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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

The Prognostic Impact of Determining Resection Margin Status for Multiple Colorectal Metastases According to the Margin of the Largest Lesion

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ABSTRACT

Background. Although the prognostic role of surgical margin status after resection of colorectal liver metastasis (CRLM) has been previously examined, controversy still surrounds the importance of surgical margin status in patients with multiple tumors.

Methods. Patients who underwent curative-intent surgery for CRLM from 2000 to 2015 and who presented with multiple tumors were identified. Patients with R1 resection status determined by the closest resection margin of the non-largest tumor were classified as R1-Type 1; patients with R1 status determined by the resection margin of the largest tumor were defined as R1-Type 2. Data regarding surgical margin status, size of tumors, and overall survival (OS) were collected and assessed.

Results. A total of 251 patients met inclusion criteria; 156 patients (62.2%) had a negative margin (R0), 50 had an R1-type 1 (19.9%), and 45 had an R1-type 2 (17.9%) margin. Median and 5-year OS in the entire cohort was 56.4 months and 48.0%, respectively. When all R1 (Type 1 + Type 2) patients were compared with R0 patients, an R1 was not associated with worse prognosis ($P = 0.05$). In contrast, when R1-type 2 patients were compared with R0 patients, an R1 was strongly associated with worse OS ($P = 0.009$). On multivariate analysis, although the prognostic impact of all R1 was not associated with OS (hazard ratio [HR] 1.56; $P = 0.08$), R1-Type 2 margin status independently predicted a poor outcome (HR 1.93; $P = 0.03$).

Conclusions. The impact of margin status varied according to the size of the tumor assessed. While R1 margin status defined according to the non-largest tumor was not associated with OS, R1 margin status relative to the largest index lesion was associated with prognosis.

Liver resection is generally recognized as the best potentially curative modality for patients with colorectal liver metastases (CRLM).[1,2] Although hepatectomy for CRLM can be performed with low short-term morbidity and mortality, long-term prognosis remains guarded as up to 50% of patients experience intrahepatic recurrence after curative-intent resection.[3–5] Much attention has been devoted to identifying potentially modifiable factors that may influence the risk of intrahepatic recurrence among patients with CRLM. In particular, the prognostic implications of the resection margin (RM) following resection of CRLM have been extensively studied.[6–15] Traditionally, a RM width of at least 10 mm was widely considered the gold standard.[6–8] With the introduction of effective modern chemotherapy regimens, numerous studies have demonstrated, however, that subcentimeter or even submillimeter margin widths were not associated with worse survival.[9–15] In fact, some recent studies have questioned the negative prognostic impact of microscopically positive (R1) resections, in cases where R0 resections are technically unfeasible.[9]

The rationale underlying the resection of additional macroscopically nontumorous tissue around the index

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TABLE 1 Baseline patient demographic and clinical characteristics

