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RESEARCH ARTICLE

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The optimal cut-off values for tumor size, number of lesions, and CEA levels in patients with surgically treated colorectal cancer liver metastases: An international, multi-institutional study

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Abstract

Background and Objectives: Despite the long-standing consensus on the importance of tumor size, tumor number and carcinoembryonic antigen (CEA) levels as predictors of long-term outcomes among patients with colorectal liver metastases (CRLM), optimal prognostic cut-offs for these variables have not been established.

Carsten Kamphues and Nikolaos Andreatos contributed equally to this manuscript.

Methods: Patients who underwent curative-intent resection of CRLM and had available data on at least one of the three variables of interest above were selected from a multi-institutional dataset of patients with known KRAS mutational status. The resulting cohort was randomly split into training and testing datasets and recursive partitioning analysis was employed to determine optimal cut-offs. The concordance probability estimates (CPEs) for these optimal cut offs were calculated and compared to CPEs for the most widely used cut-offs in the surgical literature.

Results: A total of 1643 patients who met eligibility criteria were identified. Following recursive partitioning analysis in the training dataset, the following cut-offs were identified: 2.95 cm for tumor size, 1.5 for tumor number and 6.15 ng/ml for CEA levels. In the entire dataset, the calculated CPEs for the new tumor size (0.52), tumor number (0.56) and CEA (0.53) cut offs exceeded CPEs for other commonly employed cut-offs.

Conclusion: The current study was able to identify optimal cut-offs for the three most commonly employed prognostic factors in CRLM. While the per variable gains in discriminatory power are modest, these novel cut-offs may help produce appreciable increases in prognostic performance when combined in the context of future risk scores.

KEYWORDS
colorectal cancer, metastases, prognostic factors

1 | INTRODUCTION

Hepatic resection is part of the accepted standard of care for colorectal cancer liver metastases (CRLM). In turn, patients who undergo metastasectomy have a median overall survival (OS) that has been reported to reach up to 6.6 years, compared to a median OS of 18–26.7 months for those with unresectable disease.[1,2] Despite improvements in prognostic tools, such as the development of nomograms, and the utilization of biologic markers (e.g., KRAS and BRAF mutational status) in anticipating long-term outcomes, survival among patients undergoing resection of CRLM remains highly unpredictable.[3–5] Specifically, past attempts to combine traditional clinicopathologic predictors into clinical risk scores have yielded relatively low c-indices, particularly when applied to external cohorts (0.6–0.7).[6] Surprisingly, incorporating biological markers (e.g., *KRAS* status) into earlier risk scores has so far resulted in only modest improvements in prognostic power.[7,8] This emphasizes the value of traditional clinicopathologic variables, and suggests that future prognostic tools should attempt to employ them more effectively alongside biomarkers, rather than discard them in favor of new predictors.

Of note, prior efforts to incorporate traditional clinicopathologic factors into risk scores were limited by the lack of uniform cut-off values. Despite a widespread consensus on the importance of several quantifiable clinical factors (especially tumor size, tumor number, and carcinoembryonic antigen [CEA] levels) in predicting long-term outcomes, there is little agreement on which cut-offs would maximize their prognostic power. Instead, a wide variety of cut-offs have been proposed for each variable, which have largely been derived from small, single-institution cohorts.[9–11] Moreover, determination of cut-offs has been somewhat unsystematic in many of these earlier reports with the employed methodologies not following a standardized approach and, on occasion, not being clearly described.[9–11] To address these limitations, we employed a formal statistical technique known as recursive partitioning (recently employed by Allen et al to define the optimal cut-offs for the American Joint Committee on Cancer [AJCC] staging schema) to identify the optimal contemporary cut-off values for tumor size, number of lesions, and CEA levels in one of the largest, international, multi-institutional cohorts of patients with surgically treated CRLM assembled to date.[12] To reinforce the applicability of the findings to the contemporary setting, only patients treated after 2000 were incorporated and the identified cut-offs were subjected to internal validation.

2 | MATERIALS AND METHODS

2.1 | Study protocol

The shared database of the nine major academic institutions participating in the International Genetic Consortium for Colorectal Liver Metastasis (IGCLM; The Johns Hopkins University, Baltimore, Maryland; Stanford University School of Medicine, Stanford, California; Digestive Disease Institute, Cleveland Clinic, Cleveland, Ohio; Yokohama City University, Yokohama, Japan; Kumamoto University, Kumamoto, Japan; University of Berlin–Charite, Berlin, Germany; Medical University of Vienna, Vienna, Austria; Medical University of Graz, Graz, Austria and Haukeland University Hospital, Bergen, Norway) was queried for patients who underwent resection for CRLM between January 1st, 2000 and December 31st, 2015. Patients who only underwent ablation or palliative liver resection (R2 resection) were excluded from the analysis, as were patients with missing data on all three variables of interest (tumor size, tumor number, and CEA levels). These variables were selected a priori because of their prognostic importance and frequent use in clinical risk scores; in fact, a recent systematic review identified tumor size, tumor number and CEA levels as the three most commonly used predictors across all prognostic models for patients with CRLM.[6]

