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HEPATOBILIARY-PANCREAS

Assessment of the residual tumour of colorectal liver metastases after chemotherapy: diffusion-weighted MR magnetic resonance imaging in the peripheral and entire tumour

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Abstract

Objectives To evaluate the value of diffusion-weighted imaging (DWI) in detecting residual tumours (RTs) in colorectal liver metastases (CLMs) following chemotherapy, with a focus on tumour periphery.

Methods From January 2009–January 2012, 57 patients who underwent liver resection for CLMs with preoperative MRI (<3 months) including DWI were retrospectively included. CLMs were classified into three response groups on pathology: (1) major histological (MHR, RTs≤10 %), (2) partial histological (PHR, RT=10–49 %), and (3) no histological (NHR, RT≥50 %). On DWI, regions of interest (ROIs) were drawn around the entire tumour and tumour periphery. Apparent diffusion (ADC) and pure diffusion (D) coefficients were calculated using a monoexponential fit, and compared using Kruskal-Wallis test on a lesion-per-lesion analysis.

Results 111 CLMs were included. Fourteen (12.5 %), 42 (38 %) and 55 (49.5 %) CLMs presented a MHR, PHR and NHR, respectively. ADC and D of the peripheral ROIs were significantly higher in the MHR group (P=0.013/P=0.013). ADC and D from the entire tumour were not significantly different among the groups (P=0.220/P=0.103).

Conclusion In CLM treated with chemotherapy, ADC and D values from the entire tumour are not related to the degree of RT, while peripheral zone diffusion parameters could help identify metastases with MHR.

Key Points

- *Peripheral ADC and D of CLMs were higher with major pathological responses.*
- *Global ADC and D of CLMs were not different according to residual tumour.*
- *Diffusion-weighted images of CLM periphery could be an interesting biomarker of MHR.*
- *Diffusion-weighted images could be used to help tailor treatment.*

Keywords Liver metastases · Lesion periphery · Colorectal cancer · Diffusion weighted-imaging · Residual tumours

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Abbreviations

CLM	Colorectal liver metastases
DWI	Diffusion-weighted imaging
ADC	Apparent diffusion coefficient
D	Pure diffusion coefficient
RT	Residual tumour
MHR	Major histological response
PHR	Partial histological response
NHR	No histological response
RECIST	Response evaluation criteria in solid tumour
MRI	Magnetic resonance imaging

Introduction

Colorectal carcinomas are one of the most common tumours worldwide, and up to 50 % of patients develop liver metastases during the course of their disease [1]. Complete surgical resection with systemic perioperative chemotherapy has been shown to be the most effective strategy for the treatment of colorectal liver metastases (CLMs), resulting in a 5-year overall survival of approximately 50 % [2, 3]. Preoperative chemotherapy is a key element in the management of CLMs, resulting in reduction in tumour size, increase in resectability and improved curative resection rates [2, 4]. Moreover, it has been shown that patients who do not respond to preoperative chemotherapy may not benefit from liver resection [5, 6].

The reference technique to evaluate tumour response is the pathological examination of resected metastases. Tumour necrosis is not a major issue after chemotherapy, because the rate of necrosis is similar in patients with or without preoperative chemotherapy, and has been shown to be a poor predictor of patient outcome [7]. Conversely, the presence of residual cancer cells in CLMs after preoperative chemotherapy is strongly correlated to survival, with higher survival in patients with a major response [8–10]. Therefore, tumour response is assessed by determining the proportion of residual cancer cells in the tumour [7, 8, 10].

Preoperative assessment of tumour response to chemotherapy could provide earlier identification of patients who could benefit from surgical resection or in whom surgical resection should be postponed due to a non-response. Conventional criteria to evaluate tumour response in solid tumours are RECIST, based on changes in tumour size [11]. However, RECIST criteria are poorly correlated with the pathological response of CLMs and the correlation to overall survival is even weaker [12]. Recently, MD Anderson teams have proposed new morphological criteria on CT scan, based on tumour content and tumour-to-liver interface [13, 14]. Although the correlation of these criteria with the pathological response to treatment has been shown to be better than RECIST, they are subjective and can only be applied to CT [13].

MRI is clearly more effective than CT for the preoperative assessment of CLMs, in particular since the introduction of hepatobiliary contrast agents and diffusion-weighted imaging (DWI) [15–20]. DWI is an MRI technique based on the study of the Brownian movements of water molecules. Because diffusion is significantly affected by the structure and composition of tissue and is known to be correlated to cellularity [21], it is an interesting candidate for monitoring tumour response [21]. Both animal models and clinical studies in various tumours have shown that an objective RECIST-based tumoral response corresponds to an increase in diffusion parameters in tumours [22–25]. Studies have also suggested that DWI-MRI could help identify patients with CLMs with a major response to chemotherapy [26–28]. All these previous studies analysed diffusion parameters in the entire tumour and did not focus on peripheral areas where residual cells are more frequently found and which are the site of tumour regrowth [29, 30]. Moreover, these studies did not perform a reference pathological examination but compared DWI to RECIST or lesion volume variation.

