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MRI Evaluation of Hepatocellular Carcinoma Post Locoregional Therapy Using Post Processing Arterial Subtraction

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Abstract

Background: Hepatocellular carcinoma [HCC] is the commonest primary tumor of the liver and the leading cause of cancer-related death globally. Early detection is crucial for improving outcomes. For patients who are not surgical candidates, locoregional therapies like trans-arterial chemoembolization [TACE] and radio-frequency ablation [RFA] are important palliative options. Conventional magnetic resonance imaging [MRI] had limitations in differentiating viable tumor from post-treatment changes and dynamic subtraction imaging. However, it adds significant value to dynamic MRI and diffusion-weighted imaging [DWI].

Aim of Study: The purpose of this research was to evaluate the utility of dynamic subtracted MRI sequences for evaluation of HCC after locoregional therapy.

Patients and Methods: A cross-sectional study involved 60 HCC patients [aged 42–73] who had hepatic MRI. The following pictures were obtained: precontract T1, T2, and dynamic contrast enhanced sequences, diffusion-weighted. On the workstation, subtracted dynamic images and dynamic curve were produced. A radiology consultant interpreted the magnetic resonance images. For the ordinary dynamic, subtracted dynamic and diffusion images, the following metrics were determined: overall agreement, sensitivity, specificity, negative predictive value, positive predictive value

Results: Ordinary dynamic [Arterial T1 with fat sat] showed a sensitivity of 96.77%, specificity of 58.6%, PPV of 71.4% and NPV of 94.4%, While subtraction MRI showed a sensitivity of 100%, specificity of 100%, PPV of 100% and NPV of 100% compared to DWI showed a sensitivity of 100%, specificity 93%, PPV 93.9% and NPV 100%. So Dynamic subtraction imaging was found to have a significant additive value when compared to traditional dynamic MRI and DWI.

Conclusion: The subtraction approach is a valuable confirmatory tool for the diagnosis of HCC following locoregional therapy. It also had higher sensitivity, specificity, positive and negative predictive values.

Keywords: Dynamic MRI; Hepatocellular Carcinoma; Locoregional Therapy; Subtraction MRI; T1 Signal.

INTRODUCTION

Hepatocellular carcinoma [HCC] is the most prevalent primary liver cancer worldwide, with an increasing incidence rate, and ranks third in terms of cancer-related mortality [1].

Although the overall 5-year survival rate for liver cancer is still less than 20%, the prognosis is dependent on a number of clinical, laboratory, and radiologic criteria. Early diagnosis through surveillance is crucial in lowering mortality associated with HCC [2].

According to the stage of the tumor and the severity of the underlying liver disease, surgical resection and liver transplantation are the best curative options for patients with HCC. However, a recent comparative study of over 8000 HCC cases worldwide found that less than 10% of patients met the preoperative criteria for resection [3].

New liver-directed techniques are being used to treat carefully chosen individuals, and in certain circumstances, they are curative, for those who are not suitable candidates for surgery. Other aims of locoregional treatments are palliation, hypertrophy of hepatic tissue to promote liver function for additional major resection, and tumor cytoreduction for downstaging or "bridging" to retain candidacy for transplantation [3].

Improvements in locoregional medicines, such as ablative therapies and trans arterial monotherapies, have led to an increase in management strategies that improve overall survival and decrease side effects for a variety of patients over the past 20 years [4].

Accurately assessing treatment response after locoregional therapy [LRT] for hepatocellular carcinoma is critical for assessing treatment success, directing future treatment approaches, and forecasting patient prognosis [5]. In 2017, a new treatment response methodology was introduced by the Liver Imaging Reporting and Data System [LI-RADS] to enhance uniformity and standardize the imaging criteria for HCC following LRT [6].

