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Prognostic value of ADC measurements in predicting overall survival in patients undergoing ^{90}Y radioembolization for colorectal cancer liver metastases☆

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ABSTRACT

Aim: To assess the ability of diffusion-weighted imaging (DWI) in predicting the overall survival in patients who underwent Yttrium 90 radioembolization (^{90}Y-RE) for colorectal liver metastases (CLM) with other well-established clinical and imaging parameters by comparing the pre- and post-treatment apparent diffusion coefficient (ADC) values of the lesions.

Methods: A total of 81 metastatic lesions of 27 consecutive patients who underwent DWI before and after the ^{90}Y-RE session were enrolled in the study. ADC values were calculated from the entire (ADC_e) and peripheral (ADC_p) tumor on pre- and post-treatment DWI, and any relative increase in ADC > 0% accepted as a functional imaging response. The impact of functional imaging response in addition to other well-known parameters including Response Evaluation Criteria in Solid Tumors (RECIST), hepatic tumor burden, Eastern Cooperative Oncology Group performance status (ECOG–PS) and the presence of extrahepatic metastases in predicting overall survival (OS) was assessed using Kaplan-Meier curves and Cox-regression analyses.

Results: The median OS of the patients was 10 months (range, 6–20 months) while the median OS of the responders being significantly longer than the non-responders for ADC_e and ADC_p (median 11 vs 7 months, $P = 0.003$; median 12 vs. 7 months, $P < 0.0001$, respectively). The RECIST score was also significantly affected the OS (progressive or stable disease median 8 months vs. partial response 15 indent months, $P = 0.019$). The other parameters including hepatic tumor burden, gender, ECOG score, the involvement of the liver lobes, and the presence of extrahepatic metastases were not associated with the OS. In multivariate analysis, only ADC_p remained as an independent predictor of OS ($P = 0.003$, HR = 19.878).

Conclusion: Any increase in relative ADC_p or ADC_e values after Y90-RE treatment was associated with longer OS in CLM patients, and DWI seems to be valuable imaging biomarker in predicting OS in CLM patients during the early post-interventional period after ^{90}Y-RE.

1. Introduction

Approximately 30% of the patients with colorectal carcinoma (CLC) present with colorectal liver metastases (CLM) at the time of the initial diagnosis and up to 50% of the patients develop CLM during the entire course of the disease [1]. Unfortunately, only 20% of the patients with CLM are eligible to complete surgical resection [2,3]. Systemic chemotherapy is still the first line treatment option for the remaining patients with unresectable lesions [4]. However, some of the patients do not respond well to current systemic chemotherapy options or could not continue chemotherapy cycles due to severe comorbidities [5]. Intra-arterial Yttrium 90 (^{90}Y) radioembolization (RE) of the CLM using is a promising treatment option for such patients [6–8]. Traditionally, the decision of the treatment response to ^{90}Y-RE is made using

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Response Evaluation Criteria in Solid Tumors (RECIST) scoring system, in which the size of the lesions is taken into account [9]. However, recent studies have shown that novel methods, such as diffusion-weighted imaging (DWI), which are capable of to identify the functional changes of the tumors secondary to treatment, are superior to assessing size changes in detecting treatment response as well as predicting overall survival (OS), particularly at the early period after the treatment [8,10–14].

DWI exploits random Brownian movements of the water molecules, mainly protons, in a relevant voxel of tissue. Apparent diffusion coefficient (ADC) is a biophysical parameter that quantitatively assesses the motion of the water molecules against the internal resistance of the relevant tissues using DWI [15–17]. Many studies have demonstrated the value of ADC measurements in assessing the respond of CLM to treatments as well as the ability of ADC in predicting overall survival (OS) [18–23]. However, only mere studies have been published regarding the role of DWI in assessing parameters above following ^{90}Y-RE in patients with CLM [13,14,24–26].

Herein, we aimed to evaluate and compare the ability DWI in predicting the OS in patients who underwent ^{90}Y-RE for CLM with other well-established clinical and imaging parameters by comparing the pre- and post-treatment ADC values of the lesions.

