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REVIEW ARTICLE

Intra-arterial therapies for unresectable and chemorefractory colorectal cancer liver metastases: a systematic review and meta-analysis

Jordan Levy[1,2], Jesse Zuckerman[1], Richard Garfinkle[3], Sergio A. Acuna[1,2], Jacynthe Touchette[4], Tsafrir Vanounou[3] & Jean-Sebastien Pelletier[3]

[1]University of Toronto Division of General Surgery, [2]University of Toronto Institute of Health Policy Management and Evaluation, Toronto, ON, [3]Sir Mortimer B Davis Jewish General Hospital, Hepatobiliary and Pancreatic Surgery, and [4]Sir Mortimer B Davis Jewish General Hospital Health Sciences Library, Montreal, QC, Canada

Abstract

Background: A large proportion of patients with colorectal cancer liver metastases (CRCLM) not amenable to curative liver resection will progress on systemic therapy. Intra-arterial therapies (IAT) including conventional transarterial chemoembolization (cTACE), drug eluting beads (DEB-TACE) and yttrium-90 radioembolization (Y-90) are indicated to prolong survival and palliate symptoms. The purpose of this systematic review and meta-analysis is to compare the survival benefit and radiologic response of three intra-arterial therapies in patients with chemorefractory and unresectable CRCLM.

Methods: A systematic search for eligible references in the Cochrane Library and the EMBASE, MEDLINE and TRIP databases from January 2000 to November 2016 was performed in accordance with PRISMA guidelines. Methodological quality of included studies was assessed using the MINORS scale. One-year overall survival rates and RECIST responder rates were pooled using inverse-variance weighted random-effects models. Overall survival outcomes were collected according to transformed pooled median survivals from first IAT with a subgroup analysis of patients with extrahepatic disease.

Results: Twenty-three prospective studies were included and analyzed: 5 cTACE (n = 746), 5 DEB-TACE (n = 222) and 13 Y-90 (n = 615). All but five were clinical trials. Eleven of 13 Y-90 studies were industry funded. Pooled RECIST response rates with 95% confidence intervals (CI) were: cTACE 23% (9.7, 36), DEB-TACE 36% (0, 73) and Y-90 23% (11, 34). The pooled 1-year survival rates with CI were: cTACE, 70% (49, 87), DEB-TACE, 80% (74, 86) and Y-90, 41% (28, 54). Transformed pooled median survivals from first IAT and ranges for cTACE, DEB-TACE and Y-90 were 16 months (9.0–23), 16 months (7.3–25) and 12 months (7.0–15), respectively. Significant heterogeneity in inclusion criteria and reporting of confounders, including previous therapy, tumor burden and post-IAT therapy, precluded statistical comparisons between the three therapies.

Conclusion: Methodological and statistical heterogeneity precluded consensus on the optimal treatment strategy. Given the common use and significant cost of radioembolization in this setting, a more robust prospective comparative trial is warranted.

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Correspondence

Jordan Levy, Division of General Surgery, University of Toronto, Ontario, Canada. E-mail: Jordan.Levy@mail.utoronto.ca

Introduction

The liver is the most common site of metastases in patients with colorectal cancer. Approximately 30% of patients will present with synchronous colorectal cancer liver metastases (CRCLM) or develop them at some point during the course of their disease.[1–3] The majority of patients will succumb to their metastatic burden, as only 20% are resectable. Patients with unresectable disease, or

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those who recur following their initial resection, are typically treated with palliative systemic therapies, such as chemotherapy and/or biologic therapy.[4–6]

When patients progress despite systemic therapy, liver targeted procedures are indicated to prolong survival and palliate symptoms. These include ablation and intra-arterial therapies (IAT). The latter represents a group of treatments that take advantage of the liver's dual blood supply and CRCLM's predilection for hepatic artery neovascularization.[7,8] Conventional transarterial chemoembolization (cTACE), drug eluting bead transarterial chemoembolization (DEB-TACE) and Yttrium-90 radioembolization (Y-90) (also known as selective internal radiation therapy or intra-arterial brachytherapy) all deliver tumoricidal and embolizing agents to CRCLM selectively by way hepatic artery branches without disruption of the portal blood supply, thereby avoiding significant hepatic and systemic toxicity.

Although many non-randomized clinical trials have reported on safety, tumor response and survival benefits of these three IATs, evidence to support one therapy over the others is lacking. Furthermore, an important consideration is the major cost discrepancy between the three therapies.[9,10] The aim of this systematic review and pooled analysis is to report the survival and radiological response of each IAT, in order to assist in the management of patients with unresectable and chemorefractory CRCLM.

Methods

A study protocol was established prior to the conduct of the systematic review. The objectives, outcomes of interest, search strategy and criteria of inclusion and exclusion were predefined. Methods of quality appraisal were selected following study selection and were based on the nature of the included studies. This systematic review is reported in accordance with PRISMA (preferred reporting items for systematic reviews and meta-analysis) guidelines.[11] The systematic search and study selection began prior to considering registering this systematic review. Unfortunately, the study was deemed too advanced to be eligible for registration and as such, the study was not registered on Prospero.

