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Original Article

A novel score system for predicting conversion to no evidence of Disease (C-NED) in initially unresectable colorectal cancer liver metastases

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Abstract: An estimated 70-80% of cases of colorectal cancer liver metastasis (CRLM) are defined as initially unresectable. "Converting" to no evidence of disease (NED) status may prolong survival. The current study aimed to develop a novel scoring system that predicts the conversion outcome for initially unresectable CRLM. A total of 215 consecutive CRLM patients who received first-line systemic therapy from December 2012 to January 2020 at Sun Yat-sen University Cancer Center were enrolled in the internal cohort. Forty CRLM patients from the database of the Chinese Colorectal Cancer Multidisciplinary Team Alliance were enrolled in the external cohort. A logistic regression model was applied to identify risk factors associated with the conversion outcome. The tumor-to-liver volume ratio (TLVR) was calculated as the total tumor volume divided by the total liver volume, and its cutoff value was 0.23. Three predictors of conversion failure were identified in the internal cohort and incorporated into the C-NED score: poor tumor differentiation (1 point), number of liver metastases > 8 (1 point) and TLVR ≥ 0.23 (1 point). The conversion rate was significantly negatively associated with the C-NED score ($P < 0.001$). The C-indexes of the C-NED score for predicting successful conversion outcome in the internal cohort and external cohort were 0.734 (95% confidence interval (CI), 0.668-0.800) and 0.736 (95% CIs, 0.566-0.907), respectively. Median progression-free survival (PFS) time (P = 0.001) and overall survival (OS) time (P = 0.003) were statistically significant different among different C-NED score groups. Our study demonstrated that the C-NED score is an effective scoring system that indicates the actual conversion probability for initially unresectable CRLM patients before treatment, which can serve as a tool that guides optimal first-line management strategies.

Keywords: Colorectal cancer, liver metastases, three-dimensional reconstruction, conversion outcome prediction, prognosis

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, and distant metastasis is still the main cause of treatment failure and death among CRC patients [1-3]. Colorectal cancer liver metastasis (CRLM) is the most common pattern, with approximately 25% of CRC patients found to have liver metastasis at first diagnosis and with more than half of CRC patients eventually developing liver metastasis during the development of the disease [3, 4]. Moreover, an estimated 70-80% of cases with CRLM are defined as initially unresectable, and their 5-year overall survival (OS) rate is no more than 9% when treated with systemic therapy alone [5-8].

Currently, with the increasing efficacy of systemic therapy regimens, CRC patients with initially unresectable liver-only metastases should be considered candidates for "converting" to resectable disease and achieving no-evidence-of-disease (NED) status, which may prolong the survival time to a length that is similar to that of patients with initially resectable CRLM

[9-11]. Doublet or triplet chemotherapy regimens with targeted therapy (anti-vascular endothelial growth factor (VEGF) or anti-endothelial growth factor receptor (EGFR) antibody) have increased response rates to 60%-70% [12-14], creating favorable conditions for conversion therapy. However, when setting the initial treatment goal, quantified criteria for distinguishing patients receiving purely palliative treatment from those receiving curative treatment are actually nonexistent. In current clinical practice, the first-line treatment regimen and resection of liver metastases are determined mainly by a multidisciplinary team (MDT) [15]. Under these circumstances, the conversion probability is difficult to calculate before the initial treatment, due to the lack of a clear and objective scoring system, probably leading to overtreatment or undertreatment of patients. Therefore, exploring a novel scoring system for predicting conversion outcomes to guide personalized treatment is urgently needed [16].

In recent decades, clinicopathological parameters associated with tumor burden have been proven to be an essential prognostic factor for postoperative recurrence and thus consolidated into several scoring systems for CRLM patients [17-19]. Recently, a quantitative imaging model based on the geometric and radiomics analysis of whole liver tumor burden from baseline computed tomography (CT) images was revealed to yield prognostic information [20]. In the present study, we applied a three-dimensional (3D) reconstruction technology based on the imaging data from baseline CT or magnetic resonance imaging (MRI) scans for the assessment of the tumor burden of liver metastases. Subsequently, we aimed to develop a novel scoring system that predicts conversion to NED for initially unresectable CRLM.

Materials and methods

Patient population

In the internal cohort, we selected 215 consecutive patients with CRLM who received first-line systemic therapy from December 2012 to January 2020 at Sun Yat-sen University Cancer Center (SYSUCC). Demographic and clinicopathological characteristics were retrieved from the electronic medical records system of SYSUCC. In the external cohort, we collected the clinical data of 40 CRLM patients from the database of the Chinese CRC MDT Alliance. Patients in the validation cohort underwent first-line systemic therapy from April 2018 to July 2020 in 34 hospitals in 14 provinces in China. All patients in both cohorts met the following inclusion criteria: (1) histologically confirmed colorectal adenocarcinoma, (2) metastases limited to the liver, (3) initially unresectable liver metastases (impossibility or intolerance of R0 resection with ≥ 30% liver remnant presence of unresectable extrahepatic disease), (4) no previous liver resection or interventional therapy, (5) available imaging data before and after first-line treatment, and (6) an explicit conversion outcome. All the variable data prepared to be consolidated into our novel scoring systems were obtained at the first diagnosis, concurrently with the evaluation of the baseline liver tumor burden. Informed consent for the use of the imaging and clinical data was obtained from the patients before first-line treatment. The study was approved by the Institutional Research Ethics Committee of Sun Yat-sen University Cancer Center (approval number: B2020-309-01).

Evaluation of the baseline liver tumor burden

The tumor burden was assessed by a 3D reconstruction of liver metastases and total liver formation. The 3D reconstruction was developed by using the Medi-GPS 3D Visualization System (HOKAI Medical Equipment Co., Ltd., Zhuhai, China) with 5-mm-thick contrast-enhanced MRI slices or 1.25-mm-thick contrast-enhanced CT slices. The gross images of the tumor and total liver were displayed in a 3D model, and the characteristics of liver metastases, including the tumor diameter, total tumor volume, tumor number, tumor distribution and vascular invasion, were automatically generated. Subsequently, the tumor-to-liver volume ratio (TLVR) was calculated as the total tumor volume divided by the total liver volume, which was developed, validated, and compared in the internal cohort.

Determination of the cutoff value

The serum CEA cutoff value was 200 ng/mL, the same as that of the Fong score [18]; the serum CA19-9 cutoff value was 200 U/mL, which was determined by a previous study [21]. The median tumor diameter and tumor

number of the internal cohort were recognized as the cutoff values. The TLVR cutoff value was determined by receiver operating characteristic (ROC) curve analysis according to the conversion outcome.

Treatments outcome

The treatment strategy and operability of the liver metastases of each patient were determined based on the final agreement of the MDT, including staff from the Department of Colorectal Surgery, Hepatobiliary Surgery, Medical Oncology, Medical Imaging and Invasive Technology. Tumor response or progression after first-line treatment was determined according to the Response Evaluation Criteria in Solid Tumors 1.1 [22]. Conversion success was defined as liver metastases deemed to be resectable after first-line systemic treatment, and the patients achieved NED status contributing to local treatment, including surgery and radiofrequency ablation (RFA). Conversion failure was defined as liver metastases that remained unresectable after first-line systemic treatmentand failed to received curative local treatment. Progression-free survival (PFS) was defined as the interval from the date of first-line systemic treatment to the earliest documented date of disease progression, or death from any cause the date of death from any cause, or to the last follow-up. Overall survival (OS) was defined as the interval from the date of first-line systemic treatment to the date of death from any cause or to the last follow-up. The final follow-up visit occurred in October 2021.

