Recurrent Colorectal Liver Metastasis Patients Would Benefit to Repeat Hepatic Resection

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Abstract

Background

Local treatment remains the best option for recurrent colorectal liver metastasis. The current study aims to investigate predictive factors of survival outcomes and select candidates of local treatment for CRLM at first recurrence.

Methods

Data were collected retrospectively on CRLM patients who underwent hepatic resection and developed first recurrence between 2000 and 2019 at our institution. A nomogram to predict overall survival was established based on a multivariable Cox model of clinicopathologic factors. The predictive accuracy and discriminative ability of the nomogram were determined by concordance index and calibration curve.

Results

Among 867 patients who underwent curative hepatic resection, 549 patients developed recurrence. Three hundred patients were evaluated to be resectable and liver-limited disease. Among of them, repeat liver resection and percutaneous radiofrequency ablation were performed in 88 and 85 patients, respectively. The other 127 patients only received systemic chemotherapy. Multivariable analysis identified node-positive primary, tumor size > 3 cm, early recurrence, RAS gene mutation and no local treatment were independent risk factors for survival outcome. Integrating these five variables, the nomogram showed good concordance statistics of 0.707. Compared with patients who only received systemic chemotherapy, radical local treatment did not improve survival outcome significantly (median OS: 21 vs. 15 months, p = 0.126) in high risk group (total score above 13).

Conclusion

Radical local treatment is crucial to prolong the survival of recurrent CRLM patients. The proposed model facilitates personalized assessment of prognosis for patients who developed first recurrence in liver.

Key Summary

More than half of CRLM patients developed recurrence after hepatic resection. The feasible and safety of repeat local treatment have been testified. The present study created a nomogram to select recurrent CRLM patient who would benefit from repeat local treatment. It helps to design a precision medicine schedule for recurrent CRLM.

Background

The liver is the most common site of colorectal cancer metastasis and approximately 50% of patients develop liver metastasis at some point during their disease course[1]. Hepatic resection is a potentially curative treatment for colorectal cancer liver metastasis (CRLM) patients, with 5-year survival rates of 30–50%[2]. Unfortunately, more than half of patients recur after hepatic resection, and the majority of such recurrences occur within 2 years[3].

Recent advances in surgical approaches have dramatically changed the treatment strategy for patients with recurrent CRLM, which has allowed the description of risk factors for survival after second local treatment. Previous studies have provided evidence that repeat hepatic resection is feasible in selected patient with intrahepatic recurrences[4, 5]. However, who would maximum benefit from an aggressive treatment following first recurrence is not clear as there is paucity of data on the risk factors for survival on this patient population. There was no consensus introducing how to select candidates.

The present study aimed to investigate prognostic factors of survival and select candidates for local treatment of CRLM after first recurrence.

Methods

Study Population

From January 2000 to September 2019, a total of 1,027 patients underwent a curative hepatic resection for CRLM at the Hepatopancreatobiliary Surgery Department I of Peking University Cancer Hospital. The demographic and clinical data were retrospectively obtained from a prospectively collected patient database. Patients were enrolled study following criteria: 1) developed first recurrence after initial radical resection both of liver and primary tumor; 2) diagnosed to be resectable and liver-limited disease by multidisciplinary team (MDT); 3) no extrahepatic metastasis since the first hepatic resection; 4) no other simultaneous malignancies. The technical criteria of resectablitiy related to the liver remnant after resection: a) the anticipated ability to preserve two contiguous segments; b) the anticipated ability to preserve adequate vascular inflow, outflow and biliary drainage; c) the anticipated ability to preserve adequate future liver remnant volume (30% in normal liver and 40% in pretreated liver with chemotherapy) [6]. The present study was approved by an Institutional Review Board.

Preoperative Management for First Recurrence

At the first recurrence, all patients underwent routine laboratory tests, including the measurement of the serum carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)19-9 levels, and liver function tests. Routine imaging modalities, including enhanced computed tomography(CT) scan of abdominal, thoracic and pelvic region, and hepatic magnetic resonance imaging(MRI), were performed to determine the disease stage. Strict criteria were used to determine evidence of cancer recurrence (local or metastatic or second colorectal cancer). Recurrence was diagnosed by CT scans, MRI, PET-CT, or pathology proven recurrence (biopsy or specimen). All imaging reports that suggested recurrence were reviewed carefully and compared to baseline imaging reports to confirm that disease was not present at the time of liver

resection. Preoperative chemotherapy was recommended to whom developed a heavy tumor disease burden (CRS>2) and/or recurred within a short period (disease free survival time less than 6 months) after first hepatic resection. The response to chemotherapy was evaluated by MRI, according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1)[7].

