The Role of Diffusion Weighted MRI in The Assessment of Post Ablation HCC Viability

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Abstract:

Background: Hepatocellular carcinoma (HCC) is the most common primary liver malignancy. Local ablative therapies include chemical (ethanol, acetic acid) or thermal ablation [radiofrequency ablation (RFA), microwave, laser, cryoablation] are curative treatment options that treat HCC. The apparent diffusion coefficient (ADC) calculated in diffusion-weighted MRI has become a favorable biomarker of tumor. The ADC is a measure of the mobility of water in tissues **Methods**: 30 cases of patients having HCC to radiology department of Damietta Cancer Center who underwent locoregional therapies (radio frequency ablation, microwave ablation percutaneous ethanol injection and trans-arterial hepatic chemoembolization) over a period of 18 months (APR.2017–OCT.2018). Patient are scheduled for dynamic contrast enhanced (DCE) MRI and diffusion weighted images (DWI) either in the routine follow up or after inconclusive triphasic CT study to assess tumor response to treatment and detect residual or recurrent lesions. **Results:** The ADC variable was found to be a fair indicator to differentiate marginal recurrence of HCC from benign or pseudo- lesions the sensitivity of DWI was 80%, its Specificity was 76.7%, positive predictive value was 53.3% and negative predictive value was 92%. **Conclusion**: we concluded that DWI together with conventional imaging is a promising tool in the evaluation of HCC post ablation. DWI can provide information about molecular tissue characteristics; it can help to distinguish between viable and necrotic tumor areas thus facilitating the diagnosis of residual or recurrent tumor. We could recommend a cut -off value 1.024 x 10-3mm^2/sec, with t values below this level, express viability of the malignancy.

Key words: ADC, Ablation, HCC, Viability

Introduction:

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, *(1)*. Local ablative therapies include chemical (ethanol, acetic acid) or thermal ablation [radiofrequency ablation (RFA), microwave, laser, cryoablation] are curative treatment options treat HCC *(2)*.

The ultimate goal of locoregional therapy of HCC is tumor cell death and necrosis *(3)*. Imaging evaluation of HCC after therapy is of paramount importance *(4)*.

Traditional anatomical response criteria are solely based on tumor size changes *(5)*.Simple evaluation of morphological alterations may not be ideal since relevant size changes for response assessment usually take time to occur *(6)*.

The post-therapy contrast enhancement changes are not unique features of tumorous lesions and may also occur in benign post-treatment changes. *(7)*. To overcome these shortcomings, technological advancements in functional MR imaging, such as diffusion-weighted imaging (DWI), are increasingly being used and evaluated for both post-treatment response assessment and outcome prediction prior to therapy *(8)*.

The apparent diffusion coefficient (ADC) calculated in diffusion-weighted MRI has become a favorable and promising biomarker of tumor response to therapy. The ADC is a measure of the mobility of water in tissues. Viable tumors are high in cellularity, and the cells have an intact cell membrane that restricts the mobility of water molecules and causing a relatively low ADC. Conversely, cellular necrosis increases membrane permeability, allowing water molecules to move freely and causing a relative increase in ADC *(9)*.

The aim of this study was to evaluate the role of functional MRI with Diffusion Weighted technique in the assessment of hepatocellular carcinoma (HCC) viability after ablation.

Patients and Methods

This prospective study was carried on 30 cases of patients having HCC referred to radiology department of Damietta Cancer Center from outpatient clinic of medical and surgical oncology departments who underwent locoregional therapies (radio frequency ablation, microwave ablation percutaneous ethanol injection and trans arterial hepatic chemoembolization) over a period of 18 months (April, 2017–October, 2018). The patients' age ranged between 20 to 75 years, 22 patients were males and 8 were females, all patients had liver cirrhosis related to chronic

viral hepatitis. All procedures are approved by ethical committee of Damietta cancer center.

<u>Inclusion Criteria:</u>

- Patients with HCC who underwent, RFA, MWA, PEI &TACE.