Therefore the purpose of our study was to assess the value of DWI, based on the computation of ADC and D coefficients for the detection of residual tumours in CLMs following chemotherapy, focusing on the peripheral tumour and using a pathological examination as a reference.

Patients and methods

Study population

This retrospective single-centre study was institutional review board-approved. Informed consent was waived by the local institutional review board. From January 2009 to January 2012, patients who underwent liver resection for CLMs in our tertiary university hospital were selected from our prospective pathological database. Patients who underwent a preoperative MRI less than 3 months before surgery were identified and those with an MRI including a DWI sequence with our standardized protocol including 3 b values (0, 150 and 600 s/mm^2) were retrospectively included. Exclusion criteria were: (1) patients who underwent an MRI outside of our institution, and (2) MRI not suitable for interpretation due to a poor contrast-to-noise ratio or movement artefacts. The flow chart of the study is presented in Fig. 1. Finally, among the 231 patients who underwent liver resection for CLMs during the study period, 57 patients were included.

Identification of the lesions

All CLMs larger than 1 cm and seen on MRI were matched with the pathological specimen by the study coordinator (VV). CLMs for which a radio-pathological correlation was impossible were excluded. The study coordinator did not participate in either the pathological or the MRI analyses. MRI examinations were performed anonymously and CLMs were labelled. In total, 111 CLMs were included.

Evaluation of pathological response

Haematoxylin and eosin-stained slides of each lesion were retrospectively reviewed by a liver pathologist with 20 years of experience in the field of liver malignancies (VP), blinded to the MRI data. The largest diameter of each CLM was recorded. Each CLM was sectioned into 0.5-cm thick slices and all the samples for each metastasis were examined. All residual tumours were manually quantitatively assessed as the ratio

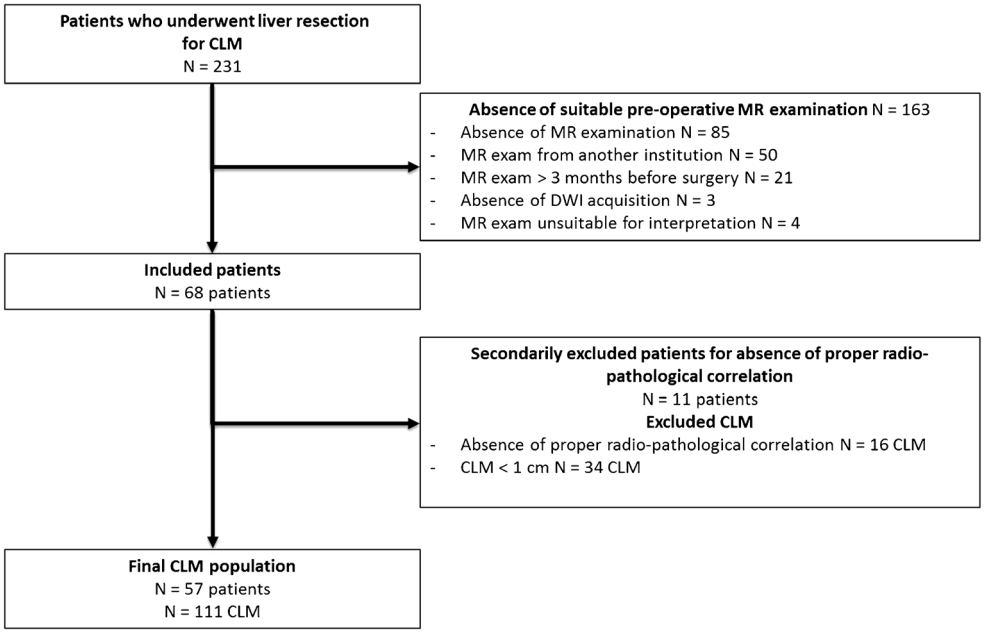

Fig. 1 Flow chart of the study

of residual tumour to the total surface of the lesion, and expressed as a percentage. CLMs were classified into three different groups: (1) major histological response (MHR) if the percentage of residual tumour was less than 10 %, (2) partial histological response (PHR) if the residual tumour percentage was between 10 % and 49 %, and (3) no histological response (NHR) if there more than 50 % of residual cancer cells remained, according to Rubbia-Brandt et al. [8].

MR imaging

MR imaging was performed on a 1.5 T clinical system (Philips Intera, Philips Medical System, Best, The Netherlands). The liver MRI protocol included transverse T2-weighted turbo spin-echo images with fat suppression, transverse T2-weighted single shot turbo spin-echo images, transverse T1-weighted gradient-echo in- and opposed-phase images, transverse single-shot echoplanar DWI with 3 b values (0, 150 and 600 s/mm^2) and dynamic three-dimensional volumetric T1-weighted gradient-echo fat suppressed images before and during the arterial, portal venous and delayed phases after a bolus injection of 0.1 mmol/kg of a non-hepatospecific gadolinium chelate, followed by a 20-ml saline flush (2 mL/s) with a power injector (Spectris, Medrad, Pittsburgh, PA, USA). Total examination time was about 30 min.