Different from a number of patient-level treatment response criteria, such as the European Association for the Study of the Liver [EASL] and the modified Response Evaluation Criteria in Solid Tumors [mRECIST], which view arterial phase hyper enhancement [APHE] as the exclusive sign of a viable tumor, Two additional characteristics of a viable tumor identified by the LI-RADS treatment response [LR-TR] algorithm are "washout" and "enhancement similar to pretreatment."; while each of these characteristics has a strong correlation with tumor viability, APHE is the characteristic that is most usually seen in viable tumors [7]. Therefore, it is very important to detect APHE during the treatment response evaluation of Hepatocellular carcinoma. Intratumorally necrosis causes HCC treated with LRT to appear bright on precontract T1-weighted imaging. This can make it more difficult to detect APHE on MRI and reduce the sensitivity for identifying viable tumors [8].

To overcome these issues, arterial subtraction pictures have been developed, which are useful for precisely determining the efficacy of HCC locoregional therapy [9].

According to a recent study by **Gordic *et al*.**[10]**,** MRI subtraction imaging has excellent diagnostic performance for predicting the pathological degree of HCC necrosis after LRT.

THE AIM OF THE WORK

The purpose of this research was to evaluate the utility of dynamic subtracted MRI sequences for evaluation of HCC after locoregional therapy.

PATIENTS AND METHODS

Patients: Sixty HCC patients, who were assessed by 3 experienced radiologists with more than 20 years of experience in hepatic imaging between January 2023 and June 2024, participated in this cross-sectional study. Patients of all ages who were sent to the radiology department for dynamic MRI evaluation following locoregional treatment for hepatocellular cancer provided data. The National Liver Institute Ethics Committee [REC] gave its approval for this work [N-00373-2022].

Inclusion criteria: Subjects with HCC who rejected surgery or were considered unsuitable for resection, received locoregional treatment, which was determined by BCLC staging. The liver volume with the tumor burden less than 50%. Serum creatinine level < 1.4 mg/dl.

Exclusion criteria: Patients who had contrast media contraindications, such as individuals with renal disease or those who are allergic to it. Patients who had contraindications to magnetic resonance imaging [MRI], such as metallic plates, pacemakers, non-MR compatible cardiac prostheses, claustrophobia in patients not suitable for anesthesia. non-hepatocellular carcinoma liver tumors.

MRI examination: All dynamic cases were performed using [Optima 450W; GE Healthcare Milwaukee, WI, USA] [1.5 Tesla MRI scanner].

MR protocol used: The conventional liver imaging protocol included the following sequences: the pre-contrast a T1 weighted image, in-phase/out-of-phase images, T2 weighted images, DWI, and phases of dynamic contrast study. A summary of the parameters which were applied in the pre- and post-contrast sequences is demonstrated **[Tables 1-3].**

Analysis of the MR images: We used Philips' IntelliSpace Portal software [Philips Medical Systems, Best the Netherlands] for the analysis and post processing of MRI images. Every lesion's morphological characteristic, such as its size, border, and signal strength, were recorded. Utilizing dynamic study analysis, the presence of residual or recurring tumor viability is evaluated. Once the single pre-contrast series was completed, we conducted arterial, portal, and delayed phases. It was investigated how the pattern of enhancement changed as the Dynamic series progressed, we also evaluated DWI to assess managed hepatic focal lesion whether restricted or not to assess tumor viability. Post processing, using an automated procedure on the workstation, subtraction images and dynamic curves were carried out. Specifically, an unenhanced T1-weighted sequence was digitally subtracted from the same sequence carried out following gadolinium injection. The pre-contrast series was digitally subtracted from the dynamic study's arterial phase in our investigation. Any native T1 signal is eliminated during this process, leaving only enhancement to account for the remaining signal on the subtracted images. Next, the subtraction dynamic imaging's pattern of enhancement was examined, we also evaluated dynamic MRI curve pattern to assess tumor viability

