THE VALUE OF SUBTRACTION MRI IN ASSESSING THE TREATMENT RESPONSE FOLLOWING TACE FOR HEPATOCELLULAR CARCINOMA

Magda Magdy Abd Rabou¹, Ahmed Mostafa Mohamed², Ahmed Mohamed Hussein³, Allam Elsayed Allam⁴

Radiology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt

ABSTRACT

Background: Hepatocellular carcinoma (HCC) is the world's fifth most frequent malignancy and the main cause of cancer-related fatalities. Early diagnosis of residual tumour or recurrence following TACE is crucial for patients' disease burden to be reduced and their survival prognosis to be improved. Imaging is critical in determining whether to treat the lesions further, repeat the same therapeutic procedure, or adjust the treatment strategy after they have been treated.

Aim: The aim of this study is to present the value of subtraction MRI study in assessing the treatment response following transcatheter arterial chemoembolization (TACE) for hepatocellular carcinoma (HCC) to differentiate between residual tumor viability and post treatment parenchymal changes.

Patients and methods: This prospective study was conducted from (2018 to 2021) on twenty four patients presented with HCC lesions who underwent TACE. Follow up Dynamic MRI with post processing subtracted images were obtained after 1-1.5 months For patients with imaging evidence of residual tumoral activity second session of TACE was achieved after 1.5 to 2 months. For patients with complete treatment follow up Dynamic MRI with subtracted images were obtained after 3 months with AFP measurement every 2 weeks for 3 months.

Results: Twenty four patients their ages ranged from 50 - 78 years were included in our study presented with twenty four lesions at time of diagnosis. All had pre TACE AFP measurement. Patients were excluded for any of the following situations HCC with normal baseline serum AFP (less than 20 ng/mL), extrahepatic metastasis, liver tumors other than hepatocellular carcinoma. Patients with no pre TACE AFP measurement. Subtracted dynamic MRI, contrast enhanced MRI and DW-MRI AUCs had a P-value of less than 0.05 indicating that only these variables could be used to reliably distinguish between patients with residual disease and completely treated patients unlike the AUC of AFP, which had a P-value greater than 0.05. The statistical analysis showed that the subtracted MRI had 87.5% sensitivity, 93.8% specificity 87.5% PPV & 93.8% NPV. The dynamic MRI had 75% sensitivity, 93.8% specificity 85.7% PPV & 88.2% NPV. DW-MRI had 75% sensitivity, 87.5% specificity 75% PPV & 87.5% NPV and finally the AFP had 62.5% sensitivity, 56.3% specificity 41.7% PPV & 75% NPV.

Conclusion: Subtraction MRI is a useful confirmative post processing application available in most commercial MRI platforms that, when used in conjunction with other techniques such as DWI, increases the radiologist's confidence in interpreting the treatment response of HCC after TACE and aids clinical management for those who require retreatment sessions.

Keywords: Hepatocellular carcinoma (HCC), Trans-arterial Chemoembolization (TACE), Subtraction MRI, Dynamic MRI , Alpha fetoprotein (AFP), Diffusion Weighted Images(DWI), Area Under Curve (AUC).

1. BACKGROUND

Hepatocellular carcinoma (HCC) is the world's fifth most frequent malignancy and the main cause of cancer-related fatalities [1]. Geographic, ethnic, infectious, and environmental variables are all linked to an increased risk of HCC. Viral hepatitis, mainly hepatitis B and C, is considered to be responsible for more than half of all HCC cases [2]. The prognosis and treatment choices for HCC are primarily determined on the stage at which the tumor is discovered [3]. As a result, early identification of HCC is crucial for improving the survival of affected patients.
Local ablation therapy for early HCC, surgical resection or liver transplantation are all viable options for treatment [5]. For individuals who cannot be treated with curative therapy, transarterial chemoembolization (TACE) is commonly performed [6]. Due to a substantial tumor burden, decompensated liver function, or extrahepatic metastases upon presentation, a considerable number of patients require nonsurgical treatment and for those patients, TACE is an important tool for extending their long-term survival [7]. Intra-arterial injection of cytotoxic drugs such as doxorubicin or cisplatin emulsified in the oil-based radio-opaque agent lipiodol is used in traditional conventional TACE. The embolic agent, such as a gelatin sponge, is then injected intra-arterially. Lipiodol promotes embolization of the tumour microcirculation and delivers cytotoxic drugs directly to the tumor in cTACE [8]. On imaging to assess the treatment response after chemoembolization is generally based on iodized oil deposition on non-contrast CT. The iodized oil's hyperattenuation makes it difficult to identify residual tumor enhancement on contrast enhanced CT, but it has no effect on MR signal intensity [9]. In contrast enhanced MRI when a tumour is adequately treated with TACE, it presents with lack of internal enhancement which indicates a non-viable tumor however, the presence of an irregular, nodular zone of arterial phase hyperenhancement inside or around a treated tumor with concomitant washout indicates recurrent or residual viable HCC at the previous TACE location. Short-term follow-up within 3 months is important for clarity when presented with findings equivocal for recurring or viable tumor following TACE [10]. The inability to identify viable cells from reactive granulation tissue is a drawback of contrast-enhanced MRI [9].

