Diffusion weighted imaging versus subtraction MRI in assessing treatment response of hepatocellular carcinoma after trans-arterial chemoembolisation (TACE)

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Aims and objectives

The aim of this study is to evaluate the efficiency of both diffusion weighted images and subtracted dynamic MRI technique in the detection of residual/ recurrent disease after (TACE) ablation of non resectable HCC lesions. Accurate judgment of tumour viability will help diagnose the need for further treatment sessions.
Methods and materials

This study included 32 patients having 54 HCC lesions that underwent Trans Arterial Chemo-Embolization procedure over a period of 12 months (August 2014 -August 2015) were followed up 1-1.5 months by dynamic MRI. 12 patients of which underwent a second follow up within 3-4 months. All patients were performed Achieva; Philips Healthcare, Eindhoven, The Netherlands

The patients' ages ranged between 59 to 73 years(mean age 53.1); 26 patients were males and 6 were females. All patients had liver cirrhosis related to chronic viral hepatitis.

Exclusion criteria:

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

2- Contraindications to magnetic resonance imaging, e.g. claustrophobia in patients contraindicated for anaesthesia, non MR compatible cardiac prosthesis, pace makers, metallic plates.

3- Liver tumours other than hepatocellular carcinoma

4- Procedures other than TACE e.g.(RF, microwave ablation)

Inclusion criteria:

1- Cases with HCC lesion undergoing only TACE as therapeutic procedure either by beads or lipidol.

2- No contraindications to MRI.

MRI protocol:

Table showing the examination parameters of all the used pre and post contrast MR sequences.

a) non contrast series included T1, T2 and heavy T2.

b) Dynamic study:
• Dynamic study was performed after manual bolus injection of 0.1mmol/kg body weight of Gd-DTPA and flushed with 20ml of sterile saline solution from the antecubital vein.
• Dynamic imaging using 3D fat-suppressed T1-weighted gradient echo sequence (THRIVE i.e. T1 high resolution isotropic volume examination). A dynamic series consisted of one pre contrast series followed by four successive post contrast series including early arterial, late arterial, and portal phases with 19-21 seconds intervals (17 seconds for image acquisition with breath-holding and 2-4 seconds for re-breathing).
• This is followed by 5-min delayed phase imaging. All patients were imaged in end expiration to limit the risk of image misregistration.

c) Diffusion weighted image:

• DWI was performed using single-shot spin-echo echo-planar imaging during one or more breath holds.
• ADC parametric maps were reconstructed from each set of DW images acquired at each slice position.

Images were sent to the workstation (Phillips Extended MR Workspace) for further image processing.

• Subtraction imaging was then performed which is an automated process available on the workstation, whereby an unenhanced T1-weighted sequence is digitally subtracted from the identical sequence performed after gadolinium administration in early angiographic and late arterial phases. Therefore, any native T1 signal is removed and the remaining signal on the subtracted images is due solely to enhancement.

All cases were viewed by 2 experienced radiologists in hepatic imaging

MRI Interpretation:

#1) Non Enhanced Study for: morphological features of each lesion were recorded including number of treated lesions, site, size, margins and signal intensity.
2) #THRIVE: pattern of enhancement and phase was recorded

3) Subtraction Dynamic study: confirmed or denied enhancement on THRIVE.

4) #DWI assessment:

Qualitatively assessment showing restriction and facilitation areas, where lesions with high signal or low signal were correlated to ADC maps to exclude T2 shine through effect or T2 black out.

Quantitatively by ADC values in the areas of restriction that appeared pathologically enhancing in the late arterial images.
Any complications were recorded.

**Standard of Reference:**

It was difficult to obtain pathologic confirmation in patients who underwent TACE embolization because most of these patients do not undergo surgery. In addition, biopsy may result in sampling error as recurrent lesions are mostly small nodules and a negative sample may be wrongly taken from a necrotic region while there may be still viable areas within the lesion.

In addition not all patients returned for their follow up

So,

**Well-treated (resolved) lesions** were considered by absence of

enhancement on both the arterial phase of the dynamic study and the

subtraction dynamic study.

