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Systematic Review With Network Meta-Analysis

Adjuvant Chemotherapy for Resected Colorectal Liver Metastases

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Abstract: There are 5 major adjuvant chemotherapies (ACTs) for hepatic metastases for colorectal cancer; however, the optimal treatment regimen remains inconclusive. Here, we aim to compare these therapies in terms of patient survival rate, intrahepatic recurrence rate, and adverse events.

Different databases were searched for controlled trials up to June 30, 2014. The pooled hazards ratios for death and odds ratios (ORs) for intrahepatic recurrence and adverse events were estimated. A mean ranking and the probability of optimal therapeutic regime was obtained for each treatment analyzed in the network meta-analysis.

Eleven eligible articles were included. Systemic chemotherapy (SCT) was ranked the most efficacious intervention among ACTs in both 1-year and 5-year survival; however, no statistical difference could be determined. Combination of bevacizumab (BEV) and hepatic arterial infusion (HAI) plus SCT was the most effective in preventing intrahepatic recurrence when compared with HAI alone (OR 1.21, 95% confidence interval [CI] 0.01–131.12), SCT (OR 2.37, 95% CI 0.03–234.16), HAI plus SCT (OR 0.97, 95% CI 0.03–35.30), SCT plus irinotecan (OR 1.01, 95% CI 0.00–278.14) and observation alone (OR 0.83, 95% CI 0.01–59.53). BEV and HAI plus SCT provided the least survival benefit after both 1 and 5 years compared with remaining therapies, and also was ranked the regiment with the least favorable adverse event profile among ACTs.

SCT may be the most efficacious intervention, however, the potential benefit should be carefully considered with the regime's associated toxicities. Combination of BEV and HAI plus SCT was effective in preventing intrahepatic relapse but was associated with the highest risk for adverse events in patients with resected hepatic metastases for colorectal cancer.

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Abbreviations: ACT = adjuvant chemotherapy, BEV = bevacizumab, CI = confidence interval, CRC = colorectal cancer, HAI = hepatic arterial infusion, HMCRC = hepatic metastases from colorectal cancer, HR = hazard ratio, IRI = irinotecan, MCRC = metastatic colorectal cancer, OR = odds ratio, SCT = systemic chemotherapy.

INTRODUCTION

Colorectal cancer (CRC) is ranked within the top 4 most common cancers worldwide and was responsible for over 500,000 deaths in 2002.[1] Up to 25% of CRC patients present with metastatic colorectal cancer (MCRC), with the most common site for metastases being the liver.[2]

Surgical resection has proved to be the most effective therapy for MCRC when isolated to the liver. However, only 15% to 20% of patients with hepatic metastases are initially eligible for such a radical surgical approach. The proportion of patients who achieve 5-year survival after resection ranges from 20% to 50%.[3,4] After liver resection, recurrences are reported in two thirds of patients with approximately half recurrences occurring in the residual liver.[5–7] Therefore, combining chemotherapy with resection of hepatic metastases from colorectal cancer (HMCRC) is of major interest.

Previous randomized clinical trials of adjuvant chemotherapy (ACT) given after liver resection, either intravenously or through the hepatic artery, both provided some indication that prognosis may improve.[8–11] A meta-analysis showed an increase in disease-free survival with the use of systemic fluorouracil and leucovorin after adjustment for poor prognostic factors.[12] Hepatic arterial infusion (HAI) with or without systemic chemotherapy (SCT), significantly increased disease-free survival when compared with SCT alone (or with no further therapy) in 3 of 4 randomized studies.[8–10,13] In addition, bevacizumab (BEV) SCT has demonstrated increased survival in patients with metastatic disease,[14] the combination of fluorouracil (FU)-based systemic therapy with irinotecan (IRI) has been reported to provide a significant improvement in the palliative treatment of MCRC patients compared with FU-based SCT alone.[15–17]

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As those clinical trials only compared pairs of strategies and opinions differ concerning a definition of optimum ACTs for resected HMCRC, network meta-analysis (also called multiple treatment comparison) is a potential consideration with which to advance our understanding of the best regimen and to help guide physicians' decision making. It combines both direct and indirect evidence for multiple treatment comparisons in order to estimate the interrelationships across all treatments and mixed treatment comparison enables indirect comparison using a common comparator when a head-to-head trial is not available.

Hence, with the introduction of these therapeutic options and the lack of clinical trials that direct compare all available treatments, it was of interest to indirectly compare these treatments by using Bayesian meta-analysis in terms of 1-year, 5-year survival rates, intrahepatic recurrence rate, and effects due to regiment toxicity.

METHODS

Search Strategy

A systematic review was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (http://links.lww.com/MD/A131) guideline (Supporting Information 1, http://links.lww.com/MD/A132).[18] We searched 4 electronic databases (*PubMed*, *Embase*, *Scopus*, and the *Cochrane Library*) up to June 30, 2014, for clinical trials investigating any ACTs for patients with resected HMCRC, with the key terms ''adjuvant chemotherapy, colorectal cancer, hepatic metastases, liver metastases'' without any language or date restrictions. Additional studies in the reference lists of all identified publications, including relevant meta-analyses and systematic reviews, were also searched. The study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University.

Selection Criteria

We included both randomized and controlled clinical trials, comparing the effects of any single or combination of ACTs with surgery only in patients with resected HMCRC >18 years. Included studies had to report at least 1 of 4 outcomes: 1-year and 5-year survival, intrahepatic recurrence rate and toxic effects. We included studies in patients receiving ACTs, including adjuvant SCT, HAI, HAI plus SCT, SCT plus IRI, or combination of BEV and SCT plus HAI, which should be administered after curative-intent surgery. Eligible studies had to be published as full-length articles or letters in peer-reviewed journals.

