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Adjuvant Hepatic Artery Infusion Chemotherapy is Associated with Improved Survival Regardless of KRAS Mutation Status in Patients with Resected Colorectal Liver Metastases: A Retrospective Analysis of 674 Patients

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Abstract

OBJECTIVE: To investigate the impact of adjuvant hepatic artery infusion (HAI) in relation to KRAS mutational status in patients with resected colorectal cancer liver metastases (CRLM).

BACKGROUND: Patients with KRAS-mutated CRLM have worse outcomes after resection. Adjuvant HAI chemotherapy improves overall survival after liver resection.

METHODS: Patients with resected CRLM treated at MSKCC with and without adjuvant HAI who had available KRAS status (wild-type, WT; mutated, MUT) were reviewed from a prospectively maintained institutional database. Correlations between KRAS status, adjuvant HAI, clinical factors, and outcomes were analyzed. Cox proportional hazard model was used to adjust for confounders.

RESULTS: Between 1993–2012, 674 patients (418 KRAS-WT, 256 MUT) with a median follow up of 6.5 years after resection were evaluated. Fifty-four percent received adjuvant HAI. Tumor characteristics (synchronous disease, number of lesions, clinical-risk score, 2-stage hepatectomy) were significantly worse in the HAI group, however, there were more patients with resected extrahepatic metastases in the no-HAI group. In KRAS-WT tumors, 5-year survival was 78% for patients treated with HAI vs 57% for patients without HAI (HR 0.51, $p<0.001$). In KRAS-MUT tumors, 5- year survival was 59% for patients treated with HAI vs. 40% for patients without HAI (HR 0.56, $p<0.001$). On multivariate analysis, HAI remained associated with improved OS (HR 0.53, $p<0.002$) independent of KRAS status and other clinico-pathologic factors.

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CONCLUSIONS: Adjuvant HAI after resection of CRLM is independently associated with improved outcomes regardless of KRAS mutational status. Adjuvant HAI may mitigate the worse outcomes seen in patients with resectable KRAS-MUT CRLM.

Mini-Abstract:

Patients with colorectal liver metastases and available KRAS data treated with resection and with or without adjuvant hepatic artery infusion chemotherapy were retrospectively evaluated. Adjuvant HAI was independently associated with improved outcomes regardless of KRAS mutational status. Adjuvant HAI may mitigate the worse outcomes seen in patients with resectable KRAS-MUT CRLM.

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide.[1] The liver is the most common site for spread with approximately 60% of patients with metastatic disease developing liver metastases.[2] Complete resection of all liver metastases is associated with the best outcomes and the only potential for cure with 10-year survival rates of 20 to 25%.[3] Despite the improvements in systemic chemotherapy, multiple randomized clinical trials have failed to show any significant survival benefit from perioperative systemic chemotherapy in patients with completely resected colorectal liver metastases (CRLM).[4,5] Since relapse occurs in 65–80% of patients after surgical resection of CRLM with the liver being the most common site of recurrence, adjuvant regional hepatic artery infusion (HAI) chemotherapy has been used for several decades.[6] Combination adjuvant treatment of HAI and systemic chemotherapy after hepatic resection has been proven in multiple randomized controlled trials to decrease hepatic recurrence, overall recurrence[7–9] and improve overall survival.[7,8]

Somatic genetic mutations such as APC, p53, PIK3CA, PTEN, BRAF, and KRAS have been shown to play a role in the biology of CRC. More specifically, KRAS mutations have been shown to be an independent prognosticator for decreased recurrence-free survival (RFS)[10–13] and overall survival (OS) in all patients with CRC.[10,12–15] Given these outcomes, some authors argue that KRAS status should be considered in the evaluation of resectability for patients with CRLM.[16] Recently, a meta-analysis assessed clinico-pathological factors in a multivariable analysis in which KRAS mutational status was consistently associated with an independent twofold increase in the risk of death or recurrence.[16] Since KRAS status also predicts response to EGFR inhibition, it is important to note that these findings were not associated with previous administration of cetuximab or panitunimab treatment.