Indications for Local Treatment

The treatment strategy at first recurrence after hepatic resection was basically same with the first hepatic resection; that is, recurrent disease was treated locally only when the overall strategy was considered curative, all detectable lesions with a tumor-free margin. The resectablitiy was discussed and clinical treatment decision was made by MDT. Systemic chemotherapy was recommended if patient refused to second local treatment because of losing the faith of future. Resection of three or more segments was considered a major hepatic resection. Percutaneous radiofrequency ablation (RFA) was performed using the Celon system (Teltow, Germany) according to the manufacturer's instructions. The bipolar electrode needles were 16G, and guidance ultrasonography was performed using the Aloka α-10 (Tokyo, Japan) and GE Logiq E9 (Connecticut, USA) devices. In general, RFA was recommended in deeply situated tumors that would require extended resection of the normal parenchyma. RFA was contraindicated for: 1) the diameter of largest tumor size exceeding 3cm; 2) tumor was adjacent to major bile ducts, larger blood vessels or colon/gallbladder were strictly restricted.

Postoperative Work-Up

After complete treatment, all patients underwent regular follow-up examinations with hepatic MRI and CT scan of abdominal/thoracic/pelvic region as well was the level of tumor marker were estimated every three months. Adjuvant chemotherapy was usually recommended[8].

Statistical Analysis

Continuous variables were summarized as means and categorical variables were summarized as frequency and percentage. The optimal cutoff points for the definition of early recurrence were determined using the minimum p value approach that was calculated using the log-rank test for OS after first recurrence. Survival analyses were carried out using the Kaplan-Meier method and were compared using the log-rank test. OS was calculated from the date of local treatment or the date of systemic chemotherapy after first recurrence until death or last follow-up. It was always the primary endpoint for studies of repeat hepatic resection[3, 9]. Cut-off values for continuous variables were determined based on the C-statistic, with a Cox regression model for survival data including censored patients. The estimated cut-off values for each variable were: tumor number, 1-5; tumor size, 20-50mm; CEA level, 5 (higher limit of normal range), 10, 20, 50, 100, 200ng/ml; CA19-9, 37 (higher limit of normal range), 50, 100units/ml[7]. All statistical analyses were performed using SPSS 26.0 and R version 3.2.6 (http://www.r-project. org), and p values <0.05 were considered statistically significant.

Establishment of the nomogram

Univariable and multivariable analyses of various clinicopathological factors by Cox's proportional hazard model were used to identify independent risk factors for OS in 300 patients. The results of the multivariable analysis developed an OS prediction nomogram with 1-,3-,5-year OS as the endpoints. The C-index was performed to assess the degree of discrimination, and calibration plots to visualize the agreement between the predicted and actual 1-, 3- and 5-year OS with bootstrapped samples. Using all categorical risk factors, we found the best separation in terms of survival by permutation and created two risk groups, a high-risk and a low-risk group.

Results

Patient Characteristics

There were 867 patients were eligible to be enrolled (Supplementary Figure 1). Recurrence was observed in 549 (64.1%). Among of them, 523 patients (95.3%) developed single site recurrence [liver (n=384), lung (n=86), lymph node (n=39), and other organ (n=14)], while 26 patients developed multiple organs recurrence. Among the patients with the single site of liver recurrence, 300 of them were defined to be technical resectablitiy by MDT. Repeat hepatic resection and percutaneous radiofrequency ablation were performed in 88 and 85 patients, respectively. There were 11 patients underwent R1 resection in repeat resection group. The other 127 patients refused to local treatment and only received systemic chemotherapy. In patients who had recurrence, the optimal cutoff point to define early recurrence was determined to be 6 months after hepatic resection, based on the results of the minimum p value approach for survival after first recurrence ($p=7.57\times10^{-17}$) (Supplementary Figure 2).