Data Extraction

Two investigators (G.-Q.Z., K.-Q.S.) independently reviewed the full manuscripts of eligible studies and extracted information into an electronic database: patients' characteristics, study design, interventions, comparisons, the number of events of interest in each group and outcomes (1-year, 5-year survival rates, intrahepatic recurrence rate, and toxic effects). Any discrepancies regarding the extraction of data were resolved by additional investigator (M.-H.Z.). When relevant information on design or outcomes was unclear, or when some needed data was unavailable directly from the study, the original authors were contacted for clarifications and assistance by email.

Quality Assessment

Methodologic quality was assessed independently by 2 reviewers using Newcastle–Ottawa Quality Assessment Scale with some modifications to match the needs of this study.[19] The quality of the studies was evaluated by examining 3 items: patient selection, comparability of ACT and observation group, and assessment of outcome (Supporting Information 2, http://links.lww.com/MD/A133).

Data Analysis

First, a traditional pairwise meta-analyses for studies that directly compared different treatment arms was performed. This was followed by a Bayesian network meta-analyses to compare different ACTs (HAI, SCT, HAI plus SCT, SCT plus IRI, combination of BEV and HAI plus SCT, as well as observation) to each other. Traditional pairwise meta-analysis was conducted using Stata software (version 10.0, StataCorp, College Station, TX). Using the method of DerSimonian and Laird random effects model, the pooled estimates of odds ratios (ORs) and 95% confidence intervals (CI) of direct comparisons were calculated between 2 strategies according to Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The heterogeneity was assessed with the I^2 statistic, a value of >50%, was considered to be representative of statistically significant heterogeneity.[20]

In addition to the direct comparison meta-analyses, a network meta-analysis was performed using the Bayesian hierarchical random effects model proposed by Lu and Ades.[21] The advantages of using a Bayesian meta-analytical approach are that direct probability statements on treatment comparisons can be made and that all evidence for a specific problem can be taken into account as it includes evidence on both indirect and direct comparisons, and as such allows estimation of the comparisons between interventions that have not been examined directly in previous trials. The software package WinBUGS (version 1.4.3, MRC Biostatistics Unit, Cambridge, UK) was used to perform the network meta-analysis, with random effects models for multi-arm trials developed by Ades et al[22] (Multi-Parameter Evidence Synthesis Research Group, University of Bristol, UK). The pooled estimates were obtained using the Markov Chains Monte Carlo method. In our Bayesian analysis, we used noninformative priors with vague normal (mean 0, variance 10,000) and uniform (0–2) prior distributions for parameters such as means and standard deviations, respectively.[21] For each model, we generated 100,000 simulations for each of the 2 sets of different initial values, and we discarded the first 50,000 simulations as the burn-in period. The achievement of convergence was assessed using the Brooks–Gelman–Rubin statistic.[22,23] The median of the posterior distribution based on 100,000 simulations was reported as the point estimate, and we obtained the corresponding 95% credible intervals using the 2.5th and 97.5th percentiles of the posterior distribution, which could be interpreted in a way similar to conventional 95% CIs.[24] When a loop connected 3 treatments, it was possible to evaluate the inconsistency between direct and indirect evidence.[25] We used the node splitting method to calculate the inconsistency of the model, which separated evidence on a particular comparison into direct and indirect evidence.[26] We then evaluated the agreement between the direct and indirect evidence and reported its Bayesian P value.[26]

Treatments were ranked for each outcome in each simulation on the basis of their posterior probabilities. We assessed the probability that each treatment was the most effective therapy, the second best, and so on, by counting the proportion of simulations in which each treatment had the smallest hazard ratios (HRs) or ORs, the second smallest, and so on. Even if the

differences in effect size among treatments obtained were small, clinical decisions about the choice of treatments may be suggested based on the probabilities of treatment ranking. The pooled HRs were reported in terms of 1-year and 5-year survival rates, whereas intrahepatic recurrence rate and toxic effects were calculated as ORs with corresponding 95% CIs, in addition to the probabilities of ranking by treatment.

RESULTS

Study Characteristics

Electronic and reference searches recovered 2065 publications (Figure 1) and after the initial screening, 1619 were excluded after screening by title and abstract (Supporting Information 3, http://links.lww.com/MD/A134). A further 435 were excluded after detailed assessment of the full text (Supporting Information 4, http://links.lww.com/MD/A135). Characteristics and quality assessment of 11 eligible trials were outlined for network meta-analysis in Table 1, with a total of 1951 patients who received 1 of the 6 treatment strategies. We included 6 regimens according to eligible studies: HAI, SCT, HAI plus SCT, SCT plus IRI, and combination of BEV and HAI plus SCT or observation.

In terms of study sample sizes, the number of patients involved in the studies ranged from 19 to 792. Eight hundred seventeen patients were treated with surgery alone, and 1134 received ACTs. Among the 11 studies, which were all two-arm trials, patients were treated with HAI chemotherapy alone in 4 studies,[10,27–29] HAI plus SCT in 5 studies,[8,9,30–32] SCT alone in 3 studies,[9,33,34] and combination of BEV and HAI plus SCT in 1 study[31] and SCT plus IRI in 1 study.[34] Table 1 summarizes the quality assessment and scores of included studies, which showed that that the quality of included studies were reliable.

