The Tumor Burden Score

A New ''Metro-ticket'' Prognostic Tool For Colorectal Liver Metastases Based on Tumor Size and Number of Tumors

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Objective: To apply the principles of the Metro-ticket paradigm to develop a prognostic model for patients undergoing hepatic resection of colorectal liver metastasis (CRLM).

Background: Whereas the hepatocellular ''Metro-ticket'' prognostic tool utilizes a continuum of tumor size and number, a similar concept of a CRLM Metro-ticket paradigm has not been investigated.

Methods: Tumor Burden Score (TBS) was defined using distance from the origin on a Cartesian plane incorporating maximum tumor size (x-axis) and number of lesions (y-axis). The discriminatory power [area under the curve (AUC)] and goodness-of-fit (Akaike information criteria) of the TBS model versus standard tumor morphology categorization were assessed. The TBS model was validated using 2 external cohorts from Asia and Europe.

Results: TBS (AUC 0.669) out-performed both maximum tumor size (AUC 0.619) and number of tumors (AUC 0.595) in predicting overall survival (OS) ($P < 0.05$). As TBS increased, survival incrementally worsened (5-year OS: zone 1, zone 2, and zone 3—68.9%, 49.4%, and 25.5%; $P < 0.05$). The stratification of survival based on traditional tumor size and number cut-off criteria was poor. Specifically, 5-year survival for patients in category 1, category 2, and category 3 was 58.3%, 45.5%, and 50.6%, respectively ($P > 0.05$). The corrected Akaike score information criteria value of the TBS model (2865) was lower than the traditional tumor morphologic categorization model (2905). Survival analysis revealed excellent prognostic discrimination for the TBS model among patients in both external cohorts ($P < 0.05$).

Conclusions: An externally validated ''Metro-ticket'' TBS model had excellent prognostic discriminatory power. TBS may be an accurate tool to account for the impact of tumor morphology on long-term survival among patients undergoing resection of CRLM.

Keywords: colorectal liver metastases, liver resection, surgical outcomes, tumor morphology

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Hepatic resection remains the only potentially curative treatment option for patients presenting with colorectal liver metastasis (CRLM). Whereas 5-year survival can be as high as 50% to 58%, the prognosis of patients can vary considerably.[1–3] Numerous clinical, morphological, and pathological factors have been proposed to estimate prognosis of patients with CRLM.[4,5] In fact, several investigators have aggregated certain sets of risk factors into prognostic scoring schemes.[4–6] Virtually, all of these risk scores include tumor size and number as important factors in estimating prognosis after resection of CRLM.[4–10] With the introduction of novel multidrug chemotherapeutic regimens and biologic agents, the current role of tumor morphologic characteristics, such as tumor size and lesion number, in determining prognosis of patients with CRLM, is unclear.[10–16] Specifically, in an era of modern chemotherapy, with reported response rates in the range of 50% to 80%, tumor morphology can be dramatically impacted by chemosensitivity.[11,12] Given this, the contemporary impact of tumor morphology, including size and number, on the long-term prognosis of patients undergoing resection of CRLM, is not well-defined.

To date, methodological approaches to understanding the impact of tumor morphology on prognosis have been relatively simplistic. For example, most reports have examined tumor size(eg, $\leq$5 cm vs >5 cm) and number(eg, solitary vs multiple; <2 vs $\geq$2) solely as binary variables.[17,18] In addition, the cut-off values utilized to define these binary categories have been somewhat arbitrary.[4,19,20] Furthermore, analysis of continuous (tumor size) or ordinal (tumor number) data using arbitrary categorical cut-off values not only can limit statistical power, but can also lead to inaccurate causal inferences.[21] Interestingly, tumor size and number of lesions have similarly been utilized to predict long-term outcomes after liver transplantation for patients with hepatocellular carcinoma (HCC).[22–26] Specifically, Mazzaferro et al[22] proposed the widely used ''Milan criteria''(single tumor $\leq$5 cm in size or $\leq$3 tumors each $\leq$3 cm in size, and no macrovascular invasion). However, unlike CRLM prognostic schemes, the original tumor size and number criteria for HCC have undergone numerous iterations culminating in a predictive tool termed the ''Metro-ticket'' system.[27,28] The HCC ''Metro-ticket'' prognostic tool utilizes a continuum of size and number, representing a paradigm shift from a dichotomous to continuous prognostic stratification of patients with HCC.[28] The ''Metro-ticket'' paradigm has been validated to stratify HCC patients accurately with regard to 5-year survival, with prognosis worsening as tumor size and number increase—just as longer trips on the ''Metro'' result in a higher monetary costs.[27,28]

A similar concept of a CRLM Metro-ticket paradigm, whereas intuitively logical, has never been investigated or developed. As such, the objective of the current study was to apply the principles of the

Metro-ticket paradigm to patients undergoing hepatic resection for CRLM. Specifically, we sought to develop a new, simple predictive tool incorporating maximum tumor diameter and lesion number to predict long-term survival among patients undergoing hepatic resection for CRLM using a large institutional database. In addition, we externally validated this novel CRLM Metro-ticket score using 2 independent international datasets.

METHODS

Data Sources and Patient Population

Patients who underwent curative-intent surgery for CRLM between January 1, 2000 and March 31, 2015 at Johns Hopkins Hospital were identified. Patients who only underwent ablation or patients who underwent a palliative liver resection (R2 resection) were excluded. Among patients with extrahepatic disease at the time of hepatectomy, only patients in whom an R0 resection of the extrahepatic disease was achieved were included in the study population. Similarly, patients who underwent combined hepatectomy and ablation who had ablation used for the tumor of maximum diameter were also excluded. The Institutional Review Board of the Johns Hopkins Medical Institution approved the study.

For each patient, sociodemographic data on age and sex, and also clinicopathologic data including the site of primary tumor, preoperative serum carcinoembryonic antigen (CEA) level, and operative details were collected. Major hepatectomy was defined as a resection of at least 3 Couinaud liver segments.[29] Additionally, details pertaining to the use and radiologic response of chemotherapy were recorded for each patient. A combined cytotoxic regimen was defined as the use of a fluorouracil-based regimen combined with oxaliplatin and/or irinotecan, whereas response to chemotherapy was assessed according to the response evaluation criteria in solid tumors (RECIST, criteria version 1.1).[30] Specifically, response was categorized as stable disease (SD), partial response (PR), and radiological complete response (rCR). Tumor-specific characteristics including primary tumor American Joint Committee on Cancer (AJCC) T stage, presence of lymph node metastasis, kirsten rat sarcoma viral oncogene homolog (KRAS) mutation status, tumor size, and the number of tumors were determined using the final histopathological report. An R1 margin was defined as microscopic tumor invasion at the margin of the pathological specimen. Overall survival (OS) was calculated for each patient from the date of surgery to the date of death or date of last follow-up.