Model establishment and validation

The C-NED score was developed in the internal cohort. The logistic regression model was applied to identify the clinical risk factors associated with the conversion outcome. Factors with a value of $P < 0.05$ in the univariable analysis were included in the multivariable analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were subsequently calculated. Factors with a value of $P < 0.05$ in the multivariable analysis were included in the C-NED score.

Internal validation was performed in the internal cohort, and further validation was performed in the external cohort. The accuracy of the model was verified by a bootstrap method with 1,000 resamples. The calibration curve was employed to detect the concentricity between the model probability curve and the ideal curve. The concordance index (C-index) was applied to validate the predictive ability of the scoring model.

Statistical analysis

Categorical variables are presented as percentages, and continuous variables as means and standard deviation. Comparison between variables were assessed with Chi-square test, Fisher's exact test, Mann-Whitney U tests and one-way ANOVA tests when appropriate. The logistic regression model was applied to identify the risk factors associated with conversion outcome. Parameters with a value of $P < 0.05$ in univariate analysis were included in the multivariate analysis. Odd ratios (ORs) and 95% confidence intervals (CIs) were subsequently calculated. Kaplan-Meier method was used to estimate OS and PFS and differences between groups were assessed with log-rank test. The Cox proportional hazards model was applied to identify the risk factors associated with OS. Parameters with a value of $P < 0.05$ in univariate analysis were included in the multivariate analysis. Results were reported as hazard ratios (HRs) and 95% confidence intervals (CIs). All analyses were conducted using SPSS 20.0 software (IBM, Chicago, IL, USA), GraphPad Prism 7 software (GraphPad Software Inc, San Diego, CA, USA), and R software packages. The calibration curve was plotted, and the C-index was calculated with the rms package (version 5.1-3.1; CRAN.R-project.org/package=rms).

Results

Patient demographics of the internal cohort

The clinical and pathological characteristics of the 215 patients in the internal cohort are presented in Table S1. The median age of all patients was 55 years (range, 28-80), and 72.6% of the patients were male. After first-line systemic therapy, 102 (47.4%) patients had a partial response (PR), 59 (27.4%) patients had stable disease (SD), and 54 (25.1%) patients had progressive disease (PD). Finally, 95 (44.2%) patients achieved successful conversion to NED. Among the 95 patients, 48 (50.5%) underwent both tumor resection and RFA, while 47 (49.5%) received curative tumor resection alone.

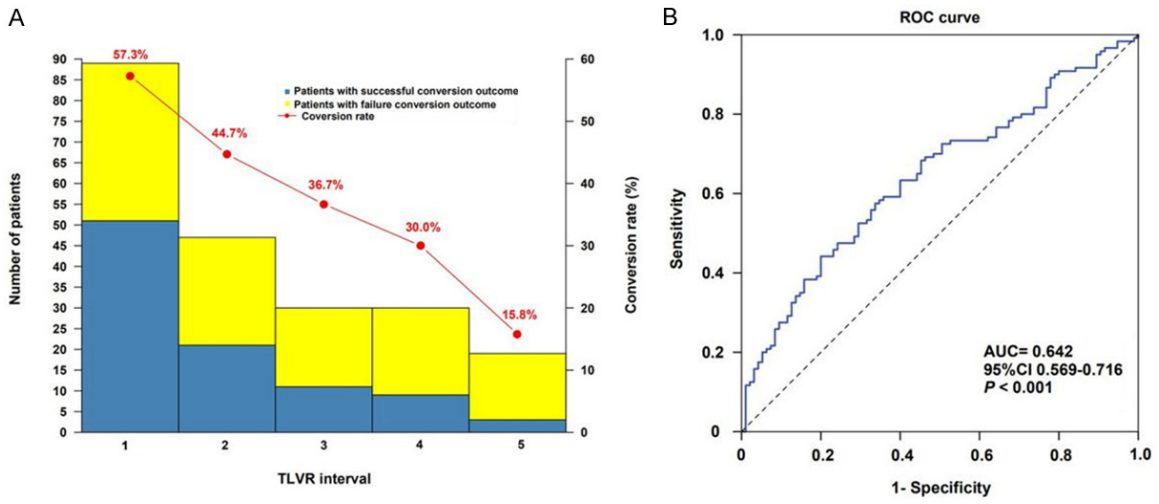

Figure 1. A. Distribution of the tumor liver volume ratio (TLVR) and its corresponding successful conversion rate of all studied patients in the internal cohort; B. Receiver operating characteristic (ROC) curves for the TLVR.

Table 1. Comparison of baseline characteristics of all patients grouped by TLVR in the internal cohort

Variables	TLVR < 0.23 (*n* = 144, %)	TLVR ≥ 0.23 (*n* = 71, %)	*P* value
Age, years			0.273
≤ 60	100 (69.4)	44 (62.0)	
> 60	44 (30.6)	27 (38.0)	
Sex			0.073
Male	110 (76.4)	46 (64.8)	
Female	34 (23.6)	25 (35.2)	
Primary tumor site			0.997
Right colon	33 (22.9)	16 (22.5)	
Left colon	69 (47.9)	34 (47.9)	
Rectum	42 (29.2)	21 (29.6)	
Tumor differentiation			0.410
Well/moderate	115 (79.9)	60 (84.5)	
Poor	29 (20.1)	11 (15.5)	
T stage			0.266
T1-3	84 (58.3)	47 (66.2)	
T4	60 (41.7)	24 (33.8)	
N stage			0.240
N0	23 (16.0)	16 (22.5)	
N1-2	121 (84.0)	55 (77.5)	
Serum CEA, ng/mL			< 0.001
≤ 200	99 (68.8)	24 (33.8)	
> 200	45 (31.2)	47 (66.2)	
Serum CA19-9, U/mL			0.177
≤ 200	81 (56.3)	33 (46.5)	
> 200	63 (43.7)	38 (53.5)	
KRAS status*			0.464
Wild type	86 (72.9)	46 (78.0)	
Mutant	32 (27.1)	13 (22.0)	

Baseline TLVR and its association with other clinicopathologic characteristics

In the internal cohort, the median total volume of liver metastases was 214 ml (range, 13-2370 ml), and the median liver volume was 1617 ml (range, 742-3819 ml). The median TLVR was 0.13 (range, 0.01-0.64). The continuous variable TLVR was divided into five "intervals": interval 1, defined as TLVR no more than 0.1, with 89 (41.4%) patients; interval 2, defined as TLVR 0.1-0.2, with 47 (21.9%) patients; interval 3, defined as TLVR 0.2-0.3, with 30 (14.0%) patients; interval 4, defined as TLVR 0.3-0.4, with 30 (14.0%) patients; and interval 5, defined as TLVR above 0.4, with 19 (8.8%) patients. The typical liver and liver tumor images of 3D reconstruction for the 5 TLVR intervals are shown in Figure S1. As shown in **Figure 1A**, interval 1 had the highest conversion rate of 57.3%, while interval 5 had the lowest conversion rate of 15.8%. The conversion rate gradually decreased with increasing TLVR interval. ROC curve analysis showed that the AUC for conversion outcome on the basis of the baseline

