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Network Meta-Analysis of Hepatic Arterial Infusion Versus Selective Internal Radiation Therapy for Colorectal Cancer Liver Metastasis

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Keywords:

Colorectal cancer liver metastasis; Hepatic Arterial Infusion; Selective Internal Radiation Therapy; Network meta-analysis.

1. Abstract

1.1. Background: Colorectal cancer liver metastases (CRLM) that cannot be surgically removed are often addressed locally with Hepatic Arterial Infusion (HAI) or Selective Internal Radiation Therapy (SIRT). This study used Bayesian network meta-analysis (NMA) to assess the differences in survival between patients treated with HAI or SIRT for CRLM.

1.2. Methods: We searched PubMed, Embase, Scopus, the Web of Science, the Cochrane Library, and ClinicalTrials.gov for articles that met the criteria before October 1, 2022. Overall survival (OS) and progression-free survival (PFS) were analyzed via NMA.

1.3. Results: Twenty-six articles containing 4,394 participants and eight distinct treatments were analyzed. Treatments were subcategorized into standard chemotherapy (SCT), HAI-based (HAI and HAI+SCT group), SIRT-based (SIRT, SIRT+SCT, multi-SIRT, and ^{90}Y-glass SIRT group), and single-agent fluorouracil intravenous chemotherapy/best supportive care (FU/BSC). HAI-based treatments were indirectly compared with SIRT-based therapy. NMA did not reveal statistically significant differences in OS or PFS when comparing patients receiving HAI-based treatments with those receiving SIRT-based treatments. Patients receiving SIRT-based treatments did demonstrate significantly better prognoses than those receiving SCT treatment. In addition, based on the rank probabilities in this analysis, multi-SIRT had the best results in terms of OS (74.27%) while SIRT+SCT ranked first in terms of PFS (95.02%).

1.4. Conclusion: Our NMA results suggest, compared with HAI- and other SIRT-based therapies, multi-SIRT may best improve OS in CRLM patients while SIRT+SCT may best improve PFS.

2. Background

Approximately 60% of colorectal cancer patients eventually develop liver metastases [1,2] and these metastases remain a major obstacle to long-term survival for colorectal cancer patients [3]. For metastatic colon cancer and metastatic rectal cancer, the hazard ratios (HR) for death in patients with versus without liver metastases were 1.32 (95 % CI = 1.28-1.37, P < 0.001) and 1.27 (95 % CI = 1.19-1.36, P < 0.001), respectively [4]. For patients with unresectable colorectal cancer liver metastases, a non-surgical, local approach to treat colorectal liver metastases (CRLM) may provide more clinically utility than systemic treatment alone [2].

Hepatic artery infusion (HAI) therapy has been developed as an attractive treatment strategy to control disease progression in patients with CRLM [5]. The hepatic artery is the main source of blood supply for liver metastases larger than 3 mm in diameter, whereas normal hepatocytes are mainly perfused through the portal circulation. Therefore, infusion of chemotherapeutics via the hepatic artery can help localize drug exposure to the area around the tumor,

thus protecting the normal functioning of unaffected areas of the liver [6].

The Selective Internal Radiation Therapy (SIRT) technique involves embolization of radiolabeled microspheres into the hepatic arterial system. These microspheres contain a radioisotope, yttrium-90, that emits high-energy particles, providing a localized, effective dose of radiation to the tumor without causing intolerable toxicity to the healthy areas of the liver [7, 8]. Non-randomized trials have shown significant activity of SIRT-based therapies against CRLM across a variety of contexts: both alone and in combination with chemotherapy, and both as a first-line treatment or in the context of chemotherapy-refractory disease [9]. To the best of our knowledge, this is the first network meta-analysis (NMA) that aimed to indirectly compare the survival prognosis of patients with CRLM under HAI-based or SIRT-based therapy.

3. Methods

This net-work meta-analysis follows the requirements of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10].