So to overcome this drawback; using subtraction imaging in which a non-enhanced T1-weighted sequence is digitally subtracted from the T1-weighted image obtained after gadolinium administration, is beneficial. Any native T1 signal related to the treatment zone which may be caused due to hemorrhage, inflammation or liquefactive necrosis is removed during this operation, and the remaining signal on the subtracted images is purely due to enhancement [10][11].

Also using Diffusion-weighted imaging is useful for detecting areas with tumor viability; however, it does not replace dynamic study for identifying characteristic enhancement patterns of tumor viability, which is why it is not currently included as a major feature in the LIRADS v2018 treatment response algorithm [12]. Many tumors, including HCC, have a restriction of water molecules movement, which can be seen on DWI. Water restriction is “improved” after treatment-induced necrosis because the molecules can move about more freely and the limitation is no longer existent. Associated rising in the ADC signal intensity reflects this alteration [13].

Serum alpha-fetoprotein (AFP) is a well-known biomarker that is overexpressed in the vast majority of human HCCs. Because mature hepatocytes lose their ability to generate AFP, it is usually low in adult serum [14]. When compared to AFP negative, AFP positive was related with less differentiated tumors, more advanced TNM stages, larger tumors, and poorer survival [15]. The AFP response after therapy could be used as a simple, objective, and non-invasive way to track treatment efficacy [16]. For the assessment of patients with HCC who undergo TACE, there are no commonly approved AFP criteria [17]. There have been a wide range of serum cutoff values proposed, ranging from 20 to 400 ng/ml. Patients with an AFP of less than 200 ng/ml at baseline, after TACE procedure they had a significantly better survival outcome than those with a higher baseline AFP of more than 200 ng/ml [18].

If newly developed lesions or enlarged non-target lesions were discovered, the overall response was classified as progressive disease (PD) ignoring any primary tumour response, according to EASL criteria. Although TACE may have resulted in the appearance of a new or enlarged non-target lesion, the primary tumor may have demonstrated an objective response, reducing tumor burden and, at the same time, decreasing or stabilizing serum AFP. As a result EASL PD not always reflect the effectiveness of treatment in primary lesions [17].

The American College of Radiology has approved the Liver Imaging Reporting and Data System (LI-RADS) for the evaluation of locoregional treatment response (LR-TR), which aims to standardize post-treatment CT and MRI evaluation. The goal of the LR-TR is to assess lesion-level therapy response in order to advise next stages in surveillance and treatment [19]. The LI-RADS system was created with the goal of improving communication, patient treatment, education, and research [20]. It provides a therapeutic response protocol for patients with liver cancer who are treated with ablation, intra-arterial treatments, or external beam radiation therapy [21]. In the LI-RADS TRA, post-treatment imaging features on contrast-enhanced CT or MRI are utilised to classify treated lesions as LR-TR nonviable (probably or certainly not viable), LR-TR equivocal (equivocally viable), or LR-TR viable, based on their LI-RADS treatment response (LR-TR) (probably or definitely viable [22].
II. PATIENT AND METHODS

This prospective study was conducted from 2018 to 2021 on 24 cases who underwent TACE procedure referred from outpatient clinic of medical and surgical oncology department. A written informed consent was obtained from each patient. Twenty four patients (20 males and 4 females) were included in this study. Their ages ranged from 50 - 78 years with a median of 62 years. Although the biopsy results are the traditional gold standard in diagnosis for HCC, nowadays it is rarely used, depending on the typical imaging finding in CT and MRI for diagnosis. And finally the decision for TACE was accomplished by the multi-disciplinary team.

Inclusion Criteria:
Patients with imaging criteria typical for HCC with no history of surgery, chemotherapy, radiotherapy or other locoregional therapy.

