Received: 25 October 2017 | Accepted: 21 February 2018
DOI: 10.1002/jso.25048

RESEARCH ARTICLE

WILEY Journal of SURGICAL ONCOLOGY

Is primary sidedness a prognostic factor in patients with resected colon cancer liver metastases (CLM)?

Márcio C Marques MD[1] | Héber S. C. Ribeiro MD, MSc[1] | Wílson L. Costa Jr. MD, PhD[1] | Victor Hugo F. de Jesus MD[2] | Mariana P. de Macedo MD, PhD[3] | Alessandro L. Diniz MD, MSc[1] | André L. Godoy MD[1] | Igor C. Farias MD[1] | Samuel Aguiar Jr. MD, PhD[4] | Rachel S. P. Riechelmann MD, PhD[2] | Maria Dirlei F. S. Begnami MD, PhD[3] | Felipe J. F. Coimbra MD, MSc[1]

[1] Abdominal Surgery Department, AC Camargo Cancer Center, São Paulo, SP, Brazil
[2] Medical Oncology Department, AC Camargo Cancer Center, São Paulo, SP, Brazil
[3] Anatomic Pathology Department, AC Camargo Cancer Center, São Paulo, SP, Brazil
[4] Pelvic Surgery Department, AC Camargo Cancer Center, São Paulo, SP, Brazil

Correspondence
Márcio Carmona Marques, MD, Department of Abdominal Surgery, AC Camargo Cancer Center, Rua Prof. Antônio Prudente 211, São Paulo, SP 01509-010, Brazil.
Email: dr.marciocarmona@gmail.com

Background and Objectives: Recent studies have suggested that sidedness of origin from colorectal adenocarcinomas is a predictor of survival, however the impact of this factor in patients with resected colon cancer liver metastases (CLM) is not clear. So, in this study, we compared clinic and pathologic characteristics and long-term survival of patients with resected CLM according to the primary tumor location.

Methods: This is a retrospective analyzes of a prospective database. Patients with resected CLM from 1998 to 2012 were included. Right colon included tumors from cecum to middle transverse colon, and left colon included tumors from splenic flexure to sigmoid.

Results: One hundred fifty-one patients were included, 27 right colon and 124 left colon. In the latter group, there were more patients with synchronous disease (67.7 × 6.2%, $P = 0.026$) and a higher CEA (22.0 × 11.7 ng/mL, $P = 0.001$). However, K-Ras mutation was more frequent in right sided tumors (75.0 × 24.1%, $P = 0.001$). There was no difference in long term survival in both groups in this series even when adjusted for the confounding variables.

Conclusion: Sidedness do not seem to be a predictor of long term survival in patients with resected colon cancer liver metastases.

KEYWORDS
colorectal neoplasms, hepatectomy, liver metastasi, sidedness

1 | INTRODUCTION

Colorectal adenocarcinoma encompasses a heterogeneous group of diseases with different biological characteristics and varying responses to different systemic treatment regimens.[1–3] Despite the advances in the understanding of the molecular and genetic mechanisms of the disease, many questions remain unanswered.[4] Retrospective studies suggest that the sidedness of origin of the primary tumor (right side vs left side) is a prognostic factor for survival in patients with metastatic colon cancer, and patient with right-sided colon tumors have a worse

Study performed at AC Camargo Cancer Center, São Paulo, SP, Brazil.

survival.[5,6] In an analysis of CALGB/SWOG 80405 presented at the American Society of Clinical Oncology (ASCO) meeting in 2016, Venook et al[5] demonstrated that patients with right-sided colon tumors had inferior survival regardless of the chemotherapy regimen employed and worse response to anti-EGFR treatment. Other authors have found similar results to those of Venook et al.[7–9]