Survival analysis

The median followed up was 39 months since the first recurrence (95% CI: 35-43 months). The 1-, 3- and 5-year OS and DFS rates were 92.3%, 59.3%, 46.2%, and 46.8%, 28.4%, 25.4% for 867 CRLM patients, respectively (Supplementary Figure 3). The 1-, 3- and 5-year OS for the local treatment group were 86.3%, 54.1% and 38.9%, respectively, and for the systemic chemotherapy group were 64.8%, 16.3% and 2.7%, respectively. The difference was significant between two groups (p<0.001) (Figure 1). Of the 173 patients who underwent second local treatment, the 5-year OS and DFS rate were 38.9% and 22.2%, respectively (Supplementary Figure 4). Among of them, 97 patients (56.1%) developed a second recurrence.

Prognostic Factors for OS after First Recurrence

In the univariable analysis, including primary N+, tumor number>1, largest tumor size>3cm, RAS mutation, early recurrence, bilateral distribution at first recurrence and no local treatment were related to a decreased OS (p<0.05). Five independent prognostic factors for OS were identified in multivariable analysis: node-positive primary (HR=1.857, 95%CI: 1.227-2.809; p=0.003), tumor size>3cm (HR=1.707, 95%CI: 1.037-2.810; p=0.036), early recurrence (HR=1.693, 95%CI: 1.142-2.511; p=0.009), RAS mutation (HR=1.553, 95%CI: 1.080-2.234; p=0.017) and local treatment (HR=0.322, 95%CI: 0.222-0.467; p<0.001) (Table 2).

Prognostic Nomogram and Calibration for OS

We developed a point based prognostic nomogram to predict OS at first recurrence based on the five independent prognostic factors (Figure 2). The sum of each score was presented in Supplementary Table 1. The C-index of the prognostic nomogram was 0.707 for predicting OS. The calibration plot suggested that the accuracy of predicted 1-,3-,5-year OS was excellent (Figure 3a,3b,3c).

Performance of the Nomogram in Predicting OS

In the development cohort, the AUCs of the nomogram score in predicting OS at 1, 3, and 5 years were higher than the Hof[10], Neal[11], and Serrano[12] recommended algorithm (Supplementary Figure 5 and Supplementary Table 2).

Stratification by Nomogram and Indication for Repeat Local Treatment

The survival curves stratified by quartiles of the nomogram predicted score are shown in Supplementary Figure 6. Compared with patients (total score above 13) who received systemic chemotherapy, radical local treatment did not improve survival outcome significantly before the decision was made (median OS: 21 vs. 15 months, p=0.126) (Supplementary Figure 7).

Discussion

Curative resection for CRLM is associated with long-term survival and cure opportunity; however, the majority of patients will develop recurrence[13]. It was well known that second hepatic resection is a safe and feasible procedure for patients with recurrent CRLM. Despite this, repeat hepatic resection may not be possible owing to anatomical or functional restraints[9, 10]. RFA is a useful alternative in this situation. In several medical centers, surgeons selected patients for second hepatic resection according the same criteria as for the first initial resection. The disease characteristics, however, were not exactly identified between initial and recurrent time-point.

The indication and concerning prognostic factors of local treatment for first recurrence have not been well studied or defined. Previous analyses have been limited by small and single cohort of patients[4, 14]. In the present study, 173 patients who underwent local treatment at first recurrence for CRLM and the survival outcome were significantly better than whom only received systemic chemotherapy. The risk factors of tumor size > 3 cm, node-positive primary, early recurrence, RAS mutation have been identified to be risk factors for survival outcome for first recurrent CRLM patients. Furthermore, in high-risk group (total score above 13), local treatment did not improve OS significantly (median OS: 21 vs. 15 months, p = 0.126). The present model might facilitate to identify whom maximum benefit from repeat local treatment before the individualized treatment decision was made.

Recurrence occured in 60−84% of CRLM patients after first hepatic resection[15, 16]. The recent expansion of indications for surgery have led to an increase in the potentially resectable pool of patients, while they can also lead to an increased risk of early recurrence. Early recurrence has been reported to

adversely influence survival after hepatic resection and therefore remains questionable for repeat hepatic resection because of their poorer prognosis[17, 18]. The present study investigated the optimal cutoff point of early recurrence was 6 months. Although it was still an independent prognostic risk factor, aggressive treatment should therefore be proactively considered even for cases of early recurrence.

