RAS Mutation Clinical Risk Score to Predict Survival After Resection of Colorectal Liver Metastases

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Objective: To determine the impact of *RAS* mutation status on the traditional clinical score (t-CS) to predict survival after resection of colorectal liver metastases (CLM).

Background: The t-CS relies on the following factors: primary tumor nodal status, disease-free interval, number and size of CLM, and carcinoembryonic antigen level. We hypothesized that the addition of *RAS* mutation status could create a modified clinical score (m-CS) that would outperform the t-CS.

Methods: Patients who underwent resection of CLM from 2005 through 2013 and had *RAS* mutation status and t-CS factors available were included. Multivariate analysis was used to identify prognostic factors to include in the m-CS. Log-rank survival analyses were used to compare the t-CS and the m-CS. The m-CS was validated in an international multicenter cohort of 608 patients.

Results: A total of 564 patients were eligible for analysis. *RAS* mutation was detected in 205 (36.3%) of patients. On multivariate analysis, *RAS* mutation was associated with poor overall survival, as were positive primary tumor lymph node status and diameter of the largest liver metastasis >50 mm. Each factor was assigned 1 point to produce a m-CS. The m-CS accurately stratified patients by overall and recurrence-free survival in both the initial patient series and validation cohort, whereas the t-CS did not.

Conclusions: Modifying the t-CS by replacing disease-free interval, number of metastases, and CEA level with *RAS* mutation status produced an m-CS that outperformed the t-CS. The m-CS is therefore a simple validated tool that predicts survival after resection of CLM.

Keywords: clinical score, colorectal liver metastases, liver resection, *RAS* mutation

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Approximately 40% of patients with colorectal liver metastases (CLM) will survive for 5 years after resection. However, it is well recognized that prognosis varies widely with approximately 40% of patients developing recurrence within 12 months.[1] There is therefore a clear need to achieve better prognostic information before surgery to personalize patient management.

Until now, prognosis has been assessed using clinicopathologic factors such as number and size of CLM, and disease-free interval between diagnosis of the primary tumor and diagnosis of CLM. These clinicopathological factors have been combined into clinical scores in an attempt to offer a potential guide to the long-term benefit of resection.[2–4] The Memorial Sloan Kettering Clinical Score [traditional clinical score (t-CS)] has been the most widely used scoring system to date, and relies on 5 factors, each attributed a single point (CEA, node positive primary, size and number of lesions, interval between primary resection and diagnosis of CLM).[2] However, this score has not been successfully validated in other centers, and may have limited clinical utility.[5] In addition, the original MSKCC t-CS was developed in patients who underwent resection between 1985 and 1998, and may therefore not reflect contemporary patient management and outcomes.

Rat sarcoma viral oncogene homolog (*RAS*) mutations are found in 15%–35% of patients with resectable CLM, and have been associated with poor overall and recurrence-free survival after liver resection.[6–8] In addition, *RAS* mutation status is used to select patients to treatment targeting the epidermal growth factor receptor, and has also been associated with radiologic and pathologic response to modern chemotherapy.[9–12] We hypothesized that in modern series of patients undergoing resection of CLM with perioperative chemotherapy, *RAS* mutation, which is a direct measure of tumor biology, may be a powerful predictor of outcome and may render traditional clinicopathological risk factors obsolete.[6] We therefore investigated the impact of *RAS* mutation on the t-CS.

METHODS

Study Population

This study was approved by the Institutional Review Board of the University Texas MD Anderson Cancer Center (protocol number PA14-0747). Patients undergoing resection of CLM with known *RAS* mutation status and known values for all 5 t-CS factors [primary tumor lymph node status, disease-free interval, number of CLM, size of CLM, and carcinoembryonic antigen (CEA) level] from 2005 through 2013 were included. Patients were excluded if concomitant radiofrequency ablation was used or if the resection was considered noncurative before surgery.

