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Prognostic factors after resection of colorectal liver metastases following preoperative second-line chemotherapy: Impact of *RAS* mutations

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Abstract

Background—After resection of colorectal liver metastases (CLM), *RAS* mutations are associated with modest survival benefit and second-line chemotherapy confers limited hope for cure.

Objective—To evaluate the impact of *RAS* mutation after second-line chemotherapy for patients undergoing potentially curative liver resection for CLM.

Methods—Among 1357 patients operated for CLM between January 2005 and November 2014, patients with known *RAS* mutational status were identified. Outcomes after second-line chemotherapy were analyzed by *RAS* status.

Results—Among 635 patients undergoing resection of CLM, 46 received second-line chemotherapy before resection, including 14 patients (30%) with *RAS* mutations. Patients who received second-line chemotherapy had significantly larger and greater number of liver metastases and were more likely to undergo major hepatectomy. Median overall (OS) and recurrence free survival (RFS) were significantly worse among patients requiring second-line chemotherapy (OS: 44.4 vs. 61.1 months, $p = 0.021$; RFS: 7.3 vs. 12.0 months, $p = 0.001$). Among patients undergoing liver resection after second-line chemotherapy, *RAS* mutations were associated with worse median OS and RFS (OS: 35.2 vs. 60.7 months, $p = 0.038$; RFS: 3.6 vs. 8.3 months, $p = 0.015$). *RAS* mutation was the only independent factor associated with OS and RFS. All patients with *RAS* mutations recurred within 18 months. Among patients with *RAS* wild-type tumors, the receipt of second-line chemotherapy did not affect OS ($p = 0.493$).

Conclusion—Among patients undergoing resection of CLM after second-line chemotherapy, *RAS* mutational status is an independent predictor of survival and outweighs other factors to select patients for liver resection.

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Conflict of interest statement

All of the authors indicate no conflict of interest.

Keywords

RAS; Colorectal; Liver; Metastases; Chemotherapy

Introduction

For patients with stage IV colorectal cancer, the liver is the most common site of distant metastases.¹ Advances in modern chemotherapy and targeted agents have significantly improved response and survival rates for patients with colorectal liver metastases (CLM).²⁻⁴ To date, surgical resection of CLM offers the only possibility for cure.⁵ Tumor progression during preoperative chemotherapy is associated with poor outcomes after resection of CLM.⁶ For patients who progress on first-line chemotherapy, a change to a second-line regimen is recommended. However, survival in patients undergoing liver resection after second-line chemotherapy is limited with a modest hope of cure.⁷ Rat sarcoma viral oncogene homolog (*RAS*) mutations, found in up to 35% of patients with resected CLM, have been reported as a major prognostic factor for patients undergoing resection of CLM, irrespective of chemotherapy regimen.⁸ The prognostic impact of *RAS* mutations in patients undergoing hepatectomy after second-line chemotherapy has not been previously reported. The purpose of this study was to determine the outcomes of patients with *RAS* mutations who received second-line preoperative chemotherapy before CLM resection.

Methods

Population and definitions

This study was approved by the Institutional Review Board (IRB) of The University of Texas MD Anderson Cancer Center (IRB protocol PA15-0113). A retrospective review of a prospectively maintained database was performed of 1357 patients undergoing resection for CLM between January 2005 and November 2014. The study population was narrowed to patients with known *RAS* mutational status. Liver resection was considered curative when a complete tumor resection was achieved. Patients who received prior liver-directed treatment at other institutions were excluded.

The electronic medical record was queried for demographic data, clinicopathologic factors, *RAS* mutation status, preoperative treatment, and surgical procedure. Pathologic response to preoperative chemotherapy was graded as previously described.⁹ A positive resection margin was defined as tumor cells within 1 mm of the margin.¹⁰

RAS mutation profiling

RAS mutational status was determined from the primary tumor or liver metastases, as previously described.¹¹ Briefly, polymerase chain reaction-based primer extension assay was performed to screen for mutations in *KRAS* codons 12 and 13 in all patients and for mutations in *KRAS* codons 61 and 146 and *NRAS* codons 12, 13, and 61 in the majority of patients since 2012. The lower limit of detection of this assay was approximately one mutant allele in the background of nine wild-type alleles. Single mutations in the various codons of *KRAS* and *NRAS* were analyzed together and reported as *RAS* mutations.

