Ann Surg Oncol (2016) 23:2635–2643
DOI 10.1245/s10434-016-5187-2

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

RAS Mutation Predicts Positive Resection Margins and Narrower Resection Margins in Patients Undergoing Resection of Colorectal Liver Metastases

Kristoffer Watten Brudvik, MD, PhD[1], Yoshihiro Mise, MD, PhD[1], Michael Hsiang Chung, BS[1], Yun Shin Chun, MD[1], Scott E. Kopetz, MD[2], Guillaume Passot, MD, PhD[1], Claudius Conrad, MD, PhD[1], Dipen M. Maru, MD[3], Thomas A. Aloia, MD[1], and Jean-Nicolas Vauthey, MD[1]

[1]Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX

ABSTRACT

Background. In patients undergoing resection of colorectal liver metastases (CLM), resection margin status is a significant predictor of survival, particularly in patients with suboptimal response to preoperative therapy. *RAS* mutations have been linked to more invasive and migratory tumor biology and poor response to modern chemotherapy.

Objective. The aim of this study was to evaluate the relationship between *RAS* mutation and resection margin status in patients undergoing resection of CLM.

Methods. Patients who underwent curative resection of CLM from 2005 to 2013 with known *RAS* mutation status were identified from a prospectively maintained database. A positive margin was defined as tumor cells <1 mm from the parenchymal transection line.

Results. The study included 633 patients, of whom 229 (36.2 %) had mutant *RAS*. The positive margin rate was 11.4 % (26/229) for mutant *RAS* and 5.4 % (22/404) for wild-type *RAS* ($p = 0.007$). In multivariate analysis, the only factors associated with a positive margin were *RAS* mutation (hazard ratio [HR] 2.439; $p = 0.005$) and carcinoembryonic antigen level 4.5 ng/mL or greater (HR 2.060; $p = 0.026$). Among patients presenting with liver-first recurrence during follow-up, those with mutant *RAS* had narrower margins at initial CLM resection (median 4 mm vs. 7 mm; $p = 0.031$). A positive margin (HR 3.360; $p < 0.001$) and *RAS* mutation (HR 1.629; $p = 0.044$) were independently associated with worse overall survival.

Conclusion. *RAS* mutations are associated with positive margins in patients undergoing resection of CLM. Tumors with *RAS* mutation should prompt careful efforts to achieve negative resection margins.

Historically, the finding of viable tumor cells at the resection margin after resection of colorectal liver metastases (CLM) has been associated with reduced overall and recurrence-free survival.[1–10] However, reports based on more recent patient series have called into question the impact of positive resection margins on survival.[11–13] This discrepancy has been attributed to more effective modern chemotherapy and targeted therapies administered preoperatively and/or postoperatively.[13] We recently showed that a positive resection margin remained significantly associated with worse prognosis, even in the era of modern preoperative chemotherapy.[14] In a recent report of a detailed pathologic analysis of resection margins in patients undergoing resection of CLM, improved survival was reported in patients with negative margins smaller than 1 mm;[15] however, the biologic factor(s) driving these margin-based differences in prognosis remain unclear.

Rat sarcoma viral oncogene homolog (*RAS*) mutations are found in 15–35 % of patients with resectable CLM and have been associated with reduced overall and recurrence-free survival after hepatectomy.[16–18] Furthermore, *RAS* mutations have been found to predict worse morphologic and pathologic response to chemotherapy, not just to monoclonal antibodies targeting the epidermal growth factor receptor.[19–22] Other reports have suggested that *RAS*

First Received: 31 December 2015;
Published Online: 25 March 2016

J.-N. Vauthey, MD
e-mail: jvauthey@mdanderson.org

mutation indicates a more migratory and invasive tumor biology.[23–25] Taken together, these findings indicate that *RAS* mutation reflects a more aggressive tumor phenotype and may have implications regarding the optimization of local therapy in patients with resectable CLM.

Previously, investigators hypothesized that a positive resection margin is a surrogate marker of worse tumor biology irrespective of the apparent correlation between a positive resection margin and poor surgical technique.[13,26] Based on this hypothesis, and in support of findings indicating that *RAS* mutation represents a more aggressive tumor phenotype, the aim of the current study was to evaluate the relationship between *RAS* mutation and resection margin status in patients undergoing resection of CLM.

METHODS

Study Population

This study was approved by the Institutional Review Board (IRB) of the University of Texas MD Anderson Cancer Center (IRB protocol PA13-0795). The prospective institutional liver database was searched to identify patients who underwent curative resection of CLM with known *RAS* mutation status at MD Anderson from 2005 to 2013 without concomitant radiofrequency ablation. For each patient, the following data were extracted from the prospective institutional liver database, or updated by journal review if missing: sex, age, location of primary cancer, lymph node status of primary cancer, disease-free interval between resection of the primary cancer and presentation with liver metastases, number of CLM, diameter of the largest CLM, *RAS* mutation status, preoperative chemotherapy, number of cycles of preoperative chemother apy, type of preoperative chemotherapy, type of liver resection, pathologic response to preoperative chemotherapy, site of any recurrence, and overall survival.

