Nomogram predicted disease free survival for colorectal liver metastasis patients with preoperative chemotherapy followed by hepatic resection

Wei Liu [a, 1], Kun Wang [a, 1], Yu Han [b], Jie-Ying Liang [c], Yu-Hong Li [c, **], Bao-Cai Xing [a, *]

[a] Key Laboratory of Carcinogenesis and Translational Research, Ministry of Education, Peking University School of Oncology, Beijing Cancer Hospital and Institute, Hepatopancreatobiliary Surgery Department I, Beijing, PR China
[b] Harbin Medical University Cancer Hospital, Department of Internal Medicine of Digestive Tumor, Harbin, Heilongjiang Province, PR China
[c] Sun Yat-sen University Oncology Hospital, Department of Internal Medicine of Digestive Tumor, Guangzhou, Guangdong Province, PR China

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ABSTRACT

Background: Hepatic resection is regarded to as a potentially curative option for colorectal cancer liver metastases (CRLM), but it is associated with a high rate of recurrence. The present study intended to establish an effective nomogram to predict disease free survival (DFS) and select candidates of hepatic resection.

Methods: The nomogram was based on a retrospective study on 447 CRLM patients treated with preoperative chemotherapy followed by hepatic resection using a multicentric database between January 1st, 2010 and December 31st, 2017. Results were validated using bootstrap resampling on 117 patients. The predictive accuracy and discriminative ability of the nomogram were determined by concordance index (C-index) and calibration curve. Overall survival, disease free survival, and local recurrence rate for patients with colorectal cancer were measured.

Results: Based on multivariate analysis of the primary cohort, independent factors for DFS included tumor size larger than 5 cm, multiple liver metastases(>1), *RAS* mutation, primary lymph node metastasis and tumor size increase after preoperative chemotherapy. These five factors were all considered in the nomogram. The C-index of the nomogram for predicting survival was 0.675. With external validation, the C-index of the nomogram for the prediction of the DFS was 0.77, which demonstrated that this model has a good level of discriminative ability. For the 382 patients (66.7%) who developed recurrence, the optimal cutoff point for early recurrence was determined to be 12 months after hepatic resection.

Conclusions: The proposed nomogram demonstrated accurate prognostic prediction of DFS for CRLM patients with preoperative chemotherapy followed by hepatic resection.

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Introduction

Colorectal cancer is currently the third most common malignancy worldwide in terms of incidence and is fourth for cancer mortality [1]. Approximately 50% of patients with primary colorectal cancer will develop liver metastasis during their disease course [2]. Upfront hepatic resection is the gold standard for curative-intent treatment, associated with a 5-year survival in 50—60% of patients.

Preoperative chemotherapy may allow unresectable colorectal cancer liver metastases (CRLM) to hepatic resection and improve long-term survival. Neoadjvuant chemotherapy is also advocated to resectable CRLM with high risk factors, while there was no survival advantage in patients with low risk profile [3]. After hepatic resection, recurrence remains a major problem as it can occur in 50%—75% of patients, especially when early recurrence is associated with worsened overall survival(OS) [4,5]. However, the definition of

* Corresponding author. Peking University School of Oncology, Beijing Cancer Hospital, Hepatopancreatobiliary Surgery Department I, No. 52, Fu-Cheng-Lu Street, Beijing, 100142, PR China.
** Corresponding author. Sun Yat-sen University Oncology Hospital, Internal Medicine of Digestive Tumor, Sun Yat-Sen University Cancer Center, 651 Dong Feng East Road, Guangzhou, 510060, PR China.
E-mail addresses: liyh@sysucc.org.cn (Y.-H. Li), xingbaocai88@sina.com (B.-C. Xing).
1 These two authors contributed equally.

early recurrence and risk prognostic factors is still ambiguous for the patients. To benefit from hepatic resection, appropriate selection of adequate surgical candidates is vital. While the criteria for selection is undergoing continuously modified and expanded [6]. There is growing recognition that careful selection of surgical interventions in patients to identify those whom the benefit will likely outweigh the risk [7].

The construction and performance characteristics of a nomogram can be applied to predict dieases free survival (DFS) and select candidates for hepatic resection in CRLM patients with preoperative chemotherapy. The proposed nomogram in present study intends to provide individualized predictions to clinicians and patients in the treatment decision making process.

Patients and methods

Study population

All patients received preoperative chemotherapy. After reevaluation, patients underwent hepatic resection if it was defined to be resectable CRLM. If not, the patient continued to receive chemotherapy. The diagnoses of CRLM were all confirmed by histopathology. Standard patient demographic, clinicopathological characteristics, response evaluation and operation related factors were collected. The inclusion criteria were as follow: 1) the patient received preoperative chemotherapy; 2) it was considered to be resectable CRLM at final line of preoperative chemotherapy before hepatic resection by multidisciplinary team(MDT); 3) preserved liver function (Indocyanine green, ICG<10%); 4) all patients underwent hepatic resection with/without intraoperative radiofrequency ablation(RFA) aimed at achieving R0; 5) no other simultaneous malignancies. Patients who underwent only ablation or palliative hepatic resection (R2) were excluded.

