Development of a Model To Predict Pathologic Response to Chemotherapy in Patients With Colorectal Liver Metastases

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Abstract

Background. Preoperative chemotherapy has widely been used in colorectal cancer liver metastasis (CRLM). Pathological response to chemotherapy is very important in evaluating tumor biology. However, there is still a lack of a non-invasive and accurate method to evaluate pathological response before surgery.

Methods. We retrospectively analyzed the clinicopathologic data of patients with CRLM who underwent liver resection after preoperative chemotherapy between January 2006 and December 2018. Pathological responses were defined as minor when there are ≥50% remnant viable cells and as major when 0-49% remnant viable cells exist.

Results: A total of 482 patients were included and randomly divided into training (n = 241) and validation (n = 241) cohorts. The proportion of major pathologic response was similar between the two groups (51.5% and 48.5%). Multivariate analysis determined the disease-free interval, tumor size, tumor number, and *RAS* status as independent predictors of major pathologic response to preoperative chemotherapy. The nomogram incorporating these variables showed good concordance statistics in the training cohort (0.746, 95% CI: 0.685-0.807) and validation cohort (0.764, 95% CI: 0.704-0.823). In addition, the nomogram showed good applicability in patients with different characteristics.

Conclusions. The established nomogram model performed well in predicting pathological response in patients with CRLM.

Introduction

Surgical resection is currently the most effective treatment for colorectal cancer liver metastasis (CRLM), with a 5-year survival rate of 40–50%[1]. Preoperative chemotherapy has been widely used in CRLM. Although the benefit in prolonging survival has long been controversial, the effect of shrinking tumor to allow for parenchymal sparing hepatectomy (PSH), controlling the micro-metastatic disease, and testing tumor biology by assessing chemotherapy response has been widely accepted[2–4]. Chemotherapy response is a very strong predictor of long-term survival. Patients who present good response in preoperative chemotherapy show significantly better survival compared with those who had poor response after hepatectomy[5]. For those who show poor response, a more effective regimen might be used rather than performing surgery directly. Thus, it is very important to evaluate the chemotherapy response with high accuracy[6].

Response evaluation criteria in solid tumors (RECIST) has long been used to evaluate chemotherapy response based on the tumor size change, however, it can be rather inaccurate in assessing tumor size change in patients with irregular tumor shapes[7]. The most accurate way to evaluate true chemotherapy response is pathologic examination, especially for patients treated with targeted drugs who are often presented as composition changes rather than size change[8, 9]. By assessing the residual tumor cell percentage, we can objectively assess the true response status. Precisely testing the pathologic response

is very helpful in deciding on the most optimal timing to perform the surgery and knowing the prognosis of patients undergoing surgery[6]. However, a pathologic response could hardly be obtained before the surgery without resected specimens. Preoperative biopsy can be invasive and not accurate enough because of the tumor heterogeneity. Recently, several studies found that some clinical factors are associated with pathologic response, including *RAS* gene status, chemotherapy regimens and clinical characteristics[10, 11]. The aim of this study is to develop a model to accurately predict pathologic response to chemotherapy in a non-invasive way.

Materials And Methods

The study design was approved by the Ethical Review Board committee of the Beijing Cancer Hospital and Institute (Beijing, China). All study participants provided written informed consent.

Study design

Pathologically confirmed CRLM patients after preoperative chemotherapy following liver resection between January 2006 and December 2018 in the HPB Surgery Ward I at the Beijing Cancer Hospital (Beijing, China) were identified from our prospective patient database. Patient exclusion criteria were: (1) having undergone palliative surgery (R2 resection); (2) having no pathologic response information; (3) being lost to follow-up.

Assessment of pathologic response following chemotherapy

All CRLM tumors of included patients were sampled and the hematoxylin & eosin stained sections were reviewed by gastrointestinal pathologists. Pathologic response to chemotherapy was categorized according to MD Anderson group[8]. Major response was defined as from 1–49% residual cancer cells, and minor response as ≥ 50% residual cancer cells remaining.

