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ONCOLOGY

Late gadolinium MRI enhancement of colorectal liver metastases is associated with overall survival among nonsurgical patients

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Abstract

Purpose To determine if late gadolinium MRI enhancement of colorectal liver metastases (CRCLM) is associated with overall survival among nonsurgical patients.

Materials and methods This retrospective study was approved by the institutional research ethics board. Late gadolinium enhancement was measured using target tumour enhancement (TTE) in all nonsurgical patients with CRCLM who received a 10-min delayed phase gadobutrol-enhanced liver MRI between March 1, 2006, and August 31, 2014. A total of 122 patients met inclusion/exclusion criteria. Patients were dichotomized into strong and weak TTE. Kaplan-Meier and Cox regression statistics were used to determine whether TTE was associated with overall survival. Noncontributory potential confounding variables (age, sex, number and size of metastases, carcinoembryonic (CEA) level, and presence of extrahepatic disease) were excluded from the final Cox regression model using the backward Wald elimination. Subgroup Kaplan-Meier survival analyses were performed on patients who were chemotherapy-naïve and chemotherapy-treated at the time of MRI.

Results Strong TTE had increased survival compared with those with weak TTE on Kaplan-Meier analysis (2-year survival: 69.8% vs. 43.5%, $p = 0.002$). Among 96 patients where data was available for multivariable analysis, weak TTE was associated with death (adjusted hazard ratio 0.25, 95% CI 0.11–0.59, $p = 0.002$), after adjusting for CEA level. Other potential confounders were noncontributory. Subgroup analyses demonstrated that strong TTE had increased survival compared with those with weak TTE in both the chemotherapy-naïve ($p = 0.047$) and chemotherapy-treated ($p = 0.008$) groups.

Conclusion Strong late gadolinium MRI enhancement of CRCLM is associated with overall survival among nonsurgical patients.

Key Points

- *MRI enhancement of colorectal liver metastases is associated with overall survival in nonsurgical patients.*
- *MRI enhancement of colorectal liver metastases is associated with overall survival in both chemotherapy-naïve and chemotherapy-treated subgroups.*

Keywords Magnetic resonance imaging · Contrast media · Neoplasm metastasis · Colorectal neoplasms · Biomarkers, tumour

Abbreviations and acronyms

CEA	Carcinoembryonic antigen
CNR	Contrast-to-noise ratio
CRCLM	Colorectal liver metastases
MRI	Magnetic resonance imaging
REB	Research ethics board
RECIST 1.1	Response Evaluation Criteria in Solid Tumours 1.1
ROI	Region of interest
SD	Standard deviation
SI	Signal intensity
TTE	Target tumour enhancement

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Introduction

Colorectal cancer is the second leading cause of cancer deaths in Europe and North America [1, 2]. The liver is the most common site for metastatic disease and colorectal liver metastases (CRCLM) lead to high morbidity and mortality [3]. In recent years, the survival of patients with CRCLM has improved significantly with advances in targeted chemotherapeutic agents and in surgical techniques. Even among patients with unresectable metastatic disease, the overall survival has increased to more than 30 months [3].

There is growing evidence to suggest that the biology of individual tumours is a significant determinant of prognosis and response to chemotherapy, particularly in the era of targeted chemotherapy agents [4]. Individual tumour subtypes can be distinguished through histology (fibrosis, necrosis, etc.) and genetic signatures (KRAS, BRAF, etc.); however, these techniques require direct tissue sampling of metastases, which is invasive, costly, and prone to undersampling [3]. Liver biopsy is often challenging and potentially dangerous [5]. In addition, there is growing evidence to suggest that tumours can be heterogeneous and are susceptible to mutations over time [6–10]. Therefore, extrapolation of tissue characterization from the primary tumour or from a single liver biopsy may not adequately reflect tissue characteristics of CRCLM [10, 11]. A simple, noninvasive biomarker of prognosis, which could be easily repeated over time, would be helpful for patient management; unfortunately, few such biomarkers are currently available [12].

