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The value of dynamic subtraction MRI technique in the assessment of treatment response of hepatocellular carcinoma to transcatheter arterial chemoembolization

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Abstract

Background: Hepatocellular carcinoma is considered to be the fifth most common cancer worldwide. Resection and liver transplantation have a high survival in the correct clinical scenarios; however, locoregional therapy has many advantages over tumor resection like preservation of hepatic parenchyma and overall less morbidity and mortality. Our aim was to present the role of dynamic subtraction MRI technique in the assessment of treatment response of hepatocellular carcinoma to transarterial chemoembolization.

Methods: The study consisted of 43 patients with 55 hepatocellular carcinoma lesions who underwent transarterial chemoembolization procedure and followed up by dynamic MRI of the liver with post processing to obtain subtraction images 1–1.5 months after the procedure. If no signs of disease activity, another follow up study was preformed 2–4 months later. Five patients were excluded due to misregistration artifact at the subtraction images. The final cohort is 38 patients having 50 lesions. Precontrast T1, T2, dynamic contrast enhanced, and diffusion-weighted images were acquired. Subtracted dynamic images were created on the workstation. Sequences were assessed by three experienced readers in hepatic imaging. The sensitivity, specificity, positive predictive value, negative predictive value, 95% confidence interval, and overall agreement were calculated for the dynamic and subtracted dynamic images.

Results: The subtraction images have sensitivity of 96%, specificity of 100%, PPV of 100%, and NPV of 100% Compared to 96%, 100%, 100%, 96%, and 96%, 100%, 100% 96% for the three readers respectively. On the other hand, the dynamic images has 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.

Conclusion: Subtraction technique is a useful confirmative tool as it had higher sensitivity, specificity, PPV, and NPV values compared to the dynamic and diffusion images with high level of agreement between the readers and also associated with significantly higher reader confidence levels.

Keywords: HCC, TACE, Subtraction MRI, Dynamic MRI, Treatment response

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Background

Hepatocellular carcinoma is considered to be the fifth most common cancer worldwide [1]. Liver cirrhosis is the major risk factor for development of hepatocellular carcinoma (HCC), particularly liver cirrhosis secondary to chronic viral hepatitis and alcohol related liver cirrhosis [2].

Surgical resection remains for a long time as the gold standard therapy for HCC. Liver transplantation is another treatment option; however, tumors are resectable or meet transplantation criteria in only 5–10% of patients at the time of diagnosis [3, 4].

Locoregional therapy (LRT) can be used for multiple purposes. It can be used in patients who are not surgical candidates. Another role is as a bridge to orthotropic liver transplant (OLT) and to down stage a patient to meet the transplantation criteria [5]. In addition, LRT has the advantages of preservation of hepatic parenchyma and overall less morbidity and mortality compared with tumor resection [4].

Accurate assessment of response to therapy, either LRT or systemic, requires evaluation of tumor size, tumor margins, and tumor necrosis, as well as early detection of residual or recurrent tumor and also for detection of new tumor. The evaluation of treatment success is essential for future treatment decisions and for prognosis [4].

Multiphasic CT and/or dynamic MRI can be used as routine follow-up modalities to evaluate the treatment response. Follow-up imaging is usually performed at 1 and 4 months after treatment then every 3 to 6 months [6].

HCC treated with transarterial chemoembolization (TACE) usually shows variable signal intensity on unenhanced T1 weighted MRI (hypo-intensity is suggestive of necrosis; hyper-intensity indicates hemorrhage) [7]. Thus limiting assessment for residual tumor enhancement [4].

Dynamic subtraction MRI is a technique used to remove the pre-existing high T1 signal from the post-processed images. The corresponding contrast-enhanced and unenhanced T1-weighted sequences are digitally subtracted image-by-image using post processing MRI software so that any native T1 signal is removed and the remaining high signal on the post processed subtracted images is solely due to enhancement [3].

There are many applications for this technique including evaluation of complicated cysts, hemorrhagic masses, and other settings in which determining the presence or absence of enhancement is critical. Subtraction imaging can make evaluation of such lesions more straight forward [8].

In this study, we aimed to evaluate the role of dynamic subtraction MRI technique in the assessment of the treatment response of HCC after TACE procedure and whether it increases the confidence level of the radiologist interpreting the post interventional MRI studies or not.

Methods

- A retrospective study comprised 43 patients with 55 HCC lesions underwent TACE procedure over a period of 12 months (from January 2017 to December 2017).
- All patients had liver cirrhosis secondary to chronic viral hepatitis.
- All cases included in the study had been subjected to:
  - Clinical assessment and revision of the laboratory investigations including creatinine level.
  - Revision of the previous radiological investigations.
  - Written consent was signed by all patients.
  - This study is approved by our institutional review board (IRB).
  - All patients underwent dynamic MRI with post processing to obtain subtraction images 1–1.5 months after the TACE procedure. If no radiological signs of tumoral activity, another follow up study is preformed after 2–4 months from the procedure.

Inclusion criteria

- Cases with HCC underwent only TACE as therapeutic procedure.
- No contraindications to MRI.

Exclusion criteria

- Contraindications to contrast media.
- Contraindications to MRI.
- Liver tumors other than HCC.
- Locoregional procedures other than TACE.
- All cases with misregistration artifact at subtraction images that interferes with proper assessment of the enhancement of the lesions were excluded.

MRI protocol

All cases were performed using Philips 1.5 Tesla MRI machine (Achieva).

I. Precontrast study: the precontrast sequences are discussed in Table 1.
II. Dynamic study:

- 0.1 mmol/kg body weight Gd-DTPA was injected manually flushed with 20 ml saline via antecubital vein.

Table 1 The parameters of pre contrast sequences

Sequence	TR (ms)	TE (ms)	FOV (ms)	Flip angle	Slice thickness
Axial T1 TFE	10	4.6	300–350	15°	7 mm
Axial T2 TSE	1000	80	300–350	90°	7 mm
Axial T2 SPAIR	1000	80	300–350	90°	7 mm

- Dynamic imaging using 3D fat-suppressed T1-weighted gradient echo sequence (THRIVE). A dynamic series was obtained consisted of one precontrast series followed by four successive post contrast series with 19–21 s intervals (17 s for image acquisition in breath holding and 2–4 s for rebreathing).This is followed by a delayed phase after 5 min. All patients were imaged at end expiration to limit the image misregistration.
- Acquisition parameters for dynamic study (THRIVE) were TR 10 msec. TE 4.6 ms flip angle 15°, matrix size, 172 × 163, field of view 300–350 mm, and slice thickness 7 mm.