Perioperative management and follow-up

Multidisciplinary team meetings were scheduled weekly in our center for patients with CRLM. Gene status was assessed in every patient and included at least the following: *KRAS* (codons 12, 13 and 61); *NRAS* (codons 12, 13 and 61); and *BRAF* (v600e). Contrast-enhanced MRI combined with diffusion-weighted MRI were routinely performed before and every 2–4 cycles after chemotherapy. Chest and pelvic CT scans were routinely performed. Positron emission tomography-CT scans were not routinely performed unless patients were suspected as having extrahepatic disease. All patients received neoadjuvant chemotherapy, including oxaliplatin- or irinotecan-based chemotherapy (mFOLFOX6/ XELOX/ FOLFIRI/ FOLFOXIRI) regimens in combination with or without targeted agents (Bevacizumab and Cetuximab). The time interval between the date of the last chemotherapy session and hepatic surgery was usually 2–4 weeks, extending to 6–8 weeks with the addition of bevacizumab. Primary tumors located in the cecum, ascending colon, and transverse colon were defined as right side (RS) tumors, and those located in the

splenic flexure, descending colon, sigmoid colon, and rectum were defined as left side (LS) tumors. Contrast-enhanced CT scans or MRI, liver function tests, and measurements of carcinoembryonic antigen levels were performed every 3 months after the surgery. For patients with liver-limited recurrence, the treatment option of choice was localized treatment, including surgical or ablation techniques.

Patient selection for liver resection and operative technique

For some patients, the primary tumor was resected at another institution. The surgical treatment of all LMs was conducted at our center. Resectable was defined as complete remove of macroscopic tumors, while maintaining at least a 30% future liver remnant (FLR) or a remnant liver to body weight ratio > 0.5 with sufficient blood inflow and outflow of the liver[6]. Intra-operative ultrasound was routinely performed during the hepatectomy to detect the presence of any further or yet undetected lesions.

Statistical analyses

Categorical variables were presented as numbers with percentages and compared using the Chi-squared test. Multivariable logistic regression analysis was performed to determine independent predictors of major pathologic response. A nomogram was formulated based on the results of multivariate logistic regression analysis. The predictive performance of the nomogram was measured by concordance (C) statistics and calibration plots. In subgroup analysis, receiver operating characteristic (ROC) curve analysis was conducted, and the area under the ROC curve (AUC) was calculated to further evaluate the predictive performance of the nomogram. All statistical analyses were conducted using SPSS software version 24.0 (IBM Corp., Armonk, NY, USA) and R version 3.5.1 (http://www.r-project.org/). A $P < 0.05$ was considered statistically significant.

Results

Characteristics of patients

A total of 482 patients met the inclusion criteria and were enrolled in this study. The included 482 patients were randomly divided into the training cohort (n = 241) and validation cohort (n = 241). The baseline characteristics of patients in the training cohort and validation cohort are summarized in Table 1. Baseline data were similar between the training cohort and validation cohort. The median number of preoperative chemotherapy cycles were 4 for both the training cohort and validation cohort. Major pathologic response was observed in 241 (50.0%) of the total patients, including 29 patients with complete pathologic responses (6.0%). The proportion of major pathologic response was similar between the training cohort and validation cohort (51.5% versus 48.5%, $P = 0.524$). Based on radiographic assessment, tumor decrease was observed in 396 (82.2%) of the total patients. For patients with tumor increase after preoperative chemotherapy, major pathologic response was observed in 19 (42.2%) and 20 (48.8%) patients in the training cohort and validation cohort, respectively. According to the RECIST criteria, complete or partial response was observed in 223 (46.1%) of the total patients.

Table 1
Baseline characteristics

Variables	Training cohort (*n* = 241)	Validation cohort (*n* = 241)	*P*
Gender			0.562
Male	158 (65.6)	164 (68.0)	
Female	83 (34.4)	77 (32.0)	
Age			
< 65 years	190 (78.8)	190 (78.8)	1.000
≥65 years	51 (21.2)	51 (21.2)	
Primary tumor			
T category			0.601
T1-2	36 (14.9)	32 (13.3)	
T3-4	205 (85.1)	209 (86.7)	
N category			0.921
N0	73 (30.3)	74 (30.7)	
N1-2	168 (69.7)	167 (69.3)	
Site			0.722
Left	199 (82.6)	196 (81.3)	
Right	42 (17.4)	45 (18.7)	
Liver metastases			
DFI			0.558
≥ 12 months	74 (30.7)	80 (33.2)	
< 12 months	167 (69.3)	161 (66.8)	
Tumor size			0.145
≥3 cm	107 (44.4)	123 (51.0)	
<3 cm	134 (55.6)	118 (49)	
Tumor number			0.525

*Evaluated based on imaging examinations. Decrease, reduction in the sum of target lesion diameters; Increase, increased in the sum of target lesion diameters. CEA, carcinoembryonic antigen; DFI, disease-free interval; RECIST, Response Evaluation Criteria in Solid Tumors.