At the same event, Schrag et al[6] presented the results of the Surveillance Epidemiology and End Results (SEER) database. These authors included patients with nonmetastatic colon tumors in the analysis and observed that patients with right-sided colon tumors and clinical stages (CS) III and IV had worse survival whereas those with right-sided colon tumors at CS I and II did not have significant differences in survival. A large Australian case series (9509 patients) included only nonmetastatic disease and had similar findings, with lower survival among patients with right-sided colon tumors and CS III.[10] Other studies that included patients with nonmetastatic disease obtained different results for patients with CS I and II. However, these studies have consistently demonstrated the negative impact of right-sided colon tumors in patients with CS III.[11–14]

Few studies to date have evaluated patients with resected metastatic disease. Retrospective analyses presented at the ASCO 2017 Gastrointestinal Cancers Symposium (including two American populations and one Japanese population) considered patients who underwent resection of liver metastases, and the results suggest that patients with right-sided colon tumors had an inferior overall survival (OS) but no significant difference in disease-free survival (DFS).[15–17] However, these results are recent have not yet been applied in clinical practice.

Therefore, the objective of this study was to evaluate patients with colon cancer who underwent resection of liver metastases to compare the clinic and pathologic characteristics according the sidedness of the tumor and determine its association with long-term survival.

2 | MATERIALS AND METHODS

This retrospective study analyzed patients with colorectal liver metastases operated on between 1998 and 2012 at the Department of Abdominal Surgery of the AC Camargo Cancer Center. The study was approved by the Research Ethics Committee of our institution.

Clinical data on the patients (sex, age, and ASA classification), disease (lymph node metastasis in the primary tumor, synchronicity, carcinoembryonic antigen [CEA] level at diagnosis of metastasis, number of hepatic nodules, diameter of largest hepatic nodule, bilobar disease, resectability, extrahepatic disease, and K-RAS status), and treatment (exposure to preoperative chemotherapy, number of cycles, treatment regimen, resection margin), and site of recurrence after hepatectomy was obtained from the patients' medical records. Patients with clinically proven liver metastases who had undergone the first resection at our institution and for whom the sidedness of origin of the primary tumor could be characterized were included in the study. Right-sided colon tumors were considered those that originated anywhere from the cecum to the transverse colon and left-sided tumors were those that originated anywhere from the splenic flexure of the colon to the sigmoid colon. Patients with rectal tumors were excluded from the final analysis because of the peculiarities of the natural course of the disease. Patients with macroscopically incomplete resections (R2) were also excluded. Patients with extrahepatic disease amenable to surgical resection with an intent to cure were included in the study. Synchronous metastases were defined as those diagnosed before, during, or until 6 months after diagnosis of the primary tumor. The resectability of hepatic metastases was defined according to the consensus of the American Hepato-Pancreato-Biliary Association, the Society of Surgical Oncology, and the Society of Surgery of the Alimentary Tract in February 2013,[18] and those initially considered unresectable were operated on after receiving conversion chemotherapy. Depending on the availability of the material, K-RAS analysis of either the primary tumor or the metastatic surgical specimen was conducted using the pyrosequencing method, with screening for mutations at codons 12 and 13. The radiological response in patients who received preoperative chemotherapy was characterized using the Response Evaluation Criteria In Solid Tumors criteria version 1.1.[19] Resection was defined as R0 in cases in which the distance from the tumor to the resection margin was ≥1 mm.

Statistical analysis was performed using the SPSS software version 20.0 (SPSS Inc., Chicago, IL). Continuous variables were expressed using the appropriate central tendency measure (mean or median). The characteristics were organized by type of variable for