MR image analysis

MRI images were retrospectively and independently reviewed by two radiologists with 6 (reader 1), and 10 years (reader 2) of experience in abdominal imaging (MW and MR). Each reader placed an ellipsoid region of interest (ROI) on the equatorial plane of the entire tumour (global ROI) of each CLM labelled on DWI. This global ROI had to be drawn to include the largest portion of the tumour with no surrounding liver parenchyma. Then, each reader was asked to draw a second ellipsoid ROI on the periphery (peripheral ROI) of the tumour. The peripheral ROI was placed anywhere on the periphery of the lesion with no surrounding liver in accordance with previous pathological studies, its small diameter was smaller than 5 mm [31, 32] (Fig. 2).

ROIs were placed on the intermediate b-value image (b= 150 s/mm^2) and pasted on the other b-values images (i.e. b=0 and 600 s/mm^2). The mean signal intensity (SI) for each b-value image was noted for each ROI. The apparent diffusion coefficient (ADC) and the pure diffusion coefficient (D) were then calculated using a monoexponential fit for the global ROI

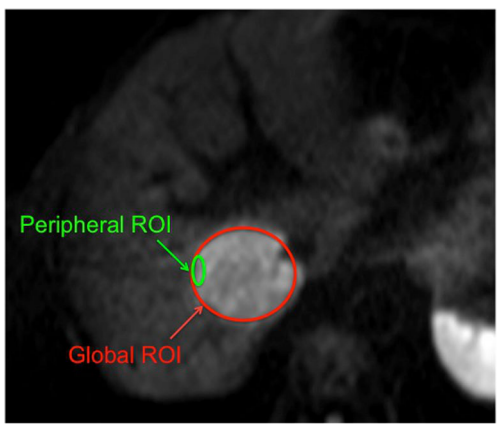

Fig. 2 Example of region of interest (ROI) placement. The global ROI is drawn to include the largest portion of the tumour with no surrounding liver parenchyma, and the peripheral ROI is placed anywhere on the periphery of the lesion with no surrounding liver

(ADC_g and D_g) and the peripheral ROI (ADC_p and D_p) using the SI values obtained at b=0, 150 and 600 s/mm^2 for ADC and only at b=150 and 600 s/mm^2 for D.

Statistical analysis

Results are presented as means±standard deviation or medians and ranges for quantitative data, and as the number of cases (percentage of cases) for categorical variables. As was previously published, intermetastatic heterogeneity is common and therefore we performed a lesion-by-lesion analysis [33, 34]. The correlation between the ADC and D values obtained by the two readers was calculated with a Pearson correlation test and with the intra-class correlation coefficient (ICC). A Bland-Altman analysis was also performed.

The ratios of the ADC and D for peripheral and global ROIs were computed ($ADC_{p/g}$ ratio and $D_{p/g}$ ratio). The values of the diffusion parameters and the ratios of the three groups, MHR, PHR and NHR were compared by a Kruskal-Wallis test for repeated measurements, followed by a Mann-Whitney test for differences between groups, with Bonferroni correction. The diagnostic value of D, ADC and the ratios for differentiating MHR from the two other groups was assessed by non-parametric receiver operating characteristic (ROC) curve analysis. Curves were compared using the DeLong test, and cutoff values were chosen by maximizing the Youden index on the estimated curves. Sensitivity and specificity were computed with exact 95 % confidence intervals.

The values of the diffusion parameters and the ratios in the CLMs depending of the treatment were compared by a Mann-Whitney test for differences between groups.

Tests were always two sided, with a level of significance set at $P<0.05$, except for post-hoc tests for which a level of significance of $P<0.017$ was chosen according to Bonferroni's correction. All analyses were performed using Statistical Package for the Social Sciences (SPSS) software (version 20.0, IBM SPSS Inc., Armonk, NY, USA) and the GraphPad Prism 5.0 software (GraphPad Software, Inc., La Jolla, CA, USA).

Results

Study population

Patient and tumour characteristics are shown in Table 1.

Histological findings

On pathological examination, 14 CLMs (12.5 %) showed a major response, 42 (38 %) a partial response and 55 (49.5 %) no response. The median diameter was 2.1 cm (10–130) in the MHR group, 2 cm (10–180) in the PHR group and 2 cm (10–55) in the NHR group (P=0.98). There was intermetastatic heterogeneity in 13/25 patients with several CLMs (≥2): one patient with CLMs classified into three categories, four patients with MHR and NHR classified CLMs, two patients with MHR and PHR classified CLMs groups, and six patients with PHR and NHR classified CLMs.

