El-Husseiny et al. Egyptian Journal of Radiology and Nuclear Medicine (2019) 50:87
https://doi.org/10.1186/s43055-019-0070-3

Egyptian Journal of Radiology and Nuclear Medicine

RESEARCH Open Access

Assessment of the percentage of apparent diffusion coefficient value changes as an early indicator of the response of colorectal hepatic metastases to chemotherapy

Nada Gamal El-Husseiny[1], Sayed Mohamed Mehana[1*] and Sherif Farouk El Zawawy[2]

Abstract

Background: Colorectal cancer is considered one of the most common causes of cancer-related deaths worldwide. We aim to evaluate the efficacy of DWI-MRI in predicting response to chemotherapy in this cohort.
The study included 30 lesions in 20 biopsy proven-colorectal cancer patients with hepatic metastasis larger than 1 cm. All patients underwent both triphasic CT with intravenous contrast, pre-chemotherapy MRI (axial T2 and DW sequences) which was repeated 21 days following chemotherapy. A follow-up CT was done 2 months later. The response of the lesions was evaluated using the RESCIST criteria. On MRI, the lesions corresponding to the ones chosen on CT were identified and the apparent diffusion coefficient (ADC) values of pre- and post-chemotherapy images were recorded and correlated with the CT results.

Results: In the study, 17 (56.7%) of the lesions showed response to chemotherapy while 13 (43.3%) were non-responding. There was no significant difference in pretreatment ADC values between responding and non-responding lesions ($p = 0.14$). The mean percentage increase in ADC values in responding lesions was 42% compared to 18% in non-responding lesions ($p < 0.001$). Lesions that showed less than 18% increase were all found to be non-responsive

Conclusion: DWI-MRI has an emerging role in early assessment of early treatment response that can be detected before morphological response for patients with hepatic metastasis from colorectal cancer. Based on our study, the use of 25 % as the cutoff point of percent difference in ADC for detection of non-responding lesions proved to be successful only 21 days after the 1st chemotherapy cycle.

Keywords: Magnetic resonance imaging, Diffusion magnetic resonance imaging, Colorectal neoplasms, Response evaluation criteria in solid tumors, Follow-up studies

Key points

Evaluation of the efficacy of DWI-MRI in predicting response to chemotherapy

Apparent diffusion coefficient (ADC) values of pre- and post-chemotherapy images for hepatic metastases from colorectal cancers

The cutoff points of percent difference in ADC for detection of non-responding hepatic metastases

Background

Colorectal carcinoma (CRC) is considered the third most common cancer in males and the second in females worldwide, it is responsible for over 9% of all cancer incidence [1]. Around 60% of patients with colorectal carcinoma develop a lymph-nodal or a distant metastasis, the liver as the initial site in 30% of hematogenous metastasis [2].

According to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, the size change is currently considered the bases of evaluation of therapeutic response after chemotherapy [3]. However, because

* Correspondence: sayedmehana9@gmail.com
[1]Department of Diagnostic and Intervention Radiodiagnosis, Medical Research Institute, Alexandria University, 165 Alhoreia Street, Alexandria 21561, Egypt
Full list of author information is available at the end of the article

therapy may result in modification in tissue composition despite constant tumor size; moreover, fatty liver infiltration after chemotherapy can affect the *liver parenchyma* impairing the assessment of lesions, functional techniques, such as dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and diffusion-weighted imaging (DWI), which reveal alterations in tissue microstructure rather than macrostructure changes [4, 5].

Apparent diffusion coefficient (ADC) depends on the tissue cellularity. Malignant lesions, such as liver metastases frequently demonstrate low ADC, except in treated lesions or internal necrosis [6]. Tumors with low ADC values before the beginning of the treatment that significantly increased following the first cycle of chemotherapy are suggested in cases of good therapeutic response with a greater decrease in tumor volume after chemotherapy [7, 8].

Despite being not considered in RECIST 1.1, recent publications considered diffusion-weighted MRI (DW-MRI) a promising technique in cancer patients and tumoral response [9]. However, studies on its use for prediction of the response of colorectal liver metastases are limited. So, we aim to investigate the efficacy of DWI-MRI in predicting the response of liver metastases from colorectal cancer to systemic treatment.

