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Impact of Primary Tumor Laterality on Adjuvant Hepatic Artery Infusion Pump Chemotherapy in Resected Colon Cancer Liver Metastases: Analysis of 487 Patients

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Abstract

Background: Hepatic artery infusion (HAI) chemotherapy is associated with overall survival (OS) in patients with resected colon cancer liver metastases (CLM). The prognostic impact of primary tumor location in CLM following hepatic resection in patients receiving regional HAI is unknown. This study sought to investigate the prognostic impact of HAI in relation to laterality in this patient population.

Methods: Consecutive patients with resected CLM, known primary tumor site treated with and without HAI were reviewed from a prospective institutional database. Correlations between HAI, laterality, other clinicopathological factors and survival were analyzed; Cox proportional hazard regression was used to determine whether laterality was an independent prognostic factor.

Results: From 1993–2012, 487 patients (182 right colon cancer (RCC), 305 left colon cancer (LCC)) were evaluated with a median follow up of 6.5 years. Fifty-seven percent (n = 275) received adjuvant HAI. Patients with RCC had inferior 5-year OS compared with LCC (56% vs. 67%, $P = 0.01$). HAI was associated with improved 5-year OS in both RCC (68% vs. 45%; $P < 0.01$) and LCC (73% vs. 55%; $P < 0.01$). In multivariable analysis, HAI remained associated with

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improved OS (HR, 0.52; 95% CI, 0.39 to 0.70; $P < 0.01$) but primary tumor site did not (HR, 0.83; 95% CI, 0.63 to 1.11; $P = 0.21$). Additional significant prognostic factors on multivariable analysis included age, number of tumors, node-positive primary, positive margins, *RAS* mutation, 2-stage hepatectomy and extrahepatic disease. Cox proportional hazard regression determined no significant interaction between HAI and laterality on OS (parameter estimate [SEM], 0.12 [0.28]; $P = 0.67$)

Conclusions: Our data show an association of adjuvant HAI and increased OS in patients who underwent curative hepatectomy, irrespective of primary tumor location. Laterality should therefore not impact decision making when offering adjuvant HAI.

INTRODUCTION

Colorectal cancer (CRC) is no longer regarded as a single disease entity. For the past decades, there has been a persistent trend in the increasing percentage of right-sided colon cancers (RCC) [1, 2]. Furthermore, a large body of literature since the 1990s has demonstrated differences in biology with regards to epidemiology, clinical behavior, and somatic genetic expression profiles in colon cancers originating in the right and left colon [3, 4]. RCC usually present at more advanced stage compared with left-sided colon cancer (LCC) [5]. Mucinous features, microsatellite instability, and *BRAF* mutations [6–8] have been found to be more common in RCC. Prognostic implications of primary tumor location have also been reported. Multiple retrospective series and post-hoc analyses of clinical trials have demonstrated worse survival outcomes in patients with unresectable, metastatic RCC compared to LCC [9–12]. Although most studies similarly show inferior outcomes for RCC compared with LCC in patients with CLM after curative hepatectomy [13, 14], long-term cure rates after hepatic resection have been reported to be similar [15].

More than 50% of colon cancers present with or develop liver metastasis and complete resection remains the only chance of cure. Despite that, relapse is a common clinical challenge and occurs in up to 80% of patients after resection of CLM. Multiple randomized controlled trials have demonstrated that adjuvant regional hepatic artery infusion (HAI) chemotherapy after hepatic resection decreases hepatic recurrence and overall recurrence, and improves overall survival [16–18]. In our largest study evaluating 2,368 consecutive patients after complete [19] resection of CLM, the median OS for patients treated with HAI ($n = 785$) was 67 months versus 44 months treated without HAI ($n = 1,583$; $P < 0.001$), despite more advanced disease in the HAI group. More recently, we showed that adjuvant HAI was associated with improved OS in patients with colorectal liver metastases after hepatic resection, irrespective of *RAS*-mutational status [20]. While numerous prognostic factors were evaluated in both studies, location of primary tumor was not. Whether adjuvant HAI is a prognostic factor for survival based on the anatomic location of the primary site for CLM after hepatic resection remains unknown. Therefore, the objective of this study was to study the differential impact of adjuvant HAI and systemic therapy on outcomes by primary tumor location in patients with resected CLM from a large institutional database.