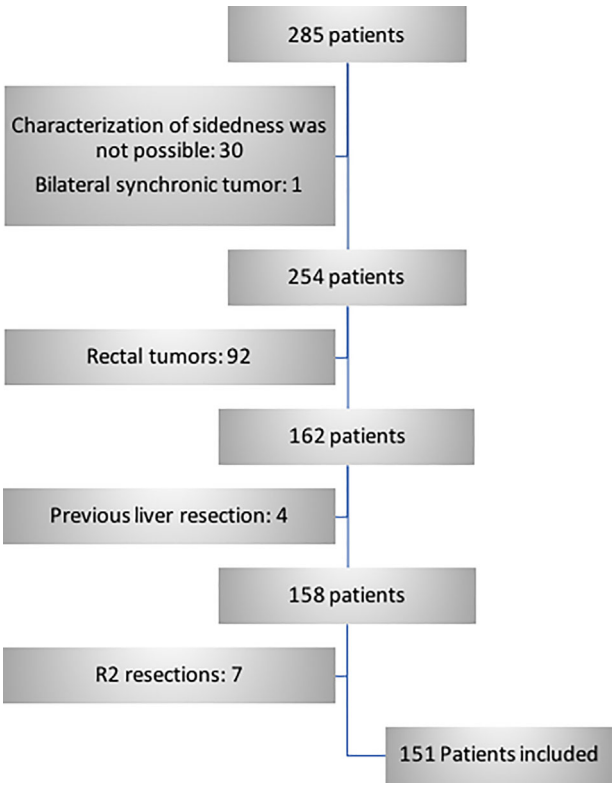

FIGURE 1 Flowchart of inclusion and exclusion criteria

TABLE 1 Characterization of the study population and comparison between right and left side tumors

		Sidedness		
Characteristic	**Total**	**Right**	**Left**	***P***
All patients	151	27	124	
Gender (M:F)	75:76	12:15	63:61	0.699
Age (median, range, years)	58 (23-80)	61 (23-73)	57 (29-80)	0.741
ASA (1/2:3/4)	127:24	23:4	104:20	1.000[a]
Lymph node status (N0:N+)	43:96	10:15	33:81	0.399
Synchronous:metachronous	95:55	1:15	84:40	0.026
CEA level (median, range, ng/mL)	18.7 (1-3200)	11.7 (1-109)	22.0 (1-3200)	0.001
Tumor number (median, range)	2 (1-20)	2 (1-9)	2 (1-20)	0.987
Largest tumor diameter (mean, range, cm)	8.6 (±4.6)	3.7 (±1.9)	8.9 (±4.8)	0.237
Bilobar:unilobar	71:80	11:16	60:64	0.611
Extra-hepatic disease	24	6	18	0.383[a]
Resectability at diagnosis (resectable:unresectable)	123:27	24:3	99:24	0.412[a]
Pre-operative chemo	91	14	77	0.574
Number pre-op. cycles (median, range)	7 (1-22)	6 (3-12)	7 (1-22)	0.102
Oxali:Irino	57:30	8:5	49:25	0.759[a]
Bevacizumab	39	6	33	0.863
Cetuximab	24	3	21	0.572[a]
Recist				
Response	63	8	55	0.204[a]
Stable disease	21	4	17	
Progression	2	1	1	
Margin (R0:R1)	136:11	27:0	109:11	0.217[a]
Recurrence (hepatic:extra-hepatic)	29:70	5:9	24:61	0.544[a]
K-RAS status (wild-type:mutated)	63:28	3:9	60:19	0.001[a]

[a]Fischer's exact test.

subsequent comparisons. For quantitative variables, Student's *t*-test was used in cases of normal distribution, and the Mann-Whitney test was used in cases of nonnormal distribution. For qualitative variables, Pearson's chi-square test or Fischer's exact test was used in cases in which the frequency was <5 in a table larger than 2 × 2. Survival was calculated using the Kaplan-Meier estimator, and comparisons were performed using the log-rank test. OS was defined as the time in months from the liver resection surgery to death by any cause, and DFS was defined as the time from liver resection surgery to relapse. The level of significance adopted was $P < 0.050$. Variables with *P*-values <0.200 determined by the log-rank test were selected for multiple regression analyses using the Cox proportional regression model.