2.2 | Study cohort

For each eligible patient, detailed information on the following variables was extracted from the electronic medical record: patient gender, age, AJCC T stage, primary tumor location (right vs. left colon), presence or absence of lymph node metastasis, administration of preoperative or postoperative chemotherapy, most recent CEA levels before hepatectomy, and disease-free interval between the diagnosis of the primary tumor and liver metastasis; a disease-free interval less than 12 months characterized synchronous (as opposed to metachronous) presentation of liver disease. With respect to CRLM, information on tumor size (maximum tumor size in the case of multiple metastatic lesions), tumor number and margin status (with R1 defined as the presence of tumor cells at the resection margin) was extracted from the pathology reports. KRAS mutational status was determined via analysis of tissue derived from the resected CRLM or the primary colorectal tumor depending on availability, as previously described.[4] Data on postoperative management and outcomes was also collected.

2.3 | Data analysis

Categorical data were summarized with frequencies and percentages, and continuous data were presented as medians and ranges. OS estimates for the study population were generated using the Kaplan–Meier method and calculated from the date of surgery to the time of death or last follow-up. Variables with a p value of less than .05 on univariable analysis were included in the multivariable survival analysis. The multivariable analysis was performed with the backward stepwise procedure for building a Cox proportional hazards model.

To calculate and validate the optimal prognostic cut-offs, the dataset was randomly split into two groups, as previously described by Allen et al; specifically, two-thirds of the cohort were assigned to a training dataset and the remaining one-third to a testing dataset.[12] This approach allowed us to strike a reasonable balance between obtaining an accurate estimate of the optimal prognostic cut-offs and retaining sufficient statistical power for a validation analysis. Recursive partitioning analysis was employed to determine the optimal cut-offs in the training dataset, similar to Allen et al.[12] Of note, only patients with available data on a given variable of interest were included in the respective cut-off analysis; data imputation was not employed. For the validation analysis, concordance probability estimates (CPEs) were calculated to assess how effectively the new cut-offs discriminated between patients at high and low risk of death, respectively. A CPE of 0.5 indicated that chance alone was as predictive as the prognostic cut-off in question, whereas a CPE of 1.0 corresponded to perfect prognostic discrimination. Finally, CPEs for the optimal cut-offs were compared to CPEs for the most widely used cut-offs in the surgical literature. Specifically, the following literature cut-offs were used: tumor size: 5[10,11,13,13,14] and 10 cm[15]; number of liver metastases: 4[10] and 3[9,15]; CEA level: 200[11,13,14,16] and 5 ng/ml.[17]

All analyses were performed using SPSS 22.0 (IBM) and R 3.3.1 (https://cran.r-project.org/), including the rpart and CPE packages.

3 | RESULTS

3.1 | Cohort characteristics

The demographic and clinicopathologic characteristics of the study cohort are presented in Table 1. A total of 1643 patients who met eligibility criteria were identified. The median patient age was 62 years (range: 18–90 years), and most patients were male (n = 1018, 62.0%). The majority of patients (86.8%) underwent resection for T3–4 tumors and had confirmed node-positive disease (63.4%); 24.2% of primary tumors were located in the right and 75.8% in the left colon. A total of 60.2% of all patients received some type of preoperative chemotherapy. The median prehepatectomy CEA level was 7.4 ng/ml (range: 0–6877 ng/ml) and around 48.8% of patients had synchronous presentation of liver metastases. Following CRLM resection, the median size of the largest metastatic lesion was 2.5 cm (range: 0.1–19 cm) and the median number of liver metastases was 2 (range: 1–36). A total of 630 (38.6%) patients harbored a KRAS mutation. Postoperative systemic chemotherapy was administered to 834 (53.1%) patients. The median follow-up for all patients was 33 months (range: 0–182 months). At the time of last follow-up, 842 patients were alive (51.2%); median OS was 54 months and the estimated 1-, 3-, and 5-year survival rates were 92.3%, 65.3% and 45.9%, respectively.

