REVIEW ARTICLE

Adjuvant intra-arterial chemotherapy for patients with resected colorectal liver metastases: a systematic review and meta-analysis

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Abstract

Background: The practice of adjuvant hepatic arterial infusion chemotherapy (HAIC) for colorectal liver metastasis (CRLM) varies widely. This meta-analysis investigates the effectiveness of adjuvant HAIC and the influence of variations in HAIC treatment in patients with resected CRLM.

Methods: PRISMA guidelines were followed for this study. The search was limited to comparative studies (HAIC vs non-HAIC) for overall survival. Subgroup meta-analyses using random-effects were performed for type of intra-arterial drug, method of catheter insertion, use of concomitant adjuvant systemic chemotherapy, and study design.

Results: Eighteen eligible studies were identified. After excluding overlapping cohorts, fifteen studies were included in the quantitative analysis, corresponding to 3584 patients. HAIC was associated with an improved overall survival (pooled hazard ratio (HR) 0.77; 95%CI 0.64–0.93). Survival benefit of HAIC was most pronounced in studies using floxuridine (HR 0.76; 95%CI: 0.62–0.94), surgical catheter insertion with subcutaneous pump (HR 0.71; 95%CI: 0.61–0.84), and concomitant adjuvant systemic chemotherapy (HR 0.75; 95%CI: 0.59–0.96). The pooled HR of RCTs was 0.91 (95%CI 0.72–1.14), of which only 3 used floxuridine.

Conclusion: Adjuvant HAIC is a promising treatment for patients with resectable CRLM, in particular HAIC with floxuridine using a surgically placed catheter and a subcutaneous pump, and concomitant systemic chemotherapy.

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Introduction

Colorectal cancer (CRC) is the second leading cause of cancer related death worldwide.[1] Synchronous and metachronous colorectal liver metastases (CRLM) account for 40% of all metastases in CRC patients. Resection and ablation are the only potentially curative treatments for CRLM, resulting in a 10-year survival rate of approximately 25%.[2,3] However, 65% of patients develop recurrences after resection, with the liver being involved in the large majority of patients.[2,4,5]

Several therapies have been introduced to reduce disease recurrence and improve survival after curative treatment of CRLM. Perioperative systemic chemotherapy is widely administered.[6] Additionally, patients with resectable CRLM may benefit from adjuvant hepatic arterial infusion chemotherapy (HAIC).[7] This therapy is based on two main principles. First, CRLM, as opposed to normal liver parenchyma, primarily derive their blood supply from the hepatic artery rather than the portal vein.[8,9] Second, systemic side effects of HAIC are limited due to

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the high first-pass effect in the liver of certain drugs (e.g., floxuridine and oxaliplatin), allowing for a high liver dosage.[10–12]

Several studies, including RCTs demonstrated promising survival benefits of adjuvant HAIC.[7] However, not all studies could confirm these findings, which may be a result of variations in intra-arterial drugs, method of drug delivery (surgical or percutaneous catheter insertion), and use of concomitant adjuvant systemic treatment.

The objective of this systematic review and meta-analysis was to investigate the effectiveness of adjuvant HAIC in patients with resected CRLM and the influence of variations in HAIC treatment.

Methods

Search strategy and study selection

The PRISMA guidelines were used to conduct this systematic review and meta-analysis.[13] A systematic search in Embase, Medline Ovid, Web of Science, Cochrane and Google Scholar was performed on April 13th 2021. A full description of the search is available in supplementary table 1. Studies comparing overall survival (OS) in patients with and without HAIC after resection of CRLM were eligible. The search was restricted to articles written in English. Non-comparative and non-original studies (e.g., systematic reviews, meta-analyses) were excluded, as were studies not reporting OS. After removing duplicates, titles and abstracts were screened for eligibility by three independent researchers (FB, WF, BoG). Then full text articles were screened based on the inclusion and exclusion criteria. At each step disagreement was resolved by consensus between two reviewers (FB, WF).

Data-extraction and qualitative assessment

Data were independently extracted by two reviewers (FB, WF). A standardized data extraction form was used. Patient characteristics, tumor characteristics, treatment characteristics of HAIC patient groups and comparative patient groups, and survival outcomes were extracted. When not reported, hazard ratios (HRs) with 95% confidence intervals (95%CIs) for OS were extracted from the Kaplan–Meier graphs and calculated using methods described by Tierney *et al.*[14] Quality assessment of the studies was performed using the RoB 2 (for randomized studies) and Newcastle Ottawa (for non-randomized studies).

Quantitative assessment

Random effects modelling was applied to create pooled estimates for OS. Heterogeneity was evaluated using the I^2 statistic. Forest plots and funnel plots were created to display pooled OS estimates and the risk of publication bias, respectively. Subgroup analysis was performed for study design (RCT vs non-randomized), for the type of intra-arterial drug (floxuridine versus other), the method of catheter insertion (surgical or subcutaneous), and the use of concomitant adjuvant systemic

chemotherapy. Statistical analyses were performed using RevMan (Review Manager version 5.4.1).

