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## **RAS mutations predict radiologic and pathologic response in patients treated with chemotherapy prior to resection of colorectal liver metastases**

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### **Abstract**

**Purpose**—*RAS* mutations have been reported to be a potential prognostic factor in patients with colorectal liver metastases (CLM). However, the impact of *RAS* mutations on response to chemotherapy remains unclear. We sought to determine the association between *RAS* mutations and response to preoperative chemotherapy and their impact on survival in patients undergoing curative resection of CLM.

**Methods**—*RAS* mutational status was assessed and its relation to morphologic response and pathologic response was investigated in 184 patients meeting inclusion criteria. Predictors of survival were assessed. The prognostic impact of *RAS* mutational status was then analyzed using two different multivariate models including either radiologic morphologic response (model 1) or pathologic response (model 2).

**Results**—Optimal morphologic response and major pathologic response were more common in patients with wild-type *RAS* (32.9% and 58.9%, respectively) than in patients with *RAS* mutations (10.5% and 36.8%;  $P = .006$  and  $.015$ , respectively). Multivariate analysis confirmed that wild-type *RAS* was a strong predictor of optimal morphologic response (odds ratio [OR], 4.38; 95% CI, 1.45–13.2) and major pathologic response (OR, 2.79; 95% CI, 1.29–6.04). *RAS* mutations were independently correlated with both overall survival and recurrence free-survival (hazard ratios,

3.25 and 2.02, respectively, in model 1, and 3.19 and 2.23, respectively, in model 2). Subanalysis revealed that *RAS* mutational status clearly stratified prognosis in patients with inadequate response to preoperative chemotherapy.

**Conclusion**—*RAS* mutational status can be used to complement the current prognostic indicators for patients undergoing curative resection of CLM after preoperative modern chemotherapy.

### Keywords

*RAS* mutation; response to chemotherapy; prognosis; colorectal liver metastasis

## INTRODUCTION

Recent developments in chemotherapy and multidisciplinary approaches have changed the prognosis of patients with colorectal liver metastases (CLM).[1, 2] As a result, traditional prognostic factors such as disease-free interval, tumor number, tumor size, serum carcinoembryonic antigen level, and lymph node status have become less reliable.[3-8] Our group has previously reported that pathologic[9] and radiologic morphologic responses[10, 11] to preoperative chemotherapy are potent prognostic indicators for patients undergoing resection of CLM. However, most patients would be classified as inadequate responders according to these criteria, with 70% experiencing a suboptimal morphologic response[11] and 55% experiencing a minor pathologic response.[9] Moreover, the molecular bases for these prognostic indicators remain unclear.

During the last decade, the study of somatic gene mutations has become a focus of colorectal cancer research.[12-16] Especially, the mutational status of the *RAS* oncogene family (*KRAS*, *NRAS*, and the rarer *HRAS*) has been shown to be a strong predictor of response to anti-epidermal growth factor receptor (EGFR) agents.[16-18] Furthermore, two recent studies have suggested that *KRAS* mutation is a predictor of worse survival in patients undergoing resection of CLM regardless of the use of bevacizumab.[19, 20] Additionally, our group previously reported that *KRAS* mutation is related to more aggressive tumor biology.[21] However, the prognostic impact of *RAS* oncogene family mutation remains unclear, and little is known about the association between *RAS* mutational status and radiologic morphologic and pathologic responses to chemotherapy.

This study aimed to identify predictors of survival after curative resection of CLM, to define associations between *RAS* mutations and pathologic and/or morphologic response to chemotherapy, and finally, to assess whether *RAS* mutational status further stratifies patient prognosis within subgroups defined according to type of response to chemotherapy.