Timing of CRLM			0.069
Synchronous	136 (94.4)	62 (87.3)	
Metachronous	8 (5.6)	9 (12.7)	
Distribution of liver metastasis			0.259
Unilobar	34 (23.6)	12 (16.9)	
Bilobar	110 (76.4)	59 (83.1)	
Size of largest liver tumor, cm			< 0.001
≤ 6	85 (59.0)	5 (7.0)	
> 6	59 (41.0)	66 (93.0)	
Number of liver tumors			0.995
≤ 8	67 (46.5)	33 (46.5)	
> 8	77 (53.5)	38 (53.5)	
Invasion of hepatic vein			< 0.001
No	69 (47.9)	2 (2.8)	
Yes	75 (52.1)	69 (97.2)	
Invasion of portal vein			< 0.001
No	108 (75.0)	11 (15.5)	
Yes	36 (25.0)	60 (84.5)	
Outcome of conversion therapy			< 0.001
Success	76 (52.8)	19 (26.8)	
Failure	68 (47.2)	52 (73.2)	

Abbreviations: TLR, tumor liver ratio; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CRLM, colorectal cancer liver metastasis. Notes: *Data of 177 patients were available.

TLVR was 0.642 (95% CI: 0.569-0.716, $P < 0.001$) (**Figure 1B**). The optimal TLVR cutoff value was 0.23 at the highest Youden index of 0.242. As a result, 144 (67.0%) patients had a low TLVR (< 0.23), while 71 (33.0%) patients had a high TLVR (≥ 0.23).

The associations between TLVR and clinicopathologic characteristics are summarized in **Table 1**. Patients in the low TLVR group were more likely to have a lower proportion of serum CEA level > 200 ng/mL and diameter of largest liver tumor > 6 cm than those in the high TLVR group (31.2% vs. 66.2%; $P < 0.001$; 41.0% vs. 93.0%; $P < 0.001$). Lower proportions of invasion of the hepatic vein and invasion of the portal vein were observed in the low TLVR group than in the high TLVR group (52.1% vs. 97.2%; $P < 0.001$; 25.0% vs. 84.5%; $P < 0.001$). There were no significant differences regarding age, sex, primary tumor site, tumor differentiation, T stage, N stage, serum CA19-9 level, KRAS status, timing of CRLM, distribution of liver metastasis or number of liver tumors. Patients with a low TLVR had a two times higher conversion rate than those with a high TLVR (52.8% vs. 26.8%, $P < 0.001$).

Identification of predictive factors and development of the C-NED score in the internal cohort

The results of the univariate and multivariable logistic regression analyses of the relationships between variables and conversion outcome are summarized in **Table 2**. The univariate analysis revealed that poor tumor differentiation, metachronous CRLM, bilobar liver metastases, number of liver metastases > 8, TLVR ≥ 0.23, hepatic vein invasion and portal vein invasion were associated with a failed conversion outcome. Multivariate analysis indicated that poor tumor differentiation (OR, 3.496; 95% CI, 1.490-8.825; $P = 0.005$), number of liver metastases > 8 (OR, 3.107; 95% CI, 1.511-6.544; $P = 0.002$) and TLVR ≥ 0.23 (OR, 2.706; 95% CI, 1.124-6.755; $P = 0.029$) were independent predictive factors for failure conversion outcome. Finally, the 3 independent variables of conversion outcome were consolidated into the C-NED score: poor tumor differentiation as 1 point, number of liver metastases > 8 as 1 point and TLVR ≥ 0.23 as 1 point.

Patient demographics of the external cohort

The variables related to the C-NED scores of 40 patients in the external cohort are summarized in Table S2. In the external cohort, 35 (87.5%) patients had a TLVR < 0.23, while 5 (12.5%) patients had a TLVR ≥ 0.23. After first-line systemic therapy, 25 (62.5%) patients had a tumor partial response (PR), 7 (17.5%) patients had stable disease (SD), and 8 (20.0%) patients had progressive disease (PD). Finally, a total of 26 (65.0%) patients achieved successful conversion outcomes.

Internal and external validation of the C-NED score

In the internal cohort, the C-NED score was allocated as follows: 0 points in 65 (30.2%) patients; 1 point in 96 (44.7%) patients; 2 points in 47 (21.9%) patients; and 3 points in

Table 2. Univariate and multivariate logistic regression analyses of baseline characteristics for conversion treatment prediction in the internal cohort

Variables	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, years (> 60 vs. ≤ 60)	1.055 (0.596-1.869)	0.855		
Sex (male vs. female)	1.200 (0.658-2.188)	0.552		
Primary tumor site (rectum vs. colon)	1.137 (0.626-2.065)	.0359		
Tumor differentiation (poor vs. well/moderately)	2.434 (1.144-5.176)	0.021	3.496 (1.490-8.825)	0.005
T stage (T4 vs. T1-3)	1.093 (0.629-1.898)	0.753		
N stage (N1-2 vs. N0)	1.680 (0.801-3.229)	0.182		
Serum CEA, ng/mL (> 200 vs. ≤ 200)	1.551 (0.895-2.687)	0.118		
Serum CA19-9, U/mL (> 200 vs. ≤ 200)	1.658 (0.961-2.859)	0.069		
KRAS status* (mutant vs. wild type)	1.455 (0.732-2.893)	0.285		
Timing of CRLM (metachronous vs. synchronous)	4.674 (1.595-17.019)	0.039	3.621 (0.963-13.611)	0.057
Distribution of liver metastasis (bilobar vs. unilobar)	2.895 (1.527-5.635)	0.001	1.577 (0.771-4.231)	0.310
Size of largest liver tumor, cm (> 6 vs. ≤ 6)	1.393 (0.811-2.392)	0.230		
Number of liver tumors (> 8 vs. ≤ 8)	4.269 (2.385-7.641)	< 0.001	3.107 (1.511-6.544)	0.002
TLVR (≥ 23% vs. < 23%)	3.059 (1.647-5.680)	< 0.001	2.706 (1.124-6.755)	0.029
Invasion of hepatic vein (yes vs. no)	2.278 (1.281-4.093)	0.005	0.873 (0.390-1.920)	0.737
Invasion of portal vein (yes vs. no)	3.407 (1.936-6.119)	< 0.001	2.035 (0.895-4.689)	0.091

Abbreviations: OR, odds ratio; CI, confidence interval; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CRLM, colorectal cancer liver metastasis; TLVR, tumor to liver volume ratio. Notes: *Data of 177 patients were available.