Table 1 Patients and colorectal liver metastases (CLM) characteristics

Age	64 (41–83)[a]
Sex	
Male	39 (68)[b]
Female	18 (32)[b]
Primary tumour	
Rectum	16 (28)[b]
Colon	41 (72)[b]
CLM	
Synchronous	29 (51)[b]
Recurrence of synchronous	4 (7)[b]
Metachronous	24 (42)[b]
CLM diameter (mm)	2 (1–18)[a]
Surgery	
Minor hepatectomy	39 (68)[b]
Major hepatectomy	18 (32)[b]
Preoperative chemotherapy	
FOLFOX	36 (63)[b]
FOLFIRI	21 (37)[b]
With targeted therapy	37 (65)[b]
Bevacizumab	26 (46)[b]
Erbitux	11 (19)[b]
Days between MRI and surgery	20 (0–75)[a]

[a] Data are presented as median (range)

[b] Date are presented as number of cases (percentage of cases)

Apparent diffusion and pure diffusion coefficients

Table 2 summarizes the ADC and D values according to the type of treatment (with or without targeted therapy). For all diffusion parameters and ratios, there was no significant difference between the two groups. Only the results for the whole population were presented.

Table 3 summarizes the ADC and D values according to the residual tumours.

For both global and peripheral ROI, the calculated ADC and D values obtained from the two readers were significantly and substantially correlated (global ROI: r=0.73, P <0.0001, ICC=0.836 and r=0.69, P <0.0001, ICC=0.813, for the ADC and D; peripheral ROI: r=0.67, P<0.0001, ICC=0.786 and r=0.62, P<0.0001, ICC=0.750, for the ADC and D). The mean difference between the measurements of the two readers was $0.081\pm0.329\times10^{-3}$ mm^2/sec for ADC_g, $0.080\pm0.374\times10^{-3}$ mm^2/sec for D_g, $0.128\pm0.412\times10^{-3}$ mm^2/sec for ADC_p

Table 2 ADC and D values obtained in entire tumour and at the periphery of the tumour, and ratios $ADC_{p/g}$ ratio and $D_{p/g}$ ratio according to treatment

	Chemotherapy alone N=37 (33)	Chematherapy + targeted therapy N=74 (67)	*P* value
Entire tumour			
ADC_g ($\times10^{-3}$ mm^2/sec)	1.476±0.456	1.474±0.396	0.925
D_g ($\times10^{-3}$ mm^2/sec)	1.306±0.440	1.332±0.441	0.788
Peripheral area			
ADC_p ($\times10^{-3}$ mm^2/sec)	1.463±0.480	1.403±0.453	0.438
D_p ($\times10^{-3}$ mm^2/sec)	1.257±0.484	1.240±0.510	0.726
Ratio			
$ADC_{p/g}$ ratio	0.994±0.159	0.956±0.200	0.173
$D_{p/g}$ ratio	0.976±0.235	0.937±0.246	0.368

ADC apparent diffusion coefficient, *D* pure diffusion coefficient

and $0.142\pm0.486\times10^{-3}$ mm^2/sec for D_p (Fig. 3). The mean ROI value for the two readers was computed and used for the rest of the analysis.

Global analysis

ADC_g and D_g values for the entire tumour were not significantly different among the 3 groups (P=0.220 and P=0.103, respectively) (Figs. 4 and 5).

Peripheral analysis

ADC_p and D_p were significantly different in the three groups (P=0.013, and P=0.013, respectively). ADC_p and D_p values were significantly higher in the MHR group than in the PHR group (P=0.004 and P=0.006), and in the NHR group (P=0.009 and P=0.013) (Figs. 4 and 5). There was no significant difference between ADC_p and D_p in the PHR and NHR groups (P=0.994 and P=0.165, respectively).

$Ratio_{p/g}$ analysis

The $ADC_{p/g}$ ratio was not significantly different for the three groups (P=0.94), while the $D_{p/g}$ ratio was significantly different for the three groups (P=0.019). It was significantly higher in the MHR than in the PHR group (P=0.015), and the NHR group (P=0.006) (Fig. 4).

The subgroup analysis separating patients with standard chemotherapy from those with chemotherapy and targeted therapy showed the same results as the whole population analysis with higher ADC_p, D_p and $D_{p/g}$ ratio in the MHR. The level of significance was not reached, likely due to the lower size of the groups.