METHODS

Patients

From 1993 to 2012, consecutive patients with liver metastases from colonic origin who underwent complete resection and treated with and without HAI chemotherapy were assessed from a prospectively maintained institutional database. Patients who presented with upfront resectable liver-only metastases, those who initially were downstaged with chemotherapy (systemic and/or HAI therapy) and then underwent complete resection, and those who had completely resected extrahepatic disease at the time of prior to liver resection were included in the final analysis. Patients who underwent ablations exclusively or had R2 resections were excluded. Patients with rectal cancer, multiple primaries, *BRAF* mutations, or unknown location of primary tumor or unknown *RAS* status were excluded. Patients with rectal cancer were excluded due to its unique therapeutic approach [3, 21, 22]. Finally, patients who received regional HAI for recurrent CLM were also excluded from this analysis. The study was approved by the Institutional Review Board of MSKCC.

Treatment

All patients completed hepatic resection, including 2-stage hepatectomy and additional intraoperative ablative therapies in some cases. Standard placement of the hepatic artery infusion pump was performed as previously described [17]. Adjuvant HAI chemotherapy consisted of infusion of FUDR mixed with dexamethasone plus heparinized saline administered for a two-week infusion alternating with 2 weeks of heparinized saline alone. With tolerable toxicity, this treatment is generally administered for a total of six cycles. HAI chemotherapy was routinely administered concomitantly with systemic chemotherapy as previously reported [17]. The treatment groups therefore were defined as adjuvant HAI + systemic therapy (HAI) versus systemic therapy alone (non-HAI). Patients who initially received HAI prior to completion of hepatic resection, were continued on adjuvant HAI therapy with systemic chemotherapy. Selection of post-operative systemic chemotherapy and details of the treatment plan were determined by the treating medical oncologist and based on prior chemotherapy exposure [17].

Variables

Laterality was defined as location of primary tumor derived from the pathology report. RCC was defined as tumors arising from the cecum through the transverse colon; LCC originated from the splenic flexure to rectosigmoid junction [23, 24]. Liver metastases diagnosed prior (within 6 months of diagnosis of the primary lesion) to or at the time of resection of the primary tumor were defined as synchronous disease. Node-positive primary tumors were staged according to 8th AJCC guidelines [25]. Total number and tumor size were derived from pathology reports. Positive surgical margins were defined as tumor cells at the resection margin. Serum CEA level was recorded closest to and within 3 months prior to liver resection. *RAS* mutational status (*NRAS* and *KRAS*) were obtained from institutional genomic platforms. Disease-free interval (DFI) was defined as time from resection of primary tumor to diagnosis of liver metastasis. Clinical risk score was calculated using DFI, CEA, node positivity and size of primary tumor, and number of metastases as previously described [26]. Surveillance scans were performed every 3 to 6 months unless

otherwise indicated. Recurrent disease was confirmed by imaging (including CT, MRI, or PET) and/or biopsy. Only initial recurrence was recorded for each patient. Overall survival (OS) was calculated from the time of hepatic resection (2nd resection in cases with 2 stage hepatectomies) to date of death, with censoring at date of last follow-up. Recurrence-free survival (RFS) was calculated from date of hepatic resection to date of first recurrence, with censoring at date of last follow-up or death prior to recurrence.

Statistical Analysis

Clinical and pathological factors were summarized by laterality and HAI using frequencies and percentages or medians and ranges, as appropriate. Chi-square tests and Wilcoxon rank sum tests were used to assess the association of each factor with laterality and HAI. Three- and five-year OS and RFS were estimated using the Kaplan-Meier method, along with their 95% confidence intervals; comparisons of these survival probabilities by laterality and HAI were performed using z-tests. The log rank test was used to compare OS and RFS with respect to laterality and HAI separately and in combination; the stepwise log-rank tests was used to assess the interaction between laterality and HAI. Multivariable Cox regression models of OS and RFS were created to estimate hazard ratios and 95% confidence intervals adjusted for clinically important variables that have been shown to be significant in previous studies [20]. A separate Cox regression model of RFS and OS including interaction between HAI and laterality was performed to determine whether the effect of HAI on RFS differed between right- and left-sided tumors. All analyses were performed in SAS version 9.3 (SAS Institute Inc, Cary, NC).

