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Evidence Summary Focal Ablation 1 ARCHIVED

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

Focal Tumour Ablation 1: Thermal Ablation of Hepatocellular Carcinoma and Metastases from Colorectal Carcinoma

Fulvia G. Baldassarre, Mark Baerlocher, Robert Beecroft, and Laura A. Dawson

Report Date: July 28, 2014

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Evidence Summary (ES) Focal Ablation 1: Thermal Ablation for Liver Cancer

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

Focal Tumour Ablation 1: Thermal Ablation of Hepatocellular Carcinoma and Metastases from Colorectal Carcinoma

Fulvia G. Baldassarre, Mark Baerlocher, Robert Beecroft, and Laura A. Dawson

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QUESTIONS

1. What is the effectiveness of liver lesion thermal ablation using radiofrequency ablation or microwave ablation, alone or in combination with other strategies for the treatment of patients with hepatocellular carcinoma (HCC) or liver metastases (e.g., from colorectal cancer)?
2. What are the subgroups of patients most likely to benefit from thermal ablation interventions?
3. What are the potential adverse events associated with thermal ablation techniques?

Target Population

Patients with HCC or colorectal liver metastases (CLM).

Target Users

Interventional radiologists, radiation oncologists, hepatobiliary surgeons, medical oncologists, healthcare professionals caring for patients with HCC or CLM.

INTRODUCTION

This report summarizes the peer-reviewed evidence regarding the use of radiofrequency ablation (RFA) and microwave ablation (MA) in the treatment of HCC and CLM.

Both RFA and MA are thermal ablative techniques that use heat to destroy cancerous cells. Permanent tissue destruction occurs once the temperature reaches 45°C, and irreversible cellular damage occurs at temperatures between 45°C and 60°C (1). Once the temperature rises above 60°C, protein coagulates almost instantly, with permanent damage occurring at the mitochondrial and enzymatic level. With thermal ablation, the goal is to heat the target tissues to a temperature between 50°C and 100°C and maintain that temperature until irreversible cellular destruction has occurred.

RFA refers to the destruction of cells by inducing coagulation with any electromagnetic energy source with a frequency less than 30 MHz, with most RFA generators working within a range of 375 to 500 kHz (2,3). There are various types of RFA applicators

currently available, including single- and multi-tined applicators, internally cooled electrodes, and perfusion electrodes. Various algorithms of energy deposition are used, including ramped energy and impedance regulated.

Microwave ablation is similar to RFA; however, cellular destruction is achieved by inducing coagulation with an electromagnetic energy source of a frequency between 30 MHz and 30 GHz.

There are ablative therapies other than RFA and MA that can be used to treat liver cancers by using either heating or cooling to destroy the tumour. External beam conformal radiation therapy or stereotactic body radiation therapy (SBRT; also known as stereotactic ablative radiotherapy, SABR) can also be used to treat liver cancers. This current review does not cover all ablative therapies or all liver cancer presentations. It focuses specifically on the use of RFA and MA in the treatment of HCC and CRC liver metastases.

METHODS

This evidence-based report was developed by the Focal Thermal Ablation Working Group in collaboration with the Program in Evidence-Based Care (PEBC). For this project, a systematic review was used to develop the evidentiary base. A review of systematic reviews was conducted by the methodologist (FGB). The evidence from the systematic reviews was complemented by a search of primary randomized controlled trials (RCTs), which was also conducted by the methodologist.

Evidence was selected and reviewed by the methodologist (FGB). The final document was independently reviewed by the other authors (MB, RB, and LD).

Search Strategy

A literature search was performed using MEDLINE, EMBASE (Ovid interface), and the Cochrane Library (to Issue 4, 2014), first for systematic reviews published from 2009 to March 7, 2014 and then for RCTs published from January 1, 2012 to April 25, 2014. The search strategies are reported in Appendices 1 and 2. The citations of the RCTs referenced by the systematic reviews retrieved were also pulled and added to the RCTs retrieved from the database searches.

Additionally, the following resources were checked for systematic reviews, practice guidelines or relevant RCTs: the National Guideline Clearing House, the National Institute for Health and Clinical Excellence, the Scottish Intercollegiate Guideline Network, the Focal Ablation Advisory Committee members' own files, and the Clinicaltrials.gov registry of ongoing trials. All databases were searched on March 7, 2014.

Study Selection Criteria

Systematic Reviews

Inclusion Criteria

Systematic reviews were eligible for inclusion if they met all the following criteria:

- Included studies with a population of patients with HCC or CLM.
- Had a research question pertaining to ablative treatments with radiofrequency and/or microwave.
- Reported on any outcomes (e.g., survival, disease control, adverse events, quality of life).
- Had a search strategy with a cut-off date of 2009 or later.
- Included RCTs and/or non-RCTs.

Exclusion criteria

Systematic reviews were excluded if they:

- Had a focus different from the treatments of interest (e.g., cryoablation).
- Were published in languages other than English.
- Examined thermal ablation used solely with palliative intent.
- Examined thermal ablation to treat metastatic disease to the liver from sources other than colorectal cancer.
- Examined thermal ablation used intraoperatively.
- Examined thermal ablation used for the ablation of biliary obstructions

The RCTs were sought to cover areas not already discussed by the systematic reviews. The time lag between the date of the most recent cut-off date for the included systematic reviews and the date of search was identified as a gap. Therefore, a search for RCTs was performed to cover the years 2012 to 2014.

Study Selection Criteria: Randomized Controlled Trials

Inclusion criteria

RCTs were included if they:

- Included a population of patients with HCC or CLM.
- Had a research question pertaining to RFA and/or MA compared to alternative strategies.
- Reported on any outcomes (e.g., survival, disease control, adverse events, quality of life).
- Were published in 2012 or later.

Exclusion criteria

RCTs were excluded if they:

- Had a focus different from the treatments of interest (RFA and MA).
- Focused on cryoablation.
- Were published in languages other than English.
- Examined thermal ablation used solely with palliative intent.
- Examined thermal ablation to treat metastatic disease to the liver from sources other than colorectal cancer.
- Examined thermal ablation used intraoperatively
- Examined thermal ablation used for the ablation of biliary obstructions

Study Selection, Data Abstraction and Analysis

The methodologist (FGB) reviewed the titles and abstracts of retrieved citations to identify potentially relevant articles which were then retrieved for full-text review. The methodologist reviewed the full text of the systematic reviews and of the RCTs. The methodologist evaluated the quality of the reviews with A Measurement Tool to Assess Systematic Reviews (AMSTAR) instrument (4) and the Cochrane Risk of Bias Tool for the RCTs (5). The AMSTAR tool is an 11-item checklist that evaluates the likelihood of bias in a systematic review by asking questions such as whether the literature search was comprehensive, the study selection was done in duplicate, the methods for combining the results were appropriate, and the quality of the included studies were assessed. The Cochrane Risk of Bias Tool is a domain-based evaluation tool, that critically assesses seven different domains representing selection bias, performance bias, detection bias, attrition bias, and reporting bias.

The data from the included systematic reviews and included RCTs and their quality assessments were summarized in tables. The results of the highest quality systematic reviews and those most relevant to the questions asked by the Panel are reported in detail in the Results section. The initial plan was to pool in a meta-analysis the RCTs if they were sufficiently clinically homogeneous, and to follow a narrative approach if the RCTs were heterogeneous.

RESULTS

Literature Search

The search for systematic reviews resulted in 75 citations from the Cochrane Library, 108 citations from EMBASE, 72 from MEDLINE, 36 from the Panel's own files, and 13 from the guidelines search. We reviewed 304 citations at the title and abstract level, and 82 articles were selected and reviewed at the full-text level. We were unable to locate the full publication of one study. A total of 21 systematic reviews met eligibility criteria and were included. Reasons for exclusion included: duplicate publication (n = 3), abstract of systematic review (n = 4), not the intervention of interest (n = 21), not in English (n = 3), search was before than 2009 (n = 14), no outcomes of interest reported (n = 4), and not a systematic review (n = 12) (see study flow chart in Appendix 3A, and list of excluded systematic reviews in Appendix 4A).

The search for RCTs resulted in 41 citations from Cochrane (CENTRAL), 14 citations from MEDLINE, 197 from EMBASE, and one from the Panel's files. We reviewed 253 citations at the title and abstract level; 13 publications were considered of potential interest and the full text was retrieved. Two RCTs were included after full-text review. Reasons for exclusion included: an abstract of an interim analysis (n = 1), already included in systematic reviews (n = 2), duplicate publication (n = 2), not written in English (n = 1), not an intervention of interest (n = 2), and not a RCT (n =3) (see study flow chart in Appendix 3B and list of excluded RCTs in Appendix 4B).

Tables 1A and 1B present the general characteristics and the summary results of the included systematic reviews. Tables 2A and 2B present the quality characteristics of the included systematic reviews. Tables 3A and 3B present the general characteristics and summary results of the included RCTs and Table 4 presents the quality of the included RCTs.

Table 1A. Focal ablation: summary table of included systematic reviews of thermal ablation – HCC.