**Residual tumor activity (unresolved) lesions** were suggested by:

- Presence of enhancement on arterial phase and wash out of contrast on
  delayed phase as well as positive enhancement on the subtracted images.
- **Focal area at the margin of the ablation zone that shows:**
  1. Early or late arterial phase enhancement that must be proved by the
     subtraction images.
  2. Contrast wash out: the lesion becomes hypointense relative to the liver
     parenchyma in the delayed phase.
  3. This should coincide with area of restriction on the DWI and ADC maps.

**Statistical method and analysis:**

- Data were coded and entered using the statistical package SPSS (Statistical
  Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 22.
- Data was summarized using mean, standard deviation, median, minimum
  and maximum in quantitative data and using frequency (count) and relative
  frequency (percentage) for categorical data.
- Standard diagnostic indices including sensitivity, specificity, positive
  predictive value (PPV), negative predictive value (NPV) and diagnostic
  efficacy were calculated as described by Galen (1980).
- ROC curve was constructed with area under curve analysis performed to
  detect best cutoff value of ADC for detection of residue. For comparing
categorical data, Chi square (c2) test was performed. Exact test was used instead when the expected frequency is less than 5.

- Agreement between the 2 readers was done using Kappa measure of agreement.
**Fig. 10:** case 1 T1WI showed high Intralesional signal denoting internal hemorrhage in addition to the high back ground T1 signal due to high fat content. Early arterial image shows peripheral thin enhancement (white arrow) and high central signal. subtracted early arterial image shows low central signal with thin marginal enhancement. late arterial image shows persistent delayed thin marginal arterial enhancement confirms the benign
reactive hyperaemia Subtraction late arterial image removed back ground high T1 signal and intralesional hemorrhagic high signal

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**Fig. 12:** case 1 DWI shows high intrallesional signal corresponding to facilitation both qualitatively and quantitatively denoting that it was a T2 shine through signal. Mean ADC value was (0.9 - 1x10-3 mm2/ sec)

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**Fig. 13:** Case 2: T1WI shows 2 focal lesions in segment VIII with high perilesional signal, and high intralesional signal as seen late arterial image shows high peri and intralesional signals in both lesions. Subtracted late arterial image shows removal of the perilesional high signal denoting perilesional hemorrhage, subtraction of intralesional high signal leaving thin ring like enhancement denoting intralesional hemorrhage and peripheral reactive hyperemia, but no residual disease in both lesions. DWI only the larger lesion could be demonstrated faintly, the smaller lesion can't be seen on DWI, mean ADC value was 1.1 x10⁻³ mm²/sec for larger lesion.

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Fig. 14: case 3 Image (a) high intralesional signal denoting post embolization hemorrhage within the lesion. Image (b)&(c) still showed the high intralesional signal but with indistinct margins of the lesion. Intralesional enhancement can’t be ruled out. Image (d) image subtraction removed the intralesional high signal and no further enhancement could be detected, i.e no residue or recurrence. But the margins of the lesion remained indistinct. Image (e)showed distinct lesion margins low signal denoting facilitation. And high internal signal ?? for restriction versus T2 shine through. Image (g)revealed over all facilitation of the lesion with over all mean ADC value of (1.7 x10-3 mm2/ sec) and peripheral mean ADC(1.6x10-3 mm2/ sec)
**Fig. 15:** case 4: Image (a) white arrow indicates areas of low signal intensity liquefactive necrosis, red arrow indicates areas of high signal. (b,c) white arrow indicates areas of necrosis and red arrow indicates areas of peripheral high signal residue. Image (d) red arrow corresponds to areas of regular rim enhancing periphery of the lesion denoting lack of residual disease and confirming good therapeutic response. Image (e) DWI qualitative assessment shows areas of peripheral restriction marginally indicated by the red arrow which correspond to quantitative restriction on image (f) with mean ADC value of $(0.4 - 0.5 \times 10^{-3} \text{ mm}^2/\text{sec})$.