Table [1]: Precontract study

	TE	TR	Field of View	Slice Thickness	Slice Spacing	Flip angle
Axial T2	92ms	2957ms	35-40cm	6mm	1.5mm	Auto corrected [100-140]
Axial T2[Fat Sat]	83ms	4286ms	35-40cm	6mm	1.5mm	Auto corrected [100-140]
Axial Heavy T2	200ms	1080ms	35-40cm	6mm	1.5mm	Auto corrected [100-140]
Coronal T2	92ms	2957ms	35-40cm	6mm	1.5mm	Auto corrected [100-140]

Table [2]: Dynamic study

	TE	TR	Field of view	Slice thickness	Slice Spacing	Flip angle
Axial Lava T1	4.2ms	6.2ms	42 cm	5.2mm	1.5mm	12
[Coronal [LAVA-Flex	4.2ms	6.2ms	42cm	5.2 mm	1.5mm	12

Phase	Timing
Early arterial	After 25 s from onset of contrast injection
Delayed Arterial	After 15 s after early arterial phase scan time
Portal phase	Over 30 s after delayed arterial phase scan time
Venous phase	After 120 s after portal phase scan time
Delayed phase	After 5 min from onset of contrast injection

Table [3]: Diffusion weighted image

	TE	TR	Field of view	Slice Thickness	Slice spare
Axial DWI B 50, 800	140ms	8131ms	38cm	5mm	1.5mm

Interpretation of the MR image:

- MR images were interpreted by radiology consultant He read the films, having the clinical data of the patients. Interpreted the Dynamic MRI and post processing subtraction MRI images and dynamic MRI curves.
- Arterial phase enhancement was recorded, suggesting residual tumoral activity.
- Absence of enhancement in the arterial phase was recorded, suggesting well tumor ablation.
- Diffusion weighted images were evaluated to assess managed hepatic focal lesions whether restricted or not [viable or not] and results will be recorded and compared with ordinary dynamic and subtraction results.
- Post processing arterial subtraction images and dynamic curve analysis to assess managed hepatic focal lesion viability, any high signal within subtracted image means true enhancement which indicates tumor viability, also dynamic curve type III means tumor viability.

Standard of reference: In our investigation dynamic curve of all included HCC patients served as the standard of reference.

- We define two groups depending on dynamic curve results as gold standard: A well-managed group with non-viable lesion and the viable group with detectable viable tumors.
- Since most patients who perform RFA or TACE do not u may result in sampling error. Therefore, assessed hepatic focal lesions were classified into two groups [Viable and Non-viable] based on Dynamic curve results as gold standard.
- We evaluated the sensitivity, specificity, and accuracy for ordinary dynamic MRI, diffusion-weighted and subtraction MRI images based on dynamic curve results as gold standard

Statistical analysis: By SPSS v26 [IBM Inc., Armonk, NY, USA], statistical analysis was done. Quantitative data were expressed as a range [minimum and maximum], mean, standard deviation, and median. Qualitative variables were presented as number and percentage [%]. The chi-square or Fisher's exact test compared well-managed and residual groups based on dynamic MRI curves. Diagnostic indices, including sensitivity, specificity, PPV, and NPV, were calculated for conventional MRI, diffusion MRI, and the subtraction image.

RESULTS

60 patients, who underwent locoregional therapy for HCC lesions, were included in this study **[Table 4].**

Experienced radiologists interpreted different MRI images [Ordinary dynamic, DWI, post processing arterial subtraction and dynamic curve] of managed HCC lesion to assess them for viability and results are demonstrated **[Tables 5, 6]**.

Arterial T1 with and without fat sat showed a sensitivity of 96.77%, specificity of 58.6%, PPV of 71.4% and NPV of 94.4%, While subtraction MRI showed a sensitivity of 100%, specificity of 100%, PPV of 100% and NPV of 100% compared to DWI showed a sensitivity of 100%, specificity 93%, PPV 93.9% and NPV 100% **[Table 7]**. So, a notable additive value of dynamic subtraction imaging to conventional dynamic MRI and DWI was identified.Figures [1 and 2] represented imaging findings of two cases.