	Author, date, funding source,	Search cut-off date	# of studies included	Review objectives/ Design	Study designs included	Population	Intervention/ comparison(s)	Outcomes	Summary results
1	Wang, 2014 (6) Funding: National Technology Support Program (China)	Nov 2012	28: 3 RCTs and 25 non-RCTs	To evaluate the efficacy and safety of RFA versus hepatic resection for early HCC meeting the Milan criteria Meta-analysis (separately of RCTs and non-RCTs)	RCTs, non-RCTs, retrospective clinical, or cohort studies	N = 11,873 meeting the Milan criteria[a]	RFA vs. SR	OS (at 1-, 3-, and 5 y), RFS (at 1-, 3-, and 5 y), DFS (at 1-, 3-, and 5 y), Safety (at 1-, 3-, and 5 y)	**Meta-analysis of RCTs** **OS**: at 1 and 3 y: p = NS; **RFS**: at 1 and 3 y: NS; RFA was lower than SR at 5 y (RR 0.56, 95% CI: 0.40-0.78, NNH= 4.4). **DFS**: 1 RCT: p =NS **Meta-analysis of non-RCTs** **OS**: at 1 and , 2 and 5 y: RFA significantly lower than SR at 1, 3 and 5 y (OR 0.78, 95% CI: 0.63–0.97, OR 0.67, 95% CI: 0.52–0.85, ; and OR 0.58, 95% CI: 0.36–0.94, respectively). **RFS:** at 1, 3 and 5 y RFA lower than SR (OR 0.78, 95% CI: 0.64–0.95, OR 0.67, 95% CI: 0.56–0.79, and OR 0.63 95% CI: 0.40–1.00 respectively). **DFS**: at 1, 3, and 5 y RFA significantly lower than SR (OR 0.46, 95% CI: 0.38–0.55, OR 0.49, 95% CI: 0.34–0.69, and OR 0.52, 95% CI: 0.32–0.84, respectively).
2	Weiss, 2013 (7) Cochrane review	Sept 2012	11 RCTs	To assess the beneficial and harmful effects of RFA versus placebo, no intervention, or any other therapeutic approach in patients with HCC. Meta-analysis (RCTs only)	RCTs	N = 578 pts with HCC without contraindications for RFA (e.g., too many or too large tumours)	RFA vs SR RFA vs PEI RFA vs MA RFA vs LA	OS EFS (recurrence and death) Local recurrence AE (Time intervals NR)	<u>RFA vs SR (3 trials):</u> **OS** NS (random effects model) (HR 0.71; 95% CI 0.44 to 1.15); favoured SR (fixed effect model) (HR 0.76; 95%CI 0.58-1.00). <u>RFA vs PEI (6 trials):</u> **OS** favours RFA (HR 1.64; 95% CI 1.31 to 2.07) **EFS** favours RFA (HR 1.55; 95% CI 1.31-1.85) Local recurrence favoured RFA (HR 2.44; 95% CI 1.71-3.49). However, no significant difference was found if only the result from the 4 trials with low risk of bias were meta-analyzed (OS: HR 1.19; 95% CI 0.79-1.77). <u>RFA vs. MA (1 trial):</u> **AE** for all comparisons: p = NS
3	Belinson, 2013 (8) **Funding:** Agency for Healthcare Research and Quality (USA)	Jul 2012	48: 6 RCTs, 4 non-RCTs, 35 case series, and 3 case reports	To examine the comparative effectiveness of local interventions for HCC	3 RCTs, 1 non-RCT, 6 case series and 1 case report.	N = 483 (RCTs only) with unresectable HCC. Pts with unresectable primary HCC who meet all	RFA vs. PEI/PAI (3 trials) RFA vs. TACE	OS Progression Length of stay AE	<u>RFA vs PEI/PAI</u> **OS** at 3 y: RFA superior to PEI (p=0.031) **TTP** and local recurrence: RFA superior to PEI (high risk of bias) **Length of stay**: shorter with PEI than RFA

	Author, date, funding source,	Search cut-off date	# of studies included	Review objectives/ Design	Study designs included	Population	Intervention/ comparison(s)	Outcomes	Summary results
				Systematic review and meta-analysis (only RCTS)		of the following criteria: • No extrahepatic spread • No portal invasion • Child-Pugh class A or B disease • Eastern Cooperative Oncology Group (ECOG) status ≤1 and/or • BCLC stage A or B, or equivalent			<u>RFA vs. TACE</u> No RCTs for this comparison available OS at 2 y: RFA: 72% vs. TACE: 58%, p = NS
4	Qi, 2013 (9) **Funding**: ND	Dec 2012	3 RCTs	To test the efficacy of RFA compared with SR Meta-analysis	RCTs	N = 559 with HCC who met the Milan criteria[a]	RFA vs SR	OS RFS Complications Hospital length of stay	**OS**: SR superior to RFA (p=0.02) **RFS**: SR superior to RFA (p=0.001) **AE**: SR had higher incidence of treatment-related AE than pts treated with RFA (p=0.002) **Hospitalization**: SR pts had longer hospitalizations than pts treated with RFA (p<0.00001)
5	Duan, 2013 (10) **Funding**: National Science Foundation of China	Jun 2013	12: 2 RCTs and 10 non-RCTs	To compare the effectiveness of RFA with SR Meta-analysis	All	N = 8,612 with early stage HCC	RFA vs SR	OS (at 1, 3, and 5 y) DFS (1, 3 and 5 y) Complications Length of hospital stay	**OS** at 3 and 5 y: RFA shorter than SR
6	Cucchetti, 2013 (11) **Funding:** Siemens, Esaote, Bayer	Dec 2012	19: 3 RCTs and 16 retrospective observational studies	To examine the available literature directly comparing surgical resection with RFA Systematic review	All	N = 12,703 with HCC	RFA vs SR	OS Complications	Unable to draw conclusions from the evidence. Includes 3 RCTs of which 2 state NS difference in OS and one favours SR. Good discussion of non-RCTs, and separate analysis because RFA is offered as an alternative not competitive strategy (i.e., prognostic factors are different in patients allocated to RFA and to SR in favour of SR)
7	Shen, 2013 (12) **Funding:** National Natural Science Foundation of	Mar 2012	4 RCTs	To perform a systematic review and meta-analysis of RCTs to	RCTs	N = 766 with HCC <3 cm	RFA vs. PEI	OS Complete tumour necrosis Recurrence Metastases	**OS**: RFA better than PEI (HR = 0.66, 95% CI 0.48-0.90, p = 0.009) **Recurrence**: RFA had lower risk of local recurrence (HR = 0.38, 95% CI

	Author, date, funding source,	Search cut-off date	# of studies included	Review objectives/ Design	Study designs included	Population	Intervention/ comparison(s)	Outcomes	Summary results
	China and Chongqing Natural Science Foundation of China			compare RFA with PEI Meta-analysis				Complications Cost Hospital stay	0.15-0.96, p = 0.04), but for distant hepatic recurrence NS. **Complete tumour necrosis**: RFA was better **Complications**: RFA caused more major complications **Cost**: RFA cost more
8	Xu, 2012 (13) **Funding:** ND	Dec 2011	13: 2 RCTs and 11 non-RCTs	To perform a meta-analysis of SR vs RFA Meta-analysis (together RCTs and non-RCTs)	All comparative	N = 2,535 with HCC	RFA vs SR	OS Recurrence	**OS**: SR better at 1, 3 and 5 y (respectively: OR, 0.60, 95% CI, 0.42 to 0.86; OR, 0.49, 95% CI, 0.36 to 0.65; OR, 0.60 95% CI, 0.43 to 0.84.) **Recurrence**: SR better at 1, 3, and 5 y (respectively: OR, 1.48, 95% CI, 1.05 to 2.08; OR, 1.76, 95% CI, 1.49 to 2.08; OR, 1.68, 95% CI, 1.21 to 2.34)
9	Li, 2012 (14) **Funding:** ND	Mar 2011	6: 2 RCTs and 4 non-RCTs	To retrospectively evaluate the long term effects of RFA and SR Meta-analysis (RCTs and non-RCTs together)	All comparative	N = 877 with HCC	RFA vs SR	OS RFS Local recurrence	**OS**: SR better at 1, 3, and 5 y (respectively: OR: 0.50, 95% CI: 0.29-0.86; OR: 0.51, 95% CI: 0.28-0.94; OR: 0.62, 95% CI: 0.45-0.84). For tumours ≥3 cm SR better than RFA for the 3-y OS (OR: 0.38, 95% CI: 0.16-0.89) **RFS**: SR better at 1, 3, and 5 y (respectively: OR: 0.65, 95% CI: 0.44-0.97; OR: 0.65, 95% CI: 0.47-0.89; OR: 0.52, 95% CI: 0.35-0.77) **Local recurrence**: RFA had higher rate of local recurrence (OR: 4.08, 95% CI: 2.03-8.20)
10	Tiong, 2011 (15) **Funding:** University of Adelaide, Discipline of Surgery (Australia)	Nov 2010	43: 12 RCTs, and 31 non-RCTs	To test the effect of RFA Meta-analysis (only RCTs)	RCTs, quasi-RCT, and non-RCTs	N = 1,558 with resectable and unresectable HCC	RFA vs. SR, chemotherapy, other ablative treatments (e.g., PEI, microwave coagulation, LITT)	OS (at 1,3 and 5 y) Disease recurrence	RFA vs SR **OS**: inside the Milan criteria: NS; outside the Milan criteria: SR was better (limited to pts with Child-Pugh grade A cirrhosis and a single HCC >3 cm) RFA vs PEI: **OS:** RFA better than PEI at 1 y: risk ratio: 0·62 (95% CI 0.41-0.94); and 3 y: risk ratio: 0·79 (95% CI 0.65-0.96)
11	Cho, 2011 (16) **Funding:** ND	Feb 2011	8: 2 RCTs and 6 retrospective analyses	To compare SR with RFA as a primary treatment for HCC. Systematic review	All comparative	N = 1,100 meeting the Milan criteria[a]	RFA vs. SR	OS Safety (perioperative mortality) Local recurrence	Cannot reach a conclusion from available evidence.
12	Salhab, 2011 (17) **Funding**: none declared	Dec 2010	17 of which 5 of percutaneous treatment and	To identify survival benefit for medical modalities in HCC	RCTs	N = 628 with HCC (included in meta-analysis)	RFA vs. PEI	OS (at 1, 2 ,and 3 yrs) Cumulative probability of no recurrence	**OS** at 3 y RFA superior to PEI (p=0.002) **AE** NS