Calculation of the Tumor Burden Score Using Tumor Size and Number of Lesions

For each patient, a ''Tumor Burden Score (TBS)'' was calculated by combining tumor size and the total number of tumors. Specifically, the TBS was defined as the distance from the origin on a Cartesian plane that incorporated 2 variables: maximum tumor size (x-axis) and number of liver lesions (y-axis). The Pythagorean theorem was then used to calculate the distance of any given point from the origin of the plane (0, 0) whereby [$TBS^2 = (\text{maximum tumor diameter})^2 + (\text{number of liver lesions})^2$] (Fig. 1A). A prognostic discrimination model using TBS cut-off values was developed. The cut-off values of TBS were selected so as to divide the cohort into 3 groups: lowest 25% of TBS (zone 1), medium TBS between the 25th and 90th percentile (zone 2), and the highest 10% of TBS (zone 3), respectively.[31] The discriminatory performance of the TBS model was compared with traditional tumor morphology categorization as defined by Fong clinical risk score [tumor size (>5 cm) and number (≥2)].[4]

External Validation Population

The accuracy of the TBS model was subsequently externally validated. Specifically, data on patients who had undergone hepatectomy for CRLM at Yokohama City University Graduate School of Medicine, Yokohama, Japan, and also University of Verona, Verona, Italy, were analyzed. Both external validation cohorts included patients who underwent hepatectomy for CRLM after 2000 and met the same inclusion criteria as the patients in our original cohort. The Institutional Review Boards of both institutes approved the study.

Statistical Analysis

Summary statistics were presented as whole numbers and percentages for categorical variables, or as medians with interquartile ranges (IQRs) for continuous variables. OS was estimated using the Kaplan-Meier method calculated from the date of surgery; differences in OS were assessed with the log-rank test. To compare the prognostic ability of the TBS, maximum tumor diameter, and tumor number, receiver-operating characteristic curve (ROC) analysis was used with the outcome of interest being OS. The nonparametric method developed by Hanley and McNeil was employed, and Z-statistics were calculated and used for comparison of the areas under the curve (AUCs) in ROC analysis.[32,33] Model fit was calculated and compared using the corrected Akaike information criterion (AICc) and also assessed visually via Kaplan-Meier plots for each model.[34,35] The lower the AICc value, the better the model fit for the prognostic model. Cox proportional-hazards regression models were used to evaluate the association of the relevant clinicopathological factors with prognosis.[17,18,36,37] The degree of association between nonparametric variables was determined using Pearson correlation coefficient. Survival estimates were reported as hazard ratios (HRs) with 95% confidence intervals (95% CIs). Variables with a $P < 0.100$ on univariable analysis were included in the multivariable analysis. All analyses were carried out with SPSS software version 23(IBM SPSS, Chicago, IL) and JMP Pro 12 statistical package(SAS Institute, Cary, CA).

RESULTS

Clinicopathologic Characteristics and Surgical Outcomes

A total of 604 patients underwent hepatectomy for CRLM and met inclusion criteria (Table 1). Median patient age was 58.1 years (IQR 49.0–66.4 years) and most patients were male (n = 354, 58.6%). Most patients had preoperative chemotherapy for the liver disease (n = 395, 65.4%); the majority of patients received a combination cytotoxic regimen (n = 343, 86.8%). Among the 343 patients who received preoperative cytotoxic chemotherapy, 264 patients received oxaliplatin regimen (77.0%), 63 patients received irinotecan regimen (18.4%), and 16 patients received both oxaliplatin and irinotecan regimens (4.7%). More than half of the patients received a combined cytotoxic regimen with a biologic agent (n = 215, 54.4%). Among the 215 patients who received a biologic agent, 193 patients received bevacizumab (89.8%) and 22 patients received other regimen (11.2%). The majority of patients (59.2%) had SD or PD; 40.2% patients had PR or rCR. The median number of metastatic lesions was 2 (IQR 1–3) and the median size of the largest metastatic lesion was 2.5 cm (IQR 1.6–4.2 cm), resulting in a median TBS of 4.1 (IQR 2.7–6.1). TBS calculated by preoperative imaging and final pathological specimens were strongly correlated ($r = 0.764$, $P < 0.001$) (Supplemental Fig. 1, http://links.lww.com/SLA/B139).

The median duration between the last imaging study and surgery, defined as ''time from preoperative imaging,'' was 20.0 days (IQR 9.0–32.5). At the time of surgery, a minority of patients

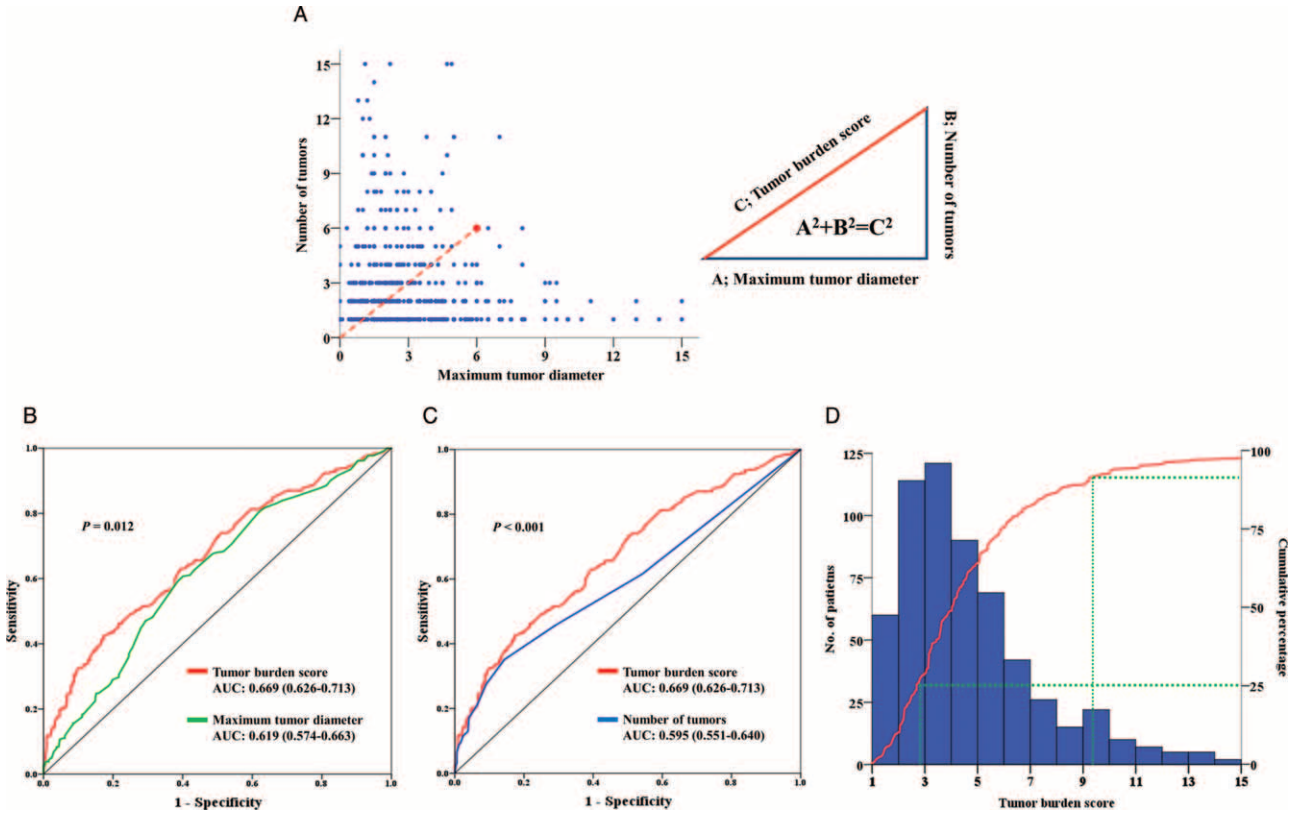

FIGURE 1. A, Tumor burden score (TBS) was defined as the distance from the origin on a Cartesian plane that incorporated 2 variables: maximum tumor size (x-axis) and number of liver lesions (y-axis). The Pythagorean theorem was then used to calculate the distance of any given point from the origin of the plane (0, 0) whereby [TBS^2 = (maximum tumor diameter)^2 + (number of liver lesions)^2]. B, Receiver-operating characteristic curve analysis comparing prognostic discrimination of TBS and maximum tumor diameter. C, Receiver-operating characteristic curve analysis comparing prognostic discrimination of TBS and maximum tumor diameter. D, The distribution of TBS values with respective cumulative percentages.