Perioperative chemotherapy

At The University of Texas MD Anderson Cancer Center, the institutional guidelines for patients with CLM included preoperative chemotherapy in almost all patients.¹² Patients with resectable CLM who developed CLM within a year after the end of adjuvant chemotherapy for primary tumor could be an exception to this strategy. First-line chemotherapy was proposed according to patient oncological history and adapted to *RAS* status for combination of anti EGFR therapy.¹³ After 4 cycles, restaging was performed to evaluate radiological response according to response evaluation criteria in solid tumor (RECIST)¹⁴ and morphological response.^{15,16} Criteria for resectability of CLM has previously been defined.¹⁷ For patients with response to chemotherapy, extrahepatic metastases identified on preoperative imaging were not considered a contraindication to liver resection with curative intent.¹⁸ Second-line chemotherapy was considered for patients with disease progression or suboptimal response after first-line chemotherapy, or for patients with unacceptable toxicity with the first-line regimen. A suboptimal response was defined as an insufficient response to allow a complete and safe resection based on preoperative volumetric assessment.

As previously described, a second-line chemotherapy was defined as any change in the chemotherapy regimen before liver resection of CLM.⁷ Adjuvant chemotherapy for primary tumor was not considered as first-line chemotherapy except in patients with synchronous CLM (CLM detected at same time as the primary tumor) and patients who developed CLM during adjuvant chemotherapy for the primary tumor. Reasons for receiving second-line chemotherapy were classified: (1) progression during first-line chemotherapy, (2) advanced metastases with suboptimal response to the first-line chemotherapy regimen, or (3) intolerable toxicity of the first-line chemotherapy regimen. Maintenance chemotherapy was not considered as a new line of chemotherapy.

Chemotherapy after liver resection was proposed to complete a total of 12 cycles, including preoperative and postoperative chemotherapy.

Statistical analysis

Quantitative and qualitative variables were expressed as median and range and frequency. Comparisons between groups were analyzed using chi-squared test for proportions, Mann–Whitney U test for median as appropriate.

Survival was calculated from the date of first liver surgery, and patients died within 90 days after liver resection from postoperative complication were excluded from the survival analysis. Overall (OS) and recurrence free survival (RFS) were calculated by using the Kaplan–Meier method and compared using the log-rank test. Variables with p value of less than 0.1 from univariate analysis were entered into cox regression survival analysis with backward conditional method. $p < 0.05$ was considered statistically significant.

Statistical analysis was performed using SPSS version 22 (SPSS Inc., IBM, Chicago, IL).

Results

Population

Among 635 patients with known *RAS* status undergoing potentially curative liver resection, 589 (93%) and 46 (7%) received <2 lines or ≥2 lines of preoperative chemotherapy, respectively. Clinicopathologic factors are listed in Table 1. Patients who received ≥2 lines of preoperative chemotherapy had significantly more and larger CLM, underwent more cycles of first-line chemotherapy and were more likely to require major hepatectomy than patients who received <2 lines of preoperative chemotherapy. Among patients who received ≥2 lines of preoperative chemotherapy, reasons to change for second-line regimens were tumor progression after first-line in 21 (46%) patients, suboptimal response after first-line in 9 (19%) patients, and first-line toxicity in 16 (35%) patients. Twenty two (48%) patients presented with suspected extrahepatic disease at time of liver resection, including 16 patients with lung metastases, 4 patients with node involvement (1 portal nodes, 1 pelvic nodes and 2 aortocaval nodes) and 2 patients with peritoneal carcinomatosis (PC). One patient with PC underwent a complete resection of PC 4 years before liver surgery and the other patient with PC underwent a complete resection during liver surgery. Clinicopathologic factors by *RAS* status among patients who received ≥2 lines of preoperative chemotherapy are listed in Table 2. Patients with *RAS* mutation had significantly smaller CLM and higher rate of positive margin.