7 (3.3%) patients. Patients with 0 points achieved the highest conversion rate of 69.2%, while patients with 3 points achieved a 0% conversion rate. The conversion rate was significantly negatively associated with the C-NED score ($P < 0.001$, **Figure 2A**). The calibration curve showed good statistical performance upon internal validation between the C-NED score and the actual observation for probability of conversion (**Figure 2B**). The C-index of the C-NED score for predicting successful conversion was 0.734 (95% CI, 0.668-0.800).

In the external cohort, the C-NED score was allocated as follows: 0 points in 22 (55.0%) patients; 1 point in 15 (37.5%) patients; 2 points in 2 (5.0%) patients; and 3 points in 1 (2.5%) patient. Patients with 0 points achieved the highest conversion rate of 81.8%, while no patient with 3 points achieved successful conversion. The conversion rate was also significantly negatively associated with the C-NED score ($P = 0.017$, **Figure 2C**). The calibration curve demonstrated that the C-NED score showed a good statistical discriminatory ability on external validation (**Figure 2D**). The C-index of the C-NED score for predicting successful conversion was 0.736 (95% CI, 0.566-0.907).

Efficacy of first-line systemic therapy among different C-NED score groups

Since patients with 3 points C-NED score in the internal cohort were relatively few, the group of 2 and 3 points will be combined into a 2-3 points C-NED score group in the further analysis. As shown in **Figure 3**, the mean duration (7.15 vs. 8.14 vs. 8.81 cycles, $P = 0.007$, **Figure 3A**) and objective response rates (ORR) (66.2% vs. 48.4% vs. 24.1%, $P = 0.001$, **Figure 3B**) of first-line systemic therapy were significant difference among patients with 0 points, 1 point and 2-3 points. However, there were no statistically significant difference among patients with different C-NED score for KRAS status ($P = 0.783$, **Figure 3C**).

Prognostic analysis of C-NED score

After a median follow-up of 43.5 months, 78 patients died of tumor and 179 patients experienced disease progression in the internal cohort. Patients with 0 points C-NED score had the highest median PFS time and OS time [PFS: 16.6 months (95% CI 12.6-20.6); OS: 64.8 months (95% CI 35.6-93.9)] of the three groups. Patients with 1 point presented intermediate median PFS time and OS time [PFS:

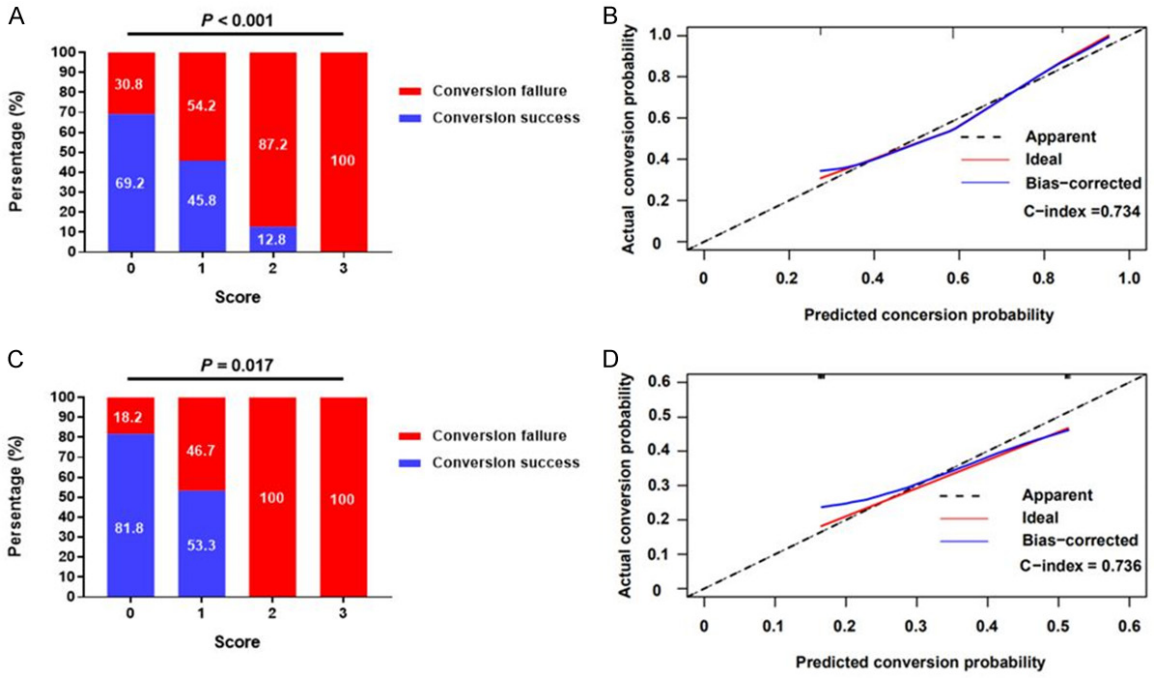

Figure 2. Internal and external validation of the C-NED score. A. Distribution of conversion to no evidence of disease (C-NED) score and its association with conversion treatment outcome in the internal cohort; B. Validation of the C-NED score using the bootstrap sampling method in the internal cohort; C. Distribution of the C-NED score and its association with the conversion treatment outcome in the external cohort; D. Validation of the C-NED score using the bootstrap sampling method in the external cohort.

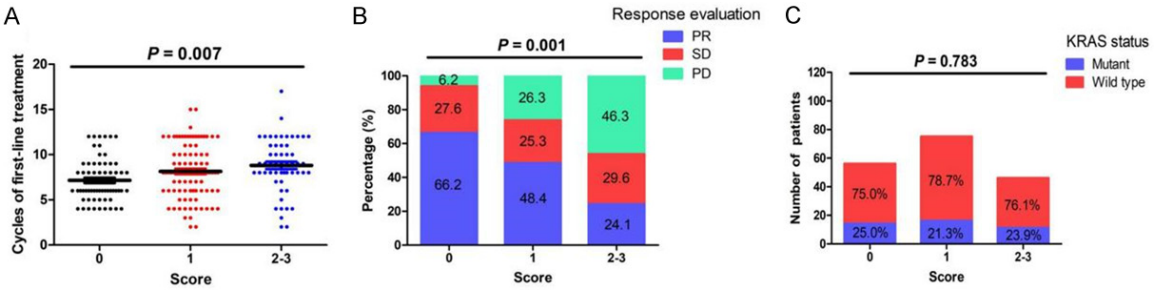

Figure 3. Comparison of duration (A) and treatment response evaluation (B) of first-line systemic therapy and KRAS mutation status (C) grouped by 0 points, 1 point and 2-3 points conversion to no evidence of disease (C-NED) score of patients in the internal cohort.

12.2 months (95% CI 10.0-14.4); OS: 43.4 months (95% CI 27.1-59.9)]. Patients with 2-3 points had the lowest median PFS time and OS time [PFS: 9.7 months (95% CI 7.9-11.6); OS: 27.7 months (95% CI 18.1-37.3)]. The C-NED score was statistically significant for PFS (P = 0.001, **Figure 4A**) and OS (P = 0.003, **Figure 4B**).

As shown in Table S3, the univariate analysis revealed that the N1-2 stage, mutant KRAS and 2-3 points C-NED score were associated with unfavorable OS. The multivariate analysis showed that mutant KRAS (HR, 1.895; 95% CI 1.060-3.387; P = 0.031), 2-3 points C-NED score (HR, 2.867; 95% CI 1.092-5.564; P = 0.002) were independent predictive factors for an unfavorable OS.