ROC curve analysis

The areas under the ROC curves (AUROCs) of ADC_p, D_p and $D_{p/g}$ ratio for differentiating CLMs with MHR from other CLMs were 0.743±0.071 (P=0.003), 0.73±0.078 (P=

Table 3 ADC and D values obtained in entire tumour and at the periphery of the tumour, and ratios $ADC_{p/g}$ ratio and $D_{p/g}$ ratio according to pathologic response

	MHR N=14 (12.5)	PHR N=42 (38)	NHR N=55 (49.5)	*P*-values
Entire tumour (mean of the two readers)				
ADC_g ($\times10^{-3}$ mm^2/sec)	1.643±0.427	1.416±0.373	1.474±0.437	0.220
D_g ($\times10^{-3}$ mm^2/sec)	1.526±0.497	1.228±0.394	1.344±0.444	0.103
Peripheral area (mean of the two readers)				
ADC_p ($\times10^{-3}$ mm^2/sec)	1.749±0.453	1.346±0.437	1.398±0.454	**0.013**
D_p ($\times10^{-3}$ mm^2/sec)	1.653±0.583	1.153±0.476	1.213±0.451	**0.013**
Ratio				
$ADC_{p/g}$ ratio	1.08±0.21	0.94±0.14	0.96±0.21	0.094
$D_{p/g}$ ratio	1.09±0.21	0.94±0.25	0.92±0.24	**0.019**

Values are expressed as mean±standard deviation. Significant *P*-values are in bold

ADC apparent diffusion coefficient, *D* pure diffusion coefficient, *MHR* major histological response, *PHR* partial histological response, *NHR* no histological response

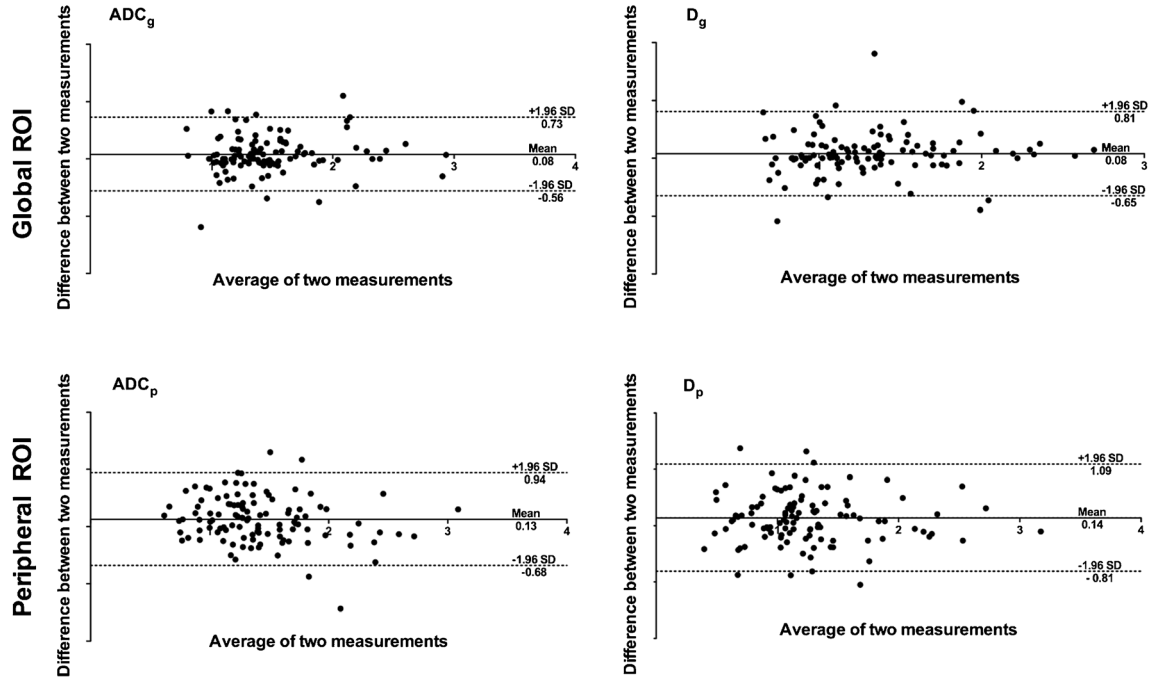

Fig. 3 Bland-Altman plot of the measurements of the two readers. Dotted lines represent the 95 % limits of agreement and solid lines represent the mean bias