Table 1 Site, number, and size of liver lesions

Variable		No. of patients	(%)
Location of liver deposits			
Segment III		4	13.3
Segment IV		6	20.0
Segment V		3	10
Segment VI		1	3.3
Segment VII		8	26.7
Segment VIII		6	20.0
Segment VIII/V interface		1	3.3
Segment VII/VIII interface		1	3.3
Initial number of lesions			
1		2	10.0
2		2	10.0
3		2	10.0
4		2	10.0
6		1	5.0
Multiple (> 6)		11	55.0
Lesion size	Median	Mean ± SD	*p* value
MRI (cm) after 21 days			0.056
Pre-treatment	3.10	4.05 ± 2.73	
Post-treatment	2.80	3.84 ± 2.78	
CT (cm) after 2 months			0.001*
Pre-treatment	2.98	3.87 ± 2.80	
Post-treatment	2.07	2.75 ± 2.38	

p value for Wilcoxon signed ranks test for comparing between pre- and post-chemo. *Statistically significant at $p \leq 0.05$

Methods

This is a prospective study of 20 colorectal cancer patients with liver metastases

Inclusion criteria

Patients having hepatic metastases from pathologically proven colorectal origin with a minimum of one liver metastasis measuring at least 1 cm

Exclusion criteria

History of any other malignant disease, pregnancy, contraindications to MR imaging, and patient with contraindications to chemotherapy

Imaging

Eighteen patients performed pre-chemotherapy baseline triphasic CT with contrast. In the two remaining patients, contrast was not given due to allergy and elevated renal function, and diagnosis of metastases was based on their new appearance compared with the older studies of the patients in US and non-contrast CT while assessment of the size in the current study was done in the T2-weighted MRI sequence.

Lesions were evaluated at the portal phase, and the selected lesion/s was the largest with the maximum number of two lesions chosen as target lesions.

Baseline pre-chemotherapy axial T2-weighted sequence and DW MRI were then done before the first cycle of chemotherapy and repeated 21 days later just before the second cycle.

A follow-up CT was done 2 months later with the measurement of the target lesions.

CT examinations were performed using 64 slice equipment (acquiring images from the top of the liver to the pubic symphysis, before and after the intravenous injection of contrast agent (1.5 ml/kg body weight), during arterial and portal venous phases (35–40 s and 70–75 s after injection, respectively).

MRI was performed using a 1.5-T MRI scanner (SIEMENS-MAGNETOM_ ESSENZA) equipped with phased-array torso surface coil.

Table 2 Descriptive analysis of the studied cases according to ADC ($n = 30$)

ADC	Min.–Max.	Mean ± SD	Median
Pre-chemo	0.65–1.90	1.07 ± 0.30	1.0
Post-chemo	0.72–1.95	1.40 ± 0.31	1.41
% difference	0.0–99.0	31.67 ±23.80	29.50

Table 3 Relation between response with ADC and % difference of size regression

	Response		Test of Sig.	*p*
	Non-responding (*n* = 13)	Responding (*n* = 17)		
ADC				
Pre-chemo				
Mean ± SD.	1.14 ± 0.37	1.01 ± 0.22	*t* = 1.171	0.256
Median	1.0	1.0		
Post-chemo				
Mean ± SD.	1.32 ± 0.33	1.46 ± 0.28	*t* = 1.305	0.203
Median	1.30	1.52		
% difference				
Mean ± SD.	16.23 ± 25.30	39.94 ± 16.98	*U* = 17.000*	< 0.001*
Median	11.0	38.0		

t, p: *t* and *p* values for Student *t* test for comparing between the two categories
U, p: *U* and *p* values for Mann-Whitney test for comparing between the two categories
*Statistically significant at $p \leq 0.05$

Axial T2-weighted free-breathing, with TR (2000), TE (80), matrix (256 × 179), slice thickness (6.5 mm), and gap (20% = 0.8 mm) in the axial plane.

Diffusion-weighted echo-planar imaging (EPI) sequence with TR (4500), TE (73), matrix (192 × 120), slice thickness (7 mm), and gap (50% = 2 mm) in axial plane. The *b* values were 50, 400, and 800 with computer-generated ADC map.

Image analysis on MRI

Images were analyzed by two radiologists independently (consultant and resident), the results were compared, and mismatching results were re-assessed in conjoint.

The lesions corresponding to the ones chosen on CT were identified.

A similar-sized ROI was placed at the same site on the pre- and post-chemotherapeutic images and the two ADC values were compared.

CT image analysis

The maximum diameter of each metastatic lesion was measured before and after treatment. Analysis of the results was done according to the Response Evaluation Criteria in Solid Tumors (RECIST).

A metastatic lesion presenting a 20% or more increase in the maximum transverse diameter with respect to time 0 was classified as progressive disease (PD), a lesion showing at least 30% of reduction in the maximum transverse diameter with respect to time 0 was classified as partial response (PR). A lesion not presenting such dimensional decrease or increase was considered stable disease (SD). From a clinical point of view, lesions with complete cure or regressing (CR and PR, respectively) were also labeled as responding (R), while those progressing and stable were classified as not responding (NR).