A recent study showed that late gadolinium enhancement of CRCLM on 10-min delayed phase preoperative MRI in patients who underwent hepatectomy was associated with overall survival post-hepatectomy [13]. No studies to date have looked at whether this imaging biomarker is also associated with overall survival in the nonsurgical population. Therefore, the goal of this study is to determine the association between late gadolinium enhancement of CRCLM and overall survival among nonsurgical patients CRCLM.

Materials and methods

The institutional research ethics board (REB) approved this retrospective study and waived the requirement for informed consent. Patients with CRCLM who received a gadobutrol-enhanced MRI between March 1, 2006, and August 31, 2014, were included in the study. Patients were excluded if they underwent hepatectomy or if they did not have 10-min delayed phase gadobutrol-enhanced MRI that was available or acceptable quality for analysis.

All MRI studies were obtained for diagnosis or staging as per institutional clinical protocols. As per standard clinical liver imaging protocols at our institution, patients received an intravenous dose of gadobutrol (Gadovist) at 0.1 mL/kg body mass up to 10 mL at 1.0 mmol/mL. As part of the contrast-enhanced series, delayed phase axial T1 imaging was performed at 10-min post-contrast injection using either a 1.5-T (GE Twinspeed™; TR 4.5; TE 2.2; flip angle 15°; slice thickness 5 mm; spacing 2.5 mm; FOV 380 mm; matrix 320 × 192) or a 3.0-T (Philips Achieva™; TR 3.0; TE 1.4; flip angle 10°; slice thickness 3 mm; spacing 1.5 mm, FOV 380 mm; matrix 250 × 250) magnet with an eight-channel body phased array surface coil covering the liver.

Clinical information and demographic information were obtained from electronic patient records and obituary databases. This includes age, sex, mean carcinoembryonic antigen (CEA) level within 6 months of the MRI, and death. All-cause mortality was taken as the primary end point in this study.

Imaging analysis

All imaging analysis was performed using clinical picture archiving and communication system (PACS) software (Agfa Impax 6.3.1, AGFA HealthCare N.V.).

Target tumour enhancement (TTE) was measured according to published protocols [13]. Up to two target CRCLM were identified on 10-min delayed phase gadobutrol-enhanced MRI. Target lesions were identified using the same method of target lesion selection in the RECIST 1.1 criteria [14]. If there were no target lesions based on RECIST 1.1 criteria, the patient was excluded from the study. If there were more than two target lesions, then the two largest lesions were used. Target lesions were measured on the single axial slice where the tumour was largest. The mean signal intensity (SI) of the target lesion was measured using a round ROI that most closely approximates the entire tumour. The mean SI of the background liver was measured by taking the mean SI of five 1–2-cm circular ROIs drawn in the surrounding liver parenchyma, avoiding major blood vessels. The standard deviation (SD) of the background noise was calculated from taking the mean SD of eight 1–2-cm ROIs drawn in the background (outside the patient's body). The lesion-liver contrast-to-noise ratio (CNR) for each target CRCLM was calculated as follows:

$$\mathrm{CNR} = \frac{\mathit{Signal\ intensity\ (lesion)} - \mathit{Signal\ intensity\ (liver)}}{\mathit{Standard\ deviation\ (background\ air)}\sqrt{\frac{2}{4-\pi}}}$$

The correction factor for standard deviation:

$$\sqrt{\frac{2}{4-\pi}}$$

was applied to correct for the use of multichannel coil and parallel imaging [15].

TTE was calculated as the mean of the CNR of the target lesions. All measurements were determined by a single reader (HMCC with 6 years of experience) using standard clinical PACS software.

The reader performing the image analysis was blinded to all clinical information other than a history of CRCLM, including the study end point (overall survival) at the time of image analysis.

Statistical analysis

Patients were dichotomized into those with strong TTE and weak TTE as previously described in the literature (Figs. 1 and 2) [13]. The cutoff for strong versus weak TTE was chosen based on the Youden Index for 2-year survival [16]. Baseline demographic data was compared between strong and weak TTE groups using a shi-square test.