## PATIENTS AND METHODS

### Study Population

We searched the prospectively maintained hepatobiliary database at The University of Texas MD Anderson Cancer Center to identify patients who had undergone curative resection of CLM (without concomitant radiofrequency ablation) after a fluorouracil-based irinotecan regimen or a fluorouracil-based oxaliplatin regimen that included bevacizumab. Patients

previously treated for hepatic and extrahepatic colorectal cancer metastases were excluded from our analysis, as were those who had received pre- or postoperative anti-EGFR agents, those who died within 90 days after hepatectomy, and those who had a viable tumor cell rate <5% in their CLM specimen. This study was approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center (PA12-0736).

### Somatic Gene Mutation Profiling

DNA extracted from formalin-fixed, paraffin-embedded resected CLM was analyzed with Sequenom MassArray technology (Sequenom, Inc, San Diego, CA) using a protocol developed in one of our institutional core facilities.[22] Tumor position was identified on slides with standard hematoxylin-eosin staining and microdissected. A total of 17 point mutations at codons 12, 13, 61, and 146 were tested in the *RAS* gene family (including *KRAS* and *NRAS*). Sequenom's MassArray system utilizes polymerase chain reaction amplification and single-base primer extension for mutation detection.[23-25]

### Assessment of Radiologic Morphologic Response to Chemotherapy

Computed tomographic scans were performed using a triphasic liver protocol or single-phase technique, as previously described.[10] The radiologic morphologic response of CLM was assessed by two independent radiologists (K.H. and E.M.L.) blinded to clinical data, according to the following previously described criteria: group 1, homogeneous low attenuation with a thin, sharply defined tumor-liver interface; group 3, heterogeneous attenuation with a thick, poorly defined tumor-liver interface; and group 2, intermediate morphology that cannot be classified as either group 1 or group 3.[10, 11] Optimal radiologic morphologic response to chemotherapy was defined as a change in morphology from group 3 or 2 to group 1. Suboptimal morphologic response was defined as a change in morphology from group 3 to group 2 or the absence of remarkable changes in morphology. In patients with multiple tumors, morphologic response was determined according to the response seen in the majority of tumors or, in patients with two CLM, in the largest one.

### Assessment of Pathologic Response to Chemotherapy

Hematoxylin-eosin-stained specimens sectioned into 5-mm-thick slices were evaluated by a gastrointestinal pathologist who was blinded to clinical data. The extent of residual carcinoma was assessed semiquantitatively as the percentage of the total tumor surface area composed of residual viable tumor cells, as previously described. Pathologic response was scored as minor if residual viable tumor cells made up  $\geq 50\%$  of the total tumor surface area and major if residual viable tumor cells made up < 50% of the total tumor surface area.[9]

### Statistical Analysis

To identify predictors of optimal morphologic response and major pathologic response, categorical variables were compared using the  $\chi^2$  test or Fisher's exact test, and continuous variables were compared using the Mann-Whitney *U* test, where appropriate. Overall survival (OS) was measured from the date of hepatectomy until the date of death or last follow-up. Recurrence-free survival (RFS) was measured from the date of hepatectomy until the date of radiographic detection of any recurrence or last follow-up. Survival curves were

generated using the Kaplan-Meier method, and survival differences were evaluated with the log-rank test.

Based on results from previous studies, 11 variables were identified as the most important factors affecting survivals after liver resection for CLM and consequently included in univariate analysis of predictors of OS and RFS: disease-free interval between primary tumor and CLM diagnosis, Primary tumor location (colon vs rectum), Primary tumor nodal status, presence of extrahepatic metastases, number of preoperative chemotherapy cycles, number and diameter of CLM, positive surgical margin, pathologic and morphologic response to chemotherapy, and RAS mutational status.