Efficacy of Adjuvant Chemotherapy From Pairwise Meta-Analysis

Pairwise comparisons were accomplished for the 6 different treatment permutations. The weighted hazard ratios for the primary outcome, 1-year and 5-year survival, were calculated for each comparison. The geometric distribution of controlled trials on survival rates (Figure 2A), intrahepatic recurrence (Figure 2B) and adverse events (Figure 2C) were displayed. Table 2 indicated that when compared with adjuvant SCT, there was no evidence favoring the regimen of SCT plus IRI (HR 1.30, 95% CI 0.47–3.59 and HR 1.38, 95% CI 0.82–2.35, respectively), HAI plus SCT (HR 0.61, 95% CI 0.17–2.18 and HR 0.53, 95% CI 0.28–1.02, respectively), observation (HR 2.07, 95% CI 0.37–11.64 and HR 1.43, 95% CI 0.78–2.61, respectively) in 1-year and 5-year survival and no statistical significance was determined.

In the current pairwise meta-analysis of the 2 outcomes, the I^2 values were 0% for the comparison of HAI versus

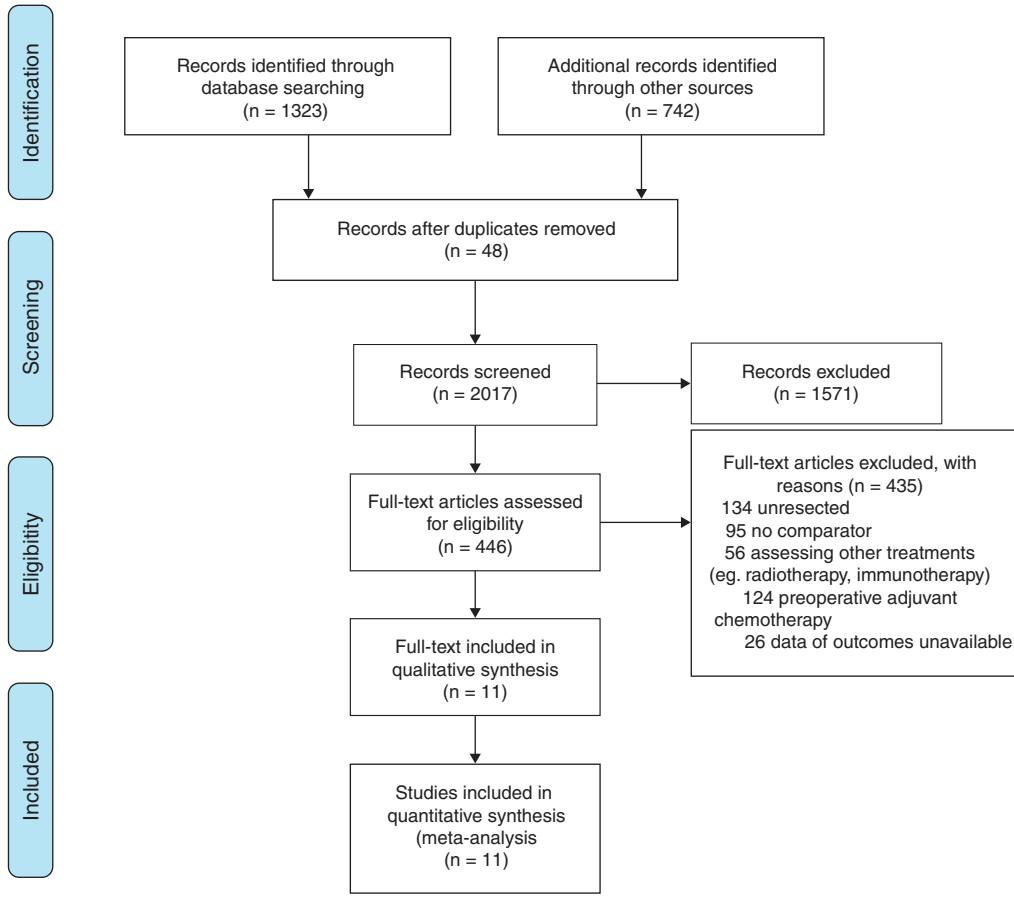

FIGURE 1. Literature search and selection.

TABLE 1. Characteristics and Quality Assessment of Included Studies

Author (Year)	Country	Investigational Interventions	Study Size	1-Year Survival (%) Treatment/ Control	5-Year Survival (%) Treatment/ Control	Intrahepatic Recurrence (%) Treatment/ Control	Toxic Effects (%) Treatment/ Control	Study Quality (*)
Wagman (1990)	United States	HAI, Observation	21	80/83	33/50	13/67	20/17	*****
Lorenz (1998)	German	HAI, Observation	226	67/72	1/4	33/37	96/1	*******
Kemeny (1999)	United States	SCT + HAI, SCT	156	91/95	52/68	37/9	NA/NA	*******
Rudroff (1999)	German	HAI, Observation	29	77/56	23/31/	50/50	NA/NA	*******
Tono (1999)	Japan	HAI, Observation	19	89/90	78/50	67/10	11/10	*******
Kemeny (2002)	United States	HAI + SCT, Observation	109	85/91	34/38	27/53	21/2	********
Portier (2006)	France	SCT, Observation	171	98/95	51/42	60/65	37/1	*******
Parks (2007)	United States	HAI + SCT, Observation	792	88/86	37/31	NA/NA	NA/NA	*******
Ychou (2009)	France	SCT, SCT + IRI	306	95/94	27/21	5/10	30/47	********
Kemeny (2011)	United States	HAI + SCT, HAI + SCT + BEV	73	97/97	84/80	47/47	32/86	********
Bolton (2012)	United States	HAI + SCT, Observation	49	92/77	31/15	64/67	78/8	*******

*: see Supporting Information 2, http://links.lww.com/MD/A133. BEV = bevacizumab, HAI = hepatic arterial infusion, IRI = irinotecan, NA = not available, SCT = systemic chemotherapy.