Characteristics	Hepatectomy for multiple tumors ($n = 251$) No. (%)			
	Negative RM ($n = 156$)	Positive RM ($n = 95$)		
		Overall	Type 1 ($n = 50$)	Type 2 ($n = 45$)
Patient characteristics				
Age (years)				
Median (IQR)	56 (47–65)	57 (51–65)	57 (48–67)	57 (52–65)
Sex				
Male	83 (53.2)	59 (55.6)	30 (60.0)	29 (64.4)
Female	73 (46.8)	36 (44.4)	20 (40.0)	16 (35.6)
Primary CRC characteristics				
Tumor site				
Right-sided	53 (34.0)	27 (28.4)	15 (30.0)	12 (26.7)
Left-sided	103 (66.0)	68 (71.6)	35 (70.0)	33 (73.3)
T stage ($n = 235$)				
T1 or T2 stage	20 (13.6)	11 (14.1)	6 (12.8)	5 (12.2)
T3 or T4 stage	127 (86.4)	77 (85.9)	41 (87.2)	36 (87.8)
Nodal metastases				
Negative	43 (27.6)	22 (28.9)	11 (22.0)	11 (24.4)
Positive	113 (72.4)	73 (71.1)	39 (78.0)	34 (75.6)
Preoperative factors				
Disease interval (months)				
<12	128 (82.0)	78 (81.8)	41 (82.0)	37 (82.2)
≥12	28 (18.0)	17 (18.2)	9 (18.0)	8 (17.8)
Preoperative chemotherapy	102 (65.4)	68 (71.6)	33 (66.0)	35 (77.8)
RECIST response ($n = 168$)				
PD or SD	67 (67.0)	43 (63.2)	20 (60.6)	23 (65.7)
PR or rCR	33 (33.0)	25 (36.8)	13 (39.4)	12 (34.3)
Preoperative CEA (ng/mL), Median (IQR)	7.9 (3.0–24.0)	11.1 (4.1–40.5)	11.1 (5.9–46.9)	10.6 (3.4–30.0)
Extrahepatic disease				
Negative	143 (91.7)	86 (90.5)	46 (92.0)	40 (88.9)
Positive	13 (8.3)	9 (9.5)	4 (8.0)	5 (11.1)
Tumor factors				
No. of CRLM, Median (IQR)	2 (2–3)	3* (2–4)	3 (2–4)	3 (2–4)
Size of largest CRLM (cm), Median (IQR)	2.3 (1.5–3.7)	2.7* (1.8–4.5)	2.5 (1.6–6.0)	2.7 (1.8–3.5)
Bilobar disease	82 (52.6)	57 (60.0)	32 (64.0)	25 (55.6)
KRAS mutation status ($n = 209$)				
Wild-type	76 (61.3)	59 (69.4)	32 (69.6)	27 (69.2)
Mutated	48 (38.7)	26 (30.6)	14 (30.4)	12 (30.8)
Postoperative factors				
Postop chemotherapy ($n = 237$)	111 (76.0)	71 (78.0)	37 (75.5)	34 (81.0)
Pattern of initial recurrence				
Total	93 (59.6)	58 (61.1)	32 (64.0)	26 (57.8)
Intrahepatic only	37 (39.8)	33 (56.9)	18 (56.3)	15 (57.7)
Extrahepatic only	37 (39.8)	13 (22.4)	8 (25.0)	5 (19.2)
Both intra and extra	19 (20.4)	12 (20.7)	6 (18.8)	6 (23.1)
Recurrence at RM	11 (11.8)	11 (19.0)	6 (18.8)	5 (19.2)

CEA carcinoembryonic antigen, *CRC* colorectal cancer, *CRLM* colorectal liver metastases, *KRAS* kirsten rat sarcoma viral oncogene homologue, *OS* overall survival, *PD* progressive disease, *PR* partial response, *rCR* radiological complete response, *RM* resection margin, *SD* stable disease