Results

Study characteristics

After screening 2512 potentially relevant studies, the full-text of 260 studies was assessed for eligibility (Fig. 1). Studies were primarily excluded when describing outcomes in patients with unresectable CRLM (n = 98) or when resectability status was unclear (n = 29). Full text was unavailable for 36 articles, none of which were RCTs (based on the abstract), and 29 articles (81%) were published before 1980. One study was excluded due to complete overlap of the cohort with another study.[15] Ultimately, eighteen studies were included, representing 2325 patients who received adjuvant HAIC and 3998 patients who did not.[5,16–33] The number of patients treated with HAIC ranged between 5 and 785 across studies.

Characteristics of the included studies are shown in Table 1.[5,16–33] Eight studies were RCTs.[16,17,19,21,22,26,31,32] Five studies included partially overlapping cohorts of patients.[5,26,27,30,33]

Baseline patient and tumor characteristics are summarized in Table 2. Large variability between study cohorts was observed in terms of patient and tumor characteristics. Four studies included patients with (a history of) extrahepatic disease (EHD), ranging from 7% to 20% of the study population.[19,29,30]

Effectiveness of HAIC

For the quantitative assessment, 15 studies were included, representing 1391 patients treated with HAIC versus 2193 patients treated without HAIC after resection of CRLM.[16–24,26,28–32] Four studies have been performed in Memorial Sloan Kettering Cancer Center (MSKCC) and had overlapping cohorts[5,26,27,30,33]; the largest study was selected for quantitative assessment.[30]

Fig. 2 displays the pooled analysis, including a subgroup analysis for RCTs only. The pooled HR for OS for all studies was 0.77 (95% CI: 0.64–0.93). Moderate heterogeneity, in terms of the effectiveness of HAIC, was present with an I^2 of 37%. When evaluating the eight RCTs, representing 312 HAIC patients and 340 patients without HAIC, the pooled HR was 0.91 (95%CI 0.72–1.14, $I^2 = 0$%).[7,16,17,19,22,26,31,32]

HAIC agents

Floxuridine was used as primary HAIC agent in seven studies (including three RCTs), representing 1036 HAIC patients (versus 1838 non-HAIC patients) and was infused continuously using a surgically placed catheter and subcutaneous infusion pump or port.[16,22–24,26,28,30] Patients were scheduled to receive six cycles of 12–14 days of continuous HAIC with floxuridine at a dosage of 0.1–0.5 mg/kg/day or 0.2–0.3/m²/day followed by 12 or 14 days of saline.[16,22–24,26,28,30] The pooled HR of studies using
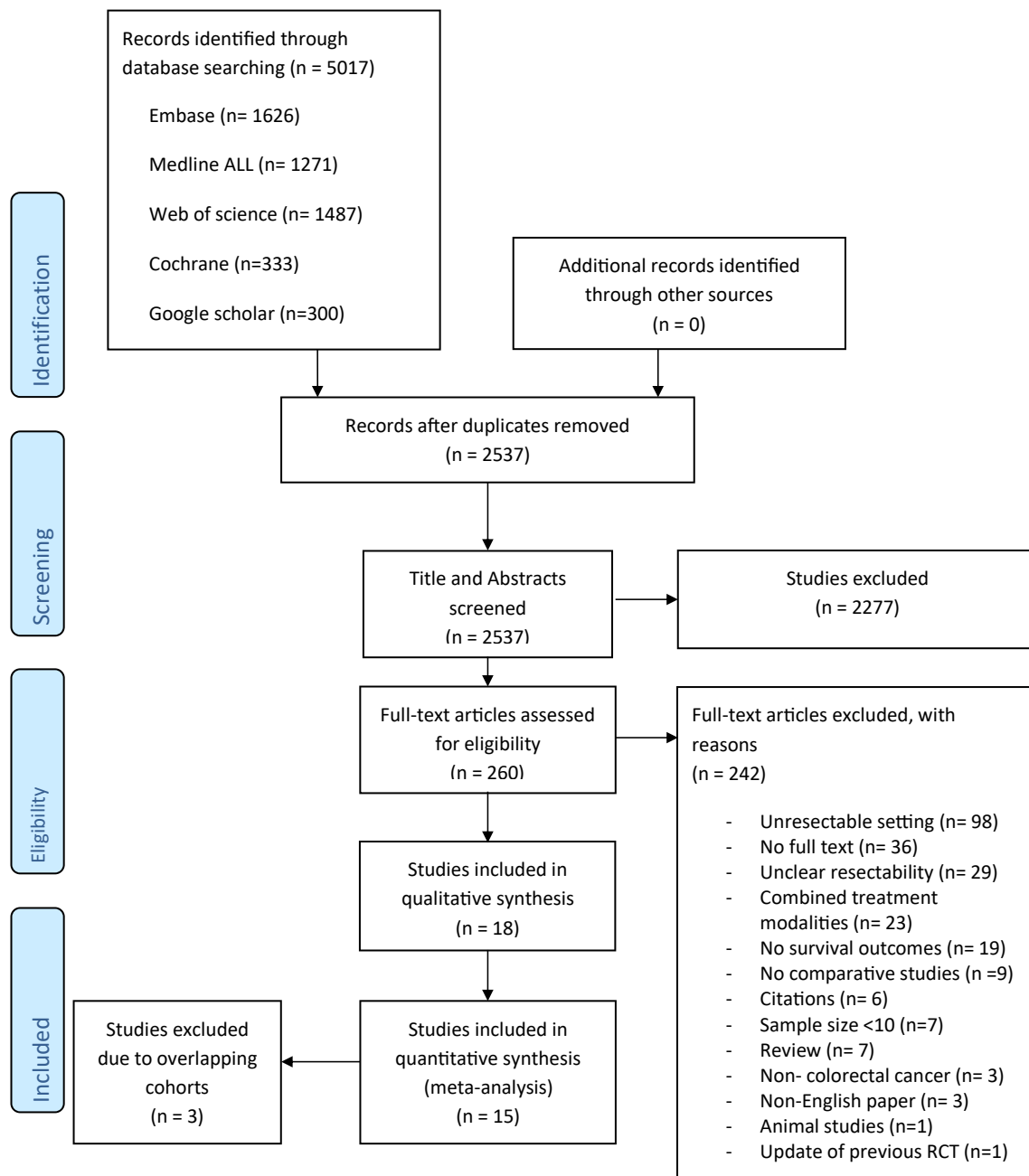
Figure 1 Prisma flowchart of study inclusions