Variables	Training cohort (n = 241)	Validation cohort (n = 241)	P
Single	56 (23.2)	62 (25.7)	
Multiple	185 (76.8)	179 (74.3)	
Distribution			0.461
Unilobar	106 (44.0)	98 (40.7)	
Bilobar	135 (56.0)	143 (59.3)	
RAS status			0.515
Wild	148 (61.4)	141 (58.5)	
Mutated	93 (38.6)	100 (41.5)	
Chemotherapy cycles			0.516
≤ 4 cycles	147 (61.0)	140 (58.1)	
>4 cycles	94 (39.0)	101 (41.9)	
Bevacizumab			0.209
No	167 (69.3)	154 (63.9)	
Yes	74 (30.7)	87 (36.1)	
CEA			0.016
≤50 ng/ml	182 (75.5)	158 (65.6)	
> 50 ng/ml	59 (24.5)	83 (34.4)	
Pathologic response			0.524
Minor	117 (48.5)	124 (51.5)	
Major	124 (51.5)	117 (48.5)	
Tumor radiographic assessment*			0.634
Decrease	196 (81.3)	200 (83.0)	
Minor pathologic response	91 (46.4)	103 (51.5)	
Major pathologic response	105 (53.5)	97 (48.5)	
Increase	45 (18.7)	41 (17.0)	

*Evaluated based on imaging examinations. Decrease, reduction in the sum of target lesion diameters; Increase, increased in the sum of target lesion diameters. CEA, carcinoembryonic antigen; DFI, disease-free interval; RECIST, Response Evaluation Criteria in Solid Tumors.

Variables	Training cohort (*n* = 241)	Validation cohort (*n* = 241)	*P*
Minor pathologic response	26 (57.8)	21 (51.2)	
Major pathologic response	19 (42.2)	20 (48.8)	
RECIST assessment			
Complete or partial response	113 (46.9)	110 (45.6)	0.784
Stable or progressive disease	128 (53.1)	131 (54.4)	

*Evaluated based on imaging examinations. Decrease, reduction in the sum of target lesion diameters; Increase, increased in the sum of target lesion diameters. CEA, carcinoembryonic antigen; DFI, disease-free interval; RECIST, Response Evaluation Criteria in Solid Tumors.

Predictors of major pathologic response in the training cohort

In the univariate logistic regression analysis, disease-free interval (DFI), tumor size, tumor number, *RAS* mutational status, and CEA level were identified as predictors of major pathologic response to preoperative chemotherapy (Table 2). Multivariate analysis determined that DFI (< 12 vs ≥ 12 months, OR [95% CI]: 1.908 [1.026–3.547], *P* = 0.041), tumor size (< 3 vs ≥ 3 cm, OR [95% CI]: 5.076 [2.849–9.010], *P* < 0.001), tumor number (single vs multiple, OR [95% CI]: 2.625 [1.302–5.291], *P* = 0.007), and *RAS* status (wild-type vs mutated, OR [95% CI]: 2.217 [1.227-4.000], *P* = 0.008) were identified as independent predictors of major pathologic response to preoperative chemotherapy (Table 2).

Table 2
Uni- and multivariable analyses to identify predictors of major pathologic response in the training cohort

Variables	Univariable			Multivariable		
	OR	95% CI	P	OR	95% CI	P
Gender (Male vs female)	0.784	0.460–1.337	0.372	-	-	-
Age (≥ 65 vs < 65 years)	0.800	0.431–1.486	0.480	-	-	-
Primary tumor						
T category (T3-4 vs T1-2)	0.721	0.352–1.477	0.372	-	-	-
N category (N1-2 vs N0)	1.045	0.603–1.811	0.875	-	-	-
Site (Right vs left)	0.740	0.379–1.443	0.376	-	-	-
Liver metastases						
DFI (< 12 vs ≥ 12months)	1.889	1.083–3.292	0.025	1.908	1.026–3.547	0.041
Tumor size (< 3 vs ≥ 3 cm)	4.739	2.747–8.197	< 0.001	5.076	2.849–9.010	< 0.001
Tumor number (Single vs multiple)	1.984	1.070–3.676	0.030	2.625	1.302–5.291	0.007
Distribution (Unilobar vs bilobar)	1.447	0.867–2.415	0.157	-	-	-
RAS status (Wild vs mutated)	1.739	1.029–2.932	0.038	2.217	1.227-4.000	0.008
Chemotherapy cycles (≤ 4 vs > 4)	1.563	0.928–2.632	0.093	-	-	-
Bevacizumab (Yes vs no)	1.162	0.672–2.012	0.591	-	-	-
CEA (≤ 50 vs > 50 ng/ml)	2.597	1.406–4.808	0.002	1.684	0.833–3.401	0.147
Tumor radiographic assessment (decrease vs increase)	1.580	0.820–3.040	0.172	-	-	-