* $P < 0.05$ between negative and positive resection margin

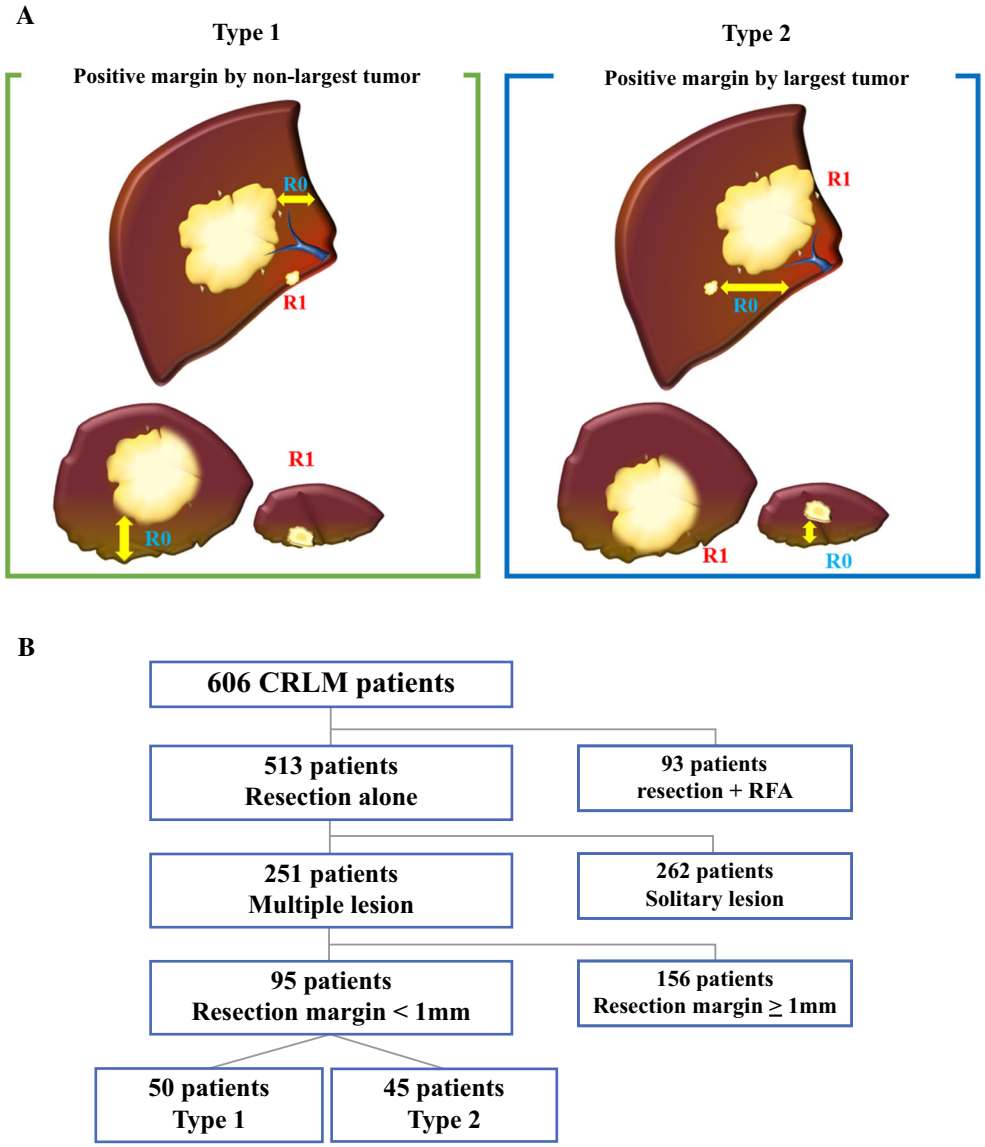

FIG. 1 **a** Illustration of positive margin by largest or non-largest tumor. **b** Derivation of the final study cohort

lesion is to remove grossly undetectable micrometastases.[8,15] Specifically, previous reports have demonstrated that most micrometastases are present within 2–4 mm of the main tumor in patients with CRLM.[16] However, other data have suggested that larger tumors may be surrounded by more widely dispersed micrometastases, leading to a higher risk of recurrence and worse long-term outcomes.[16,17] As such, it may be that RM status of resected smaller versus larger tumors has a different prognostic impact. Most previous studies examining RM width/status at the time of hepatectomy for multiple CRLMs have only considered the closest margin width among all resected tumors, rather than examining the impact of margin status on a per lesion basis.[9–13] Given that the incidence of micrometastases surrounding a CRLM lesion may vary based on lesion size, we hypothesized that the clinical impact of RM may differ among patients whose overall RM status was determined by the margin width/status of the largest tumor versus patients whose margin status was determined solely by the minimum margin width/status among all resected tumors. As such, the objective of the current study was to test this hypothesis by comparing the prognostic utility of these two different methods of determining RM status among patients with multiple CRLM.

METHODS

Patients, Clinicopathologic Data, and Assessment of Radiologic Response to Chemotherapy

Patients who underwent curative-intent hepatectomy for CRLM between January 2000 and June 2015 at Johns