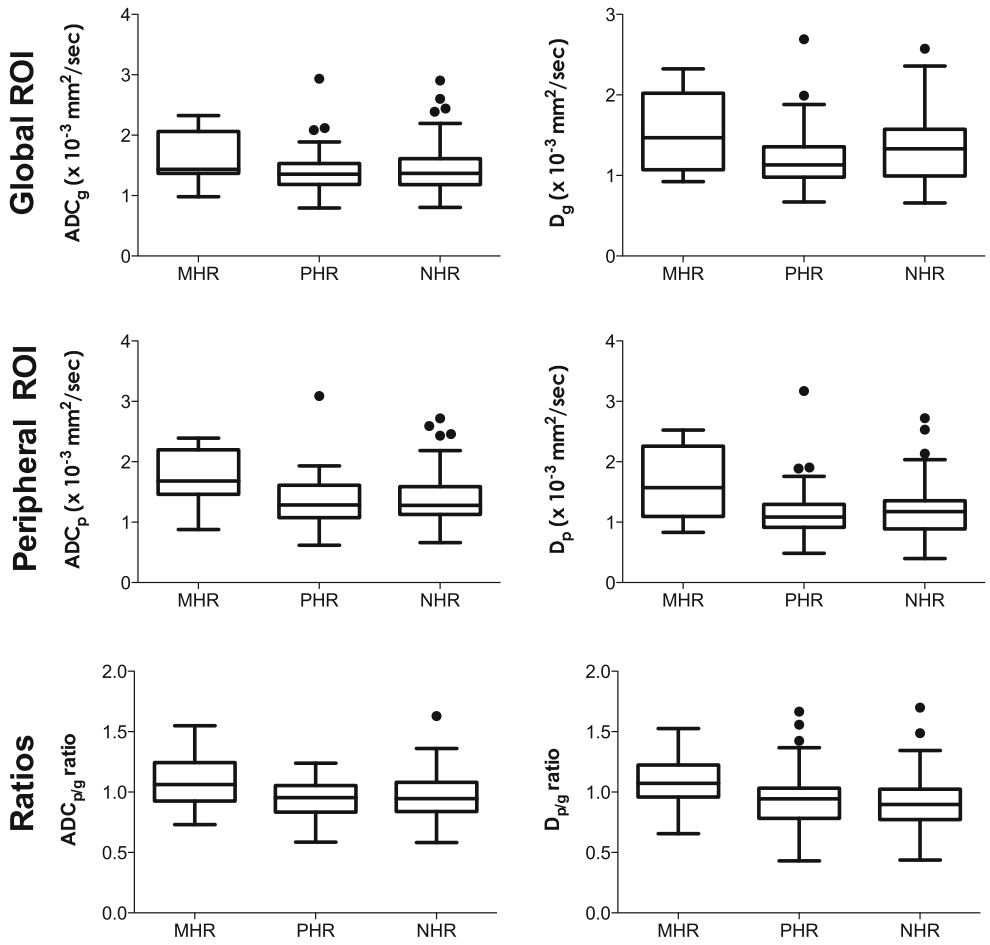

Fig. 4 Apparent diffusion coefficient (ADC) and pure diffusion coefficient (D) values in the entire tumour and in the peripheral zone, $ADC_{p/g}$ ratio and $D_{p/g}$ ratio. For the entire tumour, none of the diffusion parameters (ADC_g and D_g), was statistically different among the three groups. For the peripheral zone, both ADC_p and D_p were statistically different among the three groups. The $ADC_{p/g}$ ratio was not significantly different among the three groups, while the $D_{p/g}$ ratio was significantly different among the three groups. Line within box is the median, and top and bottom of the box are the 25th and 75th percentiles, respectively. Error bars indicate smallest and largest values within 1.5 box lengths of the 25th and 75th percentiles. Outliers are represented as individual points