underwent concurrent ablation (n = 92, 15.2%) or major hepatectomy (n = 200, 33.1%). Regarding operative procedures, 197 patients underwent partial hepatectomy, 67 patients underwent segmentectomy, 140 patients underwent bi-segmentectomy, 125 patients underwent right lobectomy, 40 patients underwent left lobectomy, and 35 patients underwent extended lobectomy. At a median follow-up of 30.3 months, 267 patients had died. Median, 1, 3, and 5-year OS was 61.7 months, 93.9%, 68.9%, and 49.9%, respectively.

Prognostic Stratification by TBS

The ability of TBS to predict OS was analyzed by ROC curve and AUC analyses; in addition, the discriminatory prognostic performance of TBS was compared using established maximum tumor size or number of cut-off values.[4] Of note, TBS (AUC 0.669) outperformed both maximum tumor size (AUC 0.619) and number of tumors (AUC 0.595) in predicting OS (TBS vs maximum tumor size, $P = 0.012$; TBS vs number of tumors, $P < 0.001$). The distribution of TBS values in the cohort with the respective cumulative percentages are depicted in Fig. 1D. The optimal cut-off points for the TBS model were set at 3 (28.8%, lowest 25%) and 9 (88.9%, highest 10%) according to the cumulative percentage of TBS distribution.

The distribution of maximum tumor diameter and tumor number among the entire cohort is shown in Fig. 2A. Patients were divided into 3 groups according to the TBS model [zone 1: TBS <3, n = 174 (28.8%); zone 2: TBS ≥3 to <9, n = 363 (60.1%); and zone 3: TBS ≥9, n = 67 (11.1%)]. Baseline characteristics stratified by each zone were largely comparable; however, patients' TBS ≥9 were more likely to have received perioperative chemotherapy (Supplemental Table 1, http://links.lww.com/SLA/B139). TBS was able to stratify patients with CRLM into distinct prognostic groups with regard to long-term prognosis (Fig. 2B). In fact, there was an incremental worsening of long-term survival as the TBS increased (5-year OS of zone 1, zone 2, and zone 3: 68.9%, 49.4%, and 25.5%, respectively; log-rank test; zone 1 vs zone 2, $P = 0.002$, zone 1 vs zone 3, $P < 0.001$, and zone 2 vs zone 3, $P < 0.001$).

To evaluate the relative predictive utility of the TBS model, prognostic discriminatory ability was compared with traditional tumor morphologic categorization by tumor size (≤5 vs >5 cm) and number (<2 vs ≥2).[4] In the traditional categorization model, patients were assigned into 3 groups [category 1: tumor size ≤5 cm and solitary, n = 199 (32.9%); category 2: size >5 cm and solitary or size≤5 cm and multiple, n = 354 (45.5%); and category 3: size>5 cm and multiple, n = 51 (8.4%)] (Fig. 2C). The stratification of survival based on traditional tumor size and number cut-off criteria was poor (Fig. 2D). In fact, long-term survival was relatively comparable among patients in each of the categories based on tumor size (≤5 vs >5 cm) and number (<2 vs ≥2). Specifically, 5-year survival for patients in category 1, category 2, and category 3 was 58.3%, 45.5%,

TABLE 1. Baseline Patient Demographic and Clinical Characteristics

Characteristics	All Patients (N = 604) No.	%
Patient characteristics		
Age, yrs, median (IQR)	58.1; 49.0–66.4	
Sex		
Male	354	58.6
Female	250	41.4
Treatment period		
2000–2007	302	50.0
2008–2015	302	50.0
Primary CRC characteristics		
Tumor site		
Right colon	191	31.7
Left colon	284	46.9
Rectum	129	21.4
T stage (n = 598)		
T1or T2 stage	91	16.7
T3 or T4 stage	454	83.3
Nodal metastases		
Negative	191	31.6
Positive	413	68.4
Preoperative factors		
Presentation of liver metastases		
Synchronous	350	57.9
Metachronous	254	42.1
<12 mos	96	37.8*
>12 mos	158	62.2*
Chemotherapy for liver disease		
Total	395	65.4
Combined cytotoxic regimen	343	86.8†
Combined cytotoxic regime and biologic agent	215	54.4†
RECIST response (n = 393)		
SD or PD	235	59.8
PR or rCR	158	40.2
Preoperative CEA, ng/mL, median (IQR)	7.4 (3.0–21.7)	
Extrahepatic disease at the time of operation	51	8.4
Tumor factors		
No. of CRLM, median (IQR)	2.0 (1.0–3.0)	
Size of largest CRLM, cm, median (IQR)	2.5 (1.6–4.2)	
Tumor burden score, median (IQR)	4.1 (2.7–6.1)	
Bilobar disease	246	40.7
KRAS mutation status (n = 502)		
Wild-type	320	63.7
Mutated	182	36.3
Operative factors		
Resection only	512	84.8
Resection plus ablation	92	15.2
Major resection	200	33.1
Resection margin, mm, median (IQR)	5.0 (1.0–10.0)	
R1	52	8.6
Postoperative factors		
Postop chemotherapy (n = 559)		
Total	402	71.9
Combined cytotoxic regimen	310	77.1†
Biologic agent	139	34.6†

*Proportion in metachronous presentation.
†Proportion in total preoperative chemotherapy for liver disease.
‡Proportion in total postoperative chemotherapy.
CRC indicates colorectal cancer; KRAS, kirsten rat sarcoma viral oncogene homolog; R1, resection margin exposure in pathology specimen.

and 50.6%, respectively (log-rank test; category 1 vs category 2, $P = 0.134$, category 1 vs category 3, $P = 0.052$, and category 2 vs category 3, $P = 0.280$).

When assessing the goodness of fit of the models, the AICc value of the TBS model (2865) was lower than the AICc value of the traditional tumor morphologic categorization model (2905). Specifically, when comparing the TBS to other established models such as Fong and Adam, which included tumor size >3 cm and tumor number ≥4 model, the AICc of TBS model were lower. Visual inspection of the curves of the 2 models also suggested that TBS had better discriminatory ability. Of note, the curves of zone 1 and zone 3 in the TBS model had a better discriminatory performance than the curves of category 1 and category 3 in the traditional morphologic model (Fig. 2B and D).

To further investigate discriminatory performance, the TBS and traditional morphologic categorization models were analyzed after stratifying patients according to preoperative chemotherapy response. Whereas the TBS model was able to stratify long-term survival among both patients who had a PD/SD, and also a PR/rCR response to preoperative therapy (Fig. 3A and B), the traditional morphologic model failed to provide any discrimination of prognosis among patients who received preoperative chemotherapy (Fig. 3C and D). In addition to a better discriminatory performance, the TBS model also demonstrated a better goodness of fit. Specifically, among patients who had a PD/SD or PR/rCR response to preoperative chemotherapy, the AICc values for the TBS model (1047 and 501, respectively) were lower than the AICc of the traditional tumor size and number model (1067 and 520, respectively).

