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ORIGINAL ARTICLE

Improved treatment of colorectal liver metastases by early response evaluation and regimen adjustment: a prospective study of clinical functional MR-based modeling

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ABSTRACT

Objective: The aim of the study was to evaluate the feasibility of functional MR in predicting the clinical response to chemotherapy in patients with colorectal liver metastases (CLM).

Methods: A total of 196 eligible patients were enrolled in the study between August 2016 and January 2023. Functional MR was performed at baseline and after one cycle of chemotherapy. The diffusion kurtosis radiomic texture features were extracted and a signature model was built using the R package. The initial 100 cases were designated as the training set, the following 48 cases were designated as the validation set, and the final 48 cases were designated as the intervention validation set.

Results: Good performance for the response prediction (AUC = 0.818 in the training set and 0.755 in the validation set) was demonstrated. The objective response rates (ORRs) in the high-risk subgroup were significantly lower than the low-risk subgroup in the training and validation sets. Worse progression-free survival and overall survival rates were noted in the high-risk population. In the intervention set 22.9% (11/48) of the chemotherapy regimens for patients were changed in response to the model-predicted results and the ORR reached 77.1% (37/48), which was significantly higher than the training and validation sets [47.97% (71/148); $P = 0.000$].

Conclusions: A functional MR signature effectively predicted the chemotherapy response and long-term survival. The adjustment of the regimen guided by the model significantly improved the ORR.

KEYWORDS Colorectal cancer; liver metastases; objective response rate; MR

Introduction

The incidence and mortality rate of colorectal cancer rank third worldwide. Distant metastases are important factors for the poor prognosis of patients with colorectal liver metastases (CLM)[1]. CLM patients comprise a unique population that have the potential to be cured through resection and chemotherapy[2].

Chemotherapy is beneficial for shrinking tumors and increasing the opportunity for R0 resection of the liver in CLM patients[3,4]. The 5-year overall survival (OS) rate reaches 30% after successful conversion treatment[5,6]. Traditional efficacy evaluation is usually performed after every 2–3 cycles of medication (6–8 weeks) using computed tomography (CT) or magnetic resonance (MR) imaging, according to the Response Evaluation Criteria In Solid Tumors (RECIST) criteria, which are based on changes in the size of the tumor. An earlier efficacy evaluation or response prediction is critical for CLM patients because the use of inappropriate treatment could be

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prevented and the drug regimen could be changed as soon as possible.

Molecular and imaging biomarkers for response prediction, such as positron emission tomography and functional MR, have received increasing attention in selecting CLM patients who will benefit from treatment[7,8]. Functional MR can provide more innate lesion characteristics and features in multiple dimensions with diffusion sequences, such as diffusion-weighted imaging (DWI), intravoxel incoherent motion (IVIM), and diffusion kurtosis imaging (DKI). DWI is based on a single exponential model of water molecular signal attenuation, which has been reported to reflect the treatment response before the tumor size changes[9]. However, DKI has an advanced non-Gaussian distribution modality of the water molecule deviation degree from the Gaussian distribution, which is superior to traditional diffusion imaging in describing tissue microstructure[10]. In recent years correlations between one or two DKI parameters and clinical response have been reported in hepatocellular carcinoma[11], nasopharyngeal carcinoma[12], gastric cancer[13], and breast cancer[14]. However, the early predictive value of the DKI sequence in liver lesions from patients with colorectal cancer has not been thoroughly investigated.

There are several issues in currently reported studies on functional imaging, which limits application in clinical practice. First, most studies retrospectively analyzed data with a limited sample size (dozens of cases) and without strict enrollment and uniform treatment. The other limitation is that only the correlation between specific parameters and efficacy was observed and there was no further intervention to verify the observations.

The current study was prospectively designed to evaluate the feasibility of a functional MR model for predicting clinical response and further applied to guide treatment regimens in patients with CLM.

Materials and methods

Study design, patient enrollment, treatment, and effect evaluation

The FDZL-MRinCLM study (NCT03088163) was approved by our Institutional Review Board (Clinical trial registration: NCT03088163) and written informed consent was obtained from all participants. Eligible patients who were ≥ 18 years of age with histologically confirmed colorectal adenocarcinoma and had at least 1 measurable liver metastatic lesion were included. No previous systemic chemotherapy or local treatment (including radiotherapy, radiofrequency ablation and/or surgery) had been performed on the liver lesions.