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0 (Armonk, NY: IBM Corp). Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation, and median. Significance of the obtained results was judged at the 5% level.

Results

Our cohort consisted of 11 males and 9 females with a mean age of 57.4 ± 11.5 years. Two different chemotherapeutic regimens were used; XELOX (Capecitabine and

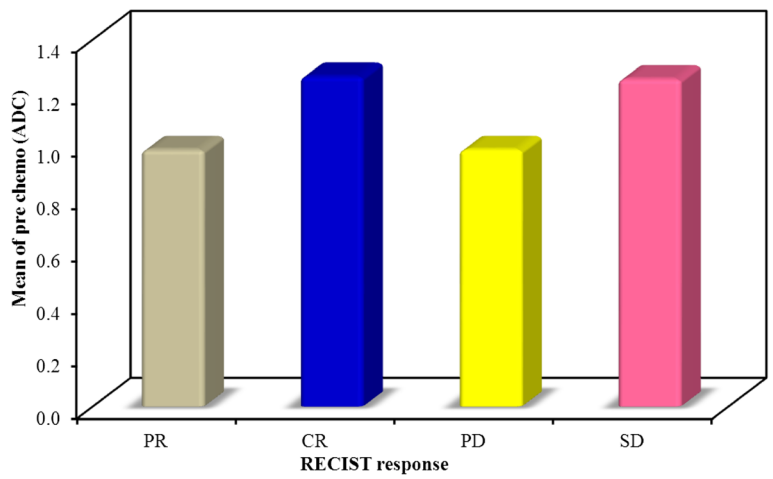

Fig. 1 Pre-treatment ADC values in different response

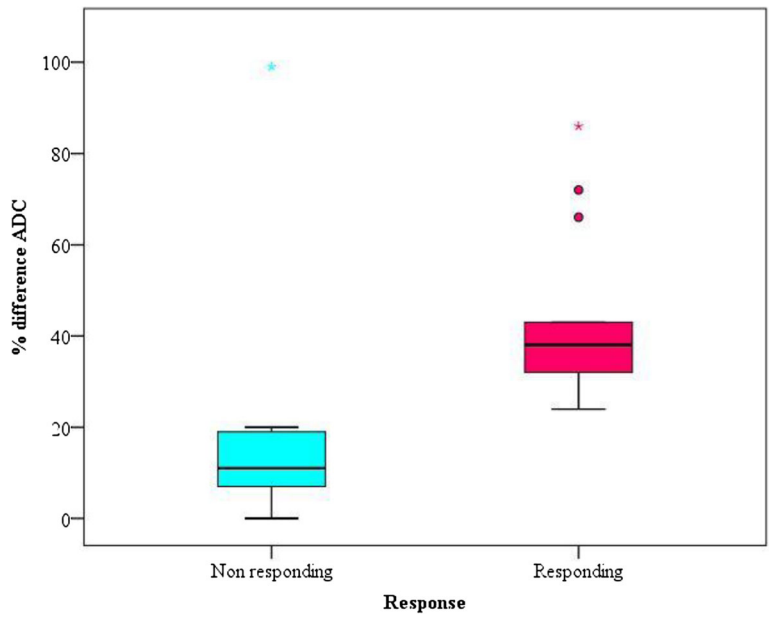

Fig. 2 Relation between response and percent difference ADC

Oxaliplatin) was used in 15/20 (75%) patients. While FOLFOX (5FU, Leucovorin and Oxaliplatin) was used in 5/20 (15%)

Details about the number, location, and size of the lesions before and after chemotherapy are presented in Table 1.

Our data show that there is no significant morphological changes in size in the initial MRI study performed 3 weeks after initiation of the treatment with mean percentage change in the size was 5% (p = 0.056) (Table 1).

The lesion response on CT was evaluated using the RECIST criteria, 15 (50 %) of the lesions showed PR. 4 lesions showed were completely disappeared (complete response (CR)), while 4 lesions showed PD. Seven lesions were characterized as stable (SD).

In view of the RECIST criteria, 19 lesions were overall classified as responding to the chemotherapy (PR and CR lesions) while 11 showed no significant response and were classified as non-responding (SD and PD).

All of the patients were subjected to diffusion-weighted MRI, pre- and post-chemotherapy. The mean percentage difference was about 31.67% (Table 2). Details presented in Table 3.