Exclusion Criteria:
Severely damaged liver function with poor overall health status that can’t tolerate the procedure. Liver tumors other than hepatocellular carcinoma. Patients with no pre TACE AFP measurement. Patients known to have severe allergy to contrast material or sever kidney disease.

TACE protocol:
Preoperatively local analgesia and antiemetic medications were used. To map vascular liver anatomy and identify arterial feeders of the tumor, digital subtraction angiography of the hepatic and mesenteric arteries was conducted immediately before TACE. Utilising microcatheter inserted within the feeding vessel. TACE was carried out with the use of an anticancer agent. The anticancer agent dosage and lipiodol amount were adjusted based on tumor size and its vasculature, and an injection of iodized oil and doxorubicin hydrochloride was given, followed by selective or even superselective arterial embolization using an emulsion of grated gelatine sponge particles. The dosage of administrated iodized oil (10–20 mL; mean 17 mL) and doxorubicin (50–75 mg; mean 55.0 mg) were decided on the basis of the number and diameter of lesions.

Follow up after TACE:
Tumor response was assessed one month following TACE using contrast enhanced MRI. Second session of TACE was performed 1.5- 2 months for those who had imaging signs of tumoral activity. If patients achieved a complete response, a three-month follow-up was conducted. This was proceeded by AFP level measurements every two weeks for three months. In the instance of ambiguous findings, interobserver agreement was reached and a conclusion was reached.

Equipment:
All patients underwent dynamic MRI on GE 3 Tesla (Discovery 720) MRI scanner.

MRI Protocol:
A T1 weighted sequence, fat sat suppressed T1, a breath hold T2 weighted single shot fast spin echo sequence, a breath hold T1 weighted dual echo (in phase and out phase) sequences, respiratory triggered diffusion weighted sequences, and dynamic contrast enhanced fat suppressed 3D T1 weighted sequences were all part of the protocol. The pulse sequences are listed in Table (1)

After injecting 0.1 mmol/kg body weight of gadolinium DTPA at a rate of 2 ml/sec and flushing with 20 ml of sterile saline, dynamic and subtraction series were obtained. The series consist of one precontrast series followed by four subsequent postcontrast series, early arterial phase (15 sec), late arterial phase (30 s), portovenous (90 s), and delayed phase (90 s) (5 min). To obtain the subtracted images, all of these dynamic series are subtracted from the unenhanced phase.

DWI was obtained using respiratory triggered diffusion weighted sequences, which were then utilized to create ADC maps, and subsequently ADC values were assessed at three b values (0,500, and 800s/mm2) using a commercially available Windows computer (GE).
Table 1: Pulse Sequences in MRI Protocol

<table>
<thead>
<tr>
<th>Parameter</th>
<th>T1</th>
<th>Fat sat</th>
<th>T2w</th>
<th>3D T1 (in&amp;outphase)</th>
<th>Dual</th>
<th>DWI</th>
<th>Contrast FS 3D T1(4 phases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR</td>
<td>4</td>
<td>110</td>
<td>1779</td>
<td>4.1</td>
<td>4.1</td>
<td>b500-3197 b800-3197</td>
<td>3.67</td>
</tr>
<tr>
<td>TE</td>
<td>1.1</td>
<td>2.1</td>
<td>81</td>
<td>2.4</td>
<td>1.1</td>
<td>b500-71 b800-76</td>
<td>1.68</td>
</tr>
<tr>
<td>DFOV</td>
<td>84.5x42 cm</td>
<td>84.5x42 cm</td>
<td>44x60 cm</td>
<td>88.5x44 cm</td>
<td>44x60</td>
<td>44x53</td>
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</tr>
<tr>
<td>FA</td>
<td>12</td>
<td>80</td>
<td>90</td>
<td>12</td>
<td>90</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Section thickness</td>
<td>5 mm</td>
<td>8mm</td>
<td>8mm</td>
<td>4mm</td>
<td>8mm</td>
<td>5mm</td>
<td></td>
</tr>
</tbody>
</table>

Criteria for diagnosis
On dynamic MRI sequences, typical imaging of rapid contrast uptake and rapid wash out was used to diagnose HCC residual activity. Patients were divided into two groups: those with no residual tumor (complete treatment response) and those with residual tumor (incomplete treatment response). Patients with complete therapeutic response underwent a second MRI examination after 3 months. In patients with residual activity, digital subtraction angiography was used as a diagnostic and therapeutic technique. In addition, angiography was performed as a confirmatory approach in cases of persistently high levels of AFP on follow-up with no imaging signs of residual activity.