2. Materials and methods

2.1. Patient population

The local ethics committee approved this retrospective single-center study, which was conducted between January 2012 and January 2018. Informed consents were not required for retrospective review of the medical and radiological data of the patients. The online database of our department was reviewed to identify the patients who underwent ^{90}Y-RE for CLM in our institute. Patients underwent magnetic resonance imaging (MRI) including DWI sequence in the pre-operative period within one month before the treatment and underwent MRI in the post-operative period within three months after the treatment were enrolled in the study. All patients had to have at least three metastatic lesions with a diameter of > 1 cm located in the treated lobe, which should be clearly visible on DWI. The exclusion criteria were; having chronic liver disease, incomplete data, MR images with significant motion or magnetic susceptibility artifacts, MR images with low contrast-to-noise ratio preventing interpretation of the images, and any history of previous local liver-directed interventional therapies including RE, transarterial chemoembolization, and radiofrequency ablation. Furthermore, patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) > 1 were excluded from the study since current guidelines discourage commencing RE in these patients [27].

2.2. MRI acquisition

All MR images assessed in the study were obtained by the same 1.5 T MRI unit (Avanto Tim®, Siemens Healthcare, Forchheim, Germany) using a phased-array body coil. Care was taken to obtain all MRI examinations using the same device since ADC values could be significantly affected by gradient linearity [28]. Our liver MRI protocol consisted of pre-contrast axial T1-weighted (T1W) and T2-weighted (T2W) sequences, pre-contrast coronal T2W sequence, post-contrast axial T1W sequences, and diffusion-weighted sequences. For the conventional MRI sequences, the manufacturer's standard MRI parameters were used. DWI was performed using echo planar imaging in the axial plane using the following parameters: repetition time/echo time = 3500/75 ms, bandwidth = 1736 kHz, number of channels = 16, slice thickness = 5 mm, time of acquisition = 1.51 s, range of field of view = 400, with b-values of 0 and 800 s/mm^2. ADC maps were generated with voxel-by-voxel basis using following equitation: ADC (mm^2s^1) = [ln (S^0/S^b)]/b in which S^0 and S^b represent the signal intensities of the images with different gradient b factors, and b is the difference between gradient b factors. To avoid measurement errors from respiratory motion, we took several precautions for our abdominal DWI protocol: (1) Use of echo planar imaging, which is considerably faster than conventional DWI technique, (2) use of phased array coils and parallel imaging method to accelerate DWI acquisition, (3) employment of respiratory-triggered DWI acquisition with a prospective acquisition correction technique, and (4) use of fat-suppression method, spectral attenuated inversion recovery, to reduce chemical shift artifacts [29]. Given our precautions, only one patient was excluded from the study given to respiration-based motion artifacts.

2.3. Radioembolization procedure

A multidisciplinary tumor review board (attended by interventional radiologists, body radiologist, radiation therapists, hepatobiliary surgeons, oncologists, and nuclear medicine specialists) determined whether the patients would benefit from internal RE procedure, and the board members made the final decision in line with previous recommendations for ^{90}Y-RE [30]. Additionally, patients who had extrahepatic metastases, which reviewed by the council members and accepted as prognostically insignificant were also approved to be eligible for the study (for instance patients with ≤3 small pulmonary metastases were eligible).

Two interventional radiologists with > 10 years of experience in interventional radiology performed all the procedures. Diagnostic catheter angiography and both planar and single photon emission computed tomography (SPECT)/CT following an intra-arterial injection of 200–400 MBq of 99mTc- macroaggregated albumin (Tc-MAA) were utilized to detect the percentage of pulmonary and intraabdominal shunting. During the angiography, if any aberrant vessels arising from the hepatic artery were detected, it was embolized using coils to prevent non-target embolization. The treatment session commenced within the interval of one to two weeks the catheter angiography. ^{90}Y microspheres (SIR-Spheres; SIRTeX Medical Europe, Bonn, Germany) were given into the relevant hepatic artery. The administered activity of 90Y microspheres was calculated with body surface area method using following formula: Activity in GBq = (BSA x 0.2) + (volume tumor/volume tumor + volume tumor-free liver) [31]. The calculation of the liver and tumor volumes was handled on MRI. We did not employ bilobar treatment at the same session the patients with bilobar liver involvement and these patients were treated with sequential RE procedures. The initial RE procedure was performed for the liver lobe with a higher tumor burden. To avoid repeated measurements for patients, ADC values of the patients were only calculated after the initial treatment sessions.