Search strategy and study selection

The resource ClinicalTrials.gov was consulted to find ongoing trials relevant to the topic of this systematic review. The Prospero registry was also searched to find any other projects similar to this one. Results found in TRIP database included "grey literature" unpublished in academic journals. In March 2015, a list of relevant MeSH terms and keywords was elaborated collaboratively between the research team and senior information analyst trained in systematic reviews (J. T.) with the concepts of "metastases to the liver", "colorectal cancer", "cTACE", "DEB-TACE" and "Yttrium-90". MEDLINE(OVID) (1946 to date) was first consulted with a preliminary search in late March 2015 and sent along with the first hundred results for approval by the team. The search strategy was also peer reviewed by another librarian. The final and revised search in EMBASE (1947 to date), MEDLINE (1946 to date), and TRIP, was performed in April to May 2015 and updated in November 2016. Functions like adjacencies, truncations and phrase searching were used where appropriate. The only limitation used was to restrict the results to human studies. No other limits such as date, language, or geographical localization were used. PubMed results were restricted to those not in MEDLINE. The Cochrane Library was also consulted; it was only searched with the concepts of treatments, favoring sensitivity over specificity. The results were de-duplicated within the OVID platform between MEDLINE and EMBASE, with priority to MEDLINE results. All the results were then imported into Endnote for further de-duplication, always with a priority to MEDLINE results. An outline of the complete search strategy can be found in the appendix.

Original studies evaluating the use of cTACE, DEB-TACE and/or Y-90 in the treatment of CRCLM were identified and their references were all manually reviewed for eligible studies. Article titles, abstracts and full-texts were sequentially screened for inclusion eligibility by two reviewers (J.L. and J.Z.). Corresponding authors were contacted when pertinent information or data was missing or unavailable.

Inclusion criteria

For inclusion into the present analysis, studies had to meet the following criteria: (i) full-text prospective studies, (ii) with contemporary publication year (2000 or later), (iii) in English language, (iv) evaluating the use of cTACE, DEB-TACE and/or Y-90 (v) in human subjects (vi) with CRCLM that are unresectable and (vii) chemorefractory (defined as failing at least one line of systemic chemotherapy), and (viii) reporting on overall survival. Studies including a minority of subjects (<10%) on the basis of chemo-intolerance rather than treatment failure were included. Mixed cancer cohorts were included if they reported on the primary outcome of overall survival specifically for the colorectal liver metastases group.

Data collection

Data from each study was independently extracted by two reviewers (J.L and J.Z.). Disagreements were resolved by consensus or, when necessary, by a third reviewer (R.G.). The reviewers systematically extracted information on authorship, publication, study design, methodology, quality criteria, patient demographics, disease characteristics (including previous treatments, concurrent treatments, hepatic and extrahepatic burden of disease status), procedural characteristics (agent, dose, number of procedures), procedural morbidity and mortality, radiological response and survival outcomes. The primary outcome was overall survival. When not reported, median overall survival was extracted from Kaplan Meier curves using DigitizeIt 1.6.1 Software (I. Bormann, http://www.digitizeit.de). All

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survival outcomes were determined from the time of first IAT procedure. Radiologic response according to RECIST guidelines (Response Evaluation Criteria In Solid Tumors),[12] was extracted at the earliest assessment reported, in order to optimize the proportion of available patients.

Quality assessment

Given the prospective and non-randomized nature of most included studies, we used the MINORS scale (Methodological Index for Non-Randomized Studies) to assess methodological quality.[13] This tool was chosen given that it was validated in both comparative and non-comparative surgical trials, and many of the included studies in this review are non-comparative. The MINORS scale includes 8 items pertinent to all studies, and 4 to comparative studies only. Each item is scored as 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate). As such, the total score is out of 16 or 24, depending on the nature of the study (comparative or not). Given the small number of studies included per IAT, assessing for publication bias was deemed inappropriate.[14]

Statistical analysis

Descriptive synthesis was used to summarize study characteristics, patient characteristics, intervention details, and risk of bias results. Pooling of median survival times using simple weighting by sample size produces biased estimates. A more appropriate approach is achieved by averaging median survival times transformed using an exponential distribution and recalculating the estimate of median survival times from the pooled distribution parameter as described by Gillen *et al.*[15] The exponential distribution assumes a time constant hazard rate. Because confidence intervals for median estimates are not calculable (given the available study-level aggregate data), ranges of median survival times were provided instead. The proportion of patients alive at 1 year (1-year overall survival rate) and RECIST responders (complete or partial response) was pooled using inverse-variance weighted

