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Preoperative CT-based morphological heterogeneity for predicting survival in patients with colorectal cancer liver metastases after surgical resection: a retrospective study

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Abstract

Objective To explore the value of preoperative CT-based morphological heterogeneity (MH) for predicting local tumor disease-free survival (LTDFS) and progression-free survival (PFS) in patients with colorectal cancer liver metastases (CRLM).

Methods The latest CT data of 102 CRLM patients were retrospectively analyzed. The morphological score of each liver metastasis was obtained, and the morphological heterogeneity difference (MHD) was calculated. The receiver operating characteristic (ROC) curve was drawn, and the cutoff value was found. The Kaplan-Meier method was used to draw survival curves of patients with or without MH. The Cox regression analysis was used to build the model with MH and clinical characteristics for predicting PFS.

Results In 78 patients without MH, median PFS was 9.0 months (95% CI:6.5–11.5), while in 24 patients with MH, median PFS was 6.0 months (95% CI:4.0-8.1), indicating that MH significantly affected PFS ($p=0.001$). MH affected PFS in both the chemotherapy group and the chemotherapy combined with targeted therapy group ($p=0.005$, $p=0.043$). MH, preoperative carcinoembryonic antigen (CEA) and chemotherapy after surgery were independent predictors for postoperative PFS in patients with CRLM.

Conclusion Preoperative CT-based MH had good efficacy for predicting LTDFS and PFS of CRLM patients after surgical resection, regardless of preoperative treatment. MH is one of the independent predictors of PFS.

Keywords Colorectal cancer, Liver metastases, Heterogeneity, Prognosis, CT

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Background

The global incidence of colorectal cancer is steadily increasing every year [1]. Liver is the most common organ for hematological metastasis of colorectal cancer. About 15–25% of newly treated patients have liver metastasis, and 25–35% of patients develop liver metastasis after surgery or during treatment of primary tumor [2]. Surgical resection remains the best curative treatment for colorectal cancer liver metastasis (CRLM) to achieve long-term survival [3]. However, studies have shown that about 55–60% of patients have recurrence within two years after surgery [4].

Preoperative neoadjuvant therapy can reduce tumor size, transform unresectable liver metastases into resectable ones [5], increase the chance of R0 resection [6] and reduce the chance of local recurrence. During the course of chemotherapy, clinicians need to monitor the response rate and the possibility of surgical resection through radiological evaluation closely to determine whether patients will benefit from surgery. Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, which is commonly used to assess the efficacy of chemotherapy, can only reflect the changes in the size of tumor lesions, but cannot reflect the content of residual tumor cells and the degree of tumor necrosis or fibrosis [7]. Studies have shown that the RECIST version 1.1 cannot accurately predict pathological response in patients treated with targeted therapy such as bevacizumab and cetuximab [8]. Due to the use of targeted therapy, the blood supply to the tumor is reduced, tumor regression and fibrotic replacement occur in the tumor [9], and the pathological response of tumor is increased [10]. In radiology, morphological changes are mainly observed as low density, low enhancement and clear boundary. The change of diameter is less common in patients with targeted therapy than in patients with chemotherapy alone [11]. Morphological response criteria can predict pathological response better than RECIST version 1.1, thus reflecting the efficacy of neoadjuvant therapy and predicting patient prognosis [8, 12].

In the process of tumor evolution, changes in molecular biology or genes cause temporal and spatial heterogeneity of the tumor [13], which can cause difference in the growth rate, invasion ability and sensitivity to drugs [14]. A previous study confirmed that there were significant differences in inter-metastatic heterogeneity between patients, and previous chemotherapy exposure is associated with higher level of heterogeneity, which is a strong prognostic factor by studying the DNA copy number of surgically removed liver metastatic lesions [15]. In addition, pathological study on patients with liver metastases who received preoperative chemotherapy showed that 19.7% of patients had pathological heterogeneity, which was defined as the difference of residual tumor cells between any two lesions > 50%, and 27.6% of patients with pathological heterogeneity had genetic heterogeneity.

The existence of heterogeneity is more likely to promote tumor progression and accelerate the formation of drug resistance [13], which can lead to progression and affect the patient outcome. However, it is impossible to know whether there is inter-metastases heterogeneity in patients at either pathological or genomic level before surgery. Previous radiology studies based on the change of lesion diameter have confirmed that heterogeneity accounts for 11–25% of patients with liver metastases [16, 17]. However, there is no research on morphological heterogeneity of CRLM after chemotherapy with or without targeted therapy. Compared with RECIST, CT-based morphological criteria can better predict the pathological response and survival. Therefore, this study was based on the morphological criteria to study the relationship between the morphological heterogeneity (MH) of metastatic lesions and prognosis.

Materials and methods

Patients

A total of 819 patients with CRLM who underwent liver surgery at our hospital between March 2011 and March 2019 were retrospectively collected. This study was approved by the Ethics Committee of our hospital, which met the ethical requirements, and informed consent was exempted.

Inclusion criteria:

1. Preoperative CT scan was available at our hospital.
2. There were at least two liver metastases (long diameter ≥ 10 mm) on the CT images.
3. Preoperative neoadjuvant therapy (chemotherapy with/without targeted therapy) was performed for at least two cycles.
4. Radical resection of all liver metastases.
5. The interval between the last chemotherapy and preoperative CT was less than 1 month, and the interval between preoperative CT and surgery was less than 1 month.
6. Postoperative pathology confirmed CRLM.

Exclusion criteria:

1. CT scan image quality was poor.
2. The morphological characteristics of CRLM could not be evaluated due to previous local treatment.
3. Peri-operative death.
4. Lost to follow-up.

