

Intra-arterial therapy for unresectable colorectal liver metastases

A patient-level meta-analysis of 70 prospective & 21 randomized studies comprising 6,655 patients.

Joseph Zhao¹, Eelin Tan², Rehena Sultana³, David Lim⁴, David Tai⁵, Too Chow Wei²

- ¹ Yong Loo Lin School of Medicine, National University of Singapore, Singapore
- ² Division of Vascular & Interventional Radiology, Singapore General Hospital, Singapore
- ³ Centre for Quantitative Medicine, Duke-NUS Graduate Medical School, Singapore
- ⁴ Diagnostic and Interventional Radiology, Changi General Hospital, Singapore
- ⁵ Division of Medical Oncology, Singapore General Hospital, Singapore



Yong Loo Lin School of Medicine



Background & Objectives

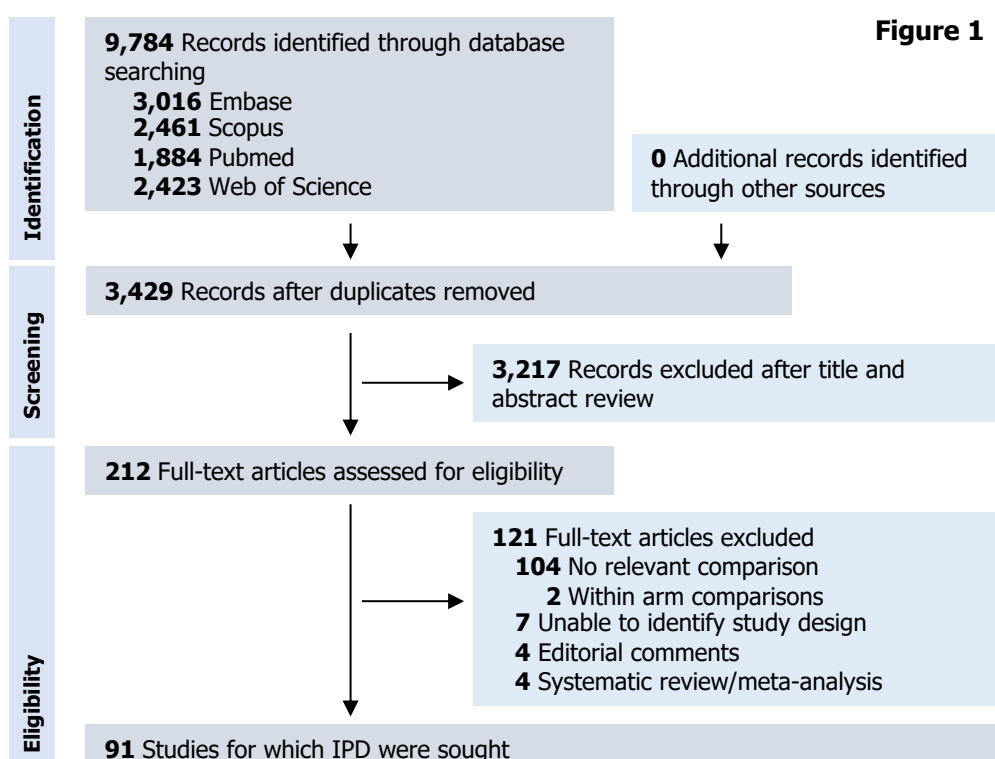
Annually, metastatic disease affects about 40–50% of the more than one million patients diagnosed with colorectal cancer (CRC) worldwide [1]. Once metastasis to the liver has occurred, 5-year survival drastically drops from 64.3% to 11.7% [1]. While outcomes have improved for the 15–20% of patients with upfront resectable metastases [2, 3], the outlook remains grim for patients with initially unresectable metastases [4].

Here, we sought to evaluate the efficacy intra-arterial approaches and their combinations with systemic chemo/immuno-therapy (SCT) for unresectable colorectal liver metastases.