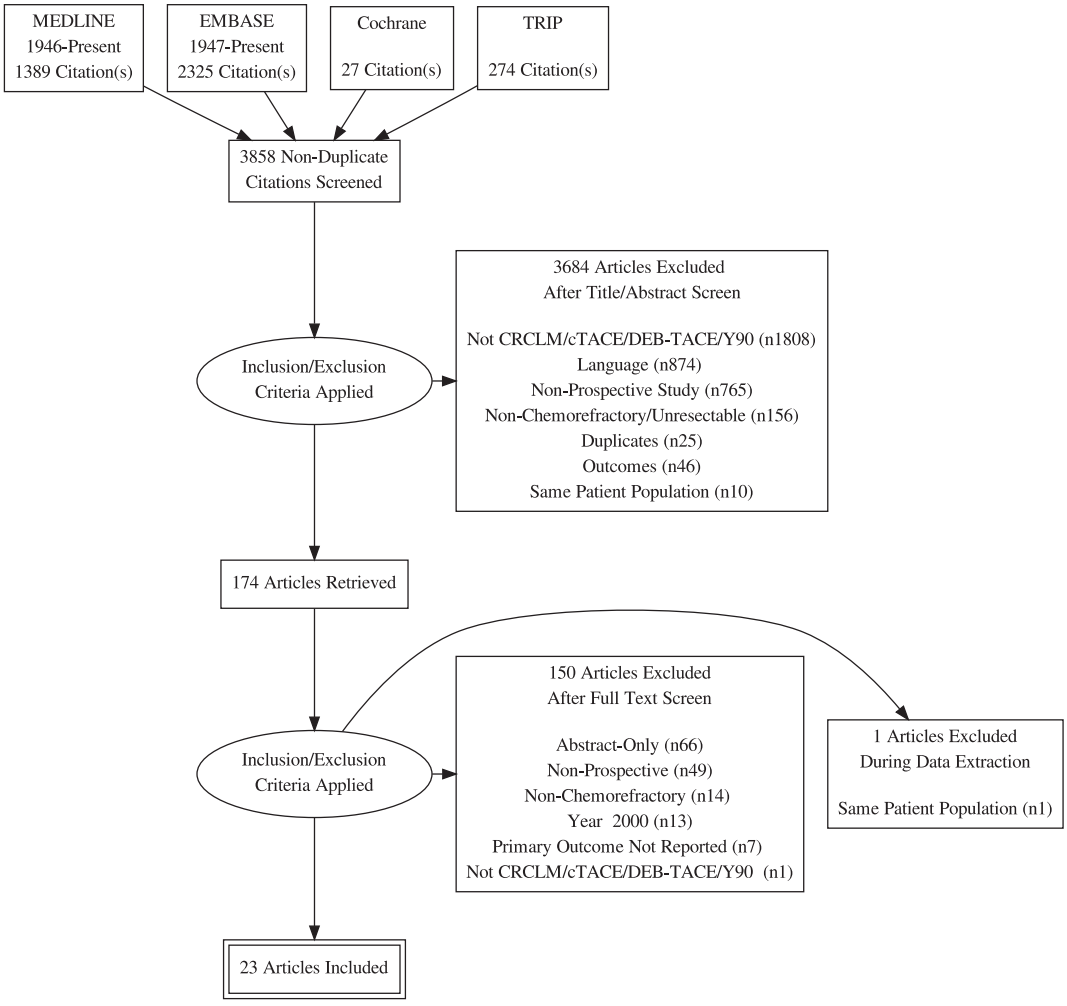

Figure 1 Study Selection Flow Diagram

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random-effects models following the conventional method of DerSimonian and Laird. Statistical heterogeneity of combined study results was assessed by the I^2 statistic. A subgroup analysis of patients with extrahepatic disease was planned prior to analysis to further define outcomes in this special patient population.

Results

Study selection

Study screening, exclusion and selection are depicted in the PRISMA diagram (Fig. 1) (Toronto Health Economics and Technology Assessment (THETA) Collaborative, PRISMA Flow Diagram Generator). Searches of the grey literature and of the references of included studies did not identify additional citations. All studies were prospective and all but five were clinical trials.[16–20] The IAT modality of interest in these five studies was Y-90.

IAT study funding

One of five cTACE, no DEB-TACE and 11 of 13 Y-90 studies disclosed some form of research support or industry ties. Salman *et al.*'s cTACE study was funded in part by an NIH National Cancer Institute grant. Industry presence was ubiquitous in Y-90 studies. Seven such studies were directly funded by industry,[17,20–25] and 10 had authors either employed or receiving some form of salary/income from pharmaceutical industries.[17,18,20–27]

Quality assessment

Most studies scored fairly well using the MINORS index. cTACE studies ranged from 12 to 15 out of 16, with one comparative study scoring 19 out of 24. DEB-TACE studies ranged from 12 to 14 out of 16, with one comparative study scoring 22 out of 24. Y-90 studies ranged from 10 to 14 out of 16, with two comparative studies scoring 20 and 22, respectively. MINORS index scoring is outlined for each included study in Appendix 1.

