# Hepatic Arterial Infusion for Unresectable Colorectal Liver Metastases Combined or Not with Systemic Chemotherapy

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**Abstract.** *Background: The hypothesis was tested that systemic chemotherapy might contribute to improving overall survival (OS) of patients with unresectable colorectal liver metastases treated with hepatic arterial infusion (HAI). Patients and Methods: We considered 153 consecutive patients retrospectively divided into group A (n=72) treated with HAI alone (floxuridine [FUDR] + leucovorin [LV]), and group B (n=81) treated with HAI combined with systemic chemotherapy (5-fluorouracil [5FU] + LV). Results: No significant difference in OS was observed between the two groups. Median OS was better in patients with <50% of liver involvement (21.3 vs. 13.2 months; p<0.0001) and in responders vs. non-responders (24.4 vs. 13.4 months; p<0.0001). The combination of low tumor load with good tumor response to HAI was the only variable retained on multivariate survival analysis, associated with a better clinical outcome (median OS: 34.2 months). Conclusion: Our study does not support the use of FUDR-based HAI combined or not with 5FU-based systemic chemotherapy as the first-line therapeutic approach to unresectable colorectal cancer liver metastases. The identification of responsive patients would improve the therapeutic index of this HAI regimen.*

Colorectal cancer (CRC) is the fourth most commonly diagnosed cancer and the second leading cause of cancer death in Western countries (1). Nearly 50% of CRC patients will develop liver metastases during the course of their disease, with half having hepatic metastases at the time of primary diagnosis and another half developing metachronous disease (2). Furthermore, over 50% of patients who die of CRC have liver metastases at autopsy, and the majority of these patients die as a result of their metastatic disease.

Surgical resection represents the standard treatment of resectable disease and is followed by 5-year overall survival (OS) rates of 20% to 40% (2, 3). Unfortunately, only 20% of patients with liver metastases from CRC present with liver-confined resectable disease and/or are candidates for major surgical operation (depending on comorbidities) (4, 5).

The therapeutic management of unresectable metastases is more controversial and is generally associated with a dismal prognosis. In fact, despite the improvements achieved with modern systemic chemotherapy (SCT) regimens (e.g. those combining 5-fluorouracil (5FU) with irinotecan, oxaliplatin and, lately, biological agents (6)), the median OS of these patients does not exceed 18-20 months, with a 5-year OS rate being very close to 0% (*i.e.* there are virtually no long-term survivors) (7, 8).

The unique differential blood supply of the liver (portal vein → healthy parenchyma; hepatic artery → metastatic disease) represents the rationale of a locoregional treatment such as hepatic arterial infusion (HAI) chemotherapy for patients with unresectable hepatic metastates from CRC (9). Floxuridine (FUDR, a pyrimidine antimetabolite transformed to 5FU in the liver) is the preferred agent for HAI owing to its short half-life and high rate (>90%) of hepatic extraction (a major advantage over 5-FU whose extraction rate is <50%) leading to a 100- to 400-fold ratio of hepatic-to-systemic drug exposure.

Despite this strong rationale, only 40-50% of patients show a clinically meaningful tumor response, which is similar to the results following modern SCT. More importantly, there is a lack of evidence of HAI efficacy in terms of overall survival (10-12). Clearly, HAI alone cannot guarantee therapeutic activity against clinically occult extrahepatic disease, which can only be treated by administering anticancer agents through the systemic route. Moreover, current eligibility criteria are likely to include patients who will not respond to HAI due to overwhelming tumor burden and/or intrinsic chemoresistance of their disease. The identification of patients who most

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benefit from FUDR-based HAI might increase the therapeutic index (the ratio between clinical benefit and side-effects) of this locoregional treatment. This objective can be mainly pursued by enrolling patients with a low likelihood of harboring extrahepatic disease and/or by identifying biological factors predicting tumor response.