According to the criteria, the present retrospective observational study enrolled 447 CRLM patients who underwent hepatic resection with preopoperative chemotherapy between January 2010 and December 2017 at the Hepatopancreatobiliary Surgery Department I of Peking University Cancer Hospital, 90 CRLM patients between January 2013 and November 2017 at Sun Yet-sen University Oncology Hospital, and 27 between January 2013 and December 2017 at Harbin Medical University Cancer Hospital (Supplementary Fig. 1). Patients from the Peking University Cancer Hosptical formed the primary cohort (n = 447), and the remaining 117 patients from another two centers formed the validation cohort.

Preoperative chemotherapy and surgical treatment

The unresectable CRLM patients and resectable CRLM patients with high risk factor of recurrence (Clinical Risk Score, CRS>2), who received preoperative chemotherapy. The response to chemotherapy was classified according to the World Health Organization criteria, which agree with the Response Evaluation Criteria in Solid Tumors (RECIST) [8]. In the present study, the tumor diameter increment after first line preoperative chemotherapy was included in patients with progressive disease (PD) and stable disease (SD) but increment is less than 30% of the diameter of the target lesion. Treatment response was evaluated to assess the possibility for through surgery in a discussion of MDT. If the disease was not controlled with chemotherapy, a new regimen of second line chemotherapy was given. Treatment response was also reevaluated to assess the possibility for through surgery in a MDT. Any resections of three or more segments was considered a major hepatic resection [9]. Normal liver parenchyma remnant volume was more than 30%. For patients with chemotherapy liver injuries,

more than 40% of the remnant volume should be preserved [10].

Statistical analysis

Continuous variables were summarized as a mean, and categorical variables were summarized as frequency and percentage. Univariate and multivariate analyses of various clinicopathological factors by Cox's proportional hazard model were used to identify independent risk factors for disease free survival. A nomogram was created based on the results of the multivariable analysis. The predictive performance of the nomogram was assessed by evaluating the degree of discrimination with the C-index, plotting Kaplan-Meier curves over the quartiles of the nomogram-predicted score and examining calibration plots with bootstrapped samples. Finally, we performed external validation, in which the nomogram was used to assess each patient in the validation cohort. Statistical analysis was performed using SPSS 19.0 (SPSS, Inc., Chicago, IL, USA) and R version 3·1.1 (http://www.r-project.org).

Results

Clinicopathologic characteristics

In the present study, 564 patients met the inclusion criteria and entered into this study, included in 447 patients of the primary cohort and 117 patients of validation cohort, respectively. The clinicopathologic characteristics of patients were listed in Table 1. There was no patient died in perioperative period and the mortality was 0%.

Tumor recurrence and OS in the primary cohort

The postoperative 1-, 3-, and 5-year disease free survival rates were 42.6%, 27.1% and 23.2%, respectively. The 1-, 3-, and 5-year OS rates were 92.1%, 55.8% and 41.4%, respectively (Supplementary Fig. 2).

Definition of early recurrence

Among the 564 patients, recurrence was observed in 382 (66.7%) during the median follow-up period of 44 months (range, 1−147 months). In patients who had recurrence, the optimal cut-off point to define early recurrence was determined to be 12 months after hepatic resection, based on the results of the minimum p value approach for survival after initial recurrence ($p = 7.8 \times 10^{-9}$) (Supplementary Fig. 3). We defined early recurrence as those that occurred within 12 months after surgery. Among the recurrence patients, early recurrence was observed in 307 (80.4%). OS in patients with early recurrence was significantly worse than those with late recurrence ($p < 0.001$) (Supplementary Fig. 4). For the 87 patients with early recurrence, local treatment was performed included in repeat surgery and RFA. OS in those patients who underwent local treatment was significantly better than in those who did not. OS at 3 and 5-year were 61.8% and 32.1%, and 17.8% and 7.9%, respectively ($p < 0.001$) (Supplementary Fig. 5).

Prognostic factors for DFS in primary cohort

In the univariable analysis, including primary N+, synchronous metastases, tumor number>1, size>5 cm at hepatic resection, serum CA19-9>100 levels at hepatic resection, *RAS* mutation, tumor diameter increased after preoperative chemotherapy at first line, major hepatic resection and R1 resection were related to a decreased DFS ($p < 0·05$). Five independent prognostic factors for DFS were identified in multivariable analysis: node-positive

Table 1
Demographic and clinical characteristics of study patients.