	Author, date, funding source,	Search cut-off date	# of studies included	Review objectives/ Design	Study designs included	Population	Intervention/ comparison(s)	Outcomes	Summary results
			4 included in meta-analysis	Meta-analysis (RCTs mixed with Observational)					
13	Xie, 2009, 2010 (18,19) **Funding**: McGill University	Jan 2009	6: 1 RCT and 5 comparative studies	To compare effectiveness and cost of RFA and SR for HCC Meta-analysis (mixed RCTs and observational)	RCTs, non-randomized comparative cohort studies, and cohort studies. (For cohort studies the min sample size was N = 50).	N = 1,014 with either primary HCC or CLM	RFA vs. SR RFA +TACE vs. RFA alone TACE vs. SR	OS DFS Recurrence AE Cost	RFA vs SR: **OS** NS **DFS** SR is superior to RFA **Recurrence**: Either comparable or SR is superior to RFA **AE** RFA has less complications than SR
14	Zhou, (20) **Funding:** ND	Nov 2009	10: 1 RCT and 9 non-RCTs	To test whether RFA is superior to SR Meta-analysis (mixed RCTs and observational)	RCTs and non-RCTs	N = 1411 Pts with a small HCC eligible for SR	RFA vs SR 2 of the studies included laparoscopic RFA and the others included percutaneous RFA	OS Recurrence DFS Safety	**OS** 1 y (all trials): p =NS **OS** 2 y (4 trials): p = NS **OS** 3 y (9 trials) OR: 0.56, 95% CI: 0.44-0.71 p<0.001 favours SR **Local recurrence** (5 trials): OR: 4.50, 95% CI: 2.45-8.27 p<0.001 favours SR **Distant recurrence**: NS **DFS**: at 1, 2, 3, 5 y: significantly better for HR (p=0.006, p<0.001, p<0.001, p=0.05 respectively) **Morbidity**: OR: 0.29, 95% CI: 0.13-0.65 p= 0.003 favors RFA **Mortality**: p = NS

AE = adverse events; BSC = best supportive care; CI = confidence interval; CLMs = colorectal liver metastases; DFS = disease free survival; EFS = event-free survival; HCC = hepatocellular carcinoma; HR = hazard ratio; LA = laser ablation; LITT = laser induced thermal therapy; MA = microwave ablation; min = minimum; ND = not declared; NNH = number needed to harm; NS = not significant; OR = odds ratio; OS = overall survival; PAI = percutaneous acetic acid injection; PEI = percutaneous ethanol injection; PRFA = percutaneous radiofrequency ablation; Pts = patients; QOL = quality of life; RCTs = randomized controlled trials; RFA = radio frequency ablation; RFS = recurrence-free survival; RR = relative risk; SR = surgical resection; Sys Revs = systematic reviews; TACE = transarterial chemoembolization; TTP = time to progression; vs = versus; y = years.

[a] Milan criteria: single HCC≤5 cm or 3 nodules <3 cm

Table 1B. Focal ablation: Summary table of included systematic reviews of thermal ablation - CLM

	Author, date, Funding source,	Search cut-off date	# of studies included	Review objectives/ Design	Study designs included	Population	Intervention/ Comparison(s)	Outcomes	Summary Results
1	Loveman, 2014 (21) **Funding**: Health Technology Assessment Programme, UK	Sep 2011	16: 1 RCT of MA	To evaluate the clinical effectiveness and cost-effectiveness of the different ablative and minimally invasive therapies for treating liver metastases	RCTs, Prospective non-RCTs, Prospective case series (sample >100), Economic evaluations	N = 2,618 with liver metastases	RFA, MA cryoablation, PEI, LA, focused ultrasound, electrolytic ablation, TACE and radioembolization vs. SR, chemotherapy and BSC	Effectiveness and cost	Narrative synthesis: low quality evidence does not permit conclusions or pooling. MA **OS**: from RCT: p = NS **DFS**: p = NS Surgical invasiveness: in favor of MA (p=0.0027) **AE:** p = NS RFA **OS** from 1 non-RCT + 5 case series: contrasting results **Recurrence:** contrasting results **AE:** low
2	Bala, 2013 (22) Cochrane review (sub group of a larger review by Riemsma 2009)	Dec 2012	1	To examine the efficacy and adverse events of MW coagulation. Systematic review	RCTs Quasi-RCTs Other controlled studies	N = 30 with liver metastases regardless of the location of the primary tumour.	MA vs. SR	All-cause mortality Survival at 1, 3-y DFS AE QOL Cancer mortality Failure to clear liver metastases TTP Tumour response	Insufficient evidence to draw conclusions. Body of the evidence of moderate risk of bias **Mortality**: p = NS **DFS**: p = NS **AE:** p = NS
3	Cirocchi, 2012 (23) Cochrane review	Jan 2, 2012	18: 1 RCT (abs), 7 CCTs, and 10 observational studies	To systematically review the role of RFA in the treatment of CLMs Systematic review	RCTs; Quasi-RCTs Observational designs	N = 2,709 with CLMs and pts with unresectable extrahepatic disease	RFA alone or in combination compared with any other intervention	OS at 2, 3, and 5 y PFS DFS at 1, 2, and 5 y Recurrence at 1, and 2 y Residual disease AE	Insufficient evidence to draw conclusions. Body of evidence at high risk of bias Data were not summarized. The only RCT showed that PFS was significantly higher for the group that received RFA.
4	Belinson, 2012 (24)	Jun 2012	30: 1 RCT, and 29 case series	To characterize the comparative effectiveness and harms of various local hepatic therapies for metastases to the liver from unresectable colorectal cancer (CRC) Systematic review	Comparative studies	N = NR 1. Pts with liver-dominant metastases not eligible for systemic chemotherapy because of refractory disease. 2. Pts candidate for local liver therapies as an	Ablation, embolization, and radiotherapy approaches.	OS QOL AE	Evidence insufficient to draw conclusions. No comparative study met the inclusion criteria.

	Author, date, Funding source,	Search cut-off date	# of studies included	Review objectives/ Design	Study designs included	Population	Intervention/ Comparison(s)	Outcomes	Summary Results
						adjunct to systemic chemotherapy.			
5	Wu, 2011 (25) **Funding:** ND	2010 (month ND)	7 non-RCTs	To compare the efficacy of RFA with SR Meta-analysis	Comparative studies	N = 847 with solitary colorectal cancer liver metastasis	RFA vs SR	OS (at 5 y) Local intrahepatic recurrence DFS (at 5 y) Safety (morbidity and mortality)	Body of evidence of low quality **OS** at 5 yrs significantly longer for SR (p=0.008) **Local recurrence**: significantly lower for SR (p<0.003) **AE**: p = NS for mortality and morbidity
6	Pathak, 2011 (26) **Funding:** No financial support	Jan 2010	75: 13 MA, 36 RFA, and 26 cryo	To systematically review the literature on ablative strategies. Systematic review	RCTs, case series	N = 4,248 with CLM	RFA, Cryoablation, and MA vs. palliative chemotherapy	OS (at 1,2,3,4, and 5 y) Recurrence (at 1,2,3,4, and 5 y) Complications (at 1,2,3,4,and 5 y)	RFA: No difference in response between pts with extrahepatic disease and those with intrahepatic disease. In the only RCT included: **PFS** at 3 y: 27.6% RFA + chemo vs. 10.7% chemo alone **OS:** p = NS at 30 mo MA: **OS:** p = NS
7	NICE, 2009 (27) **Funding**: National Institute for Health Research, UK	Aug 2009	1 sys rev 2 non-RCTs, 3 case series, and 2 case reports	To produce an evidence base for recommendations Rapid review	1 systematic reviews, 2 non-RCTs, 3 case series,2 case reports	N = 1,570 with CLM	RFA alone or in combination with SR	Efficacy AE	Narrative synthesis Survival rate was higher with SR compared to RFA. No comparative data reported for AE.

Abs = abstract; AE = adverse events; BSC = best supportive care; CI = confidence interval; CCT = clinical controlled trials; CLMs = colorectal liver metastases; DFS = disease-free survival; HCC = hepatocellular carcinoma; LA = laser ablation; LITT = laser induced thermal therapy; LR = liver resection; MA = microwave ablation; ND = not declared; NNH = number needed to harm; NS = not significant; OS = overall survival; PAI = percutaneous acetic acid injection; PEI = percutaneous ethanol injection; PFs = progression-free survival; PRFA = percutaneous radiofrequency ablation; Pts = patients; QOL = quality of life; RCTs = randomized controlled trials; RFA = radio frequency ablation; RFS = recurrence free survival; RR = relative risk; SR = surgical resection; Sys Revs = systematic reviews; TACE = transarterial chemoembolization; TTP = time to progression; vs = versus; yrs = years;

Table 2A. Quality assessment of included systematic reviews with AMSTAR - HCC

Study	An *a priori* design provided	Duplicate study selection and data extraction	Comprehen-sive literature search performed	Status of publication used as an inclusion criterion	List of studies (included and excluded) provided	Characteristics of included studies provided	Quality of included studies assessed and documented	Quality of included studies used appropriately in formulating conclusions	Methods used to combine the findings of studies appropriate	Likelihood of publication bias assessed	Conflict of interest included
Wang 2014 (6)	Y	Y	Y	N	Y[a]	Y	Y	N	N[b]	Y	Y
Weiss, 2013 (7)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Belinson, 2013 (8)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Qi, 2013 (9)	Can't determine	Y	Y	N	Y[a]	Y	Y	N	Y	N	N*
Duan, 2013 (10)	Can't determine	Can't determine	N (only MEDLINE)	N	Y[a]	Y	Y	N	N[b]	Y	N[c]
Cucchetti, 2013 (11)	Can't determine	N	Y	N	Y	Y	Y	N	Y	N	N*
Shen, 2013 (12)	Can't determine	N	Y	N	Y[a]	Y	Y	N	Y	Y	N*
Xu, 2012 (13)	Can't determine	N	Y	N	Y	Y	Y	Y	N[b]	Y	N
Li, 2012 (14)	N	N	Y	N	Y[a]	Y	Y	N	N[a]	Y	N[c]
Tiong, 2011 (15)	N	N	Y	N	Y	Y	Y	N	Y	N	N[c]
Cho, 2011 (16)	N	N	Y	N	Y	Y	N	N	Y	N	N[c]
Salhab, 2011 (17)	Can't tell	N	Y	N	Y	Y	N	N	N[b]	N	N
Xie, 2009, 2010 (18,19)	Can't tell	N	Y	N	Y	Y	N	N	N[b]	N	N
Zhou, (20)	N	N	N	N	Y	Y	Y	Y	N[b]	N	N

[a] Only included studies listed

[b] The authors combined observational & RCT studies in meta-analysis.