Discussion

In the present study, we first calculated a novel tumor burden evaluation parameter, the TLVR, that was generated by liver metastasis

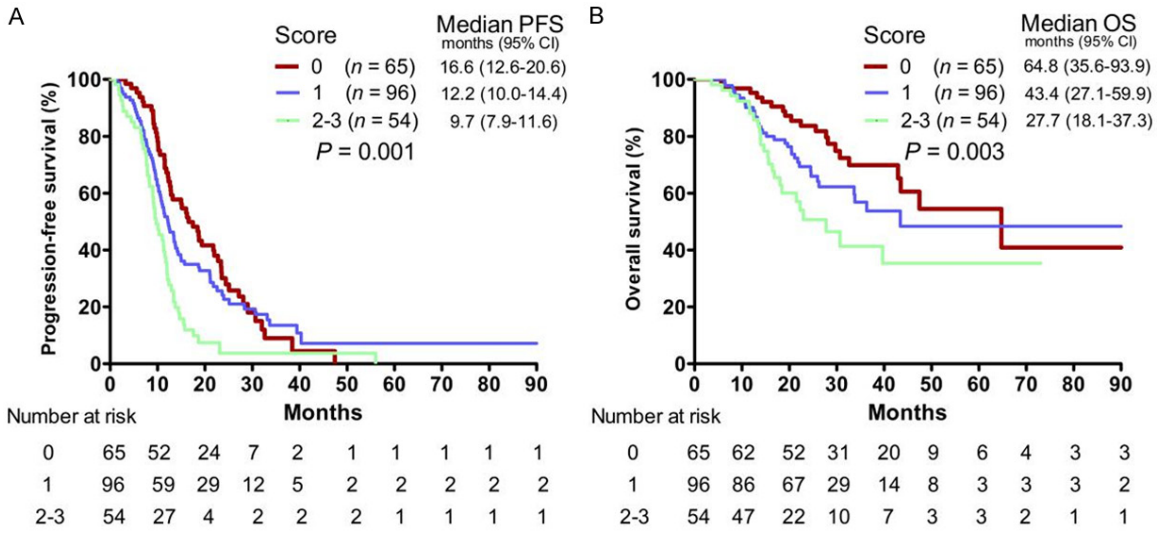

Figure 4. A. Comparison of progression-free survival of patients in the internal cohort stratified by conversion to no evidence of disease (C-NED) score from the 0 points, 1 point and 2-3 points groups; B. Comparison of overall survival of patients in the internal cohort stratified by conversion to no evidence of disease (C-NED) score from the 0 points, 1 point and 2-3 points groups.

image segmentation and 3D reconstruction technology. Then, we integrated the TLVR, the number of liver tumors and tumor differentiation into the novel C-NED scoring system. The satisfactory predictive discriminatory ability of the C-NED score was validated in both the internal cohort and external cohort. Finally, we found that initially unresectable CRLM patients with different C-NED score owned significantly different median PFS time and OS time. To the best of our knowledge, this is the first study to establish quantified criteria for selecting a potentially curative population in initially unresectable CRLM patients.

Total liver tumor volume has previously been considered a prognostic factor for several malignant cancer types with unresectable liver metastasis, such as CRC [20, 23], hepatocellular carcinoma [24] and pancreatic ductal adenocarcinoma [25]. Two previous studies [26, 27] investigated and validated the notion that tumor size was one of the most important independent predictors for tumor downstaging in locally advanced rectal cancer patients receiving neoadjuvant therapy, but its role in predicting conversion to NED has not yet been investigated. In addition, hepatic atrophy following preoperative chemotherapy was proven to predict hepatic insufficiency after resection of colorectal liver metastases [28], which is the main cause of postoperative mortality and conversion failure, suggesting that total liver volume may be a potential factor for conversion treatment. Therefore, we combined liver tumor volume with total liver volume to createa novel parameter, the TLVR. A higher TLVR value means a higher total liver tumor volume and a lower total liver volume, indicating that the TLVR is a more comprehensive assessment of tumor burden. Moreover, our results demonstrated that the TLVR could be separated into distinct intervals with different conversion rates. Differentiated by the cutoff value of 0.23, patients with a low TLVR had a two times higher conversion rate than those with a high TLVR. Therefore, we considered TLVR to serve as a simple and practical parameter for predicting conversion outcomes for unresectable CRLM patients.

Previous studies have built various models for predicting conversion therapy outcomes in initially unresectable CRLM. Modest DP et al. [29] recognized factors including lung metastases, BRAF mutation and baseline elevated alkaline phosphatase levels, which were associated with conversion failure by analysis of a prospective cohort consisting of 270 patients with wild-type RAS unresectable CRLM. This model failed to include several classical parameters, such as the size, number and distribution of liver

tumors, which are closely associated with the technical difficulty of hepatectomy. Correa-Gallego C et al. [30] evaluated the ability of PET-CT metabolic response parameters, including the standard uptake value (SUV), total lesion glycolysis (TLG) and the maximal metabolically active lesion volume, to predict conversion to resectability in patients with unresectable CRLM treated with hepatic arterial infusion (HAI) and systemic chemotherapy. However, they failed to obtain a satisfactory result due to the limited population and uninterpretable data. In the present study, the C-NED score was proven to be an effective predictive scoring system to indicate the actual conversion probability for initially unresectable CRLM patients before treatment. Moreover, the C-NED score was also proven to be a significant negative prognostic factor. In addition, the C-NED score is practical in clinical practice. The advantage of acquiring the C-NED score is that it is simple and does not expand the cause of imaging examination. And pathological biopsy is the routine baseline examination before treatment, which is easily accessible.

The combination of chemotherapy and targeted therapy was recognized as an effective first-line treatment strategy, as reported with satisfactory response rates [12, 13]. However, our data revealed that as the C-NED score increased, the duration and ORR of first-line systemic therapy was significantly prolonged and lower, presenting worse sensitivity to first-line systemic therapy. The results indicated that the C-NED score is more likely to be an inherent indicator reflecting the tumor response to systemic treatment, regardless of how effective the treatment regimen is.

Although the predictive and prognostic impact of numerous genetic markers has been evaluated, KRAS remains the most commonly used due to its wide availability and robust association with long-term outcomes, especially for CRLM patients undergoing radical hepatectomy [31-34]. And the selection of targeted therapy is also based on KRAS mutation status. Interestingly, our data found that KRAS mutation status was a prognostic factor but not a conversion outcome predictive factor. The prognostic value of a marker combining the C-NED scoring system and KRAS mutation status worth exploring in further study.

Notably, the baseline CEA level failed to become a predictive factor and was not incorporated into the presenting scoring system. Although CEA is regarded as an indicator of tumor recurrence or progression during follow-up, it has mostly been presented as a prognostic factor rather than a treatment outcome predictive factor in CRLM in previous scoring systems [18, 19, 21]. Two other worthwhile parameters, namely, invasion of the hepatic vein and invasion of the portal vein, also failed to be incorporated into the score; these have been reported to be related to treatment response and conversion treatment outcome by Tanaka K et al. [35]. Reversal of the attachment or invasion of major intrahepatic vessels by liver metastases is regarded as the key to conversion to NED. The failure of these three parameters to be included in the final scoring system might be due to collinearity with the TLVR in the current study.