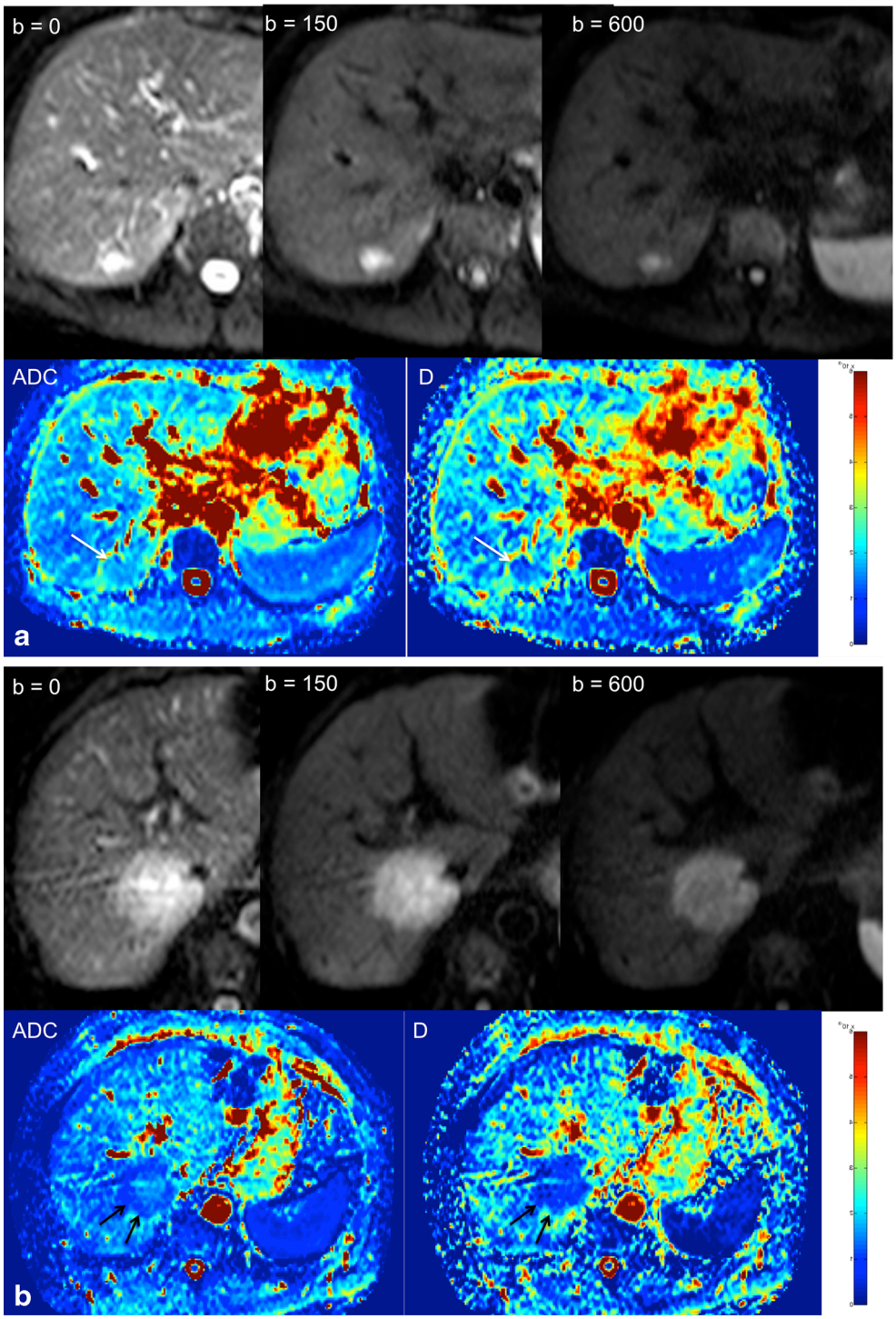

Fig. 5 Example of DW imaging, apparent diffusion coefficient (ADC) and pure diffusion coefficient (D) maps of two colorectal liver metastases (CLMs), one from the MHR group (**a**) and one from the PHR group (**b**). The CLM for the major histological response (MHR) group is homogeneous (white arrows) with no peripheral ring of viable tissue ($ADC_p=1.822\times10^{-3}$ mm^2/sec, $ADC_g=1.719\times10^{-3}$ mm^2/sec, $D_p=1.747\times10^{-3}$ mm^2/sec, $D_g=1.665\times10^{-3}$ mm^2/sec), while the CLM of the partial histological response (PHR) group is heterogeneous with a ring of viable tissue (black arrows), well seen on the ADC map ($ADC_p=1.114\times10^{-3}$ mm^2/sec, $ADC_g=1.305\times10^{-3}$ mm^2/sec, $D_p=913$ mm^2/sec, $D_g=1128$ mm^2/sec)

0.005) and 0.729±0.068 ($P=0.006$), respectively . The AUROCs were not significantly different (ADC_p vs. D_p: $P=0.779$; ADC_p vs. $D_{p/g}$ ratio: $P=0.744$; and D_p vs. $D_{p/g}$ ratio : $P=0.983$) (Fig. 6). Table 4 summarizes the diagnostic values of ADC_p, D_p and $D_{p/g}$ ratio in relation to the best and rule in/rule out cutoffs.

Discussion

Our study shows that the use of DWI-MRI on the periphery of CLMs can help differentiate tumours with a major histological response from those with a partial or without a histological response.

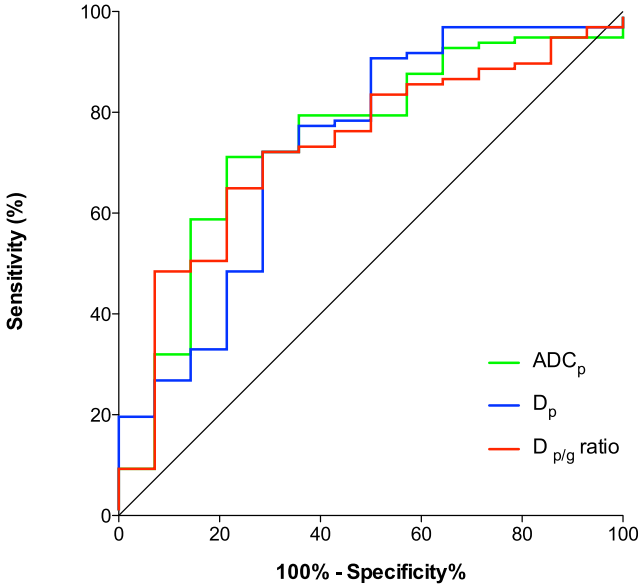

Fig. 6 Receiver operating characteristic (ROC) curves of ADC_p, D_p and $D_{p/g}$ ratio in differentiating between colorectal liver metastases (CLMs) in the major histological response (MHR) group and the other CLMs. Areas under the ROC (AUROCs) and optimal cut-off were 0.743±0.071 (P=0.003) and 1.492×10^{-3} mm^2/s (sensitivity=79 %, specificity=71 %) for ADC_p, 0.73± 0.078 (P=0.005) and 1.304×10^{-3} mm^2/s (sensitivity=71 %, specificity= 72 %) for D_p, and 0.729±0.068 (P=0.006) and 1.005×10^{-3} mm^2/s (sensitivity=71 %, specificity=72 %) for $D_{p/g}$. The AUROCs did not significantly differ (ADC_p vs. D_p: P=0.779; ADC_p vs. $D_{p/g}$ ratio: P=0.744; and D_p vs. $D_{p/g}$ ratio: P=0.983). *ADC* apparent diffusion coefficient, *D* pure diffusion coefficient