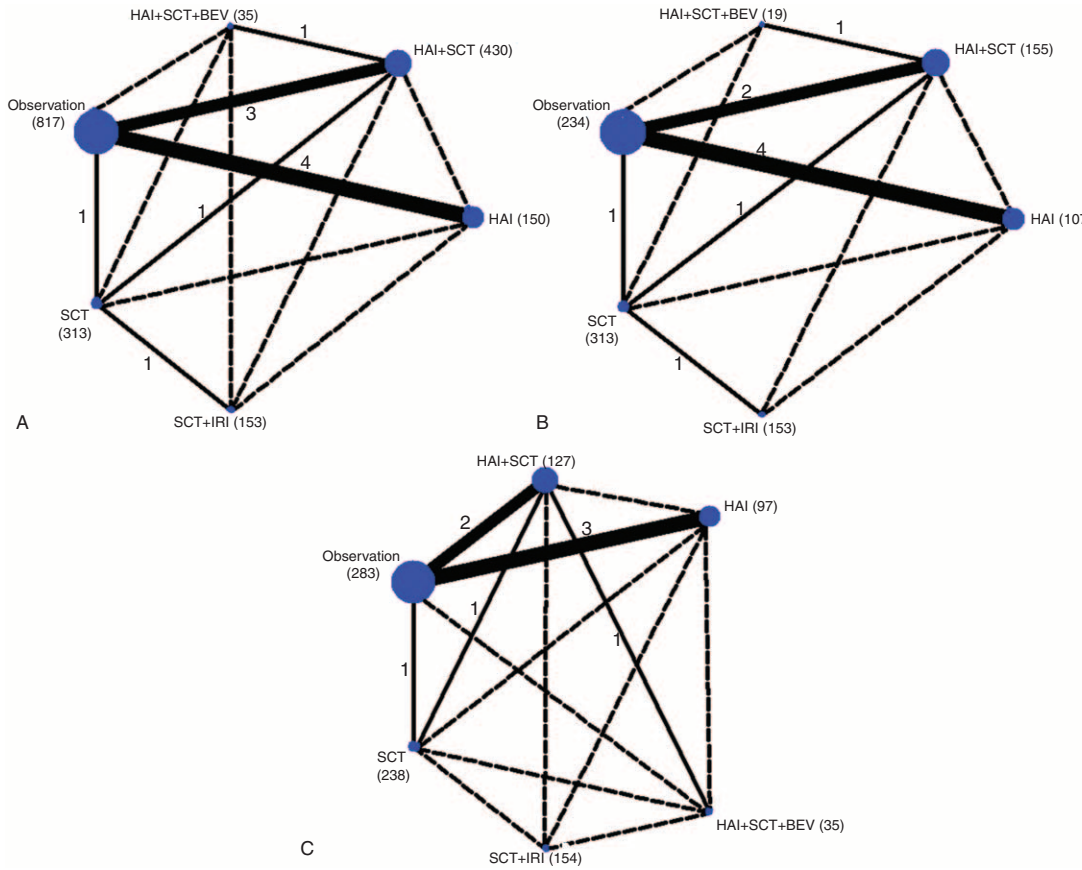

FIGURE 2. Evidence network of eligible comparisons for network meta-analysis. The numbers along the link lines indicate the number of trials or pairs of trial arms. Lines connect the interventions that have been studied in head-to-head (direct) comparisons in the eligible controlled trials. The width of the lines represents the cumulative number of trials for each comparison and the size of every node is proportional to the number of enrolled participants (sample size). BEV = bevacizumab, HAI = hepatic arterial infusion, IRI = irinotecan, SCT = systemic chemotherapy. A = 1-year and 5-year survival, B = intrahepatic recurrence, C = toxic effects.

TABLE 2. Pooled Hazards Ratios for Death by Bayesian Network Meta-Analysis and Traditional Meta-Analysis