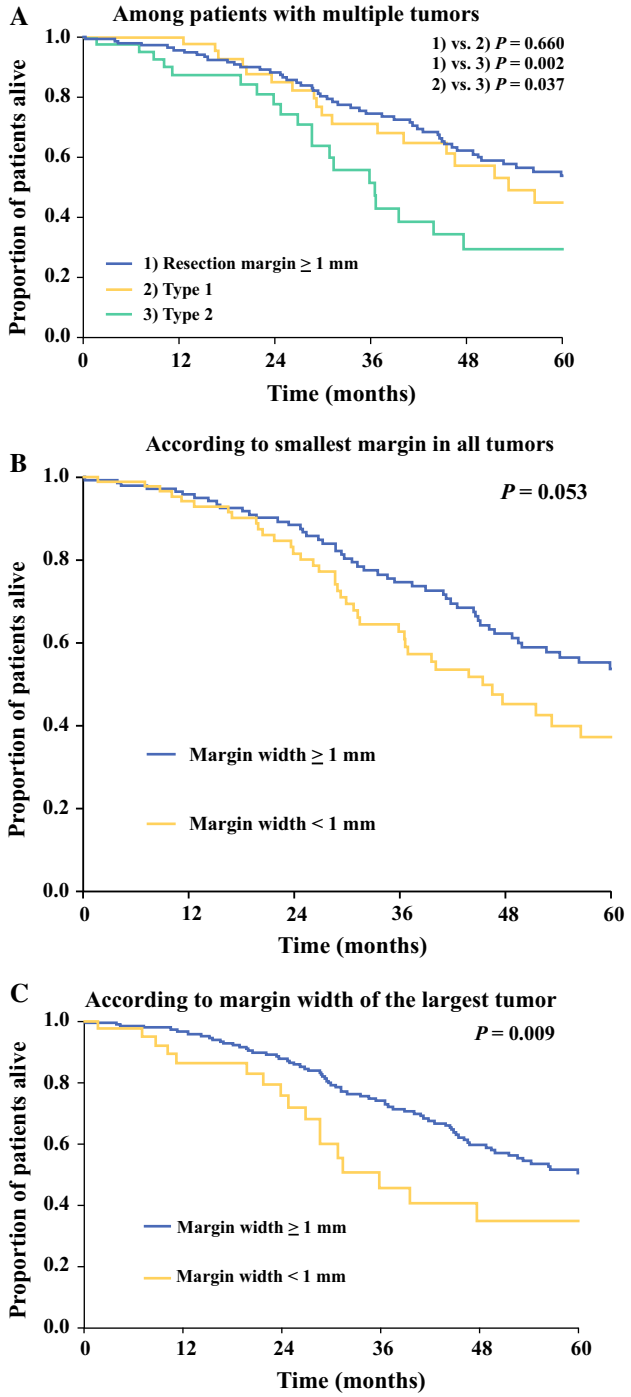

FIG. 2 **a** Overall survival stratified by R0, R1-type 1 and R1-type 2 resections. **b** Overall survival stratified by R0 and R1 defined by minimum resection margin width irrespective of tumor size. **c** Overall survival stratified by R0 and R1 defined by the largest tumor

Hopkins Hospital with available RM width data were identified. Patients who only underwent ablation or palliative liver resection (R2 resection) were excluded. Institutional review board approval was obtained for this study. For each patient, sociodemographic data and information on tumor-specific factors, such as primary tumor location (primary tumors located from the cecum to the end of transverse colon were defined as right-sided; tumors located from the splenic flexure to the rectum were defined as left-sided), American Joint Committee on Cancer (AJCC) primary tumor T stage, and nodal status were recorded. Data on preoperative chemotherapy also were recorded. A combined cytotoxic regimen was defined as any fluorouracil-based regimen combined with oxaliplatin/irinotecan. Response was defined according to the previously described RECIST criteria.[18] Major hepatectomy was defined as resection of at least three Couinaud liver segments.[19] An R1 resection was defined as the presence of tumor cells <1 mm from the transection line.[10–15] A cutoff value of 50 ng/ml was decided for CEA levels based on relevant previous findings of our group.[20] Date of last follow-up and dead-or-alive status were determined for all patients. Follow-up time was defined as the interval from the index hepatectomy to the date of death or last follow-up.

Study Design

To test the prognostic impact of R1 RM status according to index lesion size, patients who underwent hepatectomy for multiple (≥2) CRLM and who had R1 margins were divided into two groups. In the first group, R1 margin status was determined by the closest RM of the non-largest tumor (Type 1). In the second group, R1 margin status was defined as the margin width of the largest tumor (Type 2; Fig. 1a). The clinicopathological and prognostic difference between the two groups were compared. Moreover, the prognostic impact of RM width defined as either the minimum RM width among all resected lesions irrespective of tumor size or the RM width of the largest tumor also was assessed.