We have recently evaluated patients who have undergone liver resection followed by adjuvant HAI and systemic chemotherapy after liver resection and found that 3-year RFS and OS was significantly worse (30% vs. 46% and 81% vs. 95%, respectively) for KRAS-MUT versus KRAS-WT patients after adjustment for factors known to influence outcomes.[10] The impact of adjuvant HAI as compared to systemic chemotherapy alone in relation to KRAS mutational status is unknown. We therefore aimed to investigate the

impact of adjuvant HAI therapy after resection of CRLM in relation to KRAS mutational status in patients who underwent complete resection of CRLM.

Methods

Patients

Consecutive patients with resected CRLM treated with and without adjuvant HAI chemotherapy and available KRAS status (wild-type, WT; mutated, MUT) were reviewed from a prospective institutional database from 1993 −2012. Patients who underwent ablations exclusively or had R2 resections were excluded. Patients with initially unresectable disease who were downstaged with chemotherapy (systemic and/or HAI therapy) and eventually underwent complete resection, as well as patients who required 2-stage hepatectomies were included. Patients with completely resected extrahepatic disease at the time of or prior to their liver resection were included. This study was approved by the Institutional Review Board of MSKCC.

Variables

Liver metastases diagnosed prior to or at the time of resection of the primary tumor were defined as synchronous disease. Node-positive primary tumors were staged according to AJCC guidelines.[17] Total number and tumor size were derived from pathology reports. Serum CEA level was collected closest to and within 3 months of liver resection. Surgical margins were considered positive when tumor cells were present at the resection margin. 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.[18] KRAS mutational status was obtained from institutional genomic platforms (IMPACT, Sequenom, Sanger sequencing, and whole genome sequencing). The type of hepatic resection was not included in the analysis as the literature indicates that this variable does not appear to be biologically impactful and has not been shown to be associated with oncologic outcomes.

Treatment

Our general approach for HAIP therapy is to select patients with stable or responsive disease. In a small minority of selected cases, HAI therapy is offered to patients with progressive but resectable disease. About 1% of patients are ineligible for HAI therapy due to aberrant hepatic anatomy. Furthermore, patients who are unable to be present for the biweekly treatment at our institution due to social and geographic constraints, are not offered HAI. HAI pump was placed as previously reported.[7] HAI adjuvant therapy consisted of HAI with FUDR mixed with dexamethasone plus heparinized saline administered for a two-week infusion alternating with 2 weeks of heparinized saline alone every month generally for a total of six cycles if liver functions tolerate. Patients who received neoadjuvant HAI chemotherapy for unresectable disease, continued with adjuvant HAI therapy after hepatic resection with systemic chemotherapy. Post-operative systemic chemotherapy was based on prior exposure to chemotherapy at the discretion of the treating oncologist. Patients, at the time of recurrence, were treated with standard ‘modern’ chemotherapy. Treatment details were determined by the treating medical oncologist and HAI dose reduction were performed

as previously described.[9] Patients who received HAI therapy for recurrent disease but not as adjuvant therapy with their initial hepatic resection were excluded from the analysis. In the uncommon situation of disappearing lesions, MRI and intra-operative ultrasound was used for assessment and surgical guidance. If these lesions were still not visible on either study, in a small subset of patients 'disappearing lesions' were not resected.

Statistical analysis

Surveillance scans were performed every 3 to 6 months unless otherwise indicated. Recurrent disease was confirmed by imaging including CT, MRI, or PET and defined from the time of hepatic resection to date of first recurrence. OS was calculated from the time of hepatic resection to last date of follow up or date of death. OS and RFS were estimated using the Kaplan-Meier method. Log rank test was used to determine the association between KRAS mutational status and other clinical and pathological factors. Recurrence sites were recorded from the initial recurrence and calculated from the time of hepatic resection. Recurrence sites were defined as liver (liver only and multiple sites including liver), lung, and other metastatic sites. Multivariable Cox regression models using backward selection starting with all the significant variables in the univariate analysis (p-value <0.05) were created except for overlapping variables with similar biologic information, that is, those included in the clinical risk score (lymph node status, DFI <12 months, solitary metastases, median size of largest lesion, synchronous/metachronous, number of tumors) and 2-stage hepatectomy.