Disease Management

Helical computed tomography of the chest, abdomen, and pelvis with a triphasic liver protocol was used in all patients to assess resectability and extrahepatic disease. Resection of CLM in the presence of extrahepatic disease was only performed if the extrahepatic disease was judged to be completely resectable. Two-stage hepatectomy and portal vein embolization were used to extend resectability in patients with insufficient standardized future liver remnant volume.[27,28] Intraoperative ultrasonography was used in all patients to assess the vascular anatomy of the portal pedicles and the hepatic veins, and to assess previously known and undetected lesions. The parenchymal transection was performed using a two-surgeon technique with the Cavitron Ultrasonic Surgical Aspirator (Valleylab, Boulder, CO, USA) and saline-linked cautery (Dissecting Sealer DS 3.0; Tissue Link Medical, Inc., Dover, NH, USA) under total or selective hepatic inflow.[29] Preoperative oxaliplatin- or irinotecan-based chemotherapy including bevacizumab (six cycles as a standard) was used in the majority of patients. In most patients, chemotherapy was reintroduced after surgery to complete a total of 12 cycles. Radiological follow-ups were performed every 4 months after surgery to assess for recurrence.

Histological Examination and RAS Mutation Profiling

Upon histological examination of the resected specimen, the pathologist verified the presence of CLM and assessed the width of the margin and the percentage of viable tumor cells. A positive resection margin was defined as viable tumor cells <1 mm from the resection margin, as previously described[5]. Complete or major pathologic response to preoperative chemotherapy was defined as 49 % or fewer viable tumor cells.[30] DNA from CLM was used to determine *RAS* mutation status: routine 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 64 and 161 and *NRAS* codons 12, 13, and 62 in the majority of patients in the most recent years of the study period. 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.

Statistical Analysis

The Shapiro–Wilk test was used to assess whether continuous data were normally distributed and could thus be summarized in terms of mean with standard deviation and compared using independent *t* tests. Non-normally distributed continuous data were summarized in terms of median with range and compared using the Mann–Whitney *U* test. Categorical data were compared using Pearson Chi square tests. A p value <0.05 was considered statistically significant. When the continuous variables of carcinoembryonic antigen level and diameter of the largest CLM were converted into binary categories, the cutoff was set between the median/mean values of the groups to be compared. Factors with a p value <0.1 from univariate analyses were entered into multivariate analyses. Binary logistic regression with enter method for the covariates was used to perform a multivariate analysis to assess predictors of a positive margin. Cox regression survival analyses with

enter method for the covariates were conducted to determine factors associated with overall survival. Only factors with p value <0.1 in multivariate analyses were reported. The Kaplan–Meier method was used to estimate survival rates, and survival curves were compared using the log-rank test. The statistical analyses were performed using SPSS version 19.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Patient Characteristics According to the Status of the Resection Margin

RAS mutation status was available in 757 patients who underwent resection of CLM from 2005 to 2013. Of these 757 patients, 633 underwent curative resection without the concomitant use of radiofrequency ablation, and were thus eligible for analyses (Fig. 1). Patient characteristics, characteristics of the CLM, use of preoperative chemotherapy and targeted therapies, types of resection (only resection characteristics that differed significantly by margin status are shown), and pathologic response according to resection margin status are listed in Table 1. The mean age was 55.8 years (range 23–84 years), and there were 371 men (58.6 %) and 262 women (41.4 %). The primary cancer was located in the colon in 484 patients (76.5 %) and in the rectum in 149 patients (23.5 %). Positive lymph nodes in relation to the primary cancer were found in 403 patients (63.7 %). There were no associations between a positive resection margin and sex, age, location of the primary cancer, or lymph node status of the primary cancer.

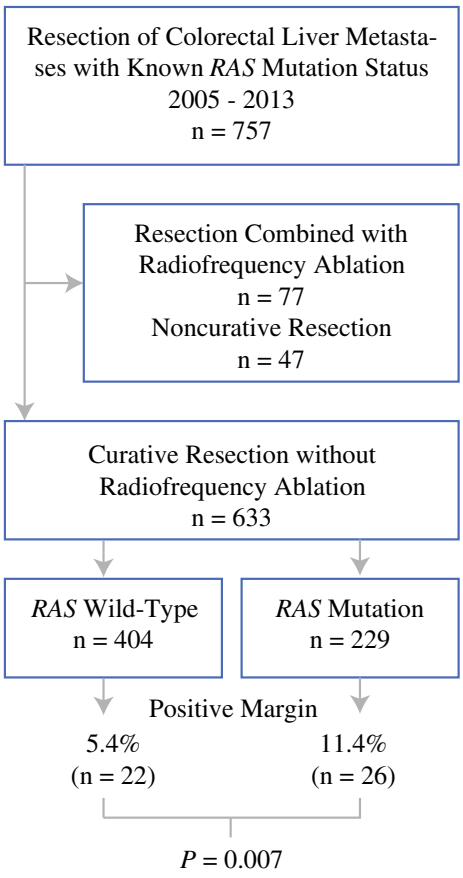

FIG. 1 Study population according to *RAS* mutation status and resection margin positivity