3 | RESULTS

A total of 285 patients underwent liver resection for colorectal hepatic metastases during the study period, but only 151 patients met the inclusion criteria (Figure 1). Of these, 27 had right-sided colon tumors (17.9%) and 124 had left-sided colon tumors (82.1%). The data on the clinical and pathological characteristics are presented in Table 1.

3.1 | Survival

The median follow-up time was 42 months. The median OS of the whole population was not reached, and 3-year OS was 84.4%. The median DFS was 18 months, and 3-year DFS was 32.6%. Tables 2 and 3 show the results of the log-rank comparison and Cox regression models for OS and DFS, respectively.

3.2 | Impact of tumor side on survival

The sidedness of origin of colon cancer did not affect OS and DFS (Figure 2). Possible confounding factors were corrected by creating two Cox regression models, including the variables that were statistically different between the two groups (disease-free interval, CEA level, and K-Ras status). The K-Ras status was included in only one of these models because most data on this variable were unavailable, and using the available data might lead to an unreliable result for the

TABLE 2 Uni and multivariate analyses of overall survival

	UV analyzes			MV analyzes		
Variables	**HR**	***P***	**95%CI**	**HR**	***P***	**95%CI**
Female	1.6	0.180	0.8-3.1	1.7	0.108	0.9-3.4
Age	1.0	0.917	0.9-1.0			
ASA 3-4	1.4	0.408	0.6-2.9			
N+	1.3	0.441	0.6-2.8			
Synchronous metastasis	1.3	0.505	0.6-2.5			
CEA	1.0	0.936	1.0-1.0			
Number liver nodules	1.2	<0.001	1.1-1.3	1.2	0.005	1.0-1.3
Diameter largest nodule	1.0	0.282	1.0-1.1			
Bilobar disease	3.0	0.002	1.5-6.0	2.0	0.094	0.9-4.5
Extra-hepatic disease	3.6	0.001	1.7-7.8	4.1	0.001	1.8-9.4
Unresectable disease	2.8	0.006	1.3-5.9	2.2	0.054	1.0-5.0
Pre-operative chemotherapy	2.0	0.049	1.0-4.1	1.6	0.235	0.7-3.5
R1 margin	1.1	0.916	0.2-4.5			

sample. Even after correction, neither DFS (hazards ratio [HR] = 1.1, $P = 0.785$, 95% confidence interval [CI] = 0.5-2.5 in the model with K-Ras; and HR = 1.0, $P = 0.971$, 95%CI = 0.5-1.8 in the model without K-Ras) nor OS (HR = 2.1, $P = 0.281$, 95%CI = 0.5-8.3 in the model with K-Ras; and HR = 1.1, $P = 0.877$, 95%CI = 0.4-2.6 in the model without K-Ras) was significantly different between the two groups.

4 | DISCUSSION

There is growing scientific evidence that the sidedness of origin of colorectal cancer originate is an independent prognostic factor of survival. This is the first series involving patients with metastatic colorectal cancer without differences in survival rates when sidedness of the tumor was considered.[5,6,20] Although this finding seems to contradict the trend observed in some studies, we believe that these contradictions are because of differences in the study samples between this study and previous studies.

The selection of patients for aggressive treatment of metastatic colorectal disease has always been an important factor for consideration.[21] In an attempt to determine the biological behavior of the disease, clinical and pathological factors such as lymph node metastasis in the primary tumor, disease-free interval, CEA level, number, and size of hepatic nodules, and extrahepatic disease have been used as selection criteria for surgical treatment.[22] Patient response to systemic treatment has gained importance recently over traditional clinical predictors.[23] Therefore, the distinctive