Table 1 Included study and population characteristics

References	Location	Study Design	Number of Participants	Mean Age (years)	Male (%)	ECOG
cTACE						
Popov 2002	Serbia	Single Arm CT	11	60[a]	18	0–2
Salman 2002	USA	RCT PII	24	60[a]	63	0–1
Vogl 2009	Germany	Single Arm CT	463	63	64	0–2[b]
Vogl 2012	Germany	Single Arm CT	224	61	64	0–2[b]
Nishiofuku 2013	Japan	Single Arm CT PI/II	24	64[a]	67	0–2
DEB-TACE						
Aliberti 2011	Italy	Single Arm CT PII	82	62	65	0–2
Martin 2011	USA	Single Arm CT	55	60[a]	58	NR
Fiorentini 2012	Italy	RCT PIII	35	64	56	NR
Huppert 2014	Germany	Single Arm CT	29	66	76	0–2[b]
Iezzi 2015	Italy	Single Arm CT PII	20	66	75	NR
Y-90						
Lim 2005	Australia	Single Arm Series	30	62[a]	73	0–2
Sato 2008	USA	Single Arm CT PII	51	63	65	0–2
Van Hazel 2009	Australia	Single Arm CT PI	25	59[a]	72	0–2
Cosimelli 2010	Italy	Single Arm CT PII	50	64	74	0–2
Hendlisz 2010	Belgium	RCT PIII	21	62[a]	48	0–2
Seidensticker 2012	Germany	Matched Pair Comparison	29	62	76	0–2[b]
Benson 2013	USA	Single Arm CT PII	61	66[a]	56	0–2
Cohen 2014	USA	Single Arm CT PI	17	60[a]	58	0–1
Lewandowski 2014	USA	Prospective Cohort	214	NR	60	0–2
Sofocleous 2014	USA	Single Arm CT PI	19	54	43	0–1
Golfieri 2015	Italy	Single Arm Series	52	63	77	0–1
Edalat 2016	USA	Correlative Study	16	62	69	0–3
Van den Hoven 2016	Netherlands	Single Arm CT PII	30	63	63	0–2

CT: Clinical Trial, PI/II/III: Phase I/II/III.
[a] Median survival.
[b] ECOG inferred according to Karnofsky Performance Status.

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Study populations

Study and patient characteristics are listed in Table 1.

Oncologic characteristics

Tumor characteristics are described in Tables 2 and 3. Hepatic tumor burden was not consistently reported across the included studies. When reported, bilobar disease was present in 92% of patients in one cTACE study, 65% in one DEB-TACE study, and 37–83% in six Y-90 studies. The overall hepatic tumor burden was variable; while 50–75% hepatic tumor burden was considered a contraindication to IAT in some studies, patients with greater than 50% hepatic replacement received treatment in one cTACE study, two DEB-TACE studies, and two Y-90 studies. Extrahepatic disease was present in 25–38% of patients in two cTACE studies, 35–55% of patients in three DEB-TACE studies, and 20–68% of patients in 11 Y-90 studies. Conversely, extrahepatic disease was reported as a contraindication to IAT in five studies (three cTACE, one DEB-TACE, one Y-90).

The number of previously failed systemic chemotherapy lines ranged from one to five in Y-90 studies compared to one to two and two to three in cTACE and DEB-TACE studies respectively. Upon extracting this data, biologic therapies were not considered as independent lines. Previous hepatic resection was inconsistently reported but was the most common pre-IAT liver directed therapy. Others, including ablation, brachytherapy and hepatic artery chemoinfusion, were rarely performed or were not reported on.

IAT characteristics

Intra-arterial and adjunct therapy characteristics can be found in Table 4.

Safety and toxicity

Seven studies graded toxicity according to the National Cancer Institute's Cancer Therapy Evaluation Program Common Toxicity Criteria v2.0 (CTC) or the more modern Common Terminology Criteria for Adverse Events v3.0 (CTCAE).

Table 2 Tumor burden

References	Number of Participants	Bilobar Disease (%)	Hepatic Burden (%)					Extra-Hepatic Disease (%)[a]
			<25%	25–50%	>50%	Median	Max	
cTACE								
Popov 2002	11	–	–	–	–	–	50	0
Salman 2002	24	–	–	–	–	–	50	38
Vogl 2009	463	–	–	–	–	–	70	0
Vogl 2012	224	–	–	–	–	–	70	0
Nishiofuku 2013	24	92	50	33	17	25–50	–	25
DEB-TACE								
Aliberti 2011	82	–	–	–	–	33	50	–
Martin 2011	55	–	55	24	22	<25	No Max	50
Fiorentini 2012	35	–	72	28	0	<25	50	0
Huppert 2014	29	–	48	24	28	25–50	75	35
Iezzi 2015	20	65	–	–	–	–	60	55
Y-90								
Lim 2005	30	–	–	–	–	–	–	20
Sato 2008	51	–	–	–	–	–	–	–
Van Hazel 2009	25	–	–	–	–	20	–	48
Cosimelli 2010	50	70	40	60	0	25–50	–	22
Hendlisz 2010	21	–	–	–	–	–	–	0
Seidensticker 2012	29	–	10	90	0	30	–	48
Benson 2013	61	77	65	34	1	<25	–	35
Cohen 2014	17	–	–	–	–	–	–	47
Lewandowski 2014	214	83	81	15	4	<25	–	42
Sofocleous 2014	19	37	–	–	–	–	–	68
Golfieri 2015	52	56	78	22[b]	–	<25	–	23
Edalat 2016	16	70	–	–	–	–	–	–
Van den Hoven 2016	30	–	90	10	0	<25	70	33

[a] 0% denotes explicit exclusion.
[b] Reported as 25% and greater.

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Descriptively, four Y-90 studies,[19,22,23,26] reported on 12–29% of patients experiencing severe to life-threatening adverse events (Grade 3–4), compared to 3–10% of patients in two DEB-TACE studies,[28,29] and 0.4% in one cTACE study.[30] Instances of 30-day mortality and/or procedure-related mortality were rare across all studies, occurring in one, two and three patients in cTACE, DEB-TACE and Y-90 studies, respectively.