Search Strategy

Date range of search: From inception to 20th June 2020, **Search keywords:** "unresectable", "non-resectable", "nonresectable", "inoperable", "colorectal", "liver", "hepatic", **Inclusion criteria:** Randomized or prospective HAI/cTACE/DEBIRI/TARE/ TAE studies including with outcomes pertaining to survival, response or conversion to resection rates, **Exclusion criteria:** Retrospective studies (in view that multiple treatment modalities may be adopted in longitudinal cohorts- and may or may not be declared - which may further increase heterogeneity) OR Combination approaches consisting multiple IATs

PRISMA Flowchart



Overall Survival – One-Stage Meta-Analysis

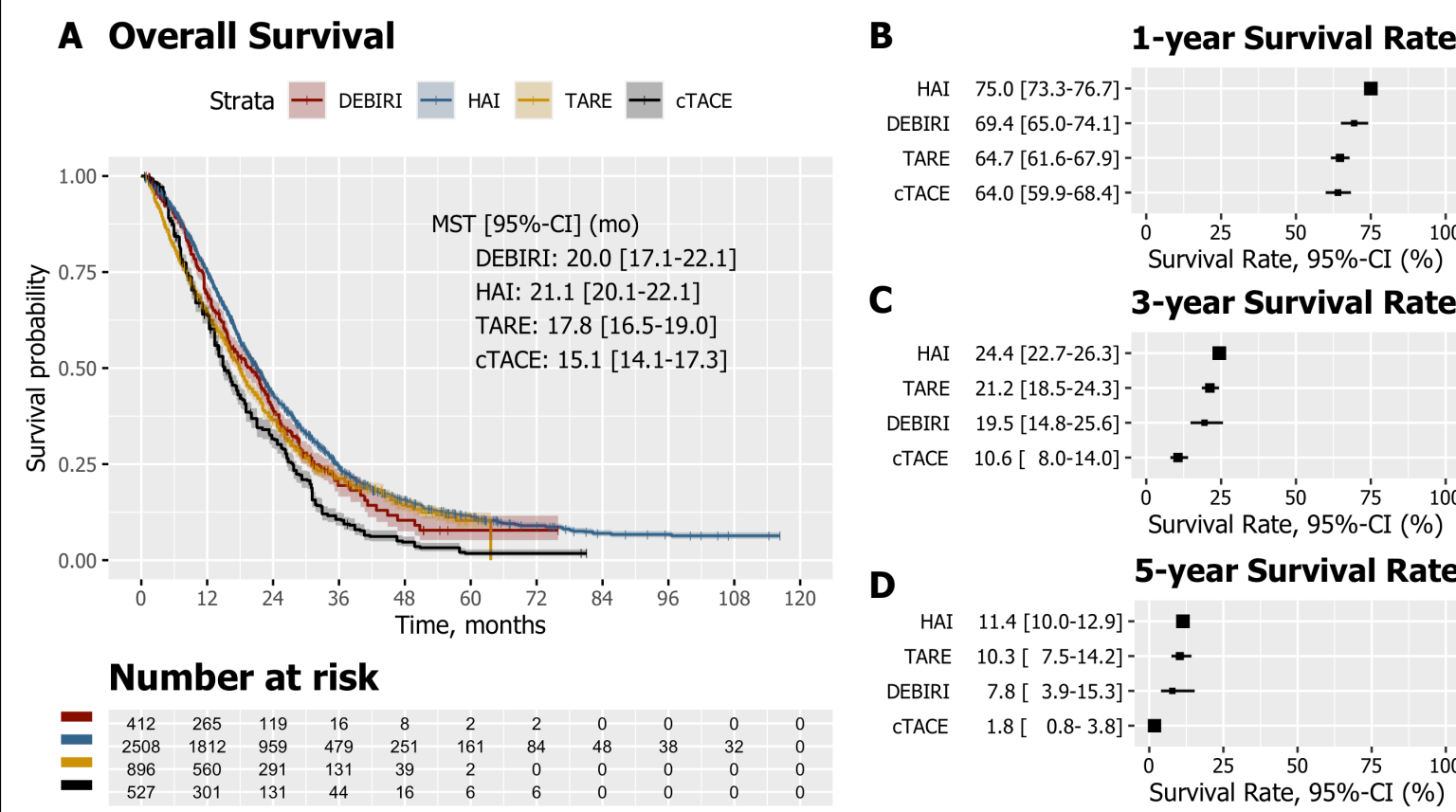


Figure 2 (N=63, n=4,343)

N, number of studies; n, number of patients; CI, confidence interval; MST, median survival time; mo, months.