Only patients who were unsuitable or could not afford the target drugs were enrolled in the first period. Patients were treated with oxaliplatin combined with 5-fluorouracil and leucovorin (FOLFOX), oxaliplatin combined with capecitabine (XELOX), or irinotecan combined with 5-fluorouracil and leucovorin (FOLFIRI) at the discretion of the medical oncologists. After the functional MR model was constructed the protocol was amended in 2019 to increase patient enrollment for validation. Because the target drugs (bevacizumab and cetuximab) were both approved for insurance coverage in China at that time, the study allowed the enrolled patients to receive target drug combined with chemotherapy. Performance of the MR model was evaluated after completion of the validation cohort. The area under the receiver operating characteristic (ROC) curve (AUC) exceeded 0.75 and the study proceeded into the intervention validation component. In the third period treatment intervention was carried out according to the model prediction. If the predicted score of the model exhibited low risk (i.e., a predicted response), no change to the regimen was made. If a patient was at high risk (i.e., a predicted non-response), the oxaliplatin-based regimen was switched to the irinotecan-based regimen considering the low probability of the response, which allowed addition of the target drug and vice versa. **Figure 1** shows the flowchart of this study.

The functional MR scan with the DKI sequence of the liver was performed at baseline and within 3 days before the second treatment cycle. The traditional response evaluation of CT/MR scanning was conducted every 6–8 weeks according to the RECIST criteria. A complete response (CR) or partial response (PR) was considered a response, whereas stable disease (SD) or progression of disease (PD) was considered a non-response.

The primary endpoint of the study was the accuracy of the MR-predicted response rate (ORR) of liver metastases, and the secondary endpoints were progression-free survival (PFS) and OS in the predicted response and non-response subgroups.

Functional MR imaging

Functional MR imaging was performed using a MAGNETOM Skyra 3T MR scanner (Siemens Healthcare, Erlangen, Germany). The inline-generated parametric maps included K and D. The whole-lesion histogram and texture features were extracted from the above parametric maps using a prototype post-processing MR multiparametric analysis software (Siemens Healthcare).

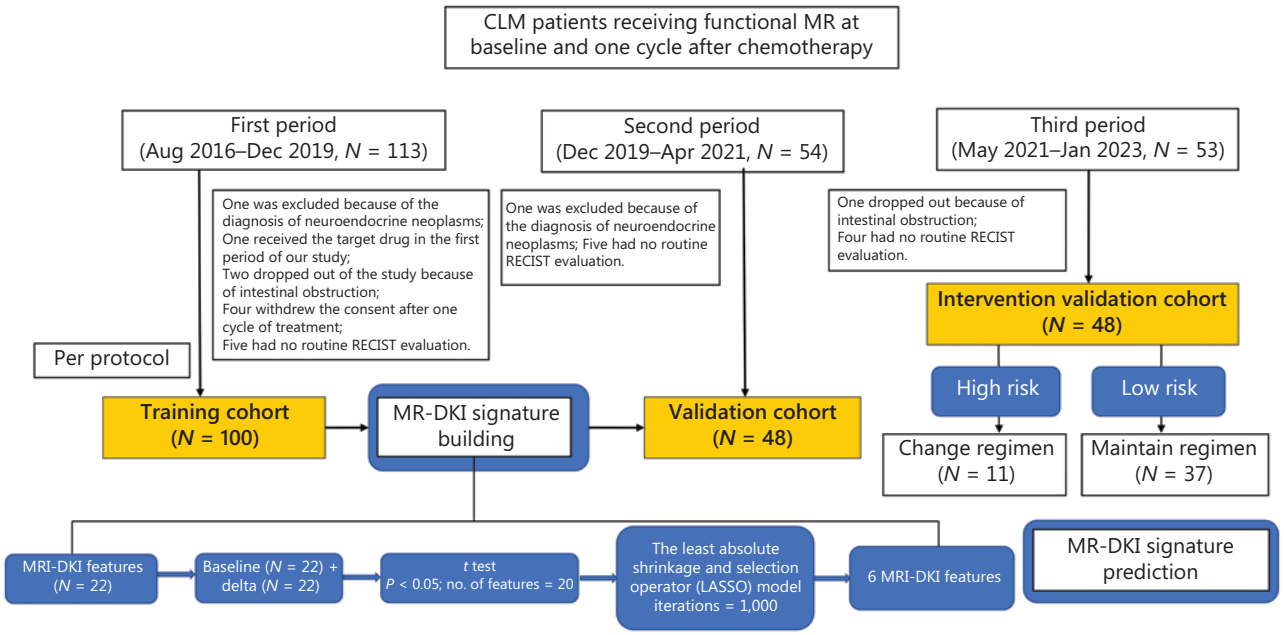


Figure 1 Study flowchart. This study was conducted in three parts. A total of 196 eligible patients were enrolled and received functional MR scanning of liver metastases at baseline and one cycle after chemotherapy, and further radiologic examinations for response evaluation were routinely performed. A total of 113 patients were enrolled and 100 per protocol of patient functional MR radiologic parameters and clinical response data were collected in the training period to build the MR-DKI signature model. In the second part, the following consecutive 54 patients were enrolled to validate the prediction ability of the model prospectively, 6 patients were excluded due to diagnosis mistake or incompletion of response evaluation, and 48 patients were analyzed. In the final part, the MR-DKI model was used to guide treatment strategy. Among the 48 eligible patients, 11 who were predicted to have a non-response after two functional MR scanning changed the regimen earlier before the routine efficacy evaluation and 37 patients who had a predicted response continued the previous regimen. The efficacy of the model-guided treatment was analyzed.

