Network Meta-Analysis of Adjuvant Chemotherapy following Resection of Colorectal Liver Metastases

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Abstract
Objective: Six principal adjuvant chemotherapy treatments (ACTs) are currently available for patients with resected colorectal liver metastases. This meta-analysis was designed to determine the optimal ACT, as evaluated by 2-year disease-free survival (DFS) and 5-year overall survival (OS) rates as well as by hepatic recurrences and adverse events (AEs). Methods: A systematic literature search of the PubMed, EMBASE, Medline, Cochrane Library, and Google Scholar databases was performed. The probability of the optimal therapeutic scheme and the mean ranking were estimated for each treatment using network meta-analysis. Results: Systemic chemotherapy (SCT) had the best 2-year DFS rate (hazard ratio [HR] = 0.78, 95% confidence interval [CI] = 0.48–1.27, 95% prediction interval [PI] = 0.17–3.56, surface under the cumulative ranking area [SUCRA] = 73) and the lowest AE rate (estimated SUCRA = 65 and predicted SUCRA = 62). Hepatic arterial infusion (HAI) plus SCT had the best 5-year OS rate (HR = 0.81, 95% CI = 0.64–1.01, 95% PI = 0.50–1.29) and the lowest hepatic recurrence rate (odds ratio = 2.87, 95% CI = 1.56–5.30, 95% PI = 0.61–13.62). Conclusion: Both SCT and HAI plus SCT showed superior efficacy and safety. Clinical trials in homogeneous populations with strict selection criteria are needed to compare these two ACTs.
Introduction

Up to 65% of patients who undergo curative hepatic resections for colorectal liver metastases (CRLM) will experience recurrence of metastases, with two-thirds having recurrences in the remnant liver. Their 2-year disease-free survival (DFS) rate has been reported to be 50%, with their 5-year recurrence-free survival rate ranging from 15 to 35% [1, 2].

Since the blood supply to hepatic metastases is arterial, randomized controlled trials (RCTs) have assessed the applicability, safety, and efficacy of hepatic arterial infusion (HAI), with or without systemic chemotherapy (SCT) [3–10]. These trials found that HAI increased DFS when compared with surgery alone or an SCT regimen. However, associated technical difficulties and complications have restricted the applicability of HAI [3–10]. Although retrospective studies have shown superior results when HAI was compared with modern chemotherapy regimens (FOLFOX, FOLFIRI) [11, 12], RCTs are required to confirm these results. Similarly, SCT was reported to enhance survival and reduce intrahepatic metastases when compared with surgery alone [13, 14].

Although bevacizumab (BEV) has been reported to increase survival in patients with metastatic colorectal cancer [15], the addition of BEV to HAI plus SCT did not increase recurrence-free survival or overall survival (OS), but increased biliary toxicity [8]. Another RCT assessing the effects on DFS of the addition of BEV to SCT reported no results because it was terminated early [16]. Irinotecan (IRI) showed clinically meaningful improvements in palliative treatment of patients with metastatic colorectal cancer [17, 18]. However, the addition of IRI to SCT did not significantly improve DFS in patients with resected CRLM [19].

To date, all of these treatment regimens and associated strategies have been assessed using standard statistical methods. Moreover, assessments of treatment effect size have utilized only the tools of standard meta-analysis.

In the present study, Bayesian network meta-analysis based on probabilistic statistics was used to compare both direct and indirect evidence and to estimate the interrelationships across all adjuvant chemotherapy treatment (ACT) strategies for resected CRLM. Therefore, the aim of this study was to use Bayesian network meta-analysis to calculate the probability of the optimal ACT strategy, as evaluated by 2-year DFS and 5-year OS rates, and by rates of intrahepatic recurrences and adverse events (AEs).

Methods

This study followed the PRISMA statement checklist for reporting the results of systematic reviews and meta-analyses.

Definitions

ACT, including both HAI and SCT, was defined as therapy administered after potentially curative hepatic resections. Modern SCT regimens included 5-fluorouracil, leucovorin, and oxaliplatin or IRI.