Dynamic & subtracted images interpretation:
Lesions are classified as either enhancing or non-enhancing lesions based on the pattern of enhancement seen in HCC. The enhancing lesions are those that have non-rim enhancement with early arterial hyper enhancement and wash out in the delayed phases. The non-enhancing lesions include rim marginal enhancement, geographic regional enhancement that is considered as a temporary post-procedural perfusion alteration or granulation tissue with persistent or delayed enhancement.

DWI interpretation:
Section by section, DWI images of lesions were examined, and the image with the largest diameter was chosen as the region of interest (ROI) for measuring the DWI quantitative signal intensity and the opposite ADC value.

Qualitative image analysis: the interpretation of images are done qualitatively with analysis of signal intensity and morphology of anatomical structures on each of the sequences. For areas of diffusion restriction correlated with the ADC map to exclude the T2 shine through.

Quantitative image analysis: ADC values are calculated automatically by the software that reflect the degree of diffusion of water molecule through different tissues. It achieved by use of dedicated work station, ADC measurement was recorded for a given region by drawing region of interest which was placed just inside the outer margin of the lesion on each slice to minimize partial volume error and is expressed in units mm²/s.

- Restricted diffusion if treated lesions showing obvious high signal on back ground of hepatic parenchyma on DWI with opposed obvious low signal on ADC.
- Facilitated diffusion if treated lesions showing iso intense signal on DWI or ADC series or showing T2 shine through effect.

AFP response was classified as follows: Complete response (CR) = normalization of AFP; partial response (PR) = > 50% decrease from baseline; stable disease (SD) = (− 50 to + 30%) change from baseline; or progressive disease (PD) = > 30% increase from baseline.
Objective response was defined as the sum of CR and PR, whereas non-response was defined as the sum of SD and PD.

III. RESULTS

Twenty four patients (20 males and 4 females) were included in this study. Their ages ranged from 50 - 78 years with a median of 62 years.

By contrast-enhanced dynamic MRI abnormal enhancement was seen at the treatment area in 6 out of 8 patients with residual disease and in 1 out of the 16 completely treated patients while no enhancement was seen in 15 of the 16 completely treated patients and in 2 out of 8 patients with residual disease with a significant difference among complete treatment and residual disease groups as regards the presence or absence of enhancement on dynamic MRI \( (x^2=11.7, P = 0.0006) \) (FIG 1).

![Figure 1](image1.png)

**Figure 1:** Clustered column chart showing the incidence of abnormal enhancement detected on dynamic MRI in complete treatment and residual disease groups.

By subtracted dynamic MRI abnormal enhancement was seen at the treatment area in 7 out of 8 patients with residual disease and in 1 out of the 16 completely treated patients while no enhancement was seen in 15 of the 16 completely treated patients and in 1 out of 8 patients with residual disease a significant difference among complete treatment and residual disease groups as regards the detection of enhancement in the treatment area by subtracted dynamic MRI \( (x^2=15.2, P = 0.0001) \) (FIG 2).

![Figure 2](image2.png)

**Figure 2:** Clustered column chart showing the incidence of abnormal enhancement detected by subtracted dynamic MRI in complete treatment and residual disease groups.

By diffusion weighted MRI (DW-MRI) restricted diffusion was seen at the treatment area in 6 out of 8 patients with residual disease and in 2 out of 16 patients in the complete treatment group while facilitated diffusion was seen in 14 out of 16 of the completely treated patients and in 2 out of 8 patients with residual disease with a significant difference among complete treatment and residual disease groups as regards the presence or absence of restricted diffusion on DW-MRI \( (x^2=8.98, P = 0.003) \) (FIG 3).
According to their AFP levels patients were characterized as responders or non-responders. 7 out of the 16 completely treated patients and 5 out of the 8 patients with residual disease were classified as non-responders while 9 out of the 16 completely treated patients and 3 out of the 8 patients with residual disease were classified as responders with no significant difference among complete treatment and residual disease groups ($x^2=0.72, P = 0.40$) (FIG 4).