III. Diffusion weighted images:

- Diffusion images were acquired using respiratory triggered single-shot spin echo echoplanar sequence (TR 2500 ms, TE 82 ms, slice thickness 8 mm, *b* values 0, 400, 800 mm^2/s). ADC parametric maps were reconstructed from each set of diffusion images acquired at each slice position.

Analysis of the MR images

- Image processing was done at the available workstation (Phillips Extended MR workspace2.6.3.5 Netherlands 2011).
- The morphological features of the lesions were assessed including lesion's number, size, site, margins, and signal pattern at T1 and T2 weighted images.
- Subtraction imaging was performed which is an automated process on the workstation removing the precontrast high T1 signal and the remaining signal on subtracted images is due to enhancement.
- The enhancement patterns of the lesion at different phases of the study and at the subtracted images were studied.

Interpretation of the MR image

- The MRI datasets were independently evaluated on the workstation by three readers (subspecialty abdominal radiologists with 18, 11, and 4 years of experience). For each case, the reader commented whether there was either "complete treatment" or "residual disease" at the treatment zone and the degree of confidence on a five-point scale (ranging from 1 = no confidence to 5 = total confidence).

I. Dynamic study

- Arterial phase enhancement is defined as high signal at the arterial phase which is higher than the non-contrast signal and proved by the subtraction images.
- Delayed wash out is defined as lower signal of the lesion compared to the liver parenchyma at the delayed phase.
- Each reader classified the lesions as "enhancing" or "non-enhancing"

II. Subtraction images

- Similarly, the subtraction images were interpreted to confirm or correct the findings that were detected by the dynamic images.

III. Interpretation of perilesional enhancement

- Reactive liver parenchymal changes were defined as early enhancement of the liver parenchyma surrounding the treatment zone that persists in the delayed phase.
- Perfusion abnormalities (transient hepatic intensity difference) are ill defined parenchymal enhancement during the arterial phase. This might occur in cases complicated with vascular injury or arterio-portal shunts.
- Well-defined enhancement along the margins of the treatment zone can be either granulation tissue formation which shows persistent/delayed enhancement or tumor recurrence which shows nodular or hallow arterial enhancement and delayed wash out.

IV. Diffusion weighted images analysis

- Qualitative assessment for areas of restriction on diffusion images and correlated to ADC maps to exclude T2 shine through effect.

- ADC measurement: ADC maps were generated on the workstation. A circular region of interest (ROI) was including the area of interest
- If no areas of diffusion restriction could be identified in the vicinity of the lesion, the whole treatment zone was measured.
- Each reader then classified the treatment zone as "facilitated" or "restricted."

The patients were then categorized into two groups:

- Complete treatment group: if there were no MRI signs of tumoural activity at the treatment zone regardless the presence of newly developed lesions.
- Residual disease group: if there is evidence of residual or recurrence.

Reference standard

- Pathological confirmation was difficult to be obtained because most of the patients do not undergo surgery. Also, tissue biopsy may result in sampling error as the 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.

So, the reference standard was as follows:

- In complete treatment group, benign changes are considered if the findings either regressed or disappeared in the follow up studies (Fig. 1).
- In residual disease group (Fig. 2), the tumoral activity is considered in case of:
  - Progressive increase in the size of the treatment zone in the follow up studies with arterial enhancement and delayed wash out.