floxuridine as the primary HAIC agent was 0.76 (95%CI 0.62−0.94, I^2 21%) in favor of HAIC (Fig. 3).

Eight studies (including five RCTs) administered intra-arterial drugs other than floxuridine and represented 355 HAIC and 355 no-HAIC patients[17−21,29,31,32]; seven studies administered intra-arterial 5-FU[17−21,31,32] and in one study intra-arterial oxaliplatin was used.[29] Intra-arterial 5-FU was delivered continuously using a subcutaneous infusion pump or port[17,18,21] or with bolus injections.[19,20,29,31,32] In two studies, patients also received intra-arterial Mitomycine C with or without aclarubicine.[18,19] HAIC

with oxaliplatin was used in one study. The pooled HR of studies using intra-arterial 5-FU or oxaliplatin was 0.74 (95%CI 0.52−1.06, I^2 52%) (Fig. 3).

Catheter insertion technique
Thirteen studies used a surgically placed catheter, corresponding to 1324 HAIC patients and 2125 no-HAIC patients.[16−24,26,28−30] A catheter was secured in the gastroduodenal artery (GDA) with the tip at hepatic artery. The catheter was then connected to a subcutaneous infusion pump or port that can be accessed

Table 1 Study characteristics

Author	Inclusion period	Center	HAIC Catheter implantation	Infusion rate	HAIC agent	Concomitant adjuvant systemic	Comparative cohort treatment
Randomized trials							
Wagman, 1990	1982–1986	City of Hope	Surgical	Continuous	FUDR	None	None
Lorenz, 1998	1991–1996	Johann Wolfgang Goethe-University	Surgical	Continuous 96 h	5-FU + FA	None	None
Rudroff, 1999	1984–1985	Friedrich Schiller University	Surgical	Bolus 4 h	5-FU + MMC	None	None
Tono, 2000	1993–1995	Osaka National Hospital	Surgical	Continuous 5 days)	5-FU	5-FU	5-FU
Kemeny, 2002	1990–1997	Multicenter	Surgical	Continuous 14 days	FUDR	5-FU	None
Kemeny, N 2005	1991–1999	MSKCC	Surgical	Continuous 14 days	FUDR	5-FU/LV	5-FU/LV
Kusano, 2017	2000–2003	Kushiro Rosai Hospital	Percutaneous	Bolus 24 h	5-FU	UFT/LV	UFT/LV
Kusano, 2018	2005–2007	Kushiro Rosai Hospital	Percutaneous	Bolus 24 h	5-FU	UFT/LV	UFT/LV
Non-randomized cohorts							
Ambiru, 1999	1984–1998	Chiba University School of Medicine	Surgical	Continuous 14 days	5-FU + MMC + aclarubicine	5-FU	None
Kusunoki, 2000	1990–1995	Hyogo College of Medicine	Surgical	Bolus unspecified	5-FU	UFT	UFT
Moroz, 2002	1989–1999	Royal Perth Hospital	Surgical	Continuous 12 days	FUDR ± LV	None	None
Onaitis, 2003	NR	Duke university Medical Center	Surgical	Continuous 14 days	FUDR	Various	Various
Bolton, 2011	1993–1999	Mayo Clinic Rochester	Surgical	Continuous 14 days	FUDR	5-FU/LV	None
House, 2011	2000–2005	MSKCC	Surgical	Continuous 14 days	FUDR	IRINO/OXA	IRINO/OXA
Goéré, 2013	2000–2009	Institut Gustave Roussy	Surgical*	Bolus 2 h	OXA	5-FU/LV	FOLFOX/FOLFIRI
Groot Koerkamp, 2017	1992–2012	MSKCC	Surgical	Continuous 14 days	FUDR	Various	Various
Buisman, 2019	1991–2012	Multicenter	Surgical	Continuous 14 days	FUDR	FOLFOX/FOLFIRI	FOLFOX/FOLFIRI
Srouji, 2020	2000–2007	MSKCC	Surgical	Continuous 14 days	FUDR	Various	Various