RESULTS

Patient Characteristics

Between 1993 and 2012, a total cohort of 2690 patients underwent complete resection of CLM at our institution. Seven-hundred seventy-five patients had verified location of the primary tumor based on pathology with available *RAS* mutational status. Patients with rectal tumors ($n = 215$) and multiple primary tumors ($n = 11$) were excluded from the analysis. Lastly, patients who received HAI for recurrent liver metastases ($n = 54$) and those who did not complete 2-stage hepatectomy and/or resection of their extrahepatic disease ($n = 8$) were excluded from the final analysis (Figure 1).

The final analysis included 305 LCC (63%) and 182 RCC (37%) cases. Patients with RCC tumors were of older median age (62.5 years (27.2–90.7) vs. 56.5 years (25.3–87.0); $P < 0.001$). Right sided tumors more commonly harbored *RAS* mutation (53%) compared to patients with LCC (30%; $P < 0.001$). There was also a trend towards more extensive disease ($P = 0.07$), and more extra-hepatic disease in patients with RCC ($P = 0.07$). The demographics and clinical characteristics of the patients in these 2 groups are summarized in Table 1.

HAI Chemotherapy

Adjuvant HAI was administered to a total of 275 patients (56%). Patients with LCC were more likely to receive HAI therapy (63%) compared to patients with RCC (46%; $P <$

0.01). Patients who received HAI were younger and were more likely to have higher risk disease demonstrated by higher CRS (3–5), synchronous disease, higher number of tumors, and larger tumor size. Furthermore, rates of ablations (28% vs. 13%) and 2 stage-hepatectomy (13% vs. 2%) were higher for the HAI group. Table 1 demonstrates the baseline characteristics of the patients in the 2 treatment groups included in the final analysis.

Predictors of Recurrence-Free Survival

In the entire cohort, 3- and 5-year overall RFS were 36% and 31%, respectively. There was no difference in 5-year RFS observed in patients between RCC (31%) and LCC (30%). Three- and five-year RFS rates were similar in the adjuvant HAI and the non-HAI groups (38% vs. 33%; $P=0.47$ and 34% vs. 27%; $P=0.2$, respectively). Among patients with LCC adjuvant HAI was associated with improved 5-year RFS (34% vs. 22%; $P=0.038$). For RCC, 5-year RFS for patients treated with and without HAI were 33% and 29%, respectively ($P=0.65$). In a Cox model of time to first recurrence, there was no significant interaction between HAI and laterality ($P=0.12$).

In multivariable analysis, RFS was longer for patients who received HAI compared to patients who received systemic therapy only (HR, 0.68; 95% CI, 0.53–0.87; $P=0.002$). The multivariable model confirmed additional significant prognostic factors of earlier recurrence including DFI < 12 months, number of tumors, node-positive primary, positive margins, size of largest tumor, lesions ablated, *RAS* mutation, extrahepatic disease (Table 2).

Predictors of Overall Survival

The median 3- and 5-year OS for the entire cohort was 79% and 63%, respectively. Considering all patients, the 5-year OS rates after hepatic resection in the RCC (56%) group was lower than that in the LCC (67%; $P=0.01$; Figure 2) group. Adjuvant HAI therapy was associated with significantly prolonged 5-year OS (71%) compared to systemic therapy only (50%; $P<0.01$; Figure 3). HAI was associated with prolonged 5-year OS for RCC (68% vs. 45%; $P<0.01$) and LCC (73% vs. 55%; $P<0.01$) as demonstrated in Figure 4. In a separate Cox model of OS, no significant interaction between HAI and laterality was observed (parameter estimate [SEM], 0.12 [0.28]; $P=0.67$).

In multivariable analysis, adjuvant HAI was independently associated with improved OS with a HR of 0.52 (95% CI, 0.38–0.69; $P<0.01$). Location of primary tumor was not a statistically significant independent predictor of OS (HR, 0.83; 95% CI, 0.63–1.11; $P=0.21$). The multivariable model confirmed additional significant prognostic factors of worse survival including younger age, number of tumors, node-positive primary, positive margins, extrahepatic disease, 2-stage hepatectomy, and *RAS* mutational status as shown in Table 3.

DISCUSSION

Differences in patient demographics, clinical presentation, tumor biology, and molecular carcinogenic pathways between right- and left-sided colon cancers have been long reported in the literature [27–30]. The prognostic impact of laterality has been well established in patients with stage IV unresectable metastatic CRC [11, 31]. However, it is unknown

whether laterality determines the treatment effect of HAI and should guide the decision to offer HAI chemotherapy. We sought to investigate the impact of adjuvant HAI on outcome by location of the primary tumor for patients with resected CLM.