The two largest hepatic metastatic lesions of multiple liver metastases were selected as regions of interest (ROIs) in each patient. Two experienced radiologists who were blinded to the clinical information independently placed the circular ROI over the entire lesion on each slice with a diameter exceeding 1 cm to generate the corresponding mean values. A senior abdominal radiologist with > 20 years of experience was consulted for final arbitration in cases of disagreement (**Figure S1**).

Statistical analysis

Analyses were performed using R software version 3.6.0 (https://www.r-project.org/). The correlations between the parameters and clinical response were analyzed using a chi-square test or Fisher's exact test for categorical variables. The log-rank test was used to estimate PFS and OS. A two-sided P value < 0.05 was considered significant.

The sample size for the modeling cohort was estimated based on the number of independent variables expected to be included in the model. Given that 10 texture features were anticipated, the study adopted the empirical rule of thumb that suggests a sample size should be 10–20 times the number of variables for reliable model estimation and inference. Consequently, the modeling cohort was set at 100 subjects with a 2:1 ratio allocated between the modeling and validation cohorts. A single-arm phase II study design was used in the intervention cohort to quickly assess the effectiveness of model-based interventions. Using PASS 15 software with an α of 0.05, the power was 0.905 in detecting a significant difference with 48 cases, assuming that an increase in ORR from 55% to 75% was clinically significant.

Results

Study population and response evaluation

The initial 100 patients were selected as the training cohort for model building, the following 48 patients comprised the

Table 1 Clinical and pathologic characteristics of patients in the training, validation, and intervention validation groups

	Training (n = 100)		Validation (n = 48)		Intervention (n = 48)		P value
	No.	%	No.	%	No.	%	
Age, years (range)	61 (23–84)						
Median (range)	60.5 (23–78)		62.5 (29–84)		60 (27–80)		0.439
Gender							0.559
Male	64	64	32	66.7	35	72.9	
Female	36	36	16	33.3	13	27.1	
Treatment regimen							
2- or 3-week regimen							0.499
2-week	46	46	23	47.9	27	56.3	
3-week	54	54	25	52.1	21	43.8	
Drug regimen							0.312
Oxaliplatin-based	67	67	29	60.4	36	75	
Irinotecan-based	33	33	19	39.6	12	25	
Target therapy							< 0.001
No	100	100	41	85.4	15	31.3	
Plus bevacizumab	/	/	5	10.4	26	54.2	
Plus cetuximab	/	/	2	4.2	7	14.6	
Primary tumor location							0.258
Right-sided	24	24	19	39.6	13	27.1	
Left-sided	51	51	16	33.3	21	43.8	
Rectum	25	25	13	27.1	14	29.2	
Timing of metastasis to liver							0.461
Metachronous	13	13	5	10.4	3	6.3	
Synchronous	87	87	43	89.6	45	93.8	
KRAS/NRAS status							0.790
Wild-type	31	40.3	16	41	15	36.6	
Mutated-type	46	59.7	23	59	26	63.4	
Unknown	23		9		7		
BRAF status							0.316
Wild-type	75	97.4	36	92.3	42	100	
Mutated-type	2	2.6	3	7.7	0	0	
Unknown	23		9		8		
Baseline characteristics of liver metastases							
Numbers of lesions							0.105
< 5	34	34	9	18.8	8	16.7	

Table 1 Continued

	Training (n = 100)		Validation (n = 48)		Intervention (n = 48)		P value
	No.	%	No.	%	No.	%	
5–9	15	15	6	12.5	8	16.7	
≥ 10	51	51	33	68.8	32	66.7	
Distribution							0.215
Right lobe	16	16	5	10.4	3	6.3	
Left lobe	1	1	2	4.2	0	0	
Caudate lobe	2	2	0	0	0	0	
Multiple lobes	81	81	41	85.4	45	93.8	
Size of the largest lesion (cm)							0.23
Mean diameter	5.77		5.39		6.56		
Range	1.71–15.51		1.66–13.31		1.88–15.61		

validation cohort, and the remaining 48 patients comprised the intervention validation cohort. The clinical and pathologic characteristics were well-balanced except for the proportion of patients receiving combined targeted therapy (**Table 1**).

The ORR was 46% (46/100) in the training cohort and the median PFS and OS were 7.6 months (range, 5.91–9.35 months) and 23.5 months (range, 16.95–30.05 months), respectively.