Disease Management

Contrast-enhanced computed tomography of the chest, abdomen, and pelvis with arterial, venous, and portovenous phase

imaging of the liver was used in all patients to assess the resectability of CLM and extrahepatic disease. Unresectable extrahepatic disease was considered a contraindication for resection of CLM. Intraoperative ultrasonography was used to assess all known and unknown lesions and vascular anatomy before resection. Number and size of lesions were assessed using preoperative measurements, before any preoperative chemotherapy. The 2-surgeon technique was used to transect the liver parenchyma with the Cavitron ultrasonic surgical aspirator (Valleylab, Boulder, CO) and saline-linked cautery (Dissecting Sealer DS 3.0; Tissue Link Medical, Inc, Dover, NH).[13] Selective or total hepatic inflow was applied during parenchymal transection in major resections.[13] Portal vein embolization and 2-stage hepatectomy were used in patients with insufficient future liver remnant, according to previously reported guidelines.[14] Routinely, all patients received perioperative fluorouracil-based chemotherapy with oxaliplatin and/or irinotecan including bevacizumab (6 cycles before and 6 cycles after resection of CLM as standard), unless contraindicated due to comorbidities or poor tolerance. A marking technique was used to facilitate resection of small lesions likely to disappear after preoperative chemotherapy.[15] Imaging was performed to check for recurrence every 4 months after resection of CLM. Overall survival (OS) was defined as days from hepatectomy to death. Recurrence-free survival (RFS) was defined as days from hepatectomy to date of the first radiological imaging diagnosing the first recurrence, regardless of site.

RAS *Mutation Profiling*

RAS mutations were assessed in DNA from CLM (resected specimen). 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 61 and 146 and *NRAS* codons 12, 13, and 61 in patients treated in the most recent years of the study period. Mutations in the various codons of *KRAS* and *NRAS* were reported and analyzed together as *RAS* mutations. With this method, the lower limit of detection is about 1 mutant allele in the background of 9 wild-type alleles.

International Multicenter Validation Cohort

An international multicenter cohort of 608 patients who underwent resection of CLM was used to validate the m-CS. The cohort included 335 patients from an Italian center, 112 patients from 1 Japanese center and 50 patients from another Japanese center, 76 patients from a Norwegian center, and 35 patients from a UK center. Patient data (days overall survival, *RAS* mutation status, and t-CS factors) were received anonymously and used to validate the m-CS.

Statistical Analysis

Continuous data were expression as the mean with standard deviation. Categorical data were expressed as frequencies of total population. $P < 0.05$ was considered statistically significant. All factors from the univariate analyses were included in the multivariate analyses regardless of P value. Multivariate analyses were carried out with Cox regression survival analyses; the covariates were entered with backward conditional method. Only significant factors in multivariate analyses were reported. Receiver operating characteristics (ROC) curves and area under the curve (AUC) analysis were used to identify optimal cutoff values for continuous variables. Log-rank analyses were used to assess survival differences (curve separation) in Kaplan–Meier plots. Concordance index (c-index) was calculated using survivalROC function in R. The survivalROC function creates a time-dependent ROC curve from censored survival data using nearest neighbor estimation method of Heagerty and Zeger.[16] Bootstrap method was used to generate 95% confidence intervals (CIs). All data analyses and figure preparations were performed using SPSS version 21.0 (SPSS Inc., IBM, Chicago, IL) and R (www.r-project.org).

TABLE 1. Demographic and Clinicopathologic Characteristics of Patients Undergoing Resection of Colorectal Liver Metastases (CLM) (n = 564)