Treatment arms are inclusive of IAT only or IAT-SCT combinations

Methodology: Survival data of patients were recovered from original Kaplan-Meier curves by exploiting graphical reconstructive algorithms [5].

Response & Conversion Rates – Two-Stage Meta-Analysis

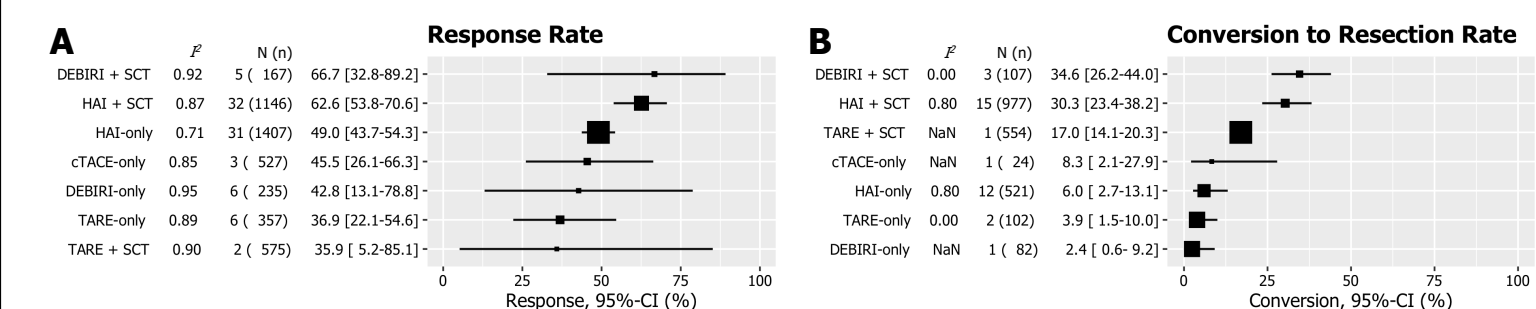


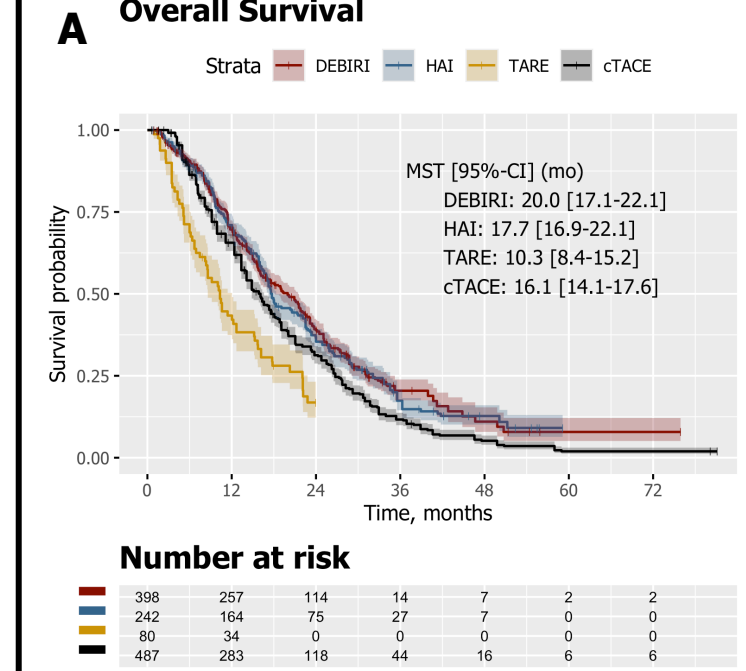
Figure 3A (N=78, n=4,309); Figure 3B (N=33, n=2,303)

N, number of studies; n, number of patients; CI, confidence interval; NaN, not applicable – meta-analysis not conducted; RR, response rate; CRR, conversion to resection; IPD, individual patient data

Methodology: Meta-Analysis of proportions was conducted using 'metaprop' command in R Studio. Random-effects model was opted for analyses in view of the significant clinical heterogeneity in patient selection.