Seven patients in the validation cohort received chemotherapy plus the target drug regimen (two plus bevacizumab; five plus cetuximab). The ORR was 52.1% (25/48). The median PFS was 9.1 months (range, 7.23–12.3 months) and the median OS was not reached.

Eleven patients in the intervention validation cohort were included in the high-risk group and the chemotherapy regimen was changed (**Table S1**). The ORR was 77.1% (37/48). The median PFS was 11.3 months (range, 10.2–18.5 months) and the median OS was not reached.

Functional MR signature construction and predictive value for response and survival

Twenty-two DKI sequence features were extracted from the liver MR of each patient in the training cohort. Most of the D-value features increased after one treatment cycle, whereas several K-value features decreased. Twenty texture features, which exhibited the ability to predict chemotherapy efficacy (**Table S2**), were subjected to a binary logistic regression model with a lasso penalty to construct the best texture feature model. One thousand iterations were performed and a texture feature model consisting of 6 MRI texture features had the highest frequency (334). The formula is as follows: risk score = (0.000239681 × baseline-D-std) + (1.174238162 × delta-D-mean) + (4.228526688 × delta-D-DiffEntropy) + (0.034209315 × delta-K-95%) + (0.212348049 × delta-K-DiffEntropy) − (0.002927063 × baseline-K-median). ROC analysis was used and the AUC for the signature was 0.818 (**Figure 2**).

Patients were divided into low- (n = 58) and high-risk groups (n = 42) based on the median value of risk score (−2.325). The ORR in the low-risk group was significantly higher than the high-risk group (72.41% *vs.* 9.52%; $P < 0.001$). Furthermore, the median PFS (5.43 months *vs.* 9.03 months) and median OS (13.67 months *vs.* 25.77 months) in high-risk patients were significantly shorter than high-risk patients, which also indicated the prognostic value of the signature (**Figure 3**).

Validation of the functional MR signature model

The AUC was 0.755 in the validation cohort. The ORRs in low- and high-risk patients were 74.07% (20/27) and 23.81% (5/21), respectively (P = 0.001). In addition, a worse median PFS (7.1 months *vs.* 11.4 months; P = 0.039) and median OS (19.5 months *vs.* not reached; P = 0.0095) were observed in the high-risk group (**Figure 4**).

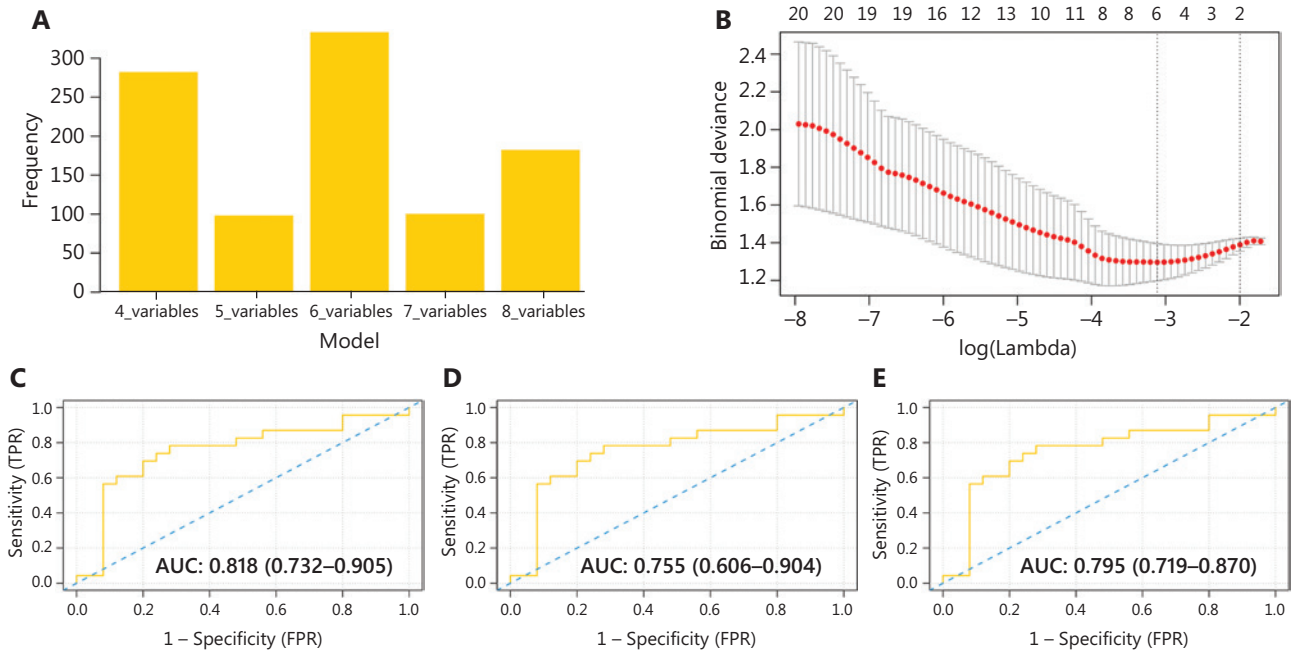


Figure 2 Construction of the MR signature. (A) Models generated after 1,000 iterations. (B) Ten-fold cross-validation for tuning parameter selection in the LASSO model. (C) ROC curve in the training set. (D) ROC curve in the validation set. (E) ROC curve in the training and validation populations.