Characteristic	Value
Sex, no. (%)	
Female	237 (42.0)
Male	327 (58.0)
Age, mean (SD), y	56 ± 11
Primary tumor site, no. (%)	
Colon	439 (77.8)
Rectum	125 (22.2)
Node-positive primary tumor, no. (%)	421 (74.6)
Disease-free interval <12 mo, no. (%)	390 (69.1)
>1 liver metastasis, no. (%)	320 (56.7)
Largest liver metastasis >50 mm in diameter, no. (%)	63 (11.2)
CEA level >200 ng/mL, no. (%)	7 (1.2)
RAS mutation in CLM, no. (%)	205 (36.3)
Perioperative chemotherapy, no. (%)	
5-FU-based with oxaliplatin and/or irinotecan	492 (87.2)
Bevacizumab	377 (66.8)
Cetuximab or panitumumab	21 (3.7)
≤6 Preoperative cycles	322 (57.1)
>6 Preoperative cycles	170 (30.1)
% Viable tumor cells on pathologic evaluation after preoperative chemotherapy, average per metastases (%)	
0–1%	30 (5.3)
1–49%	190 (33.7)
50–100%	151 (26.8)
No preoperative or missing	193 (34.2)
Resection of >3 liver segments, no. (%)	292 (51.7)

CEA indicates carcinoembryonic antigen; 5-FU, fluorouracil; SD, standard deviation.

RESULTS

During the study period, 564 patients underwent resection of CLM and had known *RAS* mutation status and t-CS factors. The mean age was 56 years, and 42.0% of the patients were female. Patient and clinicopathologic factors are presented in Table 1.

Perioperative fluorouracil-based chemotherapy with oxaliplatin and/or irinotecan was administered to 492 patients (87.1%); of these, 322 (57.1%) received 6 or fewer preoperative cycles and 170 (30.1%) received >6 preoperative cycles. Bevacizumab was coadministered to 377 patients (66.8%). Cetuximab/panitumumab was administered to only 21 patients (3.7%) before resection of CLM and among patients with wild-type *RAS*, OS and RFS were similar in patients who received perioperative cetuximab/panitumumab and those who did not (Supplemental Figure 1A, http://links.lww.com/SLA/B240).

On multivariate analysis of the classical t-CS factors and *RAS* mutation status (Table 2), the only factors significantly associated with overall survival were primary-tumor positive lymph node status, diameter of the largest liver metastasis more than 50 mm, and *RAS* mutation. Disease-free interval less than 12 months, more than 1 liver metastasis, and CEA level more than 200 ng/mL were not significantly associated with overall survival.

The nonsignificant t-CS factors (disease-free interval, number of CLM, and CEA level) were entered into ROC-AUC analyses to determine whether an optimal cutoff value could be established (Supplemental Figure 2, http://links.lww.com/SLA/B240). The cutoffs with the best combined sensitivity and specificity were 12

TABLE 2. Association of Clinical Score Factors and *RAS* Mutation With Overall Survival in Patients Undergoing Resection of Colorectal Liver Metastases (n = 564)

	Univariate Analyses			Multivariate Analysis		
Factor	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Node-positive primary tumor	2.207	1.448–3.365	<0.001	2.075	1.361–3.165	0.001
Disease-free interval <12 mo	1.240	0.862–1.783	0.246			
>1 liver metastasis	1.245	0.887–1.748	0.205			
Largest liver metastasis >50 mm in diameter	1.636	1.047–2.558	0.031	1.852	1.180–2.905	0.007
CEA level >200 ng/mL	1.541	0.381–6.242	0.544			
RAS mutation in CLM	2.752	1.966–3.851	<0.001	2.693	1.922–3.772	<0.001

CEA indicates carcinoembryonic antigen; HR, hazard ratio.

months for the disease-free interval (AUC, 0.516; $P = 0.557$), more than 2 metastases for the number of CLM (AUC 0.561; $P = 0.028$), and more than 3 ng/mL for CEA level (AUC = 0.490; $P = 0.734$). A further multivariate analysis was then performed. However, the new cutoffs defined by ROC-AUC analysis were associated with only slightly improved *P* values (number of CLM, from $P = 0.205$ to $P = 0.177$; CEA level, from $P = 0.544$ to 0.272), and both number of CLM and CEA level remained nonsignificant in the multivariate analysis (Supplemental Table 1, http://links.lww.com/SLA/B240).

The t-CS was then modified by replacing the nonsignificant factors (disease-free interval, number of CLM, CEA level) with *RAS* mutation status. The resulting m-CS was therefore based on 3 factors: (1) primary tumor lymph node status (1 point assigned for positive nodes), (2) diameter of the largest liver metastasis (1 point for diameter >50 mm), and (3) *RAS* mutation status (1 point for mutation) (Table 3).