CEA, carcinoembryonic antigen; DFI, disease-free interval; OR, odds ratio.

Development and validation of a nomogram for predicting major pathologic response

The above four independent predictors of major pathologic response were integrated into a major pathologic response estimation nomogram (Fig. 1). The c-statistic of the nomogram in discriminating major pathologic response in the training cohort was 0.746 (95% CI: 0.685–0.807), and the calibration plot showed good agreement between the predicted probability of major response and the observed incidence of major response (Fig. 2a). In the validation cohort, the C statistic of the nomogram was 0.764 (95% CI: 0.704–0.823), and the calibration plot also showed good agreement between predictions and actual observations (Fig. 2b). The optimized cutoff of the nomogram score for predicting major pathologic response was 124. With this optimized cutoff, the sensitivity and specificity of the nomogram for predicting major pathologic response were 75.0% and 65.0% in the training cohort and 66.7% and 71.0% in the validation cohort.

Subgroup analysis

To evaluate the applicability of the nomogram in patients with different characteristics, subgroup analyses were performed based on primary tumor site (left or right colon), *RAS* status (wild-type or mutated), and the use of bevacizumab (yes or no). In each subgroup, the nomogram performed well in predicting major pathologic response to preoperative chemotherapy (all AUCs > 0.700, Fig. 3a-f).

Discussion

Many previous studies have tried to predict pathologic response to chemotherapy. However, a comprehensive model for predicting pathologic response[10–13] is still lacking. This study established a prognostic model to predict pathologic response after chemotherapy based on several clinical factors that are obtainable in a non-invasive fashion. The weight and correlation of each factor influencing pathologic response was fully considered. The validation results suggest that the model could predict pathologic response with precision, as well as good sensitivity and specificity.

The RECIST criteria are currently widely used to evaluate chemotherapy response based on radiographic tumor change. As systematic treatment protocols and targeted drugs are refined, tumor response would also present as internal composition changes. Tumor tissue was replaced by necrosis and inflammatory cells in pathologic examination, causing tumor size to remain stable or even increase. Previous studies shown that although some patients were evaluated as unresponsive by RECIST criteria, major response could still be found by pathological examinations[14]. Consistently, in this study, major pathologic response was also observed in 39 (45.3%) patients of those with tumor increase after preoperative chemotherapy. This finding indicates that tumor radiographic changes after chemotherapy are not completely in consistent with the pathological response. Hence, the model for predicting pathological response in this study could be considered as a supplement to evaluate chemotherapy response and helps to make treatment strategies more comprehensively. For patients who were predicted to show major pathologic response despite stable tumor size, hepatectomy could be performed if the liver metastasis was resectable. If the metastases were still unresectable, our nomogram could allow for continuing with chemotherapy in pursuit of maximum pathologic response, and even complete pathologic response[15, 16]. In addition, patients with major pathologic response would show clearer

tumor-normal liver interface (TNI) [17, 18], allowing for narrower or even R1 margins to be acceptable during surgery[19]. However, if patients were predicted to have minor pathologic response and still stable or progressing in size, it would be more reasonable to select a second-line chemotherapy regimen with higher efficiency to control tumor growth instead of pursuing sugery[4, 20].