2.4. Image interpretation

Two radiologists with > 6 years experience in body radiology performed all the measurements in a consensus. The observer was blinded to clinical data except for the side of the treatment. All measurements were performed using a dedicated workstation (Extreme workstation, Extremepacs system Ankara/Turkey). First, the observers determined three index lesions from the treated lobe of the liver on baseline MR images. The lesions with the largest diameter likely to represent the hepatic tumor burden were chosen as index lesions. The observers placed three ellipsoid regions of interests (ROIs) onto the entire tumor while caring to drew the largest ROI as possible with avoiding adjacent liver parenchyma. Next, the observers randomly drew three ROI with a minor diameter < 5 mm onto the peripheral parts of the lesions. ADC measurements of the tumor-free liver parenchyma were performed from the treated lobe using the ellipsoid ROIs. Care was taken to avoid vessels, biliary ducts, and focal liver lesions during parenchyma measurements. During all the measurements, the observer was free to use any of the DW images for a guide. All ROI first was drawn onto the axial

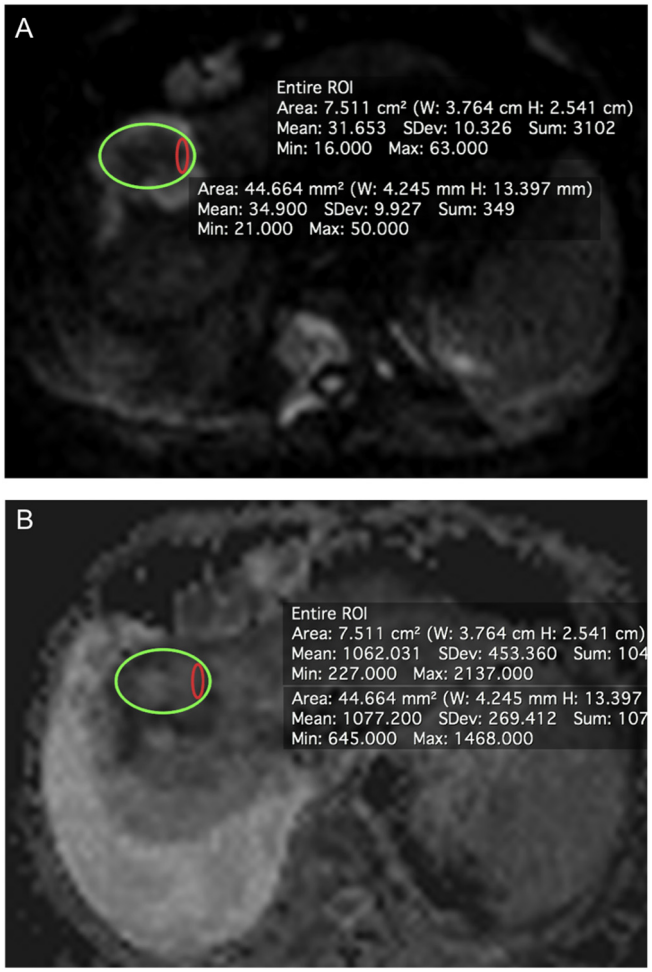

Fig. 1. Diffusion-weighted image (a) and ADC map (b) of a patient with colorectal metastasis in segment 8. Entire (green) and peripheral (red) ROIs were first placed onto the diffusion-weighted image then automatically transferred to the ADC map. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

DWI then these ROIs were automatically transferred to the relevant ADC map. The average ADC value was calculated for parenchymal ROIs, entire lesion ROIs (for ADC_e), and peripheral ROIs (for ADC_p). The maximal diameters of three index lesions were also noted. The average values were calculated for the measurements. The observer performed all the steps for the same lesions using the post-treatment MRI images. All images were achieved using our picture archiving and communication system (PACS, Extremepacs system Ankara/Turkey). Fig. 1 depicts ADC_p and ADC_e measurements of a metastatic lesion.