An *RAS* mutation was found in 229 patients (36.2 %), and *RAS* mutation was associated with a positive resection margin in univariate analysis (rate of positive margins, 11.4 % in patients with mutant *RAS* vs. 5.4 % in patients with wild-type *RAS*; $p = 0.007$) [Table 1; Fig. 1]. Furthermore, *RAS* mutation status was not associated with metastasis size ($p = 0.753$), numbers ($p = 0.476$), disease-free interval ($p = 0.774$), carcinoembryonic antigen level ($p = 0.090$), or primary tumor lymph node status ($p = 0.215$).

Preoperative chemotherapy was used in 545 patients (86.1 %) and the rate of a positive margin was 7.5 %, compared with 8.0 % in patients not treated with preoperative chemotherapy ($p = 0.887$). After exclusion of patients receiving multiple and complex preoperative regimens, patients receiving oxaliplatin-based ($n = 273$) and irinotecan-based ($n = 125$) preoperative chemotherapy had similar rats of positive margins. Furthermore, the *RAS* mutation rate was similar in patients treated with oxaliplatin-based (35.9 %) and irinotecan-based (30.4 %) preoperative chemotherapy ($p = 0.283$). A total of 420 (66.4 %) patients received bevacizumab preoperatively, and the rate of a positive resection margin was the same in these patients as in those who did not receive bevacizumab. Thirty-one patients (4.9 %) received cetuximab or panitumumab perioperatively, and the rate of a positive resection margin was the same in these patients as in those who did not receive these treatments.

Factors Associated with a Positive Resection Margin

In univariate analyses (Table 2), factors associated with a positive resection margin were diameter of the largest CLM of 30 mm or more, carcinoembryonic antigen level 4.5 ng/mL or more, *RAS* mutation, extended liver resection, left hepatectomy, and non-partial hepatectomy. Major hepatectomy (more than three segments), right hepatectomy, the second stage of two-stage hepatectomy, and bilateral resection were not associated with a positive resection margin. The only independent factors predicting a positive resection margin were carcinoembryonic antigen level 4.5 ng/mL or more (hazard ratio [HR] 2.060, 95 % confidence interval [CI] 1.090–3.893; $p = 0.026$) and *RAS* mutation (HR 2.439, 95 % CI 1.300–4.575; $p = 0.005$).

TABLE 1 Patient, disease, and treatment characteristics and pathologic response according to resection margin status

Characteristic	All patients	Resection margin status		*p* Value
		Positive	Negative	
Total number of patients	633	48 (7.6)	585 (92.4)	
Sex				
Female	262	23 (8.8)	239 (91.2)	0.340
Male	371	25 (6.7)	346 (93.3)	
Age, years [mean (SD)]	55.8	56.6 (12.1)	55.8 (10.7)	0.626
RAS mutation status of CLM				
Wild-type	404	22 (5.4)	382 (94.6)	0.007
Mutant	229	26 (11.4)	203 (88.6)	
Disease-free interval[a]				
>12 months (metachronous CLM)	187	11 (5.9)	176 (94.1)	0.295
≤12 months (synchronous CLM)	446	37 (8.3)	409 (91.7)	
Number of CLM				
Single	296	22 (7.4)	274 (92.6)	0.851
Multiple	332	26 (7.8)	306 (92.2)	
Diameter of largest CLM, mm [mean (SD)]	28	35 (30)	27 (22)	0.024
CEA, ng/mL [median (range)]	3 (0–2915)	6 (1–1993)	3 (0–2915)	0.031
Preoperative chemotherapy				
Yes	545	41 (7.5)	504 (92.5)	0.887
No	88	7 (8.0)	81 (92.0)	
Cycles of preoperative chemotherapy				
≤6	374	24 (6.4)	350 (93.6)	0.216
>6	182	17 (9.3)	165 (90.7)	
Preoperative chemotherapy regimen[b]				
Oxaliplatin-based	273	22 (8.1)	251 (91.9)	0.561
Irinotecan-based	125	8 (6.4)	117 (93.6)	
Preoperative bevacizumab				
Yes	420	33 (7.9)	387 (92.1)	0.743
No	197	14 (7.1)	183 (92.9)	
Preoperative cetuximab/panitumumab				
Yes	31	2 (6.5)	29 (93.5)	0.807
No	602	46 (7.6)	556 (92.4)	
Extended liver resection				
Yes	144	18 (12.5)	126 (87.5)	0.011
No	489	30 (6.1)	459 (93.9)	
Left hepatectomy				
Yes	43	7 (16.3)	36 (83.7)	0.023
No	586	40 (6.8)	546 (93.2)	
Partial (including wedge) resection				
Yes	461	28 (6.1)	433 (93.9)	0.019
No	172	20 (11.6)	152 (88.4)	
Pathologic response, *n* (%)				
Complete or major (0–49 % VTCs)	255	19 (7.5)	236 (92.5)	0.222
Minor (50–100 % VTCs)	175	19 (10.9)	156 (89.1)	