On multivariable analysis, factors associated with long-term survival included primary tumor nodal metastases (HR 1.55. 95% CI 1.11–2.16, $P = 0.009$), preoperative CEA level ≥50 ng/mL (HR 2.26, 95% CI 1.56–3.29, $P < 0.001$), KRAS mutation (HR 1.56, 95% CI 1.15–2.13, $P = 0.004$), concurrent ablation (HR 1.45, 95% CI 1.03–2.04, $P = 0.034$), resection margin <1 mm (HR 1.81, 95% CI 1.30–2.51, $P = 0.004$), and extrahepatic disease (HR 1.92, 95% CI 1.13–4.81, $P = 0.003$). After accounting for these competing clinicopathologic factors, TBS (<3, ≥3 to <9, and ≥9) remained strongly associated with OS (Table 2). In fact, an increasing TBS was associated with an incremental higher risk of death (referent TBS <3, TBS ≥3 to <9, HR 1.66, 95% CI 1.09–2.54, $P = 0.018$; TBS ≥9, HR 2.60, 95% CI 1.52–4.43, $P < 0.001$).

External Validation

The novel TBS prognostic model was then validated in 2 separate external validation cohorts. The distribution of maximum tumor diameter and tumor number among patients in the external validation cohorts are shown in Fig. 4A and Fig. 5A. The distribution of each TBS zone in the Asian cohort (n = 430) was zone 1: TBS <3 [n = 106 (24.7%)], zone 2: TBS ≥3 to <9 [n = 237 (55.1%)], and zone 3: TBS ≥9 [n = 87 (20.2%)]; the distribution of each TBS zone in the European cohort (n = 198) was zone 1: TBS <3 [n = 51 (25.8%)], zone 2: TBS ≥3 to <9 [n = 93 (47.0%)], and zone 3: TBS ≥9 [n = 54 (27.3%)]. Survival analysis revealed excellent prognostic discrimination using the TBS model among patients in both external cohorts. Specifically, the 5-year OS among patients in the Asian cohort stratified by zone 1, zone 2, and zone 3 was 82.3%, 52.8%, and 19.8%, respectively (log-rank test; zone 1 vs zone 2, $P < 0.001$; zone 1 vs zone 3, $P < 0.001$; and zone 2 vs zone 3, $P < 0.001$) (Fig. 4B). Similarly, the 5-year OS in the European cohort for zone 1, zone 2, and zone 3 was 58.4%, 34.9%, and 29.9%, respectively (log-rank test; zone 1 vs zone 2, $P = 0.004$; zone 1 vs zone 3, $P < 0.001$; and zone 2 vs zone 3, $P = 0.200$). The AICc values for the TBS model in the external validation cohorts were lower (Asian 1811 and European 716)

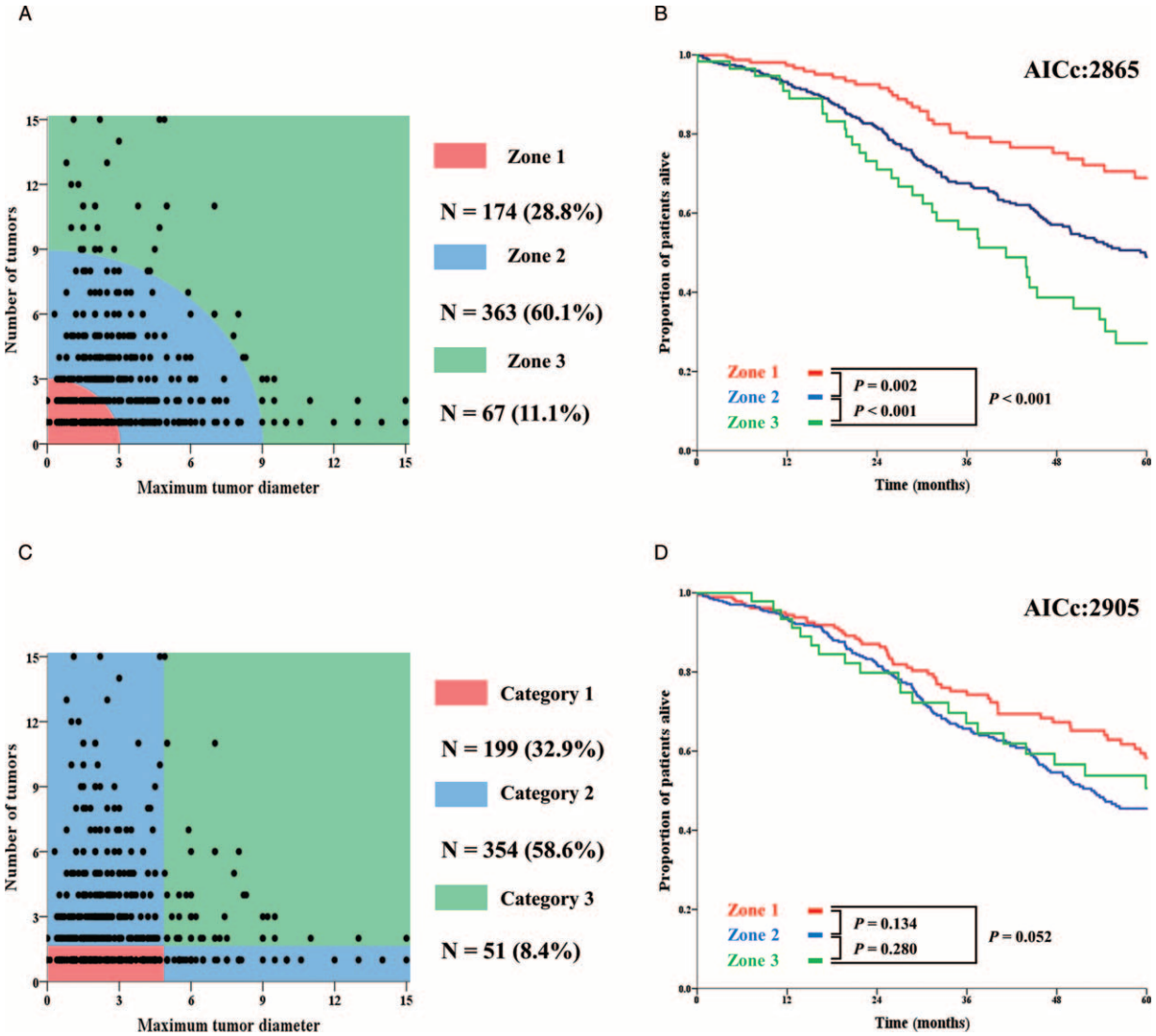

FIGURE 2. A, Distribution of patients according to tumor burden score (TBS) model. B, Kaplan-Meier estimates of overall survival stratified by TBS. C, Distribution of patients according to traditional tumor size and number model (tumor size >5 cm and number ≥2). D, Kaplan-Meier estimates of overall survival stratified by traditional tumor size and number model.

than the AICc values of the traditional tumor morphologic categorization model (Asian 1834 and European 724), indicating a better goodness of fit for the TBS model.