3.1. Search Strategy: We performed a systematic literature search of PubMed, Embase, Scopus, Web of Science, the Cochrane Library, and ClinicalTrials.gov before October 1, 2022. The following MeSH terms and text words were used: "Colorectal Neoplasms"[Mesh], "Colorectal Neoplasm", "Colorectal Tumor", "Colorectal Cancer", "Colorectal Carcinoma", "Neoplasm Metastasis"[Mesh], "Neoplasm Metastases", "Neoplasm Metastasis", "Metastase", "Metastasis", "Hepatic Metastase", "Liver Metastase", "Selective Internal Radiation Therapy", "SIR-Spheres Y-90 resin microspheres", "Internal Radiation", "SIRT", "Infusions, Intra-Arterial"[Mesh], "Intra-Arterial Infusion", "Intraarterial Infusion", "Intra Arterial Infusion", "Regional Arterial Infusion", "Hepatic Arterial Infusion", "HAI", "Survival"[Mesh], "Mortality"[Mesh], "Survival Analysis"[Mesh], "Survival Rate"[Mesh], "Survival", "overall survival", "progression-free survival", "OS", "PFS". The "AND" or "OR" operators are used to combine these terms in different combinations. Two authors independently reviewed the titles and abstracts identified during the search process. Any disagreements could be resolved through discussion or by involving a third evaluator.

3.2. Selection Criteria: We developed the following inclusion criteria in accordance with Population, Intervention, Comparison, Outcomes and Study (PICOS) principles [11].

3.3. Population: Patients with CRLM.

3.4. Intervention/Comparison: Comparison of different treatments for CRLM. 8 protocols were included, namely HAI, HAI+standard chemotherapy (SCT), SIRT, SIRT+SCT, multi-SIRT, ^{90}Y-glass SIRT, SCT, and single agent fluorouracil intravenous chemotherapy/best supportive care (FU/BSC). Notably, since most clinical applications and experimental studies around SIRT are conducted with ^{90}Y-resin SIRT, we use SIRT directly to represent ^{90}Y-resin SIRT for brevity, while ^{90}Y-glass SIRT is specifically denoted as such. Trials were only included if each arm applied only one of the above treatments.

3.5. Outcome: Clinical outcome data need to be extractable so that hazard ratios (HR) and their 95% confidence intervals (CI) could be gathered for overall survival (OS) and progression-free survival (PFS).

3.6. Study Design: Randomized controlled trials (RCTs) or qualified cohort studies.

3.7. Data Extraction: The following contents were extracted: name of first author, year of publication, region, total sample size, treatment regimen, follow-up time, HR with 95% CI of OS and PFS.

3.8. Quality Assessment: Two review authors independently assessed the risk of bias for each study. The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the quality of the cohort studies [12]. A study with NOS > 5 was regarded as a qualified study.

3.9. Statistical Analysis: Microsoft Excel was used for data management, correlation, duplicate removal, and eligibility assessment according to PRISMA guidelines. Bayesian analysis was performed using the Gemtc package and Rjags package in the statistical software "R 4.2.1" to draw network plots, forest plots and rank probability plots. The random-effects model was used for analysis. A total of 300,000 simulated iterations were updated (100,000 per chain). Annealing value was set at 100,000. If the convergence is not satisfied, we will increase the operation time. Contour-enhanced funnel plots after trim-fill analysis were drawn using the Metafor package in the statistical software "R 4.2.1", and the presence of selection bias was detected by Egger linear regression.

4. Results

4.1. Search Results and Study Characteristics: The literature search returned a total of 324 potential articles from the aforementioned databases. After screening, 26 studies met the inclusion criteria [13-24]. (Figure 1) shows the PRISMA 2020 flow diagram for new systematic reviews [25]. As shown in (Table 1), the 26 included cohort studies were published from 1984 to 2021 and involved a total of 4,394 patients with CRLM. Twenty of the studies were in European and American patients, six were in Australian patients, and only two involved Asian patients. Of the 26 studies, 18 provided comparative results for OS only, 1 provided comparative results for PFS only, and 7 provided comparative results for both OS and PFS. The quality assessment is also shown in (Table 1). In general, the studies included in our analysis were of moderate quality (NOS scores greater than 5 for all studies).

Table 1: Descriptive Characteristics of the Included Studies.

