% vs 3%; Gastrointestinal hemorrage: 0% vs 3%	*nr*	4% vs 10% vs 0%
Meyer, 2013 [28]	TAE vs sTACE	Pain: Gr3: 7 vs 10; Gr4: 1 vs 2; Fever: 1 vs 1 Vomiting: Gr 3: 1 vs 3	AST, ALT, bilirubin, alkaline phosphatase, GGT Gr 3: 19 vs 28 Gr 4: 2 vs 2 Intrahepatic abscess: Gr 3: 0 vs 2	Leukocytosis: Gr 3: 0 vs 2	*nr*	*nr*	*nr*	*nr*	Grade 3/4 toxicity:63.5% vs 83.7%, p=0.019	1 vs 1
DEB-TACE vs TACE										
Golfieri, 2014 [22]	DEB-TACE vs cTACE	Pain (postprocedural): 24.7% vs 71.6%, p=0.001 Fever: 7.9% vs 11.4% p=NS Nausea/nomiting: 2.2% vs 3.4%, p=NS	Liver function worsening: 1.1% vs 5.7%, p=NS Liver abscess: 1.1% vs 1.1%, p=NS	*nr*	*nr*	*nr*	*nr*	Cholecystitis: 2.2% vs 1.1%, p=NS	6.7% vs 5.7%, p=NS	*nr*
Lammer, 2010 [24] Vogl, 2011 [33] PRECISION V	DEB-TACE (doxorubicin) vs cTACE	Postembolization syndrome and symptoms: DEB-TACE: 72%; cTACE: 72.2%, p=NS	Liver toxicity: ALT increase post procedure was 50% less in DEB-TACE than in cTACE (95% CI, 39% to 65%; p<0.001); at 6 mo follow-up, p=NS. AST	*nr*	Cardiac function: DEB-TACE: +2.7 ± 10.1 percentage points and cTACE: 1.5 ±	*nr*	*nr*	Alopecia: 1.1% vs 20.4%, P *nr* Marrow suppression : 5.4% vs 5.6%	20.4% vs 19.4%, p=NS	1% vs 0%

Author, year (reference)	Intervention/ control	Post-embolization syndrome	Liver function derangements	Hematological	Cardiac impairment	Respiratory failure	Renal failure	Other	All adverse events	Treatment-related deaths
			increase post procedure 2 was 41% less in the DEB-TACE than in cTACE (95% CI, 46% to 76%; P<0.001); at 6 mo follow-up p=NS.		7.6 percentage points (95% CI, 0.71 to 7.3; p=0.018), however >41% pts data missing in both groups.			Mucositis: 4.3% vs 5.6% Skin discoloration: 2.2% vs 1.9% P values: *nr*		
Sacco, 2011 [31]	cTACE and DEB-TACE	cTACE: 55.9%; DEB-TACE: 63.6, p=0.51 (NS)	Greater increase of ALT 24 hrs after the procedure in the cTACE vs DEB-TACE, P=0.007. Bilirubin: p=NS	Prothrombin: p=NS	*nr*	*nr*	*nr*	2 major complications, one in each arm.	*nr*	*nr*
Maleux, 2010 [abs] [27]	cTACE vs Doxorubicin-eluting HepaSpheres (SAP).	*nr*	Better liver function in the SAP vs cTACE group (P=0.027)	*nr*	*nr*	*nr*	*nr*	Gr 3 AE: SAP 33% vs cTACE: 53% Gr 4 AE: 0% vs 27%	*nr*	*nr*
DEB-TACE vs bland embolization (TAE)										
Malagari, 2010 [26]	DEB-TACE vs TAE	80.4% vs 81.4%; p=NS	Liver failure: 4.8% vs 4.6%, p=NS cholecystitis: 4.8% vs 0%, p=NS	*nr*	*nr*	Pleural effusion: 4% vs 4%, p=NS	*nr*	p=NS for all; and skin erythema: 2.4% vs 0%	*nr*	*nr*
Brown, 2014 [abs][21]	HAE vs DEB-TACE	Postembolization syndrome HAE: 84.3%, vs LCB 83.7% P=NS	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	Overall Gr3, Gr4, or Gr5 toxicity occurred in 45.7% of HAE and 54.3% of DEB-TACE patients	*nr*
TACE vs hepatectomy										
Yin, 2014 [35]	PH vs	NA	Liver failure: 1% Bile leak: 5%	NA	*nr*	*nr*	*nr*	Bleeding: 2%	*nr*	at 30-d and 90-d: 1 vs *nr*, p=NS