Statistical Analysis

Summary statistics were presented as whole numbers and percentages for categorical variables or as medians with interquartile ranges (IQR) for continuous variables. Differences between the two groups were assessed using the Chi squared test, Fisher's exact test, and Mann–Whitney *U* test, as appropriate. Overall survival (OS) was estimated using the Kaplan–Meier method calculated from the date of surgery; differences in OS were assessed with the log-rank test. The proportional hazard regression analysis (Cox) model was used to determine predictors of long-term survival, with results presented as hazard ratios (HRs) and 95% confidence intervals (95% CI). Factors included in the multivariable model were selected based on

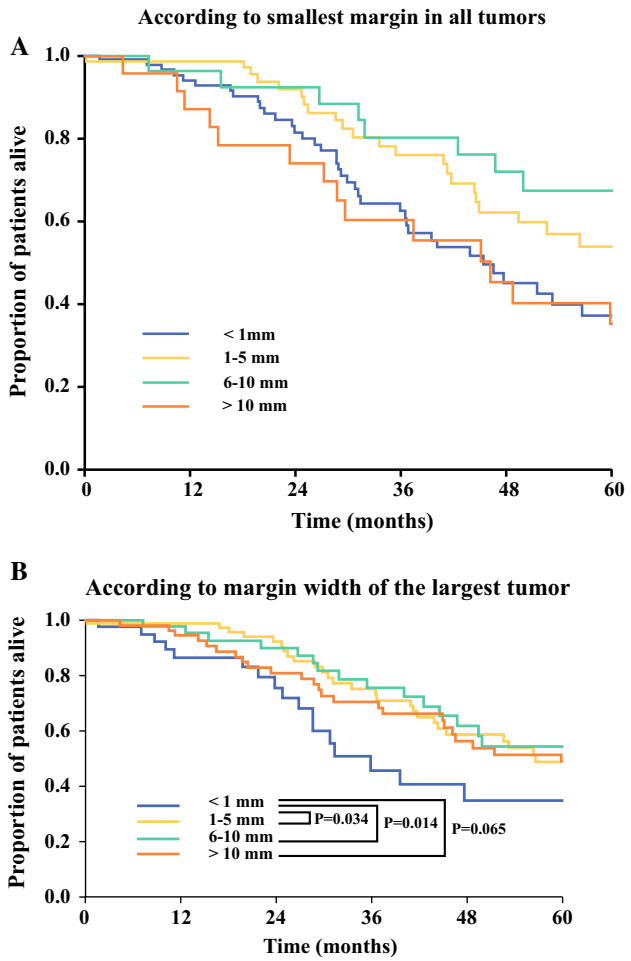

FIG. 3 **a** Overall survival stratified by the minimum resection margin width irrespective of tumor size. **b** Overall survival stratified by margin width of the largest tumor

clinical relevance, as well as statistical significance on univariable analysis ($P < 0.100$). Similar to the original clinical risk scoring system developed by Fong et al., we hypothesized that the largest (index) liver tumor has a higher prognostic significance compared with the other lesions in the case of multiple tumors.[6] As such, we hypothesized that it may better "reflect" tumor biology and, consequently, that it might be more appropriate to define margin positivity (and an R1 resection) according to the margin status of the largest liver tumor. To account for the prognostic impact of the size of the largest lesion and thus limit the possibility of bias in our analysis, we included both tumor size and number as independent factors in the univariable and multivariable analyses. P value < 0.05 (2-tailed) was considered statistically significant in the multivariable analysis. All analyses were performed with SPSS software version 23 (IBM SPSS, Chicago, IL).

RESULTS

Clinicopathologic Characteristics of the Study Cohort

A total of 606 patients met inclusion criteria. Of these 606 patients, 93 were excluded from the study population as these patients underwent combined resection and ablation. Of the remaining 513 patients, 251 had a hepatectomy for multiple CRLM and 95 (37.8%) had R1 margin status (Fig. 1b). Clinicopathologic characteristics according to RM status among patients with multiple CRLM are summarized in Table 1. Among 95 patients with multiple CRLM and R1 margin status, 50 patients were categorized as having type 1 R1 margin status, whereas 45 patients had type 2 R1 margins. Patients with type 1 and type 2 R1 margin status were similar in terms of clinicopathological characteristics (all $P > 0.05$; Table 1).