5-FU: Fluorouracil; FA: Folinic Acid; FOLFOX: Folinic acid/Leucovorine/Oxaliplatin; FOLFIRI: Folinic acid/Leucovorine/Irinotecan; FUDR: Floxuridine; HAIC: Hepatic Arterial Infusion Chemotherapy; LV: Leucovorine; MMC: Mitomycin C; MSKCC: Memorial Sloan Kettering Cancer Center; NR: Not Reported; OXA: Oxaliplatin; UFT: Tegafur/uracil; IRINO: Irinotecan.
*79% surgically implanted HAIC catheter, in 21% percutaneously implanted HAIC catheter.

percutaneously for drug delivery. The pooled HR of studies using surgically placed catheters for HAIC was 0.71 (95% 0.61−0.84, I^2 19%, p < 0.001), which represented 1325 HAIC patients and 2124 non-HAIC patients (Fig. 3).

Two studies, representing 67 HAIC patients and 68 no-HAIC patients, used a percutaneous intra-arterial catheter placement.[31,32] The HAI catheter was inserted via the femoral or subclavian artery. A catheter with a side hole was positioned and fixed with the tip of the catheter in the GDA such that the side hole lies at the arterial flow towards the liver. The GDA, right gastric artery, and aberrant or accessory hepatic arteries were embolized to prevent extrahepatic perfusion via the catheter. The pooled HR

Table 2 Baseline characteristics of HAIC patient group

Author, publication year	HAIC group n	no-HAIC group n	Follow-up months Median	Age median (range)	N+ primary CRC n (%)	Synchronous n (%)	Number CRLM median (range)	Tumor size (cm) median (range)	CEA preoperative median (range)	Prior SYS n (%)	EHD n (%)
Randomized trial											
Wagman, 1990	5	6	NR	61 (43–74)	9 (56)	9 (56)	2 (1–7)	NR	NR	NR	0 0
Lorenz, 1998	113	113	At least 18 months	61 (30–76)	53 (50)	34 (32)	NR	NR	NR	NR	0
Rudroff, 1999	14	16	NR	58 (39–70)	14 (100)	6 (46)	NR	4.5 (1–13)	NR	NR	1 (7)
Tono, 2000	9	10	62.2	59 (±5.8)	2 (22)	4 (44)	>1, 3 (33%)	26.3 (SD 14.9)	NR	NR	NR
Kemeny M, 2002	30	45	51	62 (29–78)	NR	9 (30)	NR	NR	NR	16 (53)	0
Kemeny N, 2005	74	82	123	59 (28–79)	NR	23 (31)	NR	NR	11.5 (0.9–258.9)	39 (53)	0
Kusano, 2017	45	46	66	63 (40–80)	NR	15 (33)	>5, n = 3 (7%)	≥4: n = 12 (27%)	NR	0	0
Kusano, 2018	22	22	19.9	62 (45–78)	NR	10 (46)	>6, n = 3 (14%)	≥4, n = 7 (32%)	NR	8 (36)	0
Non-randomized cohorts											
Ambiru, 1999	78	66	NR	63 (21–80)	NR	31 (40)	NR	NR	NR	NR	0
Kusunoki, 2000	30	28	60	60 (25–71)	NR	12 (40)	≥4: n = 3 (10%)	2.5 (1.0–10.0)	12 (1–1020)	7 (23)	0
Moroz, 2002	85	38	NR	NR	NR	NR	NR	NR	NR	NR	0
Onaitis, 2003	21	71	29	53 (mean, SD = 11)	12 (21)	NR	1.8 (mean)	2.2 (mean)	114 (mean)	NR	0
Bolton, 2011	36	13	NR	62 (25–75)	NR	NR	4.0 (0–10)	NR	NR	NR	0
House, 2011	125	125	43	55 (28–80)	84 (68)	NR	2.0 (1–10)	2.8 (0.2–17)	12 (1–1235)	69 (55)	0
Goéré, 2013	44	54	60	55 (SD = 8)	30 (68)	38 (86)	>6, 35 (80)	2.9 (1.7–4.0)	4 (3–10)	44 (100)	9 (20)
Groot, Koerkamp 2017	785	1583	55	56 (SD = 12)	905 (65)	468 (60)	3.5 (NR)	3.9 (NR)	>200: n = 57 (8%)	NR	42 (5)
Buisman, 2019	601	1527	96	57.2 (49.0–65.5)	371 (62.2)	>12mths: n = 432 (72%)	NR	>5: 360 (23.8%)	>200: 131 (9.6%)	441 (73)	0
Srouji, 2020	208	153	142	59 (26–96)	120 (58)	NR	2 (1–9)	3 (0.3–20)	8.4 (0.6–12,325,0)	157 (76)	0