Kaplan-Meier statistics were used to determine the univariate relationship of TTE and overall survival.

Cox regression statistics were used to determine the association of TTE and overall death independent of potential confounders. Potential confounders considered in this study included age (≤ 65 years vs. >65 years), sex (male vs. female), carcinoembryonic antigen (CEA) level within 6 months of the MRI (≤ 200 ng/mL vs. >200 ng/mL), number of liver metastases (≤ 5 lesions vs. >5 lesions), size of liver metastases (<5 cm vs. ≥ 5 cm), and presence of extrahepatic disease at the time of MRI (yes vs. no). The backward Wald elimination method was used in order to exclude noncontributory variables.

Subgroup analyses were performed among patients who had received chemotherapy prior to MRI and among patients who had not received chemotherapy prior to MRI using Kaplan-Meier survival analysis.

A p value <0.05 was considered statistically significant. All analyses were performed using SPSS (IBM SPSS Statistics for Macintosh, Version 22.0, 2013. IBM Corp.).

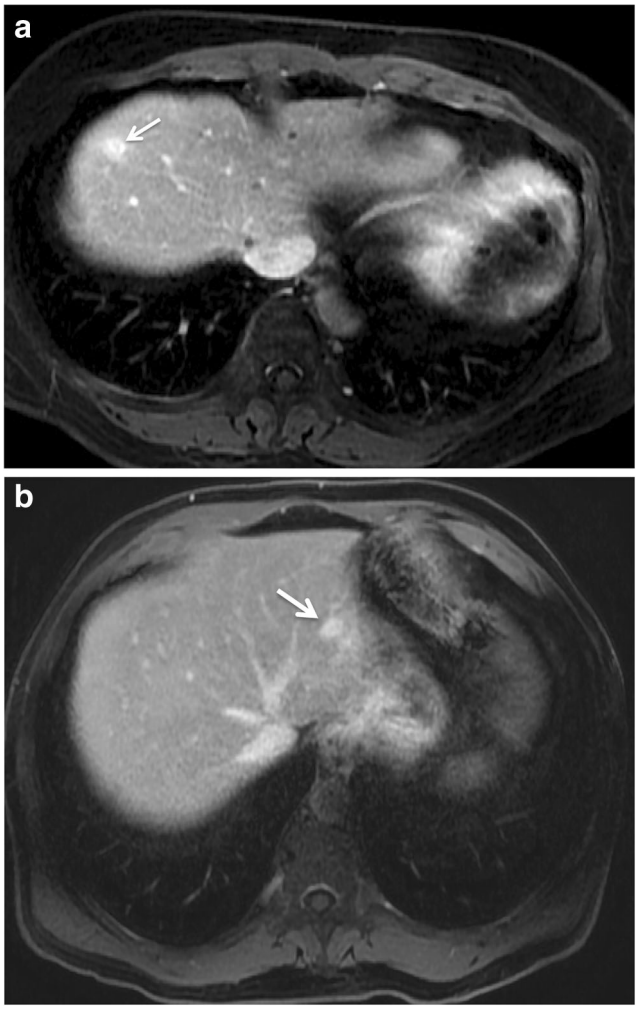

Fig. 1 Abdominal MR image demonstrating strong TTE in colorectal liver metastases in (**a**) a 59-year-old female and (**b**) a 73-year-old male