3.2 | Tumor size

Following recursive partitioning analysis in the training dataset (n = 1030), a new prognostic cut-off for tumor size was identified: 2.95 cm. According to this cut-off, 597 patients were assigned to the lower risk group (≤2.95 cm) and 433 patients to the higher risk group (>2.95 cm). Survival by tumor size according to the aforementioned cut-off in the training dataset is presented in Figure 1A. In an effort

TABLE 1 Demographic data and tumor characteristics of the entire, training and testing cohort

	Entire cohort (*n* = 1643)		Training cohort (*n* = 1153)		Testing cohort (*n* = 490)	
	*n**	No. of patients (% of the available data)	*n**	No. of patients (% of the available data)	*n**	No. of patients (% of the available data)
Age (years), median	1643 (100)	62 (18–90)	1153 (100)	61 (18–89)	490 (100)	62 (22–90)
Gender	1643 (100)		1153 (100)		490 (100)	
Male		1018 (62.0)		719 (62.3)		300 (61.2)
Female		625 (38.0)		434 (37.7)		190 (38.8)
Primary tumor:						
Tumor stage	1551 (94.4)		1091 (94.6)		460 (93.9)	
T1		28 (1.7)		18 (1.6)		10 (2.2)
T2		176 (11.3)		122 (11.2)		54 (11.7)
T3		945 (60.9)		658 (60.3)		287 (62.4)
T4		402 (25.9)		293 (26.9)		109 (23.7)
Grading	1071 (65.2)		755 (65.5)		316 (64.5)	
Well		154 (14.4)		109 (14.4)		45 (14.2)
Moderate		499 (46.6)		350 (46.4)		149 (47.2)
Poor		418 (39.0)		296 (39.2)		122 (38.6)
Lymph node+	1613 (98.2)		1132 (98.2)		481 (98.2)	
Positive		1023 (63.4)		709 (62.6)		314 (65.3)
Negative		590 (36.6)		423 (37.4)		167 (34.7)
Primary tumor location	1468 (89.3)		1034 (89.7)		434 (88.6)	
Right		355 (24.2)		231 (22.3)		124 (28.6)
Left		1113 (75.8)		803 (77.7)		310 (71.4)
Hepatectomy:						
CEA (ng/ml), median	1392 (84.7)	7.4 (0–6877)	985 (85.4)	7.4 (0–6877)	407 (83.1)	7.5 (0.3–4869)
Prehepatectomy chemotherapy	1642 (99.9)		1152 (99.9)		490 (100)	
Yes		989 (60.2)		692 (60.1)		297 (60.6)
No		653 (39.8)		460 (39.9)		193 (39.4)
Number of metastases, median	1636 (99.6)	2 (1–36)	1147 (99.5)	2 (1–28)	489 (99.8)	2 (1–36)
Tumor size (cm), median	1466 (89.2)	2.5 (0.1–19)	1030 (89.3)	2.5 (0.1–19)	436 (89.0)	2.6 (0.2–18)
Time of metastases	1454 (88.5)		1015 (88.0)		439 (89.6)	
Synchronous		710 (48.8)		501 (49.4)		209 (47.6)
Metachronous		744 (51.2)		514 (50.6)		230 (52.4)
Liver resection	999 (61.6)		702 (60.9)		297 (60.6)	
Major		329 (32.9)		229 (32.6)		100 (33.7)
Minor		670 (67.1)		473 (67.4)		197 (66.3)
Extrahepatic disease	1643 (100)		1153 (100)		490 (100)	
Yes		201 (12.2)		140 (12.1)		61 (12.4)
No		1442 (87.8)		1013 (87.9)		429 (87.6)
Resection margin	1612 (98.1)		1130 (98.0)		482 (98.4)	
R0		1315 (81.6)		924 (81.8)		391 (81.1)
R1		297 (18.4)		206 (18.2)		91 (18.9)
KRAS status	1631 (99.3)		1144 (99.2)		487 (99.4)	
wildtype		1001 (61.4)		698 (61.0)		303 (62.2)
mutation		630 (38.6)		446 (39.0)		184 (37.8)

TABLE 1 (Continued)

	Entire cohort (n = 1643)		Training cohort (n = 1153)		Testing cohort (n = 490)	
	n*	No. of patients (% of the available data)	n*	No. of patients (% of the available data)	n*	No. of patients (% of the available data)
Posthepatectomy chemotherapy	1571 (95.6)		1097 (95.1)		474 (96.7)	
Yes		834 (53.1)		571 (52.1)		263 (55.5)
No		737 (46.9)		526 (47.9)		211 (44.5)
Recurrent disease	1635 (99.5)		1150 (98.6)		485 (99.0)	
Yes		1090 (66.7)		763 (66.3)		327 (67.4)
No		545 (33.3)		387 (33.7)		158 (32.6)

Note: n* = available data cohort (% of cohort).

Abbreviation: CEA, carcinoembryonic antigen.

to evaluate the statistical validity of this cut-off value, we proceeded with a validation analysis in the testing dataset (n = 436). Survival by tumor size according to the aforementioned cut-off in the testing dataset is presented in Figure 1B. Importantly, in the entire dataset, the calculated CPE for this cut-off (0.52) was higher than the CPEs for the two most commonly employed cut-offs in the relevant literature (5 cm: CPE = 0.50; 10 cm: CPE = 0.50) (Table 2).