It should be acknowledged that there were several limitations to the current study. First, this model was built based on a retrospective study that included an uncontrolled methodology and a limited number of patients recruited from a single cohort with selective bias. The number of patients in the internal cohort and external validation cohort was limited. The findings must be validated in a prospective, multicenter clinical trial with a larger population in the future. Additionally, several tumor molecular markers were not included in the current study. It has been reported that BRAF, TP53, and SMAD4 mutations, microsatellite status, CpG island methylator phenotype (CIMP) status and tumor immune infiltration were significantly associated with long-term survival and treatment response prediction in CRLM [36, 37]. Thus, it is necessary to include pathological, immunological and molecular markers for conversion risk stratification in further studies.

Conclusion

The TLVR can be a valuable representative parameter with conversion outcome. The C-NED score is an effective tool for predicting conversion outcome can help determine optimal first-line management strategies for initially unresectable CRLM patients.

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The datasets used and analyzed during the current study are available from the corresponding author on reasonable request. The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit public platform (www.researchdata.org.cn, RDDA2022856781).

Disclosure of conflict of interest

None.

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References

[1] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017; 67: 7-30.

[2] Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A and Jemal A. Colorectal cancer statistics, 2017. CA Cancer J Clin 2017; 67: 177-193.

[3] Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, Aranda Aguilar E, Bardelli A, Benson A, Bodoky G, Ciardiello F, D'Hoore A, Diaz-Rubio E, Douillard JY, Ducreux M, Falcone A, Grothey A, Gruenberger T, Haustermans K, Heinemann V, Hoff P, Köhne CH, Labianca R, Laurent-Puig P, Ma B, Maughan T, Muro K, Normanno N, Österlund P, Oyen WJ, Papamichael D, Pentheroudakis G, Pfeiffer P, Price TJ, Punt C, Ricke J, Roth A, Salazar R, Scheithauer W, Schmoll HJ, Tabernero J, Taïeb J, Tejpar S, Wasan H, Yoshino T, Zaanan A and Arnold D. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016; 27: 1386-1422.

[4] O'Reilly DA and Poston GJ. Colorectal liver metastases: current and future perspectives. Future Oncol 2006; 2: 525-531.

[5] Tzeng CW and Aloia TA. Colorectal liver metastases. J Gastrointest Surg 2013; 17: 195-201; quiz p.201-2.

[6] Chiche L. Surgical management of hepatic metastases from colorectal cancer. J Chir (Paris) 2003; 140: 77-89.

[7] Maeda Y, Shinohara T, Nagatsu A, Futakawa N and Hamada T. Long-term outcomes of conversion hepatectomy for initially unresectable colorectal liver metastases. Ann Surg Oncol 2016; 23 Suppl 2: S242-248.

[8] Maughan TS, Adams RA, Smith CG, Meade AM, Seymour MT, Wilson RH, Idziaszczyk S, Harris R, Fisher D, Kenny SL, Kay E, Mitchell JK, Madi A, Jasani B, James MD, Bridgewater J, Kennedy MJ, Claes B, Lambrechts D, Kaplan R and Cheadle JP. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet 2011; 377: 2103-2114.

[9] Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, Giacchetti S, Paule B, Kunstlinger F, Ghémard O, Levi F and Bismuth H. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg 2004; 240: 644-657; discussion 657-648.

[10] Bolhuis K, Kos M, van Oijen MGH, Swijnenburg RJ and Punt CJA. Conversion strategies with chemotherapy plus targeted agents for colorectal cancer liver-only metastases: a systematic review. Eur J Cancer 2020; 141: 225-238.

[11] Morris EJ, Forman D, Thomas JD, Quirke P, Taylor EF, Fairley L, Cottier B and Poston G. Surgical management and outcomes of colorectal cancer liver metastases. Br J Surg 2010; 97: 1110-1118.

[12] Van Cutsem E, Köhne CH, Láng I, Folprecht G, Nowacki MP, Cascinu S, Shchepotin I, Maurel J, Cunningham D, Tejpar S, Schlichting M, Zubel A, Celik I, Rougier P and Ciardiello F. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol 2011; 29: 2011-2019.

[13] Venook AP, Niedzwiecki D, Lenz HJ, Innocenti F, Fruth B, Meyerhardt JA, Schrag D, Greene C, O'Neil BH, Atkins JN, Berry S, Polite BN, O'Reilly EM, Goldberg RM, Hochster HS, Schilsky RL, Bertagnolli MM, El-Khoueiry AB, Watson P, Benson AB 3rd, Mulkerin DL, Mayer RJ and Blanke C. Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in Patients With KRAS wild-type advanced or metastatic colorectal cancer: a randomized clinical trial. JAMA 2017; 317: 2392-2401.