Imaging examination

This retrospective study analyzed preoperative enhanced CT scans of the upper abdomen. CT examinations were

performed using multi-slice spiral CT scanners, which included GE LightSpeed VCT (GE Healthcare), Discovery 750 HD (GE Healthcare) and Philips Brilliance iCT (Philips Healthcare). The default setting for all CT scanners was 120 KV tube voltage, automatic current, tube speed of 0.8-1.0 r/s, collimation of 64×0.625 mm. The slice thickness and slice spacing of the scanned image was 5 mm. Enhanced scanning was performed with a high-pressure syringe, and iohexol (300 mgI/ml) or ultravist (300 mgI/ml) was injected through the median cubital vein at 3.0 ml/s, at a total dose of 80–100 ml (600 mg/kg). The hepatic arterial and portal vein phases were obtained 25–30 s and 60–80 s after injection, respectively.

For patients with baseline images, enhanced CT scans were prioritized for the study. The scanning equipment and parameters were consistent with those of preoperative CT scans. For patients without baseline enhanced abdominal CT, if baseline MRI examinations were available, the MRI scans were used in the study. The GE OPTIMAL 355 1.5T device (GE Healthcare) and GE Discovery 750 3.0T device (GE Healthcare) were used for MRI examinations. The MRI protocols were showed in the supplementary material.

Preoperative and postoperative treatment

Preoperative neoadjuvant therapy included FOLFOX (oxaliplatin, calcium folate, fluorouracil), XELOX (oxaliplatin, capecitabine) or FOLFIRI (irinotecan, calcium leucovorin, fluorouracil), with or without bevacizumab or cetuximab.

They received almost the same therapy as the preoperative neoadjuvant therapy after surgery. The total duration of preoperative and postoperative chemotherapy was within 6 months.

Morphological score

All CT and MR images were acquired, scored and measured on the Picture Archiving and Communication System (PACS). All CRLMs were scored and measured in the portal phase. The number of measurable liver metastases, size and morphological score of each measurable lesion was recorded.

Morphological evaluation of preoperative abdominal CT scans of 65 patients was independently performed blinded by two radiologists with six years' experience in abdominal radiology. Any disagreement in the evaluation of liver metastases was reviewed by the two radiologists together to reach a consensus. Morphological evaluation of the other 37 patients was performed blinded by one of the radiologists.

The boundary characteristic (scored 1–3) and enhancement characteristic (scored 1–3) of each lesion were evaluated, respectively. The evaluation criteria were based on the morphological response criteria of CRLM, which was shown in the supplementary material. The evaluation criteria was as follows: lesion with clear boundary was scored 1, lesion with partially clear boundary was scored 2, lesion with vague boundary was scored 3; lesion with no enhancement was scored 1, lesion with ring enhancement or heterogeneous enhancement was scored 3, lesion with other type of enhancement (could not be scored as 1 or 3) was scored as 2 (included homogenous enhancement, partial ring enhancement and scattered patchy enhancement). The scoring criteria is shown in Table 1. All measurable liver metastases were evaluated based on the morphological criteria.

Morphological heterogeneity (MH)

Morphological heterogeneity difference (MHD) is defined as the sum of difference between maximum and minimum boundary characteristic score and difference between maximum and minimum enhancement characteristic score of all liver metastases in the same patient, with a range of 0–4. The receiver operating characteristic (ROC) curve was drawn to determine the cutoff value of MHD to predict local tumor disease-free survival (LTDFS) and progression-free survival (PFS). MHD smaller than the cutoff value indicated patient without MH. MHD greater than the cutoff value indicated patient with MH.

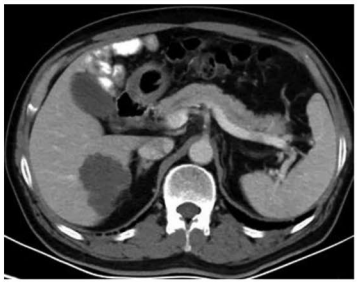
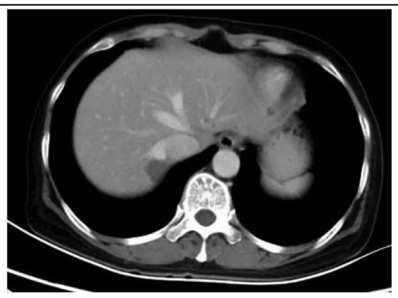
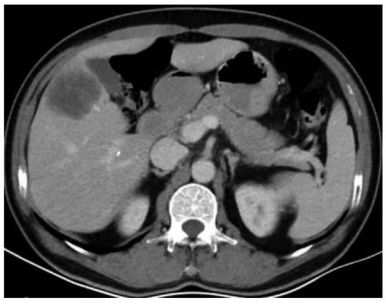
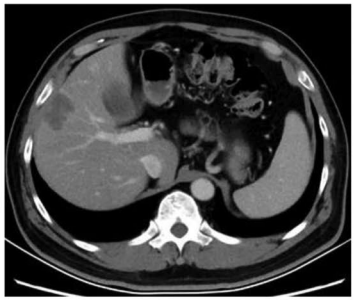
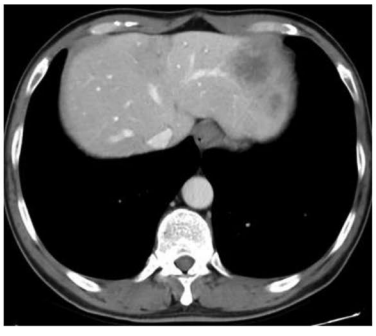
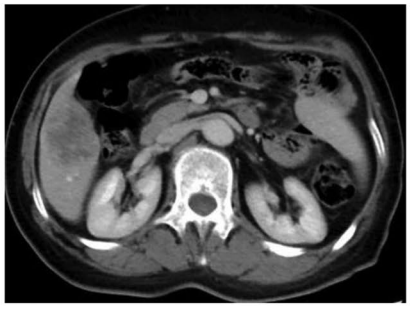
RECIST version 1.1

For a subset of patients who had undergone baseline CT/MRI scans at our hospital, the long diameter of the two largest liver metastases in the baseline examination was measured and recorded. The long diameter of the same lesions in the preoperative examination was also measured in order to calculate the change rate [18]. Complete response (CR) indicated disappearance of all liver lesions. Partial response (PR) indicated a decrease of ≥30% compared with baseline. Progressive disease (PD) indicated an increase of ≥20% compared with baseline, or appearance of new lesions. Stable disease (SD) indicated a diameter change range from 30% decrease to 20% increase. PR and CR belonged to the good response group, PD and SD belonged to the poor response group.

