The role of dynamic subtraction MR technique in characterization of focal hepatic lesions with high T1 signal

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Authors: B. E. M. H. Mahmoud, S. Fatooh, A. H. K. Abdelmaksoud; Cairo/EG
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Learning objectives

- Causes of focal hepatic lesions with high T1 signal. We will focus on lesions in cirrhotic liver.
- What is the dynamic subtraction technique and its role in assessment of enhancing lesions.
- Pitfalls of dynamic subtraction technique.

Background

- **Common hepatic focal lesions with high T1 signal in cirrhotic liver:**
  1. Regeneration nodules.
  2. Dysplastic nodules.
  3. Hepatocellular carcinoma.
  4. post interventional changes:
     - Coagulation necrosis after thermal ablation.
     - After transarterial chemo or radio embolization.

- **Other hepatic focal lesions with high T1 signal:**
  1. Hepatocellular adenoma.
  2. Hematoma (subacute stage due to presence of methemoglobin).
  3. Lipoma and angiomyolipoma.
  5. Complicated cysts (high proteinaceous and hemorrhagic contents).
  6. Calcified lesions.
  7. Fat containing metastasis.

- **Problems in detection of enhancing lesions:**
  1. During the arterial phase of the dynamic study, the liver is mildly enhancing (about 15-20% of blood supply come from the hepatic artery), so the focal lesion will still exhibiting high T1 signal relative to the mildly enhancing background parenchyma.
  2. During the subsequent phases, the liver will progressively enhance, so the lesion will appear of low signal relative to the enhancing parenchyma.
  3. This process is difficult to be differentiated from the true arterial phase enhancement and delayed wash out that is noted in many neoplastic lesions.
  4. So the high signal in the post contrast T1-weighted images may be a result of enhancement, pre-existing high T1 signal, or a combination of these.
• **What is the dynamic subtraction MR technique:**

Subtraction MRI is a technique whereby corresponding contrast-enhanced and unenhanced T1-weighted sequences are digitally subtracted image-by-image using post-processing MRI software Fig. 1 on page 4.

The objective of this process is to remove pre-existing T1-weighted high signal from the post-processed images so that the remaining high signal is solely due to enhancement\(^1\).

It's an automated process available on the software of most of the recent MR scanners and their provided workstations. It does not need any additional time during image acquisition as it is a post processing technique not an image sequence.

• **Advantages of subtraction MR imaging:**

1. Characterization of hyperintense T1 lesions.
2. Detection of mildly enhancing lesions by suppressing the background parenchyma.
3. Differentiating bland from malignant portal vein thrombosis.

• **Pitfalls of subtraction MR technique (misregistration artifact):**

** It is essential that the patient's position remain unchanged within the magnet during the unenhanced and contrast enhanced sequences. The patient should be able to maintain a breath-hold throughout the acquisition, and the breath-hold should be reproducible from sequence to sequence. Not fulfilling one or more of these criteria will result in misregistration artifact and image degradation on the subtraction series\(^2\) Fig. 2 on page 4.

Small subcentimetric peripheral subcapsular lesions are more vulnerable to this artifact.

** How to identify??

Misregistration artifact can be identified by high signal intensity that outlines the liver surface or enhancing structures, meaning that the subtracted images are not corresponding to each other at the pre contrast and contrast enhanced series Fig. 3 on page 5.

minimal degree of slice misregistration is physiologically inevitable\(^3\).

** How to overcome?
**Imaging at end expiration** may yield more consistent data sets than imaging at end inspiration \(^{(2)}\).

**Image by image subtraction** by choosing the images that will be subtracted manually (Fig. 4 on page 6). This is not available at all post processing softwares.

**Post-processing software algorithms** have been developed to improve image matching by performing registration correction on the source data \(^{(1)}\).

**Images for this section:**

![Schematic diagram illustrating the principles of subtraction MRI in treatment zones of varying characteristics.](image-url)

**Fig. 1:** Schematic diagram illustrating the principles of subtraction MRI in treatment zones of varying characteristics.
Fig. 2: Schema of misregistration and erroneous determination of enhancement between unenhanced and contrast-enhanced source images. On upper row images, level of contrast-enhanced image is lower than level of unenhanced image. In this case, high-signal lesion on unenhanced image (1) is subtracted from isointensely enhanced liver parenchyma on contrast-enhanced image, which can result in signal void artifact (2) on subtracted image. Also at more inferior level, normal unenhanced liver parenchyma is subtracted from hyperintense (but not enhanced) lesion that is present on contrast-enhanced image set. This results in appearance of hyperintense nodule (3) on subtracted image giving false impression of hypervascular tumor. To contrary, hypointense lesion (4) on unenhanced image when subtracted from normally enhanced parenchyma can create hyperintense signal (5) at more superior level and hypointense signal on more inferior level after subtraction. On lower row images, level of contrast-enhanced image is higher than unenhanced image, and same effect yields reciprocal result compared with upper row images.
**Fig. 3:** Male patient with history of transarterial chemoembolization of right hepatic lobe focal lesion. MRI revealed misregistration artifact during subtraction of the whole series from each other as a package. (A) (left lower quadrant) pre-contrast T1 (image No. 34 in the pre-contrast series). (right lower quadrant) arterial phase image (No. 34 in the arterial series). Note that the images are not at the same level, the high T1 lesion will be subtracted from a normal parenchyma "red arrows", the resultant subtracted image (right upper quadrant) showed low signal area "yellow arrow". (B) (left lower quadrant) pre-contrast T1 (image No. 40 in the pre-contrast series). (right lower quadrant) arterial phase image (No. 40 in the arterial series). Note that the images are not at the same level, the normal parenchyma will be subtracted from the high T1 lesion "red arrows", the resultant subtracted image (right upper quadrant) showed false positive result of arterial enhancement "yellow arrow".
**Fig. 4:** A method of correction of misregistration artifact by manual choice of the images that will be subtracted from each series. The same patient in figure 3, here we choose the appropriate corresponding images from the precontrast series (image no. 34) and arterial phase series (image no. 40). The resultant subtracted image show no enhancement within the lesion. N.B. This image is processed on the Phillips extended MR workspace ver 2.6.6.3 Netherlands.
Findings and procedure details