Patients Treated Beyond 1st Line & NMA of RCTs only

One-Stage Meta-Analysis of Patients Treated Beyond 1st Line



Two-Stage Component Network Meta-Analysis of RCTs

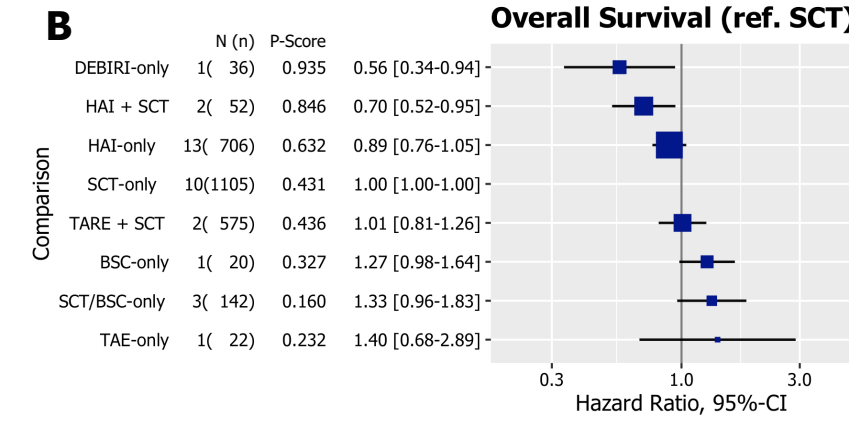


Figure 4A (N=20, n=1,207), Figure 4B (N=16, n=2,715, I²=25.4%, Q=13.4, Q_{diff}=0.05, P of Q_{diff}>0.05)

N, number of studies; n, number of patients; CI, confidence interval; TAE, trans-arterial embolisation; BSC, best supportive care; N, number of studies; n, number of patients; CI, confidence interval; MST, median survival time; mo, months.

Methodology: A network meta-analysis was conducted for randomized trials within a random-effects frequentist setting with the 'netmeta' package in R Studio. Owing to the complexity of treatment modalities, we incorporated an additive model to appreciate the individual effects of each arm.