There was no statistically significant difference between the mean pre-chemotherapeutic ADC values of the responding lesions (PR and CR) and non-responding lesions (PD and SD) (p = 0.139). Therefore, in our study, the pretreatment ADC value was not a good predictor of tumor response (Fig. 1).

The mean percentage increase in ADC value seen in responding lesions was 39.8% while in non-responding lesions was only 16.2%. The p value was < 0.001 (Table 3) which proved that there was indeed a positive relationship between the percentage increase in ADC and the response. In our study, out of the 30 lesions evaluated, lesions that showed less than 20% increase were all found to be non-responding (12 lesions) while 17 out of 18 lesions that showed more than 20% increase were responding (Fig. 2, Table 4).

According to the previously stated results, the use of 25% as the cutoff point of percent difference in ADC for detection of non-responding lesions proved to be successful with a sensitivity of 92.3%, 100% specificity, and

Table 4 Relation between RECIST response and mean pre-, post-chemotherapy ADC, and % difference of ADC (n = 30)

ADC	RECIST response				Test of Sig.	p
	PR (n = 15)	CR (n = 2)	PD (n = 5)	SD (n = 8)		
Mean pre-chemo	0.98 ± 0.21	1.26 ± 0.25	0.98 ± 0.33	1.25 ± 0.38	F = 2.001	0.139
Mean post-chemo	1.43 ± 0.27	1.74 ± 0.30	1.21 ± 0.29	1.39 ± 0.36	F = 1.540	0.228
Mean percentage difference	42.40 ± 18.07	36.50 ± 3.54	25.80 ± 39.58	12.63 ± 8.48	H = 16.280*	0.001*

F, p: F and p values for ANOVA test
H, p: H and p values for Kruskal-Wallis test
*Statistically significant at $p \leq 0.05$

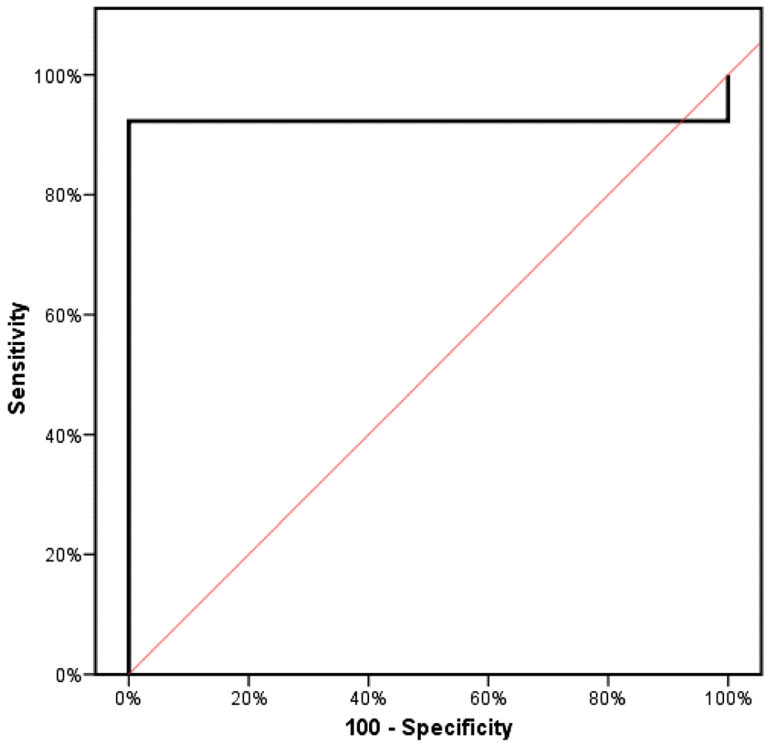

Fig. 3 ROC curve for % difference of ADC to diagnose non-responding cases

positive predictive value of 100%, and a negative predictive value was about 94% (Fig. 3).

In conclusion, our results revealed that there was no significant difference between the mean pre-therapeutic ADC of the responding and non-responding lesions. On the other hand, the responding lesions had significantly higher mean percentage difference of their ADC value showing a positive relationship between the increase in ADC and the chances of a better response.

Discussion

Tumors could respond to therapy in ways other than size reduction such as modified tissue composition which can be assessed by functional imaging such as the DWI which can detect tissue microstructure alteration rather than macrostructure [5].

Our results regarding location, number, and size of the liver lesions are all similar to the literature published about colorectal cancer with liver deposits [1].

The mean age of our cohort was 56. This is quite young compared to data from the American Cancer Society in 2017 in which the median age at diagnosis for colon cancer is 68 in men and 72 in women [10].