Literature Search

The PubMed, EMBASE, Medline, Cochrane Library, and Google Scholar databases were systematically searched for literature published over the last 20 years using the search terms in both their free text and MESH terms (“colorectal liver metastases,” “adjuvant chemotherapy,” “hepatic arterial infusion,” “systemic chemotherapy”). The clinicaltrials.gov and NEAR websites were also searched. References of the retrieved studies were inspected manually to identify additional studies.
Study Selection, Inclusion Criteria, and Exclusion Criteria

The study included both randomized and controlled clinical trials comparing HAI and/or SCT following surgery alone or SCT and any combinations of modern SCTs in patients aged > 18 years with resected CRLM. The following six combinations were assessed: HAI, HAI+SCT, HAI+SCT+BEV, SCT, SCT+BEV, and SCT+IRI.

Data Extraction and Outcomes

Using predesigned forms, two reviewers (P.G. and K.J.R.) independently extracted the following data from the included studies: authors’ names, study design and time period, number of patients included in the treatment and control groups, investigational interventions, rates of intrahepatic recurrences and AEs, 2-year DFS, and 5-year OS. The primary outcomes were 2-year DFS and 5-year OS rates. Secondary outcomes were intrahepatic recurrences and AEs. Any disagreements between the reviewers were resolved by consensus.

Statistical Analysis

The validated Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality of all included studies [20]. Studies with NOS scores ≥7 were considered of high quality. All statistical analyses were performed using the Stata software (version 15; StataCorp LP, College Station, TX, USA).

The six ACTs were compared by Bayesian network meta-analysis. DFS and OS were analyzed by combining the hazard ratios (HRs) and 95% confidence intervals (CIs) from the included studies. As these were rarely reported, they were estimated as described [21]. Dichotomous variables were analyzed by calculating odds ratios (ORs) and 95% CIs.

Both hierarchical random-effects and fixed-effects models were used to estimate size effects and to assess any discrepancy between them [22].

Quantitative data from the included studies were synthesized using the software package WinBUGS (1.4.3, MRC Biostatistics Unit, Cambridge, UK) [23].

Pooled estimates were determined using the Markov chains Monte Carlo method, involving minimally informative priors with a vague normal prior [22]. For each model, 200,000 simulations were generated for the two sets of initial values, with the first 5,000 discarded as the burn-in period. The point estimate was the median of the posterior distribution based on 200,000 simulations, and the corresponding 95% credible intervals were determined using the 2.5th and 97.5th percentiles of the posterior distribution, which can be interpreted similarly to 95% CIs [24].

The inconsistency and heterogeneity of the direct and indirect evidence of the six ACTs were estimated. A random-effects model was used to calculate 95% prediction intervals (PIs), which were reported to assess further statistical heterogeneity. These 95% PIs demonstrate the effect variance among studies and can predict a more conservative summary treatment effect of a future similar trial [25, 26].

The node splitting method was used to calculate the inconsistency of the model that separated direct from indirect evidence; the agreement between the two was evaluated and reported with Bayesian values [25, 26].

Treatment efficacy was measured by calculating the probability of each treatment being the best. Plots of cumulative ranking probabilities (rankograms) were created to rank treatments, with a larger area under the cumulative probability ranking curve indicating a better treatment [27]. The ranking of all ACTs was estimated with both estimated and predicted probabilities, using the surface under the cumulative ranking area (SUCRA) method [28].

Multidimensional scaling techniques were also used to estimate relative ranking and to detect any discrepancies with the SUCRA ranking [28].

Publication bias and small-study effects in the network were not explored because less than 15 studies were included in the review [29].

Results

Study Selection, Characteristics, and NOS

Of the 1,856 studies initially selected, 14 met our inclusion criteria [3–14, 16, 19] (Fig. 1). Thirteen of these 14 studies were of high quality, as shown by NOS scores ≥7 [3–9, 11–14, 16, 19]. There were no significant differences in the demographic characteristics among the
studies. Four studies were retrospective [9, 11, 12, 14] and ten were RCTs [3–8, 10, 13, 16, 19] (Table 1).

The network of direct evidence of the six ACTs was demonstrated with two closed triangle loops; moreover, all treatments anchored to the node of the SCT in a stellar pattern, permitting an estimation of the indirect evidence (Fig. 2).