In this study, we found several clinical factors that predicted the pathologic response of patients with CRLM to preoperative chemotherapy. Patients with *RAS* wild-type were more likely to experience a major response after preoperative chemotherapy. *RAS* status has long been known to be associated with long-term survival and the sensitivity to chemotherapy[21, 22]. Previous studies also found similar results showing that major responses were more common in patients with *RAS* wild-type compared with those with *RAS* mutant [10, 13]. Tumor size and tumor number has also been proven to correlate with degree of pathologic response. Zimmitti et al. and Georgios et al. showed that CRLM size > 3 cm was an independent predictor of poor response to chemotherapy[10, 13]. Patients with larger tumors and higher tumor number reflected a heavier tumor burden, which is already known to be a negative factor for survival[23]. DFI < 12 months is another factor shown to be in association with major pathological response. It might be explained by the following reason. Patients with metachronous liver metastases (DFI ≥ 12months) might have received adjuvant chemotherapy after resection of primary tumors. Therefore, it is often needed to change to 2nd-line chemotherapy when liver metastases occur. Previous literature shown that the efficiency of second-line chemotherapy was only about 20%[24], so it might be difficult for these patients to develop major pathologic response. However, patients with simultaneous liver metastases usually don't receive any treatment previously, so their pathologic response after preoperative chemotherapy would be relatively higher.

It was interesting that some other factors, such as primary tumor site and the use of bevacizumab[11, 25], which were previously shown to be related to chemotherapy response, were found not to be independent factors influencing pathologic response in our study. Georgios et al. also found that adding bevacizumab was not associated with pathologic response in multivariate analysis (P = 0.3)[10]. Primary tumor location was also an important factor for chemotherapy response. Wang et al. and Serayssol et al. found that it was associated with poor pathologic response[11, 12]. However, other studies did not find similar results. In order to avoid bias arising from to patient selection and operating within a single-center sample, we choose three important factors - primary tumor site, *RAS* mutational status, and the use of bevacizumab and performed a subgroup analysis to assess the predictive power of this model in different subgroups. The results showed that the nomogram performed well in predicting major pathologic response to preoperative chemotherapy in patients with different characteristics.

There are several limitations in this study. The main disadvantage of this study is that it uses data collected retrospectively with a limited sample size, which makes selection bias unavoidable. A certain degree of heterogeneity in terms of diagnosis and treatment might influence the results of the study. In addition, metastatic liver tumors are highly heterogeneous suggesting that there may be differences in pathologic response rates between different tumors. Thus, we chose the average pathologic response

rate according to the method of Blazer et al. Finally, in this study we only performed internal validation since there was no external validation cohort. Because of this, the reliability of the model was suboptimal.

Conclusion

In conclusion, we found that preoperative characteristics such as DFI, metastatic liver tumor size and number, and *RAS* mutational status were independent factors influencing pathologic response. The model we established for predicting pathologic response in patients with surgically treated CRLM after preoperative chemotherapy was highly sensitive and specific. We found that the model also performed well in subgroup analyses. This model could be very helpful for clinicians seeking to make better informed decisions regarding whether to perform surgery. A second-line therapy might be acceptable for patients with minor response. Thus, the current results may contribute to personalized care in the treatment of CRLM. However, future studies with larger sample sizes and multiple centers need to be conducted to verify the accuracy of the model proposed in this study.

Declarations

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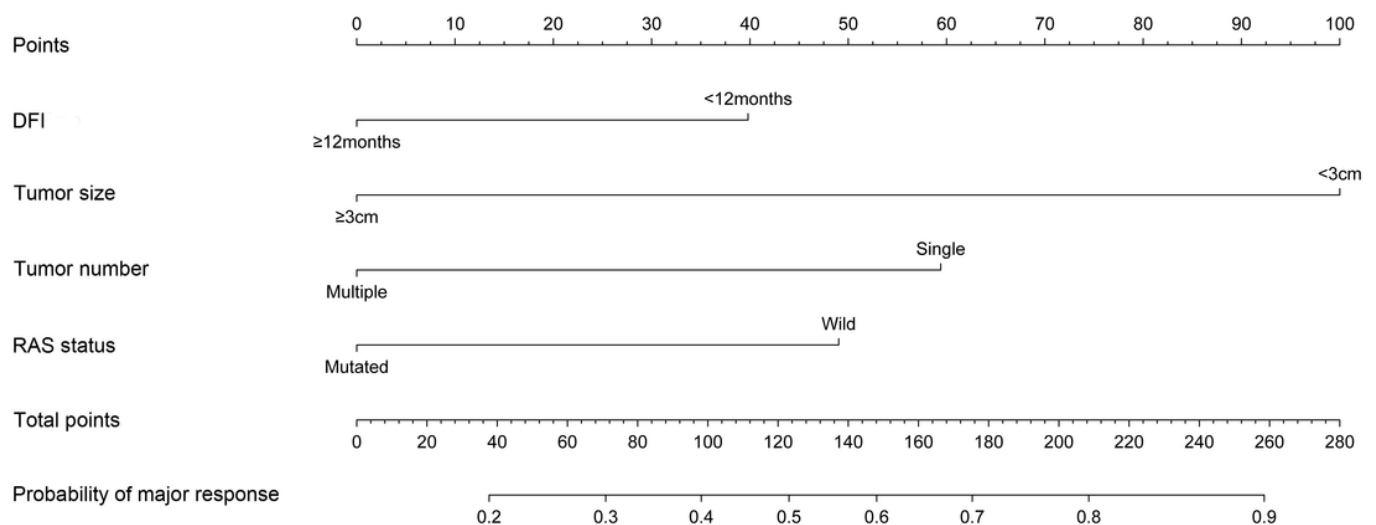
Figures