We reviewed 487 patients who completed with curative-intent hepatic resection with known primary location. Rectal tumors were excluded as they constitute a distinct clinical and prognostic subgroup [3, 21, 22]. For all patients, no difference in RFS was observed between RCC and LCC, however, OS was significantly shorter for RCC compared to LCC tumors ($P = 0.001$). Furthermore, adjuvant HAI was associated with prolonged RFS and OS regardless of primary tumor location. Although RFS rates were similar in patients who received HAI and those who did not, in multivariable analysis, HAI was a significant prognostic factor for RFS with a HR of 0.68 after accounting for other confounding factors. These findings are likely explained by the fact that patients who received HAI had overall worse prognostic indicators and more extensive disease. In multivariable analysis, laterality was not an independent prognostic factor associated with RFS (HR, 1.13; $P = 0.32$) or OS (HR, 0.83; $P = 0.21$), while adjuvant HAI therapy was (RFS: HR, 0.68; $P < 0.01$ and OS: HR, 0.52; $P < 0.01$).

While the prognostic value of laterality on OS in patients with metastatic CRC has been well established [3], it is controversial if the same holds true for patients with resectable CLM. Several studies report positive prognostic value of sidedness of primary tumor in resected CLM [11, 32, 33]. A recent retrospective analysis of 475 patients demonstrated that patients with RCC undergoing hepatic resection had an associated improved RFS but worse OS ($P = 0.03$) and survival after recurrence ($P = 0.01$). The authors attributed these findings to higher number of recurrent lesions in patients with RCC, concluding that higher tumor burden in RCC translated into worse survival. Our recent analysis of 907 CLM patients undergoing hepatectomy showed no difference in RFS stratified by primary tumor location. In that report, left-sided primary tumors had a significantly improved median OS, but the observed cure rates were not different (RCC: 20% vs. LCC: 22%). Both studies have limitations. Sasaki's group had a shorter follow up, and molecular data was not considered in Creasy's analysis [15]. Similar results have been demonstrated by others showing shorter OS for RCC compared to LCC metastatic CRC undergoing curative hepatectomy. However, these studies included rectal tumors [34, 35] and therefore can't be directly compared to other reports.

Similar to the results of the current analysis, other groups have published no prognostic value of laterality on survival outcomes in resected CLM. Wang et al. showed similar OS and RFS rates for RCC and LCC (5-year OS: 46.5% vs. 38.3%; $P = 0.69$ and 5-year RFS: 29.1% vs. 22.4%; $P = 0.54$) in 420 patients with CLM after hepatectomy [14]. Similarly, Marques et al. showed no difference in long term survival comparing RCC and LCC in 151 patients after hepatic resection [36]. It should be emphasized that in all these studies, RCC harbored higher rates of *RAS* mutation which could influence study findings. Moreover, variability in study design and selection bias may contribute to inconsistent results across all studies. For the entire cohort, current study shows lower overall survival for RCC compared to LCC, consistent with those seen in other studies [13, 15, 34]. However, laterality was not an independent predictor of survival in multivariable analysis for patients with resected CLM treated with adjuvant HAI and systemic therapy. We therefore do not

think that laterality should not be a clinical factor to be included in the decision-making for consideration of HAI therapy.

In the metastatic setting, the anatomic location of the tumor appears to make a difference in OS and response to biologic treatments. Retrospective analysis from the CALGB/SWOG 80405 trial comparing bevacizumab and cetuximab in combination with chemotherapy as initial therapy for metastatic CRC suggests that the relative effectiveness of cetuximab and bevacizumab may differ depending on primary tumor location [36]. In the primary analysis, among patients with RCC, treatment with bevacizumab was associated with longer survival than that seen with cetuximab (24.2 vs. 16.7 months). Conversely, among patients with LCC, treatment with cetuximab was associated with longer OS than bevacizumab (36 vs. 31.4 months). In the setting of metastatic liver-only disease, studies have suggested that peri-operative chemotherapy may be more effective in high-risk tumors undergoing resection [36, 37]. Imai et al. looked at the impact of primary tumor location on the effectiveness of pre-operative chemotherapy and demonstrated that pre-operative chemotherapy is more effective in patients with RCC compared to those who received upfront hepatectomy. However, this study had a small size and did not account for *RAS* mutational status. To the contrary, no significant interaction of primary tumor location and HAI treatment was observed in the current study. Adjuvant HAI was associated with improved overall RFS and OS in all groups, irrespective of sidedness of the primary tumor. Finally, there was no difference in the effect of HAI on RFS or OS between RCC and LCC. These findings further demonstrate that when considering HAI therapy, tumor sidedness should not be a determining factor for patient selection.