Regarding the size of the lesions, the mean size in a study done by Schulz et al. [11] was 1.4 cm compared to about 3.8 cm in this study which might be explained by better screening and earlier detection due to the established screening programs.

Prediction of response based on pre-treatment ADC is still controversial in some studies from the literature. Necrotic tumors are often surrounded by hypoxic viable cells that are less sensitive to ionizing radiation, more prone to aggressive behavior and probably less sensitive to cytotoxic agents [12]. Probably, these lesions would present a higher pre-treatment ADC and a worse treatment outcome [13]. Studies done by Chi et al. [14] and Kim et al. [15] confirm this theory while others like the ones done by DeVries et al. [16], Harry et al. [17] and Nilsen et al. [18] do not show significant correlation between pre-treatment ADC and response to chemo- or radiotherapy. Moreover, other studies done by Kol et al. [19] and Mardor et al. [20] even show negative correlations between these two variables. In our series, there was no significant difference between the ADC values between responsive and non-responsive lesions (Fig. 1) and our result cannot confirm the above hypothesis.

The second issue we tried to address in this study is that if DWI would be able to provide an early marker for treatment efficacy. Most published studies [14, 15, 21, 22] have shown that ADC changes could precede changes in tumor size; however, changes may disappear after a certain time due to repair mechanisms such as decrease of edema and organization of necrosis [23]. In a study done by Mungai et al. [24], assessment of the chemotherapeutic response