To identify independent prognostic factors for RFS and OS, all variables included in the univariate analysis (except pathologic response in model 1 and morphologic response in model 2) were subsequently included in a multivariate regression analysis, performed using the Cox proportional hazards model with backward elimination for variables with  $P < .1$ . Given the strong colinearity between pathologic and morphologic responses to chemotherapy, prognostic factors influencing survival were analyzed using two different multivariate models that included either pathologic response (model 1) or morphologic response (model 2).[10, 11] To identify factors associated with optimal morphologic or major pathologic response, a multivariate analysis was performed using the logistic regression model for clinical variables with  $P < .1$  in univariate analysis. Statistical analyses were performed using IBM SPSS software (version 19.0; SPSS Inc., IL, USA). All statistical tests were two-sided, and significance was set at  $P < .05$ .

## RESULTS

### Patient Characteristics and comparison of patients according to RAS mutational status

Of the 308 patients initially eligible for this study, we excluded 36 patients who lacked tissue samples for DNA extraction owing to complete pathologic response, 30 patients whose DNA samples were of insufficient quality for Sequenom analysis, and 58 patients whose computed tomographic images were of insufficient quality or whose lesions were too small (<10 mm after preoperative chemotherapy) for morphologic response to be determined. Baseline characteristics of the remaining 184 patients included in the current study are summarized in Table 1. *RAS* mutations were seen in 38 patients (21% of the population; 32 had *KRAS* mutation and 6 had *NRAS* mutation). There was no significant difference in demographic and clinical characteristics between the patients with *RAS* mutation and those without, except for optimal morphologic and major pathologic response, which were significantly more frequent among *RAS* wild-type patients, compared to *RAS* mutants. *BRAF* mutation was observed only in 1 patient with *RAS* wild type.

### Predictors of Pathologic and Morphologic Response to Chemotherapy

Optimal morphologic response was observed in 52 of the 184 patients (28%), and major pathologic response was observed in 100 patients (54%). Tumor cell viability differed according to morphologic response (median viability, 30% [range, 5%-70%] in patients with optimal response vs. 50% [range, 5%-90%] in patients with suboptimal response [ $P < .001$ ]).

Optimal morphologic response and major pathologic response were more common in patients with wild-type *RAS* (32.9% and 58.9%, respectively) than in patients with *RAS* mutations (10.5% and 36.8%;  $P = .006$  and  $.015$ , respectively). Multivariate analysis showed that wild-type *RAS* (odds ratio [OR], 4.38; 95% confidence interval [CI], 1.45-13.2) and largest CLM size  $\geq 3$  cm (OR, 1.98; 95% CI, 1.02-3.87) was associated with optimal morphologic response. Wild-type *RAS* (OR, 2.79; 95% CI, 1.29-6.04) and CLM size  $\geq 3$  cm (OR 2.39; 95% CI, 1.25-4.59) was also associated with major pathologic response (Table 2).

When classifying patients according to percentage of viable tumor cells, *RAS* mutation rate decreased as the percentage of viable tumor cells declined. *RAS* mutation rate was 33% in patients with more than 80% of viable tumor, 29% in those with viable tumors cells ranging between 61 and 80%, 26% among patients with 41-60% of viable tumor cells, 15% in those with 21-40% of viable cells, and 13% in those with 5-20% viable cells ( $P = .021$ ).

### Risk Factors for Decreased OS and RFS

Multivariate analysis showed that independent predictors of decreased OS were *RAS* mutation (hazard ratio [HR], 3.25), minor pathologic response (HR, 1.78), and having undergone  $>6$  preoperative chemotherapy cycles (HR, 1.70) in model 1 and *RAS* mutation (HR, 3.19), suboptimal morphologic response (HR, 2.32), and positive nodal status for the primary tumor (HR, 1.95) in model 2 (Table 3). Multivariate analysis for RFS revealed that independent predictors of decreased RFS were *RAS* mutation (HR, 2.02), having undergone  $>6$  chemotherapy cycles (HR, 1.57), and minor pathologic response (HR: 1.78) in model 1 and *RAS* mutation (HR, 2.23), suboptimal morphologic response (HR, 1.81), having undergone  $> 6$  chemotherapy cycles (HR, 1.44), and largest CLM  $>5$  cm (HR, 1.89) in model 2.