To address these issues, we retrospectively queried our database of patients treated with FUDR-based HAI combined or not with SCT as a first-line treatment. Besides comparing the survival rates of patients undergoing HAI alone with those of patients also treated with SCT, we analyzed the prognostic and predictive value of clinical, pathological and molecular factors.

## Patients and Methods

By retrospectively querying the database of our institution, we found that 162 consecutive patients underwent HAI with or without systemic chemotherapy for unresectable hepatic metastases from CRC between March 1994 and October 2003. Of these, full data were available for 153 patients, whose records were used for the following analyses.

*Treatments*. At the time of the enrollment, no patient had any extrahepatic disease and liver parenchyma replacement was equal to or less than 66%, as assessed by preoperative total body computed tomography (CT) scans.

HAI (combined or not with SCT) represented the first-line chemotherapeutic treatment for all patients.

In the first cohort (group A, n=72), patients were treated with HAI alone (FUDR 0.2 mg/kg + leucovorin (LV) 4 mg/m$^2$ + desamethasone 20 mg 14 days/month) between March 1994 and April 1999. In the second cohort (group B, n=81), patients were treated with the same HAI regimen combined with systemic chemotherapy (5FU 450 mg/m$^2$ + LV 20 mg/m$^2$) between May 1999 and October 2003.

Treatment (HAI alone or in combination with SCT) was continued until disease progression (hepatic and or extra hepatic), or complete response. In some patients (group A, n=8; group B, n=8) shrinkage of liver metastases induced by treatment allowed for surgical resection of residual disease.

Upon progression, patients were submitted to second-line *i.v.* multi-drug chemotherapy (mainly oxaliplatin-containing regimens). Systemic and locoregional (HAI) chemotherapy were interrupted in cases of grade 3-4 toxicity. Under these circumstances, patients underwent the subsequent cycles with 25-50% drug dosage reduction, upon clinician judgment; then, if grade 3-4 toxicity occurred, treatment was stopped and second-line chemotherapy was taken into consideration.

*Follow-up and evaluation of clinical outcome*. Clinical examination and peripheral blood withdrawal were performed every 15 days (or more often according to the patient's condition and the physician's judgment). Disease stage was assessed every three months by means of CT scans. Plasma levels of carcinoembryonic antigen (CEA) and cancer antigen CA19.9 were used to indicate but not to make diagnosis of disease progression. When CT findings were doubtful, positron emission tomography (PET) or magnetic resonance imaging (MRI) scans were performed. Changes in disease staging were considered certain only when imaging findings were confirmed by two independent radiologists.

Tumor response was assessed by means of CT scan performed at three-month intervals. The best response seen at two consecutive examinations was considered for analysis. Patients were considered responders if they showed a complete (tumor disappearance) or partial (tumor shrinkage <50%) response, or non-responders if minimal change (25-50% tumor shrinkage) or stable disease was recorded.

Overall survival was considered as the time elapsing from the patient's enrollment to their death (for any cause), or last follow-up.

Postoperative complications were classified into surgery-related and medical complications. Systemic and hepatic toxicities were graded according to the NCI Common Toxicity Criteria (13).

*Prognostic and predictive factor.* The following factors were considered for their ability to correlate with patients' survival: patient age (continuous variable) and sex, TNM stage at the time of primary tumor diagnosis (AJCC TNM stage), site of primary tumor (colon *vs.* rectum), adjuvant therapy after primary tumor resection (yes *vs.* no), onset of liver metastatic disease (synchronous *vs.* metachronous), percentage of liver replacement by metastatic disease (high load [≥50%] *vs.* low load [<50%]), performance status (ECOG 0-1 *vs.* 2), previous liver resection (yes *vs.* no), type of treatment (group A [HAI alone] *vs.* group B [HAI + systemic chemotherapy]), tumor response to HAI (complete + partial responders *vs.* others).