Results

A total of 2690 patients with CRLM who had undergone complete resection were evaluated. Of these 2690 patients, 674 had known mutational KRAS status (418 KRAS-WT, 256 KRAS-MUT) and were assessed in this analysis. The median follow-up for these 674 patients was 6.5 years. Fifty-four percent (n=366) received HAI chemotherapy: 308 (84%) in the adjuvant setting and 59 (16%) prior to and after resection for patients with initially unresectable disease. Almost all patients (n=649, 96%), whether they received HAI or not, received perioperative systemic chemotherapy.

Baseline tumor characteristics were significantly worse in the HAI group, with the exception that extrahepatic metastases being greater in the no-HAI group (Table 1). Patients treated with HAI were more likely to have advanced disease including higher rates of synchronous disease, larger number of tumors, higher clinical-risk scores, and rates of 2-stage hepatectomy. Median age was younger in the HAI group (55; 47–63 years) compared to the no-HAI group (62.5; 52–71 years) (p<0.001).

Recurrence Free Survival

For the entire cohort, the median RFS was 1.4 years [95% CI: 1.27 – 1.57] with a 5-year RFS of 29% [95% CI: 26–33%]. A total of 214 patients (31.8%) experienced a hepatic recurrence at their initial recurrence (KRAS-WT (n=121), KRAS-MUT (n=93)), of whom 135 (20%) were observed within the liver only. Patients treated with adjuvant HAI and systemic therapy had a lower initial recurrence rate involving the liver (28.4 vs. 35.8%,

p<0.04) compared to patients in the no-HAI group. A total of 243 patients experienced an extra-hepatic recurrence as their first recurrence. One hundred and forty-three (21%) had received pump therapy compared to 100 (32%) who had systemic therapy only (p=0.06). Two-hundred and two patients (30%) recurred within the lungs (KRAS-WT (n=106), KRAS-MUT (n=96). Out of the 202 patients with lung as their initial site of recurrence, 119 (59%) had received HAI therapy compared to 83 (41%) who had systemic therapy only. Pump chemotherapy was not associated with a statistical difference in the lung recurrence rate (p=0.12). Five-year RFS for patients with KRAS-WT was 33% (29%−38%) and KRAS-MUT 23% (18%−29%), respectively (p<0.0001). 5-year RFS for patients treated with HAI vs. no HAI was 33% (28%−38%) and 25% (20%−30%), p<0.006), respectively. On univariate analysis, factors associated with shorter RFS were lack of adjuvant HAI, KRAS-MUT, positive margins, CRS greater than 3, EHD, node positive primary tumors, and presence of synchronous disease. Adjuvant HAI remained associated with improved RFS (HR= 0.68, 95% CI 0.52–0.89, p<0.005) independent of KRAS status and other clinico-pathologic factors on multivariate analysis (Table 2).

Overall Survival

Median OS for all patients was 6.6 years (6.0 – 8.3 years) with a 5-year OS of 62% (58%−66%). Five-year OS for patients with KRAS-WT was 69% (63%−73%) and KRAS-MUT 50% (43%−57%), HR= 1.65, p<0.0001; Supplemental Figure 1). Five-year OS for patients treated with HAI vs. no HAI was 70% (65%−75%) and 50% (43%−57%), HR= 0.52, p<0.0001; Supplemental Figure 2), respectively. Adjuvant HAI was associated with improved OS in both KRAS-WT patients (5-year OS 76% vs. 57%, HR= 0.51, p<0.001), as well as KRAS-MUT (5-year OS 59% vs. 40%, HR= 0.56, p<0.001) (Figure 1). On multivariate analysis, HAI was an independent predictor of OS independent of KRAS status and other clinico-pathologic factors (HR= 0.53, p<0.002, Table 3).