### Survival Outcomes

After a median follow-up of 33 months, 64 patients had died (61 of cancer and three of other causes), 40 were alive with disease recurrence, and 80 were alive with no evidence of disease at last follow-up. OS rates for the entire cohort were 97.8% at 1 year, 72.6% at 3 years, and 52.4% at 5 years. The 5-year OS rate was higher for patients with major pathologic response (64.2%) than for those with minor pathologic response (44.6%;  $P = .005$ ) (Fig 1A), higher for patients with optimal morphologic response (72.9%) than for those with suboptimal morphologic response (42.9%;  $P = .007$ ) (Fig 1C), and higher for patients with wild-type *RAS* (61.6%) than for those with *RAS* mutation (23.2%;  $P < .001$ ; Table 3). Likewise, the 5-year RFS rate was higher for patients with major pathologic response (35.8%) than for those with minor pathologic response (16.5%;  $P < .001$ ), higher for patients with optimal morphologic response (39.8%) than for those with suboptimal morphologic response (22.2%;  $P = .002$ ), and higher for patients with wild-type *RAS* (31.7%) than for those with *RAS* mutation (NA;  $P < .001$ ).

Additional subanalysis revealed that among patients with minor pathologic response (Fig 1B), patients with *RAS* mutation had a significantly worse 3-year OS rate than patients with wild-type *RAS* (30.9% v 72.3%). Similarly, among patients with suboptimal morphologic

response (Fig 1D), patients with *RAS* mutation had a significantly worse 3-year OS rate than patients with wild-type *RAS* (41.8% v 76.8%).

## DISCUSSION

In this study, we analyzed 184 patients who underwent curative resection after receiving a fluorouracil-based irinotecan regimen or a fluorouracil-based oxaliplatin regimen that included bevacizumab. *RAS* mutational status independently predicted both morphologic response and pathologic response to this type of chemotherapy. *RAS* mutational status also independently predicted both OS and RFS, and further subanalysis revealed that *RAS* mutational status stratified survival outcomes in patients with suboptimal morphologic response or minor pathologic response to chemotherapy.

In the era of modern chemotherapy, pathologic response[9, 26, 27] and morphologic response[10, 11] have been proposed as new endpoints to predict long-term outcomes in patients undergoing resection of CLM after chemotherapy. However, these response criteria can be used only after chemotherapy, and the molecular bases for differences in susceptibility to chemotherapy remain unclear. *RAS* mutation is a well-known predictor of lack of response to anti-EGFR agents in both patients with advanced metastatic colorectal cancer[16, 18] and patients with metastases limited to the liver.[28] Additionally, a growing body of evidence suggests that the *RAS* mutational status of CLM might be associated with tumor aggressiveness.[19-21]

In this study, optimal morphologic response was less common in patients with *RAS* mutation (10.5%) than those with wild-type *RAS* (32.9%). Likewise, major pathologic response was less common in patients with *RAS* mutation (36.8%), than in those with wild-type *RAS* (56.8%). As confirmed in the present study, there was an association between *RAS* mutation rate and percentage of viable tumor cells after preoperative chemotherapy. These results suggest that *RAS* mutational status would be a strong predictor of response to chemotherapy not only in patients receiving anti-EGFR antibodies as previously reported, but also in patients receiving preoperative modern chemotherapy containing bevacizumab.

Another important result was that the prognosis of patients with optimal morphologic or major pathologic response was favorable independent of *RAS* mutational status. In contrast, among patients with suboptimal morphologic or minor pathologic response to chemotherapy, those with *RAS* mutation had a significantly lower OS rate than did those with wild-type *RAS* (Fig 1). These results indicate that *RAS* mutational status is not only associated with response to preoperative chemotherapy, but is also a strong prognostic factor in patients with poor response to chemotherapy.