The following factors were considered as predictors of tumor response to treatment: patient age (≥50 years *vs.* <50 years) and sex, TNM stage at the time of primary tumor diagnosis, site of primary tumor, adjuvant therapy after primary tumor resection, onset of liver metastatic disease, percentage of liver replacement by metastatic disease, performance status, previous liver resection, type of treatment (group A *vs.* group B), p53 expression by hepatic metastatic disease (immunohistochemistry positive *vs.* negative).

*Statistical analysis*. When comparing the characteristics of patients, *t*-test and Chi-square statistics were used as appropriate.

Survival estimates were calculated according to the Kaplan-Meier method and compared by means of the log-rank test (categorical variables). Univariate (continuous variables) and multivariate survival analyses were performed according to the Cox proportional hazard model.

An alpha error lower than 5% was considered significant to reject the null hypothesis.

Considering the median survival of patients with unresectable liver metastases from colorectal cancer is approximatively 18 months and expecting a survival advantage of 12 months in the combined-treatment group, we calculated a minimum sample size of 70 patients per group to achieve a statistical power ≥80%.

## Results

Patients and tumor-related characteristics are illustrated in Table I. The two study groups were similar, as no statistical differences were found for any of the factors analyzed (*i.e.* mean age, sex distribution, TNM stage at primary presentation, site of primary tumor, adjuvant therapy after primary tumor

Table I. *Characteristics of 153 patients with unresectable liver metastases from colorectal cancer treated with hepatic arterial infusion (HAI) ± systemic chemotherapy (SCT).*

| | Group A | Group B | Group A *vs*. group B | Group A + group B |
|---|---|---|---|---|
| Treatment | HAI | HAI + SCT | - | - |
| Patients (no.) | 72 | 81 | - | 153 |
| Age (years) (median, range) | 55 (44-71) | 56 (41-72) | NS | 56 (41-72) |
| Sex (M/F) | 38/34 | 46/35 | NS | 94/69 |
| TNM stage (II, III, IV)[1] | 6/55/11 | 7/57/17 | NS | 13/112/28 |
| Colon/rectum[2] | 52/20 | 59/22 | NS | 111/42 |
| Adjuvant therapy[3] | 45 | 52 | NS | 97 |
| Synchronous/metachronous[4] | 13/59 | 15/66 | NS | 28/125 |
| Liver replacement[5] | 43/29 | 50/31 | NS | 93/60 |
| Performance status[6] | 48/24 | 58/23 | NS | 106/47 |
| Previous surgery[7] | 17 | 22 | NS | 39 |

NS: Not significant. [1]At the time of primary tumor diagnosis; [2]site of primary tumor; [3]after resection of primary tumor; [4]liver metastatic disease; [5]equal to or lower than 50% /greater than 50% ; [6]ECOG classification (0-1/2); [7]liver resection.

resection, synchronous *vs*. metachronous metastatic disease, percentage of liver replacement by metastatic disease, performance status, and previous liver resection).

*Treatment-related morbidity and mortality*. Three postoperative deaths (mortality rate: 1.9% ) occurred: two in group A and one in group B. Hemoperitoneum, sepsis and massive pulmonary embolism were the causes of death, respectively.

Grade 3-4 systemic toxicity (mainly hematological) occurred in 6 (8.3% ) and 28 (34.6% ) patients in group A and group B, respectively (Chi-square $p<0.001$). Grade 3-4 hepatic toxicity was recorded in 21 (29.1% ) and 26 (32.1% ) patients in group A and group B, respectively (Chi-square $p>0.05$).

Catheter complications (occlusion or dislocation) was reported in 7 (9.7% ) and 6 (7.4% ) cases in group-A and group-B, respectively (Chi-square $p>0.05$).

*Tumor response*. The overall (complete + partial) tumor response rate in group A (52.7% ) was not different from that observed in group B (50.6% ) (Table II). Partial responses led to successful liver resection of the residual disease in eight patients both in group A and group B (resectability rate: 11.1% and 9.9% , respectively; Chi-square $p>0.05$).