Results from Network Meta-Analysis of Primary Outcomes

2-Year DFS – Direct Evidence. Direct evidence showed that SCT had a significantly superior 2-year DFS rate (HR = 0.78, 95% CI = 0.48–1.27, 95% PI = 0.17–3.56) compared with the other treatments, a finding confirmed by SUCRA rankings (estimated SUCRA = 73, PrBest = 14, predicted SUCRA = 66 (Fig. 3).

2-Year DFS – Indirect Evidence. Indirect evidence showed that HAI+SCT had a significantly better 2-year DFS rate than SCT+IRI (HR = 1.15, 95% CI = 0.44–3.01, 95% PI = 0.15–8.73) and SCT+BEV (HR = 1.30, 95% CI = 0.45–3.73, 95% PI = 0.15–11.12).

5-Year OS – Direct Evidence. HAI+SCT had a significantly superior 5-year OS rate (HR = 0.81, 95% CI = 0.64–1.01, 95% PI = 0.50–1.29) compared with the other treatments. This
Table 1. Characteristics of the included studies (NOS)

| Reference (first author), period, study type, country | Number of patients | Investigational interventions T/C | Intrahepatic recurrences T/C | AEs T/C | 2-year DFS | 5-year OS T/C | NOS max: 9 |
|-------------------------------------------------------|-------------------|----------------------------------|-----------------------------|---------|------------|--------------|------------|
| Kusano, 2017 [10] 2000-2003, RCT Japan                | 44/46             | HAI + SCT                         | 30 (68%) 21 (45%) 3 (5%) | 21 (54%) | 45%/65%/ p = 0.004 35%/59%/ p = 0.146 | 6            |
| Snoeren, 2017 [16] NR-2010, RCT The Netherlands       | 38/39             | SCT + BEV+SCT                     | 30 (79%) 26 (68%) 21 (54%) | 18 (50%) | 55%/54%/ p = 0.73 75%/75%/ p = 0.54 | 7            |
| Goéré, 2013 [12] 2000-2009, RS France                | 44/54             | HAI + SCT                         | 22 (50%) 42 (78%) 28 (78%) | 26 (68%) | 45%/65%/ p = 0.004 35%/59%/ p = 0.146 | 7            |
| Bolton, 2012 [9] 1993-1999 USA                        | 36/13             | HAI + SCT observation             | 23 (64%) 28 (78%) 21 (54%) | 18 (50%) | 45%/65%/ p = 0.004 35%/59%/ p = 0.146 | 7            |
| House, 2011 [11] 2000-2005, RS USA                    | 125/125           | HAI + SCT                         | 26 (21%) 56 (45%) 22 (50%) | 42 (78%) | 45%/65%/ p = 0.004 35%/59%/ p = 0.146 | 7            |
| Kemeny, 2010 [8] NR, RCT USA                           | 35/38             | HAI + SCT + BEV+HAI + SCT         | 16 (47%) 12 (32%) 16 (47%) | 12 (32%) | 41%/46%/ p = 0.15 81%/84%/ p = 0.5 | 8            |
| Ychou, 2009 [19] 2001-2006, RCT Multicenter          | 153/153           | SCT + IRI                         | 15 (10%) 72 (47%) 9 (21%) | 46 (30%) | 51%/46%/ p = 0.44 30%/24%/ p = 0.283 | 4            |
| Parks, 2007 [14] 1991-1998, RS Multicenter           | 274/518           | SCT observation                   | NR 108 (96%) 10 (1%) 1 (1%) | 8 (50%) | 78%/30%/ p = 0.04 78%/50%/ p = 0.349 | 7            |
| Portier, 2006 [13] 1991-1998, RCT France              | 86/87             | SCT observation                   | 52 (60%) 55 (65%) 32 (37%) | 1 (1%) | 50%/34%/ p = 0.02 51%/42%/ p = 0.13 | 7            |
| Kemeny, 2002 [7] 1990-1998, RCT Multicenter          | 35/45             | HAI + SCT observation             | 12 (27%) 9 (21%) 16 (53%) | 1 (2%) | 90%/60%/ p = 0.001 34%/38%/ p = 0.19 | 8            |
| Tono, 2000 [5] 1993-1995, RCT Japan                   | 9/10              | HAI + SCT                         | 1 (10%) 1 (11%) 1 (10%) | 1 (10%) | 78%/30%/ p = 0.04 78%/50%/ p = 0.349 | 7            |
| Rudroff, 1999 [4] 1984-1985, RCT Germany              | 14/16             | HAI observation                   | 7 (50%) 8 (50%) 5 (50%) | 5 (50%) | 50%/50%/ p = 1.00 25%/31%/ p = 1.00 | 7            |
| Kemeny, 1999 [6] NR, RCT USA                            | 74/82             | HAI + SCT                         | 7 (9%) 29 (39%) 30 (37%) | 18 (22%) | 90%/60%/ p = 0.001 61%/49%/ p = 0.105 | 8            |
| Lorenz, 1998 [3] 1991-1996, RCT Germany               | 113/113           | HAI observation                   | 37 (33%) 42 (37%) 108 (96%) | 1 (1%) | 33%/37%/ p = 0.86 1%/4%/ p = 0.369 | 7            |