Data are expressed as *n* (%) unless otherwise specified

SD standard deviation, *CEA* carcinoembryonic antigen level at resection of CLM, *Preop* preoperative, *Chemo* chemotherapy, *VTC* viable tumor cells

[a] Interval between resection of the primary colorectal cancer and diagnosis of CLM

[b] Patients treated with multiple chemotherapy regimens preoperatively excluded

TABLE 2 Logistic regression analyses of factors associated with a positive resection margin

Factor	Univariate analyses			Multivariate analysis		
	HR	95 % CI	*p* Value	HR	95 % CI	*p* Value
Diameter of largest CLM ≥ 30 mm	1.897	1.030–3.495	0.040			
CEA ≥ 4.5 ng/mL	2.283	1.256–4.150	0.007	2.060	1.090–3.893	0.026
RAS mutation	2.224	1.229–4.023	0.008	2.439	1.300–4.575	0.005
Extended resection	2.186	1.180–4.050	0.013			
Left hepatectomy	2.654	1.111–6.341	0.028			
Non-partial hepatectomy	2.035	1.114–3.718	0.021			

HR hazard ratio, *CI* confidence interval, *CLM* colorectal liver metastases, *CEA* carcinoembryonic antigen

Width of the Resection Margin in Patients with RAS-Mutant and RAS Wild-Type Colorectal Liver Metastases

Among all patients, the median width of the resection margin was similar between patients with *RAS*-mutant CLM (5 mm, range 0–80) and patients with *RAS* wild-type CLM (6 mm, range 0–90) [$p = 0.131$]. However, in the group of patients with resection margins of 10 mm or less ($n = 448$), the median width of the resection margin was significantly smaller in patients with *RAS*-mutant CLM: 3 mm (range 0–10) versus 4 mm (range 0–10) [$p = 0.045$].

The mean follow-up time for the entire cohort was 26 months, during which 407 patients (64.3 %) developed recurrence. Of the 407 patients with recurrence, 225 (55.3 %) developed liver-first recurrence (Fig. 2). Among these patients with liver-first recurrence, the median width of the resection margin at initial resection of CLM was smaller in patients with *RAS*-mutant CLM than in patients with *RAS* wild-type CLM: 4 mm (range 0–70) versus 7 mm (range 0–67) ($p = 0.031$). Among the same patients, the mean diameter of the largest metastasis at initial resection of CLM (*RAS* mutant, 28 mm; *RAS* wild-type, 30 mm; $p = 0.476$) and the mean number of metastases at initial resection of CLM (*RAS* mutant, 2.6 mm; *RAS* wild-type, 2.5 mm; $p = 0.825$) were similar between patients with *RAS*-mutant and *RAS* wild-type CLM.

Impact of Resection Margin Status and RAS Mutation Status on Overall Survival

Factors potentially associated with overall survival after resection of CLM were analyzed (Table 3). Factors independently associated with reduced overall survival in multivariate analysis were a positive resection margin (HR 3.360, 95 % CI 1.741–6.485; $p < 0.001$) and *RAS* mutation (HR 1.629, 95 % CI 1.013–2.620; $p = 0.044$). Kaplan–Meier plots of overall survival by *RAS* mutation status and margin status are shown in Fig. 3.

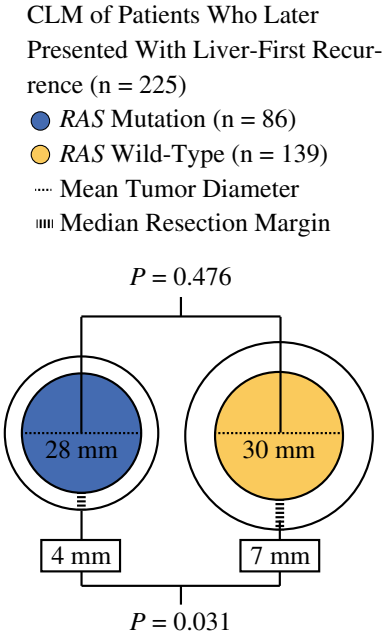

FIG. 2 Mean diameter of the largest tumor and median width of the resection margin according to *RAS* mutation status in patients who presented with liver-first recurrence ($n = 225$) after resection of CLM. *CLM* colorectal liver metastases

DISCUSSION

Several studies have recently reported worse overall and recurrence-free survival in patients with *RAS* mutation after resection of CLM, independent of perioperative chemotherapy or targeted therapy.[16–18,31,32] In the current study, the resections were performed without knowledge of *RAS* status, and *RAS* mutations were associated with double the positive margin rate (11.4 vs. 5.4 %), suggesting