Variable	All patients	Primary cohort	Validation cohort
Patients demographics	**n = 564(%)**	**n = 447(%)**	**n = 117(%)**
Age(years)	55.5 ± 10.4	55.8 ± 10.2	54.4 ± 11.1
Sex ration(M:F)	384:180	305:142	79:38
Primary T category			
T1-2	51(3.0%)	46(10.3%)	5(4.3%)
T3-4	513(97%)	401(89.7%)	112(95.7%)
Primary N category			
N0	167(23.6%)	125(28.0%)	42(35.9%)
N1-2	397(76.4%)	322(72.0%)	75(64.1%)
Primary tumor location			
Colon	346(51.3%)	255(57.0%)	91(77.8%)
Rectum	218(48.7%)	192(43.0%)	26(22.2%)
Right	79(14.0%)	66(14.8%)	13(11.1%)
Left	485(86.0%)	381(85.2%)	104(88.9%)
Timing of liver metastasis			
Synchronous	504(83.4%)	397(88.8%)	107(91.5%)
Metachronous	60(16.6%)	50(11.2%)	10(8.5%)
Metastasis no.	3(1–36)	3(1–30)	3(1–36)
Metastasis size(mm)	31.2 ± 19.8(3–110)	30.7 ± 19.1(3–110)	33.1 ± 22.5(3–110)
Localization of liver metastases			
Unilobar	231(46.4%)	197(44.1%)	34(23.1%)
Bilobar	333(53.6%)	250(55.9%)	83(76.9%)
CEA level(ng/ml)	45.41 ± 13.28 (0.56–1607)	42.61 ± 126.74 (0.6–1607)	56.33 ± 56.35 (0.56–1430)
CA199 leverl(IU/ml)	276.8 ± 83.8 (0–20000)	271.9 ± 104.6 (0.1–1590)	295.4 ± 212.1 (0.6–20000)
Pre-treatment			
Conversion	160(23.4%)	111(24.8%)	49(41.9%)
Neoadjuvant	404(76.6%)	336(75.2%)	68(58.1%)
Ras mutation			
Wild	337(53.8%)	263(58.8%)	74(63.2%)
Mutation	227(46.2%)	184(41.2%)	43(36.8%)
Extrahepatic metastases	106(18.8%)	71(15.9%)	35(23.9%)
Cycles of chemotherapy	4(2–22)	4(2–22)	5(2–14)
No. of lines			
First line	457(81.0%)	368(82.3%)	89(76.1%)
Other	107(19.0%)	79(17.7%)	28(23.9%)
Regimen			
XELOX	185(32.8%)	149(33.3%)	36(30.8%)
FOLFOX	141(25.0%)	112(25.1%)	29(24.8%)
FOLFIRI	158(28.0%)	126(28.2%)	32(27.4%)
Other	80(14.2%)	60(13.4%)	20(17.1%)
Use of biological agents	278(43.3%)	227(50.8%)	51(43.6%)
Bevacizumab	155(27.5%)	124(27.7%)	31(26.5%)
Cetuximab	123(21.8%)	103(23.0%)	20(17.1%)
Response to first-line chemotherapy			
Complete	4(0.7%)	4(0.9%)	0(%)
Partial	264(46.8%)	195(43.6%)	69(59.0%)
Stable disease	246(43.6%)	204(45.7%)	42(35.9%)
Progressive disease	50(8.9%)	44 (9.8%)	6(5.1%)
Response to first-line chemotherapy			
Tumor diameter reduction	475(84.2%)	372(83.2%)	103(88.0%)
Tumor diameter increment	89(15.8%)	75(16.8%)	14(12.0%)
Surgery details			
Operation time(min)	226.3 ± 89.7	215 ± 112.0	252.3 ± 105.2
Blood lose(ml)	188 ± 112.0	182.0 ± 120.0	196 ± 130.0
Concomitant ablation therapy	66(11.7%)	50(11.2%)	16(13.7%)
RBC transfusion	69(12.2%)	57(12.8%)	12(10.3%)
Hepatic resection			
Major resection	228(40.4%)	202(45.2%)	26(22.2%)
Minor resection	336(59.6%)	245(54.8%)	91(77.8%)
Margine status			
Positive	112(19.9%)	102(22.8%)	10(8.5%)
Negative	452(80.1%)	345(77.2%)	107(91.5%)
Complication			
Major(Clavien grade≥3)	45(0.2%)	33(7.4%)	12(10.3%)

primary (HR = 1.341, 95%CI: 1.033–1.788; p = 0.038), tumor size at hepatic resection larger than 5 cm (HR = 1.517, 95%CI: 1.062–2.168; p = 0.022), tumor diameter increased during first-line chemotherapy (HR = 1.415, 95%CI: 1.033–1.939; p = 0.030), *RAS* mutation (HR = 1.316, 95%CI: 1.030–1.682; p = 0.028) and multiple liver metastases (HR = 1.485, 95%CI: 1.034–2.133; p = 0.032) (Table 2).

Creation of a prognostic nomogram and external validation for DFS

Applying the five independent prognostic factors, we developed a point based prognostic nomogram to predict DFS after hepatic resection (Fig. 1). Based on the multivariable Cox model, each factor was assigned a specific score as follows: tumor number>1, 10 points; tumor size at hepatic resection larger than 5 cm, 8 points;

Table 2
Univariable and multivariable analysis of factors associated with DFS of Primary Cohort.