Follow-up

Follow-up ended in November 2022. LTDFS was defined as the time from the date of hepatic surgery to the appearance of new metastatic lesions or recurrence in liver, or the time of death. PFS was defined as the time from the date of hepatic surgery to the primary tumor recurrence, or appearance of new metastatic lesions, or in patients with extrahepatic metastases who developed PD, or the time of death. Overall survival (OS) was defined as the time from the date of hepatic surgery to the time of death or the time of last follow-up. If there

Table 1 The CT morphological score criteria

Morphological score	Tumor-liver interface	Overall enhancement
1		
	Clear boundary	Homogeneous and without enhancement
2		
	Partial clear boundary	Variable (homogeneous enhancement/ partial ring enhancement/ scattered patchy enhancement)
3		
	Vague boundary	Heterogeneous or with ring enhancement

was no recurrence, metastasis or death, LTDFS and PFS was defined as the time of last follow-up.

Statistical methods

SPSS 25.0 software was used for statistical analysis. Kappa statistics were used to determine the agreement between the two radiologists for boundary characteristic and enhancement characteristic of CRLM. Kappa value < 0.2 was considered as poor consistency, 0.2–0.4 was considered as average consistency, 0.4–0.6 was considered as medium consistency, 0.6–0.8 was considered as good consistency and > 0.8 was considered as very good consistency.

Count data was expressed by frequency and compared using Pearson's chi-square test or Continuity Correction Chi-square test. Measurement data of normal distribution was expressed by mean ± SD. Measurement data of non-normal distribution was expressed by median (upper and lower quartiles) and compared using Mann-Whitney U test.

The ROC curve was drawn, and area under the curve (AUC) was calculated to evaluate the effectiveness of MHD for predicting survival. The predictive value of the maximum Youden index (sensitivity + specificity − 1) was considered as the cutoff value. Kaplan-Meier method was used to draw survival curves, and log-rank method was used for comparison. Cox proportional hazard model was established to test the effect of confounding variables on PFS. A $p < 0.05$ was considered as statistically significant difference.

Results

Clinical characteristics

A total of 102 patients were enrolled in this study (Fig. 1). There were 39 females and 63 males, age range 28–82 years. The number of liver metastases ranged from 2 to 16. 70 patients had primary tumor in colon and 32 in rectum. All patients received radical treatment for primary tumor and liver metastases. Furthermore, 90 patients underwent surgery and 12 patients underwent surgery combined with radiofrequency ablation (RFA). Patients with surgery was confirmed R0 resection by pathology, while for patients received treatment with RFA, they all received imaging examination after surgery to confirm that the tumor had no active component. 23 patients had genetic mutation, including 22 RAS gene mutations and 1 BRAF mutation.

The clinical characteristics of patients are shown in Table 2. There were statistical differences in the number of liver lesions and genetic mutations between the groups with MH and without MH ($p < 0.001$, $p = 0.023$).

Among the 102 patients enrolled in this study, 89 had recurrence or appearance of new metastatic lesions, including 74 in liver, 8 in lung, 5 in lymph node, 1 in brain and 1 in ovary.

Agreement for morphological scores

A total of 237 lesions in 65 patients were evaluated by the two radiologists. Kappa values of boundary characteristic and enhancement characteristic were 0.968 ($p < 0.001$) and 0.975 ($p < 0.001$) respectively, which indicated a very high agreement between the two radiologists in the two characteristics. Moreover, 132 lesions in the remaining 37 patients were evaluated by one of the radiologists.

MH

The MHD was between 0 and 4. The AUC for predicting PFS and LTDFS by MHD was 0.635 (95% CI: 0.492–0.778) and 0.561(95% CI:0.429–0.694) (Supplementary Fig. 1). The cutoff value was 2.5, indicates that when MHD is 2, both the two models have the best efficiency.

Among the 78 patients without MH, the MHD ranged from 0 to 2, median LTDFS was 11.0 months (95% CI:7.3–14.7), median PFS was 9.0 months (95%