Author	Year	Region	Sample size	Intervention	Comparator	Follow-up (months)	OS	PFS	NOS	Selection	Comparability	Exposure
							HR (95% CI)	HR (95% CI)				
Allen[13]	1994	UK	100	HAI	FU/BSC	68	0.63 (0.41, 0.97)	-	7	★★★★	★	★★
Bester[14]	2012	Australia	253	SIRT	FU/BSC	36	0.57 (0.41, 0.82)	-	8	★★★★	★★	★★
Chang[15]	1987	U.S.	64	HAI	SCT	50	0.74 (0.42, 1.28)	-	7	★★★★	★	★★
Fiorentini[18]	2006	Italy	82	HAI+SCT	HAI	20	0.70 (0.55, 0.89)	-	7	★★★★	★	★★
Ghiringhelli[16]	2019	France	27	HAI	FU/BSC	23	0.90 (0.41, 1.97)	0.32 (0.14, 0.76)	8	★★★★	★★	★★
Gray[17]	2001	Australia	70	HAI+SCT	HAI	24	0.71 (0.43, 1.16)	-	7	★★★★	★	★★
Hafstrom[19]	1994	Sweden	60	HAI	FU/BSC	37	0.39 (0.19, 0.79)	-	7	★★★★	★	★★
Hendlisz[20]	2010	Belgium	44	SIRT+SCT	FU/BSC	26	0.92 (0.47, 1.78)	0.51 (0.28, 0.94)	8	★★★★	★★	★★
Hine[21]	1984	UK	52	SCT	FU/BSC	61	0.96 (0.25, 3.78)	-	7	★★★★	★	★★
Hohn[22]	1989	U.S.	143	HAI	SCT	53	0.97 (0.68, 1.40)	-	7	★★★★	★	★★
Kazim[27]	2016	U.S.	606	Multi-SIRT	SIRT	40	0.85 (0.75, 0.97)	-	8	★★★★	★★	★★
Kemeny[23]	1987	U.S.	99	HAI	SCT	36	0.83 (0.55, 1.26)	-	7	★★★★	★	★★
Kemeny[24]	2006	U.S.	135	HAI	SCT	72	0.56 (0.38, 0.82)	-	7	★★★★	★	★★
Kerr[28]	2003	UK	290	HAI	FU/BSC	48	1.03 (0.80, 1.33)	0.87 (0.68, 1.11)	7	★★★★	★	★★
Lorenz[29]	2000	Germany	114	HAI	FU/BSC	56	1.15 (0.81, 1.63)	-	7	★★★★	★	★★
Martin[30]	1990	U.S.	69	HAI	FU/BSC	36	0.86 (0.53, 1.39)	0.88 (0.49, 1.58)	7	★★★★	★	★★
Mary[31]	2021	North America, Europe, Asia	428	SIRT+SCT	SCT	44	0.96 (0.74, 1.24)	0.69 (0.54, 0.88)	8	★★★★	★★	★★
NGTATG[32]	1992	Sweden	182	SCT	FU/BSC	36	0.63 (0.44, 0.89)	0.51 (0.37, 0.71)	7	★★★★	★	★★
Rougier[33]	1992	France	163	HAI	FU/BSC	36	0.66 (0.47, 0.92)	-	7	★★★★	★	★★
Scheithauer[34]	1993	Austria	36	SCT	FU/BSC	37	0.39 (0.14, 1.15)	-	7	★★★★	★	★★
Seidensticker[35]	2012	Australia	58	SIRT	FU/BSC	16	0.30 (0.16, 0.55)	-	8	★★★★	★★	★★
Shyam[36]	2016	U.S.	28	^{90}Y-glass SIRT	SIRT	35	4.00 (1.30, 12.30)	-	8	★★★★	★★	★★
Van Hazel[37]	2004	Australia	21	SIRT+SCT	FU/BSC	36	0.39 (0.14, 1.13)	-	7	★★★★	★	★★
Van Hazel[38]	2016	Australia	126	SIRT+SCT	SCT	60	-	0.69 (0.55, 0.90)	8	★★★★	★★	★★
Wagman[39]	1990	U.S.	41	HAI+SCT	HAI	75	1.19 (0.68, 2.07)	-	7	★★★★	★	★★
Wasan(1)[40]	2017	Australia, North America, Europe, Asia	364	SIRT+SCT	SCT	60	1.04 (0.83, 1.31)	0.87 (0.69, 1.09)	8	★★★★	★★	★★
Wasan(2)[40]	2017		530	SIRT+SCT	SCT	60	1.06 (0.87, 1.28)	0.97 (0.81, 1.17)	8	★★★★	★★	★★
Wasan(3)[40]	2017		209	SIRT+SCT	SCT	60	0.95 (0.67, 1.36)	0.79 (0.59, 1.02)	8	★★★★	★★	★★