Among the patients who received the target drug (n = 7), the predicted ORR was 100% in 6 low-risk patients and 0% in 1 high-risk patient.

The good performance of the model was further proven in a total of 148 patients, independent of drug regimen, primary tumor location, and gene status (see **Figures S2**-**S7**).

Model-guided treatment intervention to improve the ORR

The ORR reached 77.1% (37/48) in the intervention validation cohort after treatment adjustment [83.8% (31/37) in unmodified patients (low-risk subgroup) and 54.6% (6/11) in modified high-risk group patients]. The median PFS of the two groups were similar after early intervention (11.3 months in unmodified patients and 15.1 months in modified patients; P = 0.47) and the OS was not reached (**Figure S8**).

The ORR in the intervention validation cohort was significantly improved [77.1% (37/48) *vs.* 47.97% (71/148); P = 0.000] and the median PFS was prolonged (11.3 months *vs.* 8.33 months; P = 0.0085) compared to the combined training and validation cohorts. Treatment intervention guided by the model in high-risk patients contributed to a better response and longer PFS according to the subgroup analysis with ORRs of 54.6% (6/11) *vs.* 14.3% (9/63) and median PFS rates of 15.1 months *vs.* 5.6 months, with P values of 0.002 and 0.027, respectively. No significant difference in efficacy was detected in low-risk patients (**Figure 5**).

The combination of cetuximab with a double-drug regimen improves the ORR[15] unlike bevacizumab[16]. The target drugs used in the validation and intervention cohorts were analyzed (**Table S3**) and patients who received cetuximab were excluded to avoid the influence of target drugs on the response. Improvements in ORR (73.2% *vs.* 50%; P = 0.027) and PFS (10.3 months *vs.* 9.1 months; P = 0.044) were demonstrated between the intervention and validation cohorts and a greater ORR trend (50% *vs.* 23.8%) and prolonged PFS (15.1 months *vs.* 7.1 months; P = 0.017) were observed in the high-risk subgroup (**Figure S9**).

Discussion

The current study explored the functional MR signature model, which is capable of predicting the chemotherapy response of CLM patients early. The value of the functional MR signature model was confirmed in informing treatment