Long-Term Outcomes According to the Definition of RM

At a median follow up of 30.3 months, 151 patients had tumor recurrence and 103 patients had died. There was no difference in the recurrence pattern among patients who had type 1 versus type 2 R1 margin status, including the incidence of intrahepatic recurrence (type 1; 18.8% and type 2; 19.2%, $P > 0.99$). Median 1-, 3-, and 5-year OS was 56.4 months: 95.1, 70.1, and 48.0%, respectively. OS stratified by type 1 versus type 2 RM status are shown in Fig. 2a. Interestingly, median OS was similar among patients who had an R0 margin versus patients who had type 1 R1 margin status (66.6 vs. 53.3 months, respectively; $P = 0.66$). In contrast, median OS among patients with type 2 R1 status was markedly worse compared with patients who had an R0 (36.5 vs. 66.6 months, respectively; $P = 0.002$) and type 1 R1 margin status (36.5 vs. 53.3 months, respectively; $P = 0.03$). Moreover, the prognostic impact of RM status differed according to how margin status was defined (Fig. 2b, c). Specifically, when R1 margin status was defined by minimum RM width irrespective of tumor size, R1 status was not associated with prognosis (HR 1.47, 95% CI 0.99–2.19; $P = 0.05$). In contrast, when R1 margin status was defined by the margin width of the largest tumor, R1 status was strongly associated with a poor prognosis (HR 1.94, 95% CI 1.17–3.20; $P = 0.009$). Overall results were the same when R1 status was defined as tumor at the ink margin only.

Similar analyses were performed regarding the prognostic impact of various margin widths (<1, 1–5, 6–10, and >10 mm). Among patients with multiple resected CRLM, RM width of the largest tumor tended to be a better prognostic discriminator compared with the use of margin width irrespective of tumor size (Fig. 3a, b). On

multivariable analysis, the RM status defined by minimum RM width irrespective of tumor size was not associated with long-term survival (HR 1.56; 95% CI 0.95–2.57; $P = 0.08$). In contrast, among patients with multiple resected tumors, RM width associated with the largest tumor (type 2) was associated with the risk of death long-term (HR 1.93; 95% CI 1.04–3.57; $P = 0.03$).

DISCUSSION

Surgical margin status following resection of CRLM has been the focus of an ongoing debate for the past 30 years.[15,21] Previous studies have yielded conflicting results, ranging from Ekberg's "1-cm rule" in the 1980s to the 1-mm rule in the era of modern chemotherapy to more recent reports that an R1 margin is not associated with prognosis.[9,13,14,22–24] Sadot and colleagues attributed these disparate results to the lack of a universal definition of a "positive" RM.[25] In fact, particularly in the case of multiple liver tumors, the definition of an R1 margin is highly variable and arbitrary. Specifically, the current definition of a "positive" margin states that the closest margin determines margin status in the case of multiple lesions irrespective of the tumor size.[25] This definition may not accurately estimate the risk conferred by a positive margin. In fact, data from the current study would suggest that the impact of RM status varied according to which margin was being assessed relative to tumor size. Specifically, R1 margin status determined irrespective of tumor size among patients with multiple tumors was not prognostic of survival (Fig. 2b). Rather, R1 margin status was only prognostic of survival when margin status was defined according to type 2 criteria, which took into account the margin relative to the largest resected CRLM lesion (Fig. 2c). The current study is important, because no previous study had examined margin status specifically among patients with multiple CRLM tumors and defined margin status by the margin width of the largest lesion. Importantly, we noted that on multivariate analysis, an R1 resection was only associated with worse overall survival among patients with a positive margin associated with the largest CRLM lesion (HR 1.93; 95% CI 1.04–3.57; $P = 0.03$). In contrast, margin status (R0 vs. R1) was not associated with overall survival among patients whose margin status was determined by the "closest" margin irrespective of tumor size (HR 1.56; 95% CI 0.95–2.57; $P = 0.08$). These data highlight the variable prognostic impact of how margin status is defined among patients with multiple CRLM.[26]