The liver and lungs are the predominant sites of second recurrence, of which liver metastases are especially common[3, 19]. Therefore, the present study only enrolled resectable patients with liver-limited disease at the first recurrence. Repeat hepatic resection for recurrence has been reported to be associated with an equivalent long-term outcome to first hepatic resection, with a similarly low surgical risk, and the 5-year OS rate ranged from 27 to 45%[20–23]. RFA has emerged as an alternative radical treatment with less invasive and lower complication rate, which is effective for patients with comorbidities and recurrent liver disease[24, 25]. Previous studies of percutaneous RFA for recurrent CRLM are reasonable[26, 27]. It has suggested that tumor diameter and number are the most important factors that influence the effect[28, 29]. In our opinion, RFA was recommended in deeply situated tumors that would require extended resection of the normal parenchyma.

Given that the survival for patients who undergo liver resection for colorectal cancer metastases is long, surgeons and medical oncologists are now dealing with a "chronic disease" that should be treated differently depending on its presentation upon recurrence[30]. In the modern era, in addition to the current disease state of CRLM patients, recurrence should be concerned on when determining the treatment strategy. Preoperative chemotherapy might shrink and increase resectability. Especially, it also likely selected who would benefit from resection for recurrent patient. Therefore, it might be recommended for patients who developed early recurrence or heavy liver disease burden.

Limitation

The present study included its retrospective design and the gradual change in indications for resection and RFA over the study. First, although enrolled the patients were defined to be resectable, bias could still exist from patient selection in three groups. Second, it is possible that other unknown factors that will affect the accuracy of Nomogram model. At meanwhile, there was no cohort of external validation in the present study. Finally, all data were collected from a limited number of institutions.

Conclusion

Radical treatment remains the golden option for recurrent colorectal liver metastasis. The proposed model may help to predict the possibility of radical interventions (score < 13) and provide optimal individualized treatment.

Abbreviations

CRLM: colorectal liver metastases; RFA: radiofrequency ablation; OS: overall survival; DFS: disease free survival; MDT: multidisciplinary team; CEA: carcinoembryonic antigen; HR: hazard ratio; MRI: magnetic resonance imaging; CT: computed tomography;

Declarations

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. The study was performed in accordance with the Declaration of Helsinki.

Consent for publication

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

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to protecting individual patient privacy but are available from the corresponding author on reasonable request.

Competing Interest

The manuscript has not been a podium or poster meeting. We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed.

Authors' contributions

BCX contributed to the conception and design. KW and HWW are responsible for the provision of the study materials and data collection. WL and JML contributed to the data analysis and interpretation and draft writing equally. All authors read and approved the final manuscript.

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No preregistration exists for the reported studies reported in this article. We acknowledge QB who contributed towards the study by making substantial contributions to the acquisition of the data and KMJ who made substantial contributions to the analysis and interpretation of the data. They are involved in drafting the manuscript but do not meet the criteria for authorship.

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Tables

Table 1. Demographic and clinical characteristics of patients after first recurrence

Variable	Local treatment		Systemic chemotherapy
	Repeat hepatic resection	RFA	
Patients demographics	n=88	n=85	n=127
Age（years）	55.6±10.3	57.7±9.3	56.1±9.8
Sex ration(M:F)	57:31	59:26	80:47
Primary T			
T1-2	7	7	18
T3-4	81	78	109
Primary N			
N0	54	66	94
N1-2	34	19	33
Primary tumor location			
Colon	55	52	78
Rectum	33	33	49
Right side	24	17	34
Left side	64	68	93
Timing of liver metastasis			
Synchronous	72	78	110
Metachronous	16	7	17
Metastasis no.	1(1-7)	1(1-3)	2(1-5)
Metastasis size(mm)	23.1±15.8	15.6±1.7	19.6±10.2
Localization of liver metastases			
unilobar	63	70	64
bilobar	25	15	55
CEA>50	13	4	5
CA199>100	10	6	8
Ras status			
Wild	62	50	77
Mutation	26	35	50

Table 1. Demographic and clinical characteristics of patients after first recurrence