Of the 11 predictive factors considered, only the percentage of liver replacement by metastatic disease was associated with the tumor response rate. In particular, patients with low (<50% ) tumor load (n=76) showed a higher overall (complete + partial) tumor response rate as compared to patients with high (≥50% ) tumor load (61.8% *vs*. 33.7% , respectively, $p=0.0007$).

*Survival analysis*. Considering all patients (group A + group B, n=153), the median follow-up was 15.2 months (range: 4-120 months) and the median OS was 18.2 months. To date, 121 patients (79.1% ) have died of disease, three patients (1.9% ) died in the postoperative period and nine patients (5.8% ) died of other causes. Among survivors (n=20, censored data rate: 13.1% ), 14 (9.1% ) have clinical evidence of disease and six (4% ) are alive with no evidence of disease. Twenty-five patients (16.3% ) survived more than three years after enrollment (long-term survivors).

Table II. *Tumor response in 153 patients with unresectable liver metastases from colorectal cancer treated with hepatic arterial infusion (HAI) alone (group A, n=72) or HAI + systemic chemotherapy (group B, n=81).*

| Response | Group A | Group B | Group A *vs*. group B | Group A + group B |
|---|---|---|---|---|
| Complete | 6.9% | 8.6% | NS | 12 (7.8% ) |
| Partial | 45.8% | 42.0% | NS | 67 (43.8% ) |
| Overall | 52.7% | 50.6% | NS | 79 (51.6% ) |
| Minimal change | 20.8% | 27.1% | NS | 37 (24.2% ) |
| Stable disease | 18.0% | 17.3% | NS | 27 (17.6% ) |
| Progressive disease | 8.3% | 4.9% | NS | 10 (6.5% ) |
| Resectability | 11.1% | 9.9% | NS | 16 (10.4% ) |

NS: Not significant.

No difference in OS was observed between group A and group B (median OS: 18.0 and 19.1 months, respectively; log-rank test $p>0.05$) (Figure 1). Among the other ten variables considered in this study, only tumor burden and response to treatment were correlated with patients' survival. In particular, on univariate analysis, OS was better in patients with less than 50% as compared to more than 50% liver parenchyma involvement (21.3 *vs*. 13.2 months, respectively; $p<0.0001$) and in responders (complete or partial response) *vs*. non-responders (24.4 *vs*. 13.4 months, respectively; $p<0.0001$) (Figure 2).

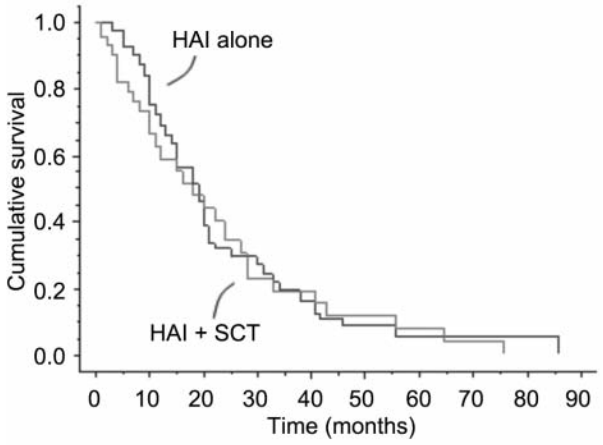


Figure 1. *Overall survival of patients with unresectable liver metastases from colorectal cancer treated with hepatic arterial infusion (HAI) (group A, blue line, n=72) or HAI + systemic chemotherapy (SCT) (group B, red line, n=81). Log-rank test p=0.589.*

The combination of low tumor load with good tumor response to HAI was the only variable retained on multivariate analysis and identified a subgroup of patients with a very favorable clinical outcome (n=47, median survival: 34.5 months) as compared to the remaining cases (n=106, median OS: 15.0 months; hazard ratio: 2.66, 95% confidence interval (CI): 1.77-4.01; $p<0.0001$) (Figure 3).