Compared with patients who had an R0 resection, patients who underwent an R1 resection (both type 1 and type 2) were more likely to have advanced disease characterized by larger and more CRLM lesions. This finding was perhaps not surprising as more advanced metastatic disease can sometimes preclude complete resection due to the need to spare hepatic parenchyma. In contrast, among patients with an R1 resection, CRLM disease characteristics were comparable regardless of whether the positive margin was defined relative to the largest CRLM lesion or by the "closest" margin irrespective of tumor size. Given the similar baseline clinicopathological characteristics between the type 1 and type 2 R1 margin groups, it was particularly interesting to note that the impact of margin status differed between the two groups. Specifically, a "traditionally" defined R1 margin was not prognostic after controlling for other clinical and pathological factors (Table 2). In contrast, when margin status was defined relative to the largest CRLM resected, R1 margin status was indeed prognostic. In fact, even after controlling for all other factors, R1 status defined relative to the largest CRLM was associated with almost a twofold increased risk of death long-term.

Vigano and colleagues reported that larger CRLM tumors are more likely to harbor tumor cell nests in their vicinity, such as satellite tumors or micrometastases.[27] Other investigators have described intrahepatic micrometastases as being separated from the index lesion by a thin rim of normal parenchyma, being only visible microscopically.[28,29] These same authors have suggested that such micrometastases represent tumor invasion of vascular structures, lymphatics, and bile ducts.[28,29]

Consistent with findings in the current study, Adam et al. reported previously that the distance from the tumor where micrometastases proliferate increases with the size of CRLM and subsequently can adversely worsen overall survival.[30] Tumor size also was associated with an increased density of these tumor nests. In turn, by not assessing the margin status/width associated with the largest CRLM, patients may erroneously be misclassified as R0 when indeed an assessment of a wider margin width around the largest lesion may have demonstrated micrometastases or tumor nests. Consistent with this theory, Gomez et al. reported that a "true" R0 margin only benefited patients with a large CRLM tumor size.[31] The authors hypothesized that patients with larger tumors have a higher incidence of micrometastases disease that may be underappreciated when the margin status specifically associated with the largest lesion is not assessed.

The disparate impact of R1 margin status also may be related to different tumor growth patterns. Sadot et al. reported that the prognostic importance of a positive margin was influenced by the underlying tumor growth pattern.[24] In fact, CRLM tumor growth pattern has been correlated with both the risk of an R1 resection and long-term survival.[25,32,33] Specifically, three histological

TABLE 2 Uni- and multivariate analysis for overall survival in cohort study stratified by traditional and proposed R1 margin definition

Factors	According to standard definition				According to largest tumor			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (years)								
<60	Ref				Ref			
≥60	1.13 (0.76–1.39)	0.544			1.13 (0.76–1.39)	0.544		
Gender								
Male	Ref				Ref			
Female	0.72 (0.48–1.07)	0.104			0.72 (0.48–1.07)	0.104		
CRC anatomical site								
Right-sided	Ref				Ref			
Left-sided	0.77 (0.52–1.15)	0.205			0.77 (0.52–1.15)	0.205		
CRC nodal metastases								
Negative	Ref				Ref			
Positive	1.42 (0.91–2.22)	0.119			1.42 (0.91–2.22)	0.119		
Disease-free interval (months)								
≥12	Ref				Ref			
<12	1.09 (0.65–1.81)	0.749			1.09 (0.65–1.81)	0.749		
Preoperative chemotherapy								
No	Ref				Ref			
Yes	1.16 (0.78–1.74)	0.462			1.16 (0.78–1.74)	0.462		
Preoperative CEA (ng/mL)								
<50	Ref		Ref		Ref		Ref	
≥50	2.39 (1.43–3.97)	**0.001**	2.96 (1.69–5.16)	**<0.001**	2.39 (1.43–3.97)	**0.001**	2.93 (1.68–5.10)	**<0.001**
Extrahepatic disease								
Negative	Ref				Ref			
Positive	1.67 (0.86–3.23)	0.129			1.67 (0.86–3.23)	0.129		
Maximum tumour diameter (cm)								
<3	Ref				Ref			
≥3	1.34 (0.73–2.44)	0.347			1.34 (0.73–2.44)	0.347		
No. of CRLM								
<4	Ref		Ref		Ref		Ref	
≥4	1.52 (1.00–2.30)	**0.051**	1.64 (0.98–2.77)	0.062	1.52 (1.00–2.30)	**0.051**	1.65 (0.98–2.77)	0.060
Bilobar disease								
Negative	Ref		Ref		Ref		Ref	
Positive	0.70 (0.48–1.03)	**0.072**	0.70 (0.42–1.15)	0.158	0.70 (0.48–1.03)	**0.072**	0.74 (0.45–1.21)	0.224
KRAS mutation status								
Wild-type	Ref		Ref		Ref		Ref	
Mutated	1.49 (0.95–2.32)	**0.082**	1.95 (1.18–3.24)	**0.010**	1.49 (0.95–2.32)	**.0.082**	1.86 (1.12–3.10)	**0.016**
RM width (mm)								
≥1	Ref		Ref		Ref		Ref	
<1	1.47 (0.99–2.19)	**0.054**	1.56 (0.95–2.57)	0.077	1.94 (1.17–3.20)	**0.010**	1.93 (1.04–3.57)	**0.036**
Adjuvant chemotherapy								
No	Ref				Ref			
Yes	0.82 (0.52–1.29)	0.396			0.82 (0.52–1.29)	0.396		