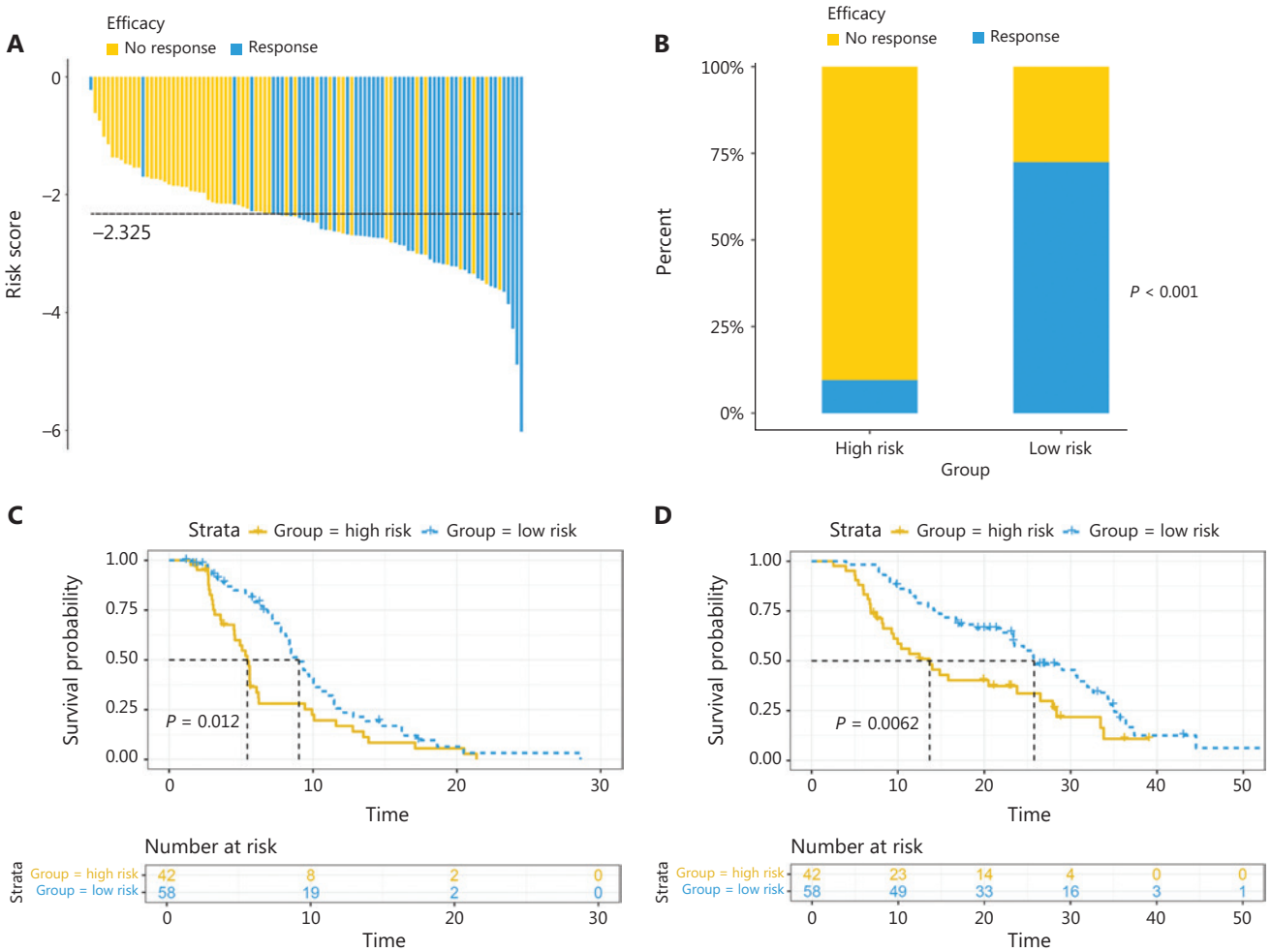


Figure 3 Response and survival of the training set. (A) The waterfall plot showed the treatment response in the training set. (B) The ORR of liver lesions in the training set. (C) The Kaplan-Meier survival curve of PFS in the training set. (D) The Kaplan-Meier survival curve of OS in the training set.

decision-making. This is the first prospective clinical study to investigate and validate a functional MR model in > 100 patients. This model was also applied to guide regimen changes in intervention validation.

Tumor shrinkage is urgently needed in conversion therapy and in patients with a high tumor burden. It is clinically meaningful to adjust the therapeutic regimen to improve the ORR, increase the likelihood of resection, and prolong survival. The ORR is nearly 70% in patients receiving anti-EGFR therapy (e.g., cetuximab) combined with a double- or triple-drug regimen in the first-line setting[17]. However, greater than 50% of patients have RAS/RAF mutations and are not suitable for EGFR antibodies[18]. The ORR is 40%–50% for patients receiving a double-drug regimen with or without bevacizumab. The ORR can reach 70% when a triple-drug regimen is given[19] but increased toxicity and poor tolerance limit use. In addition, not all drugs in triple-drug regimens are effective. In the current study a double-drug regimen with or without bevacizumab guided by an MR model was obtained and an ORR of 73.2% was achieved, which is similar to the triple-drug regimen, excluding patients who received anti-EGFR antibodies. Early response prediction by the MR model can help adjust regimens promptly and avoid unnecessary treatment and toxicity, which has important practical clinical value.

MR-DKI is an advanced non-Gaussian distribution modality introduced by Jensen et al. in 2005 to estimate and quantify the skewed distribution of water diffusion based on a probability distribution function[10]. DKI extracts the kurtosis coefficient (K) in addition to a diffusion coefficient, which shows diffusion deviance from a Gaussian approach and the