- Prior informed consent

- At least one measurable lesion.

<u>Exclusion Criteria:</u>

- Life expectancy <6 months.

- Contraindications to contrast media, e.g. patients with renal failure,

- Patients allergic to contrast media.

- Contraindications to magnetic resonance imaging, e.g. claustrophobia,

- Patients having cardiac prosthesis, metallic plates….etc

- Other tumors other than hepatocellular carcinoma.

All patients underwent locoregional ablation therapy scheduled for dynamic contrast enhanced (DCE) MRI and diffusion weighted images (DWI) either in the routine follow up or after inconclusive triphasic Ct study to assess tumor response to treatment and detect residual or recurrent lesions.

All cases were viewed by 2 experienced radiologists in hepatic imaging

<u>MR images were analyzed for the following:</u>

- The morphological features of each lesion were recorded including size, border,

signal characteristics at T1 and T2 signal characteristics.

- Pattern of enhancement in the dynamic imaging.

- Signal intensity on diffusion images with ADC values using a commercially windows workstation.

<u>The region of interest (ROI) used to measure the ADC value is applied as following:</u>

- The ROI included nearly the entire lesion if it displayed diffuse homogeneous or heterogeneous signal on ADC map.

- If the lesion shows well defined areas of restriction and other areas of facilitation the ROI is placed on each area separately and two ADC values are calculated.

- The ADC values were measured three times and the average was taken.

Data were tabulated, coded then analyzed using the computer program SPSS version 23.0 (Chicago, Ill, USA)

Results:

All DWI images using different p values, ADC maps and ADC values were interpreted and classified eventually into two groups: -

1- Diffusion Free lesions were considered when hypo-intense signals in diffusion weighted images are noted or concomitant hyper-intense signals in diffusion weighted images with hyper-intense signals in ADC maps (shine through effect) is noted.

2- Diffusion restricted lesions were considered when hyper-intense signals in diffusion weighted images are noted simultaneously with hypo-intense signals in ADC maps.

- Out of the 40 locally treated lesions (25) lesions showed free diffusion (62%) while (15) lesions showed restricted diffusion (38%) .

The lesion margin and perilesional area on DWI:

The margins of all lesions showed free diffusion while the perilesional area showed restricted diffusion in one lesion and free diffusion

Quantitive analysis of ADC Values: -

- The highest intralesional ADC values RANGED FROM .677: 1.663.

- The Mean ADC value and SD 1.087±.256. (table 8)

- The ADC values among the diffusion free lesions ranged from 1.040: 1.663 while the ADC values among the diffusion restricted lesions ranged from .667 :1.008

- The mean ADC values among the diffusion free lesions (1.131×10^{-3} mm2/sec) while the mean ADC values among the diffusion restricted lesions ($.957 \times 10^{-3}$ mm^2/sec)

Analysis of Dynamic MRI diagnostic criteria According to the pattern of enhancement characteristic for HCC, lesions are sorted into either enhancing or non-enhancing groups.

1- Enhancing group: - include lesions which showed arterial enhancement and washout in the portal and delayed phases.

2- Non-enhancing group: - include lesions which showed no intra lesion enhancement pattern of HCC or showed reactive marginal and surrounding area persistent enhancement yet no washout.

Out of the 40 locally treated lesions (30) lesions showed no intralesional enhancement (75%) while (10) lesions showed intralesional enhancement (25%).

Marginal assessment: -

The margin of the locally treated lesions showed no enhancement in 6 lesions (15%) and persistent enhancement in 34 lesions (85%).

Perilesional area assessment: -

The perilesional area of the locally treated lesions showed no enhancement in 30 lesions (75%) and persistent enhancement in 10 lesions (25%).