TABLE 3 Cox regression analyses of factors associated with overall survival

Factor	Univariate analyses			Multivariate analysis		
	HR	95 % CI	*p* Value	HR	95 % CI	*p* Value
Positive resection margin	2.423	1.414–4.153	0.001	3.360	1.741–6.485	<0.001
Positive lymph nodes in relation to primary cancer	1.539	1.053–2.247	0.026			
Disease-free interval >12 months	1.293	0.891–1.877	0.176			
Diameter of largest CLM ≥30 mm	1.564	1.106–2.214	0.012			
CEA ≥4.5 ng/mL	1.288	0.919–1.804	0.141			
RAS mutation	2.181	1.547–3.077	<0.001	1.629	1.013–2.620	0.044
Minor pathologic response (50–100 % VTCs)	1.728	1.095–2.727	0.019	1.562	0.973–2.506	0.065

HR hazard ratio, *CI* confidence interval, *CLM* colorectal liver metastases, *CEA* carcinoembryonic antigen, *VTCs* viable tumor cells

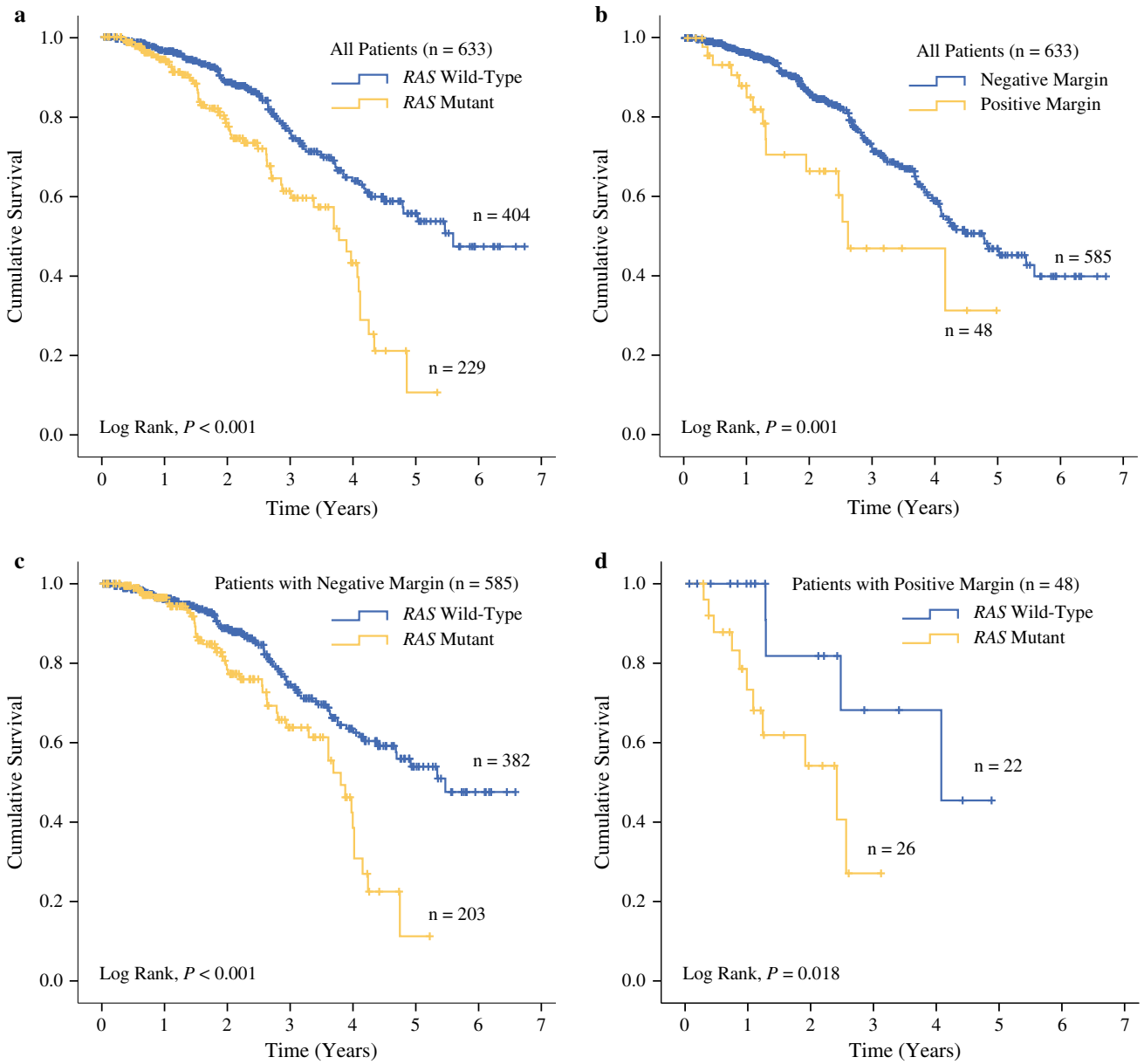

FIG. 3 Kaplan–Meier plots of overall survival in all patients according to (**a**) *RAS* mutation status and (**b**) resection margin status, and in patients with (**c**) negative resection margins and (**d**) positive resection margins stratified by *RAS* mutation status

phenotypic differences associated with the mutational status of the tumor. In multivariate analysis, both *RAS* mutation and a positive margin independently predicted worse survival, confirming the importance of adequate local surgical therapy for curative treatment of CLM.[14,15,33] To our knowledge, this is the first study reporting an association of a higher positive margin rate with a feature indicating worse tumor biology.