Figure 1

Nomogram for predicting major pathologic response to preoperative chemotherapy in patients with CRLM. DFI, disease-free interval
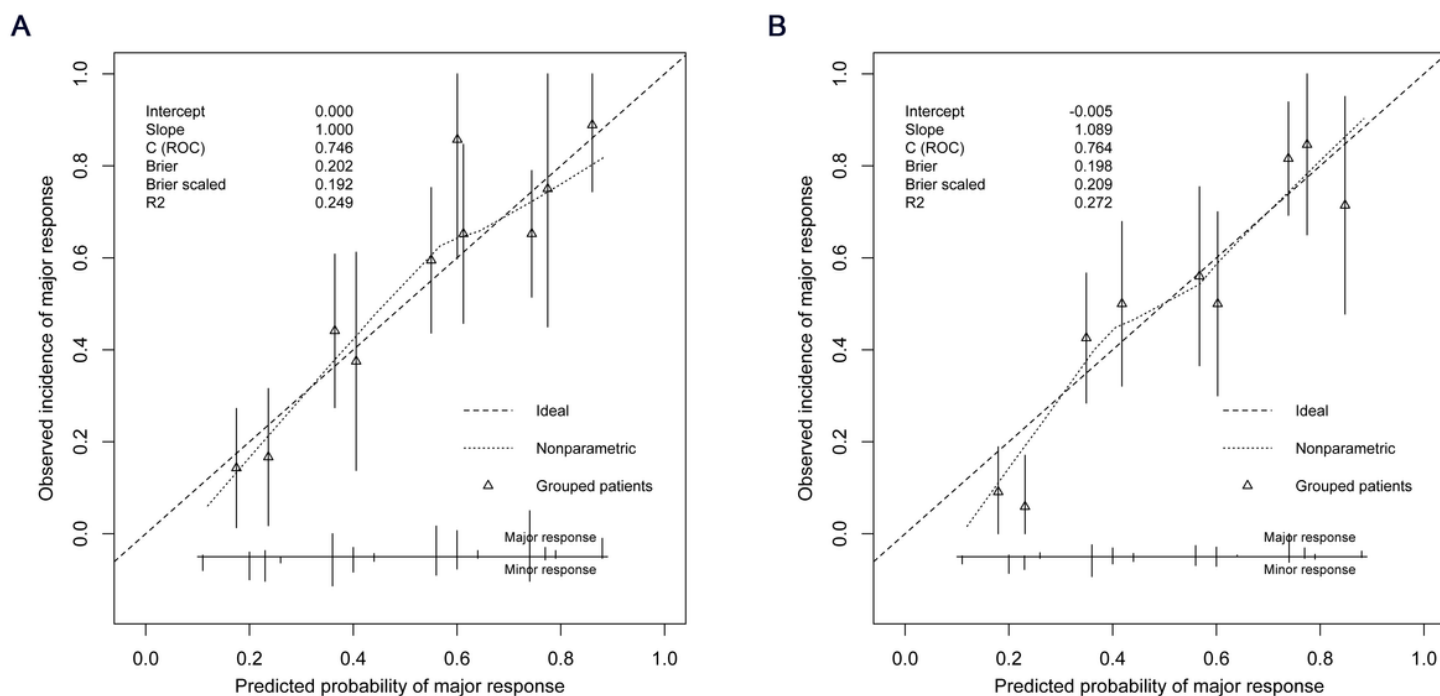
Figure 2