The current work is a retrospective analysis and subject to biases associated with retrospective data. This study was conducted at a single center with significant experience on HAI treatment and consequently may not be generalizable. It needs to be recognized that at our center and most others, systemic therapy is in general given with adjuvant HAI. Furthermore, specific timing and details of chemotherapy regimens were not collected for this analysis. In this study, systemic chemotherapy was given according to standard of care and based on modern systemic chemotherapy in the later time periods as published before by our group. One would therefore not expect any significant differences in the treatment groups comparing HAI vs. non-HAI treated patients with regards to the systemic treatment received. Lastly, while this is the largest cohort addressing the effect of HAI on location of primary tumor, a large number of patients treated were excluded due to missing molecular marker data or unknown primary tumor location. Even though we considered *RAS* mutations and excluded patients with *BRAF* mutations, worse outcomes of patients with RCC may have been partially driven by other mutational factors not accounted for in this analysis. Further work is needed to more clearly elucidate genetic differences between RCC and LCC and mechanistic relationship between these mutations and primary tumor location and their prognostic significance. Moving forward, the implementation of broader Next Generation Sequencing approaches and tumor mutational burden may help to identify potential underlying reasons related to the survival differences noted in this and other studies.

CONCLUSIONS

In summary, this is the first study to evaluate the impact of adjuvant HAI and chemotherapy on outcomes by primary tumor location for resected CLM. Our data show an association of adjuvant HAI chemotherapy and increased OS in all patients who underwent curative hepatic resection, irrespective of location of primary tumor. Laterality was not a significant prognostic factor for OS. Therefore, we believe that primary tumor location should not be a determining factor for decision-making in selecting patients for adjuvant HAI treatment

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SYNOPSIS

A retrospective review of patients with resected colon cancer liver metastases. Our data show an association of adjuvant HAI and increased OS in patients who underwent curative hepatectomy, irrespective of primary tumor location. We conclude feasibility of HAI irrespective of tumor laterality.

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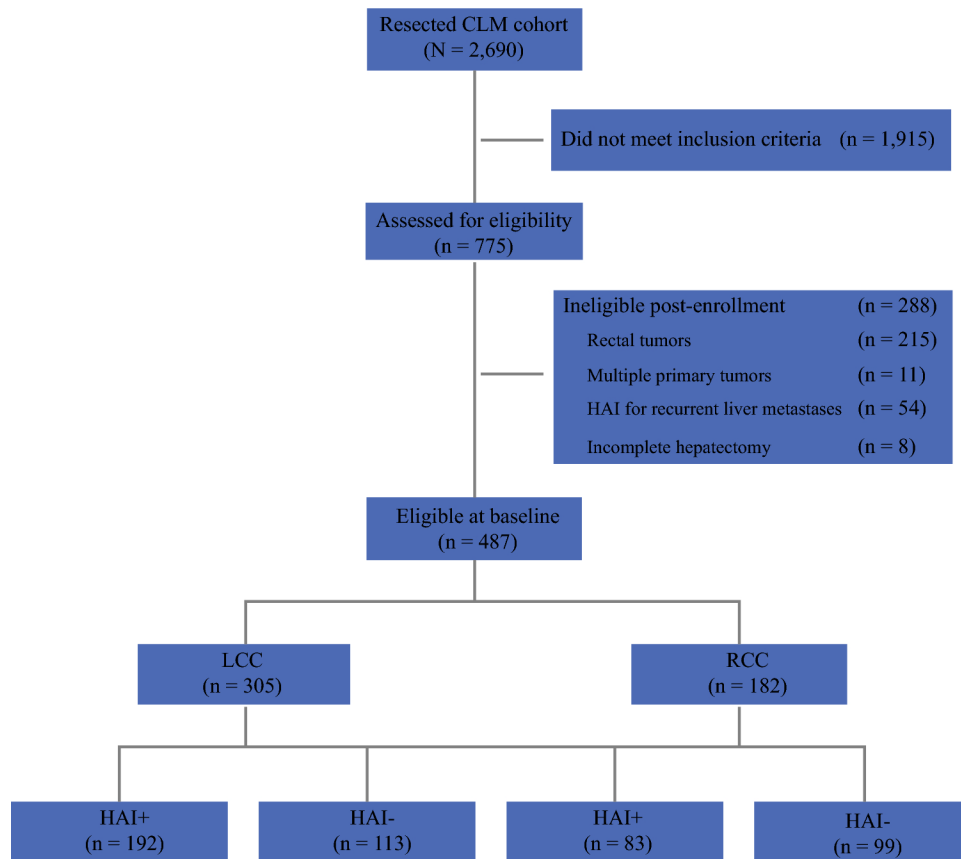


