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3T diffusion-weighted MRI in the response assessment of colorectal liver metastases after chemotherapy: Correlation between ADC value and histological tumour regression grading

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ABSTRACT

Purpose: The purpose of the study was to correlate the apparent diffusion coefficient (ADC) values of diffusion-weighted MR imaging (DW-MRI) by 3T device with the histological tumour regression grading (TRG) analysis of colorectal liver metastases after preoperative chemotherapy.

Materials and methods: Our study included thirty-five patients with colorectal liver metastases who had undergone MRI by 3T device (GE DISCOVERY MR750; GE Healthcare) after preoperative chemotherapy. DW-MRI was performed using a single-shot spin-echo echo-planar sequence with multiple *b*-values (0, 150, 500, 1000, 1500 s/mm^2), thus obtaining an ADC map. For each liver lesion (more than 1 cm in diameter) the fitted ADC values were calculated by two radiologists in conference and three ROIs were drawn: around the entire tumour (ADC_e), at the tumour periphery (ADC_p) and at the tumour center (ADC_c). All ADC values were correlated with histopathological findings after surgery. Hepatic metastases were pathologically classified into five groups on the basis of TRG. Statistical analysis was performed on a per-lesion basis utilizing the one-way analysis of variance (ANOVA). This retrospective study was approved by our institutional review board; written informed consent was obtained from all patients.

Results: A total of 106 colorectal liver metastases were included for image analysis. TRG1, TRG2, TRG3, TRG4 and TRG5 were observed in 4, 14, 36, 35 and 17 lesions, respectively. ADC_e and ADC_p values were significantly higher in lesions classified as TRG1 ($2.40 \pm 0.12 \times 10^{-9}$ m^2/s and $2.28 \pm 0.26 \times 10^{-9}$ m^2/s, respectively) and as TRG2 ($1.40 \pm 0.31 \times 10^{-9}$ m^2/s and $1.44 \pm 0.35 \times 10^{-9}$ m^2/s), compared to TRG3 ($1.16 \pm 0.13 \times 10^{-9}$ m^2/s and $1.01 \pm 0.18 \times 10^{-9}$ m^2/s), TRG4 ($1.10 \pm 0.26 \times 10^{-9}$ m^2/s and $0.97 \pm 0.24 \times 10^{-9}$ m^2/s), and TRG5 ($0.93 \pm 0.17 \times 10^{-9}$ m^2/s and $0.82 \pm 0.28 \times 10^{-9}$ m^2/s). ADC_e, ADC_p and ADC_c values were significantly different in TRG classes ($p < 0.0001$). Statistical correlations were found between the ADC_e, ADC_p, ADC_c values and the TRG classes (Spearman correlation coefficient were -0.568, -0.542 and -0.554, respectively).

Conclusion: Our study showed a significant correlation between ADC values of 3T DW-MRI and histological TRG of colorectal liver metastases after preoperative chemotherapy.

1. Introduction

Colorectal carcinoma is the third most common tumour worldwide and up to 50% of patients develop liver metastases; however, colorectal carcinoma is also one of a few malignant tumours in which complete surgical resection, associated with good response to systemic chemotherapy, grants a favourable long-term outcome [1].

Systemic chemotherapy contributes to reducing the risk of recurrence after surgery, increases lesion resectability, and improves the survival of unresectable patients [2–5].

Conventionally, the assessment of tumour response to chemotherapy is radiologically determined by using RECIST (response evaluation

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criteria in solid tumours), based on the reduction in tumour number and size (tumour shrinkage) [6–8]. However, tumour shrinkage is not always concordant with pathologic tumour response [9]. Recently, a histological tumour regression grading (TRG) system has been introduced by Rubbia-Brandt et al. [8], in order to evaluate the degree of histological response to different types of neo-adjuvant chemotherapy regimens in colorectal liver metastases.

Several studies have indicated the potential usefulness of diffusion-weighted MR imaging (DW-MRI), focusing on the added value of apparent diffusion coefficient (ADC) semi-quantitative analysis, to tell apart patients with major metastatic response to chemotherapy (responders) from patients without any response (non-responders) [10–12]. However, in those studies a reference pathological examination using the tumour regression grading (TRG) system [8,12] was not performed.

Taking into account the research available, the purpose of our study was to correlate ADC values of DW-MRI with the histological TRG analysis of colorectal liver metastases after preoperative chemotherapy.

2. Material and methods

This retrospective single-institution study was approved by our institutional review board and a written informed consent was obtained from all patients.