Radiologic response

Radiologic response to IAT according to RECIST criteria was measured one to three months after treatment. RECIST response, defined as complete response or partial response, ranged from 0 to 50% in cTACE, 2–69% in DEB-TACE and 5–48% in Y-90 patients. The pooled RECIST response rates with 95% confidence intervals for all three IAT were: cTACE 23% (10, 36), DEB-TACE 36% (0, 73) and Y-90 23% (11, 34). The results are depicted in Fig. 2. Note that RECIST was not reported in every study and that heterogeneity was high in all IAT groups.

Survival and follow-up

Transformed pooled median survivals and length of follow-up is reported in Table 5. Given the substantial differences in the number of failed chemotherapy lines between IAT groups, a sensitivity analysis restricting this variable was performed. When excluding Y-90 studies with patients receiving four or more (4 studies) and three or more (7 studies) chemotherapy lines transformed pooled median survival for patients receiving Y-90 increased to 14.3 and 13.5 months from 12.3 months, respectively. A subgroup analysis of two cTACE, three DEB-TACE and nine Y-90 studies with explicit inclusion of patients with extrahepatic disease found transformed pool median survivals and ranges of 14 months (10, 21), 11 months,[7–19] and 12 months.[7–15] One-year

Table 3 Previous therapy

References	Number of Participants	Previous Systemic Therapy Lines (%)					Previous Hepatic Resection (%)	Previous Hepatic Ablation (%)	Previous Other Therapies (%)
		1	2	3	≥4	Median			
cTACE									
Popov 2002	11	36	64	0	0	2	100	0	0
Salman 2002	24	92	8	0	0	1	75	0	0
Vogl 2009	463	48	52	0	0	2	–	–	–
Vogl 2012	224	56	44	0	0	1	Resection NOS	0	0
Nishiofuku 2013	24	50	50	0	0	2	–	–	–
DEB-TACE									
Aliberti 2011	82	39	61	0	0	2	–	–	–
Martin 2011	55	31	25	44	0	2	20	9	0
Fiorentini 2012	35	0	64	36	0	2	–	–	–
Huppert 2014	29	–	–	–	–	–	34	17	0
Iezzi 2015	20	0	50	50[a]	0	3	20	0	0
Y-90									
Lim 2005	30	54	46	0	0	1	–	–	–
Sato 2008	51	–	–	–	–	–	–	–	–
Van Hazel 2009	25	68	24	8	0	1	–	–	–
Cosimelli 2010	50	0	0	24	76	4	24	0	0
Hendlisz 2010	21	100	0	0	0	1	–	–	–
Seidensticker 2012	29	0	28	31	41	3	24	3	Brachy 14, cTACE 3
Benson 2013	61	–	–	–	–	–	–	–	–
Cohen 2014	17	–	–	–	–	2	0	0	cTACE 6
Lewandowski 2014	214	9	16	28	47	3	9	7	cTACE 2
Sofocleous 2014	19	0	16	21	63	4	53	0	HAI 100
Golfieri 2015	52	5	49	46[a]	0	2	43	0	0
Edalat 2016	16	–	–	–	–	–	–	–	–
Van den Hoven 2016	30	40	37	23[a]	0	2	–	–	–

NOS: Not otherwise specified, Brachy: Brachytheray, HAC: Hepatic Artery Infusion.
[a] Reported as 3 or more.

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survival was reported or extractable in four cTACE, three DEB-TACE and five Y-90 studies; the study level outcomes are reported in Fig. 3.

Discussion

Despite significant advances in the management of colorectal cancer, including widespread screening programs, improved surgical locoregional control and effective systemic therapies, a large proportion of patients will develop incurable colorectal liver metastases. Unfortunately, in patients with unresectable and chemorefractory CRCLM, there is no standard treatment algorithm. In appropriate patients, guidelines recommend considering IATs to palliate symptoms and prolong life.[31] However, due to a lack of comparative studies, significant cost variations, and institutional differences, there is little consensus as to which IAT should be used.

This systematic review, limited to prospective designs, identified 23 relevant studies investigating three different IATs for CRCLM. Five studies evaluated the use of cTACE, five the use of DEB-TACE, and 13 the use of Y-90. None of the trials were head to head comparisons between two or more IATs and nearly all Y-90 studies were industry funded. The primary outcome was to report on the pooled survival from first IAT, and to provide an overview of the most current and highest quality studies available to clinicians on this subject.

At first glance, it appears that DEB-TACE offers the highest survival advantage, followed by cTACE and then Y-90. This was consistent according to pooled median survivals, 1-year survival rates and RECIST responder proportions. This rank was not