Final total indices

Upon correlating the diffusion findings to the final diagnoses, among the (30) ablated lesions (23) lesions showed free diffusions (76.7%) and (7) lesions showed restricted diffusion (23.3%) while among the (10) residual lesions (8) showed restricted diffusion (80%) and (2) lesions showed free diffusion (20%)

Table (1) Number and frequency of enhancement pattern of the lesions:-

		No	%
	NO NHANCEMENT	28	70.0%
Main lesion	ENHANCEMENT	10	25.0%
	PERSISTENT ENHANCEMENT	2	5.0%
	NO ENHANCEMENT	6	15.0%
Margin	PERSISTENT ENHANCEMENT	34	85.0%
surrounding area	NO ENHANCEMENT	30	75.0%
	PERSISTENT ENHANCEMENT	10	25.0%

Table (2) DWI-MRI & Dynamic MRI results

		No	%
Dynamic	Ablated	30	75.0%
	Residual	10	25.0%
DWI	Free	25	62.5%
	Restricted	15	37.5%

Table (3): Correlation of the DWI results to in dynamic MRI results.

		Dynamic				P
		Ablated		**Residual**		
		No	**%**	**No**	**%**	
DWI	**Free**	23	76.7%	2	20.0%	<0.001*
	Restricted	7	23.3%	8	80.0%	

Table (4):- According to DWI, false and true positive lesions & false and true lesions

		No
DWI	**True Positive**	8
	False negative	2
	True negative	23
	False Positive	7

Table (5): shows the different indices of the DWI

Sensitivity	80.0%
Specificity	76.7%
PPV	53.3%
NPV	92.0%
Accuracy	77.5%

PPV: Positive predictive value   NPV: negative predictive value

Qualitative analysis of the ADC value:-

The different ADC values elicited from the corresponding ADC maps were calculated. The difference between ADC variables among the malignant and benign groups were statistically significant, p value 0.03. The ROC curve obtained by plot at different cut off values is shown in Figure. The best cut off that maximizes sensitivity and specificity is 1.024×10^{-3} mm^2/sec. At this ADC value, the sensitivity is 80% and specificity is 76.7%. A statistical software showed that the AUC=0.73 with 95% CI from 0.540 to 0.920. It seems from the ROC that ADC variable is a fair indicator to detect residual of HCC after ablation. (Area under the curve:- excellent 0.9-1, good 0.8-0.9, fair 0.7-.8, poor 0.6-0.7, fail 0.5-0.
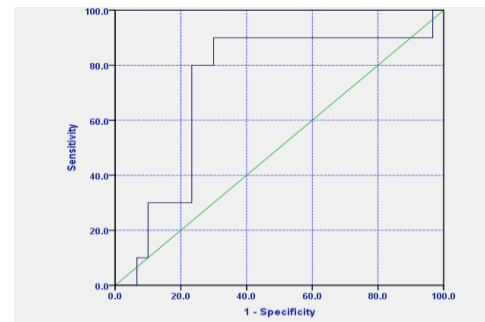

Figure (1):- Results of receiver operating curves for ADC values in distinguishing viable and non-viable groups
.

Table (6): The different indices of the ADC

AUC(95%CI)	0.73(0.54-0.92)
p value	0.03*
Cutoff value	<1.024
Sensitivity	80.0%
Specificity	76.7%
PPV	53.3%
NPV	92.0%
Accuracy	**77.5%**

Table (7):- According to ADC, false and true positive lesions & false and true lesions

| ADC		No
	True Positive	8
	False negative	2
	True negative	23
	False Positive	7

Case No.1 (Fig.2):

• Clinical history: A 70 years old female with hepatocellular carcinoma (HCC) was candidate for microwave ablation.

• MRI six months After Microwave ablation:

- Pre-contrast T1WI: isointense lesion with surrounding hypointense rim (Fig.2 a).

- Pre-contrast T2WI: the lesion is hyperintense (Fig.2 b).