Figure 1. Flowchart of study cohort. CLM, colon cancer liver metastases; RCC, right colon cancer; LCC, left colon cancer; HAI, hepatic artery infusion.

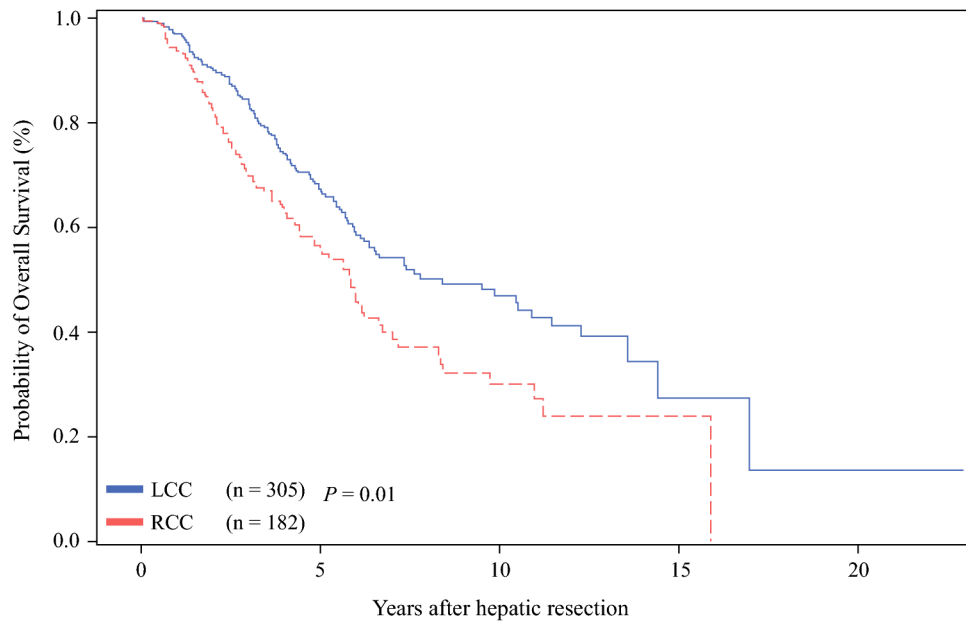


Figure 2. Overall survival (OS) rates after curative hepatectomy in RCC (right colon cancer) and in LCC (left colon cancer).