The current data, if confirmed in larger studies, could be used to predict clinical outcomes precisely, not only after resection but also when resection is being considered. Among patients with multiple ill-located metastases necessitating extended, risky resections, a combination of radiologic response of CLM and *RAS* mutational status (determined by analyzing the primary tumor or by using biopsy specimens from the primary tumor or CLM) could help select patients who might benefit from a more aggressive surgical approach. In this study, among patients with a suboptimal morphologic response, those with wild-type

*RAS* had a 3-year OS rate of 76.8%, which was significantly higher than the OS rate for patients with *RAS* mutation (41.8%;  $P < 0.001$ ) (Fig 1C). Thus, while patients with a combination of suboptimal morphologic response and *RAS* mutation should generally be considered candidates for small/not technically demanding liver resection if negative margins can be reasonably expected, the same patients should be considered more cautiously for complex hepatectomy because the risk related to extensive hepatectomy may outweigh the limited potential survival benefit (Fig 2).

One criticism of this study is that *RAS* mutational status was determined on resected CLM and not on the primary tumor and that the two tumor sites might differ in mutational status. However, a growing body of evidence suggests a high rate of concordance in somatic gene mutational status between primary tumor and related metastases, strengthening the validity of our results.[29-33] Other potential criticisms of this study include its retrospective nature and the selected population. Although this study was conducted using data from a prospectively constructed database of patients undergoing resection of CLM, a number of patients were excluded from the initial population because of a lack of sufficient tumor for DNA extraction and Sequenom analysis. However, even after exclusion of patients with extremely good pathologic response to chemotherapy, morphologic and pathologic response independently predicted survival, consistent with results from previous studies based on large cohorts of patients[9, 11]. Moreover, *RAS* mutational status remained a powerful prognostic factor. Although OS may have been affected by anti-EGFR therapy after recurrence, the impact of *RAS* status on RFS suggests that anti-EGFR therapy has a minimal confounding effect.

In conclusion, we investigated the genetic backgrounds affecting pathologic response and morphologic response in patients treated with bevacizumab and found that *RAS* mutational status is associated with both morphologic and pathologic response to chemotherapy. *RAS* mutations, pathologic response, and morphologic response independently predict survival outcomes in patients undergoing resection of CLM after preoperative chemotherapy. *RAS* mutations clearly stratify survival outcomes in patients with inadequate response to chemotherapy. Finally, *RAS* mutational status should be used as a complementary molecular marker of response to chemotherapy and of prognosis both before and after preoperative chemotherapy for CLM. Wild-type *RAS* status may encourage some surgeons to pursue resection in patients with borderline resectable disease and suboptimal response to chemotherapy. As such, the current results may contribute to personalized care in the treatment of CLM.