3.3 | Tumor number

Following recursive partitioning analysis in the training dataset (n = 1147), an optimized prognostic cut-off for tumor number was identified: 1.5. Based on this cut-off, 519 patients were assigned to the lower risk group (≤1.5 tumors), whereas 628 patients were assigned to the higher risk group (>1.5 tumors). Survival by tumor number according to the aforementioned cut-off in the training dataset is presented in Figure 2A. To evaluate the statistical validity of this cut-off value, we proceeded with a validation analysis in the testing dataset (n = 489). Survival by tumor number according to the aforementioned cut-off in the testing dataset is presented in Figure 2B. Importantly, in the entire dataset, the calculated CPE for this cut-off (0.56) was higher than the CPEs for the two most commonly employed cut-offs in the relevant literature (3 tumors: CPE = 0.55; 4 tumors: CPE = 0.55).

3.4 | CEA levels

Preoperative CEA levels were available for 1392 patients. Following recursive partitioning analysis in the training dataset (n = 985), a new

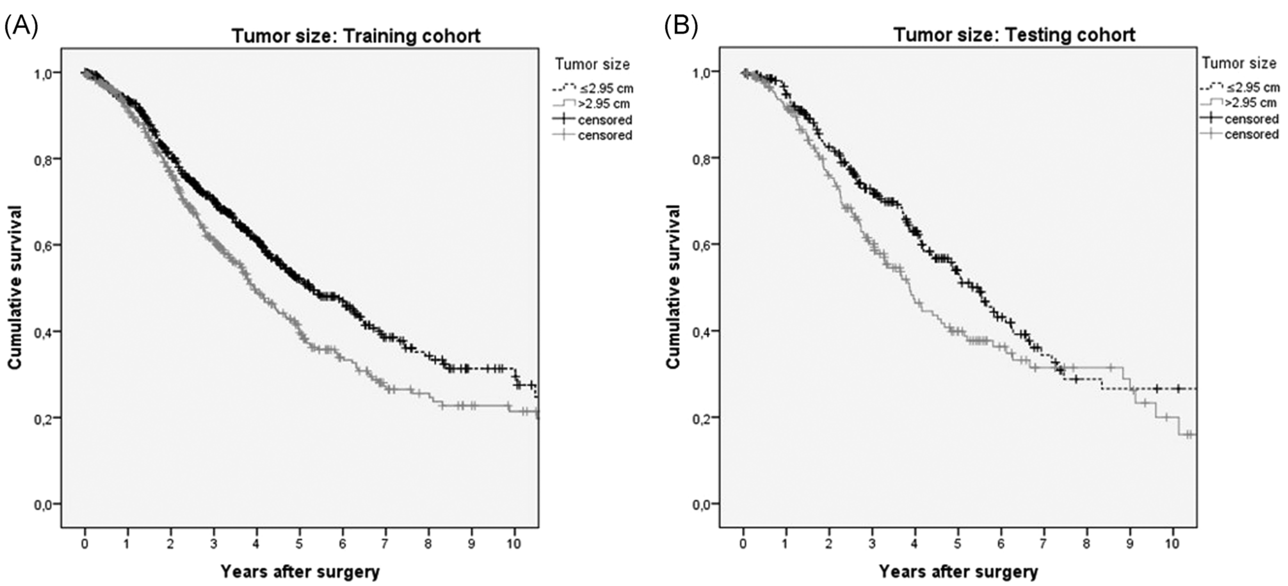

FIGURE 1 (A and B) Kaplan–Meier curves depicting survival for patients undergoing CRLM resection according to tumor size. Patients with tumor size ≤2.95 cm showed significantly better survival compared to patients with tumor size more than 2.95 cm in both the training cohort (p = .001) and the testing cohort (p = .036). CRLM, colorectal liver metastases [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 CPE values of new cut-offs compared to standard literature

	Cut-off	CPE value
Tumor Size		
Optimal cut-off	2.95 cm	**0.52**
Standard literature	5 cm	0.50
	10 cm	0.50
Number of metastases		
Optimal cut-off	1.5	**0.56**
Standard literature	4	0.55
	3	0.55
CEA		
Optimal cut-off	6.15 ng/ml	**0.53**
Standard literature	5 ng/ml	0.52
	200 ng/ml	0.50

Abbreviation: CPE, concordance probability estimate.

prognostic cut-off for CEA was identified: 6.15 ng/ml. 435 patients had a CEA level ≤6.15 ng/ml and 550 patients had CEA levels higher than 6.15 ng/ml. Survival by CEA level according to the aforementioned cut-off in the training dataset is presented in Figure 3A. In an effort to evaluate the statistical validity of this cut-off value, we proceeded with a validation analysis in the testing dataset ($n = 407$). Survival by CEA level according to the aforementioned cut-off in the testing dataset is presented in Figure 3B. Importantly, in the entire dataset, the calculated CPE for the aforementioned cut-off (0.53) was higher than the CPEs for the two most commonly employed cut-offs in the relevant literature (5 ng/ml: CPE = 0.52; 200 ng/ml: CPE = 0.50).