	1-Year Survival		5-Year Survival	
Author, Year	**Hazards Ratios (95% CI)**	**Weight (%)**	**Hazards Ratios (95% CI)**	**Weight (%)**
HAI vs observation				
Lorenz, 1998	0.81 (0.46, 1.43)	82.56	0.24 (0.03, 2.21)	19.69
Rudroff, 1999	2.59 (0.51, 13.16)	10.06	0.66 (0.12, 3.50)	31.91
Tono, 1999	0.89 (0.05, 16.66)	3.09	3.50 (0.47, 25.90)	23.40
Wagman, 1990	0.80 (0.07, 9.67)	4.28	0.50 (0.07, 3.43)	25.00
Subtotal	0.91 (0.55, 1.53)	100.00	0.75 (0.27, 2.11)	100.00
Network meta-analysis	0.99 (0.44, 2.69)	—	0.70 (0.26, 2.08)	—
HAI + SCT vs observation				
Kemeny, 2002	0.55 (0.17, 1.81)	23.31	0.86 (0.39, 1.88)	12.96
Bolton, 2012	3.30 (0.57, 18.98)	12.49	2.42 (0.46, 12.79)	2.88
Parks, 2007	1.20 (0.77, 1.86)	64.20	1.29 (0.95, 12.76)	84.16
Subtotal	1.13 (0.58, 2.21)	100.00	1.25 (0.94, 1.66)	100.00
Network meta-analysis	1.15 (0.53, 2.63)	—	1.17 (0.62, 2.22)	—
SCT vs observation				
Portier, 2006	2.07 (0.37, 11.64)	100.00	1.43 (0.78, 2.61)	100.00
Subtotal	2.07 (0.37, 11.64)	100.00	1.43 (0.78, 2.61)	100.00
Network meta-analysis	2.08 (0.52, 8.99)	—	1.76 (0.73, 4.30)	—
HAI + SCT vs HAI + SCT + BEV				
Kemeny, 2011	1.09 (0.07, 18.09)	100.00	1.33 (0.40, 4.44)	100.00
Subtotal	1.09 (0.07, 18.09)	100.00	1.33 (0.40, 4.44)	100.00
Network meta-analysis	1.04 (0.03, 38.71)	—	1.37 (0.28, 6.21)	—
SCT + HAI vs SCT				
Kemeny, 1999	0.61 (0.17, 2.18)	100.00	0.53 (0.28, 1.02)	100.00
Subtotal	0.61 (0.17, 2.18)	100.00	0.53 (0.28, 1.02)	100.00
Network meta-analysis	0.57 (0.13, 2.01)	—	0.66 (0.28, 1.53)	—
SCT vs SCT + IRI				
Ychou, 2009	1.30 (0.47, 3.59)	100.00	1.38 (0.82, 2.35)	100.00
Subtotal	1.30 (0.47, 3.59)	100.00	1.38 (0.82, 2.35)	100.00
Network meta-analysis	1.32 (0.30, 5.85)	—	1.41 (0.47, 4.19)	—

BEV = bevacizumab, CI = confidence interval, HAI = hepatic arterial infusion, IRI = irinotecan, SCT = systemic chemotherapy.

observation, SCT versus observation, SCT versus SCT plus IRI for 1-year survival, whereas in terms of 5-year survival, I^2 values for the comparisons of SCT versus SCT plus IRI (0.0%), HAI plus SCT versus combination of BEV and SCT plus HAI (0.0%), HAI versus observation (13.5%), HAI plus SCT versus observation (0.0%) were <25%. These results indicated that heterogeneity of the results was low overall.

Results From the Network Meta-Analysis of Primary and Secondary Outcomes

Figure 3A and B illustrates the HRs for 1-year and 5-year survival rates, respectively, and 95% CIs obtained from the indirect comparisons of the included regimens. Following Figure 3A from left to right, all interventions, except HAI and combination of BEV and HAI plus SCT, were associated with greater survival benefit than observation for both 1-year and 5-year survival rates. Although not differing significantly, there was a trend that SCT was more efficacious than SCT plus IRI (HR 1.31, 95% CI 0.31–5.82), HAI plus SCT (HR 0.57, 95% CI 0.14–2.20), observation (HR 2.08, 95% CI 0.52–8.99), HAI (HR 0.49, 95% CI 0.09–2.59), and combination of BEV and HAI plus SCT (HR 2.27, 95% CI 0.03–157.12) for 1-year survival. SCT and SCT plus IRI appeared to be superior to HAI plus SCT (HR 0.66, 95% CI 0.27–1.57 and HR 0.90, 95% CI 0.21–3.86, respectively), observation (HR 1.76, 95% CI, 0.73–4.30 and HR 0.79, 95% CI 0.18–3.28, respectively), HAI (HR 0.43 95% CI 0.11–1.63 and HR 0.61, 95% CI 0.10–3.49, respectively), and combination of BEV and HAI plus SCT (HR 1.97, 95% CI 0.37–12.42 and HR 0.73, 95% CI 0.08–5.60, respectively) in 5-year survival. For intrahepatic recurrence rate (Figure 3C), SCT plus IRI was more likely to cause intrahepatic relapse than observation (OR 1.24, 95% CI 0.02–100.65), HAI plus SCT (OR 0.99, 95% CI 0.01–81.80), SCT (OR 0.42, 95% CI 0.01–13.77), HAI (OR 1.20, 95% CI 0.01–147.37), and combination of BEV and HAI plus SCT (OR 1.01, 95% CI 0.00–278.14). With respect to adverse events, although not differing significantly, the combination of BEV and HAI plus SCT appeared to be associated with more toxicities than SCT (OR 2.46, 95% CI 0.00–15648693.10), HAI (OR 0.13, 95% CI 0.00–57422.61), HAI plus SCT (OR 0.07, 95% CI 0.00–867.74), observation (OR 199.77, 95% CI 0.00–26472283.23), SCT plus IRI (OR1.19, 95% CI 0.00–96326203.82).