With regard to the performance of the various parameters (contrast enhanced dynamic MRI, subtracted dynamic MRI, DW-MRI and AFP level) in differentiation of patients with residual disease from successfully treated patients, the number of true positive (TP), true negative (TN), false positive (FP), and false negative (FN) cases as well as the calculated sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), accuracies, area under curves (AUC) and their associated P values of all parameters are listed in Table 2

**Table 2:** The diagnostic performance of all parameters in differentiation of patients with residual disease from successfully treated patients as determined by the number of true positive (TP), true negative (TN), false positive (FP), and false negative (FN) cases as well as the calculated sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), accuracies, area under curves (AUC) and their associated P values of all parameters.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>TP</th>
<th>TN</th>
<th>FP</th>
<th>FN</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
<th>AUC</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast enhanced dynamic MRI</td>
<td>6</td>
<td>15</td>
<td>1</td>
<td>2</td>
<td>75%</td>
<td>93.8%</td>
<td>85.7%</td>
<td>88.2%</td>
<td>87.5%</td>
<td>0.84</td>
<td>0.0001</td>
</tr>
<tr>
<td>Subtracted dynamic MRI</td>
<td>7</td>
<td>15</td>
<td>1</td>
<td>1</td>
<td>87.5%</td>
<td>93.8%</td>
<td>87.5%</td>
<td>93.8%</td>
<td>91.7%</td>
<td>0.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DW-MRI</td>
<td>6</td>
<td>14</td>
<td>2</td>
<td>2</td>
<td>75%</td>
<td>87.5%</td>
<td>75%</td>
<td>87.5%</td>
<td>83.3%</td>
<td>0.81</td>
<td>0.0007</td>
</tr>
<tr>
<td>AFP</td>
<td>5</td>
<td>9</td>
<td>7</td>
<td>3</td>
<td>62.5%</td>
<td>56.3%</td>
<td>41.7%</td>
<td>75%</td>
<td>58.3%</td>
<td>0.59</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Subtracted dynamic MRI, contrast enhanced MRI and DW-MRI AUCs had a P-value of less than 0.05 indicating that only these variables could be used to reliably distinguish between patients with residual disease and completely treated patients, unlike the AUC of AFP, which had a P-value greater than 0.05. Subtracted dynamic MRI had the largest AUC followed by contrast enhanced MRI and finally DW-MRI, yet no significant difference was seen between their AUCs indicating the absence of a significant difference between diagnostic performance of these parameters in distinguishing between patients with residual disease and completely treated patients (Table 1).

**Figure 5:** Receiver operating characteristic curve analyses. The specificity and sensitivity of using subtracted dynamic MRI and contrast enhanced dynamic MRI were compared. No significant difference was seen between the AUCs of subtracted dynamic MRI, contrast enhanced dynamic MRI and DW-MRI.
Table 3: Difference between the ROC curves of all parameters and their statistical significance

<table>
<thead>
<tr>
<th></th>
<th>Subtracted dynamic MRI</th>
<th>Contrast enhanced dynamic MRI</th>
<th>DW-MRI</th>
</tr>
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<tbody>
<tr>
<td>Diff a</td>
<td>P</td>
<td>Diff a</td>
<td>P</td>
</tr>
<tr>
<td>Subtracted dynamic MRI</td>
<td>-</td>
<td>-</td>
<td>0.063</td>
</tr>
<tr>
<td>Contrast enhanced dynamic MRI</td>
<td>-</td>
<td>-</td>
<td>0.32</td>
</tr>
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</table>

Statistical Methods:

Statistical analysis was performed using MedCalc statistical software for Windows (MedCalc Software, Mariakerke, Belgium). Data for continuous variables were expressed as either median, interquartile range and range or mean ± standard deviation and as both number and percentage for categorical data. Mann–Whitney was used to evaluate the differences in quantitative variables. Categorical data were evaluated using the Chi–squared test. Receiver operator characteristic (ROC) curve analysis was performed to determine the diagnostic accuracy of the various variables in distinguishing the different groups. The diagnostic accuracy of all variables was evaluated in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the ROC curve (AUC). For all tests all P values were two-tailed and a P-value <0.05 was considered significant.
Figure (6): 67–years old male patient presented with single HCC seen at segment I underwent TACE ablation, Dynamic MRI liver pre TACE showing A) Hypointense signal on precontrast T1 Fat sat B) contrast uptake in arterial phase C) washing out in delayed phase. Confirmed on the corresponding subtraction images D) in arterial and E) delayed phases F) Digital subtraction angiography with tumoral blush. G) CT showing homogenous lipidol deposition. The 1st follow up after 1 month. H) Hypointense signal on non-contrast T1 fat sat. I) Iso to hyperintense signal on T2. J) No contrast uptake on arterial, K) portovenous and L) delayed phases confirmed on subtracted images of the corresponding phases M) arterial N) portovenous O) delayed phases. P) No diffusion restriction at 800 b value Q) with corresponding isointense signal on ADC mapping series R) ADC value measures about 1.4x10^-3 s/mm2. The patient was AFP non responding (PD) presented with increase, angiography was performed as a confirmatory approach that revealed no tumoral residue. Patient presented with increase PCR due to hepatitis c flares.
Figure (7): 67–years old male patient presented with single HCC 2nd follow up after 3 months showing A) hypointense signal on precontrast T1 Fat sat. No appreciable contrast uptake on B) early arterial phase or washing out on C) delayed phase. confirmed on subtracted images of the corresponding phases D) arterial E) portovenous F) No diffusion restriction at 800 b value G) with corresponding increase signal on ADC mapping series H) relative increase in ADC value measures about 1.5x10^-3 s/mm².
Figure (8): 66–years old male patient presented with single HCC seen at segment III underwent TACE ablation CT triphasic liver pre-TACE A) contrast uptake in arterial phase B) washing out of contrast in delayed phase. C) Digital subtraction angiography with tumoral blush. D) CT showing homogenous lipidol deposition. The 1st follow up after 1 month. E) Hyperintense signal on non contrast T1 fat sat. F) Hyperintense signal on T2. G) intralosomal component of early arterial enhancement with washing out on, H) portovenous and I) delayed phases confirmed on subtracted images of the corresponding phases J) early arterial J) portovenous K) delayed phases. L) with diffusion restriction at 800 b value M) with corresponding low signal on ADC mapping series N) ADC value measures about 0.88x10^-3 s/mm². The patient was AFP responding (PR)
Figure (9): Follow up study after second session of TACE 1 month A) Hyperintense signal on non contrast T1 fat sat. B) Hyperintense on T2. C) No intralesional enhancement on early arterial, D) portovenous and E) delayed phases confirmed on subtracted images of the corresponding phases F) early arterial G) portovenous H) delayed phases. I) No diffusion restriction at 800 b value J) with corresponding heterogenous signal on ADC mapping series K) with increase ADC value measures about 1.4x10^-3 s/mm². The patient was AFP responding (PR).
Figure (10): 70–years old male patient presented with single HCC seen at segment IV underwent TACE ablation CT triphasic liver pre TACE A) contrast uptake in arterial phase B) washing out on delayed phase. C) Digital subtraction angiography with tumoral blush. The 1st follow up after 1.5 month. D) Hyperintense signal on non contrast T1 fat sat. E) Heterogeneous signal on T2. F) No intraltesional enhancement on early arterial, G) portovenous and H) delayed phases confirmed on subtracted images of the corresponding phases I) early arterial J) portovenous K) delayed phases. L) No diffusion restriction at 800 b value M) with corresponding bright signal on ADC mapping series N) ADC value measures about 1.58x10^{-3} s/mm². The patient was AFP non responding (SD).
Figure (11): Follow up study after 3 months with still AFP non response A) Hyperintense signal on non-contrast T1 fat sat. B) No intralesional enhancement on early arterial, C) portovenous and D) delayed phases confirmed on subtracted images of the corresponding phases E) early arterial F) portovenous G) delayed phases. H) No diffusion restriction at 800 b value J) with corresponding bright signal on ADC mapping series K) with increase ADC value measures about 2x10^-3 s/mm². The patient was AFP non responding (PD).
Figure (12): Follow up study after 6 months with still AFP non response newly developed adjacent lesion A) isointense on non contrast T1 B) hyperintense on T2 C) of abnormal faint enhancement early arterial phase D) with washing out on portovenous and E) delayed phases confirmed on corresponding subtracted images on F) arterial, G) portovenous and H) delayed phases. I) It shows restricted diffusion with corresponding J) low signal on ADC mapping series K) ADC value about 0.7 x10^-3 s/mm^2.

IV. DISCUSSION

Hepatocellular carcinoma (HCC) is a type of cancer that affects the liver and is the fifth highest cause of cancer-related death globally. Surgical resection is a better curative alternative than nonsurgical treatments, however it is not an option for the majority of patients due to poor hepatic function and the disease’s often advanced form upon presentation [1][23]. TACE has been shown to be an effective bridging therapy for patients awaiting liver transplantation and can help patients with inoperable HCC have a better prognosis [24]. Because the objective response may become a surrogate marker of better survival, evaluating treatment response is a critical element of cancer therapy [25]. After TACE, accurate and early detection of residual tumors or intrahepatic recurrences is crucial for determining treatment success and guiding subsequent therapeutic planning [24]. Imaging is critical in determining the treatment respond of the embolized lesions. After loco-regional treatment, the most common method for determining whether to treat further, repeat the same therapeutic modality, or change the treatment plan is to employ CT or MRI.