Note: HAI, Hepatic artery infusion; SIRT, 90Y-resin Selective Internal Radiation Therapy; 90Y-glass SIRT, 90Y-glass Selective Internal Radiation Therapy; SCT, standard chemotherapy; FU/BSC, single agent fluorouracil intravenous chemotherapy/best supportive care; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

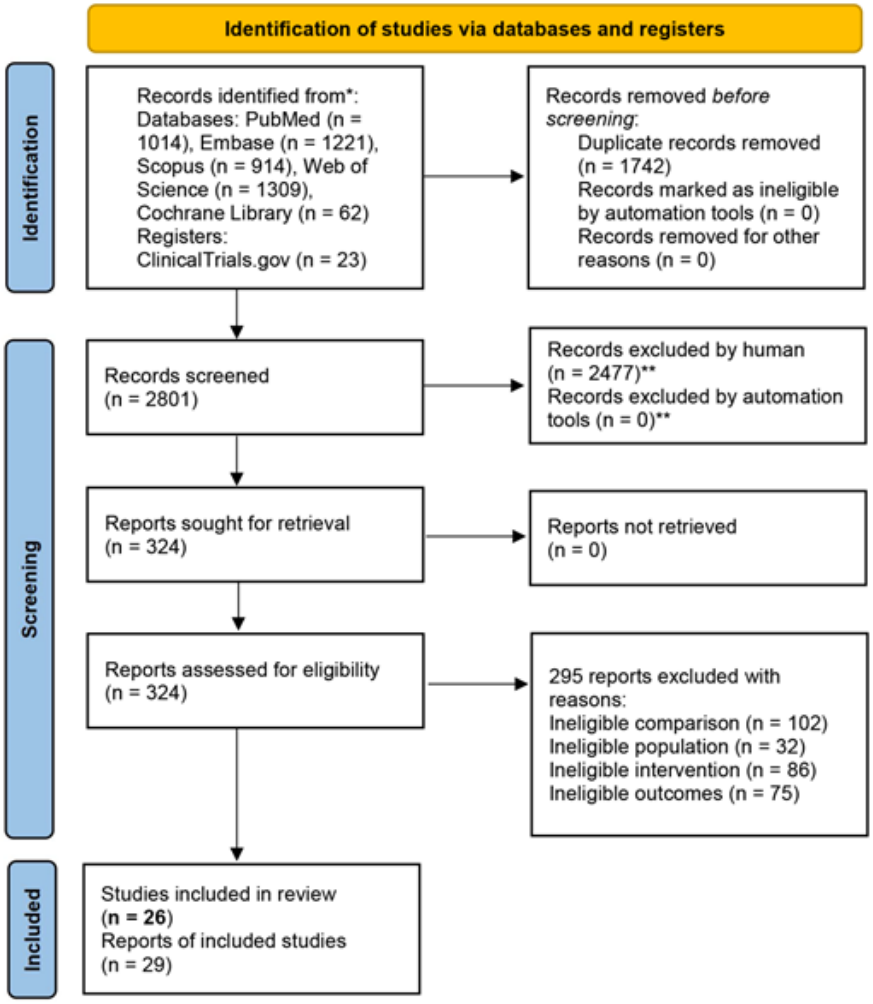

Figure 1: Flow chart of study selection

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

4.2. NMA: The network structure is illustrated in (Figure 2), reflecting the relationships between the different treatment options. The number of comparisons between two treatments is represented by the thickness of the line connecting them, while the number of patients who received a given treatment is represented by the diameter of the circle itself.

(Figures 3 and 4) provide forest plots of OS and PFS when different treatments are used as references, and the HRs and their corresponding 95% CIs are summarized in (Figure 5).

Rank probabilities for the role of each treatment regimen in OS and PFS prognosis are shown in (Figure 6). We will present these results in terms of both OS and PFS, respectively.

4.3. OS: The results of the NMA in the OS section were generated from 25 studies with a total of 4,268 participants, including 8 treatment regimens (HAI, HAI+SCT, SIRT, SIRT+SCT, multi-SIRT, ^{90}Y-glass SIRT, SCT, and FU/BSC). The reticulation between the different regimens is shown in (Figure 2A), the forest plot of OS when different treatments were used as reference is shown in (Figure 3), and the efficacy of different treatment modalities on HRs and corresponding 95% CIs is shown in (Figure 5A).