Author, year (reference)	Intervention/ control	Post-embolization syndrome	Liver function derangements	Hematological	Cardiac impairment	Respiratory failure	Renal failure	Other	All adverse events	Treatment-related deaths
	TACE							Infection: 2%		
		Nausea/Vomiting: 98% Pain: 56%	Increase in ALT/AST: 66% Increase in GGT: 40% Decrease in albumin: 29% Increase in bilirubin: 53%	Leukopenia: 39%	*nr*	*nr*	*nr*	*nr*	*nr*	
TACE vs radiotherapy										
Mohnike, 2013 [abs] [29]	BT vs TACE	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*
Kolligs, 2013 [abs] [23]	SIRT with yttrium-90 microspheres vs TACE	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	6 vs 4, P =0.433	*nr*
TACE vs systemic therapy										
Mabed, 2009 [25]	TACE vs Systemic chemotherapy	92%	Gr 1 increase of liver enzymes: 64% Deterioration of liver function: 36% Liver failure 22% Liver abscess: 2%	*nr*	*nr*	*nr*	*nr*	Puncture site bleeding: 6% Esophageal varicies rupture: 4% Cholecystitis: 2%	*nr*	4% vs 0%, p=*nr*
		NA	*nr*	Hematological toxicity: 38%	Gr2 cardiotoxicity: 4%	*nr*	*nr*	GI toxicity: 28%	*nr*	
TACE vs symptomatic treatment										
Lo, 2002 [4]	TACE vs	Fever: 32% Pain: 26% Vomiting: 16.7%	Liver abscess: 0.5%	*nr*	Bradycardia: 0.5% Hypotension: 0.5%	Pleural effusion: 1%	Hematuria: 0.5%	Ascites: 5.2% GI bleeding: 4.2%	1%	*nr*

Author, year (reference)	Intervention/ control	Post-embolization syndrome	Liver function derangements	Hematological	Cardiac impairment	Respiratory failure	Renal failure	Other	All adverse events	Treatment-related deaths
	symptomatic treatment							Puncture site bleeding: 1.6% Encephalopathy: 1.6%		
		nr	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	
Llovet, 2002 [3]	TAE vs TACE vs Control	*nr*	*nr*	nr	*nr*	*nr*	*nr*	*nr*	*nr*	4% vs 10% vs 0%

[A] Grade 1 and 2; [B] 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.

Study Design	Subgroups	Results
cTACE vs DEB-TACE		
Lammer, 2010 [24] Design: preplanned analysis	**Patients with more advanced disease[A]**	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] Design: post hoc analysis	**Patients with less advanced disease[B]**	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])
TEA vs TACE		
Yu, 2014 [36] Design: pre-planned analysis	**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
	Subclasses of TTP and PFS: Intrahepatic, extralesional and extrahepatic progression:	NS difference

[A]Child Pugh class B, ECOG-1, bilobar or recurrent disease; [B]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 7. Ongoing trials as of February 13, 2015