DISCUSSION

Several investigators have previously proposed tumor morphologic factors, including tumor size and number, as important predictors of prognosis for patients treated for CRLM.[38–41] In fact, various cut-off values of maximum tumor diameter and number have been incorporated into several prognostic nomograms utilized to estimate long-term prognosis of patients with CRLM.[6,42,43] Recent studies have questioned the prognostic utility of these previous scoring systems, most of which analyzed tumor size and number as binary variables.[44,45] Unlike previous reports, the model presented in the current study represents the first attempt to stratify patients with CRLM along a continuum of outcome probabilities that incorporated a wide range of tumor size and number. By adopting a ''Metro-ticket'' approach, we were able to develop a dynamic prognostic model that reflected underlying tumor morphology and extent of disease more completely. The current study was important because it demonstrated that the ''Metro-ticket'' concept, which was developed for HCC patients, was also directly applicable to estimating prognosis of patients with CRLM. By combining tumor size and number into a ''Metro-ticket,'' the prognostic performance of TBS was much better than its 2 constituent variables. Moreover, the new TBS prognostic model had a better prognostic discriminatory ability than the traditional categorization model, which used binary values for tumor size and number. In addition, the TBS was associated with survival on multivariable analysis and maintained prognostic

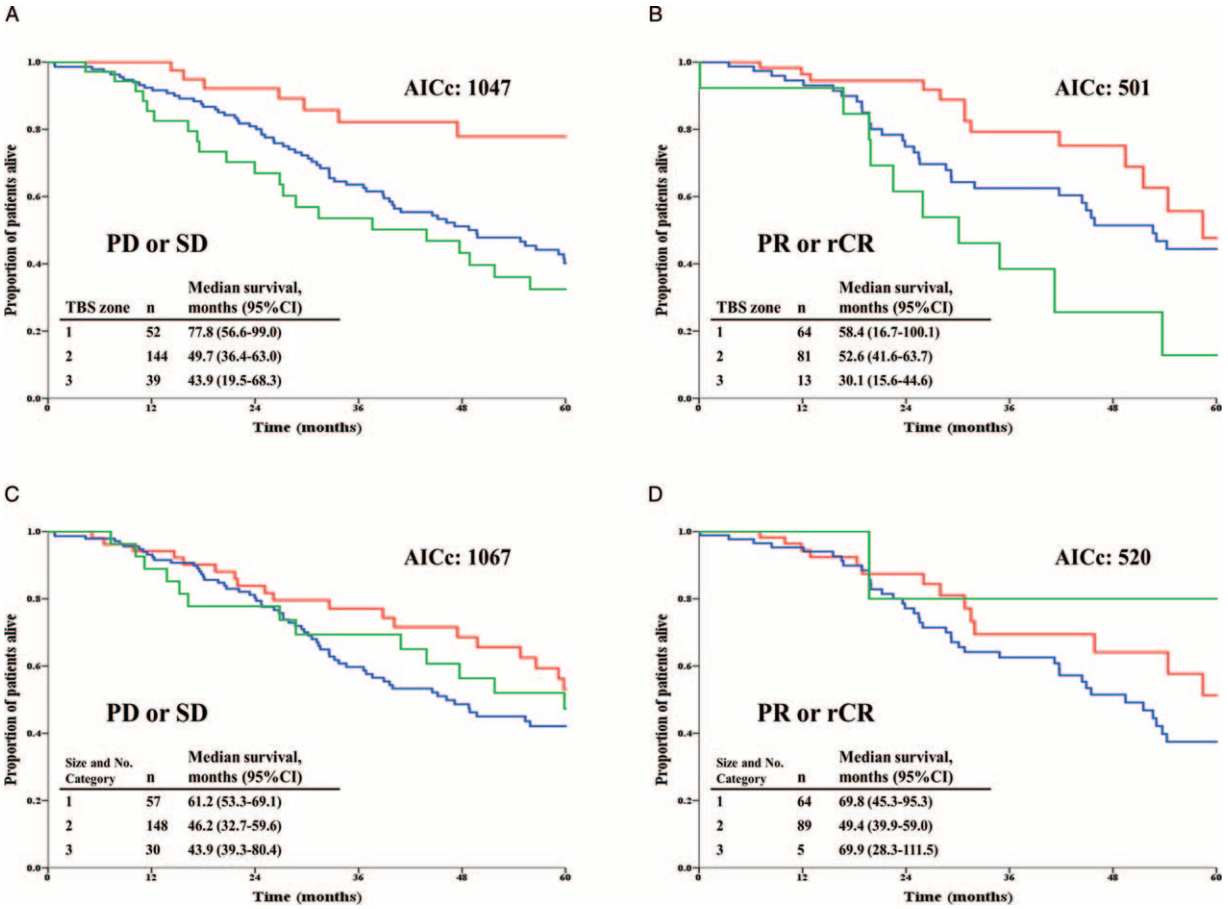

FIGURE 3. A, Kaplan-Meier estimates of overall survival among patients who had PD/SD response to preoperative chemotherapy stratified by TBS. B, Kaplan-Meier estimates of overall survival for patients who had PR/rCR response to preoperative chemotherapy stratified by TBS. C, Kaplan-Meier estimates of overall survival for patients who had PD/SD response to preoperative chemotherapy stratified by traditional tumor size and number model. D, Kaplan-Meier estimates of overall survival for patients who had PR/rCR response to preoperative chemotherapy stratified by traditional tumor size and number model.

discriminatory power among patients treated with preoperative therapy. Importantly, the TBS performed well on external validation when applied to 2 distinct cohorts of patients from Asia and Europe.

The ''Metro-ticket'' system concept was established in liver transplantation for HCC.[27,28] Similar to the model used for HCC, we modeled tumor size and number on a Cartesian plane and forecasted 5-year survival of patients undergoing resection of CRLM based on this model (Fig. 1A). Figuratively, each point on the chart may be said to represent a potential ''destination'' with the origin of the Cartesian plane (0, 0) serving as the ''central Metro station.'' The longer the ''trip'' away from the origin (increased maximum tumor diameter and greater number of lesions), the higher the price of the ''ticket'' (reduction in expected survival).[27] Applying this approach for the first time to patients with CRLM, we developed a new prognostic TBS model that was a robust predictor of long-term survival. The predictive utility of this new prognostic model was examined and compared with the ''gold-standard'' tumor morphology categorization, as defined by Fong clinical risk score.[4] Fong clinical risk score has been used extensively as a predictor of OS, although it was originally developed to predict recurrence.[46–50] In the current study, TBS was a much better tool to predict long-term survival compared with the traditional categorization of tumor size and number based on Fong score. In fact, categorization of patients according to traditional tumor size and number cut-off values resulted in very poor prognostic discrimination (Fig. 2D). In contrast, the TBS was strongly associated with survival, as it stratified patients into distinct prognostic groups (Fig. 2B). In fact, even after for controlling for other risk factors on multivariable analysis, an increasing TBS was associated with an incremental higher risk of death (referent TBS <3, TBS ≥ 3 to <9, HR 1.66, 95% CI 1.09–2.54, $P = 0.018$; TBS ≥ 9, HR 2.60, 95% CI 1.52–4.43, $P < 0.001$). Importantly, the utility and validity of the TBS model were independently confirmed in 2 external cohorts derived from Asia and Europe (Figs. 4 and 5).