Table 4 IAT characteristics and subsequent therapies

References	Antineoplastic Agents	Embolizing Agent	Mean Number of IAT (Range)	Concomitant Therapy	Post-IAT Therapy
cTACE					
Popov 2002	M	Lipiodol	1.6 (1–3)	–	–
Salman 2002	F + IF	Polyvinyl Alcohol Foam (Ivalon)	1 (1–6)[a]	–	Chemo 17%
Vogl 2009	M/M + G/M + I	Lipiodol + Starch Microspheres	5.3 (3–24)	–	LITT 12.9%
Vogl 2012	M/M + G/M + I	Lipiodol + Starch Microspheres	3.4 (1–10)	–	LITT 100%
Nishiofuku 2013	Cis	Starch Microspheres	2.2 (1–4)	Excluded	Chemo 83%, Resection 4%, Resection and RFA 4%
DEB-TACE					
Aliberti 2011	Iri	DC Bead (Biocompatibles)	2.3 (1–4)	–	–
Martin 2011	Iri	LC/DC Beads (Biocompatibles)	1.8 (1–5)	Cap or F 29%	–
Fiorentini 2012	Iri	–	2.0	–	Chemo 54%
Huppert 2014	Iri	Hepasphere (Merit Medical)	2.4 (1–3)	–	Chemo 17%
Iezzi 2015	Iri	DC Bead (Biocompatibles)	2.7 (2–4)	Cap	–
Y-90					
Lim 2005	Y-90	SIR-Spheres (Sirtex)	1	5FU	Resection 3.3%, Chemo NOS
Sato 2008	Y-90	TheraSphere (Nordion)	–	–	–
Van Hazel 2009	Y-90	SIR-Spheres (Sirtex)	1	Iri	Chemo 100%
Cosimelli 2010	Y-90	SIR-Spheres (Sirtex)	1 (1–2)	–	Chemo 28%, Resection 4%
Hendlisz 2010	Y-90	SIR-Spheres (Sirtex)	1	5FU	Chemo 100%, Brain Radiation 5%
Seidensticker 2012	Y-90	SIR-Spheres (Sirtex)	–	–	Chemo 31%
Benson 2013	Y-90	TheraSphere (Nordion)	–	Excluded	–
Cohen 2014	Y-90	SIR-Spheres (Sirtex)	–	Cap	–
Lewandowski 2014	Y-90	TheraSphere (BTG)	1.8 (1–3)	Excluded	–
Sofocleous 2014	Y-90	SIR-Spheres (Sirtex)	1.3	Excluded	Chemo 90%, HAI 47%, Ablation 21%
Golfieri 2015	Y-90	SIR-Spheres (Sirtex)	–	–	Chemo 13%, Resection 4%, RFA 2%, Peritonectomy 2%
Edalat 2016	Y-90	SIR-Spheres (Sirtex)	1.25	–	–
Van den Hoven 2016	Y-90	SIR-Spheres (Sirtex)	–	–	–

M: Mitomycin C, 5FU: 5-Fluorouracil, IF: Interferon Alpha 2a, G: Gemcitabine, Iri: Irinotecan, Cis: Cisplatin, Cap: Capecitabine, Chemo: chemotherapy, LITT: Laser Induced Thermo Therapy, RFA: Radiofrequency Ablation, NOS: Not Otherwise Specified Proportion, HAC: Hepatic Arterial Infusion.
[a] Median.

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Study	Year	% RECIST Responders	Total Patients	Estimate (95% CI)
cTACE				
Popov et al	2002	0	11	4.2 (0.0 to 15.5)
Vogl et al	2009	68	463	14.7 (11.5 to 17.9)
Vogl et al	2012	70	224	31.2 (25.2 to 37.3)
Nishiofuku et al	2013	12	24	50.0 (30.0 to 70.0)
Overall		150	722	23.1 (9.7 to 36.4)
I^2 = 92.1%, P<0.001				
DEB-TACE				
Martin et al	2011	35	53	66.0 (53.3 to 78.8)
Fiorentini et al	2012	24	35	68.6 (53.2 to 84.0)
Huppert et al	2014	0	29	1.7 (0.0 to 6.2)
Iezzi et al	2015	2	20	10.0 (0.0 to 23.1)
Overall		61	137	36.2 (0.0 to 72.5)
I^2 = 97.9%, P<0.001				
y90				
Lim et al	2005	10	29	34.5 (17.2 to 51.8)
Van Hazel et al	2009	11	23	47.8 (27.4 to 68.2)
Cosimelli et al	2010	12	46	26.1 (13.4 to 38.8)
Hendlisz et al	2010	2	20	10.0 (0.0 to 23.1)
Seidensticker et al	2012	12	28	42.9 (24.5 to 61.2)
Benson et al	2013	3	58	5.2 (0.0 to 10.9)
Sofocleous et al	2014	1	19	5.3 (0.0 to 15.3)
Edalat et al	2016	4	18	22.2 (0.3 to 41.4)
Overall		55	241	22.5 (11.4 to 33.5)
I^2 = 83.3%, P<0.001				