Interventions	Official title	Status	Protocol ID	Completion Date	Last updated
TACE vs TARE	A Randomized, Multi-center, Open Label, Phase 3 Trial Comparing Conventional TACE and Transarterial Radioembolization in Patients With Unilobar Advanced Hepatocellular Carcinoma	Recruiting	NCT02004210	April 2018	November 26, 2014
TACE vs HR	Hepatic Resection Versus Transcatheter Arterial Chemoembolization for Hepatocellular Carcinoma Complicated by Portal Vein Tumor Thrombosis.A Prospective and Randomized Clinical Trial	Unknown	NCT01350206	May 2013	Not available
TACE vs non-TACE	The Efficacy and Safety of Retreatment With Transarterial Chemoembolization (TACE) for Patients Who Showed TACE-resistant: a Randomized Controlled Trial	Recruiting	NCT02220088	January 2016	August 18, 2014
Chemoembolization and Response-Dependent Resection vs Immediate Resection	Hepatic Resection Versus Transarterial Chemoembolization as the Initial Treatment for Resectable Hepatocellular Carcinoma Beyond Milan Criteria	Recruiting	NCT02138981	August 2018	May 14, 2014
TACE vs radiotherapy	Adjuvant Radiotherapy Comparing Transarterial Chemoembolization for Curative Hepatocellular Carcinoma: a Randomized Controlled Trials	Recruiting	NCT02125396	June 2016	Not applicable
DEB-TACE vs ^{90}Y-RE	Transarterial RAdioembolization Versus ChemoEmbolization for the Treatment of HCC: A Multicenter Randomized Controlled Trial (TRACE Trial)	Recruiting	NCT01381211	December 2016	December 2014
TACE vs CT-guided brachytherapy	Phase-III-Study to Evaluate the Efficacy of CT-guided Brachytherapy Versus Transarterial Chemoembolization in Patients With Unresectable Hepatocellular Carcinoma	Recruiting	NCT00807300	December 2015	January 2015
TACE vs Sorafenib	An Open Label, Phase 2 Trial Comparing Sorafenib And TACE in Advanced Hepatocellular Carcinoma With Portal Vein Invasion	Recruiting	NCT01480817	December 2015	November 26, 2014
SBRT after incomplete TAE vs TACE vs Exclusive TAE or TACE	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)	Recruiting	NCT02323360	May 2018	December 22, 2014
cTACe vs hepasphere1quadrasphere microspheres	Phase 3 Prospective, Randomized, Blinded, and Controlled Investigation of HepaSphere/QuadraSphere Microspheres for Delivery of Doxorubicin for the Treatment of Hepatocellular Carcinoma	Recruiting	NCT01387932	December 2022	December 2, 2014
Transarterial embolization vs: Transarterial infusion chemotherapy vs: Transarterial iodinated poppyseed oil iodinated poppyseed oil chemotharepy	Chemoembolization of Unresectable Hepatocellular Carcinoma With or Without iodinated poppyseed oil Chemotherapy: Effectiveness and Safety. A Prospective and Randomized Clinical Trial.	Recruiting	NCT01229839	November 2016	August 3, 2013
TACE with mitomycin C, doxorubicin hydrochloride, and cisplatin vs ^{90}Y-RE	An Investigator Initiated Multicenter Prospective Randomized Study of Chemoembolization Versus Radioembolization for the Treatment of Hepatocellular Carcinoma (PREMIERE Trial)	Recruiting	NCT00956930	August 2018	November 11, 2014
TACE+ sorafenib vs sorafenib	A Randomized, Controlled Phase III Trial of Sorafenib With or Without Conventional Transarterial Chemoembolization in Patients With Advanced Hepatocellular Carcinoma (STAH Study)	Recruiting	NCT01829035	October 2016	April 2, 2014

^{90}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

Prajapati 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.

Author, year (reference)	Objectives, Design	Population, data collection period	Intervention, (control)	Outcomes	Summary results
Prajapati, 2012 [38]	To investigate safety and feasibility of same-day discharge after DEB-TACE and to explore prognostic factors for hospital admission Observational comparative	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	Superselective 100-300 µm DEB-TACE	(1) Hospital stay and discharge (2) Median recovery duration (3) Median hospital stay (4) Safety	(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. (2) Median recovery duration: Group A: 3 hrs and 42 min (range 2.5 to 10 hrs) Group B: 22 hrs and 35 min (range 16.5 to 49 hrs) (3) Median hospital stay: Group A: 7 hrs (range 3.5 to 14.0 hrs) Group B: 25 hrs and 40 min (range 10 to 51 hrs) (4) Safety: Mortality: 0 Complications: vomiting and nausea: Group A: 6.45%; Group B: 41.17% Abdominal pain: Group A: 24.73%, Group B: 70.58% PES: 32.7%
Nasser, 2014 [39]	To evaluate the safety and feasibility of same-day discharge, and to uncover the prognostic factors for hospital admission Observational, single arm, prospective	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	DEB-TACE performed with an outpatient protocol before liver transplantation as a bridging or downstaging method	(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	(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)[A], increased doxorubicin dose (p=0.004), and the use of more than one vial of embolic agent (p=0.007)[A]. Prognostic factors associated with decreased hospitalizations: Preprocedural use of oxycodone (p=0.043)
Todd, 2014 [abs] [41]	To evaluate the safety of outpatient TACE in pts with intermediate and advanced HCC Retrospective chart review	n=26 pts in Child-Pugh B and C receiving 69 procedures Age: NR Gender: NR Follow-up: NR	TACE	(1) Readmission to hospital (48 hrs post discharge), (2) ER visit (48 hrs post discharge)	(1) Readmissions: None (2) ER visit: 1 pt with intermediate disease in the outpatients group; 0 in the inpatient group