Table [4]: Demographic data and loco regional therapy of the studied patients.

		N=60
Age [years]	Mean ± SD	59.55 ± 6.7
	Median [Min-Max]	59 [42-73]
Sex	Male [%]	42 [70.0%]
	Female [%]	18 [30.0%]
Loco regional therapy	TACE [%]	37 [61.6%]
	RFA [%]	21 [35.0%]
	MWA [%]	2 [3.0%]

Table [5]: Distribution of the studied cases according to qualitative MR imaging features

		N=60
Response according to dynamic curve	Non-viable [%]	29 [48.0%]
	Viable [%]	31 [52.0%]
Arterial T1 with and without fat sat	Non-enhanced	18 [30.0%]
	Enhanced	42 [70.0%]
Subtraction	Non-enhanced	29 [48.0%]
	Enhanced	31 [52.0%]
Diffusion	Facilitated	27 [45.0%]
	Restricted	33 [55.0%]

Table [6]: Relationship of Subtraction MRI with Conventional dynamic and diffusion findings

		Subtraction MRI		[Total [n=60	P value
		[Non-viable [n=29	[Viable [n = 31		
Arterial T1 without fat sat	Non-enhanced	17 [58.6%]	1 [3.2%]	18 [30.0%]	< 0.05*
	Enhanced	12 [41.4%]	30 [96.8%]	42 [70.0%]	
Arterial T1 with fat sat	Non-enhanced	17 [58.6%]	1 [3.2%]	18 [30.0%]	< 0.05*
	Enhanced	12 [41.4%]	30 [96.8%]	42 [70.0%]	
Diffusion	Facilitated	27 [93.0%]	0 [0.0%]	27 [45.0%]	0.7
	Restricted	[2 [7.0%	[31 [100.0%	[33 [55.0%	

*: Statistically significant at $p \leq 0.05$.

Table [7]: Sensitivity, specificity, and accuracy for diffusion, subtraction, and dynamic MRI

		Activity		Sensitivity	Specificity	PPV	NPV	Accuracy
		Non-viable [n =29]	Viable [n = 31]					
Arterial T1 without fat sat	Non-enhanced	17 [58.6%]	1 [3.2%]	96.77 %	58.6 %	71.4 %	94.4 %	78.33 %
	Enhanced	12 [41.4%]	30 [96.8%]					
Arterial T1 with fat sat	Non-enhanced	17 [58.6%]	1 [3.2%]	96.77 %	58.6 %	71.4 %	94.4 %	78.33 %
	Enhanced	12 [41.4%]	30 [96.8%]					
Subtraction	Non-enhanced	29 [100%]	0 [0%]	100 %	100 %	100%	100%	100 %
	Enhanced	0 [0%]	31 [100%]					
Diffusion	Facilitated	27 [93%]	0 [0%]	100%	93 %	93.9%	100 %	96.66 %
	Restricted	2 [7%]	31 [100%]					

PPV: Positive predictive value. NPV: Negative predictive value.