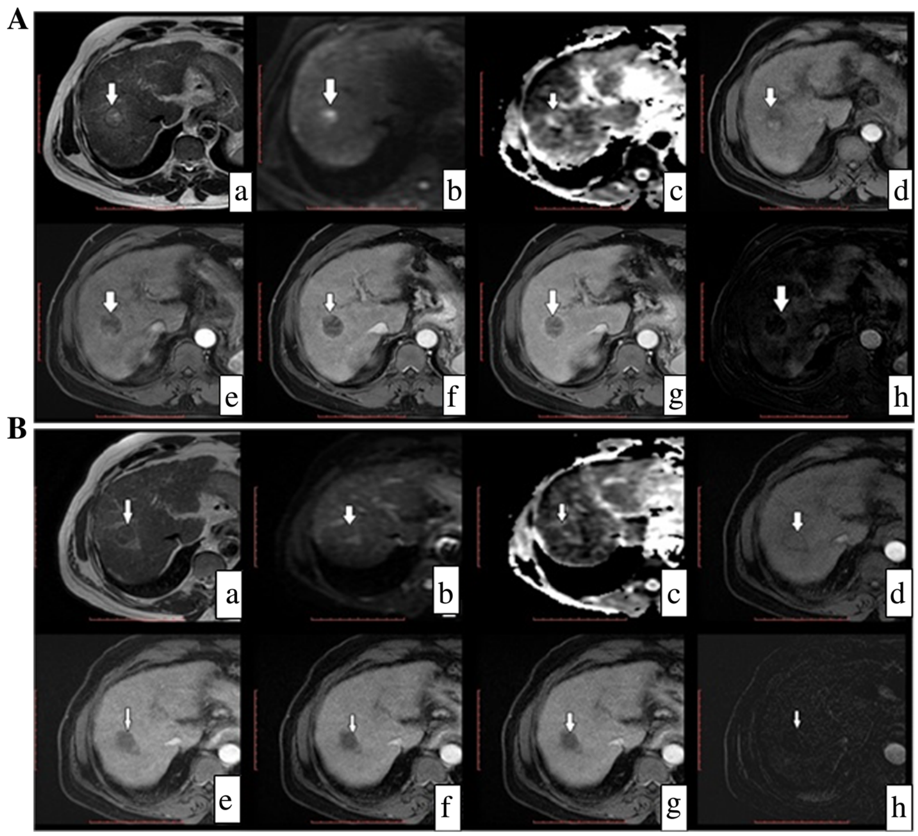

Fig. 1 A 55-year-old male patient with hepatitis-related liver cirrhosis and single segment VIII HCC lesion. He had a TACE session and came for follow up 1 and 3 months later. (A) Follow up dynamic MRI 1 month post TACE. **a** T2WI, **b** DWI image, **c** ADC image, **d** T1WI, **e** late arterial phase, **f** portal phase, **g** delayed phase, and **h** late arterial subtracted image. The treatment zone exhibits high signal in T1WIs and mildly increased signal in T2WIs with peripheral marginal enhancement. Subtraction removed the central high signal thus excluding residual disease. (B) Follow up dynamic MRI 3 months post TACE. **a** T2WI, **b** DWI image, **c** ADC image, **d** T1WI, **e** late arterial phase, **f** Portal phase, **g** delayed phase, and **h** late arterial subtracted image. Note that the lesion became of low to intermediate signal in T2WIs and iso to high signal intensity in T1WIs. The marginal enhancement became inconspicuous. High signal that was detected on the DWI is decreased in the follow up. No enhancement detected at the subtraction images confirming the complete response

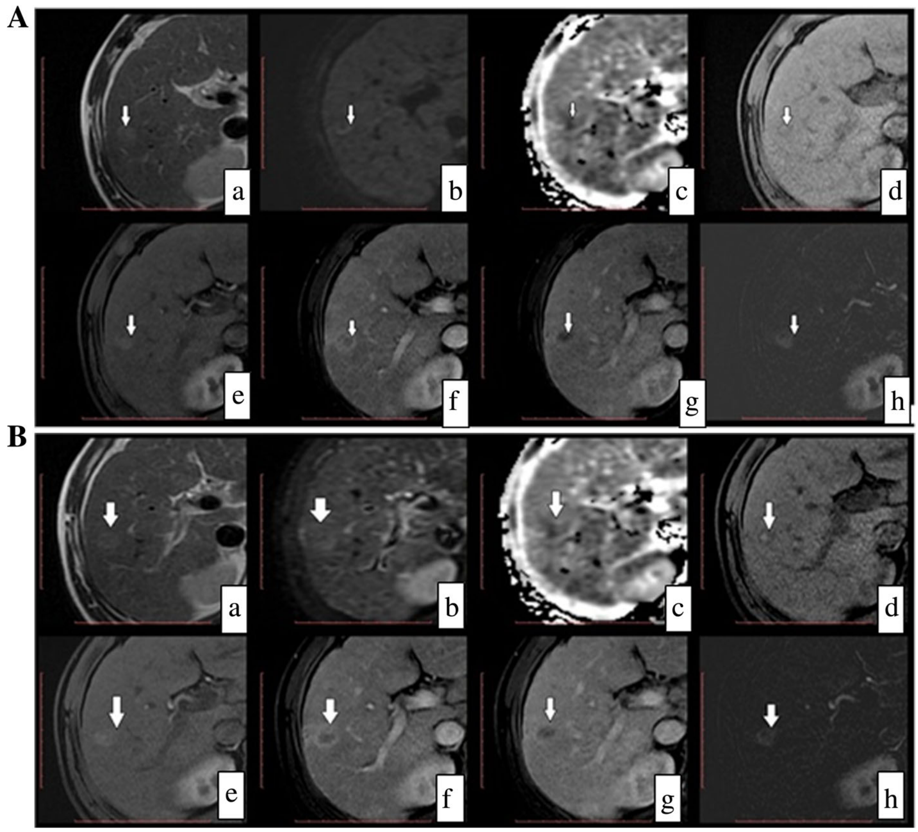

Fig. 2 A 67-year-old male patient with hepatitis-related liver cirrhosis and single segment V/VI HCC lesion. He had a TACE session and came for follow up 1 month post TACE and another short term follow up after 2 months. (A) Follow up dynamic MRI 1 month post TACE. **a** T2WI, **b** DWI image, **c** ADC image, **d** T1WI, **e** late arterial phase, **f** portal phase, **g** delayed phase, and **h** late arterial subtracted image. The treatment zone exhibits high signal in T1WIs and intermediate to high signal in T2WIs with thick peripheral area of enhancement suggestive of residual disease. Subtraction clarified this pattern of enhancement by removing the native high T1WIs signal. (B) Short-term follow up dynamic MRI 2 months post TACE. **a** T2WI, **b** DWI image, **c** ADC image, **d** T1WI, **e** late arterial phase, **f** portal phase, **g** delayed phase, and **h** late arterial subtracted image. Note that the lesion appears with same pattern of contrast enhancement and slight increase in size confirming the residual disease

- Focal area along the margins of treatment zone that shows arterial enhancement and delayed wash out.
- The arterial enhancement must be confirmed by the subtraction images. Diffusion restriction of the lesion is considered as a sign of tumoural activity only if positive dynamic findings are present.

Statistical analysis

- The acquired data were analyzed using the statistical package SPSS version 22. Data were expressed as means and standard deviations. For comparing categorical data, Chi-square test was used. Kappa measure of agreement was performed for assessment of the agreement between the readers. A P value less or equal to 0.05 was considered significant and less than 0.01 was considered highly significant.

Results

This study included 43 patients with 55 HCC lesions who underwent TACE procedure. Five patients were excluded due to misregistration artifact at the subtraction images. Our final study cohort included 38 patients with 50 HCC lesion and their ages ranging between 40 to 80 years with mean age 63.78 years. Of the 38 patients included in the study, there were 13 females and 25 males.

Correlation of the readers' results to standard of reference

Tables 2, 3, and 4 and Figs 3, 4, and 5 interpreted the results for each reader correlated to the standard of reference in both dynamic, subtraction and diffusion images in the form of enhancing or not in subtraction and dynamic images and facilitated or restricted in the diffusion images. The results were expressed as a percentage from the total number of lesions.