	Univariable analysis			Multivariable analysis		
	HR	95%	P value	HR	95%	P value
Age						
>70	Ref			Ref		
≤70	0.757	0.584–1.479	0.757	0.897	0.413–1.951	0.785
Sex						
Male	Ref			Ref		
Female	0.957	0.750–1.121	0.722	0.847	0.537–1.334	0.473
Primary T stage						
1-2	Ref			Ref		
3-4	1.318	0.875–1.987	0.187	1.274	0.831–1.951	0.266
Primary N stage						
N0	Ref			Ref		
N1-2	1.501	1.099–2.255	0.006	1.341	1.033–1.788	0.038
Location tumor						
Colon	Ref			Ref		
Rectum	1.214	0.835–1.765	0.310	1.279	0.827–1.976	0.268
Primary tumor location						
Left	Ref			Ref		
Right	1.101	0.799–1.518	0.555	0.925	0.662–1.293	0.648
Disease free interval						
>12 month	Ref			Ref		
≤12 month	1.682	1.116–2.535	0.013	1.356	0.877–2.098	0.171
CEA						
>200	Ref			Ref		
≤200	1.479	0.928–2.358	0.100	1.002	0.576–1.745	0.994
CA199						
>100	Ref			Ref		
≤100	1.511	1.093–2.090	0.013	1.376	0.949–1.994	0.093
Tumor size						
≤5 cm	Ref			Ref		
>5 cm	2.425	1.622–3.628	0.000	1.517	1.062–2.168	0.022
Tumor no						
≤1	Ref			Ref		
>1	1.770	1.329–2.358	0.000	1.485	1.034–2.133	0.032
Extrahepatic disease						
No	Ref			Ref		
Yes	1.411	0.936–1.691	0.128	1.267	0.932–1.721	0.131
Ras type						
Wild	Ref			Ref		
Mutation	1.342	1.065–1.692	0.013	1.316	1.030–1.682	0.028
Hepatic resection						
Minor	Ref			Ref		
Major	1.377	1.096–1.732	0.006	1.473	0.920–2.357	0.107
Ablation						
No	Ref			Ref		
Yes	1.237	0.840–1.820	0.281	1.078	0.708–1.642	0.727
Margin status						
R0	Ref			Ref		
R1	0.738	0.565–0.962	0.025	0.865	0.652–1.147	0.313
Pre-treatment						
Conversion	Ref			Ref		
Neoadjuvant	1.211	0.934–1.570	0.149	0.849	0.617–1.167	0.849
Response in diameter						
Decrease	Ref			Ref		
Increase	1.399	1.044–1.876	0.025	1.415	1.033–1.939	0.030
Regimen						
XELOX	Ref					
FOLFOX	1.702	0.731–2.524	0.355	0.961	0.584–1.585	0.591
FOLFIRI	1.224	0.664–2.286	0.651	0.874	0.572–1.327	0.286
Other	1.583	0.829–1.705	0.389	1.306	0.813–2.084	0.184
Red blood transfusion						
No	Ref			Ref		
Yes	1.103	0.790–1.540	0.564	1.009	0.703–1.449	0.961
Target therapy						
No	Ref			Ref		
Yes	0.859	0.678–1.731	0.277	1.236	0.951–1.606	0.114
Bevacizumab	Ref			Ref		
Cetuximab	0.744	0.483–1.221	0.478	0.884	0.692–1.293	0.447
Chemotherapy line						
≤1	Ref			Ref		
>1	0.939	0.603–1.463	0.781	1.428	0.742–3.129	0.165
Cycle						
>4	Ref			Ref		

Table 2 (*continued*)

	Univariable analysis			Multivariable analysis		
	HR	95%	P value	HR	95%	P value
≤4	0.991	0.733–1.635	0.347	1.084	0.829–1.417	0.555
Distribution						
Unilobar	Ref			Ref		
Bilobar	0.844	0.694–1.911	0.668	1.239	0.932–1.646	0.140
Complication						
Minor	Ref			Ref		
Major	0.446	0.708–1.241	0.781	1.185	0.762–1.845	0.451

node-positive primary, 6 points; tumor size increased during first-line chemotherapy, 5 points; *RAS* mutation, 5 points (Supplementary Table 1). The sum of the scores for each variable was plotted on the total points axis (left side), and the estimated probabilities of DFS at 1, 3 and 5 years were obtained by drawing a line horizontally from the plotted total points axis straight to the survival axis (right side). The total scores ranged from 0 to 34, and the C-statistic for DFS prediction was 0.675. A calibration plot for the probability of survival at 1, 3 and 5 years (Fig. 2) demonstrated good calibration between the prediction by the nomogram and the actual observation. The nomogram was externally validated by the calibration plot in Fig. 3, and by computing the bootstrap C-index in an independent validation cohort of 117 patients. The C-index of the nomogram for the prediction of the DFS was 0.77 in the external validation step, which demonstrated that it is a model with a good level of discriminative ability. The calibration curve suggests that the nomogram was well calibrated; the 1-, 3- and 5-year DFS showed an optimal agreement between the actual observation and the nomogram prediction (Fig. 3).

The survival curves stratified by quartiles of the nomogram-predicted score are shown in Supplementary Fig. 6. Patients with the lowest predicted DFS (quartile 3, total score above 24) exhibited substantially worse survival (median DFS: 3 months, 3-year DFS rate 0%) than those in quartile 1 (total score 0–10; median DFS: 17 months, 3-year DFS rate 40.0%) and quartile 2 (score 11–23; median DFS: 8 months, 3-year DFS rate 28.3%).

Discussion

Based on present study, we developed a prognostic nomogram model to predict DFS for CRLM with preoperative chemotherapy followed by hepatic resection. Externally validation also exhibited a good level of discriminative ability. Five variables were identified as independent prognostic factors by the Multivariable Cox regression analysis and were incorporated into a nomogram model. Each factor plays a different weight in the course of CRLM development, which should be quantified and specified when the treatment decision was made in personalized cancer therapy. Surgical candidate would be carefully selected in order to identify who maximum benefit from hepatic resection for CRLM patients with preoperative chemotherapy.