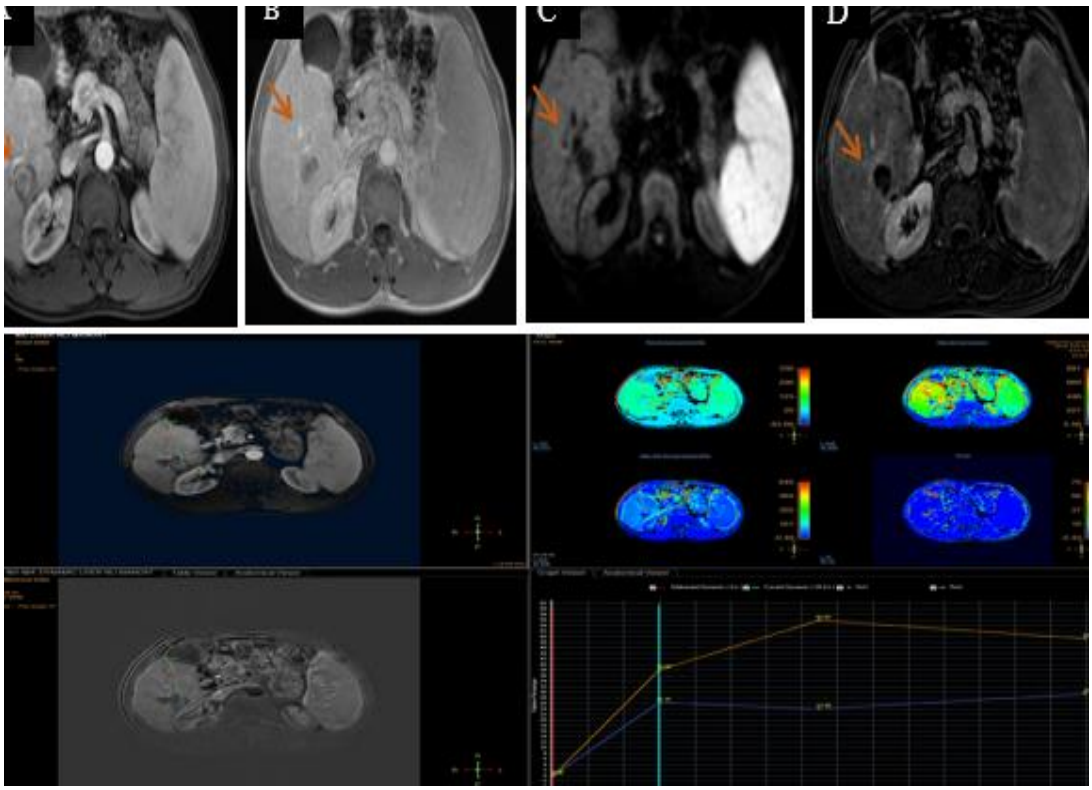

Figure [1]: A 55-year-old male discovered accidentally right hepatic lobe segment VI hepatic focal lesion [HCC] during follow up of HCV cirrhosis and the patient underwent one session of RFA. The early 3 weeks MRI showed: [A] T1W1, fat sat, post contrast [Arterial phase] showed mild enhancement. [B] T1W1, without fat sat, post contrast [Arterial phase] showed mild enhancement. [C] DWI displayed facilitated diffusion. [D] Arterial phase subtraction showed low signal [confirming that T1W1 [arterial phase] high signal was due to coagulative necrosis not true enhancement]. [E] Dynamic curve pattern demonstrated non-viable lesion.