[c] Does not report source of funding for the included studies, although it does report authors' conflict of interests and funding source for the review.

Table 2B. Quality assessment of included systematic reviews with AMSTAR - CLM

Study	An *a priori* design provided	Duplicate study selection and data extraction	Comprehen-sive literature search performed	Status of publication used as an inclusion criterion	List of studies (included and excluded) provided	Characteristics of included studies provided	Quality of included studies assessed and documented	Quality of included studies used appropriately in formulating conclusions	Methods used to combine the findings of studies appropriate	Likelihood of publication bias assessed	Conflict of interest included
Loveman, 2014 (21)	Y	Y	Y	Y	Y[a]	Y	Y	Y	Y	Y	Y
Bala, 2013 (22)	Y	Y	Y	Y	Y[a]	Y	Y	Y	Y	Y	Y
Cirocchi, 2012 (23)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Belinson, 2012 (24)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N*
Wu, 2011 (25)	N	N	Y	N	Y	Y	N	N	N	N	N
Pathak, 2011 (26)	N	Y	Y	Y	Y	Y	Y	N	N	N	N
NICE, 2009 (27)	Y	N	Y	Y	Y	Y	Can't determine	N	Y	N	N[b]

[a] Only included studies listed

[b] Does not report source of funding for the included studies, although it does report authors' conflict of interests and funding source for the review.

Table 3A. General characteristics and summary results of included RCTs - HCC

Study, year, funding	Objectives	Population	Intervention/comparison	Outcomes	Summary results
Di Costanzo (abs) 2013 (28) **Funding**: ND	To prospectively evaluate tumour response after RFA or LA of small HCC	N = 140 with cirrhosis and total 157 HCC nodules	RFA (n = 70 with total 77 nodules) LA (n = 70 with total 80 nodules)	CTA TTR OS	AT median follow-up 18.5 mo: **CTA:** 97.2% vs. 95.8% **TTR:** 16 mo (95% CI, 11-21) vs. 21 months (95% CI, 18-24) (p=0.08) **OS:** 93% vs. 93%

CI = confidence interval; CTA = complete tumour ablation; HCC = hepatocellular carcinoma; LA = laser ablation; mo = months; OS = overall survival; ND = not declared; PFS = progression-free survival; RFA = radiofrequency ablation; TTR = time to recurrence; vs = versus.

Table 3B. General characteristics and summary results of included RCTs – CLM.

Study, year, Funding	Objectives	Population	Intervention/Comparison	Outcomes	Summary results
Ruers, 2012 (29)[a]	To compare the efficacy of RFA + systemic treatment vs. systemic treatment alone	N = 119 with nonresectable liver metastases from colorectal adenocarcinoma without detectable extrahepatic disease	RFA + systemic treatment (n = 60) Systemic treatment alone (n = 59)	OS PFS HRQoL Toxicity	**OS:** 45.3 (95% CI 33.1–NA) mo vs. 40.5 (95% CI 29.5–50.1); HR = 0.74, 95% CI 0.46–1.19, p = 0.22 **PFS:** 16.8 mo (95% CI 11.7–22.1) vs. 9.9 mo (95% CI 9.3–13.7); HR = 0.63 (95% CI 0.42–0.95, p = 0.025) **HRQoL**: HRQoL scores were similar in both treatment groups. **Toxicity**: There was one postoperative death due to sepsis in the combined treatment arm. Toxicity from systemic treatment was comparable in both arms.

[a]*The Ruers' study was included in one of the included systematic reviews as an abstract of an ongoing study, we identified the full text publication.
CI = confidence interval; HR = hazard ratio; HRQOL = health-related quality of life; mo = months; OS = overall survival; PFS = progression free survival; RFA = radiofrequency ablation;

Table 4. Quality of the included RCTs

Risk of Bias Tool	Di Costanzo, 2013 (28)	Ruers, 2012 (29)
Random sequence generation (selection bias)	Unclear risk	Low risk[a]
Allocation concealment (selection bias)	Unclear risk	Unclear risk
Blinding of participants and personnel (performance bias)	Unclear risk	High risk
Blinding of outcome assessment (detection bias)	Unclear risk	High risk
Incomplete outcome data addressed (attrition bias)	Unclear risk	Low risk[b]
Selective reporting (reporting bias)	Unclear risk	Low risk

[a]The authors performed central randomization
[b]The authors performed an intention-to-treat analysis

Question 1: Effectiveness of Thermal Ablation

A. Hepatocellular Carcinoma

Two high-quality systematic reviews compared RFA with surgical resection, percutaneous ethanol injection (PEI), transarterial chemoembolization (TACE) and MA in patients with primary hepatocellular carcinoma who were (7) or were not (8) candidates for surgical resection. Both systematic reviews included RCTs and non-RCTs.

Radiofrequency Ablation versus Surgical Resection.

Weis et al. (7) included three RCTs, and they rated their quality according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (30). According to this system, the quality of the studies is rated with the Cochrane Risk of Bias tool (5) and the evidence for each outcome considered critical, across multiple studies, is evaluated individually. Evidence begins with a high ratings for RCTs and a low rating for observational studies. It may be then "graded down" according to evaluation of five factors: risk of bias, inconsistency, indirectness, imprecision, and publication bias. It may be "graded up" according to three factors: large magnitude of effect, dose-response gradient, and if no effect was observed when all possible confounding would reduce the effect or increase the effect. At the end of this process, systematic reviewers do not grade the overall quality of the evidence across outcomes, but they rate the evidence for each outcome as high, moderate, or low.

Weis et al. (7) used the Cochrane Risk of Bias tool to rate two of three RCTs at low risk of bias (31,32), and one at high risk of bias (33).

Overall survival. The reviewers rated the quality of the evidence for overall survival (OS) as moderate. When pooling the results from all three trials (31-33) using a random effects model, OS was not statistically significantly different between groups: hazard ratio (HR) 0.71, (95% confidence interval [CI] 0.44-1.15). However, when pooling data using a fixed effects model, OS reached statistical significance in favour of surgical resection: HR 0.76, (95% CI 0.58-1.00). Further, in a subgroup analysis, when only the two low risk of bias trials (31,32) were pooled, surgical resection yielded better results than RFA for OS (HR 0.56; 95% CI 0.40- 0.78).

Event free survival. The reviewers considered the quality of the evidence for this outcome as moderate. At three years, surgical resection produced better results than RFA: the pooled estimates for three RCTs (31-33) was: HR 0.70 (95% CI 0.54, 0.91), I^2=34%.

Local progression. The reviewers considered the quality of the evidence as low because only one trial reported on this outcome. Local progression was better for surgical resection than RFA (one RCT): HR 0.48 (95% CI 0.28- 0.82).

Length of hospital stay. The reviewers rated the evidence for this outcome as high. RFA produced shorter lengths of stay than surgery: standardized mean difference: 2.18 days, 95% CI 1.97-2.39.

Radiofrequency ablation versus Percutaneous Ethanol Injection (PEI).

Overall survival. The authors of both reviews (7,8) considered the quality of the evidence, and both evaluated it with the GRADE method (30) for OS as moderate. OS was superior in the RFA group than in the PEI group in both reviews.

Weis et al. pooled seven RCTs; five, (represented by four publications), of which they considered at low risk of bias (34-37) and two at high risk of bias (38,39). For OS, they reported a better results for RFA HR 1.64, (95% CI 1.31- 2.07) with I^2 = 0.0% (7).

Belinson et al. identified three RCTs (39), also included in the Weis review: one compared RFA to PEI alone (34,36,39); one compared RFA with high-dose PEI (34); and one compared RFA to PEI and percutaneous acetic acid injection (PAI) (36). Most patients in the included studies had a solitary tumour, and data on lesion size were not reported. The authors conducted a quantitative pooling for OS at three years; the RFA group had a significantly higher OS than the PEI/PAI group (risk difference 0.16 (95% CI, 0.03- 0.28, I^2=48%) (8).

Event-free survival. Weis et al. (7) rated the quality of the evidence for EFS as moderate, whereas Belinson et al. considered the strength of evidence as low (8). After pooling the previously mentioned seven RCTs (34-39) RFA resulted in a better EFS: HR 1.55, 95% CI 1.31 to 1.85 (7). Belinson et al. (8) reported narratively about cancer-free survival, and stated that the RFA group had significantly higher survival rates in both of the included studies (34,36).