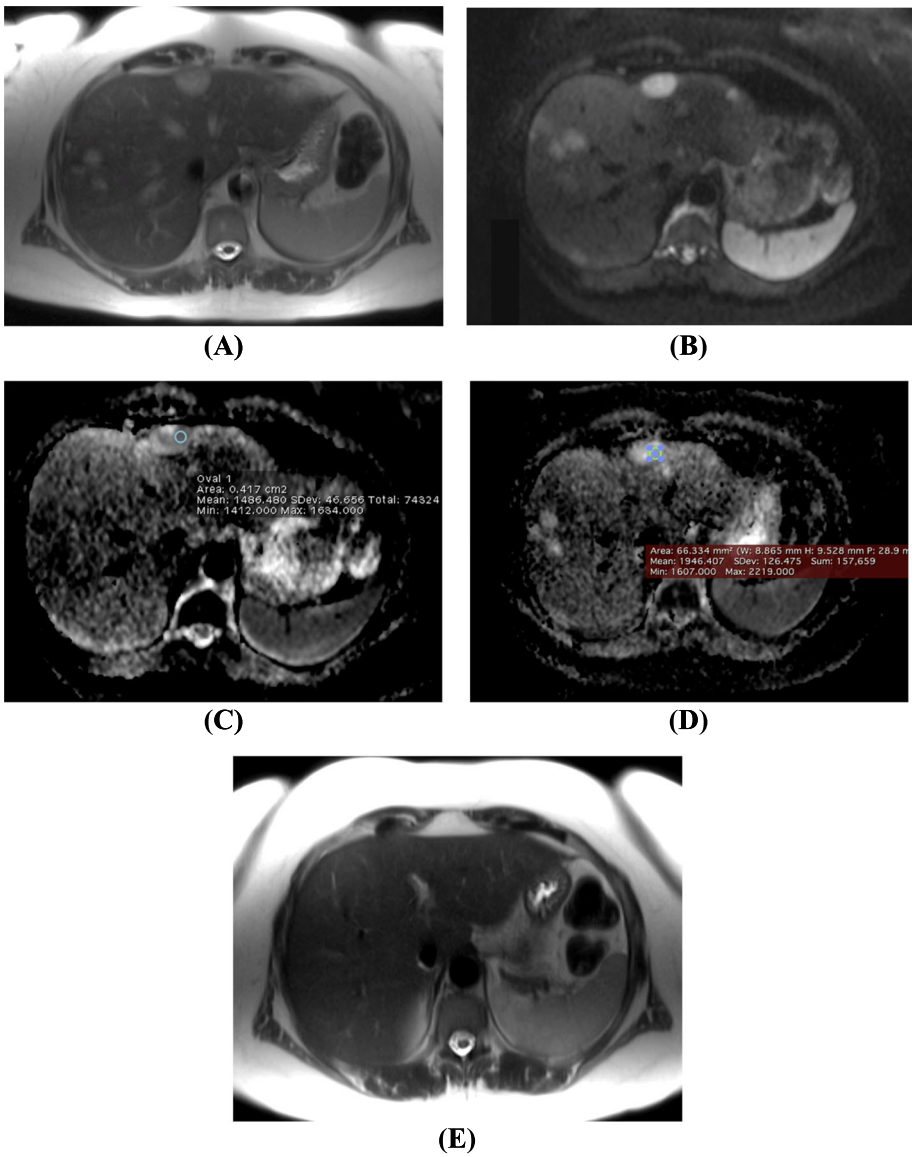

Fig. 4 Case (1): A 48 year old female patient with history of rectal adeno-carcinoma with hepatic metastasis, patient has contrast sensitivity and only non-contrast MRI was done. **a**) Base line pre chemotherapy axial T2 MRI revealed; multiple lesions, the target lesion is a well-defined sub capsular hyper intense lesion measuring about 2.5cm seen in segment III. **b**) Corresponding axial baseline diffusion weighted image of the previous T2 target lesion with b Value of (800 m2/sec) shows the lesion displaying hyper intense signal. **c**) pre therapeutic ADC image revealed diffusion restriction and ADC value of 1.49 x10-3 m2/sec (**d**) post therapeutic (21 days after chemotherapy) ADC map showing increase in the ADC value up to 1.96 x10-3 m2/sec (**e**) 2 month follow up non contrast T2 MRI revealed total resolution of the previously noted target lesion denoting complete response according to RECIST criteria

of liver metastases appears feasible after 20–25 days since the beginning of chemotherapy.

In the current study, we followed this theory and our assessment was done 21 days after the start of chemotherapy. The post-therapeutic lesion size showed almost no change with a median size of 2.6 cm compared to the pre-therapeutic median of 3.0 cm and percentage mean change of about 5%, as well as a non-significant p value of 0.056, proving that the 3-week time period is not enough to demonstrate significant morphological changes in size. Meanwhile, the mean post-therapeutic ADC values of R lesion groups (both SD and PR) become significantly higher showing a 39.94 ± 16.98% increase than the corresponding pre-treatment values compared to only 16.23 ± 25.30% increase in the mean ADC of NR lesions with a significant p value of < 0.001 (Table 4), confirming the hypothesis of reduced cellularity and increased diffusion of water molecule into the extracellular space for R lesions. We can say that an early (20–25 days after the beginning of the first cycle)