Table 2 Correlation of dynamic, subtraction, and diffusion findings obtained by reader 1 to standard of reference

		Reader's findings											
		Dynamic				Subtraction				Diffusion			
		Non-enhancing (*n* = 26)		Enhancing (*n* = 24)		Non-enhancing (*n* = 25)		Enhancing (*n* = 25)		Facilitated (*n* = 28)		Restricted (*n* = 22)	
		Count	%	Count	%	Count	%	Count	%	Count	%	Count	%
Standard of reference	Complete treatment (*n* = 25)	24	92.3	1	4.2	25	100	0	0	21	75	4	18.2
	Residual disease (*n* = 25)	2	7.7	23	95.8	0	0	25	100	7	25	18	81.8

I. Dynamic sequence: For reader 1, 92% of the lesions that interpreted in dynamic sequence by the reader 1 as non-enhancing lesion proved to be of complete treatment while about 8% of the lesions were of residual disease (i.e., false negative) (Fig. 6); on the other hand, about 96% of lesions that interpreted in dynamic sequence by the reader 1 as enhancing lesion proved to be of residual disease while 4% of the lesions were of complete treatment (i.e., false positive) (Fig. 7). For reader 2, 92% of the lesions that interpreted in dynamic sequence by the reader 2 as non-enhancing lesion proved to be of complete treatment while about 8% of the lesions were of residual disease (i.e., false negative); on the other hand, about 96% of lesions that interpreted in dynamic sequence by the reader 2 as enhancing lesion proved to be of residual disease while 4% of the lesions were of complete treatment (i.e. false positive). For reader 3, 77% of the lesions that interpreted in dynamic sequence by the reader 3 as non-enhancing lesion proved to be of complete treatment while about 23% of the lesions were of residual disease (i.e., false negative); on the other hand, about 71% of lesions that interpreted in dynamic sequence by the reader 3 as enhancing lesion proved to be of residual disease while 29% of the lesions were of complete treatment (i.e., false positive).

II. Subtraction images: For reader 1, absence of enhancement on subtraction images represent good therapeutic response in 100% of lesions while enhancement represent residual disease in 100% of lesions. For reader 2, absence of enhancement on subtraction images represent good therapeutic response in 96% of lesions while 4% were false negative. On the other hand, enhancement represents residual disease in 100% of lesions. For reader 3, absence of enhancement on subtraction images represent good therapeutic response in 96% of lesions and 4% were false negative while enhancement, on the other hand, represent residual disease in 100% of lesions.

III. Diffusion images: For reader 1, diffusion-weighted images (DWI) represents good therapeutic response in 75% of lesion, while around 25% of the facilitated lesions were proved to be of residual disease (i.e., false negative). On the other hand, about 82% of the restricted lesions were proved to be of residual disease with only about 18% being restricted and of complete treatment (i.e., false positive). For reader 2, facilitated lesions on DWI represent good therapeutic response in about 83% of lesion, while around 17% of the facilitated lesions were proved to be of residual disease (i.e., false negative). On the other hand, about 95% of the restricted lesions were proved to be of residual disease with only about 5% being restricted and of complete treatment (i.e., false positive). For reader 3, facilitated lesions on DWI represent good therapeutic response in about 75% of lesion, while around 25% of the facilitated lesions were proved to be of residual disease (i.e., false negative). On the other hand, about 82% of the

Table 3 Correlation of dynamic, subtraction, and diffusion findings obtained by reader 2 to standard of reference

		Reader's findings											
		Dynamic				Subtraction				Diffusion			
		Non-enhancing (*n* = 26)		Enhancing (*n* = 24)		Non-enhancing (*n* = 26)		Enhancing (*n* = 24)		Facilitated (*n* = 29)		Restricted (*n* = 21)	
		Count	%	Count	%	Count	%	Count	%	Count	%	Count	%
Standard of reference	Complete treatment (*n* = 25)	24	92.3	1	4.2	25	96	0	0	24	82.76	1	4.76
	Residual disease (*n* = 25)	2	7.7	23	95.8	1	4	24	100	5	17.24	20	95.24

Table 4 Correlation of dynamic, subtraction, and diffusion findings obtained by reader 3 to standard of reference

		Reader's findings											
		Dynamic				Subtraction				Diffusion			
		Non-enhancing ($n = 22$)		Enhancing ($n = 28$)		Non-enhancing ($n = 26$)		Enhancing ($n = 24$)		Facilitated ($n = 28$)		Restricted ($n = 22$)	
		Count	%	Count	%	Count	%	Count	%	Count	%	Count	%
Standard of reference	Complete treatment ($n = 25$)	17	77.3	8	28.6	25	96	0	0	21	75	4	18.2
	Residual disease ($n = 25$)	5	22.7	20	71.4	1	4	24	100	7	25	18	81.8

restricted lesions were proved to be of residual disease with only about 18% being restricted and of complete treatment (i.e., false positive).

Receiver operating characteristic curve

Receiver operating characteristic (ROC) curves are commonly used to characterize the sensitivity/specificity tradeoffs for a binary classifier. The area under the curve is viewed as a measure of a forecast's accuracy that donated by area under curve (AUC). Figure 8 shows the AUC for the three readers. For reader 1, the AUC of subtraction was 1 with 95% confidence interval range 0.929 to 1.00 producing a significant *P* value of < 0.001. For the dynamic sequence, the AUC 1 was 0.940 with 95% confidence interval range 0.835 to 0.987 producing a significant *P* value of < 0.001. And in ADC, the AUC was 0.842 with 95% confidence interval range from 0.712 to 0.930 producing a significant *P* value of < 0.001. Also the subtraction had a sensitivity of 96% and specificity of 100%, compared to 80% and 80% for ADC and 92% and 96% for the dynamic. The AUC of subtraction for reader 2 was 0.980 with 95% confidence interval range 0.894 to 0.999 producing a significant *P* value of < 0.001. Also for dynamic the AUC for reader 2 was 0.940 with 95% confidence interval range 0.835 to 0.987 producing a significant *P* value of < 0.001. And in ADC, the AUC was 0.855 with 95% confidence interval range from 0.727 to 0.939 producing a significant *P* value of < 0.001. Also, subtraction had a sensitivity of 96% and specificity of 100%, compared to 80% and 96% for ADC and 92% and 96% for the dynamic. For reader 3, the AUC of subtraction was 0.980 with 95% confidence interval range 0.894to 0.999 producing a significant *P* value of < 0.001. Also for dynamic, the AUC for reader 3 was 0.740 with 95% confidence interval range 0.597 to 0.854 producing a significant *P* value of < 0.001. And in ADC, the AUC was 0.842 with 95% confidence interval range from 0.712 to 0.930 producing a significant *P* value of< 0.001. Also for reader 3, the subtraction had a sensitivity of 100% and specificity of 100%, compared to 80% and 80% for ADC and 80% and 68% for the dynamic.