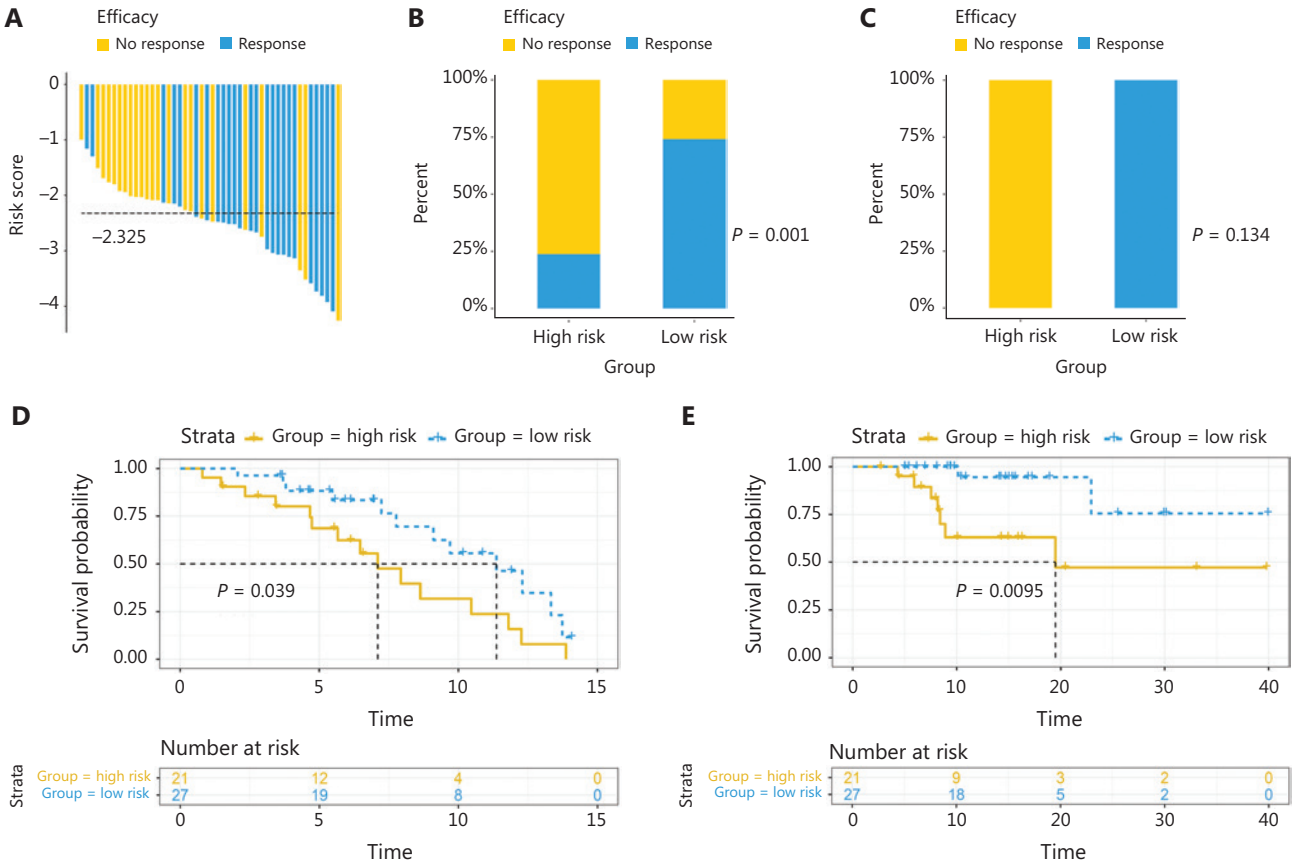


Figure 4 Response and survival of the validation set. (A) The waterfall plot showed the treatment response in the validation set. (B) The ORR of liver lesions in the validation set. (C) The objective response rate of liver lesions in patients plus target drug (n = 7). (D) The Kaplan-Meier survival curve of PFS in the validation set. (E) The Kaplan-Meier survival curve of OS in the validation set.

diffusion coefficient (D) with the correction of non-Gaussian bias. DKI is more accurate for diagnosis and tumor grading compared to traditional ADC mapping[20,21]. DKI is useful in diagnosing pathologic changes in rectal cancer[22,23] by identifying metastatic or benign lymph node status and predicting sensitivity to neoadjuvant chemoradiotherapy[24,25]. Moreover, recent studies have shown that DKI facilitates assessment of molecular gene expression or mutation. The mean K-value has been proven to be more reliable than the mean D-value for detecting positive MMR status and HER2 expression[26]. The increased standard deviation (Std) of the mean K has good diagnostic performance in detecting RAS mutations in patients with CLM[27].

However, the value of DKI in chemotherapy of patients with CLM has not been reported. Based on our previous analysis of 40 cases, pre-treatment IVIM (Dslow), DKI (D and K), and conventional DWI (ADC) parameters showed a good diagnostic performance in predicting the chemotherapeutic response[28]. In the present study there was a focus on the DKI sequence and 9 baseline variables and 11 early changes in variables related to the response were identified. Among the variables, baseline D-Std, baseline K-median, delta D-mean, delta D-DiffEntropy, delta K-95%, and delta K-DiffEntropy were included in the functional MR model. In addition, the mean kurtosis (K-mean) is related to chemotherapy response in certain tumor types[13,29]. Other variables have rarely been reported in previous studies. More importantly, the prognostic value of the model was also demonstrated. Based on the baseline data and data from only one cycle after surgery, high-risk patients not only experienced unsatisfactory tumor shrinkage but also poor survival.