Local recurrence. Local recurrence was better with RFA in both reviews: Weis et al. pooled results from six studies, four of which rated at low risk of bias (34-37) and two of which they rated of high risk of bias(38,39): HR 2.44, 95% (CI 1.71-3.49) (7). Belinson et al. (8) reported a narrative summary of the results from two RCTs (34,36) (no numerical data provided) and considered the strength of the evidence low for this outcome.

Length of hospital stay. Belinson et al. reported that patients in the RFA group stayed in hospital longer than patients in the PEI group (no numerical data provided) (8). The reviewers rated the quality of this outcome as low.

Quality of life. Quality of life was not reported by the studies included in either reviews.

Radiofrequency Ablation versus Microwave Ablation.

Weis et al (7) identified one RCT (40) that presented data by nodules and not by patient which prevented extraction of data on OS, and EFS. The Belinson et al review did not report on this comparison (8).

Local progression. Local progression was not statistically significantly different between the RFA and MA in the study by Shibata et al. (40) as reported by Weis et al (7) (HR 2.14, 95% CI 0.67-6.80)

Radiofrequency Ablation versus Laser Ablation.

When RFA was compared with laser ablation in one RCT (41) identified by the Weis et al. review (7), no statistically significant difference was detected for OS. This result is consistent with the findings of the conference abstract we identified through our search for RCTs (28). In the latter abstract, no difference was shown for complete tumour ablation or for time to recurrence. Belinson et al did not report on this comparison (8).

Radiofrequency Ablation versus Transarterial Chemoembolization.

Weis et al. (7) did not identify any study for this comparison. Belinson et al (8) identified one retrospective cohort study (42).

Overall survival. OS was not statistically significantly different between groups in the study by Chok et al. (42) and the reviewers concluded that the evidence was insufficient to draw conclusions.

B. Colorectal Liver Metastases

Four high-quality systematic reviews (21-24) and one RCT (29) were included. All these reviews concluded that the available evidence was insufficient to draw conclusions; Ruers et al. (29) concluded that RFA plus chemotherapy resulted in better progression-free survival (PFS) than chemotherapy alone, but that uncertainty remained for OS. A more detailed description of the finding of these studies follows. Bala et al. (22) evaluated the evidence with the GRADE method (30), Belinson et al. used the Agency for Healthcare Research and Quality (AHRQ) Methods Guides (43); Cirocchi et al. (23) used a component approach (i.e., generation of randomization sequence, adequacy of allocation concealment and of follow-up) to evaluate the quality of included RCTs, and Loveman et al. (21) used the approach recommended by the Centre for Reviews and Dissemination (44).

Bala et al. sought studies comparing MA with surgical resection in patients with liver metastases of any primary tumour (22) and found one RCT (45) which they rated as very low quality.

Belinson et al. sought studies examining ablation strategies in patients with unresectable or recurrent colorectal cancer liver metastases. These authors found only case series that reported no comparisons (24). The reviewers concluded that the evidence was insufficient to draw conclusions.

Cirocchi et al. included studies of RFA in patients with colorectal liver metastases (23). These authors found seven observational and six non-RCTs that compared RFA with surgical resection (46-58); one abstract publication of an RCT (the full publication of which was identified by our search for RCTs (29)) that compared RFA plus chemotherapy with chemotherapy alone, one non-RCT of RFA plus adjuvant hepatic arterial infusion chemotherapy (HAI) versus RFA plus HAI plus surgical resection (59), one observational study RFA alone versus RFA plus surgical resection versus surgical resection alone versus chemotherapy alone (60), one observational study of RFA plus surgical resection versus surgical resection plus cryosurgical ablation (61), and four non-RCTs comparing RFA with RFA plus HR (46,49,50,54). Cirocchi et al. considered all the identified studies at high risk of bias, either because patients in the intervention and control groups had different initial prognosis (i.e., in the non-RCTs) opening the possibility to selection bias, or because of lack of reporting about important data to assess quality (i.e., in the abstract publication of the only RCT included). Therefore the authors concluded that the evidence from the included studies was insufficient to recommend RFA for a radical treatment of colorectal liver metastases.

Loveman et al. (21) included studies of minimally invasive strategies in patients with liver metastases of any primary tumour, and included RCTs, prospective non-RCTs, case series with sample size >100, and economic evaluations. The authors identified 16 unique studies within 19 publications. Among these, one RCT of MA versus surgical resection that the authors considered at low risk of measurement bias (45), found no statistically significant difference in survival and less surgical invasiveness for microwave ablation; one non-RCT of RFA versus surgical resection and of RFA versus surgical resection plus RFA (46) reported few relevant data, and five studies (in seven publications) were case series of RFA (52,62-67) and therefore did not report of any comparisons. The authors concluded that the overall quality of the studies was low. The other studies included by the Loveman et al. review reported on laser ablation, chemoembolization, and radioembolization, and were out of scope for this review.

We identified the Ruers et al. RCT of patients with nonresectable colorectal liver metastases (29) by our systematic review of RCTs. This study was conceived as a phase III trial, but was stopped early because of slow accrual; it did not reach the required sample size, and was downsized to a phase II trial. In total, 59 patients were treated with systemic treatment and 60 with systemic treatment plus RFA. RFA was performed by laparotomy, laparoscopy, or percutaneously. Patients had a median of four lesions in the RFA plus chemotherapy arm, and a median of five lesions in the chemotherapy alone arm.

The quality of this study was evaluated with the Cochrane Risk of Bias tool (see Table 4). Ruers et al. (29) compared RFA and chemotherapy versus chemotherapy alone in patients with nonresectable liver metastases. We present its results in the following paragraphs.

Overall survival. At 30 months, OS was not statistically significantly different between groups: 61.7% (95% CI 48.2–73.9) for the RFA and chemotherapy group and 57.6% (95% CI 44.1–70.4) for the chemotherapy alone group. Median OS was 45.3 months (95% CI 33.1–NA) versus 40.5 months (95% CI 29.5–50.1) and HR = 0.74, (95% CI 0.46–1.19, p = 0.22).

Progression-free survival. Median PFS was 16.8 months (95% CI 11.7–22.1) in the RFA and chemotherapy group versus 9.9 months (95% CI 9.3–13.7) in the chemotherapy alone group (HR = 0.63, 95% CI 0.42–0.95, p = 0.025), corresponding to an absolute 17% increase in the PFS rate at three years from 10.6% (95% CI 4.2–20.5) to 27.6% (95% CI 16.9–39.5).

Health related quality of life (HRQoL). Health related quality of life (HRQoL) scores were similar in both treatment groups, although the limited sample size limits definite conclusions on this outcome.

Question 2: Subgroups of Patients Most Likely to Benefit from Thermal Ablation

A. Hepatocellular Carcinoma

Two systematic reviews presented results on patients subgroups (11,12). Cucchetti et al. (11) included studies of ablation techniques for patients with HCC. Shen et al. (12) included studies comparing RFA and PEI in patients with HCC. Cucchetti et al. (11) evaluated the quality of the included studies using the Newcastle Ottawa quality scale for observational studies (68), and Shen et al. (12) used the GRADE method (30).

Cucchetti et al. (11) reported on three RCTs (31-33) and on 16 observational, retrospective studies of RFA compared with surgery. The population of the RCTs was heterogeneous and had different proportions of HCC beyond early stages.

Among these three studies, Chen et al. (33) included 71 patients treated with RFA and 90 patients treated with surgery. OS and DFS were the same at three years in both RFA and surgical ablation groups for patients with tumours ≤5 cm. However, surgical resection had more adverse events (33); Huang et al. (31) included 115 patients per group. At five years OS was better with surgical resection versus RFA (RFA OS = 58.4% vs. surgical resection 75.7%, p= 0.001). Benefits of resection were maintained when patients were stratified by tumour size and number (31). Finally, Feng et al. (32) included 84 patients per group. OS at three years was not statistically significantly different between groups (RFA 67.2% and surgery 74.8%, p=0.34). This study did not provide stratification by tumour stage.

Shen et al. (12) pooled the results of four RCTs (35,36,38,39) and excluded studies with patients whose lesions were >3 cm and/or follow-up was less three years. The reviewers rated all four studies at high risk of bias; their confidence in the evidence provided was moderate for three-year survival for the subgroup of patients with HCCs <3 cm; low for four-year survival in patients with HCCs <3 cm; low for overall intrahepatic recurrence, and for risk of death when patients with liver function Child-Pugh (CP) class B were compared with patients with CP class A; and very low for three-year survival for patients with HCC >2 cm, or HCCs <2 cm and for overall local recurrence.

Single Tumours ≤ 2 cm.

Cucchetti et al (11) reported on four retrospective observational studies of patients with single tumours ≤2 cm (69-72). Not all of these studies focused on RFA and MA only, and they had populations with different prognoses in the intervention and control group; therefore, conclusions were hampered by potential for bias.

Shen et al. (12) reported that three-year OS was similar for RFA and PEI for patients with HCC <2 cm, (HR 0.79, 95% CI 0.50-1.25, p=0.32, I^2 = 0%).

Single Tumours ≤ 3 cm

Cucchetti et al. (11) reported on seven studies for this subgroup (31,33,73-77). The RCT by Chen et al. (33) reported that OS and DFS were not different between ablative strategies and surgical resection groups (data not provided). The study by Huang et al. (31) reported the three- and five-year survival rates for the hepatic resection group and the RFA group were 77.2%, 61.4% and 95.6%, 82.2%, respectively (p = 0.03). DFS and RFS were not reported. According to Cucchetti et al (11), this subgroup analysis based on 45 resected and 57 ablated patients, is the most robust evidence for the superiority of surgery over RFA. The other five studies identified were retrospective observational studies and are not discussed further here because of their high potential for bias.