Many prognostic models now rely on clinicopathological factors and tumor-specific molecular markers. Combining multiple factors within a single scoring system would better aid clinical decision-making. It has been previously proposed tumor morphologic factors, including tumor size and multiple lesions, as important predictors of prognosis for CRLM. Large tumor sizes may increase difficult extent of surgery, leading to a R1 resection. It may also represent an unfavorable tumor biology of micro-intrahepatic metastases [11]. Patients with single lesion have excellent outcomes (up to 50% overall survival at 5 years) and their benefit from surgery is undeniable [12,13]. In the present study, the multiple lesions was identified as the strongest prognostic factor which was
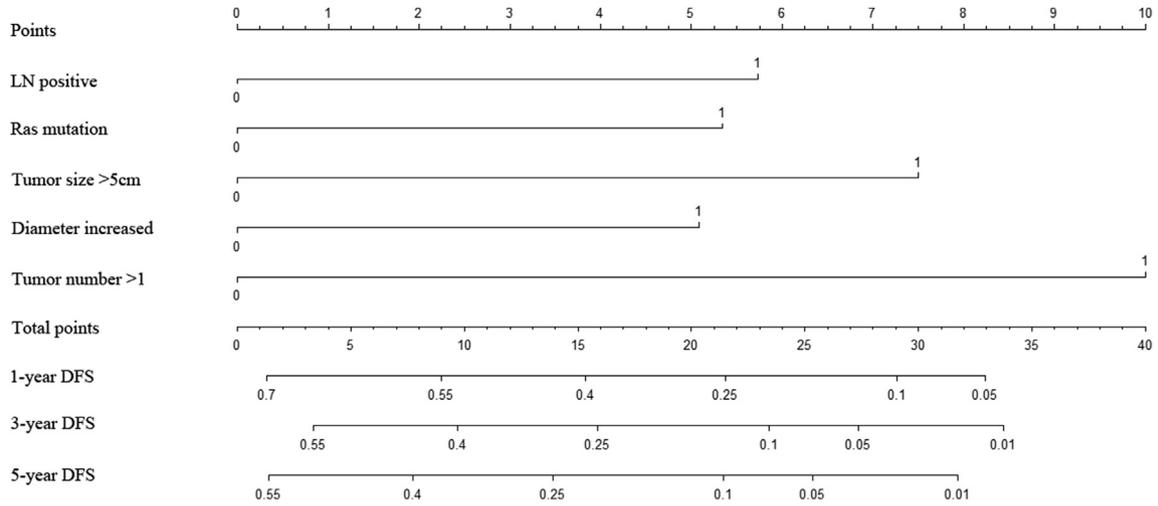
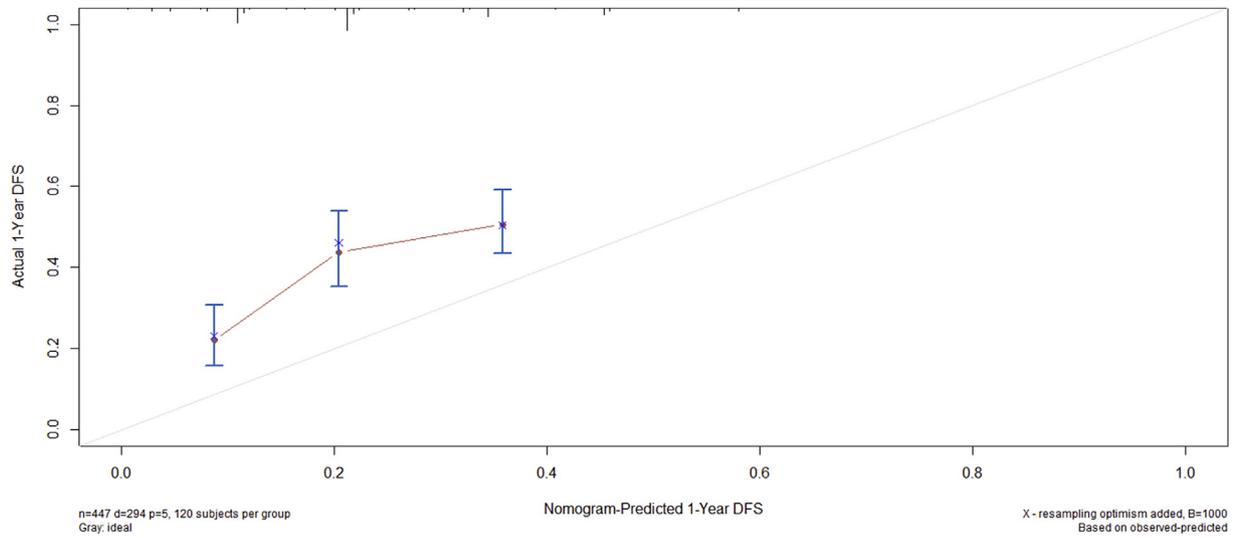**Fig. 1.** Colorectal liver metastasis Nomogram for DFS.