Zakaria et al[40] assessed the general applicability of several major risk scoring systems that utilized tumor size and number, and concluded that these models were only marginally better than chance alone in predicting disease-specific survival. A potential reason for the underperformance of these scoring systems relative to tumor size and number may be due to the fact that these scores were developed in era before the widespread use of modern chemotherapy. Many patients with CRLM now are treated with modern chemotherapy, and tumor morphology is influenced by receipt and response to preoperative chemotherapy.[10–12] As such, the role of tumor morphology on operative indications and

TABLE 2. Univariate and Multivariate Analysis of Overall Survival

	Univariate Analysis		Multivariate Analysis	
Factors	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age, yrs				
Age <60	Ref			
Age ≥60	1.11 (0.87–1.41)	0.389		
Sex				
Male	Ref			
Female	0.94 (0.73–1.20)	0.625		
Treatment period				
2000–2007	Ref			
2008–2015	0.85 (0.654–1.12)	0.243		
Tumor site				
Right	Ref			
Left	0.92 (0.72–1.19)	0.544		
CRC nodal metastases				
Negative	Ref		Ref	
Positive	1.50 (1.15–1.96)	**0.003**	1.55 (1.11–2.16)	**0.009**
Disease-free interval				
≥12 mos	Ref			
<12 mos	1.18 (0.90–1.55)	0.243		
Perioperative chemotherapy for CRLM				
No	Ref			
Yes	0.96 (0.63–1.44)	0.831		
Preoperative CEA				
<50	Ref		Ref	
≥50	2.20 (1.57–3.08)	**<0.001**	2.26 (1.56–3.27)	**<0.001**
Extrahepatic disease				
Negative	Ref		Ref	
Positive	1.90 (1.25–2.90)	**0.003**	1.92 (1.24–2.98)	**0.003**
Bilobar disease				
Negative	Ref			
Positive	1.16 (0.91–1.48)	0.230		
KRAS mutation status				
Wild-type	Ref		Ref	
Mutated	1.35 (1.02–1.78)	**0.037**	1.56 (1.15–2.13)	**0.004**
Liver resection				
Resection alone	Ref		Ref	
Resection plus ablation	1.64 (1.23–2.17)	**0.001**	1.45 (1.03–2.04)	**0.034**
Resection margin width				
≥1 mm	Ref		Ref	
<1 mm	1.72 (1.29–2.28)	**<0.001**	1.81 (1.30–2.51)	**0.004**
Tumor burden score				
<3	Ref		Ref	
≥3–9	1.61 (1.16–2.22)	**0.004**	1.66 (1.09–2.54)	**0.018**
≥9	2.85 (1.92–4.22)	**<0.001**	2.60 (1.52–4.43)	**<0.001**

CRC indicates colorectal cancer; KRAS, kirsten rat sarcoma viral oncogene homolog; Ref, reference.
Bold values indicate $P < 0.05$.

surgical outcomes in the era of modern chemotherapy has changed.[12,14] To this end, John et al[51] reported that both tumor size and number lost their prognostic significance in a cohort who underwent hepatectomy between 2000 and 2011. In the current study, we specifically examined the predictive utility of the TBS in relation to chemotherapy type and radiologic response. Of note, whereas traditional tumor size and number cut-off values were not associated with OS, the TBS model performed well both in terms of discrimination and goodness of fit among patients who received preoperative chemotherapy (Fig. 3). As such, the TBS model appears well-suited to the era of modern CRLM management, in which up to 40% to 60% of patients receive some type of preoperative chemotherapy.[36,37,51]

With respect to the distribution of tumors in each model (Fig. 2A and C), the TBS model was able to classify patients more accurately with regard to overall tumor burden. For example, the TBS classified patients who had either a solitary tumor that was large in size or small, but multifocal tumors into zone 3; in contrast, these patients were classified into category 2 by the traditional model. Similarly, the TBS model classified patients with mid-size lesions and average tumor number (2–8) into zone 2, whereas these patients were classified into category 3 using the traditional model. Of note, patients who were classified in zone 3 and category 2 had a worse 5-year OS (15.3%) compared with patients who were classified into zone 2 and category 3(55.3%) ($P = 0.009$) (Supplemental Fig. 1, http://links.lww.com/SLA/B139). As such, the superior discriminatory ability of the TBS model may, in part, be due to a more accurate classification of patients who have a solitary, large tumor, or small but more widely disseminated disease into a worse prognostic group. These data serve to emphasize how TBS can more accurately represent overall tumor burden by using a composite measure to predict long-term outcome.

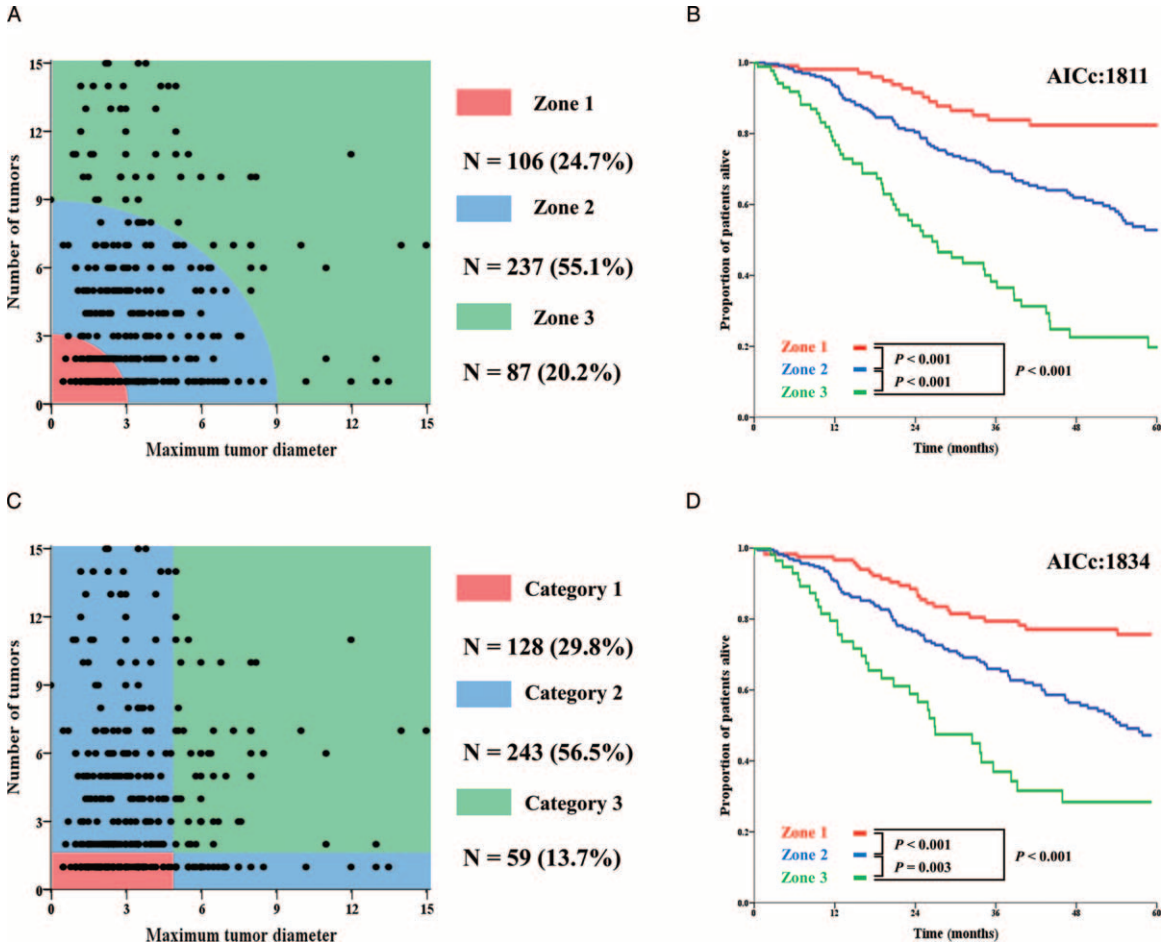

FIGURE 4. A, Distribution of patients in the external validation Asian cohort according to the tumor burden score (TBS) model. B, Kaplan-Meier estimates of overall survival stratified by TBS. C, Distribution of patients according to traditional tumor size and number model (tumor size >5 cm and number ≥2). D, Kaplan-Meier estimates of overall survival stratified by traditional tumor size and number model.