CEA: Carcinoembryonic Antigen; CRC: Colorectal Cancer; CRLM: Colorectal Liver Metastasis; EHD: extrahepatic Disease; HAIC: Hepatic Arterial Infusion Chemotherapy; N+: positive nodal status; NR: Not Reported; SD: Standard Deviation; SYS: systemic chemotherapy.
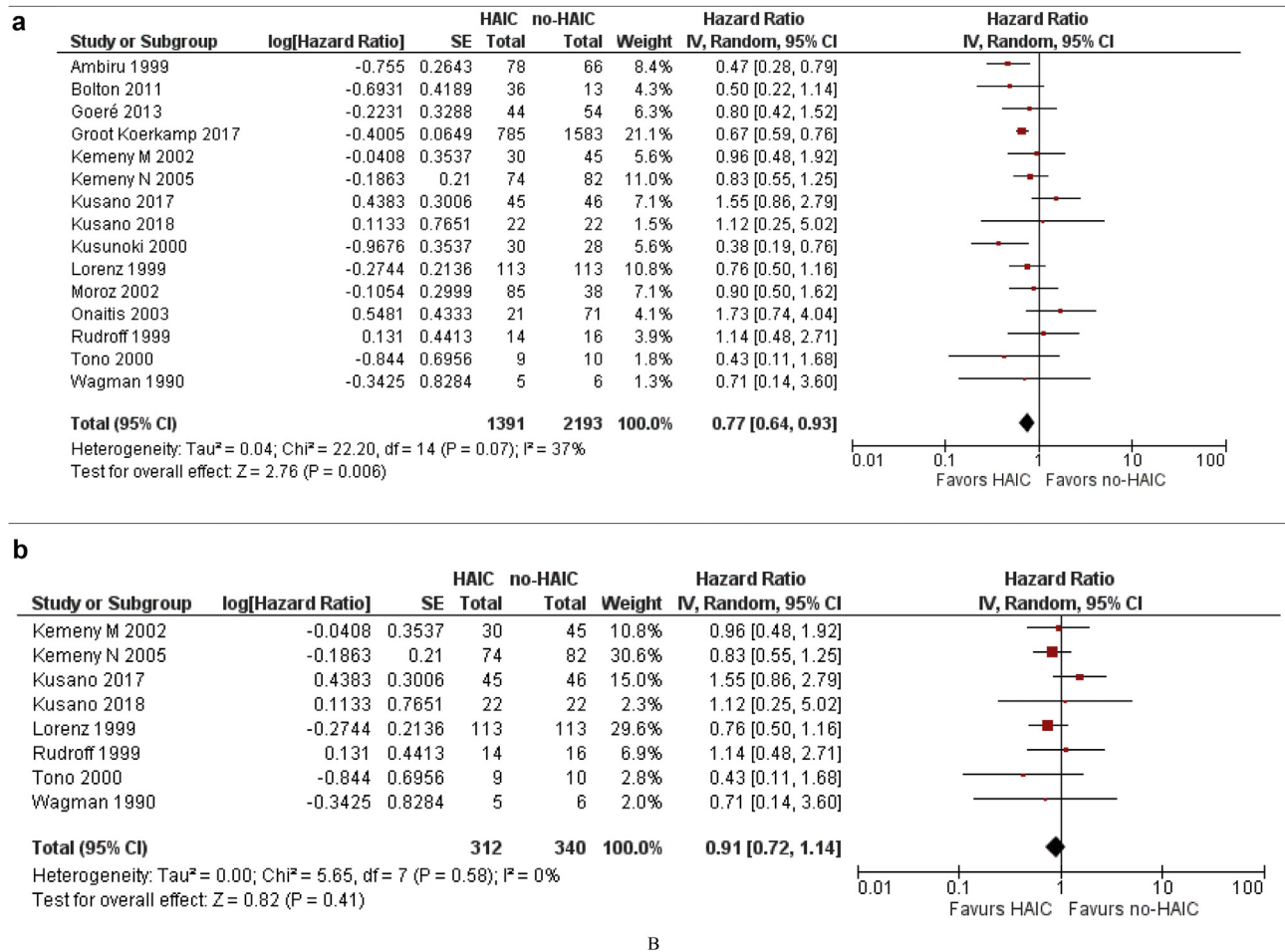
a

Study or Subgroup	log[Hazard Ratio]	SE	HAIC Total	no-HAIC Total	Weight	Hazard Ratio IV, Random, 95% CI
Ambiru 1999	-0.755	0.2643	78	66	8.4%	0.47 [0.28, 0.79]
Bolton 2011	-0.6931	0.4189	36	13	4.3%	0.50 [0.22, 1.14]
Goeré 2013	-0.2231	0.3288	44	54	6.3%	0.80 [0.42, 1.52]
Groot Koerkamp 2017	-0.4005	0.0649	785	1583	21.1%	0.67 [0.59, 0.76]
Kemeny M 2002	-0.0408	0.3537	30	45	5.6%	0.96 [0.48, 1.92]
Kemeny N 2005	-0.1863	0.21	74	82	11.0%	0.83 [0.55, 1.25]
Kusano 2017	0.4383	0.3006	45	46	7.1%	1.55 [0.86, 2.79]
Kusano 2018	0.1133	0.7651	22	22	1.5%	1.12 [0.25, 5.02]
Kusunoki 2000	-0.9676	0.3537	30	28	5.6%	0.38 [0.19, 0.76]
Lorenz 1999	-0.2744	0.2136	113	113	10.8%	0.76 [0.50, 1.16]
Moroz 2002	-0.1054	0.2999	85	38	7.1%	0.90 [0.50, 1.62]
Onaitis 2003	0.5481	0.4333	21	71	4.1%	1.73 [0.74, 4.04]
Rudroff 1999	0.131	0.4413	14	16	3.9%	1.14 [0.48, 2.71]
Tono 2000	-0.844	0.6956	9	10	1.8%	0.43 [0.11, 1.68]
Wagman 1990	-0.3425	0.8284	5	6	1.3%	0.71 [0.14, 3.60]
Total (95% CI)			**1391**	**2193**	**100.0%**	**0.77 [0.64, 0.93]**