3.5 | Univariable survival analysis

To analyze the predictive value of these newly established cut-offs, univariable survival analysis of the entire cohort was performed, which identified nine significant prognostic factors. Importantly, patient survival was strongly correlated with tumor size ($p < .001$), tumor number ($p < .001$), and CEA levels ($p < .001$), using the new optimized cut-offs. Patient age ($p < .001$), lymph node status of the primary tumor ($p < .001$), receipt of prehepatectomy chemotherapy ($p = .001$), extrahepatic disease ($p < .001$), resection margin ($p < .001$), and KRAS mutational status ($p < .001$) were similarly prognostic (Table 3).

3.6 | Multivariable survival analysis

While CPE calculation can determine the prognostic power of each cut-off value, it cannot assess the relative independence of several prognostic factors and their respective cut-offs. To address this limitation, we performed a multivariable analysis of predictors of survival in the entire cohort. Nine parameters that showed significance in the univariable analysis were included in the Cox proportional hazards model. Importantly, all new cut-offs for tumor size ($p = .01$), tumor number ($p < .001$), and CEA level ($p < .001$) were independently associated with survival. In addition, all factors shown to be significant in the univariable analyses were also independently associated with OS in the multivariable analysis (Table 4).

4 | DISCUSSION

The prognostic importance of "traditional" risk factors such as size of the largest CRLM, total number of liver metastases, and CEA level was reiterated in a recent systematic review and pooled analysis of 4855 patients with CRLM.[18] The current study is unique in that we simultaneously attempt to determine the optimal cut-offs for these three traditional clinicopathologic factors in a contemporary, international cohort of patients with surgically treated CRLM. Strengths of the study include the employment of recursive partitioning analysis to determine the cut-offs, a large and widely representative (due to the multi-institutional nature of the cohort) sample of 1643 patients, and the performance of a confirmatory validation analysis in a separate dataset. Importantly, all identified cut-offs remained significantly associated with survival even after controlling for other pertinent prognostic factors, such as KRAS mutational status. Interestingly, the identified cut-offs differ from those reported by many prior studies. Of note, previously reported cut-off values were frequently established by older studies with relatively small patient populations on the basis of unstandardized and, occasionally, incompletely described methods. Over time, many of these values became prevalent in the literature and eventually came to be employed without contemporary attempts at validation. In turn, the limited accuracy of previously reported cut-off values may partially explain why the prognostic power of several risk scores has been questioned, as CEA levels, tumor number and tumor size often constitute their principal components.[7,11,19–21]

We performed a recursive partitioning analysis to determine the optimal cut-off points for tumor size in 1030 patients (training set). A new cut-off of 2.95 cm was identified, and its value was confirmed in the validation cohort; a strong prognostic effect for this cut-off was also identified in the univariable and multivariable survival analyses. Of note, although this is the first time this cut-off has been established through a formal statistical analysis, the value we identified has been previously used by a group from Memorial Sloan Kettering.[22] Nonetheless, given that the prognostic value of tumor size is not new, different cut-offs have been used far more extensively in the literature. Specifically, the two most widely used cut-offs for tumor size have traditionally been 5 and 10 cm.[10,11,13–15] Importantly, the cut-off determined by the present analysis outperformed these previously reported values, irrespective of preoperative chemotherapy administration.

Similarly, a single cut-off value of 1.5 lesions was found to maximize prognostic discrimination in the present cohort. Of course, this cut-off can practically be equated with a cut-off of two lesions since there are no "half lesions" in real life. Indeed, patients with one tumor experienced better OS than those with more lesions (median survival: 70.7 vs.