Several limitations should be considered when interpreting the current study. While we analyzed a large cohort of patients who underwent curative-intent liver surgery for CRLM, the median follow-up time was relatively short. The median follow-up time was, however, consistent with the majority of previous institutional reports on surgery for CRLM.[2–7] The ability to achieve a longer follow-up time may surveillance at large tertiary care centers in the United States where patients are more likely to travel longer distances to undergo complex major surgery. For the purpose of analyses, TBS was calculated using data from the pathological specimen and not preoperative radiographic imaging. TBS on imaging and pathology were, however, strongly correlated (Supplemental Fig. 2, http://links.lww.com/SLA/B139). In addition, this study included patients who received combined resection and ablation. Of note, the proportion of patients who underwent a combined resection and ablation procedure was higher in zone 3 of the TBS model. Given that both the TBS model and the utilization of a combined resection + ablation procedure were independent predictors of prognosis, future studies will need to refine further how the TBS model specifically applies to patients undergoing ablation for CRLM. Although the TBS ''Metro-ticket'' model was validated in 2 external cohorts of patients, we were unable to examine the performance of TBS relative to preoperative chemotherapy at these 2 institutions due to variations in preoperative chemotherapy. Finally, the current model only considered tumor morphology. Although tumor morphology and tumor biology are intertwined, future studies will need to combine morphologic and molecular data.

CONCLUSIONS

In conclusion, the current study demonstrated that the ''Metro-ticket'' concept was applicable to patients undergoing hepatectomy for CRLM. Although traditional morphologic categorization had poor prognostic power, the TBS model was strongly predictive of OS. The performance of the TBS ''Metro-ticket'' model was validated in 2 external cohorts of patients. Furthermore, in addition to remaining predictive of OS on multivariable analysis, the TBS model had good discriminatory ability and goodness of fit in predicting outcomes among patients receiving preoperative chemotherapy. The

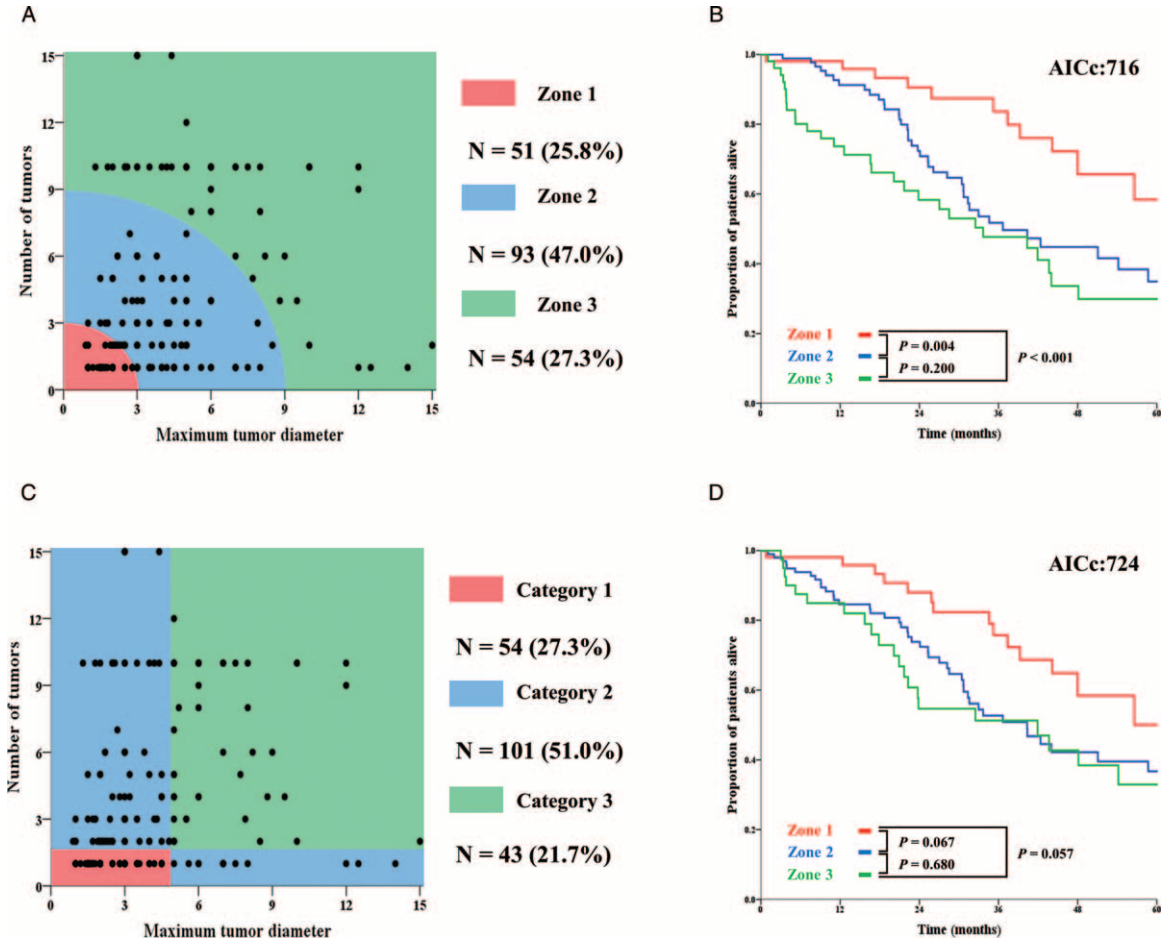

FIGURE 5. A, Distribution of patients in the external validation Italian cohort according to the tumor burden score (TBS) model. B, Kaplan-Meier estimates of overall survival for patients stratified by TBS. C, Distribution of patients according to traditional tumor size and number model (tumor size >5 cm and number ≥2). D, Kaplan-Meier estimates of overall survival for patients stratified by traditional tumor size and number model.

present model offers a useful and accurate tool to account for the impact that tumor morphology has on long-term survival among patients undergoing resection of CRLM.