2.5. Statistical analyses

Statistical Analyses were performed using the SPSS software version 21. Descriptive analyses were presented using means and standard deviations. The variables were investigated using visual (histograms, probability plots) and analytical methods (Shapiro-Wilk's test) to determine whether or not they were normally distributed. All values were presented as the mean ± SD unless otherwise specified. Dichotomous clinical variables were compared using the Mann–Whitney *U* test. A paired *t*-test was used to compare the change between pre-treatment and post-treatment ADC values of the lesions and tumor-free liver parenchyma. The Kaplan-Meier curves were used for survival estimation. We defined overall survival as the time from the intervention to death from any cause, and; patients who were known to be still alive at the time of the analysis were censored at the time of their last follow-up. The possible factors that might predict the survival including functional imaging response, RECIST, ECOG score, and hepatic tumor burden were further entered into the Cox regression analysis to determine independent predictors of survival. A P value < 0.05 was accepted as significant. For the bimodal categorical classification of the patients' response concerning the size, we used the term “responders” for patients with complete response (disappearance of all lesions) or partial response (> 30% decrease in sum of all target lesions' largest diameter) measurement (−29% to +20% change in sum of all target lesions' largest diameter) and non-responders for patients with or progressive disease (> 30% increase in sum of all target lesions or any newly developed lesion) according to RECIST [9]. For the bimodal categorical classification of the functional imaging response, any increase in relative ADC > 0% was accepted as responders and ≤ 0% non-responders for entire and peripheral ROIs analyses.

3. Results

A total of 27 patients, 12 female (44.4%) and 15 male (55.6%), with a median age of 63 years (range, 42–78 years) with 81 CLM were enrolled in the study. The average time between the RE and follow-up MRI was 53 days (range, 24–90 days). Baseline demographics and imaging findings of the patients are summarized in Table 1. Pre-treatment and post-treatment laboratory findings of the patients are listed in Table 2. The median and mean survival of the patients after the RE session were 10 months (range, 6–20 months) and 10.89 ± 4.11 months, respectively; 15 patients lived longer than the median and mean OS. The mean administered activity was 3.14 ± 1.14 GBq.

3.1. MRI assessment of the lesions' size and ADC value

The average diameter of the 81 lesions was 54.65 ± 31.72 mm on the pre-treatment MRI and 46.94 ± 31.72 mm on the post-treatment MRI. The average lesion diameter was significantly reduced after the treatment ($P = 0.011$). According to the RECIST 9 patients (33.3%) were classified as responders and 18 patients (66.7%) were classified as

Table 1
Baseline demographic and imaging findings of the patients

Demographics and clinical characteristics	Finding
Age (years)[a]	63 (36)
Gender	
Male	15
Female	12
Hepatic involvement	21
Bilateral	16 (59.3%)
Left lobe	3 (%29.6)
Right lobe	8 (%11.1)
Hepatic tumor burden	
> 50%	13 (48.1%)
< %50	14 (51.9%)
Presence of extrahepatic metastases	
No	20
Yes	7
Presence of ascites before the intervention	
No	18
Yes	9
Treated lobe of the Liver	
Right	2 2
Left	5
ECOG Score	
0	17 (63%)
1	10 (37%)
Average size of the index lesions (mm)	57.6 (39.8)

[a] Indicated as median (range) and number (percentage), Eastern Cooperative Oncology Group performance status (ECOG–PS).

Table 2
Laboratory findings of the patients before and after the RE treatment.[a]

Parameters	Pre-treatment	Post-treatment	P value
Total bilirubin (mg/dL)	0.5 (0.81)	0.54 (14.5)	NS
Creatinine (mg/dL)	0.73 (0.52)	0.69 (0.52)	NS
ALT (IU/L)	28 (80)	52 (150)	0,006
AST (IU/L)	31 (110)	52 (167)	NS
Platelet count (103/mm3)	207.28 (93.25)	202.87 (95.24)	NS
Albumin (g/dL)	4.14 (2.29)	4.12 (4.17)	0.026
GGT (IU/L)	54 (372)	140 (701)	0.008
International normalized ratio	1 (0.33)	1.06 (0.3)	0.004
Leukocyte count (103/mm3)	7400 (6600)	5600 (5400)	0.0001