For OS, multi-SIRT therapy and SIRT therapy performed better than HAI-based therapies (HR =0.53, 95% CI: 0.27-1.00; HR=0.62, 95% CI: 0.38-1.00, respectively), although only with marginal significance. Importantly, this gap disappeared when HAI was combined with SCT (HR =0.67, 95% CI: 0.31-1.40; HR=0.79, 95% CI: 0.43-1.40, respectively). Based on the results of the rankograms shown in (Figure 6A), the treatment regimens from most to least favorable for OS were multi-SIRT, SIRT, HAI+SCT, HAI, SCT, SIRT+SCT, FU/BSC, and ^{90}Y-glass SIRT.

4.4. PFS: The results of the NMA in the PFS section were generated from 8 studies with a total of 2,269 participants, including 4 treatment regimens (HAI, SIRT+SCT, SCT, and FU/BSC). The reticulation between the different regimens is shown in (Figure 2B), the forest plot of PFS when different treatments were used as reference is shown in (Figure 4), and the efficacy of different treatment modalities on HRs and corresponding 95% CIs is shown in (Figure 5B).

SIRT+SCT therapy appeared to have a favorable, albeit not significant, effect on PFS compared to HAI therapy (HR =0.57, 95% CI: 0.34-1.10). HAI therapy did not show a benefit on PFS compared to SCT and FU/BSC therapy (HR =1.40, 95% CI: 0.78-2.40; HR=0.78, 95% CI: 0.52-1.10, respectively), but SIRT+SCT therapy had a more pronounced effect on PFS compared to SCT and FU/BSC therapy (HR =0.81, 95% CI: 0.66-0.99; HR=0.44, 95% CI: 0.29-0.69, respectively). Based on the results of the rankograms in (Figure 6B), the treatment regimens from most to least favorable for PFS were SIRT+SCT, SCT, HAI, and FU/BSC.

4.5. Publication Bias: Contour-enhanced funnel plots after trim-fill analysis are shown in (Figure 7).

For OS, the funnel plot showed good symmetry, and the Egger linear regression test indicated no publication bias (z = 1.30, p = 0.19). After Trim and Fill, it showed that the two studies requiring additions were distributed in statistically insignificant areas (dotted circles in the (Figure 7A), indicating that perhaps there were statistically insignificant studies that were not published and that there was possible publication bias in the OS correlation analysis.

For PFS, the funnel plot

ad good symmetry, and the Egger linear regression test indicated no publication bias (z = 0.41, p = 0.68). As shown in (Figure 7B), after Trim and Fill, no additional studies needed to be added, indicating no publication bias in the PFS-related analyses [26-39].

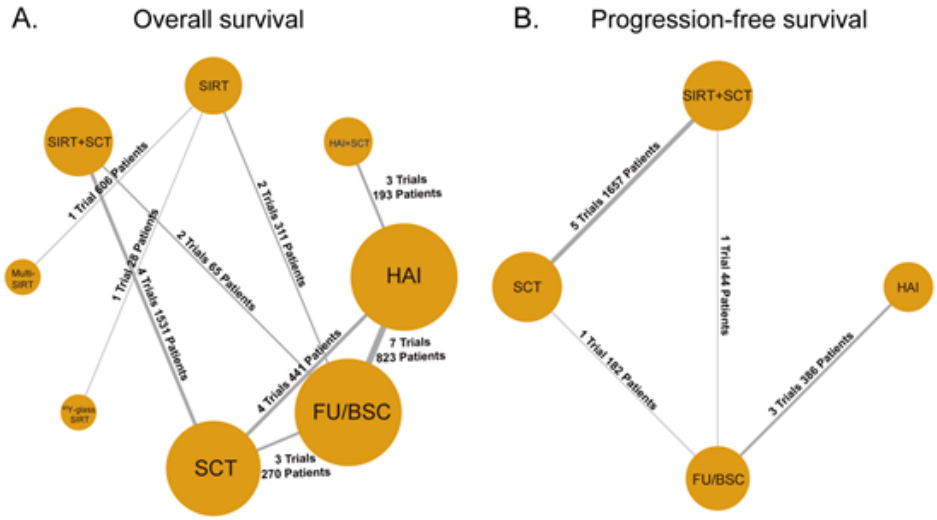

Figure 2: Summary of Network Geometry of OS(A) and PFS(B). The size of the circle indicates the number of participants per treatment. The width of the line indicates the number of direct comparisons between the two treatments.