Variable	Local treatment		Systemic chemotherapy
	Repeat hepatic resection	RFA	
Patients demographics	n=88	n=85	n=127
Preoperative chemotherapy	49	25	127
Up-front local treatment	39	60	0
No. of lines			
First line	25	12	70
Second line	24	13	47
Others	0	0	15
Regimen			
Oxaliplatin	18	9	49
Irinotecan	31	16	70
Others	0	0	8
Biological agents	39	20	95
Bevacizumab	29	18	70
Cetuximab	10	2	25
Response to chemotherapy			
Complete	0	0	0
Partial	4	2	21
Stable disease	41	23	89
Progressive disease	0	0	17
Surgery details			
Operation time	204.4±89.0	NA	NA
Blood lose	274.1±77.1	NA	NA
RBC transfusion	2	NA	NA
R1 resection	6	NA	NA
Complication	4	NA	NA
Major	1	0	NA

Table 2. Univariable and multivariable analysis of factors associated with OS of CRLM after first recurrence

	Univariable analysis			Multivariable analysis		
	HR	95%	P value	HR	95%	P value
Age						
⊠70	Ref			Ref		
≤70	1.462	0.869-2.461	0.153	1.356	0.777-2.366	0.284
Sex						
Male	Ref			Ref		
Female	0.941	0.670-1.322	0.726	0.838	0.586-1.201	0.336
Primary T stage						
1-2	Ref			Ref		
3-4	0.835	0.515-1.355	0.465	0.846	0.502-1.424	0.529
Primary N stage						
N0	Ref			Ref		
N1-2	1.860	1.265-2.734	0.002	1.857	1.227-2.809	0.003
Location tumor						
Colon	Ref			Ref		
Rectum	0.834	0.600-1.159	0.279	0.783	0.517-1.187	0.249
Primary tumor location						
Left	Ref			Ref		
Right	1.203	0.834-1.734	0.322	1.233	0.770-1.973	0.383
Timing of liver metastasis						
⊠12 month	Ref			Ref		
≤12 month	0.981	0.588-1.435	0.708	1.010	0.613-1.644	0.970
CEA						
⊠50	Ref			Ref		
≤50	0.798	0.451-1.443	0.455	0.786	0.408-1.515	0.472
CA199						
⊠100	Ref			Ref		
≤100	1.154	0.675-1.974	0.600	1.269	0.690-2.333	0.444

Table 2. Univariable and multivariable analysis of factors associated with OS of CRLM after first recurrence

	Univariable analysis			Multivariable analysis		
	HR	95%	P value	HR	95%	P value
Tumor size						
≤3cm	Ref			Ref		
⬜3cm	1.441	1.074-2.222	0.035	1.707	1.037-2.810	0.036
Tumor no.						
≤1	Ref			Ref		
⬜1	1.398	1.006-1.942	0.046	0.733	0.424-1.268	0.733
RAS status						
Wild	Ref			Ref		
Mutation	1.634	1.183-2.281	0.003	1.553	1.080-2.234	0.017
Distribution						
Unilobar	Ref			Ref		
Bilobar	1.553	1.094-2.205	0.014	1.385	0.806-2.380	0.238
Early recurrence						
No	Ref			Ref		
Yes	1.944	1.387-2.725	0.000	1.702	1.148-2.523	0.008
Local treatment						
No	Ref			Ref		
Yes	0.313	0.222-0.443	0.000	0.322	0.218-0.467	0.000