[14] Tomasello G, Petrelli F, Ghidini M, Russo A, Passalacqua R and Barni S. FOLFOXIRI Plus Bevacizumab as conversion therapy for patients with initially unresectable metastatic colorectal cancer: a systematic review and pooled analysis. JAMA Oncol 2017; 3: e170278.
[15] Lordan JT, Karanjia ND, Quiney N, Fawcett WJ and Worthington TR. A 10-year study of outcome following hepatic resection for colorectal liver metastases - The effect of evaluation in a multidisciplinary team setting. Eur J Surg Oncol 2009; 35: 302-306.
[16] Yan L and Zhang W. Precision medicine becomes reality-tumor type-agnostic therapy. Cancer Commun (Lond) 2018; 38: 6.
[17] Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P and Jaeck D. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Française de Chirurgie. Cancer 1996; 77: 1254-1262.
[18] Fong Y, Fortner J, Sun RL, Brennan MF and Blumgart LH. 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.
[19] Sasaki K, Morioka D, Conci S, Margonis GA, Sawada Y, Ruzzenente A, Kumamoto T, Iacono C, Andreatos N, Guglielmi A, Endo I and Pawlik TM. The tumor burden score: a new "Metroticket" prognostic tool for colorectal liver metastases based on tumor size and number of tumors. Ann Surg 2018; 267: 132-141.
[20] Mühlberg A, Holch JW, Heinemann V, Huber T, Moltz J, Maurus S, Jäger N, Liu L, Froelich MF, Katzmann A, Gresser E, Taubmann O, Sühling M and Nörenberg D. The relevance of CT-based geometric and radiomics analysis of whole liver tumor burden to predict survival of patients with metastatic colorectal cancer. Eur Radiol 2021; 31: 834-846.
[21] Chen Y, Chang W, Ren L, Chen J, Tang W, Liu T, Jian M, Liu Y, Wei Y and Xu J. Comprehensive Evaluation of Relapse Risk (CERR) score for colorectal liver metastases: development and validation. Oncologist 2020; 25: e1031-e1041.
[22] Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC and Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92: 205-216.
[23] Grut H, Dueland S, Line PD and Revheim ME. The prognostic value of (18)F-FDG PET/CT prior to liver transplantation for nonresectable colorectal liver metastases. Eur J Nucl Med Mol Imaging 2018; 45: 218-225.
[24] Hsu CY, Huang YH, Hsia CY, Su CW, Lin HC, Loong CC, Chiou YY, Chiang JH, Lee PC, Huo TI and Lee SD. A new prognostic model for hepatocellular carcinoma based on total tumor volume: the Taipei Integrated Scoring System. J Hepatol 2010; 53: 108-117.
[25] Strijker M, Soer EC, de Pastena M, Creemers A, Balduzzi A, Beagan JJ, Busch OR, van Delden OM, Halfwerk H, van Hooft JE, van Lienden KP, Marchegiani G, Meijer SL, van Noesel CJ, Reinten RJ, Roos E, Schokker S, Verheij J, van de Vijver MJ, Waasdorp C, Wilmink JW, Ylstra B, Besselink MG, Bijlsma MF, Dijk F and van Laarhoven HW. Circulating tumor DNA quantity is related to tumor volume and both predict survival in metastatic pancreatic ductal adenocarcinoma. Int J Cancer 2020; 146: 1445-1456.
[26] Zhang JW, Cai Y, Xie XY, Hu HB, Ling JY, Wu ZH, Lan P, Wu XJ, Huang MJ, Wang H, Kang L, Zhou ZY, Wang JP and Deng YH. Nomogram for predicting pathological complete response and tumor downstaging in patients with locally advanced rectal cancer on the basis of a randomized clinical trial. Gastroenterol Rep (Oxf) 2020; 8: 234-241.
[27] van Stiphout RG, Lammering G, Buijsen J, Janssen MH, Gambacorta MA, Slagmolen P, Lambrecht M, Rubello D, Gava M, Giordano A, Postma EO, Haustermans K, Capirci C, Valentini V and Lambin P. Development and external validation of a predictive model for pathological complete response of rectal cancer patients including sequential PET-CT imaging. Radiother Oncol 2011; 98: 126-133.
[28] Yamashita S, Shindoh J, Mizuno T, Chun YS, Conrad C, Aloia TA and Vauthey JN. Hepatic atrophy following preoperative chemotherapy predicts hepatic insufficiency after resection of colorectal liver metastases. J Hepatol 2017; 67: 56-64.
[29] Modest DP, Heinemann V, Folprecht G, Denecke T, Pratschke J, Lang H, Bemelmans M, Becker T, Rentsch M, Seehofer D, Bruns CJ, Gebauer B, Held S, Stahler A, Heinrich K, von Einem JC, Stintzing S, Neumann UP and Ricard I. Factors that influence conversion to resectability and survival after resection of metastases in RAS WT metastatic colorectal cancer (mCRC): analysis of FIRE-3-AIOKRK0306. Ann Surg Oncol 2020; 27: 2389-2401.
[30] Correa-Gallego C, Gavane S, Grewal R, Cercek A, Klimstra DS, Gewirtz AN, Kingham TP, Fong Y, DeMatteo RP, Allen PJ, Jarnagin WR, Kemeny N and D'Angelica MI. Prospective evaluation of 18F-fluorodeoxyglucose positron emission to-

mography in patients receiving hepatic arterial and systemic chemotherapy for unresectable colorectal liver metastases. HPB (Oxford) 2015; 17: 644-650.
[31] Kemeny NE, Chou JF, Capanu M, Gewirtz AN, Cercek A, Kingham TP, Jarnagin WR, Fong YC, DeMatteo RP, Allen PJ, Shia J, Ang C, Vakiani E and D'Angelica MI. KRAS mutation influences recurrence patterns in patients undergoing hepatic resection of colorectal metastases. Cancer 2014; 120: 3965-3971.
[32] Margonis GA, Kim Y, Spolverato G, Ejaz A, Gupta R, Cosgrove D, Anders R, Karagkounis G, Choti MA and Pawlik TM. Association between specific mutations in KRAS codon 12 and colorectal liver metastasis. JAMA Surg 2015; 150: 722-729.
[33] Brudvik KW, Kopetz SE, Li L, Conrad C, Aloia TA and Vauthey JN. Meta-analysis of KRAS mutations and survival after resection of colorectal liver metastases. Br J Surg 2015; 102: 1175-1183.
[34] Margonis GA, Sasaki K, Gholami S, Kim Y, Andreatos N, Rezaee N, Deshwar A, Buettner S, Allen PJ, Kingham TP, Pawlik TM, He J, Cameron JL, Jarnagin WR, Wolfgang CL, D'Angelica MI and Weiss MJ. Genetic And Morphological Evaluation (GAME) score for patients with colorectal liver metastases. Br J Surg 2018; 105: 1210-1220.
[35] Tanaka K, Nakagawa K, Yabushita Y, Hiroshima Y, Matsuo K, Ota M, Ichikawa Y, Taguri M, Tanabe M, Koda K and Endo I. Reversal of attachment to or invasion of major intrahepatic vessels by colorectal liver metastases according to prehepatectomy chemotherapy regimen. Surgery 2014; 155: 936-944.
[36] Kawaguchi Y, Kopetz S, Newhook TE, De Bellis M, Chun YS, Tzeng CD, Aloia TA and Vauthey JN. Mutation status of RAS, TP53, and SMAD4 is superior to mutation status of RAS alone for predicting prognosis after resection of colorectal liver metastases. Clin Cancer Res 2019; 25: 5843-5851.
[37] Halama N, Michel S, Kloor M, Zoernig I, Benner A, Spille A, Pommerencke T, von Knebel DM, Folprecht G, Luber B, Feyen N, Martens UM, Beckhove P, Gnjatic S, Schirmacher P, Herpel E, Weitz J, Grabe N and Jaeger D. Localization and density of immune cells in the invasive margin of human colorectal cancer liver metastases are prognostic for response to chemotherapy. Cancer Res 2011; 71: 5670-5677.

Table S1. Baseline characteristics of the total patients in the internal cohort

Variables	Total (*n* = 215)
Median age (range) - years	55 (28-80)
Sex - no. (%)	
Male	156 (72.6)
Female	59 (27.4)
Primary tumor site - no. (%)	
Right colon	48 (22.3)
Left colon	105 (48.9)
Rectum	62 (28.8)
Tumor differentiation - no. (%)	
Well/moderate	175 (81.4)
Poor	40 (18.6)
T stage - no. (%)	
T1-3	112 (52.1)
T4	103 (47.9)
N stage - no. (%)	
N0	39 (18.1)
N1-2	176 (81.9)
Serum CEA - ng/mL (%)	
≤ 200	123 (57.2)
> 200	92 (42.8)
Serum CA19-9 - U/mL (%)	
≤ 200	114 (53.0)
> 200	101 (47.0)
KRAS status* - no. (%)	
Wild type	132 (74.6)
Mutation	45 (25.4)
Timing of CRLM - no. (%)	
Synchronous	198 (92.1)
Metachronous	17 (7.9)
Distribution of liver metastasis - no. (%)	
Unilobar	46 (21.4)
Bilobar	169 (78.6)
Median size of largest liver tumor (range) - cm	6 (1-21)
≤ 6	90 (41.9)
> 6	125 (58.1)
Median number of liver tumors (range) - no.	8 (1-100)
≤ 8	100 (46.5)
> 8	115 (53.5)
Median TLVR (range)	0.13 (0.01-0.64)
Invasion of hepatic vein - no. (%)	
No	71 (33.0)
Yes	144 (67.0)
Invasion of portal vein - no. (%)	
No	119 (55.3)
Yes	96 (44.7)
First-line chemotherapy	
FOLFOX	137 (63.7)