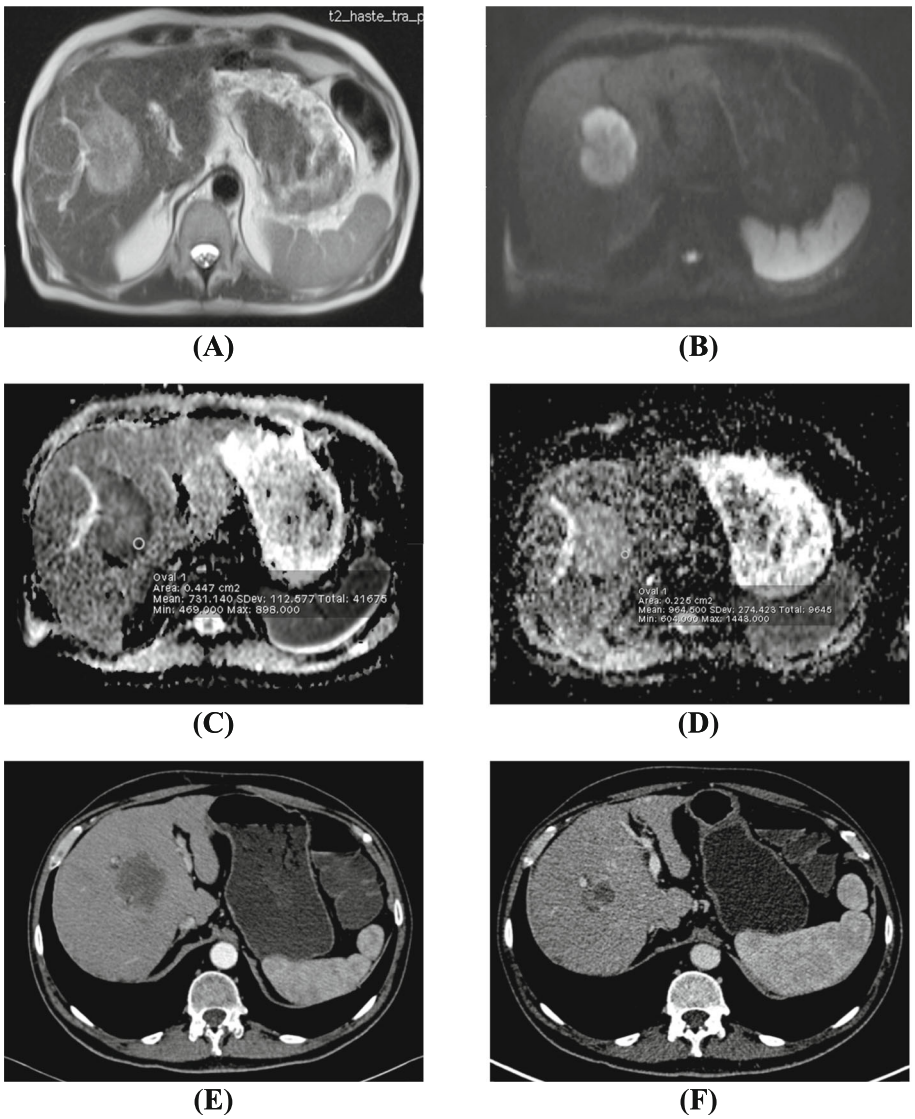

Fig. 5 Case (2): A 57 year old male patient with history of rectal adeno-carcinoma with hepatic metastasis. **a**) Baseline axial T2 MRI revealed mostly hyper intense lesion in segment VIII/V interface. **b**) Corresponding axial baseline diffusion weighted image of the previous T2 target lesion with b value of (800 m2/sec) shows the lesion displaying hyper intense signal. **c**) pre therapeutic ADC image which revealed diffusion restriction and ADC value of 0.73 x10-3 m2/sec. (**d**) post therapeutic (21 days after chemotherapy) ADC map showing increase in the ADC value up to 0.96 x10-3 m2/sec (**e**) base line pre chemotherapy CT portal phase; hypo dense lesion with relative peripheral enhancement was noted measuring about 5.6 cm. (**f**) 2 month follow up CT portal phase revealed significant reduction of the lesion currently seen measuring about 2.3cm (partial response according to RECIST criteria)

evaluation of ADC changes appears useful for an early assessment of clinical response.

Also in our limited study, we have reached a cutoff point of 25% which showed a very high sensitivity of 92.3 % and specificity of 100% in the detection of non-responding lesions. All of the non-responding lesions in our study showed a percentage change in their ADC value less than that cutoff point of 20% giving a positive predictive value of 100%, while all of the responding lesions apart from one showed a percentage change of ADC more than the cutoff value resulting in a negative predictive value of about 94%.

However, obtaining reproducible ADC measurements in liver metastases undergoing CHT is not an easy process and many possible confounding factors have to be considered. Among these factors are location of the lesion (in particular, when a lesion is located on or near organs subject to respiratory or other kinds of movement), its histotype, the presence of internal necrotic areas CHT, and others related to the MR-DWI