REFERENCES

1. Kopetz S, Chang GJ, Overman MJ, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. *J Clin Oncol*. 2009;27:3677–3683.
2. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. *Ann Surg*. 2002;235:759–766.
3. House MG, Ito H, Gonen M, et al. Survival after hepatic resection for metastatic colorectal cancer: trends in outcomes for 1,600 patients during two decades at a single institution. *J Am Coll Surg*. 2010;210:744–752. 752–745.
4. 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;230:309–318 [discussion 318–321].
5. Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. *Cancer*. 1996;77:1254–1262.
6. Kattan MW, Gonen M, Jarnagin WR, et al. A nomogram for predicting disease-specific survival after hepatic resection for metastatic colorectal cancer. *Ann Surg*. 2008;247:282–287.
7. Hughes KS, Rosenstein RB, Songhorabodi S, et al. Resection of the liver for colorectal carcinoma metastases. A multi-institutional study of long-term survivors. *Dis Colon Rectum*. 1988;31:1–4.
8. Scheele J, Stang R, Altendorf-Hofmann A, et al. Resection of colorectal liver metastases. *World J Surg*. 1995;19:59–71.
9. Gayowski TJ, Iwatsuki S, Madariaga JR, et al. Experience in hepatic resection for metastatic colorectal cancer: analysis of clinical and pathologic risk factors. *Surgery*. 1994;116:703–710 [discussion 710–711].
10. Pawlik TM, Choti MA. Shifting from clinical to biologic indicators of prognosis after resection of hepatic colorectal metastases. *Curr Oncol Rep*. 2007;9:193–201.
11. Pawlik TM, Schulick RD, Choti MA. Expanding criteria for resectability of colorectal liver metastases. *Oncologist*. 2008;13:51–64.
12. Conrad C, You N, Vauthey JN. In patients with colorectal liver metastases, can we still rely on number to define treatment and outcome? *Oncology (Williston Park)*. 2013;27:1078. 1083–1074, 1086.
13. Ekberg H, Tranberg KG, Andersson R, et al. Determinants of survival in liver resection for colorectal secondaries. *Br J Surg*. 1986;73:727–731.
14. Adam R, Wicherts DA, de Haas RJ, et al. Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? *J Clin Oncol*. 2009;27:1829–1835.

15. Folprecht G, Gruenberger T, Bechstein WO, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. *Lancet Oncol*. 2010;11:38–47.
16. Ye LC, Liu TS, Ren L, et al. Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. *J Clin Oncol*. 2013;31:1931–1938.
17. Gomez D, Cameron IC. Prognostic scores for colorectal liver metastasis: clinically important or an academic exercise? *HPB (Oxford)*. 2010;12:227–238.
18. Kanas GP, Taylor A, Primrose JN, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. *Clin Epidemiol*. 2012;4:283–301.
19. Pawlik TM, Abdalla EK, Ellis LM, et al. Debunking dogma: surgery for four or more colorectal liver metastases is justified. *J Gastrointest Surg*. 2006;10:240–248.
20. Nathan H, de Jong MC, Pulitano C, et al. Conditional survival after surgical resection of colorectal liver metastasis: an international multi-institutional analysis of 949 patients. *J Am Coll Surg*. 2010;210:755–764. 764-756.
21. Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. *Stat Med*. 2006;25:127–141.
22. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med*. 1996;334:693–699.
23. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology*. 2001;33:1394–1403.
24. Decaens T, Roudot-Thoraval F, Hadni-Bresson S, et al. Impact of UCSF criteria according to pre- and post-OLT tumor features: analysis of 479 patients listed for HCC with a short waiting time. *Liver Transpl*. 2006;12:1761–1769.
25. Kaido T, Ogawa K, Mori A, et al. Usefulness of the Kyoto criteria as expanded selection criteria for liver transplantation for hepatocellular carcinoma. *Surgery*. 2013;154:1053–1060.
26. Sugawara Y, Tamura S, Makuuchi M. Living donor liver transplantation for hepatocellular carcinoma: Tokyo University series. *Dig Dis*. 2007;25:310–312.
27. Mazzaferro V. Results of liver transplantation: with or without Milan criteria? *Liver Transpl*. 2007;13:S44–S47.
28. Mazzaferro V, Llovet JM, Miceli R, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol*. 2009;10:35–43.
29. Strasberg SM. Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. *J Hepatobiliary Pancreat Surg*. 2005;12:351–355.
30. 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.
31. Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. *J Clin Oncol*. 2015;33:550–558.
32. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982;143:29–36.
33. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology*. 1983;148:839–843.
34. Akaike H. A new look at the statistical model identification. *Automatic Control IEEE Transactions on*. 1974;19:716–723.
35. Burnham KP, Anderson DR. Multimodel inference understanding AIC and BIC in model selection. *Sociol Meth Res*. 2004;33:261–304.
36. Margonis GA, Spolverato G, Kim Y, et al. Effect of KRAS mutation on long-term outcomes of patients undergoing hepatic resection for colorectal liver metastases. *Ann Surg Oncol*. 2015;22:4158–4165.
37. Vauthey JN, Zimmitti G, Kopetz SE, et al. RAS mutation status predicts survival and patterns of recurrence in patients undergoing hepatectomy for colorectal liver metastases. *Ann Surg*. 2013;258:619–626 [discussion 626-627].
38. Dexiang Z, Li R, Ye W, et al. Outcome of patients with colorectal liver metastasis: analysis of 1,613 consecutive cases. *Ann Surg Oncol*. 2012;19:2860–2868.
39. Malik HZ, Prasad KR, Halazun KJ, et al. Preoperative prognostic score for predicting survival after hepatic resection for colorectal liver metastases. *Ann Surg*. 2007;246:806–814.
40. Zakaria S, Donohue JH, Que FG, et al. Hepatic resection for colorectal metastases: value for risk scoring systems? *Ann Surg*. 2007;246:183–191.
41. Iwatsuki S, Dvorchik I, Madariaga JR, et al. Hepatic resection for metastatic colorectal adenocarcinoma: a proposal of a prognostic scoring system. *J Am Coll Surg*. 1999;189:291–299.
42. Beppu T, Sakamoto Y, Hasegawa K, et al. A nomogram predicting disease-free survival in patients with colorectal liver metastases treated with hepatic resection: multicenter data collection as a Project Study for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. *J Hepatobiliary Pancreat Sci*. 2012;19:72–84.
43. Kanemitsu Y, Kato T. Prognostic models for predicting death after hepatectomy in individuals with hepatic metastases from colorectal cancer. *World J Surg*. 2008;32:1097–1107.
44. Konopke R, Kersting S, Distler M, et al. Prognostic factors and evaluation of a clinical score for predicting survival after resection of colorectal liver metastases. *Liver Int*. 2009;29:89–102.
45. Ayez N, Lalmahomed ZS, van der Pool AE, et al. Is the clinical risk score for patients with colorectal liver metastases still useable in the era of effective neoadjuvant chemotherapy? *Ann Surg Oncol*. 2011;18:2757–2763.
46. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol*. 2007;25:4575–4580.
47. Castaing D, Vibert E, Ricca L, et al. Oncologic results of laparoscopic versus open hepatectomy for colorectal liver metastases in two specialized centers. *Ann Surg*. 2009;250:849–855.
48. Maithel SK, Gonen M, Ito H, et al. Improving the clinical risk score: an analysis of molecular biomarkers in the era of modern chemotherapy for resectable hepatic colorectal cancer metastases. *Surgery*. 2012;151:162–170.
49. Merkel S, Bialecki D, Meyer T, et al. Comparison of clinical risk scores predicting prognosis after resection of colorectal liver metastases. *J Surg Oncol*. 2009;100:349–357.
50. Small RM, Lubezky N, Shmueli E, et al. Response to chemotherapy predicts survival following resection of hepatic colo-rectal metastases in patients treated with neoadjuvant therapy. *J Surg Oncol*. 2009;99:93–98.
51. John SK, Robinson SM, Rehman S, et al. Prognostic factors and survival after resection of colorectal liver metastasis in the era of preoperative chemotherapy: an 11-year single-centre study. *Dig Surg*. 2013;30:293–301.