AEs, adverse events; BEV, bevacizumab; C, control group; DFS, disease-free survival; HAI, hepatic arterial infusion; IRI, irinotecan; NOS, Newcastle-Ottawa Scale; NR, not reported; OS, overall survival; RCT, randomized controlled trial; RS, retrospective study; SCT, systemic chemotherapy; T, treatment group.
finding was confirmed by SUCRA rankings (estimated SUCRA = 76, predicted SUCRA = 70) (Fig. 4).

5-Year OS – Indirect Evidence. Indirect evidence showed that HAI+SCT had a significantly better 5-year OS rate than SCT+IRI (HR = 1.23, 95% CI = 0.84–1.80, 95% PI = 0.66–2.29) and SCT+BEV (HR = 1.24, 95% CI = 0.53–2.89, 95% PI = 0.39–3.99).
Results from Network Meta-Analysis of Secondary Outcomes

Intrahepatic Recurrences – Direct Evidence. There was significant evidence that HAI+SCT had the lowest intrahepatic recurrence rate (OR = 2.87, 95% CI = 1.56–5.30, 95% PI = 0.61–13.62). Moreover, rankograms of the cumulative ranking probabilities of competing treatments estimated HAI+SCT as the ACT with the lowest recurrence rate (estimated SUCRA = 89, predicted SUCRA = 88.7) (Fig. 5). In addition, multidimensional scaling showed no discrepancy with SUCRA ranking.

Intrahepatic Recurrences – Indirect Evidence. There was statistically significant indirect evidence that HAI+SCT has a lower hepatic recurrence rate than SCT+IRI (OR = 2.87, 95% CI = 0.76–10.88, 95% PI = 0.29–28.28) and SCT+BEV (OR = 5.39, 95% CI = 1.20–24.20, 95% PI = 0.45–64.96).

AEs – Direct Evidence. SCT was ranked as the treatment with the lowest rate of AEs, with an estimated SUCRA = 65 and a predicted SUCRA = 62. However, the 95% CIs and PIs crossed the line of no effect when compared with HAI+SCT (OR = −0.64, 95% CI = −1.42 to 1.29, 95% PI = −5.03 to 4.90) (Fig. 6).

AEs – Indirect Evidence. There was statistically significant indirect evidence that HAI+SCT has lower AE rates than SCT+IRI (OR = 1.94, 95% CI = 0.19–19.55) and SCT+BEV OR = 1.35, 95% CI = 0.12–15.41).

Sensitivity, Heterogeneity, Inconsistency Analysis, and Publication Bias

Pairwise comparisons showed no significant discrepancies between 95% CIs and 95% PIs. Loop-specific heterogeneity showed that inconsistently was estimated to be nonsignif-
significant, with a relative OR of 1.86 (95% CI = 1.00–5.55, \(z = 1.124, p = 0.261\)) for observation-HAI+SCT-SCT and an relative OR of 1.28 (95% CI = 1.00–68.28, \(z = 0.125, p = 0.901\)) for observation-HAI-SCT.