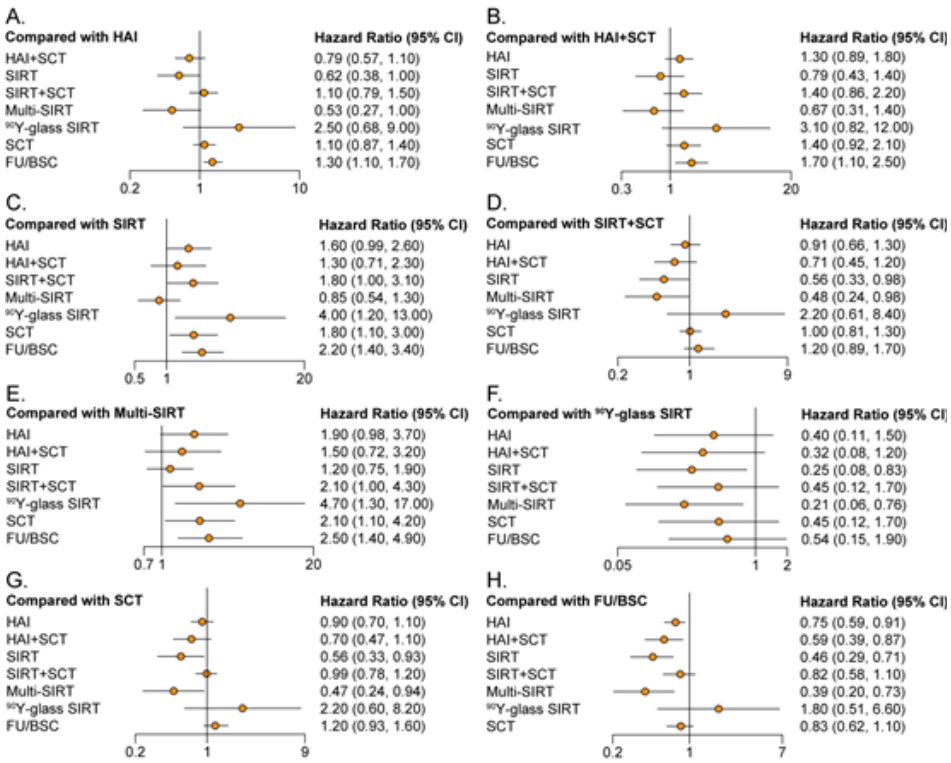

Figure 3: Forest Plots of OS compared with HAI(A), HAI+SCT(B), SIRT(C), SIRT+SCT(D), Multi-SIRT(E), ^{90}Y-glass SIRT(F), SCT(G), and FU/BSC(H).

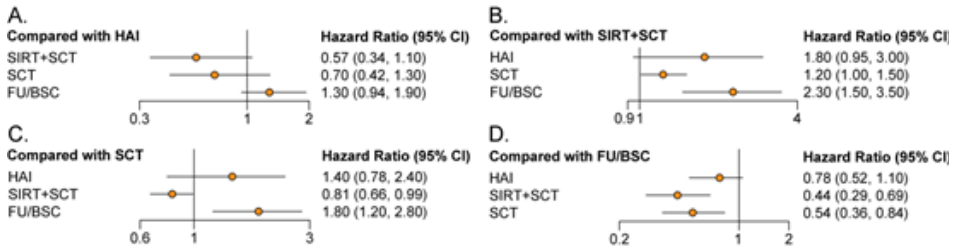

Figure 4: Forest Plots of PFS compared with HAI(A), SIRT+SCT(B), SCT(C), and FU/BSC(D).

A.

HAI							
1.30 (0.89, 1.80)	HAI+SCT						
1.60 (0.99, 2.60)	1.30 (0.71, 2.30)	SIRT					
0.91 (0.66, 1.30)	0.71 (0.45, 1.20)	**0.56 (0.33, 0.98)**	SIRT+SCT				
1.90 (0.98, 3.70)	1.50 (0.72, 3.20)	1.20 (0.75, 1.90)	2.10 (1.00, 4.30)	Multi-SIRT			
0.40 (0.11, 1.50)	0.32 (0.08, 1.20)	**0.25 (0.08, 0.83)**	0.45 (0.12, 1.70)	**0.21 (0.06, 0.76)**	^{90}Y-glass SIRT		
0.90 (0.70, 1.10)	0.70 (0.47, 1.10)	**0.56 (0.33, 0.93)**	0.99 (0.78, 1.20)	**0.47 (0.24, 0.94)**	2.20 (0.60, 8.20)	SCT	
0.75 (0.59, 0.91)	**0.59 (0.39, 0.87)**	**0.46 (0.29, 0.71)**	0.82 (0.58, 1.10)	**0.39 (0.20, 0.73)**	1.80 (0.51, 6.60)	0.83 (0.62, 1.10)	FU/BSC

B.