Discussion

In this study, we analyzed 674 consecutive patients who underwent complete resection of CRLM at a single institution who also had available KRAS data. With a median follow up of 6.5 years (0–22.9), we observed that patients with KRAS-MUT tumors had lower rates of hepatic recurrence at their initial recurrence episode as well as worse overall RFS and OS. Patients who received combination adjuvant HAI and systemic therapy had an associated prolonged RFS and OS compared to patients treated with adjuvant systemic therapy alone, independent of KRAS-status. Adjuvant HAI therapy was also independently associated with a lower rate of hepatic recurrence at the initial recurrence episode.

The liver is the most common site of metastatic disease developing in about 60% of all patients diagnosed with CRC. Complete resection is currently the only therapy associated with long term cure in CRC patients with hepatic metastases. Recurrence after complete resection remains high and a clinical challenge, with half of the recurrences involving the liver.[19] As such, understanding molecular alterations to identify new therapeutic targets and prognostic factors has received much attention in the field. KRAS, an oncogene located downstream of the epidermal growth factor receptor (EGFR), is a known mutation in

approximately 14–37% in resectable metastatic CRC patients and described in a recent meta-analysis as an independent poor prognostic factor, associated with worse survival outcomes.[20] A study by Karagkounis documented a 5-year survival of 49.8% versus 57.4% and 3-year RFS of 27.7% compared with 34% for KRAS-MUT versus KRAS-WT tumors after hepatic resection, respectively.[12] Similarly, MD Anderson Cancer Center reported lower 3-year RFS 13.5% versus 33.4% and OS of 52% versus 81% for KRAS-MUT versus KRAS-WT after hepatic resection, respectively.[13] Our previous results corroborate these findings, demonstrating that patients with KRAS mutations have increased risk of overall recurrence, shorter RFS (30% vs. 46%) and OS (81% vs. 95%).[10] In the current study, we see comparable results with 3-year RFS (28% vs. 38%) and OS (69% and 86%) for KRAS-MUT versus KRAS-WT tumors ($p<0.05$).

Although newer systemic chemotherapy regimens such as oxaliplatin and irinotecan have resulted in higher response rates, second and third line therapies have very limited efficacy in progressive disease. As such, regional HAI has been used for decades to improve regional control and prolong survival. HAI has been evaluated as adjuvant treatment in CRC patients who undergo hepatic resection and 3 randomized controlled trials have shown improved hepatic-free survival. The largest trial, performed at our institution, demonstrated improved hepatic and overall RFS rates for patients with HAI and systemic chemotherapy compared with systemic treatment alone. Median RFS was 31 versus 17 months and median hepatic RFS was not reached versus 42 months for HAI along with systemic versus systemic therapy alone, respectively.[8] Our most recent report of 2368 patients who completed resection for CRLM found that patients treated with adjuvant HAI and systemic chemotherapy had a median survival of 67 months compared with 44 months for those treated without HAI ($p<0.001$). Looking specifically into the era of modern chemotherapy, a matched cohort analysis revealed that adjuvant HAI was independently associated with improved disease-free and overall survival.[21] And although response rates have improved with modern chemotherapy, modern adjuvant therapy has not been proven to impact overall survival. [4,5] In fact, comparison to surgery alone or 5-FU alone, modern agents have not been shown to make a difference in oncologic outcomes in randomized trials.