Shen et al. (12) reported that three-year OS was better with RFA than with PEI for patients with HCC < 3cm, (HR 0.66, 95% CI 0.48-0.90, p=0.009; I^2=14.2%). However, the difference between groups narrowed with longer follow-up times (four-year survival, RFA vs. PEI, HR = 0.71, 95% CI: 0.52–0.97, p = 0.03; I^2 = 0.0%). For tumours >2 cm the authors found also a similar result (HR = 0.56; 95% CI 0.31 to 0.99, p=0.045; I^2 = 0%).

RFA was better than PEI also for recurrence and metastasis (HR = 0.38, 95% CI: 0.15–0.96, p = 0.040; I^2 = 65.6%).

In a subgroup analysis, Shen et al. (12) found that patients with liver function CP class B had a higher risk of death than patients with CP class A, irrespective of the treatment modality (HR = 2.23, 95% CI 1.26–3.97, p = 0.006; I^2 = 56.8%).

No significant difference was found in distant intrahepatic recurrence events (HR = 0.95, 95% CI: 0.75–1.22, p = 0.707; I^2 = 0.0%) by the three studies that reported on this outcome (35,36,39).

Single Tumors 3-5 cm

Cucchetti et al. (11) identified four articles that reported on this subgroup of patients: two RCTs (31,33) and two observational studies (74,78). Chen et al. (33) reported no between-arm difference, but survival rates and p values were not reported. Huang et al. (31) reported a five-year OS rate of 72.3% after surgery vs 51.5% after ablation (p = 0.046), and did not provide results for disease free survival (DFS) or recurrence-free survival (RFS). Cucchetti et al. (11) reported that the results of the observational studies, which were retrospective with very small sample size, did not show any between-group differences for DFS or OS, and the reviewers recommended more studies for this subgroup of patients.

Shen et al. (12) did not report on this subgroup of patients.

Multiple Tumors

Cucchetti et al. (11) included two studies that reported analyses for patients with multiple tumours: one RCT (31), and one observational study (74). The RCT by Huang et al. reported a better survival after surgery than after RFA (surgical resection: 69.23%, RFA: 45.16, p=0.04) in a subgroup of 26 resected patients compared with 31 ablated patients with multifocal disease, but did not report on DFS. On the other hand, Ueno et al. (74) reported OS favouring RFA over surgical resection: at five years, survival was not reached in the surgical group (n = 13) and the three-year survival was better for RFA (n = 54; surgical resection: 67%, RFA: 93% p = 0.002), although DFS was similar. The reviewers pointed out that in most of the non-RCT studies, having multifocal disease was a criterion to be allocated to thermal ablation as opposed to surgical resextion (11).

B. Colorectal Cancer Liver Metastases

The systematic reviews by Loveman et al. (21) and Bala et al. (22) identified a RCT that compared MA with surgical resection (45). Loveman et al. considered this trial of reasonable quality, whereas Bala et al. rated it at high risk of bias. The Shibata et al. RCT (45) included 40 patients with multifocal disease (MA group: mean number of lesions 4.1, largest tumour 27 mm; surgical resection group: mean number of lesions 3.0, largest tumour 34 mm), and did not find any statistically significant between-group differences in OS at one, two, and three years (MA group: 71%, 57%, 14%, respectively; surgical resection group 69%, 56%, 23% respectively p = 0.83). Similar results were found for DFS (MA group: mean DFS: 11.3 months, surgical resection group: mean DFS 13.3 months, p = 0.47).

Cirocchi et al. (23) included the non-RCT by Kim et al. (46) which analyzed subgroups of patients with different tumour size and single versus multiple lesions. Kim et al. (46) reported

for patients with a single metastatic lesion (n=226) <3 cm in size: the DFS rate was 33.6% in the RFA group and 31.6% in the surgical resection group at five years. In patients with a single lesion ≥ 3 cm, the five-year DFS rates were 23.1% in the RFA and 36.6% in the surgical resection group (p=0.01). As well, RFA resulted in lower DFS rates in patients with multiple liver lesions (6.4% in the RFA group vs. 16.2% in hepatic resection group). All of the studies in the Cirocchi et al. (23) review included patients with a worse prognosis in the RFA group than they did in the surgical resection group.

Belinson et al. (24) performed a multivariate analysis to identify characteristics that could improve overall survival (entered as dependent variable). Characteristics that were associated with improved survival were: Eastern Cooperative Oncology Group (ECOG) status (0 vs. ≥1 and in another study 0 or 1 vs. ≥2), performance status (0 or 1 vs. ≥ 2), number of extrahepatic metastases sites (0 or 1 vs. ≥2), number of lines of previous chemotherapy (0–1 vs. ≥ 2), performance status (0 or 1 vs. ≥ 2), carcino-embryonic antigen response (yes, no), and Response Evaluation Criteria in Solid Tumors (RECIST).

Question 3: Potential Adverse Events

Serious adverse events considered included: gastric bleeding, hemoperitoneum, hemothorax, thrombosis, treatment-related death.

A. Hepatocellular carcinoma

Radiofrequency Ablation versus Surgical Resection

Weis et al. (7) in a meta-analysis of three RCTs reported that the rate of complications was higher in the surgical groups compared with the RFA groups, (OR 8.24, 95% CI 2.12-31.95). The reviewers considered the evidence for rate of complications as high.

Radiofrequency Ablation versus Percutaneous Ethanol Injection.

Adverse events. Weis et al. (7) reported that the proportion of patients with serious adverse events was not significantly different between groups (PEI/PAI vs. RFA; OR 0.70, 95% CI 0.33- 1.48), and they rated the quality of the evidence for this outcome as moderate. Belinson et al. reported that none of the included studies reported on liver failure, hepatic hemorrhage or abscess; two studies reported hemoperitoneum: 1.4% in each group (36,39); hemothorax in the RFA group: 3.2% (36) and 1.4% (39); one death in the PEI group (39); and 1.6% gastric bleeding and perforation (36). The reviewers rated the quality of evidence as insufficient to draw conclusions (8).

The studies included by Shen et al. (12) reported only minor adverse events for both RFA and PEI procedures and no statistically significant difference in major adverse events such as hemothorax.

Radiofrequency Ablation versus Microwave Ablation (MA).

Adverse events. Adverse events were not statistically significant different between groups in the Shibata study (40) identified by Weis et al (7).

Radiofrequency Ablation versus Laser Ablation

Adverse events. None of the included systematic reviews reported on complications for this comparison.

Radiofrequency Ablation versus Transarterial Chemoembolization

Adverse Events. None of the included systematic reviews reported on complications for this comparison.

B. Colorectal Liver Metastases

Adverse events. Ruers et al. (29) reported of one postoperative death due to sepsis in the RFA and chemotherapy arm. Adverse effects from systemic treatment was comparable in both arms.

MA versus surgical resection

Shibata et al. (45) (in Loveman et al. (21)) reported statistically significantly less intraoperative blood loss in the MA group compared with the surgical resection group (MA: mean 360 mL, standard deviation [SD] 230 mL]; surgical resection 910 mL, SD 490 mL, p = 0.03). No difference was detected in adverse events (p=0.87).

DISCUSSION AND CONCLUSIONS

The following points summarize the conclusions of the Working Group:

Hepatocellular Carcinoma:

1. There is strong evidence in support of percutaneous RFA or MA in the treatment of nonresectable HCC. Evidence for MA is less extensive. Excellent outcomes can be expected when RFA and MA are used to treat HCC measuring ≤3 cm, and moderate outcomes in the treatment of nonresectable HCC measuring 3-5 cm.

2. RFA is equivalent in the treatment of small nonresectable HCC compared with MA, and superior compared with PEI. There is insufficient evidence comparing RFA to TACE/TABE in the treatment of nonresectable HCC (although in clinical practice RFA and TACE are generally used with different intent - curative vs. "palliative", respectively).

3. Percutaneous ablative therapies are associated with lower complication rates, and shorter hospital admission stays compared with surgery.

Colorectal liver metastases:

1. There is preliminary evidence in support of percutaneous RFA in the treatment of nonresectable colorectal metastases. Evidence for MA is less extensive. Outcomes are best when used to treat tumours measuring ≤3 cm, and moderate when used to treat tumours measuring 3-5 cm.

2. Percutaneous ablative therapies are associated with lower complication rate, and shorter hospital admission stays compared with surgery.

There is preliminary evidence suggesting that combination therapy with one or more percutaneous ablative therapies and/or TACE/TABE may provide additional DFS benefit versus singular intervention. Additional data are necessary to further delineate the effectiveness and indication(s) for combination therapy.
Additional data are necessary in order to determine specific scenarios of when a given ablative technology would be superior to another.

CONFLICT OF INTEREST

RB declared he was the director of the industry sponsored "Master Class in Interventional Oncology" 2013 at Toronto General Hospital, and declared he spoke at an industry sponsored symposium. For these activities, he received an honorarium of less than $5000. MB declared he was a temporary consultant for documents related to intravenous lines for Cook Inc. The other two authors (LAD and FGB) declared no conflict of interest.

All the members of the Advisory Committee completed a conflict of interest statement. Their conflict of interest disclosures are summarized in Appendix 4.

Updating

This document will be reviewed in three years to determine if it is still relevant to current practice and to ensure that the recommendations are based on the best available evidence. The outcome of the review will be posted on the CCO website. If new evidence that will result

in changes to these recommendations becomes available before three years have elapsed, an update will be initiated as soon as possible.

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For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322, ext. 42842 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

APPENDIX 1: Search strategies for systematic reviews and practice guidelines.