Interobserver agreement analysis

In our study, we noted a high level of agreement between the three readers through all of the studied sequences with the higher agreement value with the subtraction imaging.

- Dynamic significant agreement of (kappa = 0.601) and $P < 0.001$.

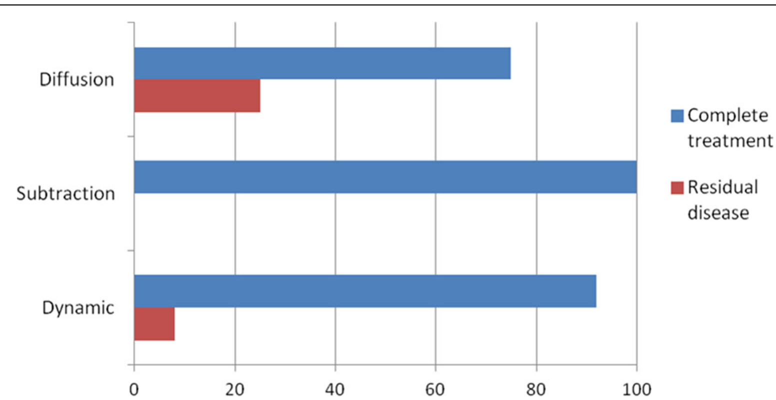

Fig. 3 Horizontal graph showing the correlation of reader 1 findings to standard of reference (expressed as percentage)

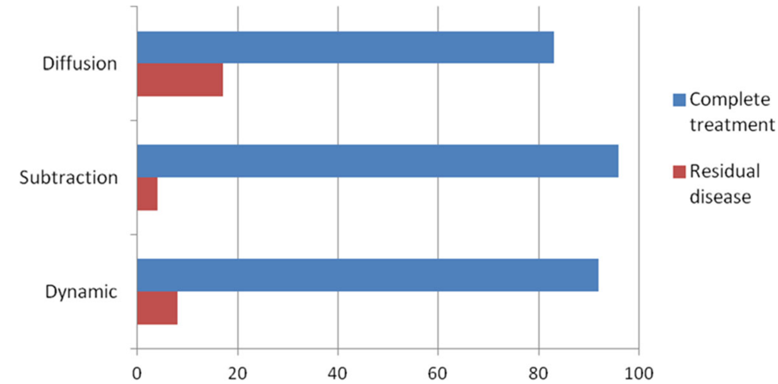

Fig. 4 Horizontal graph showing the correlation of reader 2 findings to standard of reference (expressed as percentage)

- Subtraction significant agreement of (kappa = 0.947) with $P < 0.001$.
- DWI significant agreement of (kappa = 0.837) with $P < 0.001$.

Analysis of the reader confidence levels

- The confidence levels are ordered to range from 1 to 5, where 1 refers to non-confident and 5 refers to very confident. In the following table, we compare between subtraction and dynamic images according to their confidence levels for each reader (Table 5 and Fig. 9).
- According to reader 1, the subtraction appeared to have greater mean value (4.86) with minimum value (4) and maximum value (5) than the dynamic which has mean value (3.46) with minimum and maximum values equals (1) and (5).
- Also for reader 2, the subtraction again appeared to have greater mean value (4.9) with minimum value (4) and maximum value (5) than the dynamic which has mean value (3.34) with minimum and maximum values equals (1) and (5).
- For reader 3, the subtraction appeared to have greater mean value (4.84) with minimum value (4) and maximum value (5) than the dynamic which has mean value (2.88) with minimum and maximum values equals (1) and (5).
- So from the previous results, we can conclude that the three readers noticed subtraction results to have greater confidence levels than those of the dynamic.

Discussion

HCC is considered as the fifth most common cancer worldwide and the most common liver malignancy [1]. It is one of the leading causes of morbidity and mortality, with an estimated incidence of more than 500,000 new cases per year [9].

In Egypt, almost two and half fold increase in the HCC incidence was noticed between 1993 and 2009 among the hepatic patients. HCC is expected to continue rising in the upcoming years forming major health problem this could be explained by the highest prevalence of hepatitis C worldwide, increasing urbanization, environmental exposures and aging [10].

The assessment of the treatment response after TACE by cross-sectional imaging is crucial to assess the

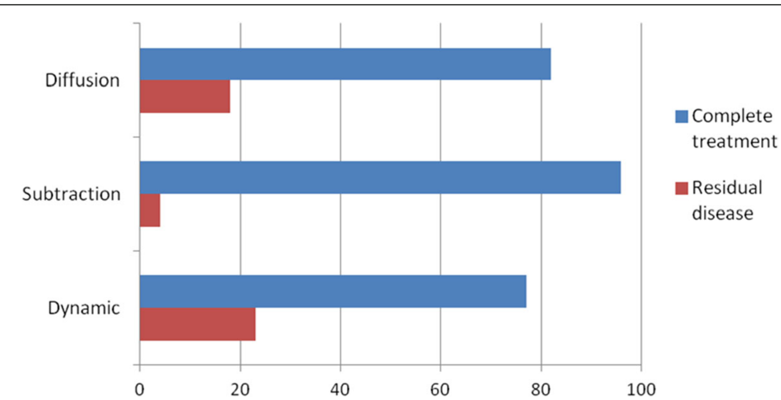

Fig. 5 Horizontal graph showing the correlation of reader 3 findings to standard of reference (expressed as percentage)