- Final conclusion: Successfully ablated lesion showing free diffusion and high ADC values.
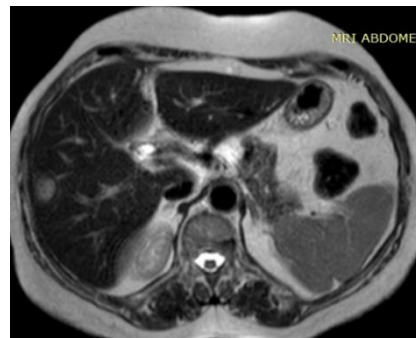
(2a) T1   **(2b) T2**

DWI: the lesion is hyperintense **(Fig. 2 c, d & e).**
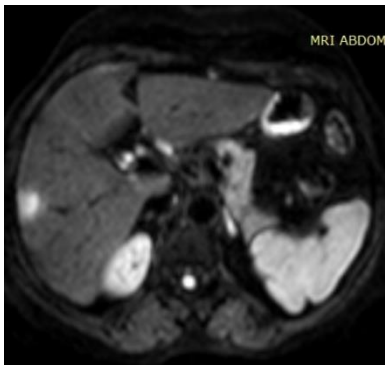
(2C) DWI   **(2d) DWI**   **(2e) DWI**

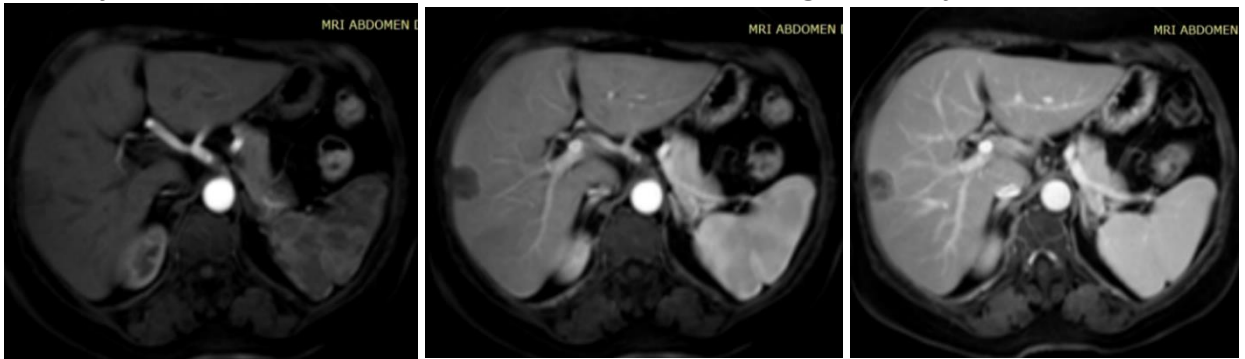**ADC map:** The lesion is hyperintense to liver parenchyma.
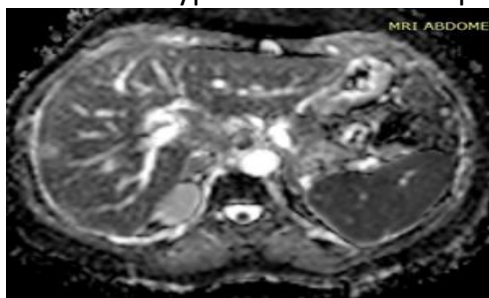
(2f) ADC

Mean ADC value = 1.593 x10^{-3} mm^2/sec (Fig. 2g).
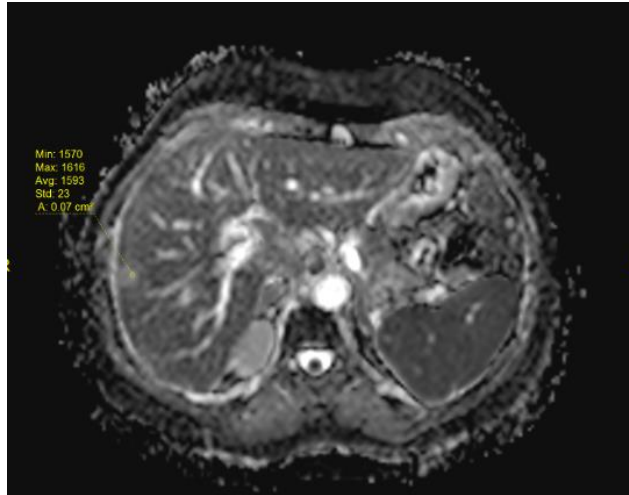
(2g) ADC value