[a] Variables are expressed as median (range), ALT alanine aminotransferase, AST aspartate transaminase, GGT gamma glutamyl transferase, NS not significant.

non-responders. The average value of the absolute lesion size change was −8.11 ± 18.84 mm with the relative change of −14.56%. The ADC_e value of the index lesions in the pre-treatment period was 1190 ± 352 mm^2/s and in the post-treatment period was 1228 ± 305 mm^2/s with a relative increase of 8.19% and without any significant difference ($P = 0.32$). The ADC_p value of the index lesions in the pre-treatment period was 1110 ± 251 mm^2/s and in the post-treatment period was 1185 ± 305 mm^2/s with a relative increase of 1.18% and without any significant difference ($P = 0.20$). There was no significant difference between the mean ADC values of the treated tumor-free liver parenchyma before (1319 ± 128 mm^2/s) and after (1363 ± 124 mm^2/s) the treatment ($P = 0.13$). Significant differences were observed between the mean ADC_p and ADC_e values and the mean liver parenchyma ADC value in the pre-treatment period; the mean liver parenchyma had significantly higher ADC values ($P = 0.015$ and $P < 0.0001$, respectively). However, no differences were observed on post-treatment MR images ($P < 0.05$). We categorized patients according to the relative ADC value changes as responders (any ADC change > 0 mm^2/s) and non-responders (any ADC change ≤0 mm^2/s). In the study cohort, 20 patients (74.1%) were classified as the responders and 9 (25.9%) were the non-responders using ADC_e, and 18 (66.7%) patients were classified as the responders and 9 patients (33.3%) were classified as non-responders for ADC_p. Table 3 shows detailed information concerning the measurements and imaging parameters. Of to 20 patients classified as responders according to ADC_e, 13 patients classified as responders (65%) according to RECIST while 7 patients classified as non-responders (35%). Despite the higher proportion of responders according to RECIST, no difference was identified ($P = 0.57$). Among 18 patients classified as responders according to ADC_p, 11 patients classified as responders according to RECIST (61.1%) while 6 patients classified as non-responders (38.9). Despite the higher proportion of responders according to RECIST, no difference was identified ($P = 0.33$).

3.2. Assessment of the impact of imaging and clinical parameters on overall survival

For the ADC_e measurements, the median survival length of the responders was significantly longer than the non-responder OS length (median 11 months, 95%CI 9.2–12.7 vs. 7 months, 95%CI 6.8–8.5; $P = 0.003$). For the ADC_p measurements, the median OS length of the responders was significantly longer than the non-responder survival length (median 12 months, 95%CI 9.9–14 vs. 7 months, 95%CI 6.5–7.4; $P < 0.0001$). The response according to the RECIST scores was also significantly affected the OS (median 15 months, 95%CI 3.3–26 vs. 8 months, 95%CI 6.9–9; $P = 0.019$). The other parameters, hepatic tumor burden, gender, ECOG score, the involvement of the liver lobes, the presence of extrahepatic metastases before the treatment, did not significantly affect the OS. Fig. 2 shows the Kaplan-Meier curves of ADC_p, ADC_e, RECIST and hepatic tumor burden effect on the OS. Parameters including functional imaging responders and non-responders for peripheral and entire ROIs, responders and non-responders according to RECIST, hepatic tumor burden (having more or less than %50), hepatic involvement (Unilobar or bilobar), and ECOG score were further evaluated using multivariate Cox-regression model. In our model, none but one parameter, functional imaging response according to peripheral ROI derived ADC_p being significant (For non-responders, $P = 0.003$, HR = 19.878 95%CI 2.69–32.353). Table 4 shows the multivariate Cox-regression analysis in detail.

During the follow-up period of the study, 12 patients died within eight months after the treatment; hence, did not undergo long-term scans. Among remaining 15 patients, ten patients underwent Positron emission tomography/computed tomography (PET/CT) scan at six and twelve months, and only five patients underwent MRI (three patients underwent MRI at six months and twelve months, while two patients underwent MRI only at six months). Of the five patients, three were responders while two were non-responders according to the ADC changes, and all three of responders had higher ADC values compared to early post-treatment scans. The mean ADC values did not significantly change in one of the two non-responders while the other patient had an increase in ADC values on long-term MRI examination. Nevertheless, we did not thoroughly assess follow-up MRI of the patients since it would not be appropriate to draw any conclusions from such a small cohort.