## Discussion

Despite its theoretical advantages, fluoropyrimidine-based HAI has not been demonstrated to guarantee any consistent survival advantage for patients with liver-confined unresectable metastatic disease from CRC as compared to fluoropyrimidine-based SCT (*i.e.* 5-FU combined or not with LV) (10-12). This lack of clinical benefit is even more evident when considering that the randomized clinical trials so far performed compared HAI with 5-FU SCT, which has now been superseded by modern more effective antineoplastic regimens containing oxaliplatin or irinotecan (7, 8). Moreover, it must be remembered that SCT trials include a significant percentage of patients who also have extra hepatic metastases (greater tumor burden → worse prognosis), a substantial bias in favor of HAI trials where extra hepatic disease is considered a typical eligibility exclusion criterion. Overall, although HAI yields high tumor response rates (up to 40-50%) that well compare with those observed with modern SCT, the median OS is reported to be lower (12-14 months *vs.* 18-20 months, respectively) (11, 14). According to these considerations, the future of HAI as a first-line treatment of patients with unresectable hepatic metastases from CRC appears to be linked to its use for the

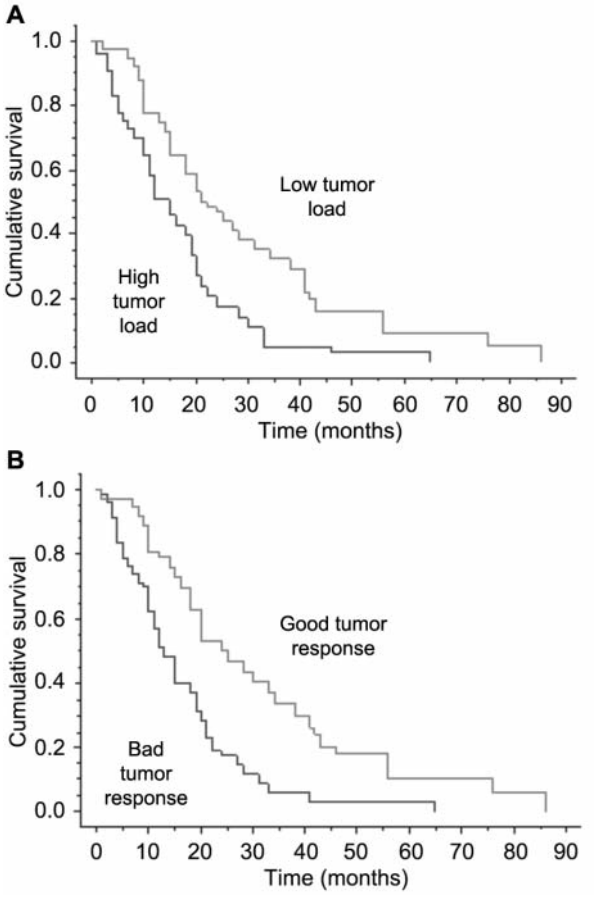


Figure 2. *Overall survival of 153 patients with unresectable liver metastases from colorectal cancer treated with hepatic arterial infusion (HAI) or HAI + systemic chemotherapy according to A)the tumor load (greater (blue line) or lower (red line) than 50; log rank p<0.0001) and B) the tumor response (complete or partial (red line) versus other (blue line); logrank, p<0.0001).*

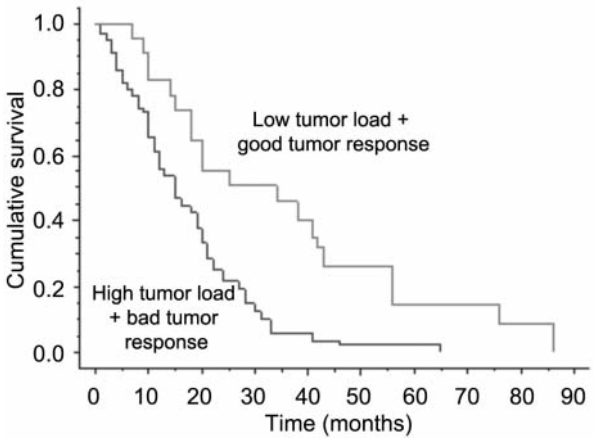


Figure 3. *Overall survival of 153 patients with unresectable liver metastases from colorectal cancer treated with hepatic arterial infusion (HAI) or HAI + systemic chemotherapy according to the combination of tumor load and tumor response (low tumor load and good tumor response (red line) versus other (blue line), log rank test p<0.0001).*