Congruent with those results, we demonstrate in this study that adjuvant HAI was associated with improved OS in patients with KRAS-WT tumors compared with systemic therapy alone. However, the main finding of the current study is that adjuvant HAI was also associated with improved outcomes for patients with KRAS-MUT (5-year OS 59% vs. 40%, HR= 0.56, $p<0.001$) tumors. We demonstrated a nearly significant trend towards increased extrahepatic recurrence in the group of patients receiving pump chemotherapy ($p=0.06$), however we believe that this is likely related to selection bias as patients in the HAI group had overall worse prognostic factors at baseline. On multivariate analysis, HAI remained associated with improved OS (HR 0.53, $p<0.002$) independent of KRAS status and other clinico-pathologic factors. Comparing 5-year OS, our data revealed similar outcomes for KRAS-MUT patients treated with HAI and systemic therapy (59%) than for KRAS-WT patients treated with systemic chemotherapy only (57%). To that affect, an argument can be made that adjuvant HAI can potentially enhance the worse clinical outcomes of KRAS-MUT tumors with comparable survival rates to that of KRAS-WT. Although administration of HAI takes a specialized team, its low cost and acceptable toxicity profile make it a very

attractive treatment strategy as an adjunct to systemic therapy given its impact on overall survival.

This study has several limitations inherent to its retrospective nature including a highly selected study population presenting to a tertiary care center and unknown confounding factors. Although this study was conducted using data from a prospectively constructed database of patients undergoing resection, a number of patients were excluded from the initial population because of missing genetic data. We also acknowledge that there has been significant evolution in systemic therapy over the study period and this analysis does not include details of the type of systemic therapy administered. However, all patients were treated at a single high-volume cancer center in which modern systemic therapy was used in both arms. The HAI group at our institution receives on average a dose reduction of 10–15% to decrease overall systemic side effects when receiving combination therapy compared to systemic only group. Moreover, in our most recent work, we show that the difference in OS remained similar after excluding patients who did not receive modern systemic chemotherapy (median OS, 67 *v* 47 months; $p < .001$). Finally, multiple randomized trials have documented that adjuvant modern systemic chemotherapy does not improve overall survival.

In conclusion, we investigated the impact of HAI in relation to KRAS mutational status in patients with resected CRLM and found that HAI is independently associated with improved OS regardless of KRAS mutational status. Adjuvant HAI may mitigate the worse prognosis in patients with resectable KRAS-MUT CRLM. With regards to using mutational analysis to guide treatment planning, we believe that KRAS status should not affect patient selection and be an exclusion criteria for adjuvant regional HAI therapy. Adjuvant HAI should be considered for patients with KRAS mutations given the known poor outcomes with systemic chemotherapy alone.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Ferlay J, Soerjomataram I, Ervik M, et al.Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. GLOBOCAN 2012:1. Lyon, France: International Agency for Research on Cancer; 2013.
2. Siegel R, Naishadham D, Jemal A. Cancer Statistics. CA Cancer J Clin. 2012;62:10–29. [PubMed: 22237781]
3. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al.Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol. 2007;25:4575–4580. [PubMed: 17925551]
4. Nordlinger B, Sorbye H, Glimelius B, et al.Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol. 2013;14:1208–1215. [PubMed: 24120480]