T-ranked at each of the possible 6 permutations (Figure 4A–F). SCT and SCT plus IRI had the highest probabilities of reduction in mortality rate for 1-year and 5-year survival rates (Figure 4), suggesting SCT and SCT plus IRI were more efficacious than the other remaining interventions, the cumulative probabilities of being among the most efficacious

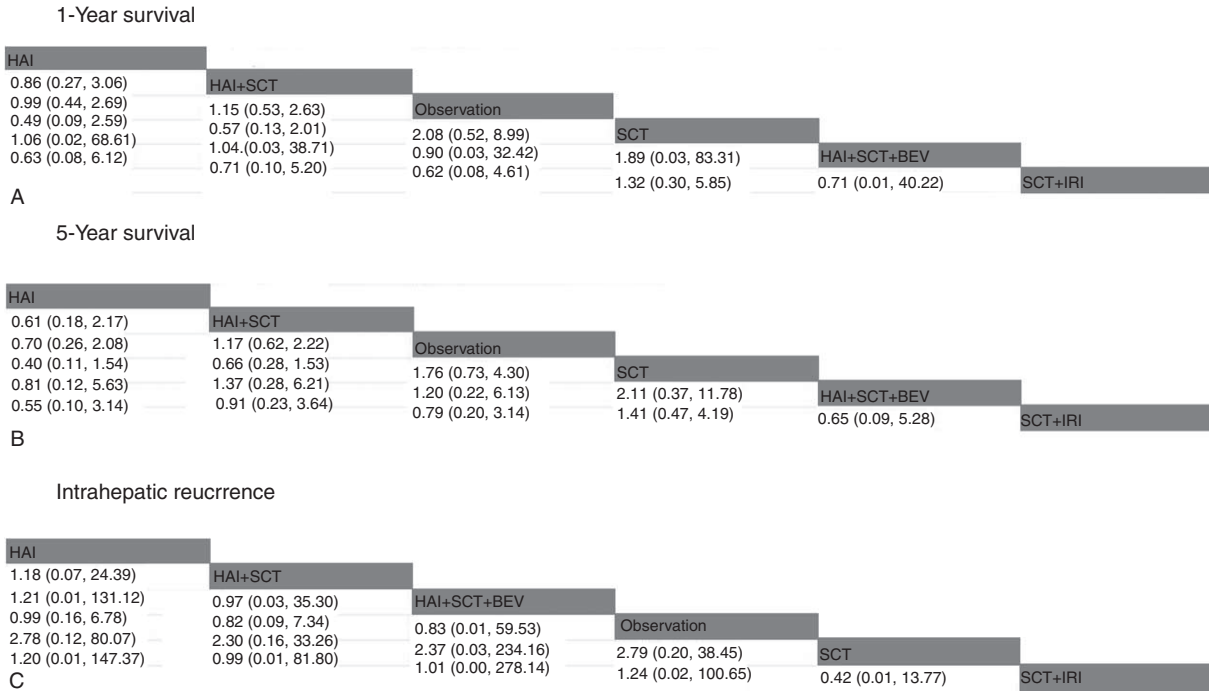

FIGURE 3. Pooled hazard ratios for death and pooled odds ratios for intrahepatic recurrence. The column treatment is compared with the row treatment. Numbers in parentheses indicate 95% credible intervals. BEV = bevacizumab, HAI = hepatic arterial infusion, IRI = irinotecan, SCT = systemic chemotherapy. A = 1-year survival, B = 5-year survival, C = intrahepatic recurrence.

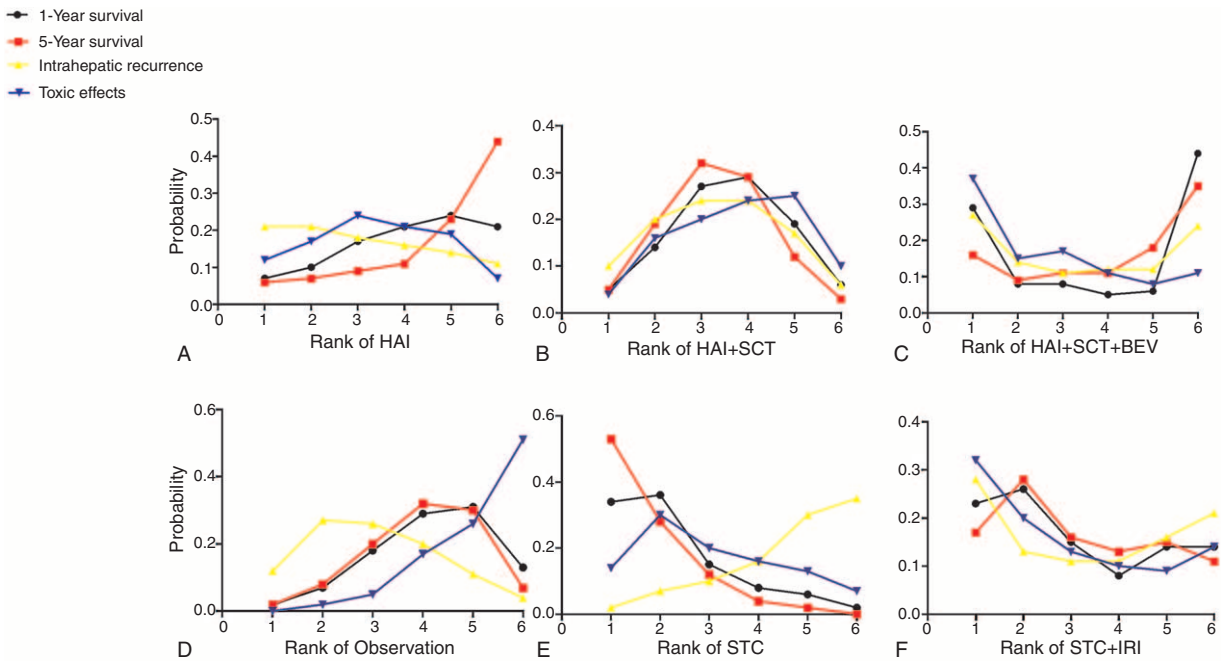

FIGURE 4. Rankograms showing probability of each strategy having each specific rank (1–6) for 1-year and 5-year survival, intrahepatic recurrence and toxic effects. Ranking indicates the probability to be the best treatment, the second best, the third best, and so on. Rank 1 is worst and rank N is best. BEV = bevacizumab, HAI = hepatic arterial infusion, IRI = irinotecan, SCT = systemic chemotherapy. A = rank of HAI, B = rank of HAI + SCT, C = rank of HAI + SCT + BEV, D = rank of observation, E = rank of SCT, F = rank of SCT + IRI.