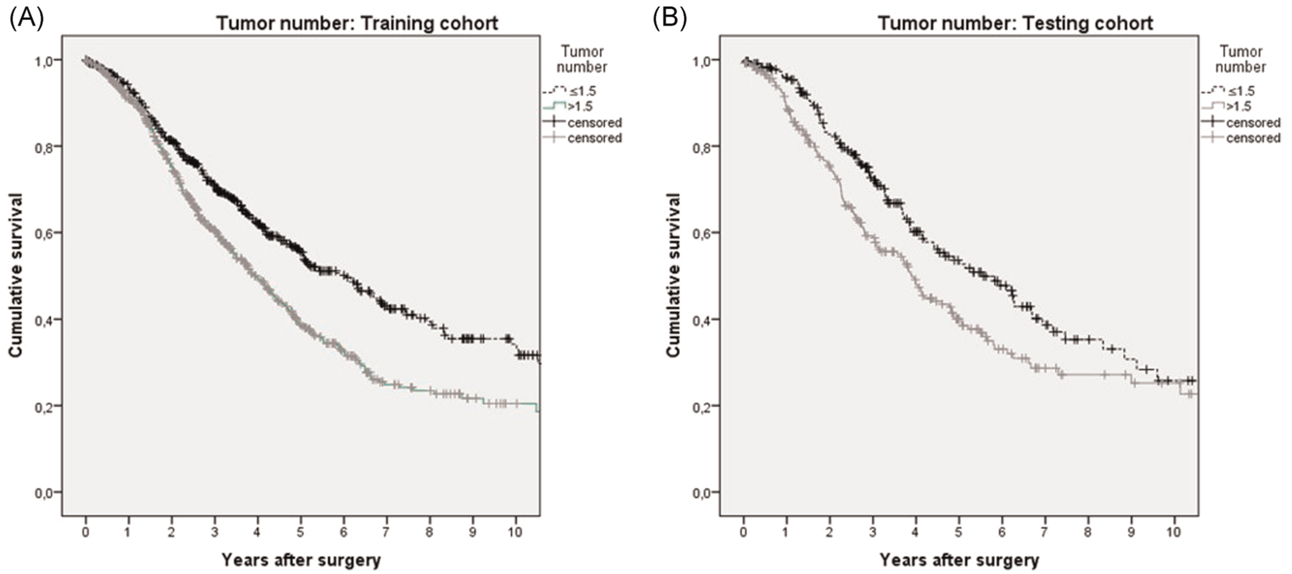

FIGURE 2 (A and B) Kaplan–Meier curves depicting survival for patients undergoing CRLM resection according to tumor number. Patients with tumor number ≤1.5 showed significantly better survival compared to patients with more tumors both in the training cohort ($p < .001$) and the testing cohort ($p = .006$). CRLM, colorectal liver metastases [Color figure can be viewed at wileyonlinelibrary.com]

47.1 months, $p < .001$). Although this is the first time that this cut-off has been established through a formal statistical analysis, the value in question has been previously used by several groups, including our own.[4,23] For example, a group from MD Anderson has consistently used this cut-off in their studies.[5,24,25] However, several other cut-offs have been employed in survival analyses, with most previous reports based on small, single-institution studies. Thus, determination of the optimal cut-off for this variable has proved elusive so far. For example, a previous systematic review noted that although five studies reported that patients with fewer metastases had significantly better outcomes, eight studies were unable to detect any such difference.[26] In contrast, another systematic review reported that patients with four or more liver metastases had a median 5-year OS of 17.1%, compared to 39% for those with fewer than 4.[27] Other cut-offs have been proposed by different groups, with 3 and 4 being the values most commonly employed in the literature.[9,10,15,15,28] As with tumor size, the tumor number cut-off determined by the present analysis outperformed these values, irrespective of preoperative chemotherapy administration.