5. Portier G, Elias D, Bouche O, et al.Multicenter randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: FFCD ACHBTH AURC 9002 trial. J Clin Oncol. 2006;24:4976–4982. [PubMed: 17075115]
6. Kemeny NIs hepatic infusion of chemotherapy effective treatment for liver metastases? Yes! In: Important Adv Oncol. 1992:207–227. [PubMed: 1533847]
7. Kemeny N, Huang Y, Cohen a M, et al.Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. N Engl J Med. 1999;341:2039–2048. [PubMed: 10615075]
8. Kemeny NE, Gonen M. Hepatic Arterial Infusion after Liver Resection. N Engl J Med. 2005;352:734–735. [PubMed: 15716576]
9. Kemeny MM, Adak S, Gray B, et al.Combined-modality treatment for resectable metastatic colorectal carcinoma to the liver: surgical resection of hepatic metastases in combination with continuous infusion of chemotherapy--an intergroup study. J Clin Oncol. 2002;20:1499–1505. [PubMed: 11896097]
10. Kemeny NE, Chou JF, Capanu M, et al.KRAS mutation influences recurrence patterns in patients undergoing hepatic resection of colorectal metastases. Cancer. 2014;120:3965–3971. [PubMed: 25155157]
11. Cejas P, López-Gómez M, Aguayo C, et al.KRAS mutations in primary colorectal cancer tumors and related metastases: A potential role in prediction of lung metastasis. PLoS One. 2009;4(12):e8199. [PubMed: 20020061]
12. Karagkounis G, Torbenson MS, Daniel HD, et al.Incidence and prognostic impact of KRAS and BRAF mutation in patients undergoing liver surgery for colorectal metastases. Cancer. 2013;119:4137–4144. [PubMed: 24104864]
13. Vauthey J, Zimmitti G, Kopetz SE, et al.RAS mutation status predicts survival and patterns of recurrence in patients undergoing hepatectomy for colorectal liver metastases. Ann Surg. 2013;258:619–626; discussion 626–627. [PubMed: 24018645]
14. Petrowsky H, Sturm I, Graubitz O, et al.Relevance of Ki-67 antigen expression and K-ras mutation in colorectal liver metastases. Eur J Surg Oncol. 2001;27:80–87. [PubMed: 11237496]
15. Nash GM, Gimbel M, Shia J, et al.KRAS Mutation Correlates With Accelerated Metastatic Progression in Patients With Colorectal Liver Metastases. Ann Surg Oncol. 2010;17:572–578. [PubMed: 19727962]
16. Brudvik KW, Kopetz SE, Li L, et al.Meta-analysis of KRAS mutations and survival after resection of colorectal liver metastases. Br J Surg. 2015;102:1175–1183. [PubMed: 26206254]
17. Edge SB, Byrd DR, Compton CC, et al.TA. AJCC Cancer Staging Handbook: from the AJCC Cancer Staging Manual (7th edition). Am Jt Commitee Cancer. 2010;38:2011.
18. Fong Y, Fortner J, Sun RL, et al.Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg. 1999;230:309–318. [PubMed: 10493478]
19. de Jong MC, Pulitano C, Ribero D, et al.Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. Ann Surg. 2009;250(3):440–8. [PubMed: 19730175]
20. Passiglia F, Bronte G, Bazan V, Galvano A, Vincenzi B, Russo A. Can KRAS and BRAF mutations limit the benefit of liver resection in metastatic colorectal cancer patients? A systematic review and meta-analysis. Crit Rev Oncol Hematol. 2016;99:150–157. [PubMed: 26775732]
21. Groot Koerkamp B, Sadot E, Kemeny NE, et al.Perioperative Hepatic Arterial Infusion Pump Chemotherapy Is Associated With Longer Survival After Resection of Colorectal Liver Metastases: A Propensity Score Analysis. J Clin Oncol. 2017;35:1938–1944. [PubMed: 28426374]