IAT + SCT vs IAT-only

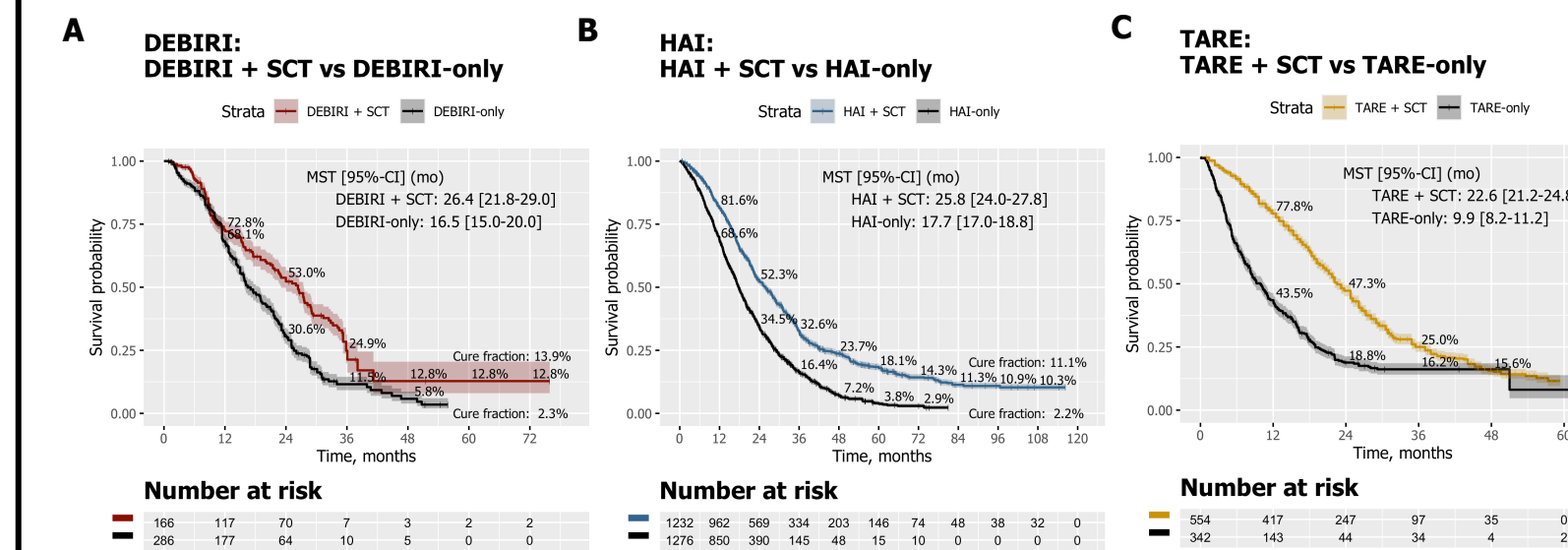


Figure 5A DEBIRI; Figure 5B HAI; Figure 5C TARE

N, number of studies; n, number of patients; CI, confidence interval; NR, not reached; MST, median survival time; mo, months.

Methodology: Survival data of patients were recovered from original Kaplan-Meier curves by exploiting graphical reconstructive algorithms [5]. One-stage meta-analysis of IAT-SCT vs IAT-only was repeated for patients treated beyond first line, demonstrating analogous results for HAI & DEBIRI (not shown here). To account for the subset of patients who no longer contribute to excess hazard (as observed by long plateaus), we fitted Weibull mixture or flexible parametric cure models and estimated the cure fraction using an identity link.

Discussion & Conclusion

While heterogeneity & paucity of available evidence forestalled any definitive consensus, the overall evidence suggests that DEBIRI or HAI may have a slight survival advantage against other IAT approaches. [Figure 2,3] Modelled cure fractions (13.9% vs 11.1%), response rates (66.7% vs 62.6%) and conversion to resection rates (34.6% vs 30.3%) in DEBIRI + SCT were slightly higher compared to HAI + SCT. [Figure 3, 5] Likewise, a subgroup component network meta-analysis demonstrates that patients treated with DEBIRI-only (HR=0.56, P-Score=0.94, 1st) and HAI + SCT (HR=0.71, P-Score=0.85, 2nd) were associated with longer survival when compared to SCT-only. [Figure 4B] Results were consistent amongst patients treated beyond 1st line. [Figure 4A]

In view of significant heterogeneity, these results should be interpreted as exploratory & to guide future trials. Randomized trials between combination IAT + SCT (preferably DEBIRI or HAI) against SCT-only are warranted to better elucidate the survival advantage, if any, of concurrent use of IAT.

References

- [1] R. L. Siegel *et al.*, "Colorectal cancer statistics, 2017," (in eng), *CA Cancer J Clin*, vol. 67, no. 3, pp. 177-193, May 6 2017, doi: 10.3322/caac.21395.
- [2] S. Kopetz *et al.*, "Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy," (in eng), *J Clin Oncol*, vol. 27, no. 22, pp. 3677-83, Aug 1 2009, doi: 10.1200/jco.2008.20.5278.
- [3] H. Bismuth *et al.*, "Resection of Nonresectable Liver Metastases from Colorectal Cancer After Neoadjuvant Chemotherapy," *Annals of Surgery*, vol. 224, no. 4, 1996. [Online]. Available: https://journals.lww.com/annalsurgery/Fulltext/1996/10000/Resection_of_Nonresectable_Liver_Metastases_from.9.aspx.
- [4] R. Adam *et al.*, "Patients With Initially Unresectable Colorectal Liver Metastases: Is There a Possibility of Cure?," *Journal of Clinical Oncology*, vol. 27, no. 11, pp. 1829-1835, 2009/04/10 2009, doi: 10.1200/JCO.2008.19.9273.
- [5] P. Guyot, A. E. Ades, M. J. N. M. Ouwens, and N. J. Welton, "Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves," *BMC Medical Research Methodology*, vol. 12, no. 1, p. 9, 2012/02/01 2012, doi: 10.1186/1471-2288-12-9.

Acknowledgements: Dr Gerta Rucker, Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany – for clarifying our queries on the usage of component network meta-analyses. Prof Thomas Debray, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands – for clarifying our queries on the synthesis of individual patient data from randomized and non-randomized studies.

Financial disclosure: J.Z. is supported by the SingHealth SMSTDA Talent Development Award administered by SingHealth, Singapore and NUS Enterprise Innovation & Entrepreneurship Practicum Award awarded by National University of Singapore, Singapore.