4. Discussion

The findings of the present study suggest that ADC_p, ADC_e, and size of the CLM between pre- and early post-interventional period are associated with OS with any increase in overall ADC_p and ADC_e (> 0% mm^2/s) and decrease in average size (> 30%) being associated with longer median survival. However, none of the other recognized parameters (the presence of extrahepatic metastases, ECOG score, hepatic tumor burden) were associated with the OS of the patients. Additionally, only increase in ADC_p > 0% was independently predicted longer OS in the multivariate analysis.

Increased ADC values of the tumors after chemotherapy is a well-recognized phenomenon [18–23]. In general, tissues with high cellularity substantially reduced the extracellular space and restrict the extracellular random movement of the water protons; thus, invariably result in diffusion restriction and lower ADC values [15–17]. ^{90}Y-RE of the lesions leads cancerous cells to undergone apoptosis, lysis and losing cell membrane integrity; hence, increase extracellular space and increase in water protons diffusion and ADC values [18–23]. To date, several authors have investigated the diagnostic value of DWI in

Table 3
Imaging characteristics of the study cohort.

Parameters	Pre-treatment	Post-treatment	Relative difference (%)	P value
The mean entire ADC values of the lesions (mm^2/s)	1190 ± 352	1228 ± 305	8.19%	NS
The mean peripheral ADC values of the lesions (mm^2/s)	1110 ± 251	1185 ± 305	1.18%	NS
The mean ADC values of the treated lobe lesions (mm^2/s)	1319 ± 128	1363 ± 124	%3.3	NS
The average size of the lesions (mm)	54.65 ± 31.72	46.94 ± 31.72	−14.56%.	P = 0.011

All values are expressed as mean ± SD.