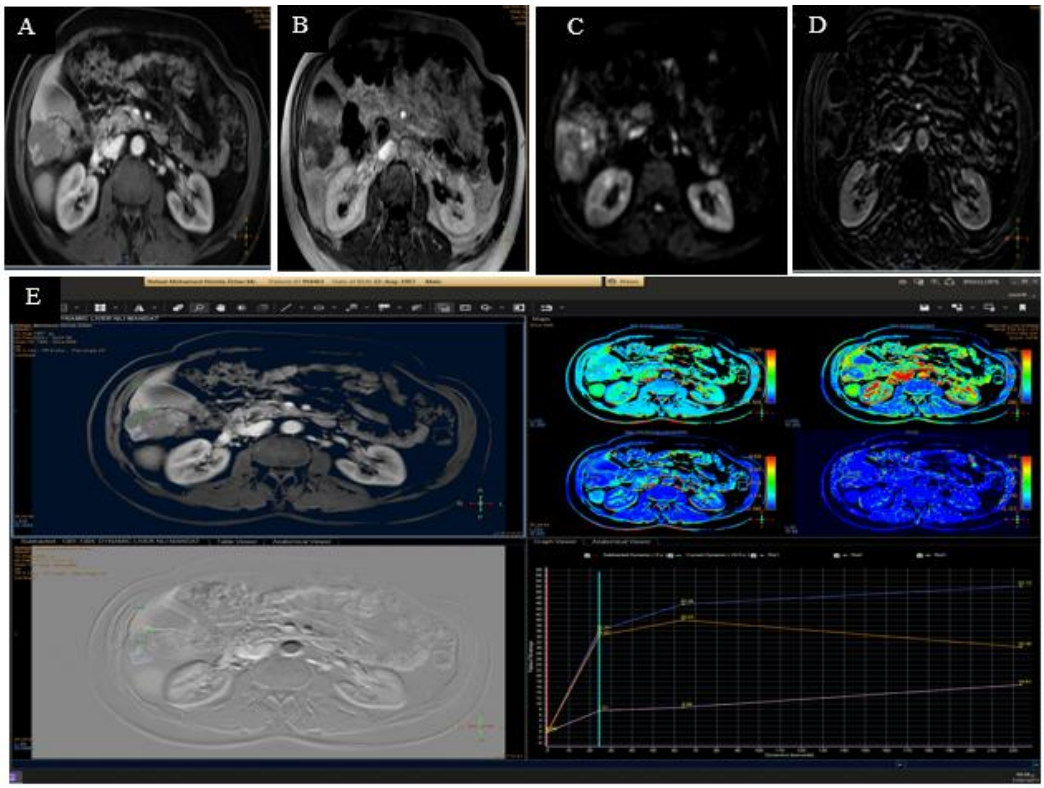

Figure [2]: A 59-year-old male discovered right hepatic lobe segment V\VI hepatic focal lesion [HCC] during follow up of HCV cirrhosis and the patient underwent TACE. The early 3 weeks MRI showed: [A] T1W1 fat sat, post contrast [arterial phase] showing peripheral nodular tissue within posterior lateral aspect of HFL showing enhancement. [B] T1W1 without fat sat, post contrast [arterial phase] showing peripheral nodular tissue within posterior lateral aspect of HFL showing enhancement. [C] DWI displayed Peripheral nodular tissue within posterior lateral aspect of HFL showing restricted diffusion. [D] Arterial phase subtraction showed peripheral nodular tissue within posterior lateral aspect of HFL showing high signal, [confirming viability and that high signal due to truly enhance not tissue necrosis]. [E] Dynamic curve pattern demonstrated Peripheral nodular tissue within posterior lateral aspect of HFL showing viability confirming that high signal due to true enhancement

DISCUSSION

As palliative therapy for hepatocellular carcinoma [HCC], image-guided loco-regional therapies are currently advised for patients who are not candidates for surgery [11].

Monitoring the tumor's response to these therapies is becoming vital in oncologic imaging. A favorable early response generally indicates the therapy's effectiveness and can lead to significant survival benefits. Conversely, early identification of treatment failure is crucial for patient management, allowing for the repetition of treatment cycles [12].

MRI provides detailed information to assess HCC response to treatment. It helps distinguish between viable and non-viable tumors, with MRI enhancement characteristics indicating treatment efficacy and potentially suggesting the need for further intervention [13].

While reduction in tumor size is a validated parameter for assessing treatment response according to the Response Evaluation Criteria in Solid Tumors [RECIST], it does not account for non-viable HCC that may not reduce in size shortly after treatment [14].

The American Association for the Study of Liver Disease [AASLD] and the European Association for the Study of the Liver [EASL] developed the modified RECIST, which takes tumor enhancement into account as a biomarker for disease response [13].

It's possible that standard gadolinium-enhanced MRI cannot distinguish between granulation tissue and inflammation brought on by therapy and a viable tumor [15]. Thus, in order to accurately capture tumor response, different MRI techniques are required [11].