CEA carcinoembryonic antigen, *CRC* colorectal cancer, *CRLM* colorectal liver metastases, *CI* confidence interval, *HR* hazard ratio, *KRAS* kirsten rat sarcoma viral oncogene homologue, *OS* overall survival, *PD* progressive disease, *PR* partial response, *rCR* radiological complete response, *Ref* reference, *SD* stable disease

Bold values were used for the variables that were significantly associated with the outcome. As stated in the "Methods" section, a cut-off $P < 0.1$ and $P < 0.05$ was used for the univariable and the multivariable analysis, respectively

patterns have been described, including the pushing-type, desmoplastic-type, and replacement-type.[34,35] Among these, the desmoplastic type has been associated with tumor size.[34] In particular, a smaller tumor size corresponded to a desmoplastic CRLM growth pattern and superior survival. While histologic growth patterns were not specifically examined in the current study, these data may explain, in part, why an R1 margin status associated with larger tumors conferred a worse survival.

Several limitations should be considered when interpreting the results of the current study. Histopathologic techniques used to define margin status harbor inherent limitations; specifically, a standard, biopsy-derived tissue section (5-μm thick) represents approximately 1:1000 of the area that is macroscopically suspicious for margin involvement.[16,36] Therefore, RM involvement by cancer cells can be missed, particularly in tumors with a diffuse, infiltrating growth pattern. Moreover, the use of argon coagulation or CUSA may influence margin status.[37] Specifically, these techniques may provide a "true" RM that is larger than that assessed by the pathologist, through their capacity to destroy several millimeters of surrounding liver parenchyma. However, in the current study, the same technique was largely used to divide the hepatic parenchyma, thereby minimizing case variation. Furthermore, we cannot comment on how these data relate to patients with multiple tumors that have a positive surgical margin, because no patient in the current cohort had two lesions with an R1 margin. Another limitation of this study is that while the receipt of neoadjuvant and adjuvant chemotherapy was accounted for in our analysis, we did not have sufficient data on the duration of postoperative chemotherapy to analyze its impact. Of note, further analysis of the impact of an R1 resection as defined by the largest liver lesion on the rates and patterns of recurrence (particularly on RM recurrence) was not feasible due to the limited sample size of the study. Lastly, R1 margin status was defined as the margin width of the largest tumor compared to other tumors in the same patient; the importance of the absolute and not the relative size of the positive margin tumor should be investigated in future studies.

CONCLUSIONS

The impact of R1 margin status among patients with multiple resected CRLM varied according to how margin status was defined. Whereas R1 margin status defined by traditional criteria was not associated with prognosis, margin status was prognostic when determined relative to the margin width of the largest tumor. As such, the current study suggests that the definition of an R1 resection should perhaps be reconsidered in the context of multiple lesions compared with a solitary lesion. Future studies should validate the prognostic impact of surgical margin relative to the largest surgical margin to facilitate the formulation of a universal definition of R1 margin status among patients undergoing resection of multiple CRLM.

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