Database: Ovid MEDLINE(R) without Revisions, MEDLINE Daily Update, MEDLINE in-Process and Other non indexed citations <March 6, 2014>
Search Strategy:
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1 meta-Analysis as topic/
2 meta analysis.pt.
3 (meta analy$ or metaanaly$).tw.
4 (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
5 (systematic adj (review$ or overview?)).tw.
6 (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7 or/1-6
8 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9 (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10 (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11 (study adj selection).ab.
12 10 or 11
13 review.pt.
14 12 and 13
15 exp Carcinoma, Hepatocellular/
16 exp Liver Neoplasms/
17 ((Hepat* or liver) and (carcinom* or tumo?r* or neoplasm* or malign* or cancer*)).mp.
18 HCC.mp.
19 15 or 16 or 17 or 18
20 exp Catheter Ablation/
21 ((radiofrequenc* or radio-frequenc* or radio frequenc*) and (ablation* or therap* or treat*)).mp.
22 (RFTA or RFA or RFT of RFCA).mp.
23 thermotherapy.mp. or exp Hyperthermia, Induced/
24 exp microwaves/ or coagulation therapy.mp. or exp Electrocoagulation/
25 7 or 8 or 9 or 14
26 20 or 21 or 22 or 23 or 24
27 19 and 25 and 26
28 limit 27 to english language
29 animal/
30 human/
31 29 not 30
32 28 not 31
33 (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.
34 32 not 33
35 remove duplicates from 34

Database: EMBASE <1996 to 2014 Week 10>
Search Strategy:
---
1 exp Meta Analysis/ or exp "Systematic Review"/
2 (meta analy$ or metaanaly$).tw.
3 (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
4 (systematic adj (review$ or overview?)).tw.
5 exp Review/ or review.pt.
6 (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7 (study adj selection).ab.
8 6 or 7
9 5 and 8
10 1 or 2 or 3 or 4 or 9
11 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab. (55190)
12 (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
13 10 or 11 or 12
14 exp liver cell carcinoma/
15 ((Hepat* or liver) and (carcinom* or tumo?r* or neoplasm* or malign* or cancer*)).mp.
16 HCC.mp.
17 14 or 15 or 16
18 exp radiofrequency ablation/
19 exp Catheter Ablation/
20 ((radiofrequenc* or radio-frequenc* or radio frequenc*) and (ablation* or therap* or treat*)).mp.
21 (RFTA or RFA or RFT of RFCA).mp.
22 Hyperthermic Therapy.mp. or hyperthermic therapy/
23 microwave radiation#.mp. or exp microwave radiation/
24 ((coagulation adj therapy) or ablation).tw.
25 18 or 19 or 20 or 21 or 22 or 23 or 24
26 13 and 17 and 25
27 limit 26 to english language
28 Animal/
29 Human/
30 28 not 29
31 27 not 30
32 (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
33 31 not 32

Database Cochrane Library:
Search terms: “Ablation” AND “Cancer”

Database: National Guidelines Clearinghouse (http://www.guideline.gov/) :
Search terms: “Ablation” AND “Cancer”

National Institute for Health and Care Excellence
(http://guidance.nice.org.uk/CG/Published)
Search terms: “Ablation” AND “Cancer”

APPENDIX 2. Search strategies for randomized controlled trials.

Database: Ovid MEDLINE up to April 25, 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 random allocation/ or double blind method/ or single blind method/
4 (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
5 1 or 2 or 3 or 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 9 or 10 or 11 or 12 or 13
15 exp Carcinoma, Hepatocellular/
16 exp Liver Neoplasms/
17 ((Hepat* or liver) and (carcinom* or tumo?r* or neoplasm* or malign* or cancer*)).mp.
18 HCC.mp.
19 15 or 16 or 17 or 18
20 exp Catheter Ablation/
21 ((radiofrequenc* or radio-frequenc* or radio frequenc*) and (ablation* or therap* or treat*)).mp.
22 (RFTA or RFA or RFT of RFCA).mp.
23 thermotherapy.mp. or exp Hyperthermia, Induced/
24 exp microwaves/ or coagulation therapy.mp. or exp Electrocoagulation/
25 20 or 21 or 22 or 23 or 24
26 animal/
27 human/
28 26 not 27
29 (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.
30 19 and 25 and 14
31 30 not 28
32 31 not 29
33 limit 32 to english language
34 limit 33 to yr="2012 -Current"

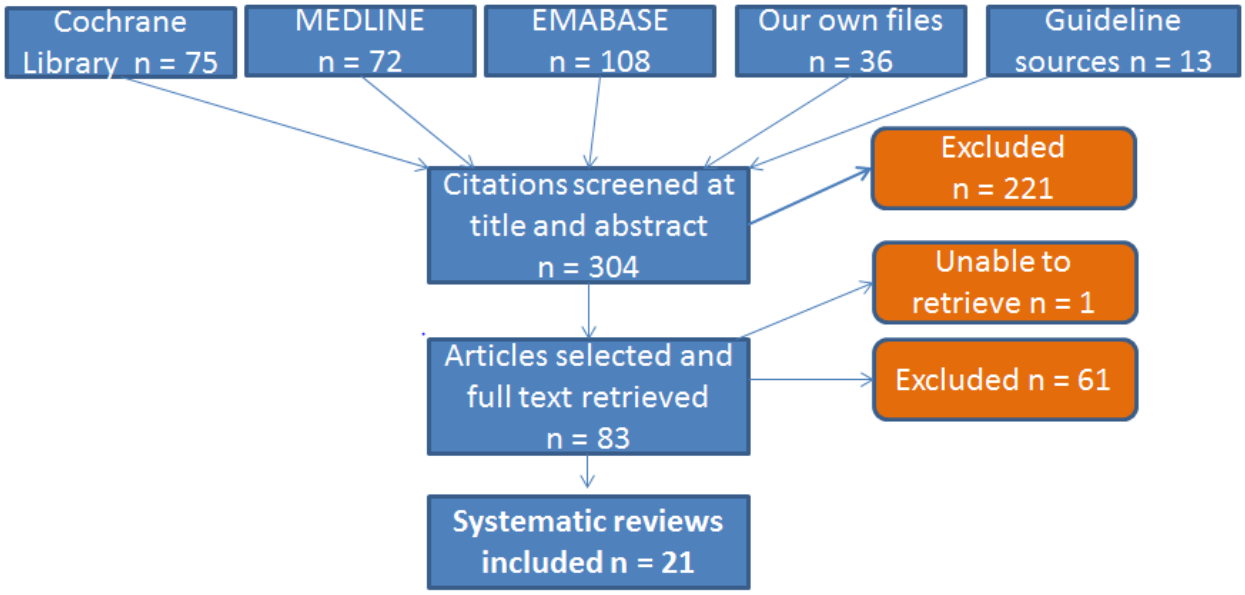
Database: EMBASE <2012 to 2014 Week 16>
Search Strategy:
---

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 1 or 2 or 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.

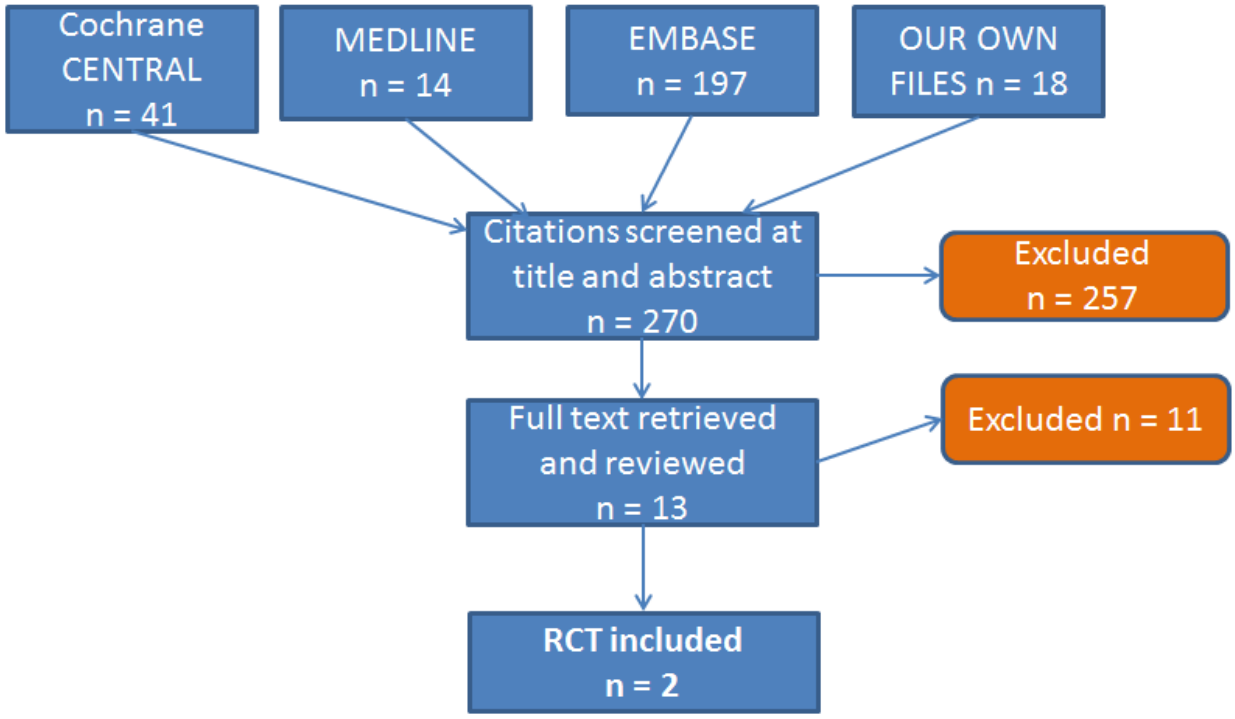
9 placebo/
10 (placebo? or random allocation or randomly allocated or allocated randomly).tw.
11 (allocated adj2 random).tw.
12 7 or 8 or 9 or 10 or 11
13 4 or 6 or 12
14 (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
15 13 not 14
16 limit 15 to english
17 animal/
18 human/
19 17 not 18
20 16 not 19
21 exp liver cell carcinoma/
22 ((Hepat* or liver) and (carcinom* or tumo?r* or neoplasm* or malign* or cancer*)).mp.
23 HCC.mp.
24 21 or 22 or 23
25 exp radiofrequency ablation/
26 exp Catheter Ablation/
27 ((radiofrequenc* or radio-frequenc* or radio frequenc*) and (ablation* or therap* or treat*)).mp.
28 (RFTA or RFA or RFT of RFCA).mp.
29 Hyperthermic Therapy.mp. or hyperthermic therapy/
30 microwave radiation#.mp. or exp microwave radiation/
31 ((coagulation adj therapy) or ablation).tw.
32 25 or 26 or 27 or 28 or 29 or 30 or 31
33 20 and 24 and 32
34 (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
35 33 not 34
36 animal/
37 human/
38 36 not 37
39 35 not 38
40 limit 39 to english
41…..Limit 40 to yr=2012 to current