HAI			
1.80 (0.95, 3.00)	SIRT+SCT		
1.40 (0.78, 2.40)	**0.81 (0.66, 0.99)**	SCT	
0.78 (0.52, 1.10)	**0.44 (0.29, 0.69)**	**0.54 (0.36, 0.84)**	FU/BSC

Figure 5: HRs and corresponding 95% CIs for OS(A) and PFS(B). Results with statistical significance are bold.

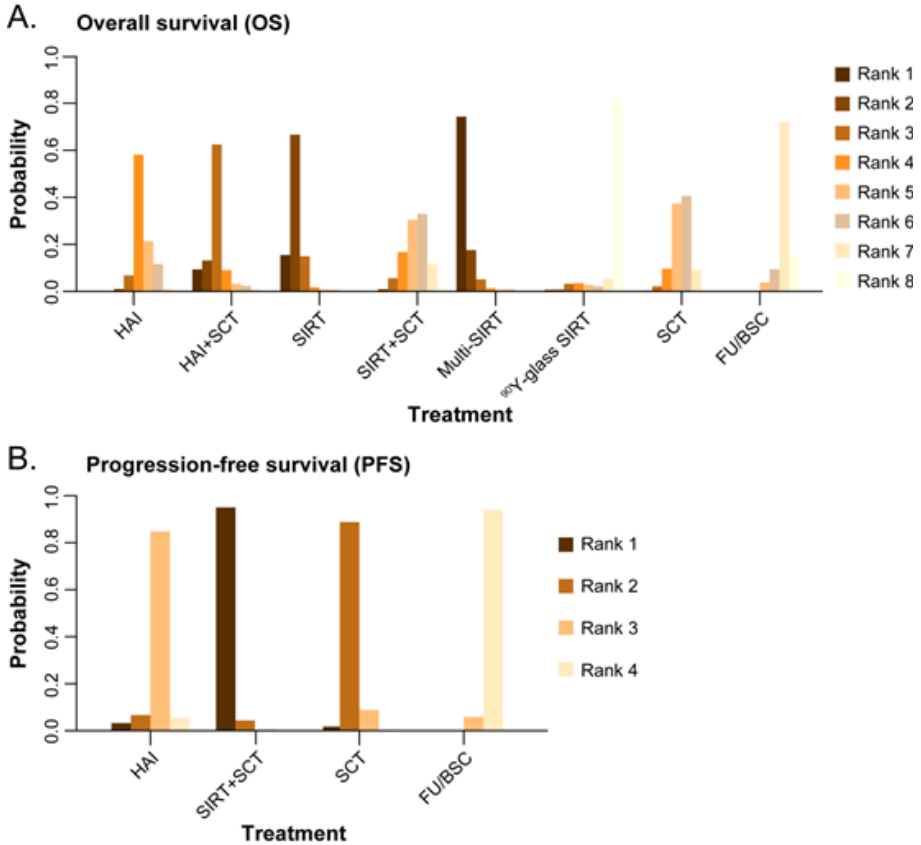

Figure 6: Rankograms for OS(A) and PFS(B). The figure shows the probability of each treatment from best to worst. The heights of the columns "Rank 1, Rank 2, etc." refer to the probability of each rank.

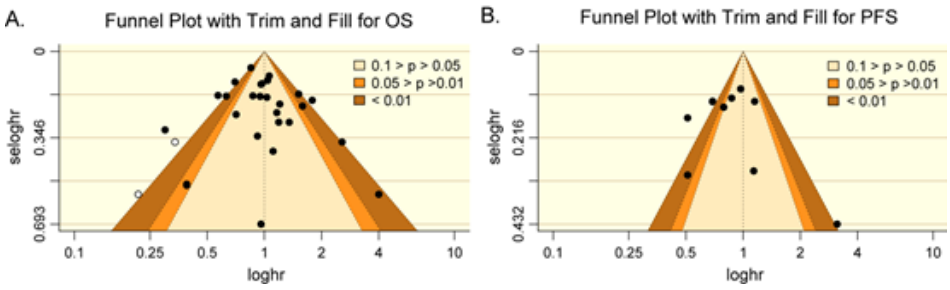

Figure 7: Funnel plots with Trim and Fill for OS(A) and PFS(B).