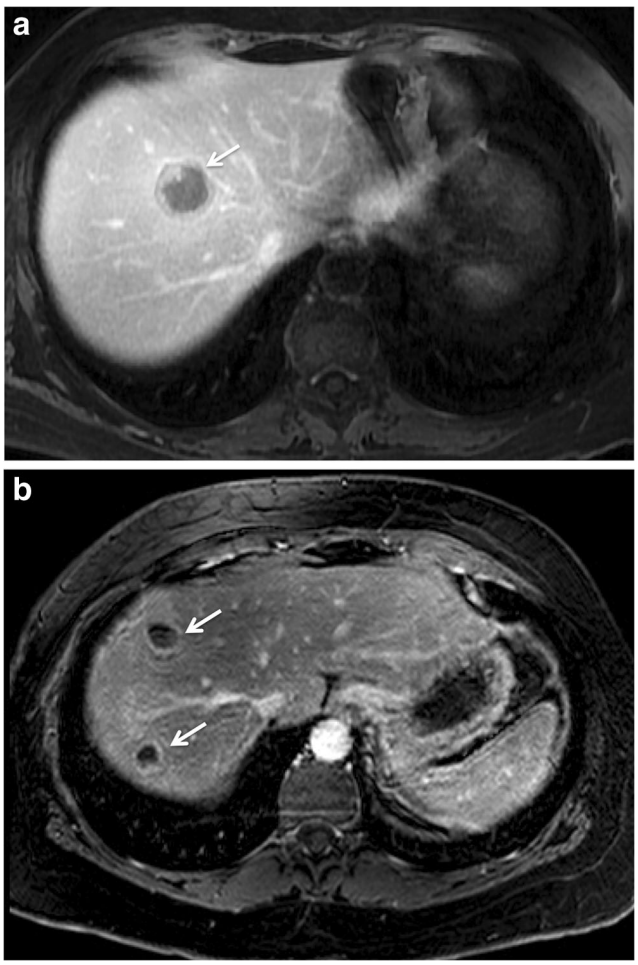

Fig. 2 Abdominal MR image demonstrating weak TTE in colorectal liver metastases in (**a**) a 56-year-old female and (**b**) a 43-year-old female

Results

Patient demographics

A total of 122 patients met inclusion/exclusion criteria for this study. The mean age was 64.7 years (SD, 11.5 years) and 66.2% of the patients were male. A summary of the baseline characteristics of all the patients is shown in Table 1. There were 27 patients who were excluded from the study: 14 patients who had received prior hepatectomy, 6 patients where no 10-min delayed phase imaging was available for analysis, 5 patients where image quality was unacceptable for analysis, and 2 patients with liver metastases from multiple primary cancers.

Using the Youden Index for 2-year survival, a cutoff of TTE = 5 was used to dichotomize patients into strong TTE (TTE ≥ 5) and weak TTE (TTE < 5). There were 37 patients with 9 deaths in the strong TTE group versus 85 patients with 46 deaths in the weak TTE group. There was no difference in baseline demographics between the strong and weak TTE groups. Baseline demographic information is provided in Table 1.

Survival analysis

Using Kaplan-Meier analysis, TTE was significantly associated with survival ($p = 0.002$) (Fig. 3). At 24 months, there were 69.8% (SE, 10.4%) of patients surviving in the strong TTE group (number of events, 6; number at risk, 12) versus 43.5% (SE, 7.1%) in the weak TTE group (number of events, 32; number at risk, 16).

Table 1 Baseline demographics of study patients ($n = 122$)

	Weak TTE ($n = 85$)	Strong TTE ($n = 37$)	p value
Age			
< 65 years	39 (45.9%)	16 (43.2%)	$p = 0.85$
≥ 65 years	46 (54.1%)	21 (56.8%)	
Sex			
Male	52 (61.2%)	26 (70.3%)	$p = 0.41$
Female	33 (38.8%)	11 (29.7%)	
Carcinoembryonic antigen (CEA) level			
< 200 ng/mL	55 (85.9%)	29 (90.6%)	$p = 0.75$
≥ 200 ng/mL	9 (14.1%)	3 (9.4%)	
Missing data	21	5	
Number of colorectal liver metastases			
< 5 lesions	53 (62.4%)	21 (56.8%)	$p = 0.69$
≥ 5 lesions	32 (37.6%)	16 (43.2%)	
Size of largest colorectal liver metastasis			
< 5 cm	65 (76.5%)	32 (86.5%)	$p = 0.23$
≥ 5 cm	20 (23.5%)	5 (13.5%)	
Extrahepatic disease at time of MRI			
No	37 (43.5%)	21 (56.8%)	$p = 0.24$
Yes	48 (56.5%)	16 (43.2%)	