2.1. Patients

From March 2013 to March 2016, 35 patients (25 men and 10 women; mean age, 61.8 ± 8.9 years; range 38–76 years) were retrospectively selected from a list of patients who had undergone DW-MRI as part of their diagnostic workup for colorectal liver metastases at our hospital. The inclusion criteria were: (a) MRI within 1 month prior to surgery; (b) pre-operative chemotherapy concluded less than 3 months prior to MRI; (c) liver lesions, larger than 1 cm, visible on DW-MRI, all resected and pathologically confirmed as colorectal liver metastases. The chemotherapeutic regimen used was fluorouracil-based (FOLFOXIRI, n = 5; FOLFOX, n = 19; FOLFIRI, n = 11), with or without target therapy (18 patients were treated with cetuximab; 9 patients with bevacizumab, and 8 patients with chemotherapy alone). The exclusion criteria were: (a) patients who had received liver local treatment; (b) patients with a history of any other kind of cancer. All 35 patients underwent liver resections in our surgical department using minor–but–complex liver resection ("parenchymal sparing technique" [13–15]).

2.2. MRI technique

All MRIs were performed by a 3T device (GE DISCOVERY MR750; GE Healthcare, Milwaukee, Wisconsin, USA) with an eight-channel phased-array body coil, using a standard liver MRI protocol (Table 1). Axial DW-MRI was acquired through the entire liver using a single-shot spin-echo echo-planar sequence (SE-EPI) with multiple *b*-values (0, 150, 500, 1000, 1500 s/mm^2), parallel imaging technique and with diffusion-weighted gradients applied in all the three orthogonal directions (Table 2).

2.3. Image analysis

MR images were analysed by two radiologists in consensus (with more than 15 and 5 years' experience in abdominal MRI, respectively), on a workstation (Advantage Windows VolumeShare 4.7; GE Healthcare, Milwaukee, Wisconsin, USA), both blinded to the pathological report (TRG) of the liver metastases. First, the radiologists identified the pathologically confirmed metastases, then they performed the quantitative analysis on DW-MRI. Lesions less than 1 cm or with evident artefacts (particularly lesions located on the left hepatic lobe) were excluded from evaluation. For each lesion the following features were recorded: a) lesion location (by using Couinaud segmental anatomy); b) lesion size (maximum diameter measured with a calibre tool on axial diffusion images with *b* value = 0 s/mm^2); c) fitted ADC values. ADC values were measured by drawing an ellipsoid region of interest (ROI) on the images. First, fused images were obtained by the fusion of diffusion images (with *b* value = 1500 s/mm^2) and automated ADC maps – which include all the *b* value images of diffusion acquisition – generated by the built-in software (GeniQ; GE Healthcare, Milwaukee, Wisconsin, USA); then, the ROIs were drawn on the fused images. For each lesion, three ROIs were placed: 1) on the equatorial plane of the entire tumour (entire ROI), drawn to include the largest portion of the tumour without surrounding the liver parenchyma; 2) anywhere on the periphery of the tumour (peripheral ROI), drawn in such a way that its minor axis was less than 5 mm, and its area was 10% of that of the entire tumour ROI; 3) on the isocenter of the tumour (central ROI), where a round ROI was drawn to include 10% of the area of the entire tumour ROI (Fig. 1). ADC values were calculated using a monoexponential fit for the entire, peripheral and central ROIs of all lesions and then the values were recorded.

2.4. Pathological analysis

Following surgical resection, all colorectal liver metastases were macroscopically identified, recorded (number, location and size), and fixed in formalin. Each lesion was sampled extensively at its maximum diameter. When the lesion was too large, representative areas were taken from the center and periphery. Histological hematoxylin-eosin-stained sections were reviewed by a liver pathologist with more than 20 years' experience. Tumour regression was scored for each metastasis according to the scheme of Rubbia-Brandt et al. [8] for the assessment of pathologically documented response after preoperative chemotherapy in colorectal liver metastases. The presence of necrosis or of acellular mucin were also recorded. According to the TRG scoring system, 5 grades were identified on the basis of residual tumour cells and fibrosis. Besides, based on the response to chemotherapy, the metastases were also distinguished into three groups: major histological response (MHR); partial histological response (PHR) and no histological response (NHR) (Fig. 2).

2.5. Statistical analysis

All statistical computations were performed with dedicated software packages (JMP statistical software 7.0, SAS; Cary, NC, USA). Continuous variables were reported as means ± standard deviation (SD); categorical variables were reported as frequencies or percentages. As reported in the literature [16], patients with multiple colorectal liver metastases showed pathological lesion heterogeneity in 19.7% of cases; therefore it was decided to perform a lesion-by-lesion analysis. The correlation between the values of the diffusion parameters of each lesion and the TRG class or of the histopathologic response group assigned (NHR, PHR and MHR), were evaluated (Spearman correlation).

Differences of ADC values grouped on TRG grade and histological response were evaluated according to the one-way analysis of variance (ANOVA).

Comparisons between two unpaired groups were performed using the Bonferroni-Dunn analysis.

Differences were considered statistically significant when the *p* value was less than 0.05.

3. Results

According to our inclusion criteria 114 liver metastases in 35 patients were identified; however, 8 out of 114 lesions were excluded from image analysis because of the presence of artefacts and/or