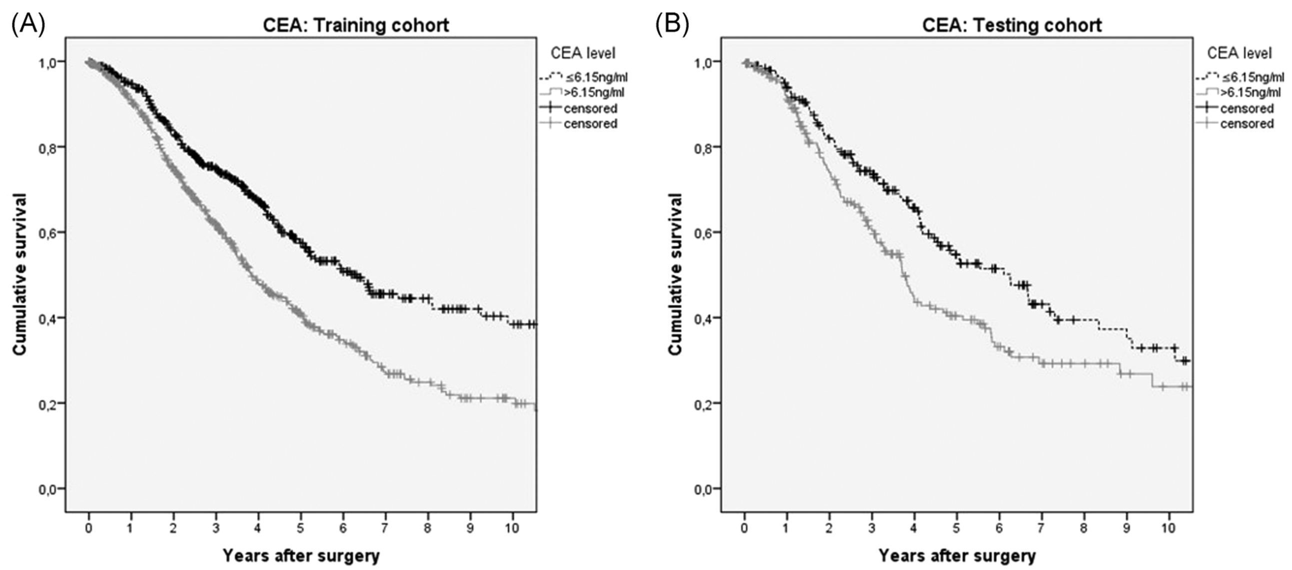

FIGURE 3 (A and B) Kaplan–Meier curves depicting survival for patients undergoing CRLM resection according to CEA levels. Patients with CEA levels ≤6.15 ng/ml showed significantly better survival compared to patients with CEA levels more than 6.15 ng/ml in both the training cohort ($p < .001$) and the testing cohort ($p = .005$). CEA, carcinoembryonic antigen; CRLM, colorectal liver metastases [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Univariate survival analysis

	No. of patients	Median survival (months)	95% CI (months)	*p* Value (log-rank test)
Gender				
Male	1018	55.9	50.8–60.9	.56
Female	625	54.2	48.0–60.4	
Age				
<65 years	997	59.8	53.3–66.3	**<.001**
≥65 years	641	48.0	42.6–53.3	
Primary tumor:				
Tumor stage				
T1	28	70.8	39.7–101.9	.07
T2	176	60.6	50.3–71.0	
T3	945	57.6	51.5–63.6	
T4	402	47.4	39.4–55.3	
Grading				
Well	154	60.7	39.5–81.9	.24
Moderate	499	65.2	52.7–77.6	
Poor	418	53.1	46.8–59.3	
Lymph node+				
Positive	1023	48.6	44.8–52.4	**<.001**
Negative	590	69.7	61.9–77.5	
Primary tumor location				
Right	355	49.9	42.6–57.0	.14
Left	1113	57.6	52.1–63.0	
Hepatectomy:				
CEA (ng/ml)				
≤6.15	621	75.0	65.5–84.5	**<.001**
>6.15	771	45.8	42.0–49.5	
Number of metastases				
≤1.5	748	70.7	62.1–79.3	**<.001**
>1.5	888	47.1	43.0–51.2	
Tumor size (cm)				
≤2.95	835	63.6	56.5–70.8	**<.001**
>2.95	631	46.8	42.1–51.5	
Prehepatectomy chemotherapy				
Yes	989	49.2	45.2–53.3	**.001**
No	653	63.2	55.5–71.0	
Extrahepatic disease				
Yes	201	32.6	26.0–39.2	
No	1442	58.5	53.6–63.5	**<.001**
Time of metastases				
Synchronous	710	57.6	48.4–66.8	.11
Metachronous	744	50.4	45.5–55.3	
Resection margin				
R0	1315	58.6	52.4–64.9	**<.001**
R1	297	42.4	36.2–48.7	
KRAS status				
wildtype	1001	60.7	54.8–66.7	**<.001**
mutation	630	44.8	39.2–50.4	

Notes: Bold values statistical significance $p < .05$.
Abbreviation: CI, confidence interval.

Finally, we sought to determine the optimal prognostic cut-off for preoperative CEA levels. Interestingly, although the determination of prognostic cut-offs for all the aforementioned variables has been inconclusive, the cut-off for CEA levels has been the most controversial. For example, Schindl et al used CEA as a continuous variable, whereas Lee employed a prognostic cut-off of 5 ng/ml, Rees of 60 ng/ml, and Fong and Konopke of 200 ng/ml.[11,19–21] If one takes into account the studies that associated CEA levels with outcomes, rather than construct a risk score, the number of reported cut-offs nearly stretches to infinity (e.g., > 5, > 7.5, ≥ 10, > 30, > 60, > 100, and > 200 ng/ml).[3,28–34] As discussed by Brudvik et al.,[7] the large proportion of missing data in previous studies, as well as a general lack of consensus on how and when to measure CEA levels, may account for these discrepancies. Another possible explanation is a shift in the prognostic value of CEA levels over time due to the introduction of modern chemotherapy. In contrast with previous studies, our analysis determined 6.15 ng/ml as the most prognostic CEA cut-off value, a result confirmed by the validation analysis.