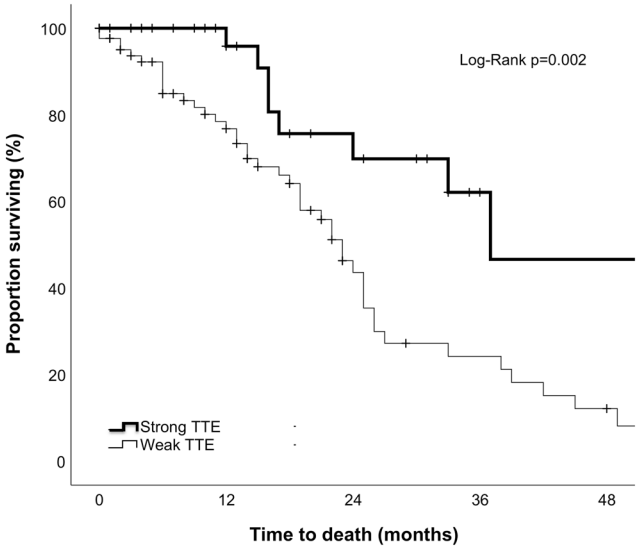

Fig. 3 Kaplan-Meier survival curve demonstrating overall survival in patients with weak vs. strong target tumour enhancement (TTE) in the entire cohort ($n = 122$)

Using Cox regression analysis, age, sex, number of metastases, size of metastases, and presence of extrahepatic disease at time of MRI were noncontributory variables based on the backward Wald elimination method. Therefore, the final Cox regression model included TTE and CEA level within 6 months of MRI. There were a total of 96 patients (with a total of 43 events) where data was available for all variables in the model. The adjusted hazard ratio of death for weak TTE was 0.25 (95% confidence interval, 0.11–0.59; $p = 0.002$), after adjusting for CEA level (Table 2).

Subgroup of patients who had not received chemotherapy prior to MRI

There were 68 patients (with 33 events) who had not received chemotherapy prior to MRI. Among these patients, TTE was significantly associated with survival using Kaplan-Meier analysis ($p = 0.047$) (Fig. 4a). At 24 months, there were

Table 2 Table showing adjusted hazard ratios for target tumour enhancement and carcinoembryonic antigen (CEA) level within 6 months of MRI in final Cox regression model ($n = 96$). Outcome was all-cause mortality

	Adjusted hazard ratio for death (95% CI)	p value
Carcinoembryonic antigen (CEA) level		
< 200 ng/mL	Reference	$p = 0.020$
≥ 200 ng/mL	2.66 (1.16–6.07)	
Target tumour enhancement		
TTE < 5	0.25 (0.11–0.59)	$p = 0.002$
TTE ≥ 5	Reference	