Author, year (reference)	Objectives, Design	Population, data collection period	Intervention, (control)	Outcomes	Summary results
		Period: July 2009 to October 2011			
Goldstein, 2014 [abs] [42]	To verify if outpatient chemoembolization is safe Retrospective chart review	N=238 pts in an outpatient setting Age: NR Gender: NR Follow-up: 4-6 wks Period: NR	Chemoembolization	Complications	Complication rate: 0.8%: HCC rupture (n=1) and hepatic abcess (n=1)
Mitchell, 2009 [40]	To evaluate the safety and feasibility of outpatient TAE and TACE Retrospective chart review	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	Bland embolization and chemoembolization	Safety	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.

[A] 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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Contact Information

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 synthes?s 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)

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Database: EMBASE <1996 to 2014 Week 37>
Search Strategy:
---
1 exp artificial embolism/ (47834)
2 (((transcatheter or transarte- rial) and (emboli* or chemoem- boli*)) or TAE or TACE).mp. (11535)
3 1 or 2 (51392)
4 exp liver cell carcinoma/ (73609)
5 (hepatocellular carci- noma* 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 synthes?s 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 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. (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)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to July 2014>, EBM Reviews - Database of Abstracts of Reviews of Effects <3rd Quarter 2014>
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.
13. (allocated adj2 random).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 transarte- rial) and (emboli* or chemoem- boli*)) 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>

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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:

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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

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1 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)

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Database: Embase <1996 to 2014 Week 41>
Search Strategy:
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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)