There were no significant overall survival differences between patients with t-CS scores of 0 and 1, 1 and 2, 2 and 3, 3 and 4, or 4 and 5 (Fig. 1A). In contrast, there were significant overall survival differences between patients with m-CS scores of 0 and 1, 1 and 2, and 2 and 3 (Fig. 1B). Five years postoperatively, the t-CS c-index for OS was 0.57 (95% CI, 0.48–0.65) and the m-CS c-index for OS was 0.69 (95% CI, 0.62–0.76). Similarly, there were no significant recurrence-free survival differences between patients with t-CS scores of 0 and 1, 1 and 2, and 3 and 4 (Fig. 1C), whereas there were significant recurrence-free survival differences between patients with m-CS scores of 0 and 1, 1 and 2, and 2 and 3 (Fig. 1D). Five years postoperatively, the t-CS c-index for RFS was 0.58 (95% CI, 0.47–0.68) and the m-CS c-index for OS was 0.66 (95% CI, 0.56–0.76).

In an international multicenter validation cohort, the m-CS outperformed the t-CS at stratifying patients by OS (Fig. 2). There were differences between both the University of Texas MD Anderson Cancer Center cohort and the international validation cohort, as well as between centers in the validation cohort, in terms of clinicopathological characteristics and therefore t-CS and m-CS (Table 4). This was reflected in the differences in median OS between centers (Table 5).

By reducing 5 prognostic factors (t-CS) to 3 factors (m-CS), it was possible that the improved stratification seen with the m-CS was a result of increased differences between larger study groups. A simplified version of the t-CS that included only the 3 factors with the lowest *P* value (primary tumor lymph node status, number of CLM, and diameter of the largest liver metastasis) was therefore assessed, but did not perform as well as the m-CS (Supplemental Figure 1B, http://links.lww.com/SLA/B240).

Pathologic response to preoperative chemotherapy was assessed in 371 patients (Table 1). On multivariate analysis, pathological response was significantly associated with OS (Supplemental Table 2, http://links.lww.com/SLA/B240). However, this data was not available for all patients and is not preoperatively assessable (unlike the other factors included in the score). For the subgroup in whom this information was available, addition of pathological response did not significantly improve the discrimination of the score (Supplemental Table 3, http://links.lww.com/SLA/B240), and so was not included in the final m-CS.

DISCUSSION

The MSKCC t-CS is the most recognized and widely used clinical score for prediction of survival after resection of CLM. However, in this study only 2 of the 5 clinicopathologic factors that constitute the score were associated with overall survival. By replacing the 3 nonsignificant factors with *RAS* mutation status, a highly significant predictor of survival, we created a novel m-CS based on primary tumor lymph node status, size of the largest liver metastasis, and *RAS* mutation status. The m-CS outperformed the t-CS in both the discovery and validation cohort.

The list of factors that have been associated with survival after resection of CLM in the literature is long: size of CLM,[17] number of CLM,[2,18] primary tumor nodal status (positive nodes and number of positive nodes),[19] differentiation grade,[3] margin status, CEA level,[4] need for perioperative blood transfusion,[5,20,21] neutrophil to lymphocyte ratio,[22] T-cell tumor infiltration,[23] age and sex,[4] disease-free interval (different intervals have been used),[24,25] primary tumor site,[4] primary tumor stage,[17] laterality of the CLM,[26] presence of circulating

TABLE 3. Traditional and Modified Clinical Scores Predicting Survival After Resection of Colorectal Liver Metastases (CLM)

Factor	**Finding Contributing to Traditional Clinical Score**	**Points**	**Finding Contributing to Modified Clinical Score**	**Points**
Primary tumor N category	N1	1	N1	1
Disease-free interval	<12 mo	1	—	—
Number of CLM	>1	1	—	—
Diameter of largest liver metastasis	>50 mm	1	>50 mm	1
CEA level	>200 ng/mL	1	—	—
RAS mutation status in CLM	—	—	Mutation	1

CEA indicates carcinoembryonic antigen level.