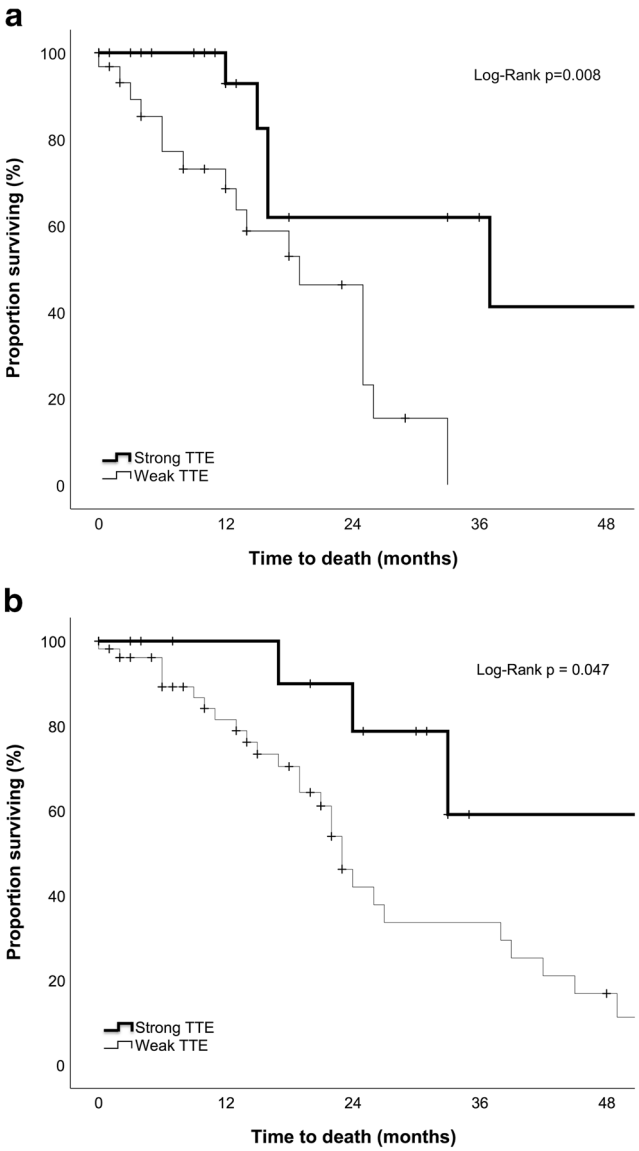

Fig. 4 Kaplan-Meier survival curves demonstrating overall survival in patients with weak vs. strong target tumour enhancement (TTE) (**a**) in the subgroup of patients who did not receive chemotherapy prior to MRI and (**b**) in the subgroup of patients who received chemotherapy prior to MRI

78.8% (SE, 13.4%) of patients surviving in the strong TTE group (number of events, 2; number at risk, 7) versus 42.0% (SE, 8.9%) of patients surviving in the weak TTE group (number of events, 19; number at risk, 12).

Subgroup of patients who had received chemotherapy prior to MRI

There were 54 patients (with 22 events) who had received chemotherapy prior to MRI. Among these patients, TTE was significantly associated with survival using Kaplan-Meier analysis ($p = 0.008$) (Fig. 4b). At 24 months, there were 61.9% (SE, 15.3%) of patients surviving in the strong TTE group (number of events, 4; number at risk, 6) versus 46.3% (SE, 11.3%) of patients surviving in the weak TTE group (number of events, 12; number at risk, 7).

Discussion

This is the first study to demonstrate that late gadolinium MRI enhancement of CRCLM is associated with overall survival in nonsurgical patients after adjusting for potential confounders. Contrast-enhanced MRI is a commonly used imaging test for diagnosis and staging and is available at most major cancer centres [17]. The image analysis used in this study is straightforward and can be performed with standard PACS software at nearly all institutions that offer MRI and requires minimal training. Therefore, this technique could be easily translated for use in clinical practice.

There has been one study to date describing the use of late gadolinium enhancement in CRCLM as a biomarker of survival in preoperative patients undergoing hepatectomy for curative intent [13]. In this population, late gadolinium enhancement is associated with histopathological evidence of tumour fibrosis, which is a known histological predictor of prognosis [18]. In this study, increased tumour fibrosis was associated with increased late gadolinium enhancement or TTE. The current study confirms that the association between late gadolinium enhancement and survival also holds in a nonsurgical population likely via a similar mechanism. However, we were unable to perform radiologic-pathologic analysis in this cohort as patients did not undergo surgery (or biopsy) and therefore pathologic specimens were not available. Future studies are required in order to determine whether the relationship between TTE and fibrosis also holds in this patient population. In addition, future studies are required in order to determine whether TTE is correlated with the degree or the area of tumour enhancement.

The proportion of patients with weak TTE in the current cohort of nonsurgical patients was 74%. In comparison, the proportion of patients with weak TTE in the prior study performed on a surgical population was 39% [13]. The greater proportion of patients with weak TTE may be due to underlying differences in biology of the CRCLM in the different populations. Patients with weak TTE may have less favourable biology, be more likely to present at a more advanced stage, and be unresectable candidates. There was an overall higher mortality rate in the nonsurgical population in the study cohort compared with the surgical population in the prior study, which is expected [13].