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**Fig. 16:** Serial non contrast CT images showing marginal stagnation of the lipidol droplets of the lesion corresponding to areas of false ADC restriction,

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Results

- Evaluation of the cases were according to mRECIST and EASL criteria by both readers in 1\textsuperscript{st} response and follow up findings post TACE. Where,
  
  1. **Good response**: was defined as disappearance of any intra tumoral arterial enhancement in treated lesions,
  2. **Residual disease** was defined as at least 30% reduction in the sum of diameters of the viable enhancing lesion in the arterial phase.
  3. **No response** was less than 30% reduction in the enhancing lesion diameters.
  4. **Progressive disease** was defined as 20% increase in the sum of diameters of the enhancing lesions in comparison to the target lesion diameter at the start of treatment.

# Although both readers agreed that 34 lesions had residual disease by conventional dynamic MRI, subtraction was able to deduct the number to 33 enhancing lesions by removing native T1 signal from enhanced images.

- It also increased the conspicuity of the embolized lesions for both readers achieving a higher confidence level.
- In spite of under estimating the disease burden in 5 cases by reader 1 and 6 cases by reader 2, DWI still presented as a useful confirmative tool with other diagnostic series in 53.7% and 52% of lesions by reader 1 and 2 respectively.

- **Correlation of DWI to THRIVE noting the efficiency of DWI in detecting residual disease post TACE by reader 1**: illustrated that facilitated lesions on DWI represent good therapeutic of 75% of non-enhancing lesions, while around 30% of the facilitated lesions were enhancing (i.e. false negative). On the other hand 70% of the restricted lesions were enhancing on THRIVE with only 5% being restricted and non-enhancing (i.e. false positive).

- **Correlation of DWI to THRIVE noting the efficiency of DWI in detecting residual disease post TACE by reader 2**: illustrated that facilitated lesions represent good therapeutic response in up to 90% of non-enhancing lesions, while around 23% of the facilitated lesions were enhancing (i.e. false negative). On the other hand 76% of the restricted lesions were enhancing on THRIVE with only 10% being restricted and non-enhancing (i.e. false positive).

- **False negative** results were attributed to 1\textsuperscript{st} high ADC value of well differentiated HCC, so these lesions still showed enhancement due to partial response to TACE while they were falsely facilitated on DWI.
• **False positive** results were attributed to lipiodol deposition in the tumour giving no enhancement but only false restriction on DWI.

• **Correlation of subtraction to THRIVE noting the efficiency of subtraction in detecting residual disease post TACE by both readers:**

  illustrates how absence of enhancement represents good therapeutic response in 100% of lesions in both THRIVE and subtraction, while enhancement represents residue in almost 97% of the lesions in both studies. False negative results were obtained in 0% of the lesions by subtraction and only 2.9% false positive.

• **Accuracy measures of both DWI and subtraction as viewed by reader1:** subtraction dynamic MRI had a sensitivity of 97.06%, a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 95%. Compared to 70.59%, 75%, 82.76% and 60% respectively in diffusion weighted imaging.

• **Accuracy measures of both DWI and subtraction as viewed by reader 2:** subtraction dynamic MRI had a sensitivity of 97.06%, a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 95%. Compared to 76.47%, 90%, 92.86% and 69.23% respectively in diffusion weighted imaging.

**AUC as calculated from ROC curve and 95% CI according to reader1:** In subtraction the AUC (95% CI) was 0.985 with range of (0.95-1.019) producing a significant P-value of <0.001.

However in ADC the AUC (95%CI) wasn't as significant, ranging from (0.3-0.63) producing an insignificant P-value of 0.64.

**AUC as calculated from ROC curve and 95% CI according to reader 2:** In subtraction the AUC( 95% CI) was 0.906 with range of(0.811-1.001) producing a significant P-value of <0.001.

However in ADC the AUC(95%CI) wasn't as significant , ranging from (0.398-0.84) producing an insignificant P-value of 0.563.

**N.B** We failed to generate a cut off value for malignant lesions due to the small scale of our study.

Furthermore it was detected that ADC values may vary according to the 1ry tumoral histological grade giving high ADC values for well differentiated HCC and vice versa.
Kappa measure for agreement between the 2 readers in DWI

1. Reader 1 and 2 agreed about 87% of the facilitated lesions & 82.7% of the restricted ones.
2. They both disagreed about 3 lesions that were seen facilitated according to reader1 were restricted according to reader 2.
3. While 4 of restricted lesions according to reader1 were noted as facilitated according to reader2.