Dynamic MRI: The lesion show no enhancement **(Fig.2 h, I & j).**


| **(2h) dynamic arte** | **(2i) dynamic venous** | **(2j) dynamic delayed** |

Case No.2 (Fig.3):

- Clinical history: A 46 years old male with hepatocellular carcinoma (HCC) was candidate for radiofrequency ablation.

- MRI one month After radiofrequency ablation (Fig. 3):
    - Pre-contrast T1WI: hypointense lesion at seg VI (Fig. 3a).

- Pre-contrast T2WI: The lesion is hyperintense (Fig. 3b).

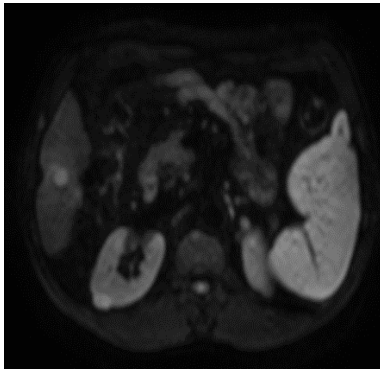- Final conclusion: residual lesion showing restricted diffusion and low ADC values (true +ve).
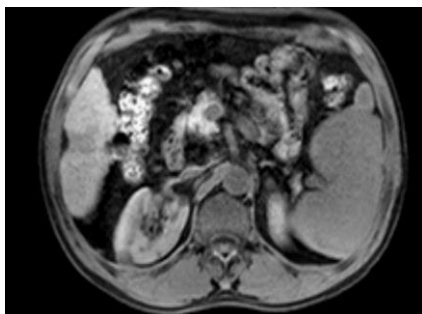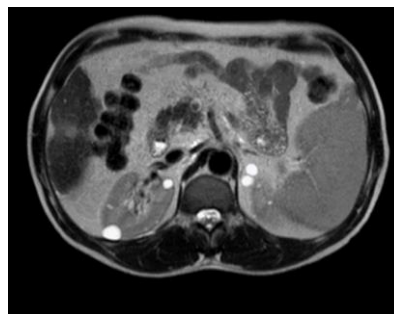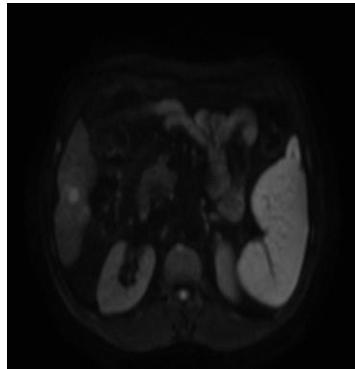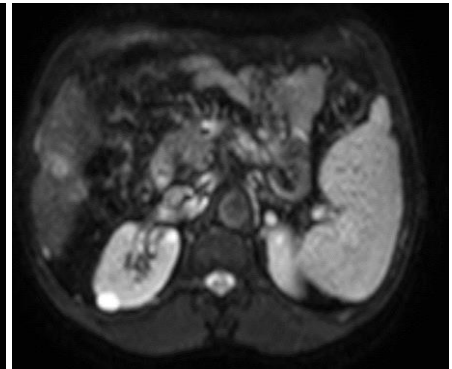

| **T1   (Fig.3 a1)** | **T2 (Fig.3 b)** |

DWI: the lesion is hyperintense at different b values **(Fig. 3 c,d&e).**
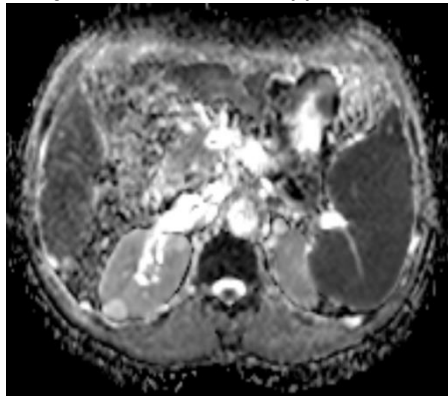