Calibration plots of the observed incidence versus predicted probability of major pathologic response of the nomogram in the training cohort and b validation cohort
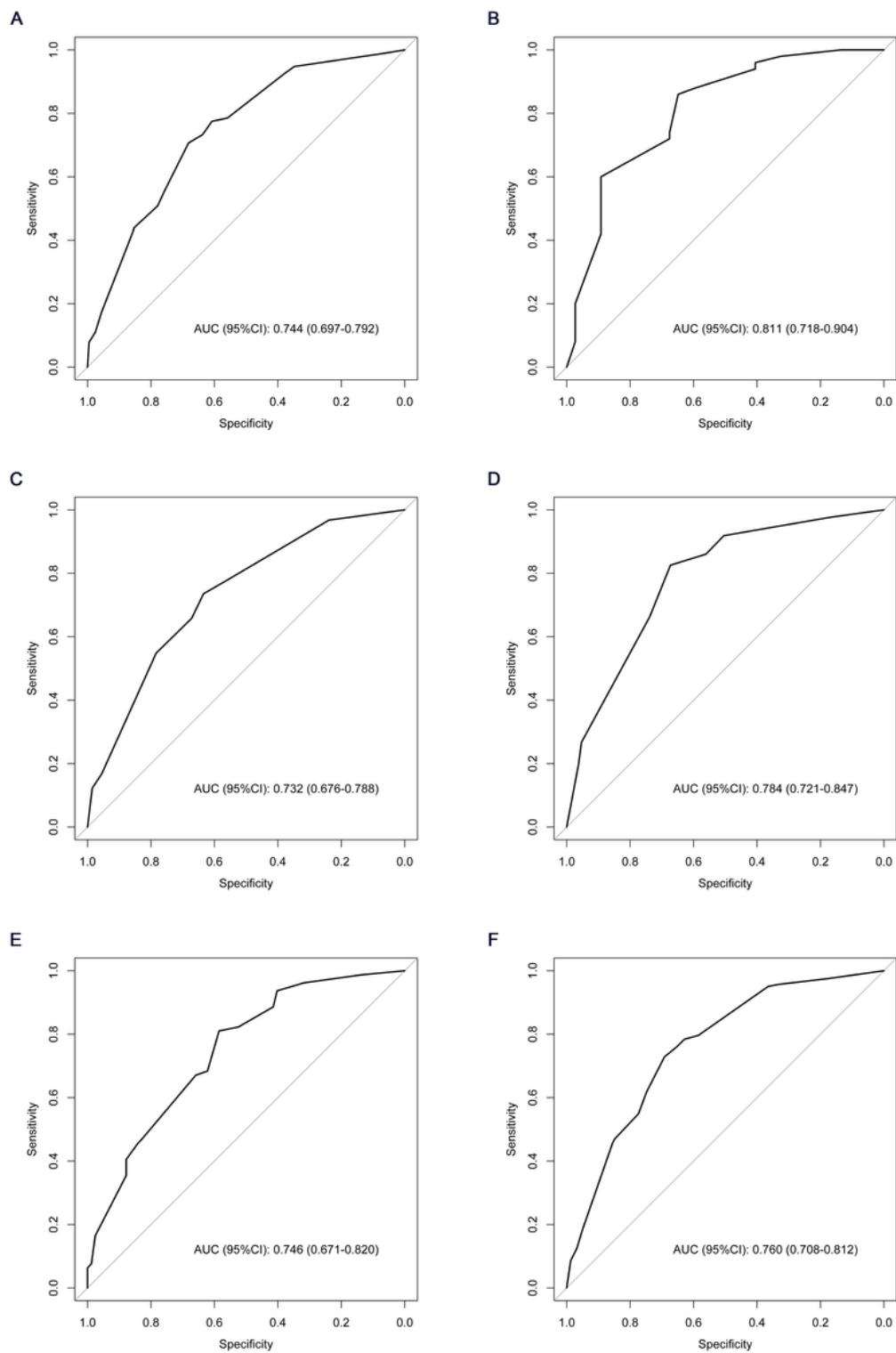
Figure 3

Validity of the nomogram performance in predicting major pathologic response in patients with different characteristics, including primary tumor located in left a or right b colon, wild-type c or mutated d RAS status, and with e or without f bevacizumab.