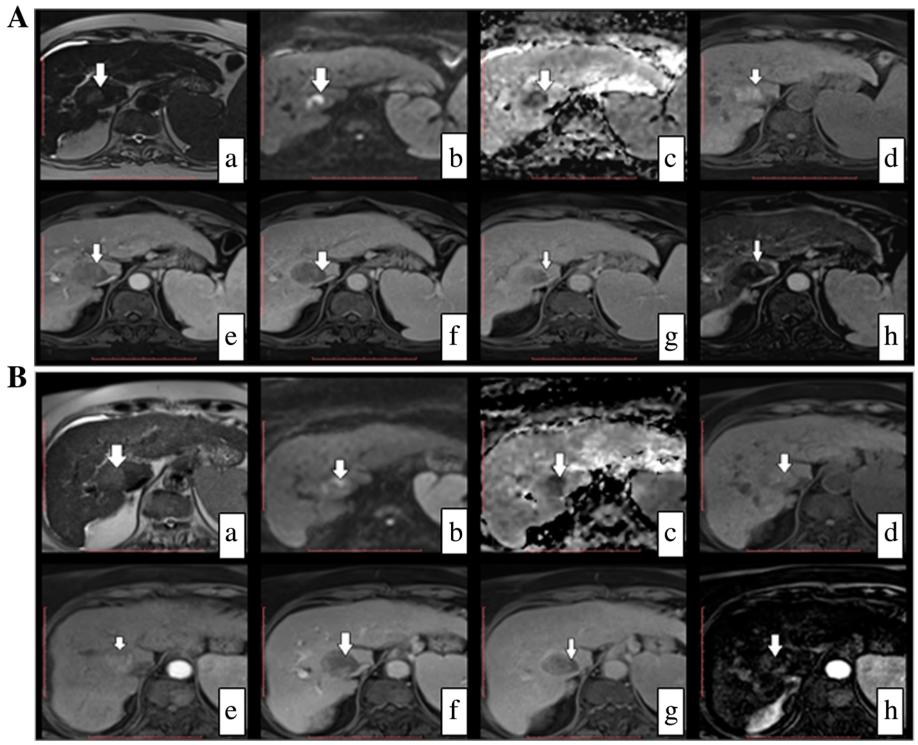

Fig. 6 A 64-year-old female patient with hepatitis-related liver cirrhosis and single segment I HCC lesion. She had a TACE session and came for follow up 1 month later. (A) Follow up dynamic MRI 1 month post TACE. **a** T2WI, **b** DWI image, **c** ADC image, **d** T1WI, **e** late arterial phase, **f** Portal phase, **g** delayed phase, and **h** late arterial subtracted image. The treatment zone elicits high heterogeneous signal in both T1WIs and T2WIs with the periphery of the lesion is seen of restricted diffusion. NO clear areas of enhancement could be seen in the dynamic study; however, the subtraction images shows faint lesion enhancement (false negative dynamic study interpretation). (B) Follow up dynamic MRI 3 months post TACE. **a** T2WI, **b** DWI image, **c** ADC image, **d** T1WI, **e** late arterial phase, **f** portal phase, **g** delayed phase, and **h** late arterial subtracted image. The enhancement became more clear and more appreciated in the dynamic and subtraction images confirming residual/recurrent disease

patient's prognosis, determine whether an additional procedures is needed or not or to select another therapeutic option. Recently, enhancement approaches, such as Liver Imaging Reporting and Data System (LiRADS), mRECIST, and European Association for the Study of the Liver (EASL) are better criteria for categorizing distinct tumor responses following TACE rather than the criteria depending on the change in the lesion's size [11, 12].

HCCs underwent coagulative necrosis after locoregional therapy. The treatment zone exhibits hyperintense T1 signal on pre-contrast images, which makes the assessment of tumor enhancement difficult on the dynamic contrast-enhanced T1WI [13]. Subtraction imaging is an available technique whereby an unenhanced T1-weighted image is digitally subtracted from the identical image performed after contrast administration aiming to remove any native T1 signal from the images and the remaining signal on the subtracted images is solely due to enhancement [8].

An important technical principle in dynamic subtraction imaging is to keep all acquisition parameters of the unenhanced and dynamic contrast-enhanced images constant throughout the different dynamic phases. Also, the patient's position should not be changed during the acquisition of the unenhanced and corresponding dynamic sequences. The patient should be able to maintain a breath-hold throughout the acquisition, the images should be done at end expiration, and the breath-hold should be reproducible from sequence to sequence [14].

Misregistration artifact and image degradation will result in cases not fulfilling one or more of the forementioned criteria [14]. A hyperintense nonenhancing lesion on unenhanced images could erroneously be designated as an enhancing lesion and yield a false impression of a hypervascular tumor. A hypointense lesions on unenhanced images subtracted by hepatic parenchyma on contrast-enhanced images can yield hyperintense pseudolesions on subtraction images [15]. If this occurs, subtracting individual images rather than entire data sets can be useful [14].

In this study, we aimed to evaluate the role of dynamic subtraction MRI technique in the assessment of the treatment response of HCC after TACE procedure. This