Survival by number of lines of preoperative chemotherapy

Three patients, 2 after one line or less of chemotherapy and one after ≥2 lines of chemotherapy died of postoperative liver failure within 3 months after surgery and were excluded from survival analysis.

After median follow-up of 39.8 months (range, 1.7–125.6 months), median overall survival (OS) was 61.1 and 44.4 months for patients who received <2 and ≥2 lines of preoperative chemotherapy, respectively ($p = 0.021$, Fig. 1). After a second-line of chemotherapy, OS was 60.656 and 35.246 months for *RAS* wild-type and *RAS* mutated patients, respectively ($p = 0.038$; Fig. 2a). No difference in OS was observed between patients who received <2 lines of chemotherapy and *RAS* wild-type patients who received ≥2 lines of preoperative chemotherapy ($p = 0.493$).

Median recurrence free survival (RFS) was 12 and 7.3 months after <2 and ≥2 lines of preoperative chemotherapy, respectively ($p = 0.001$). After a second-line chemotherapy, RFS was 8.3 and 3.6 months for *RAS* wild-type and *RAS* mutated patients, respectively ($p = 0.015$; Fig. 2b). After a second-line chemotherapy, all patients with *RAS* mutation recurred within 18 months after surgery, and 2 patients with *RAS* wild-type are alive without recurrence 5 years after surgery. No difference in RFS was observed between patients who received <2 lines of chemotherapy and *RAS* wild-type patients who received ≥2 lines of preoperative chemotherapy ($p = 0.127$).

Predictors of survival after resection of CLM after second-line chemotherapy regimen

Results of univariate and multivariate analysis for factors associated with OS and RFS after second-line chemotherapy are reported in Table 3. The only independent factor associated with OS and RFS was *RAS* mutation status.

Discussion

Radiographic and pathologic response to preoperative chemotherapy are determinants of survival in patients undergoing resection of CLM,^{15,19,20} and tumor progression on chemotherapy represents a relative contraindication to liver resection in patients with advanced CLM.⁶ For patients with advanced CLM and disease progression on first-line chemotherapy, changing to a second-line regimen before consideration of major hepatic resection is recommended. However, objective response rates to second-line chemotherapy are only 4–28%.^{21–25} Furthermore, 5-year overall survival following hepatectomy after second-line chemotherapy is 22%, which is less than half the rate after first-line chemotherapy.⁷ Previously, we showed that major pathologic response to second-line chemotherapy correlated with improved survival and recommended liver resection after second-line chemotherapy in carefully selected patients.⁷ This study demonstrates that *RAS* mutational status is an independent predictor of survival in patients undergoing liver resection after two or more lines of preoperative chemotherapy. Importantly, all of the patients with *RAS* mutated tumors experienced disease recurrence within 18 months after liver resection. In contrast, among patients with *RAS* wild-type tumors, the number of lines of preoperative chemotherapy did not impact survival.

Historically, *RAS* mutations were evaluated to guide chemotherapy and use of anti-Epithelial Growth Factor Receptor (EGFR) treatment.²⁶ Recent studies and a recent meta-analysis suggested that *RAS* mutations were a major prognostic factor of survival after CLM surgery, irrespective of anti EGFR therapy.⁸ In addition, *RAS* mutational status correlates with radiographic and pathologic response to chemotherapy in patients undergoing resection of CLM.²⁷ Mise et al. reported that the frequency of optimal morphologic response to chemotherapy identified on computed tomography was 33% and 11% in patients with *RAS* wild-type and mutated tumors, respectively. Similarly, *RAS* predicted major pathologic response, which was observed in 59% and 37% of patients with *RAS* wild-type and mutated tumors, respectively. Unlike morphological and pathological response, *RAS* status can be determined before any treatment, does not require a surgical specimen, and does not depend upon radiologic interpretation. Therefore, *RAS* status can be used at time of diagnosis to guide treatment decisions. Furthermore, *RAS* is a stable biologic factor that does not vary with time or tissue origin. Several studies have reported a high concordance in *RAS* status between the primary tumor and liver metastases.^{28,29} *RAS* status remains over time, irrespective of chemotherapy.³⁰