Heterogeneity: Tau² = 0.04; Chi² = 22.20, df = 14 (P = 0.07); I² = 37%
Test for overall effect: Z = 2.76 (P = 0.006)

b

Study or Subgroup	log[Hazard Ratio]	SE	HAIC Total	no-HAIC Total	Weight	Hazard Ratio IV, Random, 95% CI
Kemeny M 2002	-0.0408	0.3537	30	45	10.8%	0.96 [0.48, 1.92]
Kemeny N 2005	-0.1863	0.21	74	82	30.6%	0.83 [0.55, 1.25]
Kusano 2017	0.4383	0.3006	45	46	15.0%	1.55 [0.86, 2.79]
Kusano 2018	0.1133	0.7651	22	22	2.3%	1.12 [0.25, 5.02]
Lorenz 1999	-0.2744	0.2136	113	113	29.6%	0.76 [0.50, 1.16]
Rudroff 1999	0.131	0.4413	14	16	6.9%	1.14 [0.48, 2.71]
Tono 2000	-0.844	0.6956	9	10	2.8%	0.43 [0.11, 1.68]
Wagman 1990	-0.3425	0.8284	5	6	2.0%	0.71 [0.14, 3.60]
Total (95% CI)			**312**	**340**	**100.0%**	**0.91 [0.72, 1.14]**

Heterogeneity: Tau² = 0.00; Chi² = 5.65, df = 7 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.82 (P = 0.41)

Figure 2 Forest plot on Overall Survival for a) All studies b) only RCTs

of studies applying a percutaneous approach for HAIC was 1.48 (0.86−2.57, I² 0%) (Fig. 3).

Concomitant adjuvant systemic chemotherapy
Concomitant adjuvant systemic chemotherapy included any combination of 5-FU, oxaliplatin and irinotecan and was administered during HAIC in 11 studies representing 1174 HAIC and 2020 no-HAIC patients.[18,20−22,24,25,28−32] The pooled HR for OS was 0.75 (95%CI 0.59−0.96, I² 50%), in favor of HAIC (Fig. 3). In four adjuvant HAIC studies, representing 218 HAIC and 172 no-HAIC patients, no concomitant adjuvant systemic chemotherapy was administered.[16,17,19,23] The pooled HR for OS was 0.84 (95%CI 0.61−1.14, I² 0%) (Fig. 3).

Discussion

The pooled HR for overall survival of patients who underwent adjuvant HAIC after resection of colorectal liver metastases was better than without adjuvant HAIC (HR for OS of 0.77, 95% CI:

0.64−0.93). Survival benefit of HAIC was best in studies using floxuridine (pooled HR 0.76, 95%CI: 0.62−0.94), surgical catheter insertion (pooled HR 0.71, 95%CI: 0.61−0.84), and concomitant adjuvant systemic chemotherapy (pooled HR 0.75, 95%CI: 0.59−0.96).