Figures

Kaplan-Meier Curve of OS

Local Treatment Group(n=173)
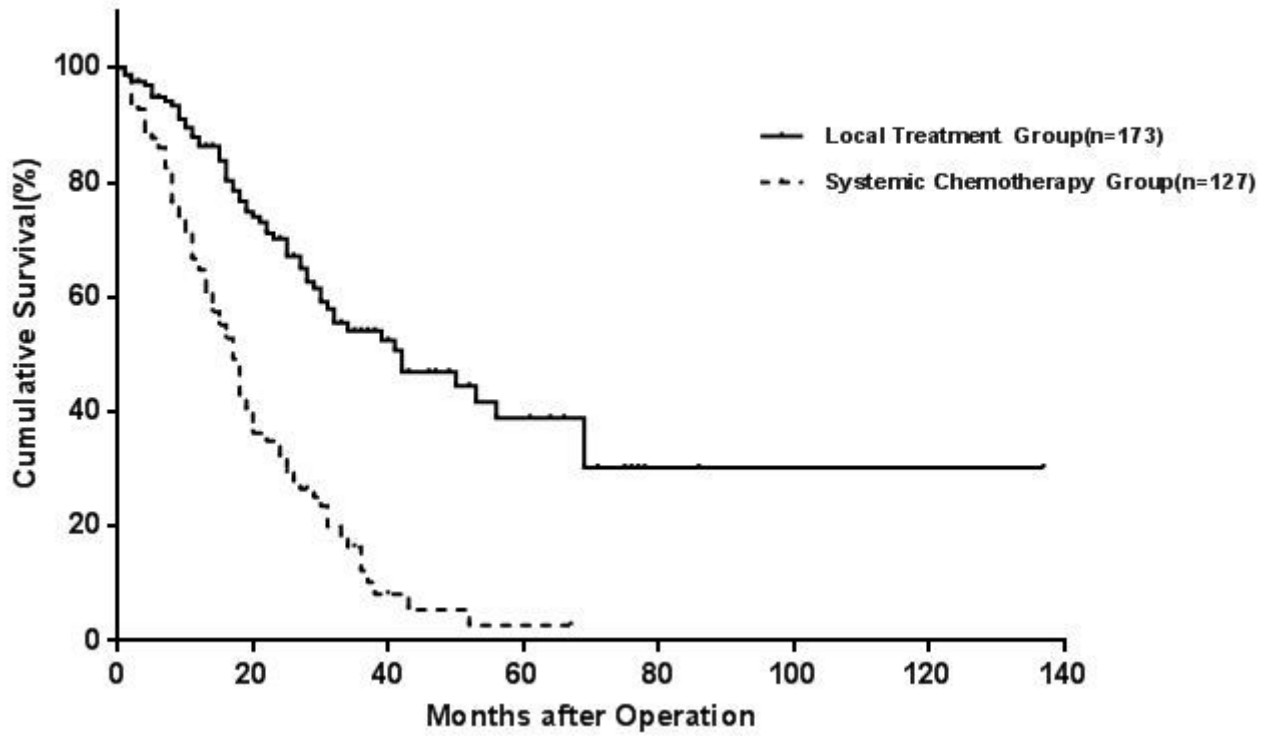
Systemic Chemotherapy Group(n=127)

Figure 1

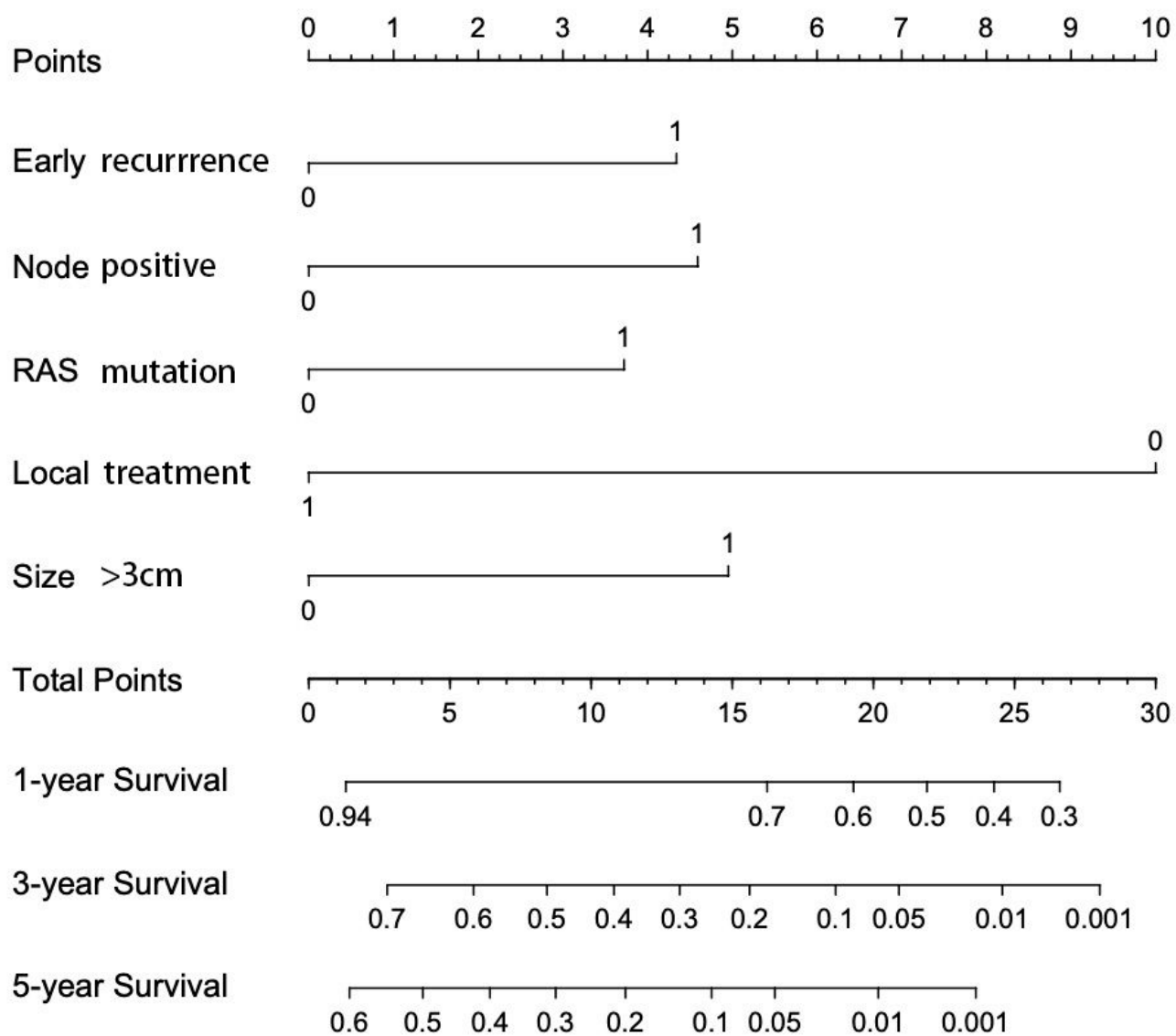The OS of local treatment and chemotherapy was showed by Kaplan-Meier Curve.