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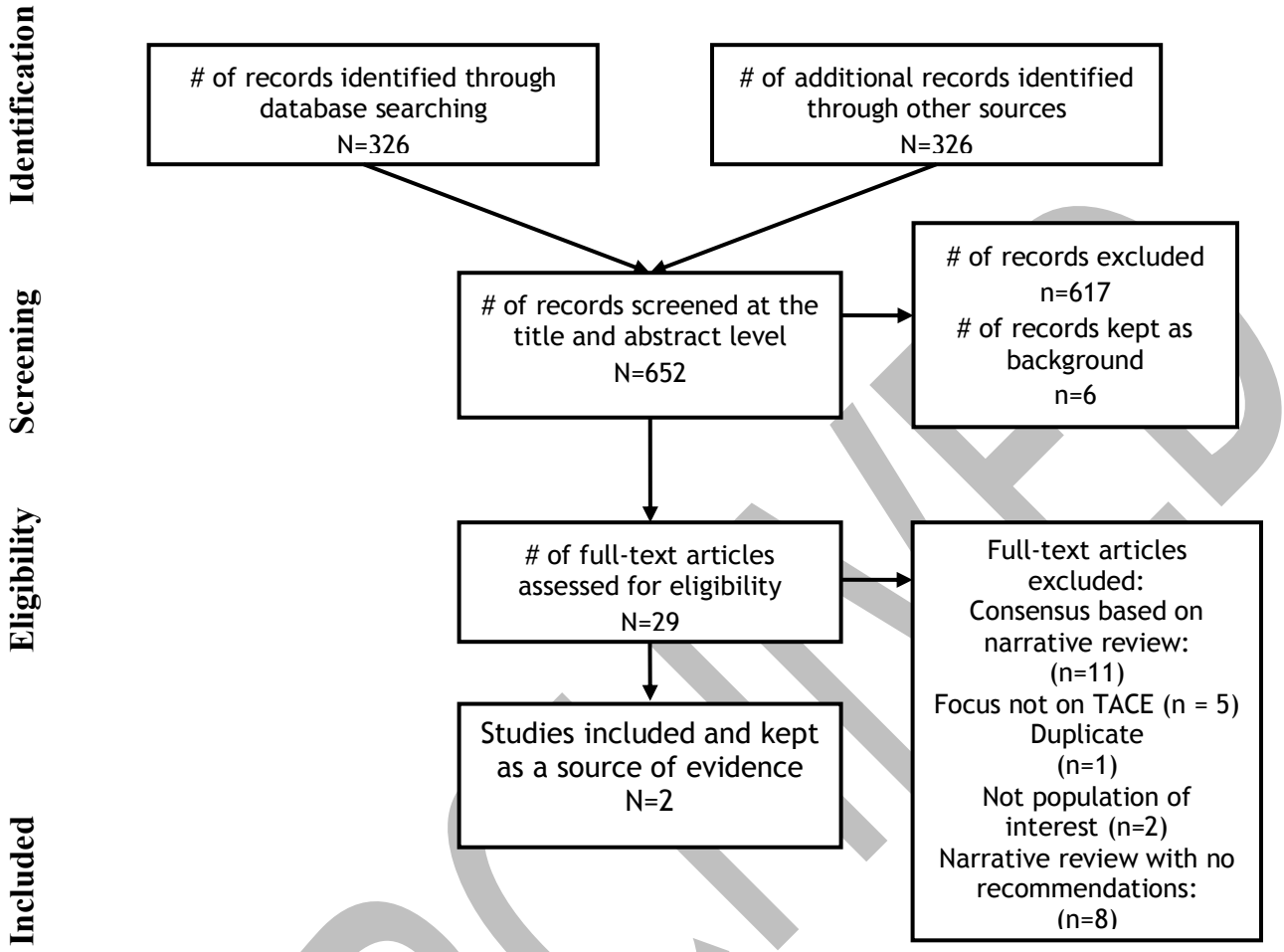
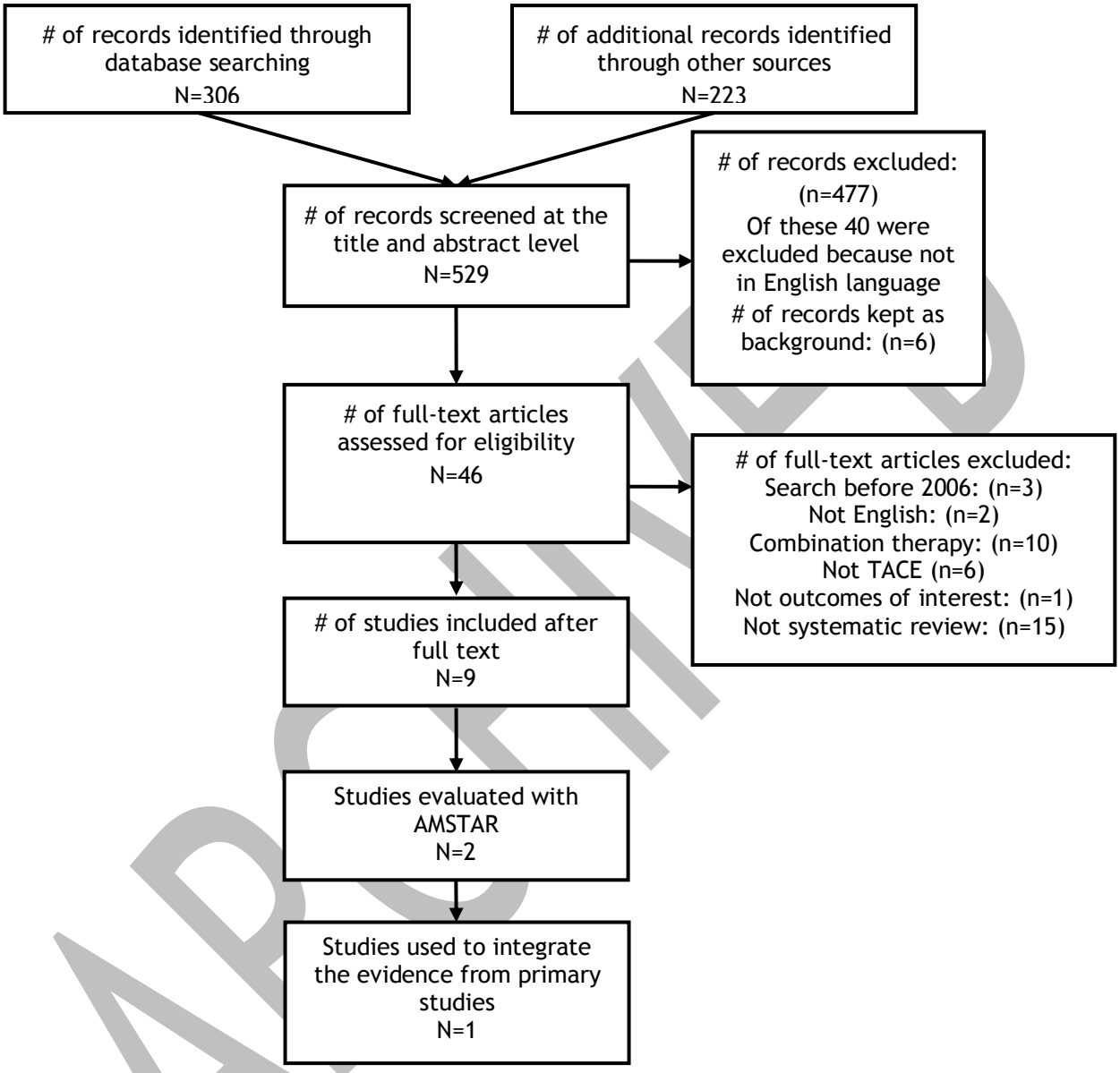
APPENDIX 2: Study Flow Charts