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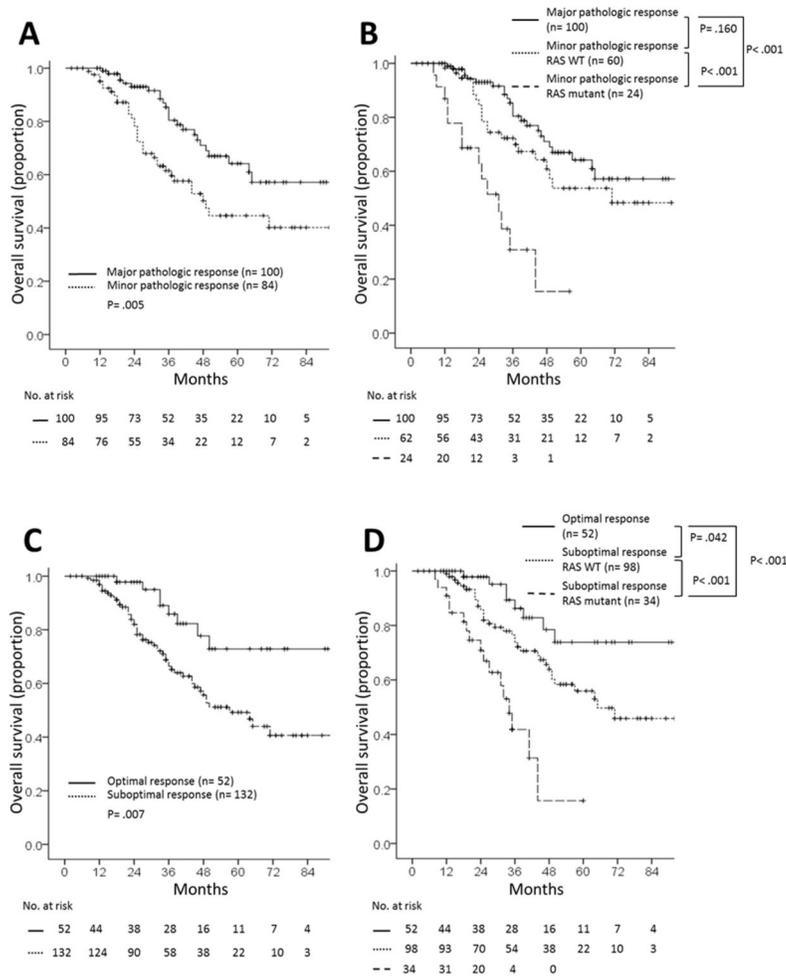
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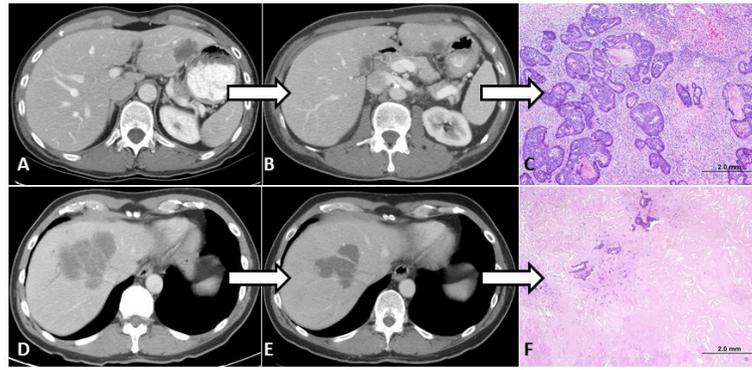
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**Fig 1.** (A-D) Cumulative overall survival curves for patients with major and minor pathologic response overall (A) and stratified according to *RAS* mutational status (B). Cumulative overall survival curves for patients with optimal and suboptimal morphologic response overall (C) and stratified according to *RAS* mutational status (D).



**Fig 2.** (A-C) A 57-year-old patient with a single CLM in segments 2-3 and *RAS* mutation. (A) Before initiation of treatment. (B) Suboptimal radiologic morphologic response after 4 months of preoperative FOLFOX (leucovorin, fluorouracil, and oxaliplatin) with bevacizumab. (C) Minor pathologic response (75% viable tumor cells in CLM) after resection. The patient died of disease 18 months after undergoing a partial left hepatectomy. (D-F) A 68-year-old patient with a single large CLM involving the origin of the right and middle hepatic veins and wild-type *RAS*. (D) Before initiation of treatment. (E) Optimal morphologic response after 3 months of preoperative FOLFOX with bevacizumab. (F) Major pathologic response (<10% viable tumor cells in CLM) after resection. As of this writing, the patient is alive and disease-free more than 5 years after extended right hepatectomy.