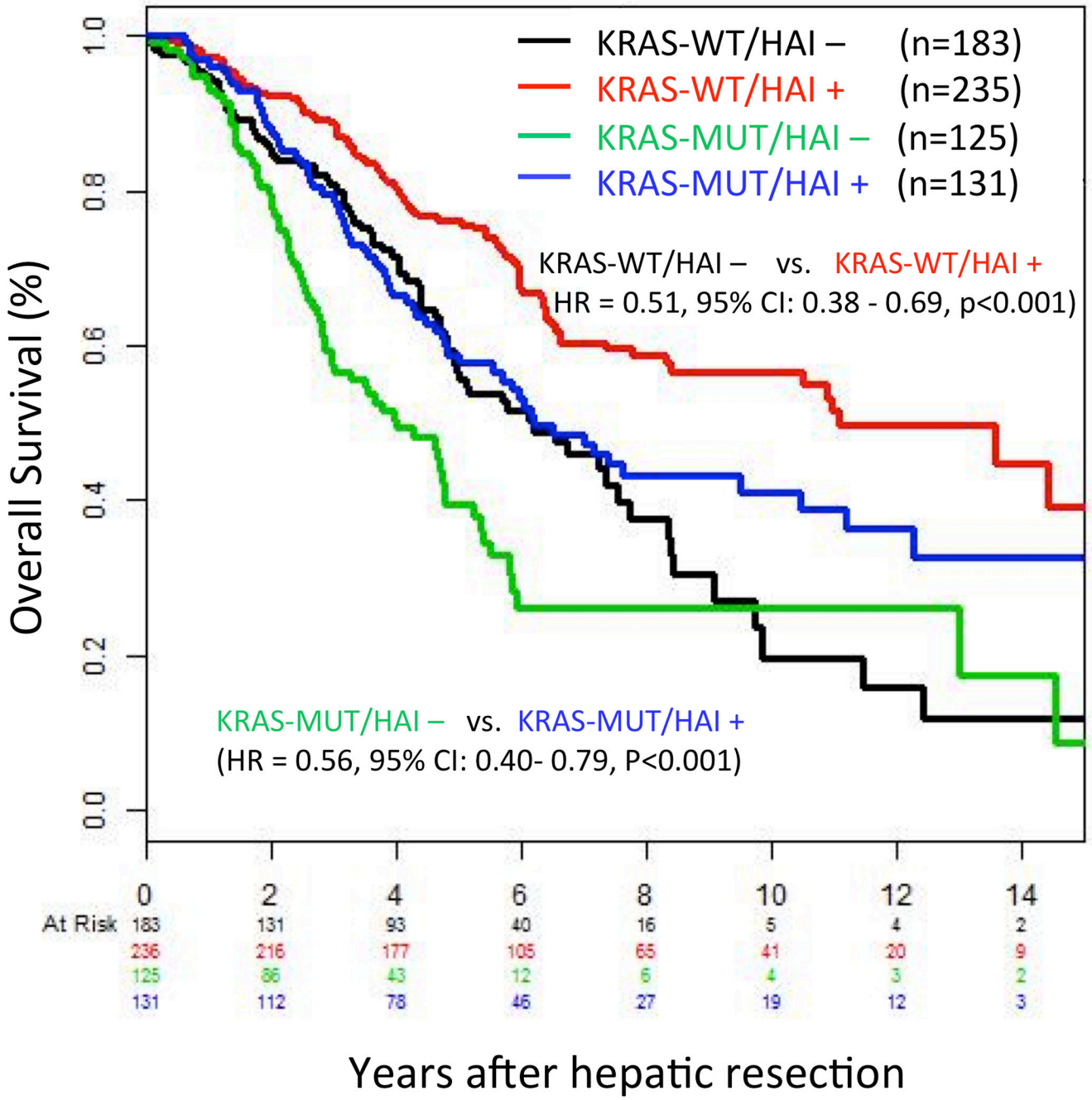

Figure 1.

Overall survival after liver resection for colorectal liver metastases (CRLM) according to KRAS status (wild-type, WT; mutant, MUT) and treatment with (HAI+) and without (HAI-) adjuvant hepatic after infusion chemotherapy.

Table 1.

Clinical and pathologic characteristics of all consecutive patients who underwent curative-intent resection with available KRAS-status from 1993–2012

Variable (median, range)	No HAI n = 308	HAI n = 366	P-value
Age	62.5 (52 – 71)	55.0 (47– 63)	<0.001
Gender			
male	179 (58)	205 (56)	0.66
female	129 (42)	161 (44)	
KRAS status			
wild-type (WT)	183 (60)	235 (64)	0.22
mutant (MUT)	125 (40)	131 (36)	
Number of metastases	1 (1–12)	3 (1–15)	<0.001
Solitary metastasis	144 (47)	80 (22)	<0.001
More than 3 CRLM	70 (22)	173 (47)	<0.001
Number of patients treated with ablation	44 (14.3)	108 (29.5)	<0.001
Extra-hepatic disease	42 (14)	26 (7)	0.02
Synchronous	183 (60)	246 (67)	0.04
Metachronous	125 (40)	120 (32)	
Extend of Surgery			
Major hepatectomy	119 (39)	154 (42)	0.36
Minor hepatectomy	189 (61)	212 (58)	
2-stage hepatectomy	5 (2)	43 (12)	<0.001
Disease-free interval <12 mo	229 (75)	300 (82)	0.02
Median size largest lesion (cm)	3.0 (2–15.6)	2.6 (1.6–20.0)	0.20
Nodal status of primary tumor			
node-positive	187 (61)	234 (64)	0.56
node-negative	118 (39)	132 (36)	
Margin status			
Positive	31 (10)	35 (10)	0.92
Negative	277 (90)	331 (90)	
CRS 3–5	129 (45)	211 (59)	<0.001