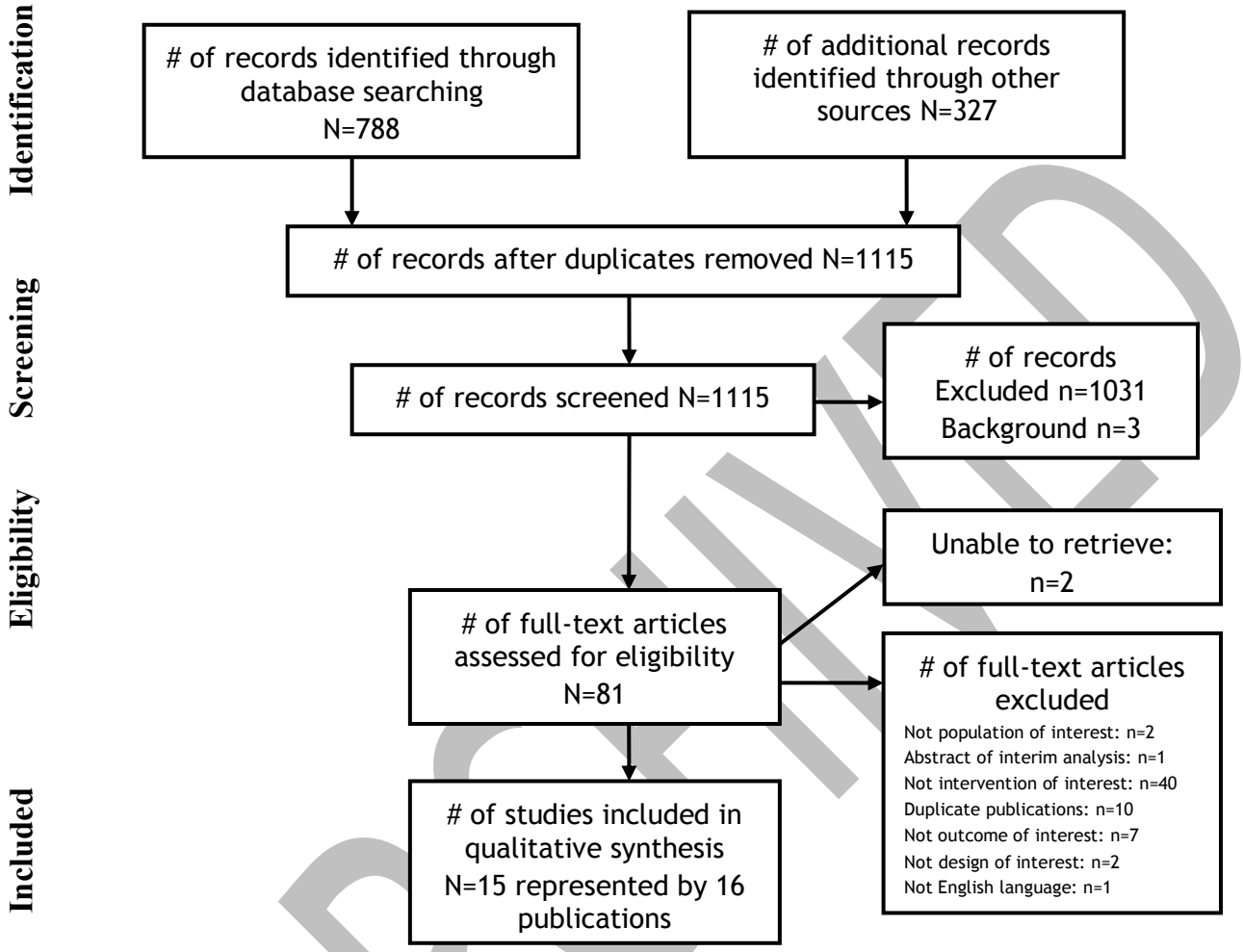
A). Figure 1: Study flow chart: guidelines.



