Intra-arterial therapy for unresectable colorectal liver metastases

*A patient-level meta-analysis of 71 prospective & 21 randomized studies comprising 6,655 patients.*

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Background & Objectives

Background

- 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].

- Compared to systemic therapy, intra-arterial therapy achieves a marked increase in the local concentration of chemotherapy/brachytherapy by direct selective/superselection injection into the hepatic arterial system [5]. This, together with a relatively slower rate of clearance of the localized region (liver), creates a concentration differential in favour of the local compartment harbouring the cancer [6].

- Presently, several randomized and non-randomized studies on IAT regimens have yielded conflicting consensus, while prior meta-analyses conducted have had incongruent conclusions [7-10]. Lamentably, their pairwise and heterogenous nature precluded any collective consensus with the manifold approaches & combinations available today.

Objectives

To evaluate the comparative efficacy of intra-arterial therapy (IAT) including:
1. Hepatic arterial infusion (HAI)
2. Conventional trans-arterial chemoembolization (cTACE)
3. Irinotecan-loaded drug-eluting beads (DEBIRI)
4. Trans-arterial radioembolization (TARE)
& their combinations with systemic chemo/immuno-therapy (SCT)
**PRISMA & Search Strategy**

**Date range of search:** From inception to 20th June 2020

**Search keywords:** “unresectable”, “non-resectable”, “nonresectable”, “inoperable”, “colorectal”, “liver”, “hepatic”

**Inclusion criteria**
1. Randomized or prospective HAI/cTACE/DEBIRI/TARE/TAE studies including with outcomes pertaining to survival, response or conversion to resection rates

**Exclusion criteria**
1. 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)
2. Combination approaches consisting multiple IATs

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**Figure 1 PRISMA Flowchart**

- N, number of studies; n, number of patients; IPD, individual patient data
91 Studies for which IPD were sought
   21 RCTs
   70 Prospective studies

63 Studies with IPD reconstructed from published Kaplan-Meier curves
   Overall survival: N=63, n=4,343
0 Studies provided IPD data

Studies with aggregate data were available for the following outcomes
   Response rate: N=78, n=4,309
   Conversion to resection: N=33, n=2,303

One-stage Meta-Analysis
   Overall survival
   1-, 3-, 5-year survival rates
   Patients treated beyond 1st line
   IAT + SCT vs IAT-only

Two-stage Meta-Analysis
   Response rate
   Conversion to resection
   Two-Stage Component Network Meta-Analysis

Statistical Methodology
- Where amenable, survival data of patients were recovered from original Kaplan-Meier curves by exploiting graphical reconstructive algorithms [11].
- One-stage meta-analyses were conducted for median survival time (MST) and survival rates (SR) while two-stage meta-analyses of proportions were conducted to determine response rates (RR) and conversion to resection rates (CRR).
- A subgroup frequentist component network meta-analysis was conducted for randomized trials.

Figure 1 PRISMA Flowchart (cont')
N, number of studies; n, number of patients; IPD, individual patient data
Methodology: Survival data of patients were recovered from original Kaplan-Meier curves by exploiting graphical reconstructive algorithms.
Response & Conversion Rates
Two-Stage Meta-Analysis

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.
Subgroup Analysis

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

Two-Stage Component Network Meta-Analysis of RCTs

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.

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

N, number of studies; n, number of patients; CI, confidence interval; TAE, trans-arterial embolisation; BSC, best supportive care; MST, median survival time; mo, months.
Subgroup Analysis
One-Stage Meta-Analysis of IAT-SCT vs IAT-only

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

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.
Which IAT approach is the best?

- 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]
Summary & Significance of Results

Should SCT be administered concurrently with IAT?

- Combination approaches appeared to have longer survival compared to IAT-only [Figure 5]. Results were consistent amongst patients treated beyond 1st line.
  - Plausible mechanisms for survival difference: In keeping with the Norton-Simon hypothesis [12] – Intra-arterial delivery of agents with high first-pass hepatic extraction may limit systemic toxicity, thereby enabling concurrent administration of systemic chemotherapy at optimal dosage intensities for tumour eradication [12-15].

Looking forward

- 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.
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