CT is widely used in analyzing the distribution of lipiodol deposition and is helpful for evaluating the therapeutic effect of TACE. However, some pitfalls occur, particularly after lipiodol-based TACE, due to beaming artifact of lipiodol hindering the proper evaluation of residual viable tumor, whose enhancement is masked with significantly lower accuracy and sensitivity. As a result, MRI has surpassed CT in terms of post-treatment surveillance for patients in order to reduce radiation exposure and the risks of contrast agents [3].
In our study twenty-four patients met the inclusion criteria, with subtraction results indicating that one of the 16 patients received complete treatment, indicating a false positive result by subtraction and conventional dynamic MRI, which was confirmed by angiographic procedure, which revealed no detectable tumoral residue and no abnormal signal on follow-up after three months. Another case with a small sized lesion was underdiagnosed by subtraction and the conventional dynamic MRI, which gave a false negative result, and was detected by the aid of the continuous elevation of AFP level on follow up, which forced the use of diagnostic angiography to detect residual tumoral blush and a second session of TACE was performed.

Our findings are consistent with those of Winter et al. (2012), [26] who found that subtraction MRI is helpful and has a high level of agreement when compared to conventional dynamic MRI. In comparison to conventional dynamic MRI, which had sensitivity 39.9%, specificity 90.9%, PPV 63.9%, and NPV 86.9%, the subtraction had sensitivity 83.3%, specificity 90.9%, PPV 76.9%, and NPV 93.8%.

Metwally et al. (2019) [27] conducted another trial and discovered that the subtraction images have a sensitivity of 96%, specificity of 100%, PPV of 100%, and NPV of 100% in comparison to the three readers scored 96%, 100%, 100%, 96%, and 96%, 100%, 100%, 96%. On the other hand, the dynamic images have sensitivity of 92%, specificity of 96%, PPV of 95%, and NPV of 92.3% compared to 92%, 96%, 95%, 92.3% and 80%, 68%, 71.4%, and 77.2% for the three readers respectively.

Kim et al. (2010) [28] also found that the qualitative assessment of HCC tumour necrosis after TACE using subtracted CE MRI datasets had a strong correlation with histopathology, higher interobserver agreement when compared to nonsubtracted datasets, and a statistically significant difference for predicting complete tumour necrosis at the arterial phase.

The subtraction at the arterial phase had sensitivity 78.1 % , specificity 92.7 %, PPV 80.7 % & NPV 91.6 % with accuracy 88.6% compare to the non-subtracted dataset at the arterial phase that had sensitivity 28.1 % , specificity 92.7 % , PPV 60 % & NPV 76.8 % with accuracy 74.6%.

Elsaid et al. (2016) [11] supported our findings, stating that the subtracted approach is even more beneficial than DWI in terms of increasing radiologists' confidence in evaluating treatment response after locoregional treatments for HCC. In this study (Reader 1) subtraction dynamic MRI sensitivity = 97%, specificity = 100% PPV = 100% and NPV = 95% compared to 70.59%, 75%, 82.76% and 60% respectively in DWI. (Reader 2) subtraction dynamic MRI sensitivity = 97%, specificity = 100% PPV = 100% and NPV = 95% compared to 76.5%, 90%, 92.8% and 69% respectively in DWI.

In our study, we encountered two false positive DWI cases with no residual tumoral tissue, which were confirmed by angiographic catheterization and follow-up. Diffusion restriction may be caused by intralesional liquefactive necrosis and haemorrhage following the procedure. Salah et al. (2019) [12] provided the same explanation, demonstrating that while dynamic contrast enhanced MRI has a higher sensitivity than DWI, the later is required to improve the diagnostic confidence of dynamic contrast enhanced MRI for post-treatment response viability detection using the LIRADS v2018 diagnostic algorithm. According to Elsaid et al. (2016), [11] this could be due to lipidol deposition in the tumour, which results in no enhancement but just incorrect restriction on DWI. Diffusion restriction could also be caused by nearby areas of hepatic parenchymal inflammation (Liu et al., 2020) [24].

Two false negative cases can be attributed to a well differentiated HCC similar to that discovered by Yuan et al. (2014) and a small sub diaphragmatic lesion influenced by the respiratory motion artifact as well as cardiac pulsetility (Salah et al 2019) [12].