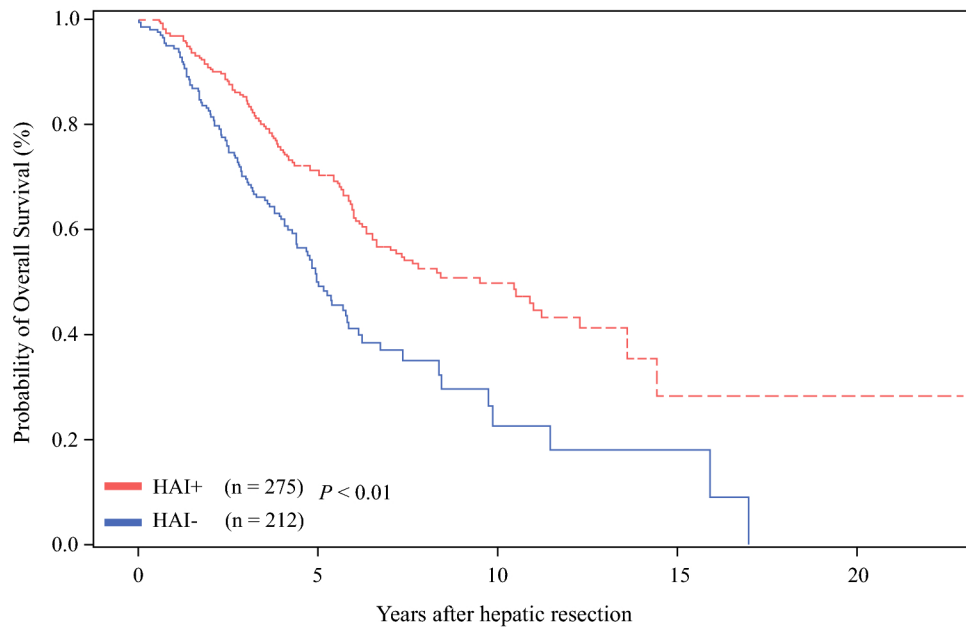


Figure 3. Overall survival (OS) rates with adjuvant HAI (hepatic artery infusion) therapy with systemic therapy (HAI +) and systemic therapy alone (HAI -).

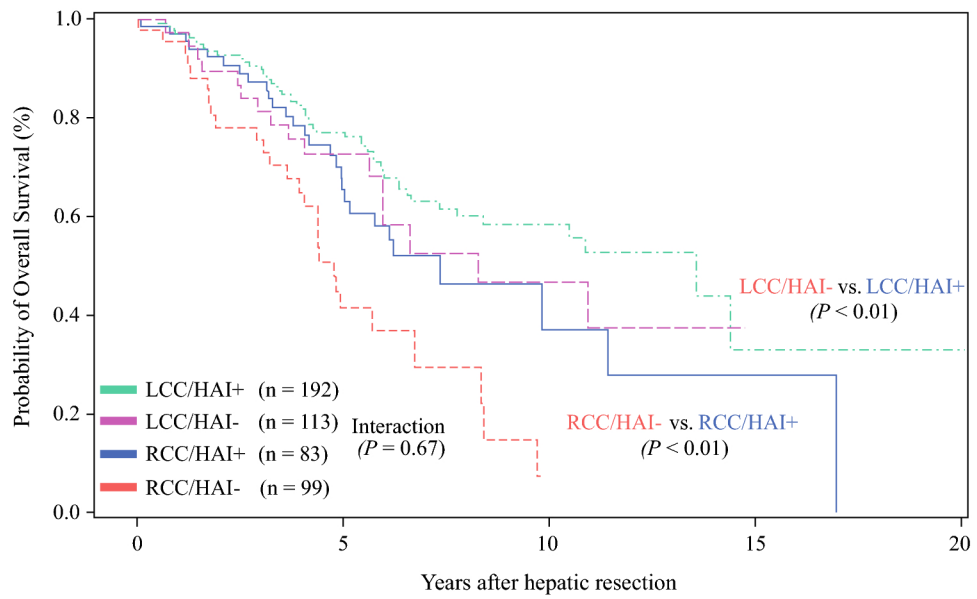


Figure 4. Overall survival (OS) rates for RCC (right colon cancer) and LCC (left colon cancer) stratified by treatment with (HAI +) and without (HAI -) therapy.

Table 1.

Clinical and pathologic characteristics of all consecutive patients who underwent curative-intent resection (n = 487)