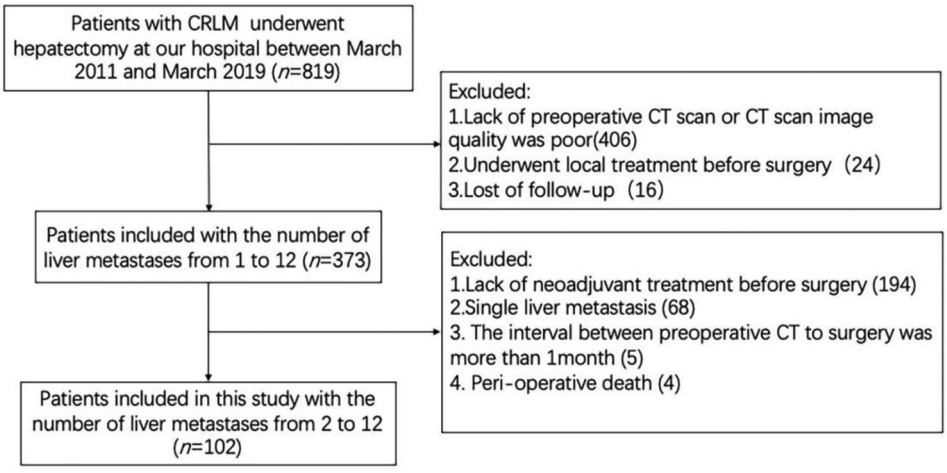


Fig. 1 Patients inclusion and exclusion flowchart of this study

Table 2 Clinical characteristics of patients

	Without MH group (*n* = 78)	With MH group (*n* = 24)	χ^2/Z	*p*-value
Age(year)	56.2 ± 11.2	56.0 ± 10.5	-0.241	0.810
Gender				
Male	47	16	0.319	0.572
Female	31	8		
Time of diagnosing CRLM				
Synchronous	60	22	1.682	0.195
Metachronous	18	2		
Number of liver lesions (median)	2.0 (2.0, 3.35)	5.0 (4.0, 6.0)	-5.594	***<0.001***
length of largest liver lesions (median) (mm)	26 (20, 40.5)	26 (21, 31)	-0.794	0.427
Primary tumor site				
Colon	55	15	0.547	0.459
Rectum	23	9		
T-stage of primary tumor				
1–2	9	0	1.665	0.197
3–4	69	23		
N-stage of primary tumor				
0–1	58	20	1.603	0.205
2	20	3		
Genetic mutation				
No	40	20	5.181	***0.023***
Yes	21	2		
Treatment before surgery				
Chemotherapy	38	9	0.930	0.335
With target therapy	40	15		
Use RFA in surgery				
No	69	21	0.000	1.000
Yes	9	3		
Chemotherapy after surgery				
No	14	2	0.552	0.457
Yes	64	21		
With extrahepatic matastasis				
Yes	13	0	3.208	0.073
No	65	24		
Preoperative CEA (ng/ml)	11.90 (3.82, 44.11)	12.60 (4.18, 23.18)	-0.165	0.869

T-stage tumor-stage, *N-stage* node stage, *RFA* radiofrequency ablation, *CEA* carcinoembryonic antigen

Note: The clinical data of the patients were not comprehensive. There were one case unclear with primary T-stage, one case unclear with N-stage, one case unclear with postoperative chemotherapy, and 19 cases unclear with gene mutation

CI:6.5–11.5). Among the 24 patients with MH, the MHD ranged from 3 to 4, median LTDFS was 7.0 months (95% CI:4.9–9.4), median PFS was 6.0 months (95% CI:4.0-8.1). MH significantly affected LTDFS (p=0.003, Fig. 2a) and PFS (p=0.001, Fig. 2b).

While OS according to MH did not show difference. Median OS was 28.5months (95%CI: 22.8–33.2) for without MH group and 31.5months (95%CI:19.0–43.0) for with MH group (p=0.817, Fig. 2c).

Relationship between MH and preoperative treatment

Preoperative chemotherapy group

There were 47 patients in the preoperative chemotherapy group. Median PFS was 5.0 months (95% CI: 2.1–7.9) in the 9 patients with MH, while median PFS was 10.0 months (95% CI:5.8–14.2) in the 38 patients without MH. MH significantly affected PFS in the chemotherapy group (p=0.005, Fig. 3a).

Preoperative chemotherapy combined with targeted therapy group

There were 55 patients in the preoperative chemotherapy combined with targeted therapy group, including 15 patients with MH and 40 patients without MH. Median PFS was 6.0 months (95% CI:4.1–7.9) for patients with MH, while median PFS was 8.0 months (95% CI:4.3–11.7) for patients without MH. MH significantly affected PFS