The association between TTE and overall survival was seen in both the subgroup of patients who had not received chemotherapy prior to MRI and the subgroup of patients who had received chemotherapy prior to MRI. It is possible that TTE may represent an inherent property of CRCLM and/or a response to chemotherapy treatment. A previous study by

Reddy et al [19] had demonstrated that histopathology evidence of tumour fibrosis post-hepatectomy is associated with overall survival even among patients who had not received any preoperative chemotherapy. The effect of chemotherapy on TTE is unclear. Further prospective studies measuring TTE pre- and post-chemotherapy, controlling for different chemotherapy regimens, and timing of chemotherapy are required in order to better elucidate this relationship.

There are several limitations to this study. This is a relatively small, retrospective study and larger, prospective studies are required for further assessment and external validation. Due to its retrospective nature, there are a number of clinical confounders and technical confounders that may affect the results. Clinical confounders such as chemotherapy regimens may affect the results. Future prospective studies controlling for the timing of MRI in relationship to the administration of chemotherapy, the type of chemotherapy administered, and the duration of chemotherapy are required. Technical confounders such as the multichannel surface coil used to acquire images and the use of parallel imaging techniques will also affect CNR measurements [15, 20]. We attempted to partially correct the effects of multichannel surface coil on noise; however, further studies using more robust methods of measuring noise such as through repeated acquisitions, which could be acquired prospectively, are required [15]. Prospective validation studies are required to standardize techniques for measuring delayed tumour enhancement, assess for the reproducibility, and control for technical MRI parameters. Future prospective studies with fixed MRI parameters are required.

Future studies are required to optimize measurement techniques. TTE was determined based on CNR of up to two target lesions. Target lesions were chosen due to practical considerations, since it was not feasible to measure the CNR of all lesions. Size-based RECIST 1.1 guidelines have previously shown that there was no loss of information using 2 lesions rather than 5 lesions for measuring tumour response [14]. However, it is unclear whether this holds true for target tumour enhancement. Additional studies are required in order to optimize how to address multiple lesions. TTE was measured as the mean signal intensity of the tumours. It is unclear how intra-tumoural heterogeneity may affect this. Future studies analyzing tumoural components including the different enhancement within the tumour would be helpful to better understand this.

Future studies are also required in order to determine the optimal timing to measure TTE. At our institution, late phase imaging is performed at 5-min and 10-min post-contrast injection. We chose to measure TTE at 10-min post-contrast because prior studies have also measured TTE at this time [13]. Prior studies in the cardiac literature suggest that late gadolinium enhancement in the myocardium is best associated with histopathologic evidence of myocardial fibrosis between 10-min and 30-min post-contrast injection [21]. However, it is unclear whether this optimal time period also applies to TTE. Further studies are required to better understand this.

Although MRI with extracellular contrast agents continues to be used routinely for diagnosis and staging of CRCLM at many institutions, some centres now use MRI with hepatobiliary specific contrast agents for this purpose [17]. One study recently demonstrated that late enhancement of CRCLM measured on MRI with hepatobiliary specific contrast agents may also be associated with survival in the surgical population; however, further studies are required to determine if this is the case in the nonsurgical population [22].

The current study provides preliminary evidence that late enhancement of CRCLM may be a potential prognostic imaging biomarker. However, it is unclear whether this could also represent a potential predictive clinical biomarker. In particular, it is unclear based on the current study whether this biomarker can be predict which patients will respond to specific types of chemotherapy. If this were found to be the case, then late gadolinium enhancement of CRCLM could be used in order to stratify patients for different chemotherapy regimens. Further prospective studies are required in order to determine whether this is the case and how late gadolinium enhancement of CRCLM can be used to guide patient management.

In conclusion, this study provides preliminary evidence that late gadolinium tumour enhancement on MRI may represent a prognostic biomarker of survival in a nonsurgical cohort of patients with colorectal liver metastases.

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Compliance with ethical standards

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Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- cross-sectional study
- performed at one institution

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