Fig. 2a. The calibration curve for predicting patients DFS at 1-year of primary cohort.
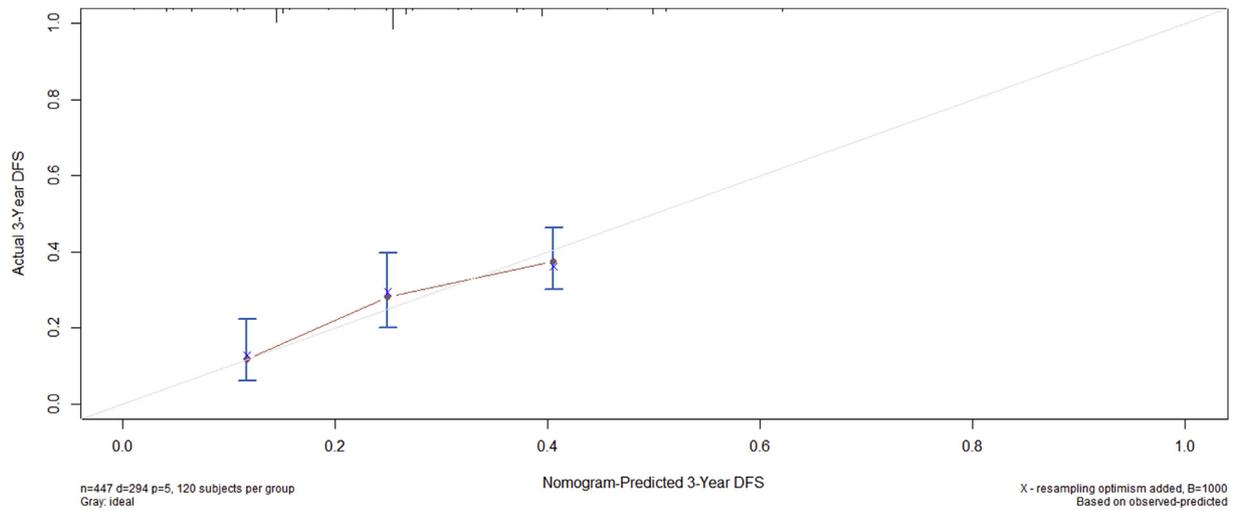

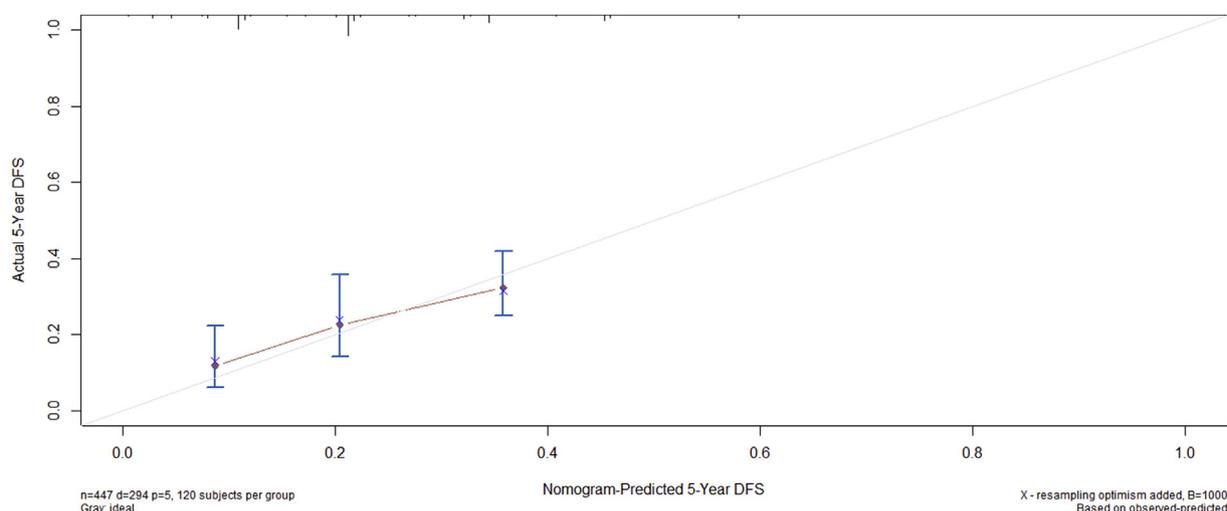**Fig. 2b.** The calibration curve for predicting patients DFS at 3-year of primary cohort.