Pooled analysis of only RCTs failed to demonstrate an OS benefit in favor of HAIC (HR 0.91 95%CI 0.72−1.14). However, these RCTs were heterogeneous regarding intra-arterial drug, method of catheter insertion, and concomitant adjuvant systemic chemotherapy. In particular, five RCTs administered intra-arterial 5-FU of which four were terminated prematurely due to lack of effectiveness or low accrual.[16,17,19,23] The largest completed RCT used intra-arterial floxuridine with a surgically placed catheter and subcutaneous pump.[26] The median progression-free survival was 31.3 months in the HAIC group versus 17.2 months in the no-HAIC group (p = 0.02); the median overall survival was 68.4 months in the HAIC group versus 58.8 months in the no-HAIC group (p = 0.10), with ten-year OS of 41.1% versus 27.3%. Of note, this is the only large
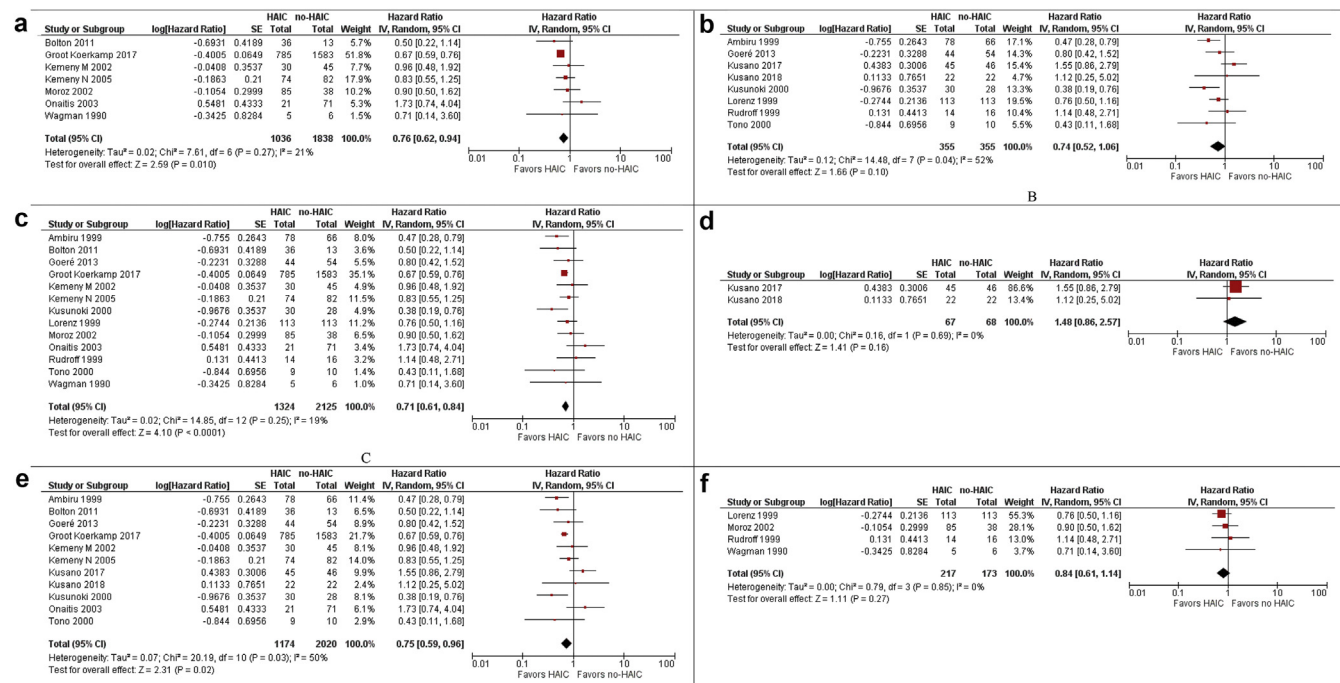
Figure 3 Forest plot for Overall Survival for a) Floxuridine, b) other HAIC agents c) surgical HAIC catheter insertion, d) percutaneous HAIC catheter insertion, e) HAIC with concomitant systemic chemotherapy f) HAIC without concomitant chemotherapy

RCT that completed accrual. In a previous meta-analyses of seven RCTs, Nelson et al. could not demonstrate a difference in OS for adjuvant HAIC (HR 1.09, 95%CI 0.89–1.34).[34] The present study included one additional RCT and long-term results of the largest RCT. Liu et al. identified nine randomized and non-randomized studies with a pooled HR for OS of 0.75 (95% CI: 0.56–0.99) in favor of HAIC.[35] However, this study included several overlapping cohorts and 5 more recent studies were not included. Additional adequately powered RCTs are needed to investigate whether HAIC can improve survival.

Zhang et al. recently published a systematic review in which a pooled analysis of seven RCTs showed a HR of 0.63 (95% CI: 0.56–0.99) for OS, significantly in favor of adjuvant HAIC with respect to no adjuvant HAIC.[36] However, two articles were incorrectly added to the analysis; one article analyses HAIC in the palliative setting for CRLM (without resection),[20] the other article was not a RCT.[37] To our knowledge, no previous published article addresses heterogeneity of treatment with HAIC and by analyzing subgroups based on treatment approach of HAIC.

In the subgroup analysis for different intra-arterial chemotherapeutics, floxuridine-based studies found an improvement in OS in favor of HAIC (HR 0.76, 95%CI: 0.62–0.94), while this could not be demonstrated for 5-FU and oxaliplatin-based studies (HR 0.74, 95%CI: 0.52–1.06). Oxaliplatin, however, was evaluated in only one retrospective study.[29] The rationale behind the superior effectiveness of HAIC with floxuridine is the high hepatic extraction rate of 95% allowing for high intra-

arterial dosages in the liver resulting in a tumor exposure 400 times greater than achieved with systemic administration with limited systemic side-effects.[10] 5-FU and oxaliplatin have a hepatic first-pass effect of approximately 50%,[11,38] allowing for a 5 to 10-fold increased drug exposure in the liver tumor, with respect to systemic administration.[10,11,39] Of note, the pooled HR of the non-floxuridine studies is similar to that of the floxuridine studies, but with a wider confidence interval, possibly corresponding to a smaller pooled sample size rather than a less effective treatment. However, based on pharmacodynamics and pooled analysis of survival data, floxuridine should be investigated in future RCTs. Floxuridine has been FDA approved since 1971, but is not yet registered in the Europe.

In the majority of studies the intra-arterial catheter was primarily inserted surgically.[16–25,28–30] The pooled analysis of studies using this method showed a survival benefit in favor of HAIC (HR 0.71, 95%CI: 0.61–0.84). Two studies administered HAIC via a percutaneously inserted catheter with a pooled HR of 1.48 (95%CI: 0.86–2.57). The percutaneous approach to HAIC catheter implantation has been largely abandoned due to the challenging procedure and high complication rate, in particular, hepatic artery thrombosis and catheter dislodgement with extrahepatic perfusion.[29,40–45] However, technical advancements in percutaneous catheter implantation may reduce complications.[46] Based on the currently published results, future RCTs should use a surgically placed catheter with a subcutaneous infusion pump.