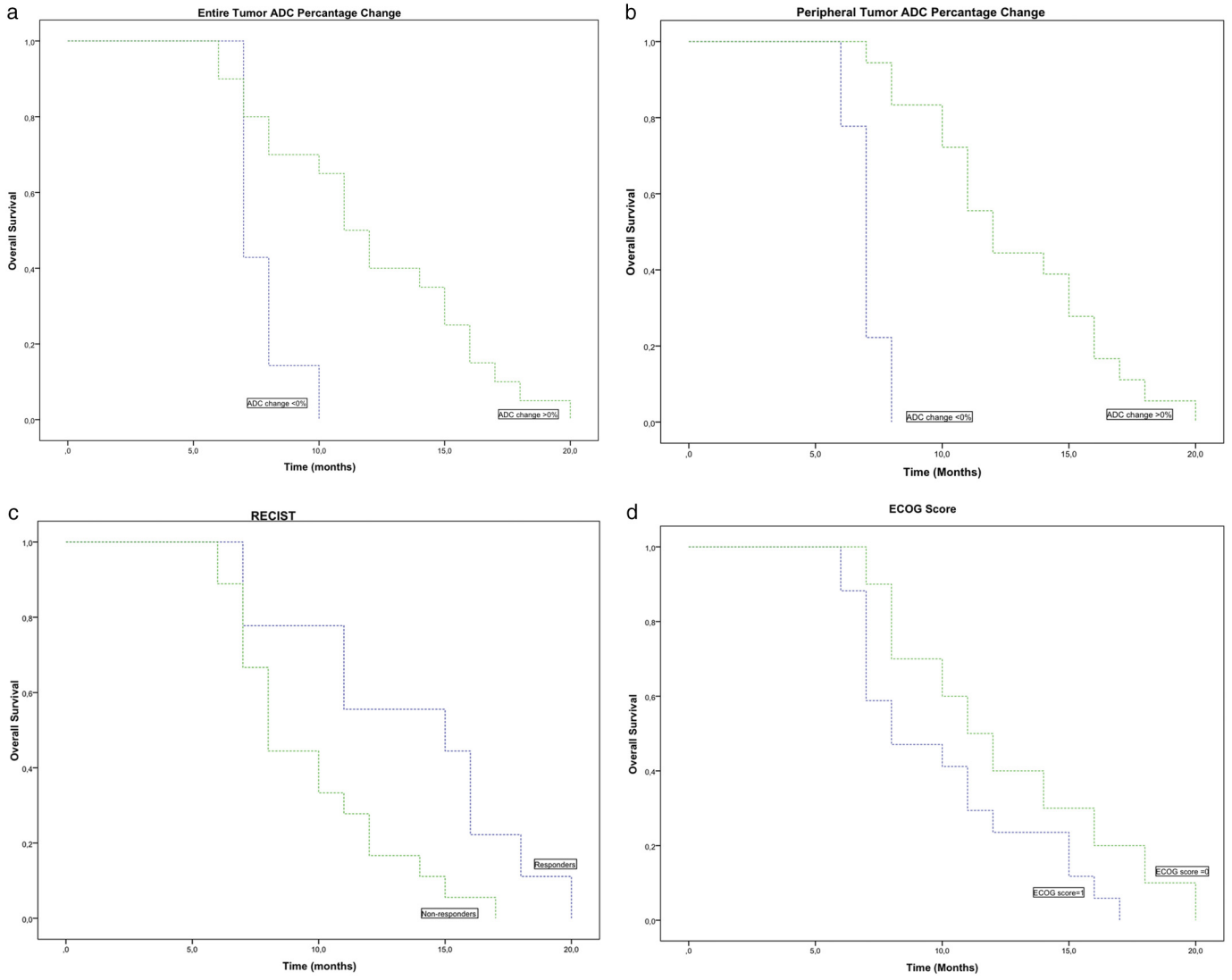

Fig. 2. Kaplan-Meier curves show survival stratification by ADC_e (a) and ADC_p (b) in addition to some of the recognized parameters including, RECIST (c) and ECOG-PS (d). The median survival length of the responders was being significantly longer for responders according to ADC_e ($P = 0.003$), ADC_p ($P < 0.0001$) and RECIST ($P = 0.019$) while no difference was observed for ECOG-PS ($P > 0.05$).

Table 4
Multivariate Cox-regression shows the effect of imaging and clinical parameters on overall survival.[a]

Variables		P value	Hazard Ratio	%95 CI
Functional imaging Response for peripheral ROI	ADC change ≤ 0% ROIADC change > 0%	0.013	14.68	1.76–27.266
Functional imaging Response for entire ROI	ADC change ≤ 0% ADC change > 0%	0.29	0.42	0.81–2.30
Liver involvement	Unilobar Bilobar	0.18	0.53	0.21–1.3
Hepatic tumor burden	> 50% < 50%	0.18	0.27	0.30–1.22
RECIST category	Non-responders Responders	0.080	0.36	0.13–1.18
ECOG-PS	1 0	0.89	0.90	0.28–2.40

(RECIST)

[a] Eastern Cooperative Oncology Group performance status (ECOG–PS), Response Evaluation Criteria in Solid Tumors.

assessing treatment response and predicting overall/progression-free survival in patients who underwent Y90-RE for CLM. Dudeck et al. [26] were one of the first to explore the role of DWI for the evaluation of CLM, yet they only evaluated the correlation between ADC change and lesion size between pre- and post-treatment period, which yielded promising results. A more recent study by Schmeel et al. [13] demonstrated that functional imaging response (ADC increase > 0%) in addition to Hepatic tumor burden (≥50%), ECOG score ≥ 1, and progressive disease according to RECIST are associated with OS. In the present work, only the functional imaging response and RECIST were found to be associated with OS, but we found no association between ECOG score and hepatic tumor burden (> 50%) and OS. However, in line with our results, a further study by Barabasch et al. [14] also demonstrated that hepatic tumor burden or ECOG score is not associated with OS, yet only the functional imaging response. Interestingly, they reported no difference between the length of survival and RECIST. We contend that despite all studies favor the success of DWI in assessing treatment response and OS, patient selection, relatively small sample sizes, the time of the application of MRI, and different categorization of continuous variables among these studies and ours might have led to inconsistent results.