On unenhanced T1-weighted images, coagulative hemorrhagic necrosis appears as a high signal in the transition zones. Subtraction MRI eliminates preexisting T1-weighted high signals from the post-processed pictures, leaving only the enhancement-related high signals. It does this by digitally subtracting unenhanced from contrast-enhanced T1-weighted sequences [15].

It is essential to keep acquisition parameters for dynamic contrast-enhanced and unenhanced images constant across multiple phases in dynamic subtraction imaging. The patient's position should also not alter, and it's critical that they be able to hold their breath during acquisition. The breath-hold needs to be consistent across sequences, and pictures should be taken as the subject expires. Image deterioration and misregistration artifacts may result from not meeting these requirements [16].

Our study categorized managed hepatic focal lesions into two groups based on dynamic MRI curves: a well-managed group with good response [29 out of 60 patients, 48.4%] and a residual group with detectable viable tumors [31 out of 60 patients, 51.6%]. Subtraction dynamic MRI proved more valuable than conventional dynamic MRI and DWI for follow-up of HCC lesions post-locoregional therapy.

Ordinary dynamic MRI demonstrated a sensitivity of 96.0% and specificity of 59.0%, while DWI showed a sensitivity of 100.0% and specificity of 93.0%. In contrast, subtraction MRI achieved a sensitivity and specificity of 100.0%. Thus, dynamic subtraction imaging adds significant value to conventional dynamic MRI and DWI.

Our results are consistent with those of ***Winters et al***. [18] and ***Newatia et al***. [19], who highlighted the additional value of subtraction MRI. By removing pre-existing T1-weighted high signals from post-processed images, the remaining high signal is solely due to enhancement, thereby improving reader confidence in detecting enhancement in targeted zones. This improvement enhances MRI assessment of treatment response following locoregional therapy.

In this study, DWI showed a sensitivity of 100.0% and a specificity of 93.0%. These results are in line with **Hassan *et al***. [17]. The high sensitivity and lower specificity of DWI are attributed to false positives from hemorrhage, coagulative necrosis, and intralesional lipiodol accumulation, so DW MRI is a useful add on technique that increases the sensitivity of the DCE MRI in the evaluation of the HCC response to locoregional therapy, especially in patients who cannot hold their breath for adequate time.

We compared statistical analyses between conventional dynamic MRI, diffusion-weighted imaging [DWI] and arterial subtraction to assess the added value of MRI subtraction, considered a gold standard. We found that MRI subtraction is more valuable than Conventional dynamic MRI and DWI, increasing radiologists' confidence in interpreting treatment responses following locoregional therapies for HCC.

Limitations: The main limitation in our study was the reference standard was not based on histopathological results to confirm whether there is a complete treatment or residual disease. However, as discussed before, this point relates to clinical practice. False negative results are commonly seen as the residual/recurrent neoplastic lesions are mostly small sized and difficult to be properly identified in the non-contrast image-guided biopsy. In fact, the only true reference standard is the liver explant. This will be done only if patients are scheduled for hepatic transplantation. Another limitation is the mis-registration artefact that could be seen in many of HCC patients especially when the patient is unable to hold his breath properly during the scan time and thus interfering with proper image assessment.

Conclusions: HCC is a major cause of cancer-related mortality in the world. Image-guided locoregional therapies like thermal ablation and TACE are recommended for non-surgical patients. Accurate monitoring of treatment response is crucial for patient management. MRI can distinguish between tumors that are viable and those that are not, although interpretation can become more challenging after treatment. Dynamic subtraction MRI overcomes challenges posed by high pre-contrast T1 signals in treated lesions, improving detection of residual tumor enhancement. This technique demonstrates higher sensitivity, specificity, and predictive values compared to conventional dynamic and DWI sequences. It also increases reader confidence. We recommend incorporating subtraction images as a routine component of liver MRI protocols for improved tissue characterization in post-treatment HCC assessment.

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