TABLE 3 Uni and multivariate analyses of disease free survival

	UV analyzes			MV analyzes		
Variables	**HR**	***P***	**95%CI**	**HR**	***P***	**95%CI**
Female	1.1	0.536	0.8-1.7			
Age	1.0	0.559	1.0-1.0			
ASA 3-4	0.9	0.867	0.6-1.6			
N+	1.7	0.027	1.1-2.7	1.5	0.070	1.0-2.5
Synchronous metastasis	1.7	0.018	1.1-2.6	1.3	0.373	0.7-2.2
CEA	1.0	0.014	1.0-1.0	1.0	0.060	1.0-1.0
Number liver nodules	1.2	<0.001	1.1-1.2	1.1	0.141	1.0-1.2
Diameter largest nodule	1.0	0.529	1.0-1.0			
Bilobar disease	2.5	<0.001	1.7-3.8	1.7	0.054	1.0-2.8
Extra-hepatic disease	2.0	0.007	1.2-3.2	1.9	0.020	1.1-3.3
Unresectable disease	3.6	<0.001	2.2-5.8	1.8	0.080	0.9-3.5
Pre-operative chemotherapy	1.9	0.003	1.2-2.9	1.6	0.093	0.9-2.7
R1 margin	1.3	0.538	0.6-2.6			

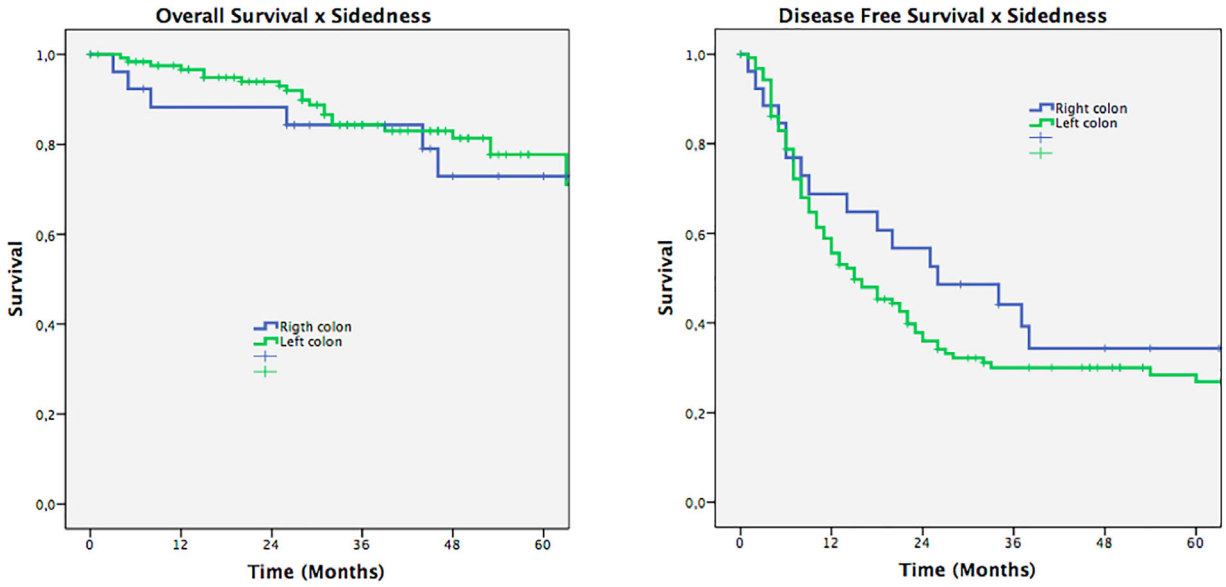

FIGURE 2 Overall and disease-free survival according to the sidedness of the tumor

feature of our series compared to previous studies may be the strict selection of patients for liver resection. A consequence of the use of this criterion was the low rate of right sided tumors and, specially, the low rate of synchronous disease in this population (6.25%) compared to that in previous studies (CALGB/SWOG 80 405 = 86.9%; Schrag et al. = 45.2%).[5,6] Another factor that was likely associated with patient selection in our study was the administration of preoperative chemotherapy in 51.8% patients with right-sided colon tumors. In general, patients who have disease progression during systemic treatment are excluded from surgery because of the little likelihood that they will benefit from the latter.