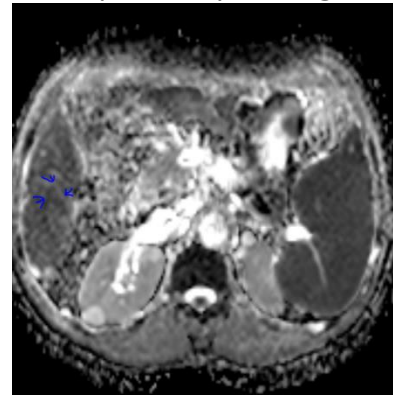**(Fig.3 c)** **(Fig.3 d).** **(Fig.3 e).**

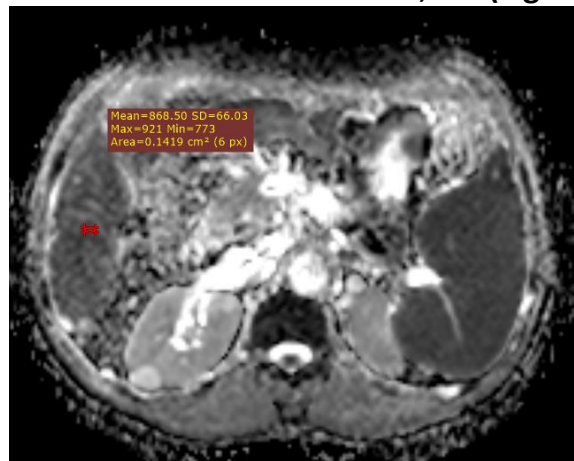**ADC map:** The lesion is hypointense to liver parenchyma **(Fig.3 f1&f2)**.

(Fig.3 f1) **ADC MAP** **(Fig.3 f2)**

***Mean ADC value = .868 x10^{-3} mm^{2}/sec* (Fig.3 g)**.

Mean=868.50 SD=66.03
Max=921 Min=773
Area=0.1419 cm² (6 px)

(Fig.3 g)

Dynamic MRI: the lesion show arterial enhancement with portal and delayed washout (**Fig.3 h, I & j).**

Arterial (Fig.3 h)   Portal (Fig.3 i)   Delayed   (Fig.3 j)
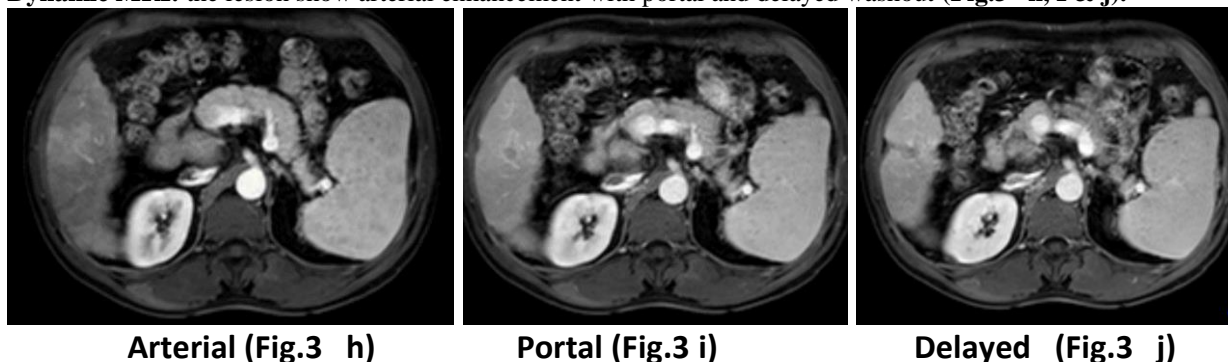
Discussion:

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. It claims more than 500,000 lives annually and is the third leading cause of cancer deaths worldwide. Most of the patients who are not fit for resection/transplantation undergo less invasive

Functional MRI techniques such as Diffusion-weighted imaging (DWI), detects early MR signal changes in tissues within several weeks of treatment, based on the degree of cell membrane integrity (10).