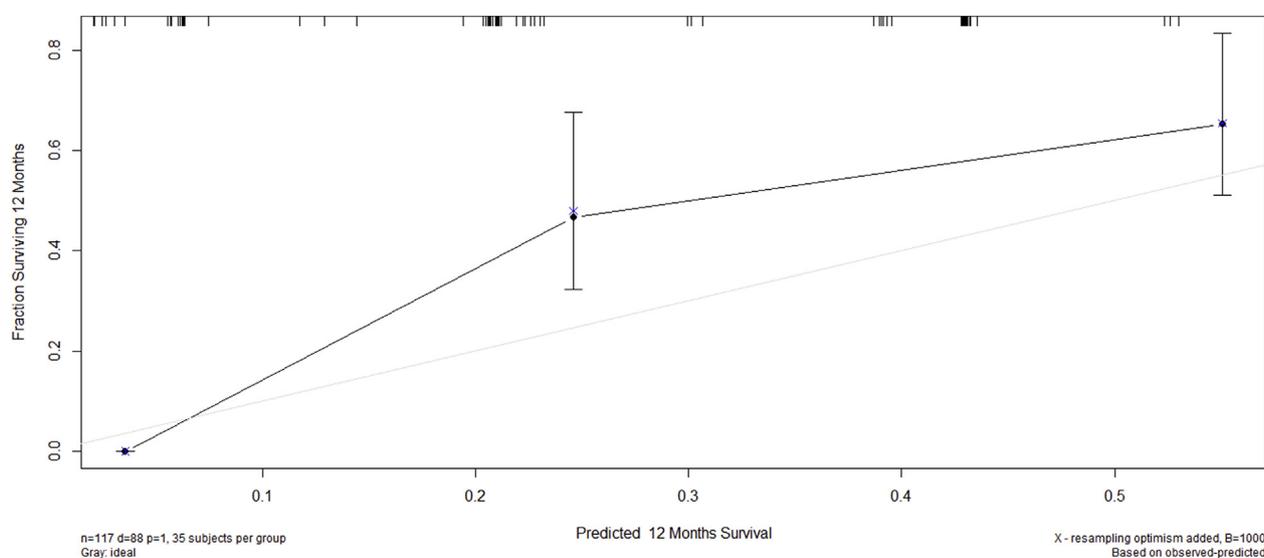**Fig. 2c.** The calibration curve for predicting patients DFS at 5-year of primary cohort.

Fig. 3a. The calibration curve for predicting patients DFS at 1-year of validation cohort.

consistent with previous studies. Most importantly, genomic analyses will be critical for personalized pharmacotherapy. *RAS* status is incorporated in the present nomogram at a time the importance of tumor biology is increasingly being recognized. Although large single-institution studies have questioned the validity and clinical usefulness of genetic markers [14,15], the prognostic impact of *KRAS* remains the most commonly used owing to its wide availability and robust association with outcomes. At meanwhile, next-generation sequencing (NGS) are getting increasing attention in CRLM care, which precisely monitored the disease burden and predicted therapeutic outcome for patients with mCRC [16]. Although it is not commonly employed for clinical purposes in present days, NGS contains more additional information for disease stratification, resistance detection, and therapy seleection, as well as prediction of drug response. The integration of all these data is required to truly individualize patient therapy [17]. It is hypothesised that incorporation of this information into existing clinico-pathological scoring systems would increase their discriminatory power. Tumor regression grade (TRG) has previously been reported to predict clinical outcome in patients with chemotherapypretreated CRLM [18]. It could be a surrogate marker of tumor biology. These factors could be integrated into a prognostic model to predict survival outcome of CRLM in the future.