Conclusions

In conclusion, the baseline value and early parameter changes in DKI are good predictive markers for chemotherapeutic response

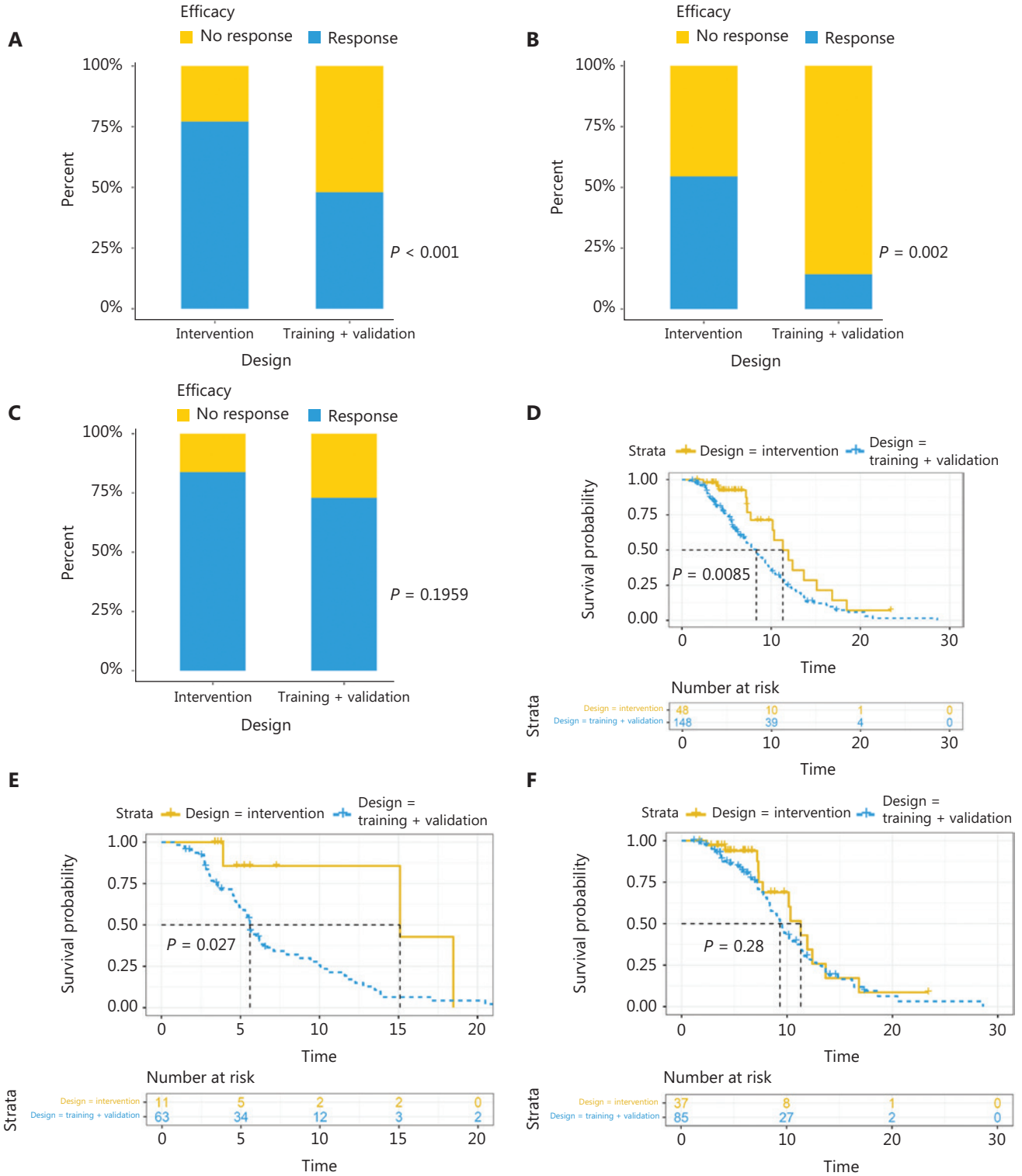


Figure 5 Efficacy comparison between the intervention validation set (n = 48) and combined training and validation sets (n = 148). (A) The difference in ORR between two sets. (B) The ORR difference in high-risk patients between the two sets. (C) The ORR difference in low-risk patients between the two sets. (D) The PFS difference in the two sets. (E) The PFS difference in high-risk patients between the two sets. (F) The PFS difference in low-risk patients between the two sets.

in patients with CLM. The functional MR model is promising for early response prediction and valuable for early guidance of treatment adjustment. The number of patients in the intervention validation cohort was limited and the model needs to be verified in randomized controlled trials with more patients.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Wenhua Li, Huan Zhang, Wen Zhang, Tong Tong, Weijian Guo.
Collected the data: Wenhua Li, Huan Zhang, Zhe Gong, Yue Li
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Performed the analysis: Wenhua Li, Huan Zhang, Zhe Gong, Yue Li.
Wrote the paper: Wenhua Li, Huan Zhang, Weijian Guo.

Data availability statement

The data generated in this study are available upon request from the corresponding author.

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