It is also important to note that the most well-known case series on this subject (CALGB/SWOG 80405, FIRE-3, CRYSTAL, PEAK, and PRIME) included only patients with wild-type K-RAS tumors because the main objective was to compare the survival rates after anti-EGFR administration in standard regimens without either monoclonal antibody or anti-VEGF.[5,7–9] This selection criterion alone creates a sample that is different from that of our study because, despite the limited data on K-RAS status, 30.8% patients were found to have the mutation, and an even higher percentage was identified in the group of patients with right-sided colon tumors (75%). Given that RAS and BRAF mutations are almost mutually exclusive[24,25] and that patients with BRAF mutations are typically less responsive to the available chemotherapy regimens,[26] these results suggest a lower percentage of patients with BRAF mutations in our series, which, in turn, could explain the similar rates of survival between the two groups.

Few studies to date evaluated cases of resected metastatic disease. The three studies presented at the ASCO 2017 Gastrointestinal Cancers Symposium demonstrated the impact of sidedness of tumor origin on OS alone,[15–17] and in the study from Japan, this impact was less evident and was observed only after the Cox regression model was fit to the confounding factors (UV: $P = 0.547$; MV: $P = 0.047$).[17] In the two studies from the United States, the proportion of patients with right-sided colon tumors was higher than that reported in our study (43.3% and 36%, respectively).[15,16] In turn, the study from Japan reported a R:L tumor ratio similar to that of our case series (15.6%). It is possible that differences in the results are because of differences in the selection criteria; however, the lack of information on these populations limits conclusions on the subject.

The limiting factor in our series was the retrospective nature of the study because of the possibility of selection biases, and the missing patient information may also have affected the results. However, considering the limited number of studies on the side of origin of colon cancer and the factors that predict survival, our results may help to bridge the information gap.

5 | CONCLUSION

Our results suggest that the sidedness of origin of colon cancer does not affect the long-term survival of patients with resected liver metastases and that the selection of patients with right-sided colon tumors for surgical treatment may play a key role in the results.

DISCLOSURES

The authors have nothing to disclose.

ORCID

Márcio C Marques http://orcid.org/0000-0002-9977-9880
Wílson L. Costa http://orcid.org/0000-0003-4460-4706

REFERENCES

1. Muzny DM, Bainbridge MN, Chang K, et al. Comprehensive molecular characterization of human colon and rectal cancer. *Nature*. 2012;487:330–337.