In addition, the random-effects standard deviation of 0.241 and the time-series standard error of 0.001 proved the consistency of the model. First, the arbitrary starting values did not have an undue influence on the sampling process, and second, the quantities of interest were estimated to sufficient accuracy. The time-series plot had the appearance of a “fat hairy caterpillar,” indicative of a converged chain that contains sufficient information for accurate inferences. The potential scale reduction factor reached stable values < 1.01, and the series plot of the estimation accuracy showed density and tapering off of the extreme values in the tails.

A comparison-adjusted funnel plot of publication bias appeared symmetric, demonstrating the absence of bias in the network.

**Discussion**

The aim of this network meta-analysis was to detect among the six ACTs the most effective and safest treatment for patients who underwent curative hepatic resections for CRLM. As most metastatic recurrences occur within 2 years after curative resection \([1, 6]\), we chose 2-year DFS and 5-year OS rates as primary outcomes and AE and hepatic recurrence rates as secondary outcomes.
The evidence network of the 14 included studies demonstrated two triangle loops that connected the three most frequent ACTs – SCT, HAI, and HAI+SCT – with trials that also included BEV and IRI connected to the node of the SCT in a star pattern. This last characteristic permitted estimates of indirect evidence among the ACTs, using SCT as a common comparator.

Evaluation using the loop-specific heterogeneity of the two closed loops indicated that inconsistency was nonsignificant. Moreover, a comparison-adjusted funnel plot demonstrated the absence of small-study effects in the network, findings indicating robustness of the model.

Based on the SUCRA methodology, SCT was classified as the ACT with the best 2-year DFS; this finding was also supported by the statistically significant credible intervals and PIs. Moreover, SCT had the lowest AE rate. However, in comparison with HAI+SCT, SCT did not achieve statistically significant credible intervals and PIs.

To date, no RCT has compared combined HAI and SCT with modern chemotherapy, consisting of oxaliplatin- or IRI-based intravenous chemotherapy. Therefore, to compare all existing ACT strategies, we intentionally included retrospective studies in our meta-analysis.

HAI+SCT was found to have the highest 5-year OS rate and the lowest hepatic recurrence rate, with both showing statistically significant credible intervals and PIs. In addition, indirect evidence comparing ACTs with SCT as a common comparator showed that HAI+SCT had higher 2-year DFS and 5-year OS rates and lower hepatic recurrence and AE rates than SCT+IRI and SCT+BEV. Thus, the direct and indirect evidence of the current network meta-analysis suggests the need for future RCTs comparing HAI+SCT with SCT.

Fig. 6. Rankogram of adverse events. BEV, bevacizumab; HAI, hepatic arterial infusion; IRI, irinotecan; SCT, systemic chemotherapy.
The above results should be interpreted cautiously. In addition to methodological heterogeneity between studies, there was clinical heterogeneity within and between the studies. In particular, one study reported that patients in the HAI+SCT cohort were more often younger, had node-negative primary tumors, showed unilobar distribution of CRLM, and underwent less extensive operations [11]. In contrast, another study selected patients for HAI+SCT if they had at least five CRLM, were undergoing second re-hepatectomy, and had bilobar CRLM; in addition, patients treated from 2007 included those with disappeared or missing CRLM [12]. A comparison of the two cohorts in the latter study showed that patients in the HAI+SCT cohort were younger, had more “missing” CRLM, had significantly more CRLM, and tended to have higher levels of carcinoembryonic antigen [12].

Studies also differed in the chemotherapeutic agent used for HAI. Floxuridine, with reported response rates of 41–62%, was the most common frequently used chemotherapeutic agent. In contrast, another study used oxaliplatin [12], based on a reported response rate of 63% in a multicenter phase II trial of patients with unresectable CRLM [30]. Another caveat was early treatment discontinuation due to technical failures of HAI and/or the biliary toxicity of the chemotherapeutic agent.

The present study had methodological limitations in that it included small RCTs and retrospective studies from single centers. The results of our analysis may also have been influenced by institutional and national differences. Furthermore, clinical heterogeneity regarding patient characteristics predictive of high risk of recurrence remains a major confounding factor. Thus, multicenter RCTs with strict selection criteria and more homogeneous populations are required to further compare the efficacy of HAI+SCT with SCT alone.

Disclosure Statement

The authors declare no conflicts of interest.

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