HAIC has been mostly administered as an addition to the standard of care of adjuvant systemic chemotherapy. Subgroup analyses found improved survival of HAIC when administered with concomitant systemic chemotherapy (HR 0.75, 95%CI: 0.59−0.96), while this could not be demonstrated in older studies without concomitant systemic chemotherapy (HR 0.84, 95%CI: 0.61−1.14). On the other hand, a systematic review of RCTs could not demonstrate an improved OS associated with perioperative systemic chemotherapy in the treatment of resectable CRLM compared with resection alone.[6] A synergistic effect of HAIC and systemic chemotherapy cannot be ruled out and should be investigated in future RCTs.

HAIC is a liver directed therapy and should therefore be directed at patients at risk of hepatic recurrence after resection of CRLM. The challenge lies in differentiating patients likely to develop hepatic recurrence, from patients that are likely to either be cured without HAIC (approximately 20%) or develop extrahepatic recurrence (about 50%).[2,5] The former represents patients that would not benefit from HAIC, as they are cured regardless of HAIC. The latter group would be unlikely to benefit from HAIC, as the liver directed treatment does not protect against initial extrahepatic recurrence. Therefore, future studies should find biomarkers to predict whether patients will develop initial extrahepatic recurrence.

The present study has several limitations. The results of the meta-analysis in this study are limited due to the poor quality of the retrospective studies and small sample size of the RCTs. The included studies varied substantially in treatment approach, requiring subgroup analysis with small cumulative sample size. Moreover, systemic oxaliplatin- or irinotecan-based chemotherapy constitutes the standard of treatment in many countries, but was not administered in any of the included RCTs and only in the more recent retrospective studies. The vast majority of patients were included one or two decades prior to the writing of this meta-analysis. Therefore, novel prognostic biomarkers, such as sidedness of the primary CRC, tumoral mutational status (e.g., KRAS and BRAF) and histological growth patterns were not considered in the included studies.[47−51] On the other hand, two recent studies showed that sidedness and genomic alterations in KRAS did not influence the effectiveness of adjuvant HAIC for CLM.[52,53] Also, most research on HAIC originates from only few centers which could impair the generalizability of the results found in this study.

An RCT that is adequately powered to detect a clinically relevant difference in OS is warranted to determine whether adjuvant HAIC after resection of CRLM provides an OS benefit. The PUMP trial (NTR7493) is an ongoing multicenter phase-III RCT in the Netherlands, in which patients are randomized between resection and resection followed by six cycles of adjuvant continuous HAIC with floxuridine via a surgically implanted catheter and infusion pump.[54,55] In this trial, 230 patients with resectable CRLM and a low Clinical Risk Score (CRS) in the Netherlands are needed.[54] This patient selection was based on the finding that in particular low CRS seemed to benefit from HAIC floxuridine.[30] The PACHA trial (NCT02494973) is accruing 220 patients with at least four CRLMs, thus targeting high risk patients. In this phase II/III trial patients are randomized between adjuvant HAI oxaliplatin via a percutaneously or surgically implanted HAIC catheter and systemic 5-FU and leucovorin or adjuvant systemic chemotherapy with FOLFOX. The authors suggested HAIC should be reserved for high-risk patients due the high technicality of the treatment. Results of the PUMP and PACHA -01 trials may determine the role of adjuvant HAIC in patients with resectable CRLM.[56] Future RCTs should also confirm the promising results of HAIC in the setting of unresectable CLM with a response rate up to 85% in pretreated patients.[57]

HAIC has been used since the 1980s in MSKCC and only a few other centers. Why has it not gained further foothold across the world? Firstly, the promising results of the initial RCT's were published at a time when oxaliplatin and irinotecan were introduced. Both were effective in the setting of unresectable metastatic colorectal cancer. With these new treatments, it appeared that HAIC was not needed anymore. Only many years later, it was shown that oxaliplatin and irinotecan do not improve OS in the perioperative setting.[58,59] Moreover, many other systemic drugs were anticipated, but did not materialize in the adjuvant setting. Secondly, floxuridine is not registered the EU. The incentive for the pharmaceutical industry to register floxuridine has been low with a price of about 75 USD for one vial. The registration process of a drug in the EU is expensive. We are currently exploring registration of floxuridine in the EU in collaboration with the pharmaceutical industry. Thirdly, HAIC requires a continuous infusion pump for drug delivery, because the half-life of floxuridine is less than 10 min. No infusion pump with the intended use of intra-arterial chemotherapy is currently registered in the EU. The Codman pump that has been used in the US contains freon gas that is banned from the EU for environmental reasons. Finally, a considerable hurdle for dissemination is that HAIC is a complex multidisciplinary treatment that requires experience and skills.

In conclusion, adjuvant HAIC was associated with better survival in patients with resectable CRLM, in particular for HAIC with floxuridine using a surgically placed catheter and subcutaneous pump and concomitant systemic chemotherapy.

Conflicts of interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2021.10.014.

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