*Yet they displayed significant agreement of (kappa=0.728) and P <0.001*

Kappa measure for agreement between the 2 readers in Subtraction:

1. Reader 1 and 2 agreed about 85.7% of the non-enhancing lesions and agreed about 90.9% of the enhancing ones.
2. They both disagreed around 6 lesions where 3 of those lesions were detected by one reader as enhancing and the other as non-enhancing and vice versa

*Yet they displayed significant agreement of (kappa=0.766) and P value less than 0.001*

Kappa measure for agreement between the 2 readers in THRIVE:

1. Reader 1 and 2 agreed about 90% of the non-enhancing lesions.
2. Both agreed about 94.1% of the enhancing ones.
3. They both disagreed around 4 lesions where 2 of those lesions were detected by one reader as enhancing and the other as non-enhancing and vice versa.

*Yet they displayed significant agreement of (kappa=0.841) and P value less than 0.001*
Fig. 1: represents the general evaluation of the cases according to mRECIST and EASL criteria by both readers. In primary response and follow-up findings post TACE. Where good response was defined as disappearance of any intra-tumoral arterial enhancement in treated lesions, residual disease was defined as at least 30% reduction in the sum of diameters of the viable enhancing lesion in the arterial phase. No response was less than 30% reduction in the enhancing lesion diameters. Progressive disease was defined as 20% increase in the sum of diameters of the enhancing lesions in comparison to the target lesion diameter at the start of treatment.

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Fig. 2: 17 lesions were assessed in detail in the 2nd follow-up

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### Table 1: Correlated data from both readers including all results of DWI, subtracted dynamic image, and THRIVE.

<table>
<thead>
<tr>
<th></th>
<th>Reader 1</th>
<th>Reader 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Count</strong></td>
<td><strong>%</strong></td>
<td><strong>Count</strong></td>
</tr>
<tr>
<td><strong>DWI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FACILITATED(-ve)</td>
<td>25</td>
<td>46.3%</td>
</tr>
<tr>
<td>RESTRICTED(+ve)</td>
<td>29</td>
<td>53.7%</td>
</tr>
<tr>
<td><strong>Subtraction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nonenhancing</td>
<td>21</td>
<td>38.9%</td>
</tr>
<tr>
<td>/ enhancing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>reactive</td>
<td>33</td>
<td>61.1%</td>
</tr>
<tr>
<td>enhancing residue</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>THRIVE</strong></td>
<td></td>
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<tr>
<td>(dynamic)</td>
<td>20</td>
<td>37.0%</td>
</tr>
<tr>
<td>nonenhancing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>/ enhancing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>reactive</td>
<td>34</td>
<td>63.0%</td>
</tr>
<tr>
<td>enhancing residue</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 3:** Correlated the data obtained from both readers including all results of DWI, subtracted dynamic image, and THRIVE.

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**Fig. 4:** Correlated the data obtained from both readers including all results of DWI, subtracted dynamic image, and THRIVE.
**Fig. 5:** Horizontal graph relating DWI to THRIVE for reader 1

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**Fig. 6:** Horizontal graph relating DWI to THRIVE for reader 1

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**Fig. 7:** Horizontal graph relating Subtraction to THRIVE for reader 1

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Fig. 8: ROC curve for detection of residue by ADC and subtraction (reader 1)

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Fig. 9: ROC curve for detection of residue by ADC and subtraction (reader 2)

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Conclusion

MRI is a powerful tool in detection of residual tumor viability, quantifying tumour necrosis and detecting complications after TACE. Imaging protocol should include dynamic study combined with post processing subtraction images for better tissue characterization. Compared to DWI, Subtraction MRI is much more valuable, where it increases radiologists' confidence in interpreting treatment response following loco-regional therapies for HCC. DWI can still provide acceptable values of accuracy and can be used for patients who can't receive GD-DTPA and to quantify tumour necrosis in large HCC. This may help to facilitate the appropriate clinical management of patients including the need for re-treatment sessions.
Salama N., Shaker M., Abd El Shafy N. and Hamed I.: Diffusion weighted imaging versus Subtraction MRI in assessing treatment response of hepatocellular carcinoma after trans-arterial chemoembolization (TACE), National Cancer Institute Cairo University