**Table 1**

Baseline Demographic and Clinical Characteristics of the study population and comparison of characteristics according to RAS mutational status.\*

Characteristic	Overall study population (n=184)		RAS mutational status		p value
			Mutant (n=38)	Wild-type (n=146)	
Age, years					
Median	58		58	57	.473
Range	25–84		33-81	25-84	
Sex					
Male	107	(58)	18 (47)	89 (61)	.130
Female	77	(42)	20 (53)	57 (39)	
Primary tumor location					
Rectum	37	(20)	6(16)	31 (21)	.476
Colon	147	(80)	32 (84)	115 (79)	
Primary tumor nodal status					
Negative	52	(28)	10 (26)	42 (29)	.765
Positive	132	(72)	28 (74)	104 (71)	
Extrahepatic metastases					
Yes	16	(9)	4(11)	12(8)	.653
No	168	(91)	36 (89)	134 (92)	
DFI, years					
<1	122	(66)	23 (61)	99 (68)	.398
1	62	(34)	15 (39)	47 (32)	
Multiple CLM					
Yes	62	(34)	14 (37)	48 (33)	.645
No	122	(66)	24 (63)	98 (67)	
CLM size at surgery, cm					
Median	2.5		2.5	2.5	.713
Range	1–15		1.2-13.5	1-15	
Fluorouracil-based chemotherapy regimen					
Oxaliplatin	137	(74)	25 (66)	112 (77)	.209
Irinotecan	47	(36)	13 (34)	34 (23)	
Number of preoperative chemotherapy cycles					
Median	6		8	6	.597
Range	5–18		6-18	5-18	

Characteristic	Overall study population (n=184)		RAS mutational status		p value
			Mutant (n=38)	Wild-type (n=146)	
Morphologic response					
Optimal	52	(28)	4(11)	48 (33)	.006
Suboptimal	132	(72)	34 (89)	96 (67)	
Pathologic response					
Major	100	(54)	14 (37)	86 (59)	.015
Minor	84	(46)	24 (63)	60 (41)	
Portal vein embolization	39	(21)	10 (26)	29 (20)	.363
Hepatectomy					
Major resection	123	(67)	25 (66)	98 (67)	.876
Minor resection	61	(33)	13 (34)	48 (33)	
Operating time, min					
Median	231		235	230	.880
Range	55-535		62-460	55-535	
Intraoperative transfusion	14	(8)	3(8)	11(8)	.915
Surgical margin					
Positive	23	(12)	7(18)	16(11)	.215
Negative	161	(88)	31 (82)	130 (89)	
Morbidity					
None	100	(54)	19 (50)	81 (55)	.168
Minor	51	(28)	8(21)	43 (30)	
Major	33	(18)	11 (29)	22(15)	
RAS mutational status					
Wild-type	146	(79)			
Mutant	38	(21)			
KRAS					
Codon 12	28/32	(88)			
Codon 13	2/32	(6)			
Codon 61	2/32	(6)			
Codon 146	0/32	(0)			
NRAS					
Codon 12	3/6	(50)			
Codon 13	0/6	(0)			
Codon 61	3/6	(50)			
Codon 146	0/6	(0)			

Abbreviations: DFI, disease-free interval; CLM, colorectal liver metastases.

\* Values in table are number of patients (%) unless otherwise specified.

**Table 2**  
Univariate and Multivariate Analysis of Predictors of Optimal Morphologic and Major Pathologic Response

Factor	Morphologic Response			Pathologic Response		
	Optimal Response (n = 52) (%)	Univariate Analysis P Value	Multivariate Analysis P OR 95% CI	Major Response (n = 100) (%)	Univariate Analysis P Value	Multivariate Analysis P OR 95% CI
DFI, years						
<1 (n = 122)	34 (27.9)	.868		61 (50)	.097	
1 (n = 62)	18 (29)			39 (62.9)		
Primary tumor location						
Rectum (n = 37)	11 (29.7)	.824		19 (51.4)	.682	
Colon (n = 147)	41 (27.9)			81 (55.1)		
Primary tumor nodal status						
Positive (n = 132)	36 (27.3)	.635		67 (50.8)	.119	
Negative (n = 52)	16(30.8)			33 (63.5)		
Preoperative chemotherapy						
>6 cycles (n = 66)	14(21.2)	.112		35 (53)	.788	
6 cycles (n = 118)	38 (32.2)			65 (55.1)		
Multiple CLM						
Yes (n = 122)	36 (29.5)	.598		66 (54.1)	.924	
No (n = 62)	16(25.8)			34 (54.8)		
Largest CLM at diagnosis						
3 cm (n = 72)	26 (36.1)	.058	.044	46 (63.9)	.037	.009
>3 cm (n = 112)	26 (23.2)		1.02-3.87	54 (48.2)		2.39 1.25-4.59
RAS mutational status						
Wild-type (n = 146)	48 (32.9)	.006	.008	86 (58.9)	.015	.009
			4.38			2.79 1.29-6.04