No statistical difference in ADC or D coefficients was found between responders and non-responders for the entire tumour (ADC_g and D_g analysis). These results confirm previously published data. Both Cui et al. [27] and Koh et al. [28] reported similar ADC values following chemotherapy between liver metastases with an objective response and the others based on RECIST criteria. More recently, researchers evaluated DWI parameters using an intra-voxel incoherent motion technique in patients with CLMs using pathological results as the reference method. They did not find any correlation between diffusion parameters and residual tumour cells [35]. Conversely, a significant correlation was found between the rate of necrosis and diffusion parameters; however, necrosis is known to be a poor indication of tumour response because the necrosis rate has been shown to be similar in patients who do and who do not receive chemotherapy. Indeed, the main pathological change associated with chemotherapy is the development of fibrosis in association with the tumoral response [7].

Table 4 Receiver operative characteristics of ADC_p, D_p and $D_{p/g}$ ratio values in predicting a MHR in the study population

	Aim	Sensitivity	95 % CI	Specificity	95 % CI
ADC_p ($\times10^{-3}$ mm^2/s)					
>1.492	Optimal	79	49–95	71	61–80
>2.218	Rule in	21	5–51	95	88–98
<0.879	Rule out	100	77–100	9	4–17
D_p ($\times10^{-3}$ mm^2/s)					
>1.304	Optimal	71	42–92	72	62–81
>1.970	Rule in	36	13–65	95	88–98
<0.813	Rule out	100	77–100	20	12–29
$D_{p/g}$ ratio					
>1.005	Optimal	71	42–92	72	62–81
>1.375	Rule in	14	2–43	95	88–98
<0.652	Rule out	100	77–100	9	4–17

Sensitivity and specificity are expressed in percentages

ADC apparent diffusion coefficient, *D* pure diffusion coefficient, *MHR* major histological response, *CI* confidence interval

We also specifically evaluated the periphery of the tumour because residual cells are more frequently found in this part of the lesion after chemotherapy [29, 30]. ADC_p and D_p values were found to be significantly higher in patients with a marked response than in those with a partial or without a histological tumour response. These results confirm recent pathological studies investigating the tumour-normal liver interface in CLMs [31, 32]. Moreover, a multicentre study [31] has shown that tumour thickness at the tumour-normal liver interface was both a predictor of a pathological response and associated with disease-free survival [31].

The higher ADC_p and D_p values observed in patients with a major response in our study are due to the ability of diffusion parameters to differentiate viable from necrotic or fibrotic regions in liver tumours because these parameters are related to cellularity and cell membrane integrity [21, 36]. As expected, no difference in D_p and ADC_p values was found between patients with a partial response and without a response, because residual cells are present in the peripheral area in both groups. Interestingly, $D_{p/g}$ ratio, as ADC_p and D_p, was significantly higher in CLMs with major response. The diffusion ratio could be less sensitive to sequence parameters.

Similarly, the CT morphological criteria described in the study by MD Anderson highlight the analysis of the tumour-to-liver interface [13, 14]. Nevertheless, these criteria are qualitative and only based on CT. Thus, quantitative data using the most recent MRI sequences could provide information to help individually tailor treatment.

In addition to its retrospective design there were several limitations to our study. First, the number of CLMs was not very high. However, to avoid bias, we preferred to carefully select patients and perform a careful radiopathological analysis. Thus, certain patients and CLMs had to be excluded. Second, lesions smaller than 1 cm were also excluded. This exclusion criterion is due to the spatial resolution of the DWI acquisition that did not allow accurate measurement for small ROIs. Moreover, as the study focused on the periphery analysis of CLMs, peripheral ROI of lesion smaller than 1 cm would result in inaccurate values of diffusion parameters due

to partial volume effect. Third, we only analysed MRI performed after chemotherapy and before surgical resection. Therefore we did not determine the variation in the ADC or D values between baseline and post-chemotherapy imaging. Most patients are referred to our centre for liver surgery and pre-chemotherapy imaging is not always available. However, our study focused on the parameters of DWI following chemotherapy in relation to the pathological tumour response. Fourth, to make it simple to draw, the peripheral ROI was not 'doughnut shaped' so that the entire periphery was not included in the analysis. Nevertheless there was a significant correlation between the two readers.

In conclusion, the ADC and D values in the periphery of CLMs were significantly different in relation to the pathological tumour response, and could help identify patients with liver metastases with a major response to chemotherapy.

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