delivery of novel more effective antineoplastic drugs (15, 16), possibly in combination with SCT (17-20) in order to balance the intrinsic limit of this locoregional treatment, that is, the lack of control over clinically occult extra hepatic metastatic disease.

Despite the above observations, there still exists a means of further exploring the potential therapeutic activity of FUDR-based HAI for the treatment of unresectable hepatic metastases from CRC. Following a personalized medicine approach (21), this relies on the identification of the subset of patients who are prone to benefit from this therapeutic approach for one or both the following reasons: i) because the metastatic disease is really confined to the liver (no extra hepatic clinically occult minimal residual disease and thus no need for systemic chemotherapy), and ii) because the metastatic cells are sensitive to the drug used (FUDR), bearing in mind that approximately half of all colorectal adenocarcinomas are resistant to fluoropyrimidines.

In the present retrospective study, we found that the addition of systemic 5-FU + LV to FUDR-based HAI did not improve tumor response rate or median OS (Figure 1): we therefore considered together group A (HAI alone) and group B (HAI + systemic chemotherapy) patients in the search for a subset of individuals who might have benefited from FUDR-based HAI.

Considering the whole series, the overall response rate (51.6%) and median OS (15.2 months) were similar to those reported by others using the same HAI regimen (11, 14). The relatively significant proportion of long (greater than 36 months) survivors (n=25, 16%) showed that a small subset of patients might actually benefit from HAI treatment, which led us to further analyze the available data. Interestingly, prognostic factor analysis showed that low hepatic tumor burden (which might be regarded as a surrogate indicator of a low likelihood of extra hepatic minimal residual disease) and high tumor response rate (which is a quite straightforward indicator of tumor chemosensitivity) were the only variables associated with patients' clinical outcome (Figure 2). In addition, the combination of these two factors identified a subset of patients (n=47, 30.7%) with a very favorable survival (median OS: 34.5 months, Figure 3). Of course, since this observation might just represent the identification of those cases with a better natural history (low tumor aggressiveness) and/or higher tumor chemosensitivity (*i.e.* factors that could improve the results of SCT as well), only randomized controlled trials conducted in this particular population could determine whether HAI plays a clinically useful therapeutic role. While tumor burden can be assessed preoperatively, tumor chemosensitivity based on tumor response is an *a posteriori* finding that is of no clinical value for the selection of patient candidates for HAI. To address this issue, the discovery of biological markers of tumor response is urgently needed (22). In our experience, no histopathological feature (including p53 expression) of the metastatic disease correlated with tumor regression, despite others havinge reported opposite findings (23). In this regard, the use of high-throughput technologies for the screening of the genome (or proteome) (24) might greatly accelerate the pace of discovery of suitable molecular candidates in the field of oncology in general (22) and in the management of CRC in particular (25, 26).

In conclusion, our study supports the thesis that 5-FU-based systemic chemotherapy does not add a survival advantage to FUDR-based HAI in the first-line therapeutic approach to unresectable liver metastases from CRC. Since fluoropyrimidine-based HAI does not improve the survival of these patients as compared to 5-FU SCT (27), one may conclude that neither HAI alone nor HAI plus 5-FU systemic chemotherapy is recommended in this setting.

However, the identification of patients with a greater likelihood of benefiting from HAI (*i.e.* those with low tumor burden + high tumor chemosensitivity) might justify the conduction of HAI trials focusing on this population with the aim of improving the therapeutic index of this locoregional treatment by personalizing its indication.

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