5. Discussion

This NMA was performed to compare which HAI-based or SIRT-based therapies have a more favorable survival prognosis for patients with CRLM. Based on the rank probabilities, multi-SIRT exhibited the most favorable results for OS (74.27%) while SIRT+SCT ranked first for PFS (95.02%). For OS, multi-SIRT therapy and SIRT therapy have better results than HAI therapy; however, this prognostic advantage disappeared in HAI combined with SCT, implying an adjuvant effect of SCT on HAI. At the same time, SIRT alone was more beneficial to OS than SIRT+SCT, implying an inverse effect of SCT on SIRT. The diametrically opposed role of SCT on HAI- and SIRT-based therapies warrants investigation. Possible explanations are that both HAI and SCT are essentially chemotherapies, with the combination enhancing the tumor-killing effect to a greater degree than it enhances the chemotherapy-related toxicity resulting from the combination. Conversely, SIRT can be classified as an internal radiation therapy, and, thus, the side effects of the combination might actually lower OS. For PFS, the SIRT+SCT model had greater benefits and was significantly more favorable than the HAI- and SCT-based regimes, and HAI treatment was even inferior to SCT treatment in the rankogram ranking. Although SIRT+SCT has limited effect on OS, its prognostic benefit on PFS is obvious, perhaps due to its obvious tumor-killing effect. As described in the introduction, HAI has evolved as an attractive strategy to expand resectability and/or control disease progression in patients with CRLM who have liver-dominant disease. HAI is usually administered through the gastroduodenal artery via surgically implanted pumps, hepatic artery ports, or percutaneously placed catheters connected to external pumps6. Intra-arterial administration of high-channel liver-extracting drugs (e.g., fluorouracil [FUDR]) limits their systemic toxic effects and allows concurrent administration of near-full-dose systemic chemotherapy [40-42]. The most common adverse event with hepatic arterial infusion of FUDR is biliary sclerosis, which can be mitigated by pump administration of dexamethasone or adjustments [43]. Thus, HAI therapy alone or HAI+SCT both have a relatively high safety profile.

In palliative care for metastatic cancer, treatment toxicity and impact on quality of life are important endpoints. In 2002, Gray et al. conducted a trial of 74 patients, ultimately gaining FDA approval for SIR-Spheres for the treatment of colorectal cancer secondary to liver metastases [17]. In studies by Van Hazel et al. in 2004 and 2016, the addition of SIRT to systemic chemotherapy did increase hematologic toxicity as well as SIRT-related side effects such as nausea, vomiting, abdominal pain, radiation hepatitis, and liver failure [36, 37]. The impact of late radiation effects associated with SIRT - such as liver fibrosis - on survival is uncertain45. Only two phase II studies and three observational studies have reported the incidence of delayed toxicity rates, which range from 4-10% [44-46]. The most common delayed toxic reactions were gastrointestinal ulcers and liver dysfunction46, with liver dysfunction mainly secondary to grade 3 or 4 radiation therapy-induced biliary strictures [46]. Therefore, the effect of addition of SCT to SIRT on OS in this study may be attributable to toxic effects.

There are several limitations of the NMA. First, only survival-related data were analyzed in this NMA, while data on adverse effects - albeit inextricably linked to survival time - were not examined due to underreporting. Second, although we had acceptable results for the funnel plot and Egger test, we found evidence for publication bias in the meta-analysis for OS by the cut-and-patch method, which may have some degree of impact on the robustness of the results. Third, the studies included in this web-based meta-analysis mainly included European, American, and Australian patients, and the applicability of the findings to Asian patients necessitates further validation with additional clinical studies.

11. Conclusion

This NMA sought to indirectly compare the survival prognosis of patients with CRLM under HAI-based and SIRT-based therapy. For OS and PFS, multi-SIRT and SIRT+SCT, respectively, may be the best treatment options.

12. Acknowledgement

Not applicable.

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