HAI = Hepatic artery infusion; CRS = Clinical Risk Score; CRLM = Colorectal liver metastases

Table 2.

Univariate and Multivariate Analysis of Predictors of Recurrence-Free Survival

VARIABLE	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS	
	HR (CI)	P-VALUE	HR (CI)	P-VALUE
HAI	0.706 (0.59–0.84)	<0.001	0.68 (0.52–0.89)	<0.005
KRAS Mutation	1.39 (1.16–1.67)	<0.001	1.35 (1.04–1.76)	0.003
Surgical margins	1.88 (1.42–2.47)	<0.001	1.99 (1.29–3.06)	<0.001
Age	0.99 (0.99–1.9)	0.47		
Gender	0.92 (0.68–1.10)	0.37		
Number of metastases	1.12 (1.07–1.17)	<0.001		
Nodal status of primary tumor	1.30 (1.10–1.60)	0.003		
Disease-free interval <12 mo	1.50 (1.20–1.89)	<0.001		
Solitary metastases	0.65 (0.53–0.79)	<0.001		
Synchronous	1.4 (1.12–1.76)	0.003		
Metachronous				
Median size largest lesion (cm)	1.05 (1.02–1.08)	0.005		
CRS >3	1.92 (1.43–2.56)	<0.001	1.76 (1.34–2.32)	<0.001
Extrahepatic disease	1.8 (1.36–2.48)	<0.001	1.74 (0.27–2.37)	<0.001
2-stage hepatectomy	1.4 (1.06–2.05)	0.02		

HAI = Hepatic artery infusion; CRS = Clinical Risk Score; CRLM = Colorectal liver metastases

Table 3.

Univariate and Multivariate Analysis of Predictors of Overall Survival after Curative-Intent Resection of CRLM

VARIABLE	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS	
	HR (CI)	P-VALUE	HR (CI)	P-VALUE
HAI	0.52 (0.42–0.65)	<0.001	0.53 (0.39–0.77)	<0.002
KRAS Mutation	1.64 (1.31–2.06)	<0.001	1.66 (1.19–2.30)	<0.001
Surgical margins	2.30 (1.68–3.27)	<0.001	2.3 (1.40–3.73)	<0.001
Age	1.00 (0.99–1.02)	0.07		
Gender	0.83 (0.66–1.05)	0.12		
Number of metastases	1.12 (1.06–1.19)	<0.001		
Nodal status of primary tumor	1.49 (1.18–1.90)	<0.001		
Solitary metastases	0.73 (0.57–0.94)	0.02		
Disease-free interval <12 mo	1.33 (1.00–1.75)	0.04		
Synchronous vs. Metachronous	0.9 (0.60–1.29)	0.56		
Median size largest lesion (cm)	1.23 (0.94–1.59)	0.13		
CRS >3	1.59 (1.2–2.01)	<0.001	1.74 (1.24–2.43)	<0.001
Extrahepatic disease	2.12 (1.48–3.05)	<0.001	2.0 (1.37–2.92)	<0.001
2-stage hepatectomy	1.5 (1.04–2.26)	0.03		

HAI = Hepatic artery infusion; CRS = Clinical Risk Score; CRLM = Colorectal liver metastases