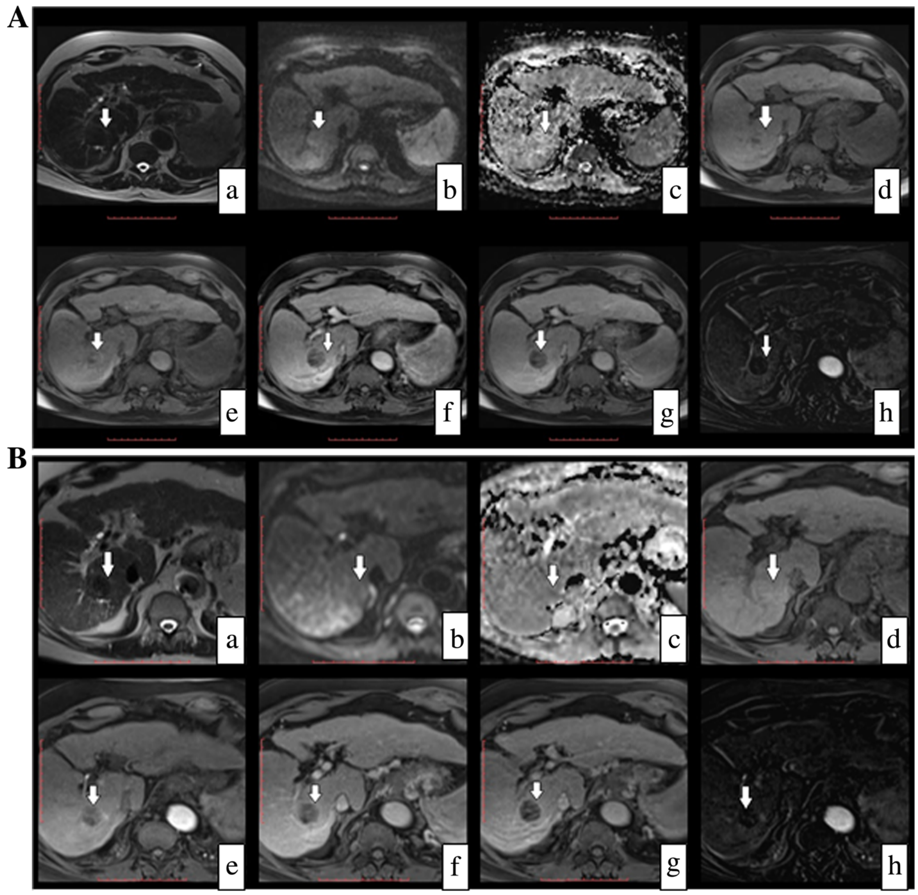

Fig. 7 A 70-year-old male patient with hepatitis-related liver cirrhosis and single segment V/VI HCC lesion. He had a TACE session and came for follow up 1 month later. (A) Follow up dynamic MRI 1 month post TACE. **a** T2WI, **b** DWI image, **c** ADC image, **d** T1WI, **e** late arterial phase, **f** portal phase, **g** delayed phase, and **h** late arterial subtracted image. The treatment zone elicits low to isointense signal in T2WIs, and iso to high signal in T1WIs. It measures about 3.4 × 2.4 cm in diameter with high central signal in the arterial phase worrisome for residue. ADC value measured (1.3×10^{-3} mm^2/s). Subtraction removed the central high signal thus excluding residual disease (false positive dynamic study interpretation). (B) Follow up dynamic MRI 3 months post TACE. **a** T2WI, **b** DWI image, **c** ADC image, **d** T1WI, **e** late arterial phase, **f** portal phase, **g** delayed phase, and **h** late arterial subtracted image. Regression in the size of the treatment zone with still no contrast uptake confirming the complete response

study included 38 patients (after exclusion of five patients due to misregistration artifact at the subtraction images).

In a previous study [2], it was found that the subtraction has a sensitivity of 97.06%, specificity 100%, positive predictive value (PPV) 100%, and negative predictive value (NPV) 95.24% by two readers which agreed with our results. Our results were also comparable with another study [16] who found that both subtraction and dynamic techniques showed excellent diagnostic performance with AUC ≥ 0.90 ($P < 0.001$). With the subtraction has sensitivity 83.3%, specificity 90.9%, PPV 76.9%, and NPV 93.8% compared to 63.9%, 86.9%, 63.9%, and 86.9% respectively for the dynamic technique.

For DWI, reader 1 found that it had sensitivity of 80%, specificity of 80%, PPV of 75%, and NPV of 78% Compared to sensitivity of 80%, specificity of 96%, PPV of 95.2%, and NPV of 82.7% for reader 2 and sensitivity of 80%, specificity of 80%, PPV of 81.8%, and NPV of 75% for reader 3. Our results were comparable with previous study [9] who found that the DWI imaging had an overall sensitivity of 83.9%, a specificity of 64.3%, PPV of 72.2%, and a NPV of 78.3% and accuracy of 74.5% and with another study [2] who found that reader 1 evaluation of DWI yielded sensitivity of 70.59%, specificity of 75%, PPV of 82.76%, and a NPV of 60% compared to 76.47%, 90%, 92.86%, and 69.23% respectively with reader 2.

As a conclusion, we found that the subtraction images had higher sensitivity, specificity, PPV, and NPV values compared to the dynamic images and DWI images as found by previous studies [2] and [16].

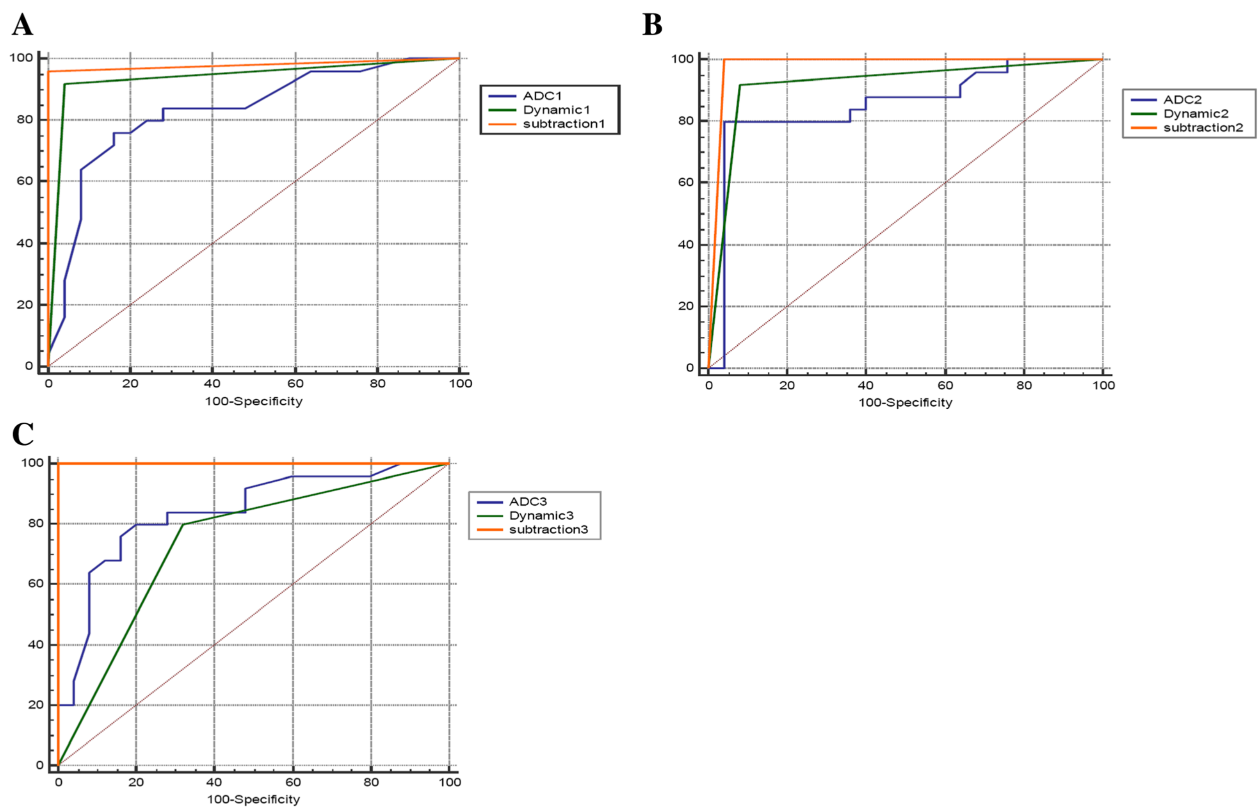

Fig. 8 Shows the area under the curve (AUC) for the three readers. **a** Reader 1, **b** reader 2, and **c** reader 3