The aim of the present study was to compare functional DWI MRI to contrast enhanced MRI to determine the usefulness of diffusion weighted imaging in detection of residual viable tumor tissue in hepatocellular carcinoma after locoregional treatment.

It has been shown that respiratory triggered DW MR imaging improves lesion detection, compared with breath-hold DW MR imaging

(sensitivity for lesion detection, 93.7% vs 84.3%) (11) and improves image quality, SNR, and ADC quantification (12).

In our study, we used respiratory-triggered DW to increase the SNR and CNR without compromising the ADC measurements. In this study the breath-hold DW MR imaging technique was used. (13)

In our work 30 patients displayed 40 HCC lesions. ten lesions displayed residual tumor tissue and (30) lesions appeared free of residual tumor tissue. The sensitivity of DWI was 80%, its specificity was 76.7%, positive predictive value was 53.3% and negative predictive value was 92%.

Different studies worldwide were established to determine the value of DW-MRI in evaluation of treatment response after loco regional therapies.

In the study done in 2017, DWI had a sensitivity of 82%, a specificity of 73.9%,

PPV value of 70%, NPV of 85% and an overall agreement of 77.5%. (14)

In ElSaid et al. (13) study of DWI, reader 1 evaluation yielded a sensitivity of 70.59%, and a specificity of 75%, a positive predictive value of 82.76% and a negative predictive value of 60% and 95% confidence interval of (64-94%) compared to, 76.47%, 90%, 92.86% and 69.23% and (76-99%) respectively in reader 2.

In a study on the qualitative DWI findings showed sensitivity of 83.9%, specificity of 64.3%, positive predictive value of 72.2%, and negative predictive value of 78.3% and overall accuracy of 74.5%. (15)

Data on DWI for response assessment can still be highly heterogeneous, most likely due to differing study protocols and MR hard- and software used (16).

On combination DWI and Gd-MRI, it was stated that DWI increased the sensitivity compared to Gd-MRI alone (92% vs. 85%; p = 0.125) only to a non-significant degree while specificity decreased from 65% to 50%. Therefore, DWI is only of little to no value for recurrence detection according to this literature.(17)

So, in our study we postulated that the false positive cases are likely originating from liquefactive necrosis or intralesional hemorrhage (hyperintense on T1WIs) that causes diffusion restriction.

In our study we used quantitative ADC calculation of the treated lesions which is dependent on multiple pre chosen b values.

In our DWI study, b values were (0, 20, 400, 800sec/mm²), with the application of parallel imaging and breath triggering technique, a satisfying image quality has been achievable on a 1.5-T scanner within an acceptable acquisition time.

In another study done in 2017, p values of 50, 400 and 800 sec/mm² to avoid intravoxel perfusion effect which result from low p values (less than 50) in addition high p value with its higher accuracy in lesion characterization, was used.(14)

In our study, the difference between ADC variables between the malignant and benign groups was statistically significant P value 0.001 and the area under the curve 0.73. The best cut off that maximizes sensitivity and specificity is 1.024×10^{-3}. At this ADC value, the sensitivity is 80% and specificity is 76.7%.

We found from the ROC that ADC variable is a fair indicator to differentiate marginal recurrence of HCC from perilesional pseudo- or benign lesions.