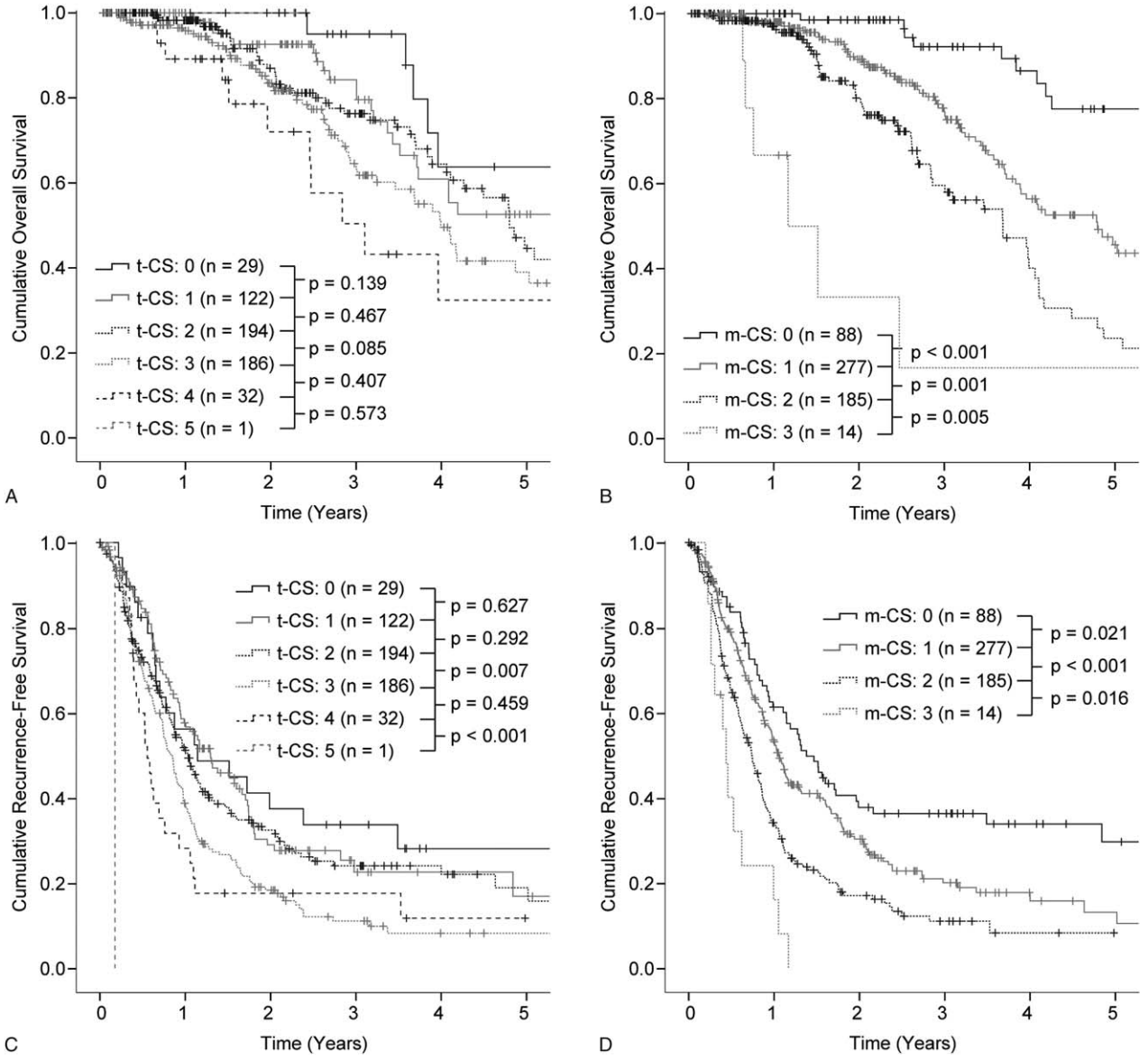

FIGURE 1. Kaplan–Meier survival plots showing overall survival (A and B) and recurrence-free survival (C and D) after resection of CLM in the cohort of the University of Texas MD Anderson Cancer Center stratified by the traditional clinical score (t-CS; A and C) and the *RAS*-mutation-modified clinical score (m-CS; B and D).