In our study, the AFP level was of insignificant value because 7 out of 16 completely treated lesions were non responders, resulting in false positive results. This could be explained by the findings of Manuc et al. (2020)[31].
and Raoul (2014) [32], who both found that the performance of AFP is suboptimal because fluctuating levels can occur in hepatitis B or C flares or decompensated cirrhosis (Case 1). He et al. (2019) [16] further argue that AFP non-responders could be owing to the treatment response was incomplete or there were occult intra or extra hepatic metastases, ignoring any initial tumour response.

Three cases of small-sized HCC are AFP responders (PR) despite residual/ recurrence tumoral component on follow-up MRI study (Case 2), which may have returned to pathological grade as suggested by Bai et al. (2017)[15] study or as reported in Carr et al. (2018) [33] study that AFP has been a poor screening tool especially in small-sized lesions less than 5 cm and recommend a new non-AFP markers especially for small-sized HCC.

Tian's (2019) [17] study, on the other hand, demonstrated that AFP could be utilised to assess tumour response, and he discovered that the AFP response was substantially linked with the EASL response and was an excellent predictor of OS. Furthermore, he discovered that varying serum AFP levels could predict tumour response rate following TACE. The higher the serum AFP level, the lower the response rate, with no response to TACE when the AFP level was greater than 999,999 ng/mL, indicating that TACE would be useless in such patients.

Lee et al. (2021) [14], who also investigated the role of AFP as a prognostic value in patients who achieved complete response to TACE, discovered that 22% of completely treated patients still had raising in AFP level, which could be explained by the presence of residual or satellite cancer cells resistant to TACE that were not identified by conventional imaging studies. Tumor multiplicity was also independently associated with prognosis regardless the complete treatment of the primary lesion.

Cerban et al. (2018) [34] discovered that another tumour marker, Des –gamma-carboxy Prothrombin (DCP), which is an abnormal form of prothrombin protein that is present at higher levels in the serum of HCC patients, is a more specific marker for HCC and a better biomarker than AFP for predicting treatment response and prognosis for HCC patients who underwent TACE.

Elevated serum AFP also occurs with tumors of gonadal origin (both germal and non germal cells) [35]. And in a variety of different cancers, the most prevalent of which is gastric cancer [36]. As a result, the level of AFP is impacted by a variety of circumstances, and a high level does not always indicate the existence of residual or recurring tumoral tissue, as well a normal level does not rule out the presence of residual or recurrent malignant lesions.

Limitation of the study

Several unanswered issues remain in our investigation. Firstly, the study cohort was rather limited due to restrictive selection criteria, reducing the strength of the statistical analysis and perhaps affecting diagnostic accuracy.

Second, misregistration artifacts occur when patients are unable to hold their breath adequately during the scan, and to address this issue, we include situations with modest misregistration of image subtraction.

Third, according to current criteria, the final diagnosis was not based on histologic evaluations. There were no biopsies taken to establish full therapy necrosis or residual illness.

Lastly, in terms of DWI, we encountered a few technical challenges in dealing with the subdiaphragmatic lesions influenced by transmitted cardiac pulsations as well as respiratory movements. And, while measuring the ADC values, we encountered partial volume averaging effects with image noise, which resulted in calculation inaccuracies.

We attempted to solve these difficulties by putting the smallest ROI and taking several measurements, therefore we urge further future investigations with a powerful magnetic gradient system and new technical improvements to improve DWI sensitivity and image quality.

As a result, our findings support the use of MRI with subtracted images as a routine follow-up examination for early detection of residual or recurrent HCC after TACE to reduce disease burden and improve survival prognosis, in conjunction with DWI for optimum image interpretation in assessing post embolized HCC viability post TACE.
V. CONCLUSION

Subtraction MRI is a useful confirmative post-processing application that is available in most commercial MRI platforms and, when combined with other techniques such as DWI, increases the radiologist's confidence in interpreting the treatment response of HCC after TACE and helps to facilitate clinical management for those who require retreatment sessions.

REFERENCES
8. Young Chang, Soung Won Jeong, Jae Young Jung et al. (2020): Recent Updates of Transarterial Chemoembolization in Hepatocellular Carcinoma Internal Journal Molecular. Science. 21, 8165
16. Dou-Sheng Bai, Chi Zhang, Ping Chen, Sheng-Jie Jin & Guo-Qing Jiang (2017). The prognostic correlation of AFP level at diagnosis with pathological grade, progression, and survival with pathological grade, progression, and survival of patients with hepatocellular carcinoma Scientific Reports 7: 12870