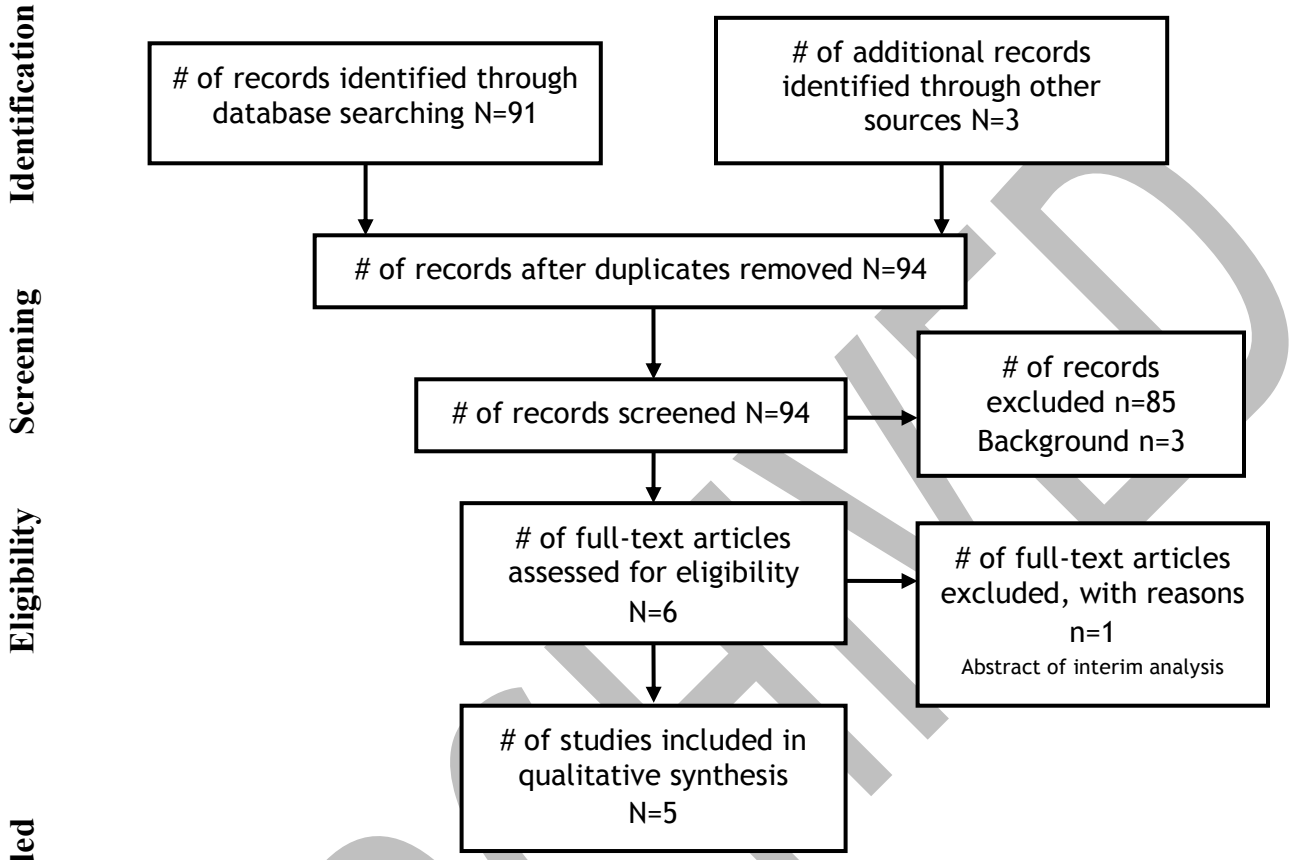
APPENDIX 2B): Figure 2: Study flow chart: systematic reviews.