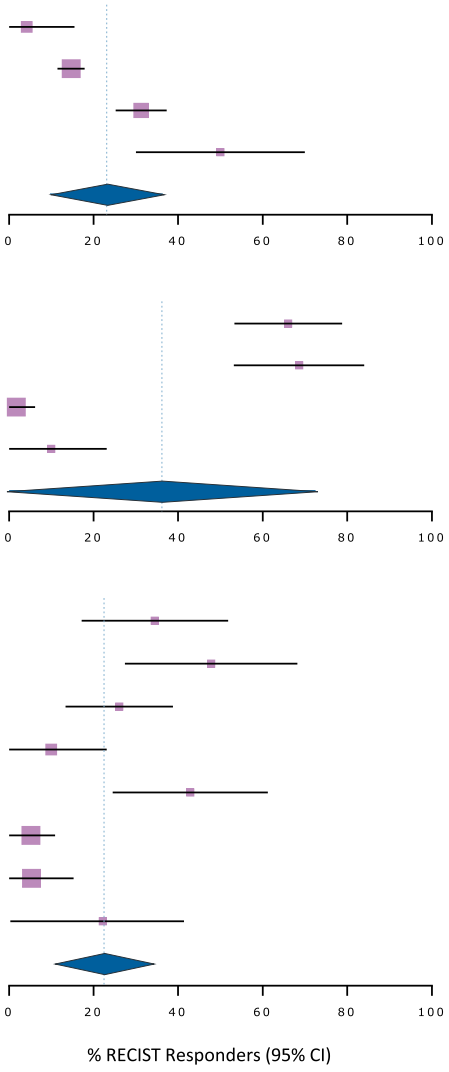

Figure 2 Pooled RECIST Response Rates

statistically confirmed and should be considered with caution. Significant confounders to the association between IAT and survival, including previous number of chemotherapy lines, tumor burden (hepatic and extrahepatic disease) and post-IAT treatments, were not standardized across the three therapies nor were they consistently reported on.

These factors can greatly affect survival outcomes. No cTACE study reported on patients receiving three or more chemotherapy lines prior to commencing IAT compared to seven Y-90 studies. Similarly, no DEB-TACE study reported on four or more chemotherapy lines compared to four Y-90 studies. It may be that Y-90 patients were further along in the course of their disease, following more lines of chemotherapy than were cTACE and DEB-TACE patients. As such, measuring survival from time of IAT introduces a systematic bias favoring patients who fail less chemotherapy lines prior to undergoing IAT. The results of the sensitivity analysis assessing survival according to number of previously failed lines was consistent with this notion. Survival from time of diagnosis would have been informative in establishing the life-prolonging effect of IATs.

Treatments following IAT may also impact survival. The two largest cTACE studies, both authored by Vogl *et al.*, in 2009 and 2012, resulted in drastically different median survivals of 14 and 23 months. These studies appeared no different in patient demographics, number of failed chemotherapy lines or cTACE agents. Patients with extrahepatic disease were excluded. The

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Table 5 Survival and follow-up

References	Median Survival, months (95% CI)	1-Year Survival (%)	Median Follow-Up, months (Range)
cTACE			
Popov 2002	9 (4–16)[a]	–	–
Salman 2002	10 (8–11)	54	–
Vogl 2009	14	62	–
Vogl 2012	23	88	11[b]
Nishiofuku 2013	21 (8–34)	67	17[b]
DEB-TACE			
Aliberti 2011	25 (6–34)[a]	83	29 (7–48)
Martin 2011	19	75	18 (12–40)
Fiorentini 2012	22 (21–23)	81	50
Huppert 2014	8 (2–38)	–	8 (1–54)
Iezzi 2015	7	–	11[b] (5–18)
Y-90			
Lim 2005	7	27	18
Sato 2008	15	54	–
Van Hazel 2009	12 (3–60)[a]	–	–
Cosimelli 2010	13 (7–18)	50	11[b] (2–29)
Hendlisz 2010	10	–	25 (2–41)
Seidensticker 2012	8	24	–
Benson 2013	9 (7–12)	–	30
Cohen 2014	8 (4–43)[a]	–	–
Lewandowski 2014	11 (9–15)	–	–
Sofocleous 2014	15 (6–26)	52	31 (19–41)
Golfieri 2015	11 (8–14)	–	7 (1–72)
Edalat 2016	9 (2–16)	–	14[b] (3–35)
Van den Hoven 2016	9 (5–12)		–

95% CI: 95% confidence interval.
[a] Range.
[b] Mean.

only notable difference was administration of LITT (laser induced thermotherapy) to 100% versus 13% of patients following IAT. Of note, hepatic tumor burden was not reported, and if selection had become more stringent between studies, it would represent an important selection bias. Interestingly, unlike cTACE, overall survival in DEB-TACE correlated inversely with publication year and decreased from 19 to 25 months in 2011 to 7 months in 2015. Barring a larger proportion of male patients, the two most recent studies by Huppert *et al.* and Iezzi *et al.* had no obvious differences in other confounders. This trend is difficult to interpret given the small sample of five studies and once again the etiology may lie in unreported data, such as time between last chemotherapy and DEB-TACE.

The current study also found that cTACE and DEB-TACE were more often repeated in a single patient compared to Y-90. This finding could be of interest for future cost-effectiveness studies as it may mitigate the price discrepancy between the two microsphere IATs. Locally, the drug cost of DEB-TACE is USD950 compared to USD12,000 for Y-90. This discrepancy was similar in a study published in 2011 which demonstrated that in metastatic neuroendocrine cancer, two treatments of Y-90 and DEB-TACE cost USD25,243 vs. USD13,400, respectively, but that Y-90 had worse symptom free, progression free and overall survival.[9] In today's healthcare environment, it is becoming increasingly evident that clinical benefit alone cannot guide practice, and as such, cost is a crucial consideration.

Despite the fact that all studies included for analysis were prospective, there was only one phase III randomized controlled trial. Hendlisz and colleagues randomized 44 patients to either infusional 5-FU alone or Y-90 with concomitant infusional 5-FU, and demonstrated that the addition of radioembolization significantly improved time to liver progression and time to tumor progression with acceptable morbidity rates. This study provided level 1 evidence for the survival benefit of Y-90, which has yet to be replicated in the other IATs of interest.