Registries:
Clinicaltrials.gov (http://www.clinicaltrials.gov/) :
Search terms: “Radiofrequency” AND “Ablation”;
“Microwave” AND “Ablation”

APPENDIX 3 A). Study flow chart: systematic reviews.



APPENDIX 3 B). Study flow chart: primary randomized controlled trials.



Appendix 4A. Excluded systematic reviews.

DUPLICATE PUBLICATION – SYSTEMATIC REVIEWS

1. Salhab M, Canelo R. An overview of evidence-based management of hepatocellular carcinoma- a meta-analysis. Hepatology. 2011;54:1395A.
2. Liao M, Huang J, Zhang T, Wu H. Will we still using chemoembolization separately? A meta-analysis of combined local therapies for hepatocellular carcinoma. Liver Transplantation. 2013;(1):S129.
3. Cucchetti A, Piscaglia F, Cescon M, Colecchia A, Ercolani G, Bolondi L, et al. Radiofrequency ablation versus hepatic resection for early hepatocellular carcinoma: A cost-effectiveness perspective. Digest Liver Dis. 2013;45:S5.

ABSTRACT of SYSTEMATIC REVIEW

1. Pleguezuelo M, Germani G, Gurusamy K, Calvaruso V, Manousou P, Arvaniti V, et al. Percutaneous treatment of hepatocellular carcinoma. Systematic review and metaanalysis [abstract]. J Hepatol. 2009;50:S297.
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3. Hu P, Zhang SJ, Sun AX, Qian GJ. Meta-analysis of survival and disease recurrence for small hepatocellular carcinoma after radiofrequency ablation and surgical resection [abstract]. HPB (Oxford). 2013;15 Suppl 2:118.
4. Cai H, Zhou T, Qiu YD. Comparison of radiofrequency ablation and surgical resection in patients with solitary hepatocellular carcinoma within 5 cm: a me [abstract]. HPB (Oxfodrd). 2013;15 Suppl 2:221.

NOT INTERVENTION OF INTEREST

1. Cucchetti A, Piscaglia F, Cescon M, Colecchia A, Bolondi L, Pinna AD. Cost-effectiveness of hepatic resection versus percutaneous ablation for hepatocellular carcinoma within the milan criteria. J Hepatol. 2013;58:S112-S3.
2. Bergenfeldt M. Palliative surgery in liver metastases from breast cancer: Is there evidence? An overview. Digest Liver Dis. 2013;45:S242-S3.
3. Huang YZ, Zhou SC, Zhou H, Tong M. Radiofrequency ablation versus cryosurgery ablation for hepatocellular carcinoma: a meta-analysis. Hepato-Gastroenterol. 2013;60(125):1131-5.
4. Carter S, Martin Ii RC. Drug-eluting bead therapy in primary and metastatic disease of the liver. HPB (Oxford). 2009;11(7):541-50.
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metastases. 2010 Jan 20 [cited 2014 Mar 11]. In: The Cochrane Database of Systematic Reviews [Internet]. Hoboken (NJ): John Wiley & Sons, Ltd. c1999 - . Record No.: CD006797.
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1. Li Z, Mi D, Yang K, Cao N, Tian J, Ma B. TACE combined with thermotherapy for primary hepatic carcinoma: a meta-analysis. Chinese J Evid-Based Med. 2012;12(6):672-8.
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carcinoma. BMC Gastroenterol. 2009;9:31.

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1. Cucchetti A, Piscaglia F, Cescon M, Colecchia A, Bolondi L, Pinna AD. Cost-effectiveness of hepatic resection versus percutaneous ablation for hepatocellular carcinoma within the milan criteria. J Hepatol. 2013;58:S112-S3.
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NOT SYSTEMATIC REVIEW

1. Cucchetti A, Piscaglia F, Cescon M, Colecchia A, Bolondi L, Pinna AD. Cost-effectiveness of hepatic resection versus percutaneous ablation for hepatocellular carcinoma within the Milan criteria. J Hepatol. 2013;58:S112-S3.
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11. Jiang K, Zhang W, Su M, Liu Y, Zhao X, Wang J, et al. Laparoscopic radiofrequency ablation of solitary small hepatocellular carcinoma in the caudate lobe. Eurn J Surg Oncol. 2013;39(11):1236-42.
12. Khajanchee YS, Hammill CW, Cassera MA, Wolf RF, Hansen PD. Hepatic resection vs minimally invasive radiofrequency ablation for the treatment of colorectal liver metastases: a Markov analysis. Arch Surg. 2011;146(12):1416-23.

Appendix 4B. Excluded RCTs

ABSTRACT OF INTERIM ANALYSIS

1. Ricke J, Bulla K, Walecki J, Schott E, Sangro B, Kolligs F, et al. Safety and toxicity of the combination of Y90-radioembolization and sorafenib in advanced HCC: an interim analysis of the European multicenter trial soramic. J Hepatol. 2013;58:S114.

ALREADY IN INCLUDED SYSTEMATIC REVIEWS

1. Tanis E, Nordlinger B, Mauer M, Sorbye H, Van Coevorden F, Gruenberger T, et al. Local recurrence rates after radiofrequency ablation or resection of colorectal liver metastases. Analysis of the European Organisation for Research and Treatment of Cancer #40004 and #40983. Eur J Cancer. 2014;50(5):912-9.
2. Feng K, Yan J, Li X, Xia F, Ma K, Wang S, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. J Hepatol. 2012;57(4):794-802.

DUPLICATE PUBLICATIONS

1. Mochizuki H, Tsukui Y, Suzuki Y, Hoshino Y, Hosoda K, Kojima Y, et al. A prospective controlled trial of radiofrequency ablation for hepatocellular carcinoma performed by two hepatogastroenterologists with different training backgrounds. Hepatol Int. 2012;6 (1):220-1.
2. Mochizuki H, Ishida Y, Kawakami S, Kuno T, Fukasawa Y, Hirose S, et al. A prospective controlled trial of radiofrequency ablation for hepatocellular carcinoma performed by two hepatogastroenterologists with different training backgrounds (4). Hepatol Int. 2013;7:S602.

NOT IN ENGLISH

1. Zhao XX, You FP, Yuan QZ, Pan GZ, Bu QA, Hao L, et al. Safety and effectiveness of radiofrequency combined with laparoscopic cholecystectomy in management of liver cancer near the gallbladder. World Chinese Journal of Digestology [Internet]. 2013 [cited 2014 Mar 18]; 21(22):2212-6. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/684/CN-00910684/frame.htmlhttp://www.wjgnet.com/1009-3079/21/2212.pdf. Subscription required to view full text.

NOT INTERVENTION OF INTEREST

1. Morihara D, Iwata K, Hanano T, Kunimoto H, Kuno S, Fukunaga A, et al. Late-evening snack with branched-chain amino acids improves liver function after radiofrequency ablation for hepatocellular carcinoma. Hepatology research [Internet]. 2012 [cited 2014 Mar 18]; 42(7): 658-67. Available from: http://onlinelibrary.wiley.com/store/10.1111/j.1872-034X.2012.00969.x/asset/j.1872-034X.2012.00969.x.pdf?v=1&t=humzumdt&s=137f69907cc0e2676762907af0599cdbf56ec569. Subscription required to view full text.
2. Mochizuki H, Kuratomi N, Kuno T, Fukasawa Y, Suzuki Y, Hosoda K, et al. A prospective controlled trial of radiofrequency ablation for hepatocellular carcinoma performed by two hepatogastroenterologists with different training backgrounds (5). Hepatol Int. 2014;(1):S270.

NOT RCT

1. Ayuso C. How to follow up and when to reintervene. Cardiovasc Intervent Rad. 2012;35:S22.
2. Lee J, Lee JM, Yoon JH, Lee JY, Kim SH, Lee JE, et al. Percutaneous radiofrequency ablation with multiple electrodes for medium-sized hepatocellular carcinomas. Korean journal of radiology [Internet]. 2012 [cited 2014 Mar 18]; 13(1):34-43. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3253401/pdf/kjr-13-34.pdf.
3. Duan JC. Percutaneous radiofrequency ablation versus repeat hepatectomy for recurrent hepatocellular carcinoma: a prospective RCT study. HPB (Oxford). 2013;15:109.

Appendix 4 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

Members	Role	Conflict of Interest
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
		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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