Notably, in our study cohort, only increase in ADC_p independently

predicted OS on multivariate analysis. Our results could be explained by the fact that residual tumor cells are more frequently localized at the tumor periphery after chemotherapy, which demonstrated by several studies using histological samples [32,33]. This phenomenon was also investigated by multicenter studies of MD Anderson teams, which proposed new criteria on computed tomography [34,35]. The underlying rationale of that study also serves the same fact that with the pathological studies, and they demonstrated that the thickness tumor-surrounding normal liver interface was a good surrogate marker for pathological response and survival. Recently two studies have investigated this phenomenon using DWI. The first of these studies was carried out by Wagner et al. [36] in which they explored the correlation between the ADC values of the entire and peripheral CLM with pathological findings. In their work, increased ADC_p values were able to discriminate CLM with a major histological response from those with a partial or without histological response after systemic chemotherapy, yet they observed no such relationship with ADC_e values. Contrarily, a further report by Donati et al. [37] claimed both ADC_p and ADC_e are good surrogate markers for the histological response after systemic chemotherapy. However, none of the authors assessed the role of ADC_p in predicting OS. In the light of these findings, using ADCp, which predominantly explore the area that has more likelihood to contain residual tumors, instead of ADCe in which measurements inadvertently include central necrosis, fibrosis, or acellular mucin, might be a better option to predict the survival and tumor response. However, our results should be interpreted with caution, and prospective studies, preferentially using multi-center larger cohorts, are needed to confirm our results and to draw more exact conclusions.

Currently, the guidelines do not offer DWI as a tool to predict OS or response assessment, and RECIST based evaluation is the recommended method whereas changes in the size of CLM after RE might not be observed before 3–4 months [38,39]. Thus, a practical imaging method is highly desirable to assess whether the patients would benefit from the ^{90}Y-RE is very crucial since ^{90}Y-RE itself is very toxic to the liver parenchyma which is already being harmed by numerous systemic chemotherapy cycles. We suggest that DWI might serve as a valuable tool in filling this gap. On the other hand, despite the change in the lesion size is expected to occur after 3–4 months, the responders in the present study according to RECIST had longer overall median survival than non-responders, which is in line with those of Schmeel et al. [13]. However, both in the present and their work, RECIST did not independently predict OS on multivariate analyses [13]. The median time of interval from the treatment to follow-up MRI was 53 (range, 23–90) days in our study, and one should be kept in mind that the required time for the size changes of the lesions after ^{90}Y-RE to be observable is not an absolute parameter. Hence, we suggest that it is not surprising that we observed macro-structural changes in some of the lesions in the present study.

We had several drawbacks in the present study. First and the foremost, we had a very small sample size, which investigated retrospectively; thus, findings of the present work suggesting the diagnostic value of DWI in predicting OS in patients with CLM after RE should be approached with caution. Second, we identified no association between the established clinical parameters and OS, which we believe might have caused due to our selection bias and small sample size. For instance, we did not include any patient with an ECOG score of > 1 or we did not include any patient with prominent extrahepatic metastases. Third, we did not evaluate interobserver variability since the two observers performed the measurements in a conference. Fourth, we did not perform lesion-by-lesion analysis and also did not evaluate the correlation between histological response and imaging response as defined by ADC measurements. Fifth, neither we did evaluate the diagnostic value of ADCe and ADCp in predicting progression-free survival nor the ability of ADCe and ADCp in predicting lesion-based response. Finally, the interval of time after the treatment for MRI was relatively longer than the similar reports, (median 53 days vs. 35 and 33 days), which might have caused inconsistent results with the literature [13,14].

In conclusion, any increase > 0% ADC_p or ADC_e values after Y90-RE treatment was associated with longer median survival in CLM patients, yet only ADC_p values remained as an independent predictor of OS in multivariate analysis. We suggest that DWI seems to be valuable imaging biomarker in predicting OS in CLM patients during the early post-interventional period after Y90-RE and it might guide clinicians to individually select the best management options for the patients. However, further comprehensive works with a larger study cohort are warranted to reveal the true potential of DWI regarding this manner.

Ethical Statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments.

Declaration of Competing Interest

Authors have no conflict of interest.

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