Interestingly, the results of the survival analyses suggested that administration of prehepatectomy chemotherapy was independently associated with worse OS, similar to a number of earlier reports, such as those by Ito et al.[16] and Passot et al.[35] It is likely that this finding stems from selection bias, as the use of preoperative chemotherapy is more frequent among patients with adverse clinicopathologic factors and high baseline tumor burden that may not be immediately amenable to resection. Other authors have suggested that prior exposure to FOLFOX (e.g., in the adjuvant setting) may result in adverse selection of resistant disease with higher mutation burden and worse outcomes following resection of CRLM. While intriguing, this question cannot be adequately addressed in the context of a retrospective study, especially given the lack of detailed data on employed chemotherapy regimens and treatment timing. Novel information on the optimal role of chemotherapy among patients with CRLM can only be obtained via well-designed clinical trials.

This study has a number of limitations that should be considered when interpreting the findings. First, the study was retrospective in nature and was inevitably affected by selection bias. Moreover, some degree of heterogeneity in terms of diagnostic, treatment, and follow-up protocols among the participating institutions is a largely unavoidable side-effect of the study design. Nonetheless, the use of aggregate data from multiple institutions and geographic locales provided greater statistical power and increased the generalizability of the results. While the identified cut-offs were successfully validated using an internal testing dataset, external validation was not performed and is warranted. Furthermore, detailed information on the administered cycles of preoperative chemotherapy was unfortunately unavailable. Similarly, very limited data on pathologic response to chemotherapy was available, thus preventing us from accounting for this factor in our analysis. Lastly, while the IGCLM dataset consists of patients with known KRAS mutational status, the latter could not be retrieved for 12 patients included in the present study cohort, likely due to accidental deletion of these data during

TABLE 4 Multivariate survival analysis showing independent prognostic factors in more than 1600 CRLM patients

	Hazard ratio	95% CI	*p*
Age			
<65 years	0.723	0.607–0.861	**<.001**
≥65 years	Referent		
Primary tumor			
Lymph node+			
Negative	0.756	0.629–0.908	**.003**
Positive	Referent		
Hepatectomy:			
CEA (ng/ml)			
≤6.15	0.644	0.541–0.767	**<.001**
>6.15	Referent		
Number of metastases			
≤1.5	0.685	0.575–0.817	**<.001**
>1.5	Referent		
Tumor size (cm)			
≤2.95	0.801	0.675–0.951	**.010**
>2.95	Referent		
Prehepatectomy chemotherapy			
No	0.632	0.525–0.761	**<.001**
Yes	Referent		
Extrahepatic disease			
No	0.586	0.465–0.740	**<.001**
Yes	referent		
Resection margin			
R0	0.711	0.578–0.874	**.001**
R1	Referent		
KRAS status			
wildtype	0.684	0.576–0.813	**<.001**
mutation	Referent		

Notes: Bold values statistical significance $p < .05$.
Abbreviations: CI, confidence interval; CRLM, colorectal liver metastases.

database updates. We decided to include these patients in the main analysis, as the determination of the ideal cut-offs for the variables of interest is independent of KRAS status; moreover, as the number of patients in question is quite small it is unlikely that the results of the multivariable analysis would have been affected even if these data were available.

5 | CONCLUSIONS

In summary, we employed recursive partitioning analysis in a large, multi-institutional cohort of patients with CRLM to determine and validate optimal prognostic cut-offs for tumor size, number, and preoperative CEA levels. Importantly, the determined cut-offs were different from those employed in the literature. As existing cut-offs vary widely (even across studies from the same group) and are largely based on older, smaller studies of questionable contemporary applicability, our findings may serve to both improve the prognostic value of traditional clinicopathologic factors and provide a uniform benchmark for future comparisons. While the gain in discriminatory ability attributable to the identified cut-offs is quite modest, the combination of multiple "optimized" risk factors into future models has the potential to yield an appreciable improvement in prognostication. In light of the limited prognostic power of existing risk scores, such gains suggest that traditional clinicopathologic factors remain relevant and standardized, formal approaches to determining optimal cut-off values have a role to play in future studies. However, our results also imply that the prognostic value of currently used clinicopathologic predictors is inherently limited and will likely prove unable to independently support robust clinical decision-making tools even when fully optimized. The discovery of novel biomarkers and their combination with optimized existing predictors will likely be necessary before more accurate prognostic and, ultimately, predictive models can be developed.[36] In turn, future models with such favorable characteristics may ultimately be used to guide clinical decision making and patient selection, goals that have so far remained unattainable for contemporary risk scores. In the interim and pending external validation of our findings, the cut-offs identified by the present analysis can be used to aid prognostication both preoperatively (in the case of CEA levels) and in the immediate postoperative period (in the case of tumor size and number). While these findings have no direct impact on operative indications, the resulting improvement in prognostic power paves the way for future predictive models and is immediately pertinent to patient-centered decision making and follow-up care.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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