interventions in improving the survival was SCT. For intrahepatic recurrence, HAI and combination of BEV and HAI plus SCT may prevent intrahepatic recurrence better than the other remaining interventions as they had the highest probabilities of reduction in intrahepatic relapse, the cumulative probabilities of being among the most efficacious in preventing intrahepatic recurrence was combination of BEV and HAI plus SCT. However, combination of BEV and HAI plus SCT rank the highest with respect to adverse events and the cumulative probabilities of being among the 3 least toxic interventions for were SCT plus IRI and HAI plus SCT. Figure 5A–D presents comparison-adjusted funnel plot for ACTs network, without the evidence of asymmetry.

Comparisons Between Traditional Pairwise and Bayesian Network Meta-Analyses

Table 2 shows the results of traditional pairwise and network meta-analyses. Although the pooled estimates showed small differences, the CIs from traditional pairwise meta-analyses and from the Bayesian network meta-analyses in general overlapped. The node splitting method showed no significant inconsistency within the networks for any of the 3 outcomes (Supporting Information 5, http://links.lww.com/MD/A136).

DISCUSSION

In this network meta-analysis, we review the efficacy of different ACTs on survival and 2 outcomes related to intrahepatic recurrence and adverse events in patients with resected HMCRC. Our results suggest that adjuvant SCT provides an overall survival advantage over the remaining interventions, but showed an increased adverse event profile. In addition, combination of BEV and HAI plus SCT was effective in preventing intrahepatic relapse but was found to be associated with the highest risk for adverse events in patients with resected HMCRC.

Our results showed that adjuvant SCT reduced both long- and short-term mortality after resection of resected HMCRC by approximately twice that suggested in the previous study.[33] A subsequent traditional meta-analysis in 2012[35] concluded that there was a trend advantage of SCT combined with surgical resection of colorectal liver metastases compared with surgery