Variable	All n = 487	RCC n = 182	LCC n = 305	P-value†	HAI n = 275	Non-HAI n = 212	P-value ^a
Age	58.8 (25.3–90.7)	62.5 (27.2–90.7)	56.5 (25.3–87.0)	< 0.01	55.5 (25.3–84.2)	64.6 (25.7–90.7)	< 0.01
Gender							
Male	265 (54)	98 (54)	167 (55)	0.85	148 (54)	117 (55)	0.76
Female	222 (46)	84 (46)	138 (45)		127 (46)	95 (45)	
Laterality							
Right	182 (37)	N/A	N/A	N/A	83 (30)	99 (47)	< 0.01
Left	305 (63)				192 (70)	113 (53)	
Adjuvant HAI							
Yes	275 (56)	83 (46)	192 (63)	< 0.01	N/A	N/A	N/A
No	212 (44)	99 (54)	113 (37)				
RAS status							
Wild-type	299 (61)	85 (47)	214 (70)	< 0.01	178 (65)	121 (57)	0.09
Mutant	188 (39)	97 (53)	91 (30)		97 (35)	91 (43)	
Number of metastases	2 (1–15)	2 (1–10)	2 (1–15)	0.09	3 (1–15)	2 (1–12)	< 0.01
Solitary metastasis							
Yes	158 (32)	60 (33)	98 (32)	0.85	62 (23)	96 (45)	< 0.01
No	329 (68)	122 (67)	207 (68)		213 (77)	116 (55)	
3+ CLM							
Yes	169 (35)	54 (30)	115 (38)	0.07	123 (45)	46 (22)	< 0.01
No	318 (65)	128 (70)	190 (62)		152 (55)	166 (78)	
Synchronous	310 (64)	115 (63)	195 (64)	0.87	185 (67)	125 (59)	0.06
Metachronous	177 (36)	67 (37)	110 (36)		90 (33)	87 (41)	
DFI < 12 months	389 (80)	149 (82)	240 (79)	0.34	228 (83)	161 (76)	0.06
Size of largest lesion (cm)	2.9 (0.2–20.0)	2.8 (0.6–20.0)	3.0 (0.2–20.0)	0.42	2.5 (0.2–20.0)	3.0 (0.6–15.6)	0.04
Nodal status of primary tumor							
Node positive	317 (65)	121 (66)	196 (64)	0.62	178 (65)	139 (66)	0.85
Node negative	170 (35)	61 (34)	109 (36)		97 (35)	73 (34)	
Margin Status							
Positive	44 (9)	13 (7)	31 (10)	0.26	24 (9)	20 (9)	0.79
Negative	443 (91)	169 (93)	274 (90)		251 (91)	192 (91)	
CRS 3–5	248 (53)	94 (54)	154 (52)	0.68	154 (62)	94 (38)	0.03
Lesions ablated							
Yes	105 (22)	39 (21)	66 (22)	0.96	78 (28)	27 (13)	< 0.01
No	382 (78)	143 (79)	239 (78)		197 (72)	185 (87)	
Extra-hepatic disease	35 (7)	18 (10)	17 (6)	0.07	15 (5)	20 (9)	0.09
2-stage hepatectomy	40 (8)	14 (8)	26 (9)	0.75	35 (13)	5 (2)	< 0.01

Abbreviations: RCC = right colon cancer; LCC = left colon cancer; HAI = hepatic artery infusion; CLM = colorectal liver metastases; DFI = disease-free interval; CRS = clinical risk score

^aP-value from chi-square test for categorical variables or Wilcoxon rank sum test for numeric variables

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Table 2:

Multivariate Analysis of Predictors of recurrence-free survival (n = 480)

Variable	Hazard Ratio	95% Hazard Ratio CI	P-value
HAI therapy	0.68	0.53 – 0.87	< 0.01
Age	0.10	0.99 – 1.01	0.89
Number of lesions	1.13	1.07 – 1.20	< 0.01
Size of largest lesion	1.08	1.04 – 1.13	< 0.01
Laterality (left)	1.13	0.89 – 1.44	0.32
Lesions ablated	1.36	1.03 – 1.79	0.03
Sex (male)	1.12	0.89 – 1.40	0.35
<i>RAS</i> (mutant)	1.49	1.17 – 1.88	< 0.01
Extra-hepatic disease	2.01	1.33 – 3.03	< 0.01
2-stage hepatectomy	1.39	0.93 – 2.08	0.11
DFI < 12 months	1.74	1.26 – 2.42	< 0.01
Node positive tumor	1.58	1.23 – 2.03	< 0.01
Positive margins	1.79	1.23 – 2.60	< 0.01

Abbreviations: HAI = hepatic artery infusion; DFI = disease-free interval

Table 3.

Multivariate Analysis of Predictors of Overall Survival after Curative-Intent Resection of CLM (n = 487)

Variable	Hazard Ratio	95% Hazard Ratio CI	P-value
HAI therapy	0.52	0.39 – 0.70	< 0.01
Age	1.01	1.00 – 1.03	0.03
Number of lesions	1.13	1.05 – 1.22	< 0.01
Size of largest lesion	1.04	1.00 – 1.09	0.08
Laterality (left)	0.83	0.63 – 1.11	0.21
Lesions ablated	1.29	0.92 – 1.81	0.15
Sex (male)	1.26	0.95 – 1.67	0.11
<i>RAS</i> (mutant)	1.60	1.20 – 2.13	< 0.01
Extra-hepatic disease	2.56	1.62 – 4.06	< 0.01
2-stage hepatectomy	1.90	1.21 – 2.97	< 0.01
DFI < 12 months	1.25	0.86 – 1.81	0.24
Node positive tumor	1.80	1.32 – 2.44	< 0.01
Positive margins	2.55	1.70 – 3.81	< 0.01

Abbreviations: HAI = hepatic artery infusion; DFI = disease-free interval