Up to now, the nomogram might be one of the most valuable tool for precision medicine. While several previously reported nomograms focused on the prediction of overall survival. The current study created a nomogram to predict DFS instead of OS, due to which might be influenced by postoperative chemotherapy and treatment patterns of recurrent tumors. The previous nomograms were considered too be complicated for use in daily practices as their total points ranged from zero to the hundreds [11,19,20]. Multi-agent systemic chemotherapy offers a median survival of over 25 months [21]. In this setting, for patients with high nomogram score who may would be better served with systemic chemotherapy rather than hepatic resection. Furthermore, internal calibration showed good predictive ability. Therefore, the authors believe that the proposed nomogram is simple and useful for determining the individual likelihood of DFS in CRLM patients with preoperative chemotherapy followed by hepatic resection. The CRLM patients nomogram >23 should be treated with caution, and
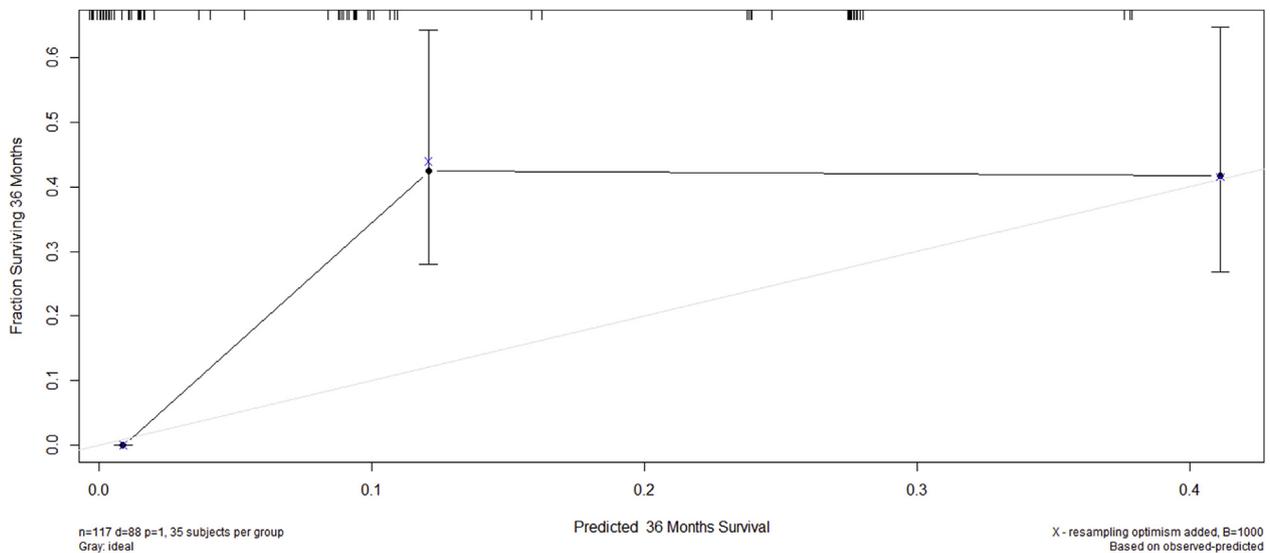
Fig. 3b. The calibration curve for predicting patients DFS at 3-year of validation cohort.
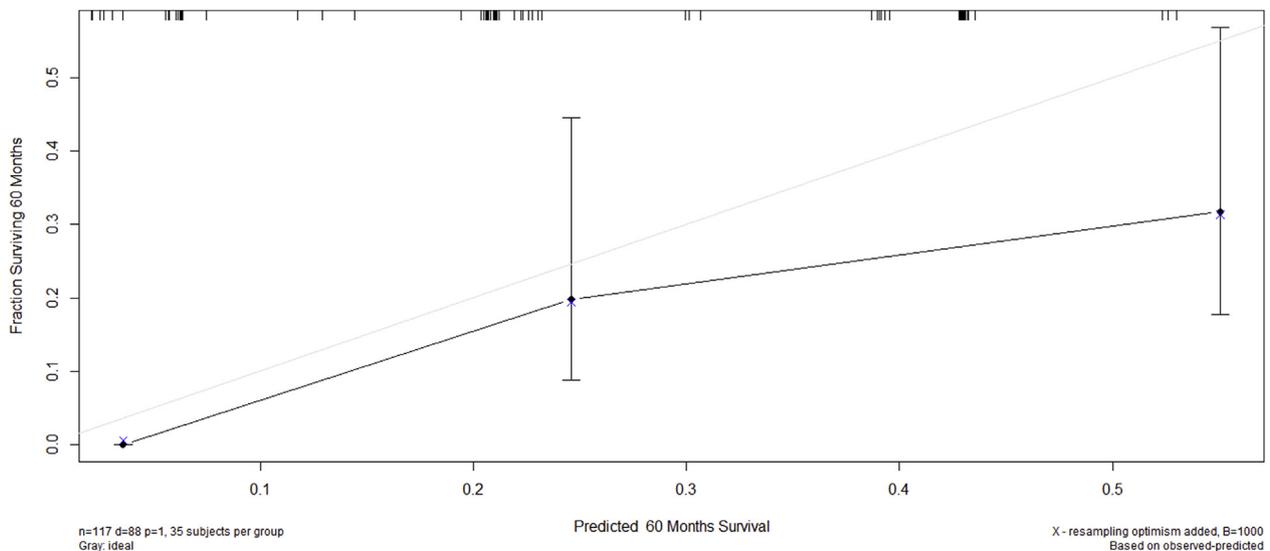

Fig. 3c. The calibration curve for predicting patients DFS at 5-year of validation cohort.

even exluded from liver resection.

In the present study, 5-year OS rate was 14.7% in the early recurrence patients. It was assumed that intensive preoperative chemotherapy should be advocated for patients with potential early recurrence by nomogram. While the purpose of treatment for non-early recurrence patients should be radical resection instead of no evidence of disease. Therefore, predicting early recurrence before surgery could remind surgeons to develop personalized cancer therapy. Repeat surgery for recurrence after hepatic resection has been shown to carry a survival benefit, even in patients with early recurrence [22–25]. Many previous studies have reported that repeat heaptic resection for recurrence provides favorable long-term outcomes and have been identified as a prognostic factor [26,27]. Similarly, in the present study, local treatment including repeat surgery and RFA could be performed in approximately 1/3 of the patients with recurrence and their 5-year OS reached 32.1%, which was significantly better than that of those who did not undergo repeat surgery.

Conclusion

This nomogram included only five preoperatvie clinicopathological variables. It can be used to accurately provide useful information to both surgeons and patients, which could identity the real tumor behaviors and select patients who would benefit from operation. Furthermore, the validation study has confirmed that this model has a good level of discriminative ability. Therefore, this nomogram could be applied for any CRC center worldwide.

Limitations

The nomogram has certain limitations. Firstly, it is a retrospective study with lack of rigid selection criteria. Secondly, we developed the nomogram in a population of CRLM patients treated with preoperative chemotherapy followed by hepatic resection. Bias could exist from the more complicated nature of the patients enrolled. Thirdly, the nomogram is not fully accurate because the

prediction calculation was based on the statistical significance within the collected factors. It is possible that other unknown factors exist that will affect the outcome. Finally, all data were collected from a limited number of institutions.

Ethics approval and consent to participate

The present study is a retrospective study and all subjects have given their written informed consent. The investigation project has been examined and certified by Ethics Committee of Beijing Cancer Hospital on June 1, 2018. The study was performed in accordance with the Declaration of Helsinki.

Consent for publication

The manuscript does not contain any individual person's data.

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Financial disclosure

There is no conflicts of interest. No drug or products were involved.

Statement

The manuscript has not been a podium or poster meeting.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.06.033.

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