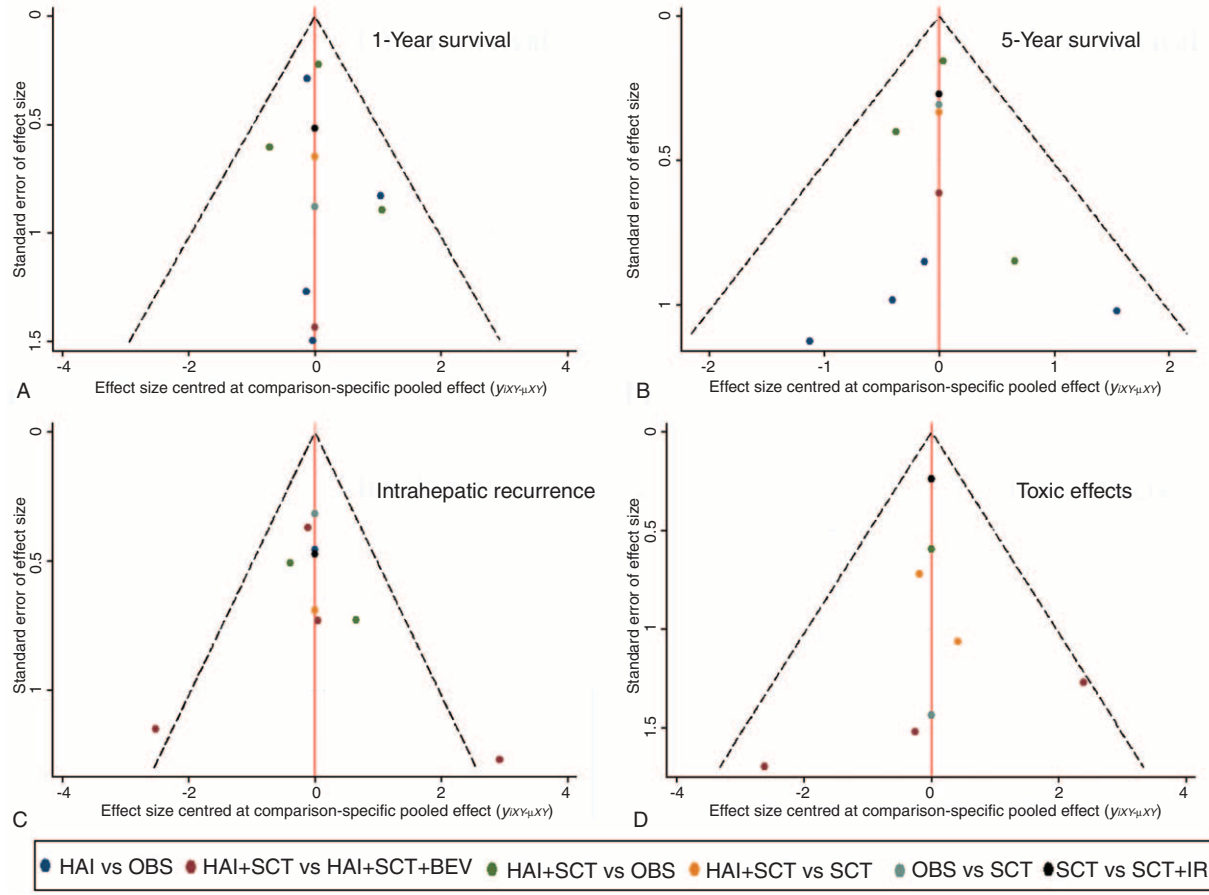

FIGURE 5. Comparison-adjusted funnel plot for the adjuvant treatments network in terms of 1-year, 5-year survival, intrahepatic recurrence, and toxic effects. The red line represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. Different colors correspond to different comparisons. Estimates below 1 indicate that the benefit of the experimental intervention is more pronounced in the trial than the pooled estimate. Observations from small studies missing on the right side of the line of null effect (ratio of rate ratios >1) indicate that small studies tend to exaggerate the effectiveness of experimental treatments. BEV = bevacizumab, HAI = hepatic arterial infusion, IRI = irinotecan, SCT = systemic chemotherapy. A = 1-year survival, B = 5-year survival, C = intrahepatic recurrence, D = toxic effects.

alone (pooled HR 0.743; CI 0.527–1.045; $P = 0.088$), but failed to reach statistical significance. The results of our meta-analysis are consistent with the results from this previous study. Similarly, 1 randomized study of Lopez-Ladron et al,[36] published as abstract, in 2003 reported a trend toward increased overall survival that did not achieve statistical significance although the sample size was small (N = 38). A further traditional meta-analysis by Mitry et al[12] also showed a marginal statistical significance in favor of using of adjuvant SCT after complete resection of colorectal cancer liver or lung metastases. Nevertheless, because of direct comparison between SCT and observations from pairwise meta-analysis, our network meta-analysis incorporates both direct and indirect comparisons of treatment strategies, including those that have never been compared directly. Furthermore, results from traditional meta-analysis in 2012[35] may be inadequate because of studies included evaluating the chemotherapy administered both before and after surgical resection. In addition, adverse events were also evaluated for adjuvant SCT, which was ranked second highest among 6 treatment strategies related to toxicities. Therefore, our results demonstrated that adjuvant SCT may prolong overall patient survival, but may increase adverse events.

There was no further survival benefit and less frequent intrahepatic recurrence with HAI, observations that are consistent with previous studies.[10,27–29] A traditional meta-analysis in 2006[37] reported that ACT delivered by HAI provided less relapse in the remaining liver, but did not yield an overall survival improvement after resection of HMCRC. In this network meta-analysis, adverse events related to an HAI treatment regimen was first evaluated and it ranked the third highest probability in causing adverse events although they appeared to be tolerated by patients. Consistently, from previously analysed studies, only 2 studies[10,29] reported frequent toxicity observed in patients treated with ACT by HAI. In addition, this meta-analysis also indicated that ACT by combination of BEV and HAI plus SCT can prevent intrahepatic recurrence but did not seem to improve survival rate and appeared to have the least favorable adverse event profile in patients after resection of HMCRC. One phase II randomized trial by Kemeny et al[31] in 2011, which was unable to provide definitive results because of its size, but did demonstrate that addition of BEV to adjuvant HAI plus SCT after liver resection appeared not to increase survival but to increase biliary toxicity, which was consistent with our results. Therefore, with the high relapse rate of patients after resection of HMCRC, combination of BEV and HAI plus SCT was effective in preventing intrahepatic relapse but was found to be associated with little benefit in overall survival and highest risk for adverse events in patients.

There are several strengths to consider in our analysis. First, our study is the largest evaluation of different ACTs on efficacy, safety, and tumor recurrence for patients with resected HMCRC to date. Second, our results are consistent with those of previous meta-analysis and extend our knowledge in this field because the network technique allows dissection of the individual drug treatment regimes to evaluate clinical outcomes of interest. This is especially of value as clinicians and scientists are faced with that very few controlled trials that have directly compared competing ACTs. Our application of a network meta-analysis based on the Bayesian model to explore the effect of indirect comparison between multiple treatments,[21,38] fills this gap, which extends our understanding and which may be of direct use for designing treatment regimes with new drug therapies. In addition, in order to reduce concerns regarding potential inconsistencies, we performed an inconsistency diagnostic for all triangular and quadrilateral loops. Furthermore, we analyzed the effects of adverse events to obtain a favorable benefit–risk ratio for resected HMCRC by the major ACTs. Finally, our up-to-date synthesis of existing evidence may provide new insights into controversies on this issue with important implications in clinical care and future research.

Our findings do also have several limitations. First, most trials included in the analysis are not randomized controlled studies and this might affect the validity of overall findings. In addition, we did not investigate the distribution of clinical and methodological variables in detail. This may provide potential sources of either heterogeneity or inconsistency in every comparison specific group of trials, although our pooled estimates were with the random effect mode. Furthermore, the sizes of most studies included in this analysis were small, although our study has established the largest sample size for trials on resected HMCRC. Therefore, this network meta-analysis provides a useful and complete picture of the associations between ACTs by using Bayesian analytical approach.

In general, our study suggested that SCT might be the most efficacious intervention, but should be weighed against associated toxicities. Combination of BEV and HAI plus SCT has effective in preventing intrahepatic relapse but was associated with highest risk for adverse events in patients of resected HMCRC.

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