tumor cells,[27] regional lymph node involvement,[5] and extrahepatic disease.[3] However, their individual impact in clinical practice is limited. Complex scoring systems based on combinations of these factors have been developed, but are cumbersome. In addition, the clinicopathological factors on which these scores are based may not be significant predictors of patient outcome in modern series.[2,3,5]

Meta-analysis has confirmed the association between *RAS* mutations and overall and recurrence-free survival after resection of CLM.[28] Addition of *RAS* mutation status to the t-CS not only improved the performance of the score, but also simplified the score from 5 factors to 3. Interestingly, the degree of improvement that resulted from changing the t-CS to the m-CS could not be reproduced by excluding 2 nonsignificant factors from the t-CS; thus, the main driver of the improved performance of the m-CS was the addition of *RAS* mutation status and not the reduction in the number of factors used to calculate the score. Furthermore, *RAS* mutation status has been associated with both resection margin status and pathologic response to chemotherapy, irrespective of antiepidermal growth factor receptor treatment.[9,29] As such, the m-CS, which is calculated preoperatively, indirectly accounts for predictors of survival that can only be determined after CLM resection. Thus, adding *RAS* mutation status to the m-CS has 3 benefits: it improves prognostication, simplifies the score, and indirectly accounts for important post-operative predictors of survival. To keep the scoring system as simple as possible, we did not weight factors by hazard ratio. Indeed, over-complexity and lack of clinical utility has been one of the key criticism of previous similar studies.[3,17] One other major strength of this study is the validation in a separate international cohort. To our knowledge, this is the first time this has been successfully performed in this setting.

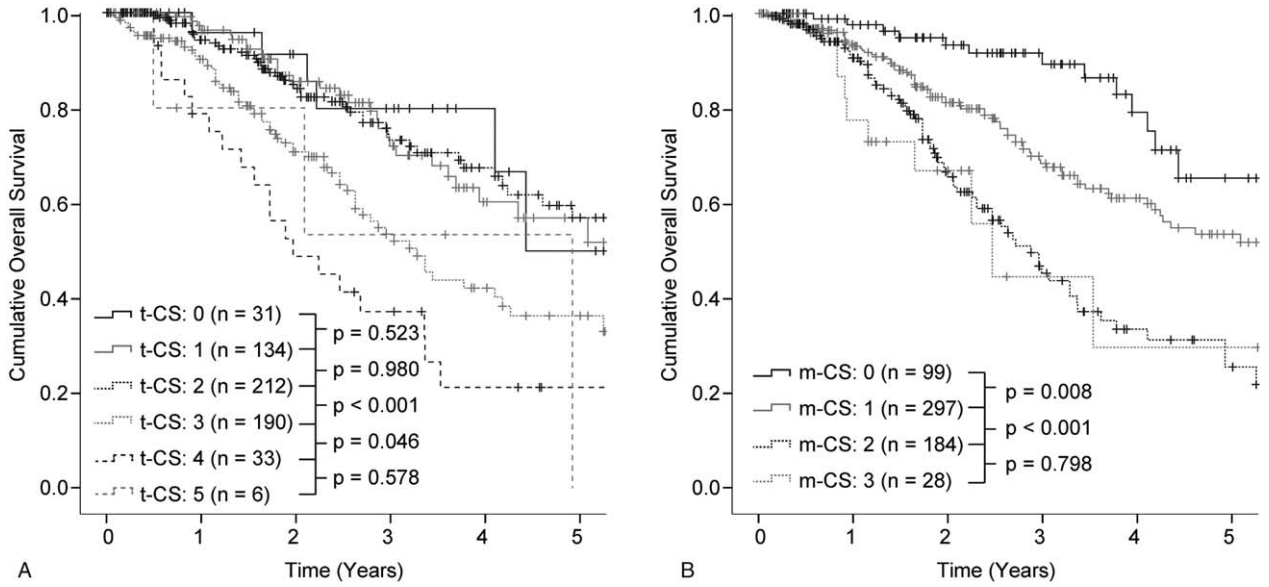

FIGURE 2. Kaplan–Meier survival plots showing overall survival after resection of CLM in the international multicenter cohort stratified by the traditional clinical score (t-CS; A) and the *RAS*-mutation-modified clinical score (m-CS; B).