APPENDIX 2C): Figure 3: Study flow chart: randomized controlled trials of TACE effectiveness.



APPENDIX 2D): Study flow chart: observational studies (inpatient vs outpatient question).



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

1. Baehr C, Zeuzem S, Raedle J. Treatment of hepatocellular carcinoma. [German] Therapie des hepatozellularen karzinoms. Verdauungskrankheiten. 2006;24(5):246-55.
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3. Doffoel M, Ananna A. [Palliative treatment of hepatocellular carcinoma]. Gastroenterol Clin Biol. 2006;30(6-7):887-90. Traitement palliatif du carcinome hepatocellulaire.
4. Mejean A, Correas JM, Thiounn N, Chretien Y, Helenon O, Dufour B, et al. [Conservative treatment of kidney cancer by cryoablation and radiofrequency]. Prog Urol. 2006;16(2):101-4. Traitement conservateur des cancers du rein par cryoablation et radiofrequence.
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10. Lu LG, Hu BS, Li Y, Luo PF. Study of interventional therapy for complications in advanced primary hepatocellular carcinoma. [Chinese]. Journal of Interventional Radiology [Internet]. 2008; 17(7):[514-7 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/785/CN-00707785/frame.html.
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Medical Journal of China [Internet]. 2009; 89(11):[754-7 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/964/CN-00802964/frame.html.
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Systematic reviews excluded at the full-text level.

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1. Lesurtel M, Mullhaupt B, Pestalozzi BC, Pfammatter T, Clavien PA. Transarterial chemoembolization as a bridge to liver transplantation for hepatocellular carcinoma: an

evidence-based analysis. Am J Transplant. 2006;6(11):2644-50.
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B) Randomized controlled trials

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APPENDIX 4: AMSTAR ratings of included systematic reviews

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

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

* 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

AMSTAR item	Rating	
	Huang 2014 [20]	Martin, 2012 [16]
1. Was an "a priori" design provided?	Y	Y
2. Was there duplicate study selection and data extraction?	Y	N
3. Was a comprehensive literature search performed?	Y	Y
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?	Y handsearch	Y
5. Was a list of studies (included and excluded) provided?	Y included only	Y Included only
6. Were the characteristics of the included studies provided?	Y	N
7. Was the scientific quality of the included studies assessed and documented?	Y	N
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Y	N
9. Were the methods used to combine the findings of studies appropriate?	Y separate analysis for RCT and nRCTs	N
10. Was the likelihood of publication bias assessed?	Y	N
11. Was the conflict of interest stated?	Y	Y

Y = yes; N = no; CA = Cannot answer; NA = not applicable

Appendix 5: Conflict of Interest Disclosures: Focal Ablation Committee.

Members	Role	Conflict of Interest
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 Kitchener/Waterloo – Grand River Regional	Member	None declared
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
Richard Malthaner	Member	None declared
Guillaume Martel	Member	Part of Fellowship conference travel stipend in 2013 was covered by a bursary from Covidien (<$5000)
Catherine. Wang	Member	Managerial responsibility on unrestricted research/education grants from Bard, Medtronic, Covidien, Gore, Boston Scientific, Sorin Medical

Members	Role	Conflict of Interest
		Managerial responsibility on research studies funded by: Cook, Medtronic, Biotronic, Teromo, Gore
Ania Kielar	Member	GE CHAR grant for MRI post RFA investigation
Calvin Law	Member	None declared
David Gast	Patient Family Advisor	None declared
Brigitta Bokkers	Patient Family Advisor	None declared

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