In this study, patients with larger size and number of CLM were more likely to require second-line chemotherapy, reflecting their significant tumor burden. In such patients with advanced CLM, *RAS* represents an important biologic factor to optimize patient selection for treatment. The present study underscores the favorable biology of *RAS* wild-type, since patients with wild-type *RAS* undergoing liver resection had similar survival rates after

second-line vs. first-line chemotherapy. Therefore, *RAS* mutational status can guide the goals of treatment, as patients with wild-type tumors may benefit from aggressive chemotherapy and surgery, even with extensive initial tumor burden.

Previously, we demonstrated an increasing number of patients over time undergoing resection of CLM after a second-line chemotherapy.⁷ The current study shows that such patients are more likely to require major hepatectomy and have had more cycles of preoperative chemotherapy. Such extensive preoperative chemotherapy is associated with increased morbidity and mortality, especially after major liver surgery.³¹ Brouquet et al.⁷ reported major complication rate of 17% and a 90-day mortality of 2% after second-line chemotherapy, comparable to rates reported after major liver surgery.³² Therefore, major liver surgery, even after a second-line of preoperative chemotherapy, is feasible for carefully selected patients.

Limitations of this study include exclusion of patients with unknown *RAS* status, limiting the analyzed population. Second, not all patients received the same chemotherapy, and due to the large diversity of chemotherapy regimens and the small population of patients who received second-line chemotherapy, we did not evaluate the impact of each regimen. Third, this study presents a selection bias due to its retrospective nature and inclusion of only patients who underwent liver resection.

Conclusion

This study shows that *RAS* mutational status represents an important prognostic factor for patients undergoing liver resection after second-line chemotherapy. Patients with *RAS* mutated tumors who required second-line chemotherapy uniformly suffered disease recurrence within two years after hepatectomy. In contrast, in patients with *RAS* wild-type tumors, the number of lines of preoperative chemotherapy did not affect survival after liver resection, highlighting their favorable tumor biology and importance of obtaining a response to chemotherapy before surgery.

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At risk, months	0	12	24	36	48	60
<2 lines	587	543	427	329	228	136
≥ 2 lines	45	40	28	21	12	9

Figure 1.
Overall survival comparing less than 2 and 2 or more lines of preoperative chemotherapy.

Figure 2.
Overall survival (a) and recurrence free survival (b) after less than 2 and 2 or more lines of preoperative chemotherapy according to *RAS* status.

Table 1Clinicopathological factors.^a

	Preoperative chemotherapy		p
	<2 lines (n = 589)	2 lines (n = 46)	
Median age, years (range)	56 (23–84)	54.6 (30–69)	0.282
Gender			
Male	341 (58)	30 (65)	0.332
Female	248 (42)	16 (35)	
Primary tumor			
Colon	458 (78)	39 (85)	0.266
Rectum	131 (22)	7 (15)	
Node-positive primary	368 (63)	30 (65)	0.313
Synchronous CLM	398 (68)	32 (70)	0.781
Two stage hepatectomy	55 (9)	7 (15)	0.196
Major resection	324 (55)	34 (74)	0.013
Number of CLM	2 (1–30)	3 (1–20)	0.001
Median size of largest CLM, mm (range)	21 (0–180)	30 (9–95)	0.003
Largest CLM size >50 mm	56 (10)	9 (20)	0.074
Solitary CLM	231 (39)	11 (24)	0.009
Positive margin	36 (6)	4 (9)	0.487
Median no of cycles of first-line chemotherapy (range)	5 (0–36)	8 (2–39)	<0.001
>7 cycles of first-line chemotherapy	146 (25)	38 (83)	<0.001
First-line chemotherapy			
Oxaliplatin	412 (70)	38 (83)	0.069
Irinotecan	107 (18)	5 (11)	0.211
Bevacizumab	414 (70)	32 (70)	0.145
Anti-EGFR	31 (5)	4 (9)	0.918
Other regime	16 ()	3 (6)	0.326
Pathological response			
Complete	30 (5)	0	0.116
Major	227 (38.5)	20 (43.5)	
Minor	159 (27)	20 (43.5)	
Missing data	173 (29.5)	6 (13)	
<i>RAS</i> mutation	222 (38)	14 (30)	0.327
Recurrence after liver resection	446 (76)	39 (85)	0.163