TABLE 4. Comparison of MD Anderson Cancer Center Cohort and International Multicenter Validation Cohort (IMVC) of Patients Undergoing Resection of Colorectal Liver Metastases (CLM)

Characteristic	MD Anderson Cohort (n = 564)	IMVC (n = 608)	*P*
Median survival after resection of CLM, months	51.8	54.0	0.477
Node-positive primary tumor, no. (%)	421 (74.6)	411 (67.6)	0.008
Disease-free interval <12 mo, no. (%)	390 (69.1)	358 (58.9)	<0.001
>1 liver metastasis, no. (%)	320 (56.7)	374 (61.5)	0.096
Largest liver metastasis >50 mm in diameter, no. (%)	63 (11.2)	120 (19.7)	<0.001
CEA level >200 ng/mL, no. (%)	7 (1.2)	34 (5.6)	<0.001
RAS mutation in CLM, no. (%)	205 (36.3)	218 (35.9)	0.861

CEA indicates carcinoembryonic antigen level.

TABLE 5. Point Distribution Into the Traditional Clinical Score (t-CS) and the RAS Modified Clinical Score (m-CS) and Median Overall Survival (OS) of the MD Anderson Cancer Center (MDACC) Cohort and the International Multicenter Cohorts (IMVC)

	MDACC	Italy	Japan	Norway	United Kingdom
t-CS, % of patients					
0	5.1	6.0	3.7	4.1	5.7
1	21.6	17.6	31.5	21.6	22.9
2	34.4	28.7	46.9	29.7	51.4
3	33.0	41.8	14.2	31.1	11.4
4	5.7	5.1	3.7	10.8	5.7
5	0.2	0.9	0	2.7	2.9
m-CS, % of patients					
0	15.6	16.7	16.7	11.8	16.3
1	49.1	51.9	45.7	42.1	48.8
2	32.8	27.5	34.0	38.2	30.3
3	2.5	3.9	3.7	7.9	4.6
Survival, months					
Median OS	51.8	60.0	NR	27.3	51.6

NR indicates not reached.

Three factors included in the t-CS were not associated with survival in the present study and so were not included in the m-CS. A long disease-free interval between diagnosis of the primary tumor and diagnosis of CLM indicates slow-growing disease with a likely survival benefit if metastatic lesions are resected. However, there is growing evidence that metastases diagnosed metachronously after the primary lesion has been resected and treated with adjuvant therapy may be associated with a worse prognosis (due to biological

selection of chemotherapy-resistant tumors) than metastases diagnosed synchronously. The second factor not included in the m-CS is the number of CLM, with the impact of modern chemotherapy likely explaining why patients with 1 liver metastasis and patients with more than 1 liver metastasis had similar survival. The third factor not included in the m-CS is CEA level. Most studies in the current literature report high numbers of missing data on CEA level, and there is no consensus regarding when to measure CEA level and the optimal cut-off for predicting a survival benefit. In this series, ROC analysis failed to identify a cutoff for CEA which was sufficiently sensitive and specific to provide useful prognostic information.