The findings of the current study should be viewed in light of several limitations. Upon completing data extraction, it became evident that a large proportion of confounders (number of chemotherapy lines, hepatic tumor burden, extrahepatic disease status and magnitude and post-IAT therapies) and statistical results (standard error and confidence intervals) were unreported. As such, statistical manipulation and estimation would have been required to perform a meta-analysis comparing the three IATs. This would blur any resulting clinical conclusions and thus statistical comparisons between IATs were felt to be inappropriate. Zacharias *et al.* published a systematic review and meta-analysis on a similar topic, comparing hepatic arterial infusion to radioembolization and TACE.[32] In addition to different inclusion criteria, particularly with respect to including non-prospective studies, the authors reported much heterogeneity and missing data between studies, which limited the analysis and ultimate conclusions. Furthermore, in the current review, there was equally as much heterogeneity in baseline patient and oncologic characteristics, IAT agents, IAT protocols and post-IATs therapies. Data and outcomes reporting was also not standardized across studies. Some of these limitations were confronted using subgroup analyses and sensitivity analyses when appropriate.

Future trials assessing IATs in this context should abide by a reporting protocol incorporating: (i) patient demographics, (ii) hepatic tumor burden (bilobar status, cumulative tumor diameter, liver volume replacement), (iii) extrahepatic tumor burden (status, location, cumulative diameter), (iv) previous systemic therapies (number of chemotherapy lines, number of biologic therapies, months of chemotherapy, time since last chemotherapy), (v) previous hepatic therapies (resection, ablation, radiation, IAT), (vi) IAT description (antineoplastic agent, embolizing agent, number of treatments), (vii) concomitant therapies (viii) post-IAT therapies.

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Study	Year	Alive at 1-year	Total Patients	Estimate (95% CI)
cTACE				
Salman et al	2002	13	24	54.2 (33.8 to 73.8)
Vogl et al	2009	287	463	62.0 (57.5 to 66.4)
Vogl et al	2012	197	224	87.9 (83.3 to 91.9)
Nishiofuku et al	2013	16	24	66.7 (46.4 to 84.4)
Overall		513	735	69.6 (49.3 to 86.7)
I^2 = 95.1%, P<0.001				
DEB-TACE				
Aliberti et al	2011	68	82	82.9 (74.8 to 91.1)
Martin et al	2011	41	55	74.5 (63.0 to 86.1)
Fiorentini et al	2012	28	35	80.0 (66.7 to 93.3)
Overall		137	172	80.1 (74.2 to 86.0)
I^2 = 0%, P=0.51				
y90				
Lim et al	2005	8	30	26.7 (10.8 to 42.5)
Soto	2008	27	51	52.9 (39.2 to 66.6)
Cosimelli et al	2010	25	50	50.0 (36.1 to 63.9)
Seidensticker et al	2012	7	29	24.1 (8.6 to 39.7)
Sofocleous et al	2014	10	19	52.6 (30.2 to 75.1)
Overall		77	179	41.0 (28.1 to 53.9)
I^2 = 69.7%, P=0.01				

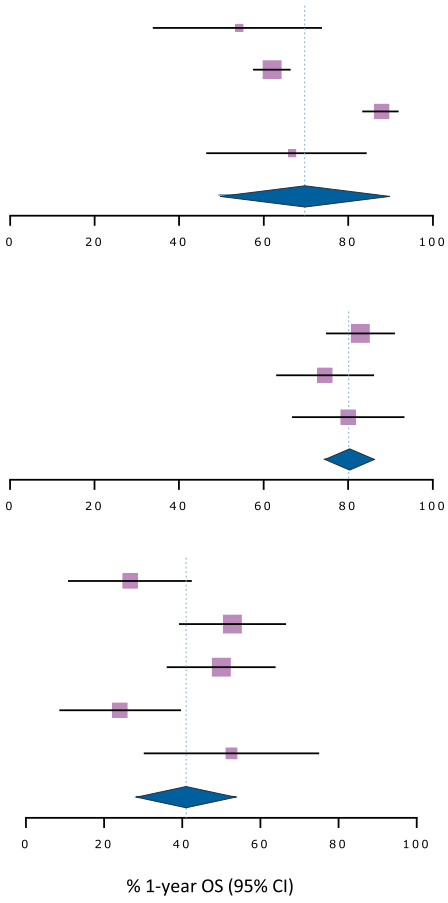

Figure 3 Pooled 1-Year Survival Rates

Conclusion

Despite a number of studies assessing intra-arterial therapies in chemorefractory and unresectable colorectal liver metastases, heterogeneous inclusion criteria and reporting protocols preclude direct comparisons. This study affirms that the highest quality of evidence available is insufficient to form a consensus on the optimal treatment strategy for these patients. A randomized trial comparing all three IATs in an evenly distributed sample population with uniform inclusion criteria is necessary to properly evaluate this question. Furthermore, if such a trial was conducted, a cost-effectiveness analysis should be undertaken as well, to frame each treatment within the context of the current healthcare environment.

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Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.hpb.2018.04.001.

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