Two types of tumor growth have been described in CLM: infiltrating growth pattern and pushing growth pattern. Tumors with infiltrating growth have been associated with worse survival and increased risk of liver recurrence after resection of CLM.[34–37] Mentha et al. further investigated the halo surrounding CLM and described a dangerous halo of viable tumor cells that infiltrated the surrounding liver parenchyma. In contrast, the good halo had the appearance of a physiological pseudocapsule where the viable tumor cells were contained within a fibroinflammatory reaction and did not penetrate the surrounding liver parenchyma.[38] *RAS* mutations were not assessed in these studies, but other studies have indicated an association between *RAS* mutations and a more migratory and invasive tumor biology.[23–25] As such, the higher rate of positive margins among patients with *RAS*-mutant CLM in the current study may indicate that *RAS* mutations are associated with a more infiltrating and/or migratory tumor phenotype.

Several studies have reported the presence of microscopic tumor deposits separate from CLM, and investigators have aimed to identify the optimal tumor-free resection margin width to clear all viable tumor cells. Kokudo et al. investigated the normal liver parenchyma surrounding CLM, and demonstrated the presence of *KRAS*-mutant tumor DNA outside the measured tumor margin in patients with *KRAS*-mutant metastases.[39] Similarly, Holdhoff et al. reported detection of mutant tumor-specific DNA 4 mm beyond the visible tumor margin.[40] Wakai et al. identified micrometastases, defined as satellites of tumor tissue undetectable on imaging and spatially separated from the gross CLM by normal liver tissue, upon histological analysis of the resected CLM specimens.[41] In the current study, the median tumor-free margin was 3 mm narrower among patients with *RAS*-mutant CLM than among patients with *RAS* wild-type CLM who later presented with liver recurrence. This finding indicates that the optimal tumor-free margin width may be inappropriate to investigate without considering differences in the underlying tumor biology. As such, for now the ideal tumor-free margin width remains unknown, and further studies evaluating tumor growth pattern, micrometastases, and *RAS* mutations are warranted.

We recently reported that a positive resection margin did not worsen survival in patients with a major pathologic response to preoperative chemotherapy;[14] however, a positive resection margin was significantly associated with reduced survival in patients with suboptimal or poor response to preoperative chemotherapy, who represented the majority of patients.[14] Mise et al. investigated *RAS* mutations in the context of pathologic and radiologic response and found a strong correlation between *RAS* mutation rate and the proportion of viable tumor cells in the specimen.[19] In the current study, administration of preoperative chemotherapy, the number of preoperative chemotherapy cycles, and the administration of bevacizumab were not associated with a positive resection margin, indicating that the association between *RAS* mutation and a positive resection margin is independent and unaffected by the association between *RAS* mutation and response to preoperative chemotherapy.

The current study had the following limitations. First, it does not provide data on margin recurrence. A previous study showed a low but definite increase in margin recurrence in patients with positive margins of resection of CLM;[5] however, given the low incidence of margin recurrence reported in that study (3.8 %),[5] an analysis of margin recurrence in the current study would not have had sufficient power to detect a difference, even if the recurrence data had been available. Second, mutations in *KRAS* codons 64 and 161 and *NRAS* mutations were not part of the standard set of mutations analyzed at the beginning of the study period, and some patients may have been misclassified with respect to *RAS* mutation status as a result; however, given the low rate of mutations at these codons (<20 %),[22,42,43] this would represent <10 % of the patients in the current study. Furthermore, if analysis of mutations in *KRAS* codons 64 and 161 and *NRAS* had been performed in all patients, the difference between patients with *RAS*-mutant and patients with *RAS* wild-type CLM would most likely have been even greater as the oncologic function of the different *RAS* mutations is similar. Finally, as *RAS* mutation status has been linked to pathologic and morphologic response to preoperative chemotherapy, poor response in *RAS* mutants may increase the chance of a positive resection margin. However, studying different regimens and no preoperative chemotherapy, we were not able to identify an impact on the positive margin status rate, and the characteristics of the *RAS*-mutated metastases were similar to the *RAS* wild-type metastases.