Response to perioperative chemotherapy is now recognized as a very strong predictor of survival after resection, and provides better prognostic information than many traditional clinicopathological factors.[30] For example, survival after resection of synchronous CLM responding to preoperative chemotherapy may be better than metachronous disease developing in the presence of adjuvant chemotherapy for the primary colorectal tumor.[31] However, a number of issues complicate the inclusion of response to chemotherapy in a clinical score. The indications and timing of chemotherapy, agents used and number of cycles varies widely between centers and countries. The optimal method of assessing treatment response is also unclear. Although histopathological scoring of response to chemotherapy is clearly predictive of outcome, the assessment can only be made following surgery on a resected specimen[30] and different scoring systems are utilized.[30,32] In the present study, pathologic response was assessed in 371 patients and was associated with OS. However, pathologic response did not improve the m-CS, possibly due to a reduced overall sample size as well as competing risk factors (RAS mutant tumors do not respond as well to cytotoxic therapies). Radiologic response is increasingly recognized as a surrogate of pathological response, but existing RECIST (Response Evaluation Criteria in Solid Tumors) criteria are too coarse and subjective, and susceptible to inherent bias which limits the utility of radiological response as an endpoint.[33] Finally, a biochemical response with a chemotherapy induced decline in CEA level may be clinically more relevant than a single preoperative CEA value, but also requires standardized pre and post chemotherapy CEA measuring and chemotherapy regiments. In addition, tumors with high CEA seem to respond differently to systemic therapy.[34] Finally, although response to chemotherapy would have to be determined after embarking on a course of preoperative chemotherapy, metastatic lesion *RAS* status is almost completely concordant with primary tumor[35] which is amenable to endoscopic biopsy, and so could be assessed at initial presentation.

This study has a number of limitations. First, the retrospective nature of this study meant only patients who had undergone *RAS* mutation status were eligible for inclusion, with indications for *RAS* typing vary between centers and countries. This difference likely explains the different median OS observed in the cohorts from different validation centers. Furthermore, complete data on the use of perioperative chemotherapy and targeted therapy was not available from the different validation centers. Second, in the international multicenter validation cohort, patients with m-CS scores of 2 and 3 did not have significantly different overall survival. This could be explained by the fact that there were differences regarding the clinicopathological characteristics between the MD Anderson cohort and the international multicenter validation cohort. However, only 28 patients in the validation cohort had an m-CS of 3 and given the individual significance and impact of the included factors, it is likely that the analysis was underpowered to detect a difference. The low numbers of patients with m-CS of 3 undergoing resection likely reflects the fact that these patients have poor prognosis and are not undergoing resection based on other disease features. Thirdly, the lymph node status of the primary tumor and *RAS* mutation status may not be available in patients with synchronously presenting liver metastases. However, with improved preoperative radiology, a tentative N category may be obtained and *RAS* mutation status can be determined from analysis of the primary tumor biopsy specimen. Finally, the importance of *KRAS* codon 64 or 161 and *NRAS* mutations were not recognized at beginning of the study period, and so were not routinely analyzed. However, all are recognized as an adverse prognosticators in metastatic colorectal cancer and as such any inadvertent inclusion of *NRAS* mutants in the wild-type cohort would lead to an underestimation of the impact of mutation on outcome.[12]

Clinical risk scores were not designed to make decisions on eligibility for resection–even in prognostically poor groups, long-term survivors are not uncommon. Although the m-CS outperformed the t-CS, the concordance index for OS and RFS was relatively low. However, risk stratification is a fundamental part of the consent process and we believe the m-CS provides a functional method of prognostication. Preoperative assessment of potential benefits of surgery could help patients make personalized decisions on the risk:benefit of any proposed intervention. In addition, the benefit of perioperative chemotherapy appears to be greater in oncologically high risk patients.[36] The m-CS may provide a better stratification for this, although this would need validation in a prospective setting. Finally, 60% of patients develop disease recurrence within 2 years of resection. m-CS may allow for a stratified follow-up approach,[1] although this would again need prospective validation.

CONCLUSIONS

The m-CS incorporates *RAS* mutation, a direct measurement of tumor biology that previously has been associated with worse survival, and also indirectly accounts for clinicopathologic factors associated with survival in modern patient series. The m-CS outperformed the t-CS and provides a quick preoperative assessment of the expected survival benefit. We find that compared to complex scoring systems with a large number of factors, the m-CS is better suited for clinical practice.

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