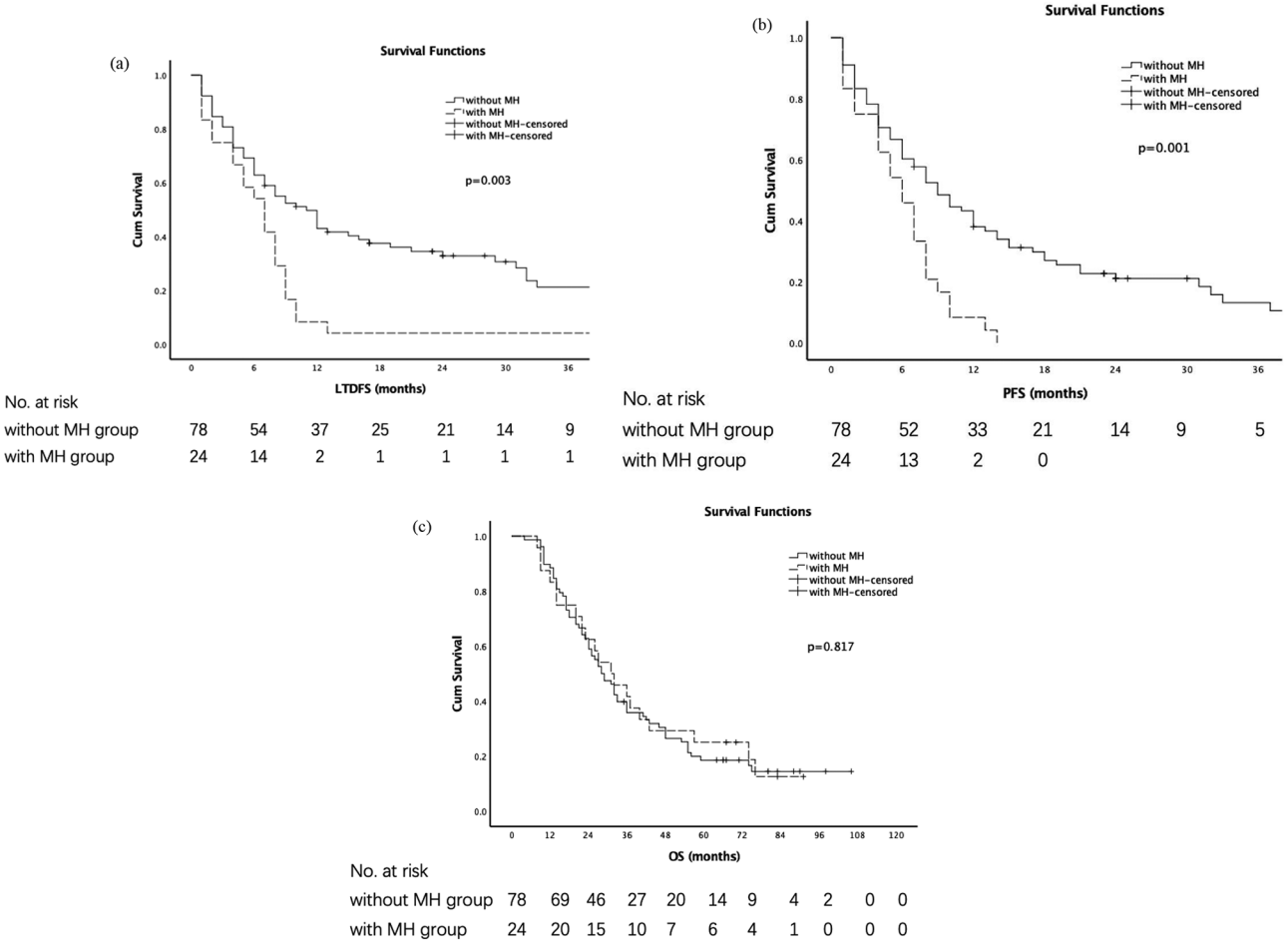


Fig. 2 Kaplan-Meier curve for LTDFS (**a**), PFS (**b**) and OS (**c**) according to MH

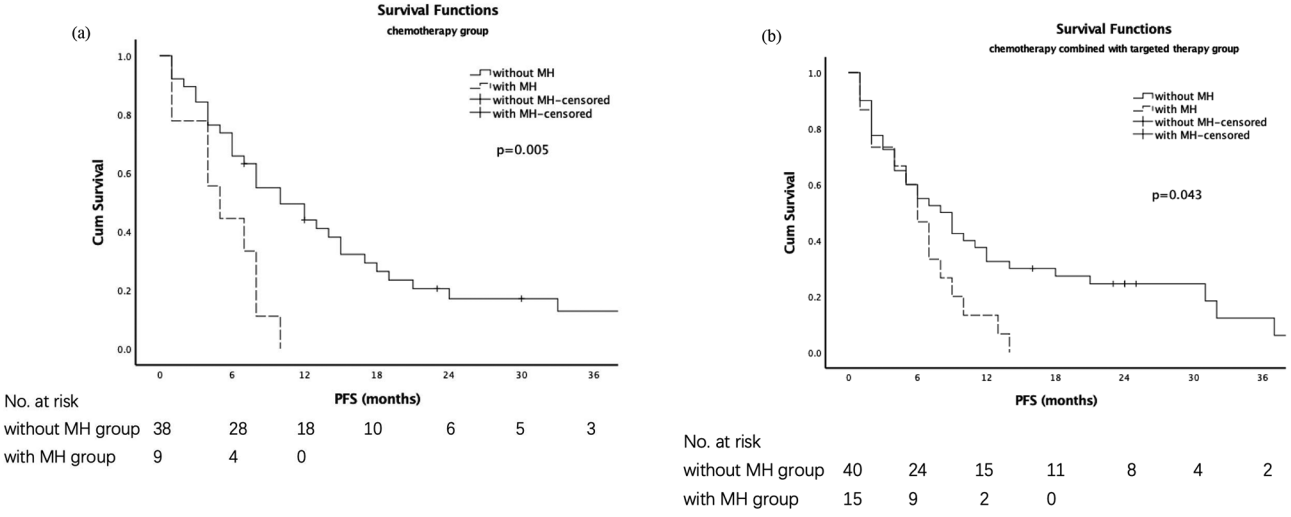


Fig. 3 Kaplan-Meier curve for PFS according to MH in the chemotherapy group (**a**) and the chemotherapy combined with targeted therapy group (**b**)

Table 3 Univariate and multivariate Cox regression model for PFS in CRLM

Characteristic	Univariate Analysis		Multivariate Analysis	
	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Sex (female vs. male)	1.247 (0.810, 1.921)	0.316		
Age (year)	0.992 (0.975, 1.010)	0.379		
Time of finding CRLM (synchronous vs. metachronous)	0.998 (0.587, 1.696)	0.993		
Number of CRLM	1.093 (1.013, 1.179)	***0.022***		
Size of largest CRLM (mm)	1.007 (0.996, 1.019)	0.232		
Primary tumor site (colon vs. rectum)	1.327 (0.851, 2.067)	0.212		
T-stage of primary tumor (1–2 vs. 3–4)	1.266 (0.584, 2.746)	0.550		
N-stage of primary tumor (0–1 vs. 2)	1.509 (0.935, 2.433)	***0.092***		
Genetic mutation (no vs. yes)	1.356 (0.824, 2.231)	0.232		
Treatment before surgery (chemotherapy vs. with target therapy)	1.141 (0.751, 1.734)	0.536		
Use RFA in surgery (no vs. yes)	1.473 (0.795, 2.731)	0.218		
Chemotherapy after surgery (no vs. yes)	0.597 (0.329, 1.084)	***0.090***	0.461 (0.244, 0.871)	***0.017***
With extrahepatic metastases (no vs. yes)	0.783 (0.413, 1.483)	0.453		
Preoperative CEA (ng/ml)	1.001 (1.000, 1.001)	***0.015***	1.001 (1.000, 1.001)	***0.006***
MH (yes vs. no)	2.269 (1.380, 3.732)	***0.001***	2.521 (1.484, 4.284)	***0.001***

T-stage tumor-stage, *N-stage* node stage, *RFA* radiofrequency ablation, *CEA* carcinoembryonic antigen *HR* hazard ratio