Figure 2

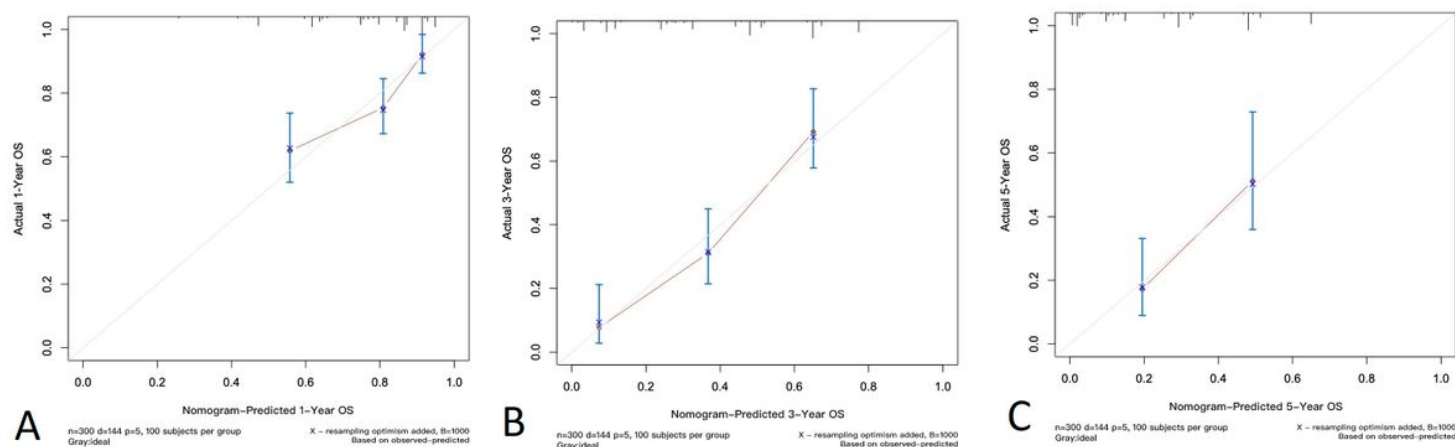Colorectal liver metastasis Nomogram for OS after First Recurrence.

Figure 3

a. The predicting OS at 1-year by calibration curve. b. The predicting OS at 3-year by calibration curve. c. The predicting OS at 5-year by calibration curve.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigure1.pdf
- SupplementaryFigure2.jpg
- SupplementaryFigure3.jpeg
- SupplementaryFigure4.jpeg
- SupplementaryFigure5.jpg
- SupplementaryFigure6.jpeg
- SupplementaryFigure7.jpeg
- SupplementaryTable1.docx
- SupplementaryTable2.docx