The ideal width of the margin for *RAS*-mutant CLM remains unknown. Therefore, in patients with *RAS*-mutant CLM, we recommend the cautious approach proposed by Are et al.[8] of obtaining a 10-mm margin if the margin is not limited by anatomical relationships, even though narrower margins have been proposed by other authors.[39,40,44]

CONCLUSION

RAS mutations are associated with a higher rate of positive margins after resection of CLM. No specific recommendations can be made as to the optimal width of margins in the subset of patients with *RAS* mutation, but future studies regarding tumor growth pattern, micrometastases, and local recurrence may contribute to optimization of local therapy for such patients. However, in the meantime, we recommend careful intraoperative assessment of the resection margins in patients with known *RAS* mutations with the goal of achieving a 1-cm margin unless the margin is limited by anatomical relationships. Inversely, these findings support the use of aggressive surgery with margins smaller than 1 cm in patients with *RAS* wild-type tumors.

ACKNOWLEDGMENT The authors thank Stephanie Deming, an employee of the Department of Scientific Publications, MD Anderson Cancer Center, for copyediting the manuscript, and Ruth J. Haynes, an employee of the Department of Surgical Oncology, MD Anderson Cancer Center, for secretarial assistance in the preparation of the manuscript. This research was supported in part by the National Institutes of Health through MD Anderson's Cancer Center Support Grant, CA016672. Dr. Brudvik is supported by the Department of Hepato-Pancreato-Biliary Surgery, Oslo University Hospital, Norway, and was awarded the Unger–Vetlesen Medical Fund for 2014. Dr Passot is supported by the French Association of Surgery (AFC).

DISCLOSURE Kristoffer Watten Brudvik, Yoshihiro Mise, Michael Hsiang Chung, Yun Shin Chun, Scott E. Kopetz, Guillaume Passot, Claudius Conrad, Dipen M. Maru, Thomas A. Aloia, and Jean-Nicolas Vauthey report no conflicts of interest relevant to this article.

REFERENCES

1. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg*. 1999;230:309–18
2. Rees M, Tekkis PP, Welsh FK, O'Rourke T, John TG. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. *Ann Surg.* 2008;247:125–35.
3. Bradpiece HA, Benjamin IS, Halevy A, Blumgart LH. Major hepatic resection for colorectal liver metastases. *Br J Surg*. 1987;74:324–6.
4. Ekberg H, Tranberg KG, Andersson R, et al. Determinants of survival in liver resection for colorectal secondaries. *Br J Surg*. 1986;73:727–31.
5. Pawlik TM, Scoggins CR, Zorzi D, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. *Ann Surg*. 2005;241:715–22.
6. Altendorf-Hofmann A, Scheele J. A critical review of the major indicators of prognosis after resection of hepatic metastases from colorectal carcinoma. *Surg Oncol Clin N Am.* 2003;12:165–92.
7. Figueras J, Burdio F, Ramos E, et al. Effect of subcentimeter nonpositive resection margin on hepatic recurrence in patients undergoing hepatectomy for colorectal liver metastases. Evidences from 663 liver resections. *Ann Oncol*. 2007;18:1190–5.
8. Are C, Gonen M, Zazzali K, et al. The impact of margins on outcome after hepatic resection for colorectal metastasis. *Ann Surg.* 2007;246:295–300.
9. Hughes KS, Simon R, Songhorabodi S, et al. Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of patterns of recurrence. *Surgery*. 1986;100:278–84.
10. Scheele J, Stang R, Altendorf-Hofmann A, Paul M. Resection of colorectal liver metastases. *World J Surg*. 1995;19:59–71.
11. de Haas RJ, Wicherts DA, Flores E, Azoulay D, Castaing D, Adam R. R1 resection by necessity for colorectal liver metastases: is it still a contraindication to surgery? *Ann Surg*. 2008;248:626–37.
12. Ayez N, Lalmahomed ZS, Eggermont AM, et al. Outcome of microscopic incomplete resection (R1) of colorectal liver metastases in the era of neoadjuvant chemotherapy. *Ann Surg Oncol*. 2012;19:1618–27.
13. Truant S, Sequier C, Leteurtre E, et al. Tumour biology of colorectal liver metastasis is a more important factor in survival than surgical margin clearance in the era of modern chemotherapy regimens. *HPB (Oxford)*. 2015;17:176–84.
14. Andreou A, Aloia TA, Brouquet A, et al. Margin status remains an important determinant of survival after surgical resection of colorectal liver metastases in the era of modern chemotherapy. *Ann Surg*. 2013;257:1079–88.
15. Sadot E, Groot Koerkamp B, Leal JN, et al. Resection margin and survival in 2368 patients undergoing hepatic resection for metastatic colorectal cancer: surgical technique or biologic surrogate? *Ann Surg*. 2015;262:476–85.
16. Vauthey JN, 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;258:619–26.
17. Stremitzer S, Stift J, Gruenberger B, et al. KRAS status and outcome of liver resection after neoadjuvant chemotherapy including bevacizumab. *Br J Surg*. 2012;99:1575–82.
18. 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;119:4137–44.
19. Mise Y, Zimmitti G, Shindoh J, et al. RAS mutations predict radiologic and pathologic response in patients treated with chemotherapy before resection of colorectal liver metastases. *Ann Surg Oncol*. 2015;22:834–42.
20. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol*. 2008;26:1626–34.
21. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med*. 2009;360:1408–17.
22. Douillard J-Y, Oliner KS, Siena S, et al. Panitumumab–FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med*. 2013;369:1023–34.
23. Pollock CB, Shirasawa S, Sasazuki T, Kolch W, Dhillon AS. Oncogenic K-RAS is required to maintain changes in cytoskeletal organization, adhesion, and motility in colon cancer cells. *Cancer Res*. 2005;65:1244–50.
24. Schramm K, Krause K, Bittroff-Leben A, Goldin-Lang P, Thiel E, Kreuser ED. Activated K-ras is involved in regulation of integrin expression in human colon carcinoma cells. *Int J Cancer*. 2000;87:155–64.
25. Serova M, Astorgues-Xerri L, Bieche I, et al. Epithelial-to-mesenchymal transition and oncogenic Ras expression in resistance to the protein kinase Cbeta inhibitor enzastaurin in colon cancer cells. *Mol Cancer Ther*. 2010;9:1308–17.
26. Mbah NA, Scoggins C, McMasters K, Martin R. Impact of hepatectomy margin on survival following resection of colorectal