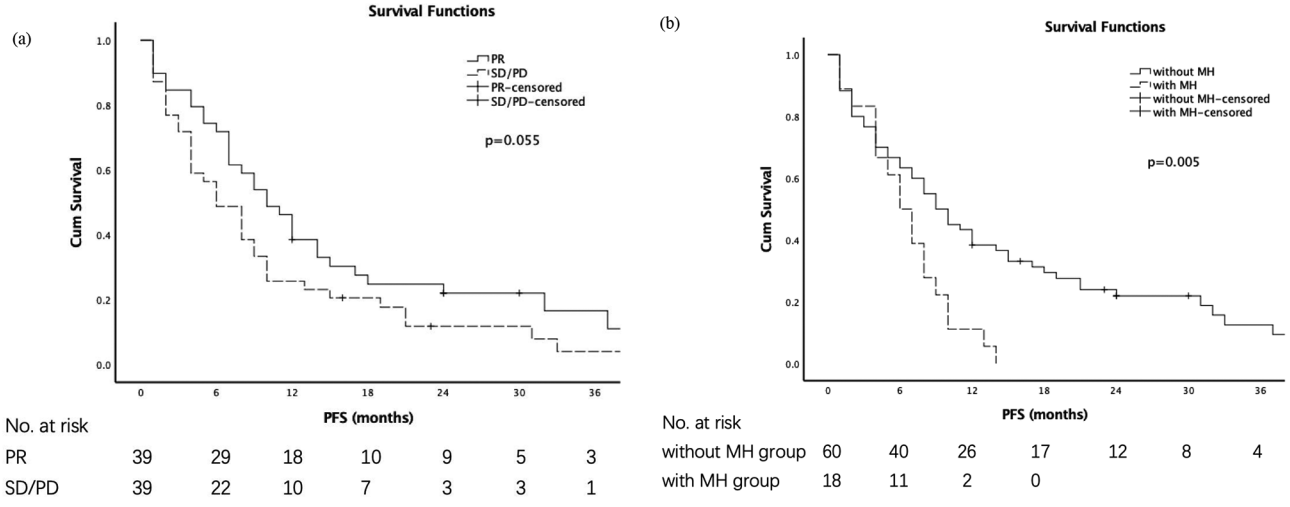


Fig. 4 Kaplan-Meier curve for PFS according to RECIST version 1.1 (**a**) and MH (**b**) in the patients with baseline CT/MR

in the chemotherapy combined with targeted therapy group ($p=0.043$, Fig. 3b).

Cox proportional hazard model for PFS

In the univariate analysis, MH, the number of liver metastases, N-stage of primary tumor, chemotherapy after surgery, and preoperative CEA were correlated with PFS ($p<0.1$). In the multivariate analysis, MH, preoperative CEA and chemotherapy after surgery had statistically significant effect on PFS ($p=0.001$, $p=0.006$, $p=0.017$, Table 3).

Compared with RECIST version 1.1

Among the 102 patients, 78 patients underwent baseline abdominal CT/MRI scans at our hospital. There were 39 patients in the good response group with PR and 39 patients in the poor response group, including 35 patients with SD and 4 patients with PD. There were no significantly difference between good response group and poor response group in PFS (median 10.0 vs.6.0 months, $p=0.055$; Fig. 4a).

Among the 78 patients, there were 60 patients without MH and 18 patients with MH. The patients without MH

had significantly longer PFS than those with MH (median 9.0 vs.6.0 months, $p=0.005$; Fig. 4b).

There are two examples of patients who were inconsistent between the RECIST criteria and MH (Figs. 5 and 6).

Discussion

Surgical treatment is crucial for patients with CRLM [19]. Previous studies have shown that patients with high clinical risk score (CRS), which was proposed by Fong et al., have a poor prognosis. However, this scoring system has not been sufficiently validated externally in the context of neoadjuvant therapy, because of the lack of indicators to evaluate the efficacy of neoadjuvant therapy [20]. The main pathological feature of untreated CRLM was the presence of the large areas of tumor glands with parts of necrosis. Response to neoadjuvant therapy mainly corresponded to the decrease of part or complete disappearance of tumor glands, a reduction of the amount of necrosis, and the appearance or an increase of fibrosis. Most tumor glands were located at the periphery in the CRLM after chemotherapy, which often showed a spiculated configuration at the borders. Because of tumor regression, the reduction of tumor glands and necrosis, the enhancement of liver lesions decreased and turned homogeneous. The more tumor glands remained, the more heterogeneous enhancement was and vaguer the boundary was. We established the morphological score based on the morphological response criteria, in order to study MH in patients with multiple liver metastases (≥2) and the correlation with survival. Compared to patients with MH, patients without MH have 34% higher PFS rate in one year, and 18% in two years. The evaluation criteria was not affected by preoperative treatment. There was statistical difference in both the chemotherapy group