FOLFIRI	19 (8.8)
FOLFOXIRI	36 (16.7)
FUDR HAI	23 (10.7)
Targeted therapy	
No	59 (27.4)
Bevacizumab	60 (44.7)
Cetuximab	96 (27.9)
Outcome of conversion therapy - no. (%)	
Success	95 (44.2)
Failure	120 (55.8)

Abbreviations: CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CRLM, colorectal cancer liver metastasis; TLVR, tumor to liver volume ratio; FUDR HAI, 5-fluoro-2'-deoxyuridine hepatic artery infusion. Notes: *Data of 177 patients were available.

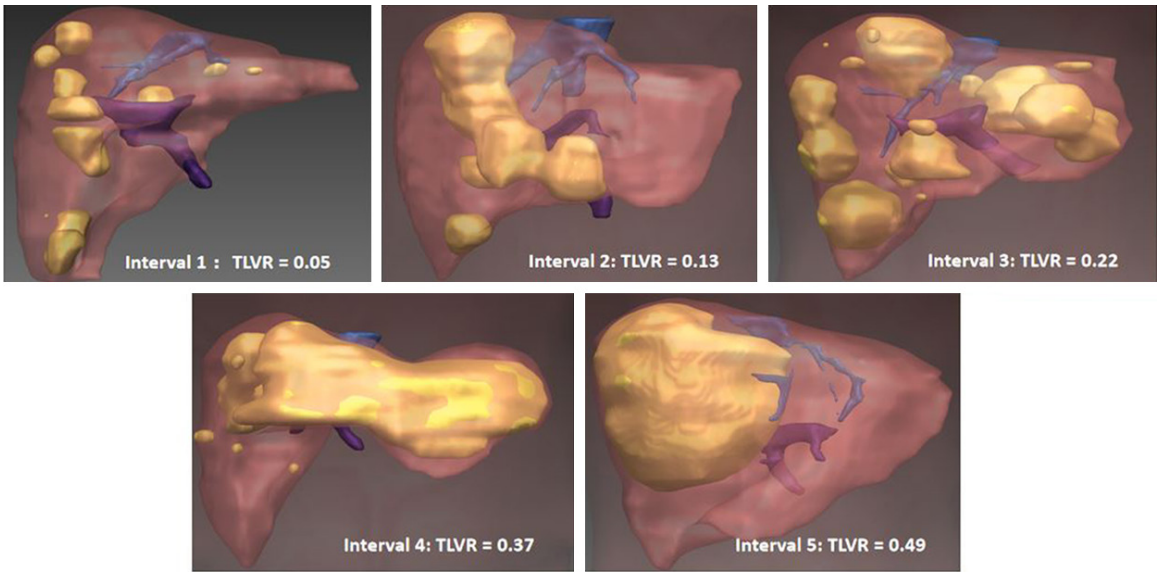

Figure S1. Typical liver and liver tumor images of three-dimensional (3D) reconstruction for the 5 tumor liver volume ratio (TLVR) intervals.

Table S2. Baseline characteristics of the total patients in the external cohort

Variables	Total (*n* = 40)
Median age (range) - years	63 (23-82)
Sex - no. (%)	
Male	35 (87.5)
Female	5 (12.5)
Primary tumor site - no. (%)	
Right colon	8 (20.0)
Left colon	11 (27.5)
Rectum	21 (52.5)
Tumor differentiation - no. (%)	
Well/moderate	36 (90.0)
Poor	4 (10.0)
Timing of CRLM - no. (%)	
Synchronous	35 (87.5)
Metachronous	5 (12.5)
Distribution of liver metastasis - no. (%)	
Unilobar	16 (40.0)
Bilobar	24 (60.0)
Size of largest liver tumor - no. (%)	
≤ 6 cm	25 (62.5)
> 6 cm	15 (37.5)
Number of liver tumors - no. (%)	
≤ 8	34 (85.0)
> 8	6 (15.0)
TLVR - no. (%)	
< 23%	35 (87.5)
≥ 23%	5 (12.5)
Invasion of hepatic vein - no. (%)	
No	23 (57.5)
Yes	17 (42.5)
Invasion of portal vein - no. (%)	
No	31 (77.5)
Yes	9 (22.5)
First-line chemotherapy	
FOLFOX	30 (75.5)
FOLFIRI	4 (10.0)
FOLFOXIRI	6 (15.0)
Targeted therapy	
No	11 (27.5)
Bevacizumab	15 (37.5)
Cetuximab	14 (35.0)
Result of conversion therapy - no. (%)	
Success	26 (65.0)
Failure	14 (35.0)

Abbreviations: CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CRLM, colorectal cancer liver metastasis; TLVR, tumor to liver volume ratio.

Table S3. Univariate and multivariate analyses of prognostic factors for overall survival in patients in the internal cohort

Variables	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, years				
≤ 60	reference			
> 60	1.058 (0.663-1.690)	0.813		
Sex				
Male	reference			
Female	0.673 (0.415-1.090)	0.107		
Primary tumor site				
Colon	reference			
Rectum	0.843 (0.510-1.392)	0.504		
T stage				
T1-3	reference			
T4	1.141 (0.723-1.800)	0.572		
N stage				
N0	reference		reference	
N1-2	2.196 (1.094-4.408)	0.027	1.110 (0.513-2.401)	0.791
Serum CEA, ng/mL				
≤ 200	reference			
> 200	1.202 (0.769-1.880)	0.419		
Serum CA19-9, U/mL				
≤ 200	reference			
> 200	1.451 (0.930-2.265)	0.101		
KRAS status*				
Wild type	reference		reference	
Mutant	1.736 (1.072-3.038)	0.048	1.895 (1.060-3.387)	0.031
Timing of CRLM				
Synchronous	reference			
Metachronous	1.900 (0.694-5.202)	0.211		
Distribution of liver metastasis				
Unilobar	reference			
Bilobar	1.691 (0.913-3.131)	0.095		
Size of largest liver tumor, cm				
≤ 6	reference			
> 6	1.023 (0.652-1.603)	0.923		
Invasion of hepatic vein				
No	reference			
Yes	1.014 (0.635-1.618)	0.955		
Invasion of portal vein				
No	reference			
Yes	1.263 (0.808-1.974)	0.305		
C-NED score				
0	reference		reference	
1	1.570 (0.901-2.735)	0.111	1.537 (0.809-2.921)	0.189
2-3	2.481 (1.363-4.518)	0.003	2.867 (1.092-5.564)	0.002

Abbreviations: CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CRLM, colorectal cancer liver metastasis.
Notes: *Data of 177 patients were available.