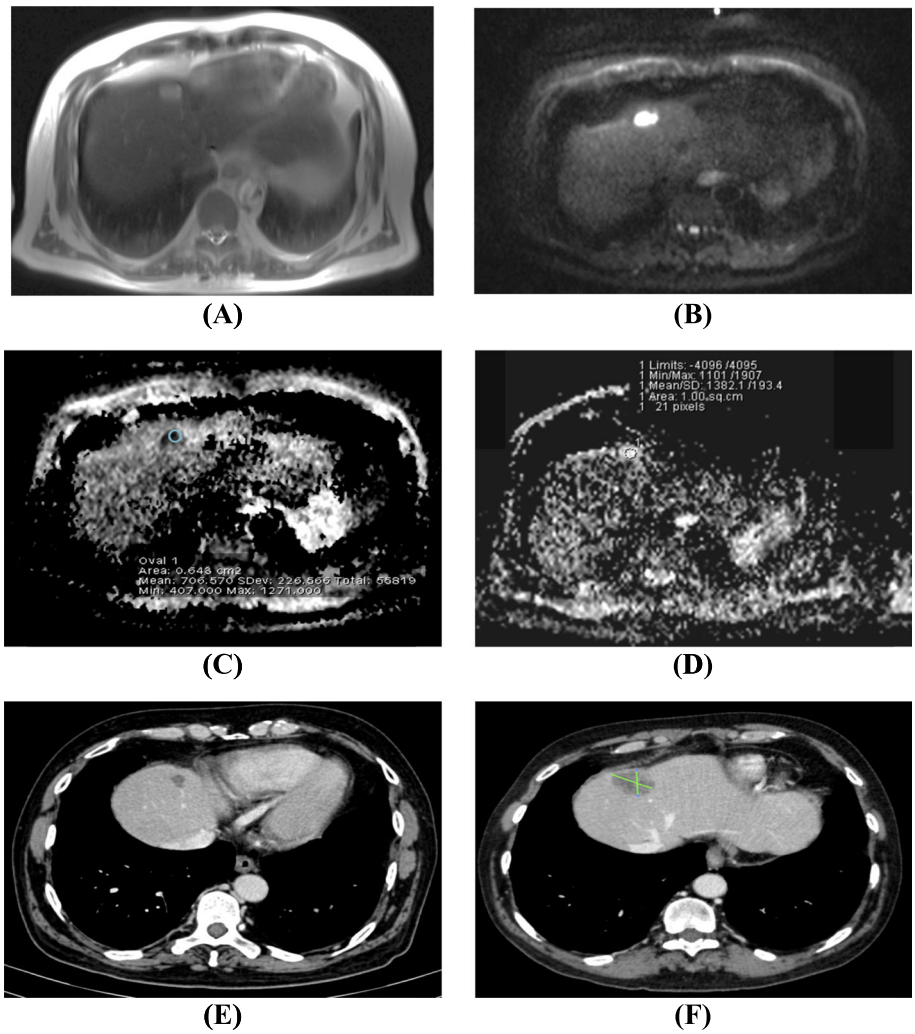

Fig. 6 Case (3): A 69 year old male patient with history of rectal adeno-carcinoma with solitary hepatic metastasis **a**) Baseline T2 axial MRI revealed a small solitary hepatic dome hyper intense lesion at segment IV A **b**) corresponding axial baseline diffusion weighted image of the previous T2 target lesion with b value of (800 m2/sec) shows the lesion displaying hyper intense signal. **c**) pre therapeutic ADC image revealed diffusion restriction and ADC value of 0.71 x10-3 m2/sec. (**d**) post therapeutic (21 days after chemotherapy) ADC map showing marked increase in the ADC value measuring 1.38 x10-3 m2/sec (**e**) base line pre chemotherapy CT portal phase; shows the same small hypo dense target lesion measuring about 1.4 cm. (**f**) 2 month follow up CT portal phase revealed significant increase in the size of the lesion which was seen measuring about 3.2 cm (progressive disease according to RECIST criteria)

acquisition technique and ADC calculation (in particular, images low signal-to-noise ratio, acquisition artifacts, *b* value adopted, and lesion sampling).

The current study included a small number of patients who received two-variable chemotherapy regimens, and although no significant relationship between the type of chemotherapeutic regimen used and the response obtained further studies with a larger population and more study sample homogeneity are needed. Also ideally to trace the diffusion or dynamic changes within tumor cells after neoadjuvant treatment, a functional map is required to detect changes within the same voxel at different examinations (Figs. 4, 5 and 6).

Conclusion

We believe that DWI-MRI has an emerging role in early assessment of early treatment response assessment that can be detected before morphological response on CT or conventional MRI for patients with hepatic metastasis from colorectal cancer.

Based on our study on 30 lesions, the use of 25 % as the cutoff point of percent difference in ADC for detection of non-responding lesions proved to be successful with a sensitivity of 92.3%, 100% specificity, positive predictive value of 100%, and a negative predictive value was about 94% only 21 days after the 1st chemotherapy cycle.

Abbreviations
ADC: Apparent diffusion coefficient; CR: Complete response; DW: Diffusion weighted; HCC: Hepatocellular carcinoma; NR: Not responding; PD: Progressive disease; PR: Partial response; R: Responding; RECIST: Response Evaluation Criteria in Solid Tumors; S: Stable disease; SD: Stable disease

Acknowledgements
To Prof. Dr. Ihab Samy Reda and Prof. Dr. Ahmed Hafez for their supervision and advise

Authors' contributions
NE collected the data and consents and performed the analysis of the study. SM revised and assessed the radiological issues of the study, performing the analysis of the study, and the corresponding author of the current paper. SZ contributed to case selection, prescribing the chemotherapy, and follow-up for the medical issues of the patients. All authors read and approved the final manuscript.

Funding
The author states that this work has not received any funding.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
This study was approved by the Ethics Committee of the Faculty of Medicine, Alexandria University on March 16, 2017; reference number of approval 01028116. All patients included in this study gave written informed consent to participate in this research (All the patients were older than 16 years old).

Consent for publication
All patients included in this research gave written informed consent to publish the data contained within this study.

Competing interests
The author of this manuscript declares no relationships with any companies, whose products or services may be related to the subject matter of the article.

Author details
[1]Department of Diagnostic and Intervention Radiodiagnosis, Medical Research Institute, Alexandria University, 165 Alhoreia Street, Alexandria 21561, Egypt. [2]Department of Oncology, Medical Research Institute, Alexandria University, Alexandria, Egypt.

Received: 9 September 2019 Accepted: 21 October 2019
Published online: 16 December 2019

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