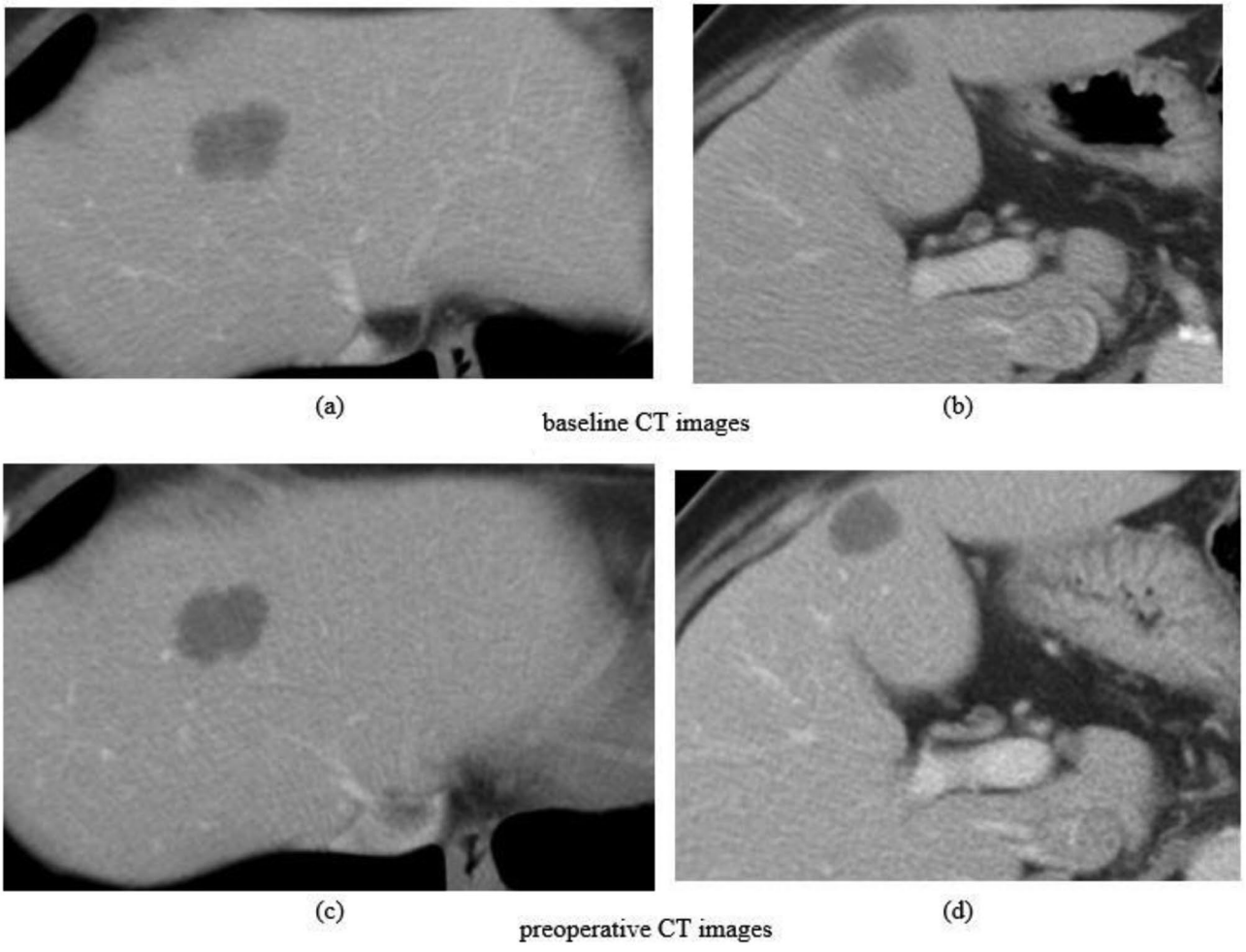


Fig. 5 A patient with a history of CRLM, who underwent radical surgery after 2 cycles of chemotherapy. (**a**) The largest liver metastasis before treatment in segment IV/VIII. It was 29 mm in long diameter. (**b**) The second largest liver metastasis before treatment in segment IV, which was 25 mm in long diameter. (**c**) The largest liver metastasis turned into 25 mm in long diameter, which had clear boundary and without enhancement. (**d**) The second largest liver metastasis turned into 19 mm in long diameter, which also had clear boundary and without enhancement. The liver lesions decreased less than 30%, so this patient belonged to the poor response group. Boundary characteristic and enhancement characteristic were all scored 1 in all liver lesions, and MHD was 0. This patient belonged to without MH group. PFS of this patient was 21 months