The readers results to standard of reference agreement

Using kappa analysis, our study showed a stronger reader to standard of reference (SOR) agreement for the subtraction MRI images compared to the dynamic MRI images. For the subtraction MRI images, the k values were 1, 0.96, and 0.96 (high significant agreement) for the three readers respectively, compared to k values of 0.88, 0.88, and 0.48 for the dynamic MRI images. These results agreed with some previous studies [13, 16–18].

Correlation between the precontrast T1 signal intensity and the mismatched finding between the SOR and the dynamic MRI images that resulted in the false positive and false negative results were occurred in lesions having high signal intensity at the precontrast T1 images. This finding agreed with previous study [16]

Our study also showed that DWI images have kappa value 0.56, 0.76, and 0.56 for the three readers respectively. That was in agreement with a previous study [13] who found that the DWI results were disappointing and ADC was not a significant predictor of complete tumor necrosis.

Interobserver agreement analysis

It was noted that a high level of agreement between the three readers through all of the studied sequences with the higher agreement value with the subtraction imaging which is comparable with recent studies [2, 18].

- Dynamic significant agreement of (kappa = 0.601) and $P < 0.001$.

Table 5 Confidence levels among three readers for subtraction and dynamic images

	Reader 1		Reader 2		Reader 3	
	Dynamic	Subtraction	Dynamic	Subtraction	Dynamic	Subtraction
Mean	3.46	4.86	3.34	4.9	2.88	4.84
Minimum	1	4	1	4	1	4
Maximum	5	5	5	5	5	5
Median	3.5	5	4	5	3	5
Standard deviation	1.0539	0.3505	1.0422	0.3030	.8722	0.3703

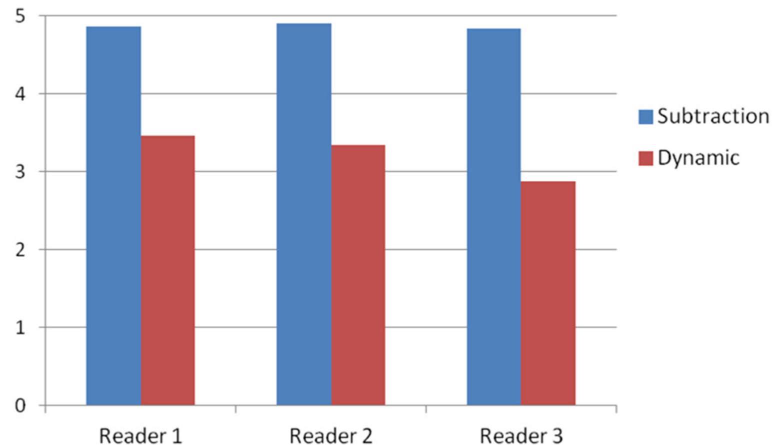

Fig. 9 Bar chart showing the confidence level for both dynamic and subtraction images among the three readers

- Subtraction significant agreement of (kappa = 0.947) with $P < 0.001$.
- DWI significant agreement of (kappa = 0.728) and $P < 0.001$.

Reader confidence level

The mean reader confidence level for the dynamic MRI protocols was 3.46, 3.34, and 2.88 for the three readers respectively. On the other hand, mean reader confidence level for the subtraction MRI protocols was 4.86, 4.90, and 4.84 for the three readers respectively. Denoting significantly higher reader confidence levels were found for all three readers when using the subtraction MRI protocol as compared to the dynamic MRI protocol.

Limitations of the study were as follows

The study design is a retrospective study which is subjected to the limitations inherent to such study design. Another limitation is a relatively small sample size reducing the power of the statistical analysis. The small sample size could be related to the strict selection criteria adopted for this highly specialized indication. However, a statistically significant higher confidence level was proven for the subtraction MRI over the dynamic MRI protocol which is an important finding not sufficiently published in the literature. Also, the reference slandered was not based on histopathological results to confirm whether there is complete treatment or residual disease. However, as discussed before, this point is related 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 on 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. One of the limitations is the misregistration artifact 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. However, in such cases, we depend on the T1 and T2 signal of the lesion as well as the diffusion images and ADC analysis. The size of the lesion was not included in our assessment criteria; however, we depend on other criteria as done in previous studies.

Conclusion

Subtraction images is a useful confirmative tool as it had higher sensitivity, specificity, PPV, and NPV values compared to the dynamic images and DWI images with high level of agreement between the readers and also associated with significantly higher reader confidence levels. We recommend post processing subtraction images to be a routine part of the dynamic liver MRI protocol for better tissue characterization.

Abbreviation

AUC: Area under curve; DWI: Diffusion weighted images; EASL: European Association for the Study of the Liver; HCC: Hepatocellular carcinoma; LiRADS: Liver Imaging Reporting and Data System; LRT: Locoregional therapy; NPV: Negative predictive value; OLT: Orthotropic liver transplant; PPV: Positive predictive value; ROC: Receiver operating characteristic; SOR: Standard of reference; TACE: Transarterial chemoembolization

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Availability of data and material

All the datasets used and analysed in this study are available with the corresponding author on reasonable request.

Authors' contributions

LM participated in the design of the study, image interpretation, and data collection. BM conceived of the study, editor of the manuscript, and image interpretation. MY participated in the design of the study, data collection, and performed the statistical analysis. All authors read and approved the final manuscript.

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Ethics approval and consent to participate
Written informed consent was signed by all patients before the examination. The study was approved by the ethics committee of faculty of medicine, Cairo University.

Consent for publication
All patients included in this research were fully conscious and older than 16 year old and gave written informed consent to publish the data contained within this study.

Competing interests
The authors declare that they have no competing interests.

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