metastasis: the role of adjuvant therapy and its effects. *Eur J Surg Oncol*. 2013;39:1394–9.
27. Vauthey JN, Chaoui A, Do KA, et al. Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. *Surgery*. 2000;127:512–9.
28. Shindoh J, Tzeng CW, Aloia TA, et al. Portal vein embolization improves rate of resection of extensive colorectal liver metastases without worsening survival. *Br J Surg*. 2013;100:1777–83.
29. Aloia TA, Zorzi D, Abdalla EK, Vauthey JN. Two-surgeon technique for hepatic parenchymal transection of the noncirrhotic liver using saline-linked cautery and ultrasonic dissection. *Ann Surg*. 2005;242:172–7.
30. Blazer DG 3rd, Kishi Y, Maru DM, et al. Pathologic response to preoperative chemotherapy: a new outcome end point after resection of hepatic colorectal metastases. *J Clin Oncol*. 2008;26:5344–51.
31. 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;17:572–8.
32. Brudvik KW, Kopetz SE, Li L, Conrad C, Aloia TA, Vauthey JN. Meta-analysis of KRAS mutations and survival after resection of colorectal liver metastases. *Br J Surg*. 2015;102:1175–83.
33. Hamady ZZ, Lodge JP, Welsh FK, et al. One-millimeter cancer-free margin is curative for colorectal liver metastases: a propensity score case-match approach. *Ann Surg*. 2014;259:543–8.
34. Yamaguchi J, Komuta K, Matsuzaki S, Okudaira S, Fujioka H, Kanematsu T. Mode of infiltrative growth of colorectal liver metastases is a useful predictor of recurrence after hepatic resection. *World J Surg*. 2002;26:1122–5.
35. Pinheiro RS, Herman P, Lupinacci RM, et al. Tumor growth pattern as predictor of colorectal liver metastasis recurrence. *Am J Surg*. 2014;207:493–8.
36. Nielsen K, Rolff HC, Eefsen RL, Vainer B. The morphological growth patterns of colorectal liver metastases are prognostic for overall survival. *Mod Pathol*. 2014;27:1641–8
37. Nagashima I, Oka T, Hamada C, Naruse K, Osada T, Muto T. Histopathological prognostic factors influencing long-term prognosis after surgical resection for hepatic metastases from colorectal cancer. *Am J Gastroenterol*. 1999;94:739–43.
38. Mentha G, Terraz S, Morel P, et al. Dangerous halo after neoadjuvant chemotherapy and two-step hepatectomy for colorectal liver metastases. *Br J Surg*. 2009;96:95–103.
39. Kokudo N, Miki Y, Sugai S, et al. Genetic and histological assessment of surgical margins in resected liver metastases from colorectal carcinoma: minimum surgical margins for successful resection. *Arch Surg*. 2002;137:833–40.
40. Holdhoff M, Schmidt K, Diehl F, et al. Detection of tumor DNA at the margins of colorectal cancer liver metastasis. *Clin Cancer Res*. 2011;17:3551–7.
41. Wakai T, Shirai Y, Sakata J, et al. Histologic evaluation of intrahepatic micrometastases in patients treated with or without neoadjuvant chemotherapy for colorectal carcinoma liver metastasis. *Int J Clin Exp Pathol*. 2012;5:308–14.
42. Netzel BC, Grebe SK. Companion-diagnostic testing limited to KRAS codons 12 and 13 misses 17% of potentially relevant RAS mutations in colorectal cancer. *Clin Chim Acta*. 2013; 425:1–2.
43. Thierry AR, Mouliere F, El Messaoudi S, et al. Clinical validation of the detection of KRAS and BRAF mutations from circulating tumor DNA. *Nat Med*. 2014;20:430–5.
44. Angelsen JH, Horn A, Eide GE, Viste A. Surgery for colorectal liver metastases: the impact of resection margins on recurrence and overall survival. *World J Surg Oncol*. 2014;12:127