Factor	Morphologic Response				Pathologic Response			
	Optimal Response (n = 52) (%)	Univariate Analysis P Value	Multivariate Analysis	95% CI	Major Response (n = 100) (%)	Univariate Analysis P Value	Multivariate Analysis	95% CI
Mutant (n = 38)	4 (10.5)				14(36.8)			

Abbreviations: OR, odds ratio; DFI, disease-free interval; CLM, colorectal liver metastases.

Table 3

Univariate and Multivariate Analysis of Predictors of Overall Survival (OS)

Factor	5-year OS, %	Median OS, mo	Univariate Analysis			Multivariate Analysis*		
			P	HR	95% CI	Model 1	Model 2	Model 2
DFI, years								
<1 (n= 122)	49.6	71.4	.252	1.39	0.79-2.44			
1 (n= 62)	65.9	79.7						
Primary tumor location								
Rectum (n= 37)	47.8	71.4	.254	1.41	0.79-2.54			
Colon (n= 147)	57.3	74.8						
Primary tumor nodal status								
Positive (n= 132)	47.4	72.8	.031	2.06	1.07-3.97	.114	1.71	0.88-3.35
Negative (n= 52)	74.1	77.8						1.95 1.01-3.81
Extrahepatic metastases								
Yes (n= 16)	31.5	83.9	.765	1.16	0.42-3.23			
No (n= 168)	56	73.3						
Preoperative chemotherapy								
>6 cycles (n= 66)	42.6	63.7	.022	1.82	1.09-3.03	.044	1.70	1.01 - 2.86
6 cycles (n= 118)	64.5	81.4						.088 1.57 0.93-2.64
Multiple CLM								
Yes (n= 122)	53.3	74.6	.775	1.08	0.62-1.88			
No (n= 62)	60.3	73.4						
Largest CLM at surgery								
>5 cm (n= 26)	48.6	61.7	.199	1.54	0.80-2.96			
5 cm (n= 158)	56.4	76.5						
Positive margin								

Factor	5-year OS, %	Median OS, mo	Univariate Analysis			Multivariate Analysis*								
			P	HR	95% CI	Model 1		Model 2		P	HR	95% CI		
Yes (n= 23)	65.8	76.8	.959	1.02	0.44-2.38									
No (n= 161)	54.6	74.4												
Pathologic response														
Minor (n= 84)	44.6	61.5	.005	2.11	1.25-3.56	.033	1.78	1.05 - 3.03	-	-	-	-	-	-
Major (n= 100)	64.2	85.3												
Morphologic response														
Suboptimal (n= 132)	49.2	68.7	.007	2.78	1.31-5.85	-	-	-	.029	2.32	1.09-4.97			
Optimal (n= 52)	72.9	89												
RAS mutational status														
Mutant (n= 38)	23.2	43.4	<.001	3.57	1.99-6.40	<.001	3.25	1.80 - 5.87	<.001	3.19	1.75-5.78			
Wild-type (n= 146)	61.6	81.2												

Abbreviations: HR, hazard ratio; DFI, disease-free interval; CLM, colorectal liver metastasis.

\* In Model 1, all factors except morphologic response were entered in the multivariate analysis. In Model 2, all factors except pathologic response were entered in the multivariate analysis.