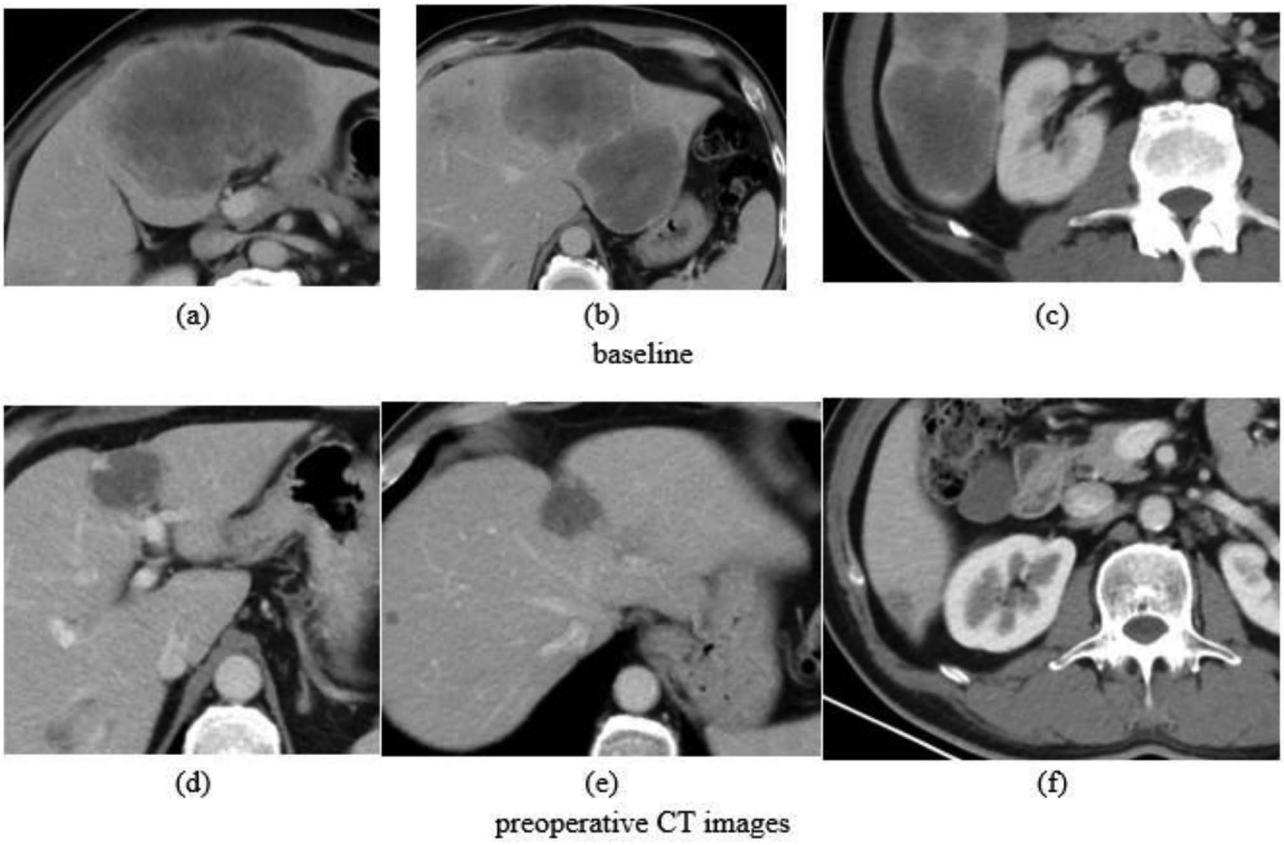


Fig. 6 A patient with a history of CRLM, who underwent radical surgery after 7 cycles of chemotherapy. (**a**) The largest liver metastasis before treatment in segment III, which was 110 mm in long diameter. (**b**) The second largest liver metastasis before treatment in segment II/IV, which was 92 mm in long diameter. (**c**) Another liver metastasis in segment VI before treatment, which was 60 mm in long diameter. (**d**) The largest liver metastasis turned into 33 mm in long diameter after treatment, which had clear boundary and without enhancement. (**e**) The second largest liver metastasis turned into 28 mm in long diameter, which also had clear boundary and without enhancement. (**f**) The same liver lesion with (**c**) after treatment, which decrease to 20 mm, had vague boundary and scattered enhancement. The boundary characteristic and enhancement characteristic were scored as 3 and 2 respectively, which were 1 in other lesions. MHD was 3, and this patient belonged to with MH group. The two largest liver metastases decreased more than 30%, and this patient belonged to the good response group. PFS of this patient was 6 months

and the chemotherapy combined with targeted therapy group.

MH is related with the number of liver lesions. The more lesions there are, the more likely the inter-metastases heterogeneity is to occur. In addition, the number of lesions is also one of the factors affecting the survival of patients. Studies have shown that the prognosis of patients with more than 5 lesions is worse than that of patients with fewer lesions. In our study, there was a statistical difference in the number of lesions between patients with MH and those without MH ($p<0.001$). In univariate analysis, MH and the number of lesions were both affecting factors of patients' PFS ($p=0.017$, $p=0.001$). However, in multivariate analysis, the influence of confounding factors (the number of lesions) could be removed, indicating that MH is an independent predictor for postoperative PFS, not the number of liver metastases.

The traditional RECIST criteria can only consider two liver metastases as target lesions, which cannot reflect the difference in the therapeutic effect of multiple lesions and the overall therapeutic effect of all liver metastases [13]. Therefore, it is not suitable for predicting prognosis.

Our research was based on morphological response criteria [12, 21]. Previous studies on heterogeneity were based on changes of lesion diameter [16, 17], however, the result of evaluation may be different according to different thresholds, which is uncertain and lacks theoretical support. In our study, heterogeneity was transformed into MHD that could be calculated, and the cutoff value of ROC curve was used to evaluate whether there was heterogeneity in morphology.

Our result shows that patients with MH accounted for 23.5% (24/102) of all patients with multiple liver metastases, which is consistent with previous studies. The existence of heterogeneity is more likely to promote tumor progression and accelerate drug resistance. The results

confirmed that patients with MH had poorer prognosis than those without MH.

Many patients had received neoadjuvant therapy before admitted to our hospital, so the baseline image data could not be obtained or was incomplete, which made the evaluation of morphological response and RECIST assessment difficult. However, in our study, we can assess the heterogeneity by evaluating the preoperative CT images alone without the use of baseline images. Compared with other methods, our evaluation method for preoperative CT images alone is simpler and more practical, without the use of baseline image data. Some research show that neoadjuvant chemotherapy improves PFS among patients with CRLM, but whether it improves OS is unclear. MH only reflects different response of liver lesions in CRLM patients to neoadjuvant therapy, which affects PFS rather than OS. Although there was no difference for OS according to MH, we can determine whether the patient can benefit from surgery for risk stratification, by evaluating the MH after neoadjuvant therapy, so as to improve the follow-up of patients with MH.

However, this study had some limitations. First, it was a retrospective study and had done for a long period. Second, the number of patients included in the study was small, especially in subset analysis. In addition, the results of this study lack external validation.

In general, many studies have focused on the morphological response assessment of CRLM, but little is known about the heterogeneity between lesions after neoadjuvant therapy by morphology. This study was based on morphological response criteria, using preoperative CT alone to quantitatively evaluate morphological response. By combining the morphological score with heterogeneity, we calculated MHD, which showed the intermetastases heterogeneity. MH, preoperative CEA and chemotherapy after surgery were independent predictors of PFS after neoadjuvant therapy.

Conclusion

MH had good efficacy for predicting LTDFS and PFS of CRLM patients after surgical resection, but not OS. MH is one of the independent predictors of PFS.

Abbreviations

CEA	Carcinoembryonic antigen
CR	Complete response
CRLM	Colorectal liver metastases
CRS	Clinical risk score
HR	Hazard ratio
MH	Morphological heterogeneity
MHD	Morphological heterogeneity difference
N-stage	Node stage
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	Radiofrequency ablation
SD	Stable disease
T-stage	Tumor stage

Supplementary Information

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Supplementary Material 1

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Author contributions

Qian Xing : Conceptualization, data curation, formal analysis, investigation, methodology, writing - original draft, writing - review & editingYong Cui : Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, writing - original draft, writing - review & editingMing Liu : Data curation, investigation, resources, writing - review & editingXiao-Lei Gu : Data curation, investigation, writing - review & editingXiao-Ting Li : Methodology, writing - review & editingBao-Cai Xing : Data curation, formal analysis, project administration, resources, writing - review & editingYing-Shi Sun : Conceptualization, data curation, formal analysis, project administration, resources, supervision, writing - review & editing.

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Data availability

Data are available through corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of Peking University Cancer Hospital, and the informed consent was waived. All methods were carried out in accordance with relevant guidelines and regulations (declaration of Helsinki).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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