2. Sadanandam A, Lyssiotis CA, Homicsko K, et al. A colorectal cancer classification system that associates cellular phenotype and responses to therapy. *Nat Med*. 2013;19:619–625.
3. Guinney J, Dienstmann R, Wang X, et al. The consensus molecular subtypes of colorectal cancer. *Nat Med*. 2015;21:1350–1356.
4. Dienstmann R, Vermeulen L, Guinney J, et al. Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer. *Nat Rev Cancer*. 2017;17:79–92.
5. Venook AP, Niedzwiecki D, Innocenti F, et al. Impact of primary (1°) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): analysis of CALGB/SWOG 80405 (Alliance). *J Clin Oncol*. 2016;34:3504.
6. Schrag D, Weng S, Brooks G, et al. The relationship between primary tumor sidedness and prognosis in colorectal cancer. *J Clin Oncol*. 2016; 34: 3505.
7. Sunakawa Y, Ichikawa W, Tsuji A, et al. Prognostic impact of primary tumor location on clinical outcomes of metastatic colorectal cancer treated with cetuximab plus oxaliplatin-based chemotherapy: a subgroup analysis of the JACCRO CC-05/06 trials. *Clin Colorectal Cancer*. 2017;16:171–180.
8. Tejpar S, Stinzing S, Ciardello F, et al. Prognostic and predictive relevance of primary tumor location in patients with RAS wild-type metastatic colorectal cancer: retrospective analyses of the CRYSTAL and FIRE-3 trials. *JAMA Oncol*. 2016 [cited 2017 Oct 10]. Available from: https://jamanetwork.com/journals/jamaoncology/issue/3/2. DOI: 10.1001/jamaoncol.2016.3797.
9. Boeckx N, Koukakis R, Op de Beeck K, et al. Primary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer: results from two randomized first-line panitumumab studies. *Ann Oncol*. 2017;28 1862–1868.
10. Brungs D, Aghmesheh M, de Souza P, et al. Sidedness is prognostic in locoregional colon cancer: an analysis of 9509 Australian patients. *BMC Cancer*. 2017; 17 251.
11. Aoyama T, Kashiwabara K, Oba K, et al. Clinical impact of tumor location on the colon cancer survival and recurrence: analyses of pooled data from three large phase III randomized clinical trials. *Cancer Med*. 2017 [cited 2017 Oct 10]. Available from: http://doi.wiley.com/10.1002/cam4.1208. DOI: 10.1002/cam4.1208.
12. Kerr DJ, Domingo E, Kerr R. Is sidedness prognostically important across all stages of colorectal cancer? *Lancet Oncol*. 2016;17: 1480–1482.
13. Dehal A, Vuong B, Graff-Baker AN, et al. Effect of colon cancer sidedness compared to tumor biology on stage-specific survival. *J Clin Oncol*. 2017; 35:543.
14. Ben-Aharon I, Goshen-Lago T, Geva R, et al. Sidedness matters: surrogate biomarkers prognosticate colorectal cancer upon anatomic location. *J Clin Oncol*. 2017; 35:523.
15. Lee-Ying RM, Bosma N, Tang PA. Impact of primary tumor sidedness on survival after resection of colorectal liver metastases (CRLM). *J Clin Oncol*. 2017; 35: 694.
16. Creasy JM, Sadot E, Groot Koerkamp B, et al. Right versus left: Impact of primary location on survival and cure in patients undergoing hepatic resection for metastatic colon cancer. *J Clin Oncol*. 2017;35:664.
17. Kizawa R, Ichikawa Y, Kumamoto F, et al. Does primary site of colorectal cancer become a prognostic factor of patients undergoing curative resection of liver metastases? *J Clin Oncol*. 2017; 35: 772.
18. Adams RB, Aloia TA, Loyer E, et al. Selection for hepatic resection of colorectal liver metastases: expert consensus statement. *HPB*. 2013;15:91–103.
19. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228–247.
20. Holch JW, Ricard I, Stintzing S, et al. The relevance of primary tumour location in patients with metastatic colorectal cancer: a meta-analysis of first-line clinical trials. *Eur J Cancer*. 2017;70:87–98.
21. Araujo RLC, Riechelmann RP, Fong Y. Patient selection for the surgical treatment of resectable colorectal liver metastases. *J Surg Oncol*. 2017;115:213–220.
22. 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;230:309–321.
23. Jones RP, Poston GJ. Resection of liver metastases in colorectal cancer in the era of expanding systemic therapy. *Annu Rev Med*. 2017;68:183–196.
24. Roth AD, Tejpar S, Delorenzi M, et al. Prognostic role of KRAS and BRAF in stage II and III resected colon cancer: results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial. *J Clin Oncol*. 2010;28:466–474.
25. Sylvester BE, Huo D, Khramtsov A, et al. Molecular analysis of colorectal tumors within a diverse patient cohort at a single institution. *Clin Cancer Res*. 2012;18:350–359.
26. Seligmann JF, Fisher D, Smith CG, et al. Investigating the poor outcomes of BRAF-mutant advanced colorectal cancer: analysis from2530 patients in randomised clinical trials. *Ann Oncol*. 2016;28562–568.

How to cite this article: Marques MC, Ribeiro HSC, Costa Jr. WL, et al. Is primary sidedness a prognostic factor in patients with resected colon cancer liver metastases (CLM)? *J Surg Oncol*. 2018;117:858–863.
https://doi.org/10.1002/jso.25048