CLM: Colorectal liver metastases.

EGFR: Epithelial Growth Factor Receptor.

^aValues in table are numbers of patients (percentages) unless otherwise indicated.

Table 2

Clinicopathologic factors by *RAS* status among 45 patients undergoing liver resection after 2 lines of preoperative chemotherapy.^a

	<i>RAS</i> wild-type (n = 31)	<i>RAS</i> mutation (n = 14)	p
Median age in years (range)	54 (30–69)	57 (35–67)	0.265
Gender			
Male	19 (61)	10 (71)	0.511
Female	12 (39)	4 (29)	
Primary tumor			
Colon	25 (81)	14 (100)	0.077
Rectum	6 (19)	0	
Node-positive primary	19 (61)	11 (79)	0.191
Synchronous CLM	23 (74)	5 (36)	0.497
Extrahepatic disease	14 (45)	8 (57)	0.457
Two stage hepatectomy	6 (19)	1 (7)	0.295
Major resection	23 (74)	10 (71)	0.846
Number of CLM	2 (1–20)	4 (1–11)	0.159
Solitary lesion	8 (26)	3 (21)	0.752
Median size of largest CLM in mm (range)	40 (10–95)	19 (9–75)	0.015
Largest CLM size > 50 mm	8 (26)	1 (7)	0.147
Positive margin	1 (3)	3 (21)	0.047
Median no of cycles of first-line chemotherapy (range)	8 (2–30)	8 (2–39)	0.684
>7 cycles of first-line chemotherapy	27 (87)	10 (71)	0.203
Regimen			
Oxaliplatin	26 (84)	11 (79)	0.667
Irinotecan	4 (13)	1 (7)	
Other	1 (3)	2 (14)	0.569
Bevacizumab	21 (68)	10 (71)	
Anti EGFR	4 (13)	0	0.159
Pathological response			
Complete	0	0	0.557
Major	14 (45)	5 (32)	
Minor	13 (42)	7 (50)	0.077
Missing data	4 (13)	2 (14)	
Disease recurrence	25 (81)	14 (100)	

CLM: Colorectal liver metastases.

EGFR: Epithelial Growth Factor Receptor.

^aValues in table are numbers of patients (percentages) unless otherwise indicated.

Table 3

Univariate and multivariate analysis of predictors of recurrence free survival and overall survival after second-line chemotherapy.

	Recurrence free survival					Overall survival				
	Univariate		Multivariate			Univariate		Multivariate		
	p	HR	95% CI	Min IC	Max IC	p	HR	95% CI	Min IC	Max IC
Age	0.491					0.649				
Gender	0.121					0.231				
Primary origin	0.391					0.753				
Primary nodes	0.188					0.627				
Synchronous CLM	0.918					0.579				
Extrahepatic disease	0.438					0.179				
Multiple tumors (>1)	0.319					0.13				
Large tumors (>50 mm)	0.687					0.503				
>7 cycles of first-line chemotherapy	0.394					0.901				
Two stage hepatectomy	0.181					0.551				
Major resection	0.357					0.152				
Positive margin	0.035					NS	0.077			NS
Pathological response	0.951					0.654				
<i>RAS</i> mutation	0.018	2.313	1.156	4.632	0.018	0.043	2.341	1.026	5.342	0.043

Primary origin: colon vs. rectum.

CLM: Colorectal liver metastases.

CI: Confidence interval, HR: Hazard ratio.

NS: non-significant, variable remove after step 1.