It was stated that quantitative measurements of diffusion showed that malignant lesions present lower ADC values than benign ones and surrounding liver parenchyma.(18)

In a study done on 2016, the measured cutoff value between the completely ablated lesions and residual/recurrent lesions was 1.05×10^{-3} mm^2/s. and showed that ablated zones can be differentiated from liver parenchyma visually in the DW-MRI and by means of ADC in all patients. There is no statistical difference in the mean ADC values between the ablated zones of the resolved 1.37×10^{-3} mm2/s and unresolved lesions 1.39×10^{-3} mm^2/s (p value 0.7). (19)

It was stated that the difference between the malignant residual and well ablated groups' ADC variables was statistically significant P value 0.009. (14)

In a study done on 2017, the measured ADC values showed significant difference (P value <0.05) between the ADC values measured in the active tumoral areas and necrotic areas. ROC analysis for ADC values showed area under curve 0.7 and maximum combined sensitivity and specificity of 79% and 69.6% respectively at cutoff ADC value of 1.395 mm^2/sec. (15)

In another study, there was no statistical difference in the mean ADC values between the entire ablation zones of the resolved and unresolved groups (p value 0.70).(20)

Completely treated lesions showed significant rising changes regarding ADC values after RF ablation and no residual enhancement was detected on subtraction images. viable tumoral tissue appeared hyperintense with significantly lower ADC values (0.8×10^{-3} mm^2/sec) than completely ablated necrotic tissue which appeared hypointense with higher ADC values (1.4×10^{-3}mm2/sec), The mean ADC of the well ablated lesion was 1.4×10^{-3} mm^2/sec and of the residual lesion 0.8×10^{-3} mm^2/sec with significant statistical difference between the residual viable tumor and the well ablated lesions, Moreover, it was recommend a cut-off value of 1.233×10^{-3} mm^2/s. The values below this level, express viability of the malignancy. (21)

It was not possible to calculate an ADC cut off value from the ROC curve because the AUC was insignificant and false-negative identification of necrotic tissue may result from well-differentiated HCC. (13)

In a study done in 2014, it was concluded that, viable and necrotic tumor tissues may occasionally be difficult to characterize with the visual assessment of the DW-MRI alone (22). Yet, we could still calculate a post treatment average for good and poor responding lesions.

In ElSaid et al. (13) study, the mean ADC value for necrotic lesions was 1.16 and 1.24×10^{-3} mm^2/sec as detected by reader 1 and 2 respectively. The mean ADC for residual disease was 1.07 and 1.05 $\times 10^{-3}$ mm^2/sec as detected by both readers respectively.

In 2012, it was found that viable lesions values were $0.97 \pm 0.39 \times 10^{-3}$ mm^2/sec and non- viable lesions were $1.18 \pm 0.34 \times 10^{-3}$ mm^2/sec (p=0.002) (23)

In 2009, Mannelli and co-workers concluded that ADC had a weaker correlation with histopathologic degree of tumor necrosis compared to contrast- enhanced subtraction MRI image. However, there was no difference between the two methods in the diagnosis of complete tumor necrosis. On the bases of their study, they believe that DWI can be used as an alternative to contrast- enhanced MRI in the care of patients who cannot administrate gadolinium contrast material, such as patients with renal insufficiency. (24)

In another study done in 2011, it was concluded that ADC value may be a useful tool in the assessment of HCC response, but it may not be sensitive to tumor recurrence as compared with DCE MR imaging. (25)

As stated in 2014, DWI can quantify HCC tumor necrosis, and the ADC value may be useful to determine necrotic and viable tumor tissues. Additionally, DW-MRI improved liver lesion detection. Therefore, DWI may be an option for the short-term follow-up of HCC patients following chemoembolization and may guide patient management for reducing radiation exposure of CT examination and the risk of contrast material-induced nephropathy. (22)

Gluskin and co-workers stated that the main strengths of diffusion MRI images are to increase the confidence in diagnosis of HCC especially when intravenous contrast administration is not possible or for small lesions adjacent to vessels.

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