- **Technique:**
  1. Images that will be presented are performed using Phillips MR scanners (Panorama 1 T, Achiva 1.5 T & Ingenia 3 T).
  2. Dynamic study was performed after manual bolus injection of 0.1 mmol/kg body weight of Gd-DTPA.
  3. Dynamic imaging using 3D fat-suppressed T1-weighted gradient echo sequence (**THRIVE** i.e. T1 high resolution isotropic volume examination).
  4. 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.
  5. All patients were imaged at end expiration.
  6. Images were sent to the workstation (Phillips Extended MR Workspace) for further image processing.

**Role of subtraction in cirrhotic liver:**

There are four classes of lesions that characteristically are found in the cirrhotic liver: regenerative nodules, dysplastic foci, dysplastic nodules and hepatocellular carcinomas. These lesions are referred to collectively as cirrhosis associated hepatocellular nodules (4).

- **Regeneration nodules:**

**Pathology:** Regenerative nodules form in response to necrosis, altered circulation, or other stimuli. Regenerative nodules may be classified according to size as either micronodules (<3 mm) or macronodules (>3 mm). Giant regenerative nodules with a diameter of 5 cm have been described, but they are rare (4). Regenerative nodules have a similar vascular profile to the surrounding cirrhotic liver and draw their blood supply from the portal venous system (5).

**MR Imaging appearance:** A small nodule exhibit intermediate or high T1 and intermediate or low T2 signal intensity. They should not enhance in the arterial phase, however enhancement may be noted during the portal phase. Fig. 5 on page 12 and Fig. 6 on page 12

- **Dysplastic nodules:**
**Pathology:** A dysplastic nodule is a nodular hepatocellular region that contains dysplastic features without histologic evidence for malignancy. Dysplastic nodules may contain architectural derangement, high nuclear density, atypia and abnormal vascular profile. Low-grade dysplastic nodules are difficult to distinguish histologically from regenerative nodules and have low malignant potential. High-grade dysplastic nodules demonstrate more advanced architectural distortion, atypia and associated vascular abnormalities. They are more likely to progress to hepatocellular carcinoma than are low-grade dysplastic nodules. The rate of that transformation is relatively slow.

**MR Imaging appearance:** Low grade dysplastic nodules show similar pattern to regeneration nodule and can't be differentiated from each other by imaging. High grade dysplastic nodules are associated with increased hepatic arterial blood supply and therefore may demonstrate hypervascularity mimicking HCC. Distinguishing feature of dysplastic nodules from HCC is that dysplastic nodules typically lack a capsule. Fig. 7 on page 13

- **Hepatocellular carcinoma:**

The most serious complication of liver cirrhosis is the development of HCC. The distorted architecture of liver parenchyma with variable signal pattern of regeneration and dysplastic nodules causes difficulties in detection of HCC.

**Pathogenesis:**

1- **De-novo in non cirrhotic liver.**

2- **Stepwise carcinogenesis in cirrhotic liver:** from regenerative nodules to dysplastic nodules to well differentiated hepatocellular carcinoma.

**Pathways of Carcinogenesis (Fig. 8 on page 14):**

- The cell origin of HCC is not well established; the tumor may derive from hepatic stem cells or from the transformation of dysplastic hepatocytes into malignant cells. HCCs arising from stem cells tend to produce #-fetoprotein and are more aggressive than those arising from mature hepatocytes.

- Ongoing hepatocyte injury from viruses, alcohol consumption, and nonalcoholic fatty liver disease results in increased liver cell turnover, leading to the formation of regenerative nodules. The formation of regenerative nodules is an attempt by the liver to replace the damaged hepatocytes and compensate for lost liver function. Within regenerative nodules, some hepatocytes can undergo further changes with atypia and hence progress to liver cell dysplasia. With these changes, the nodules increase in size and cellularity, giving rise to the formation of dysplastic nodules and, finally, HCC.
At some point during the process of carcinogenesis of HCC (most likely when regenerative nodules become dysplastic nodules), new tumor vessels begin to form. The appearance of these vessels is important in the transformation of regenerative nodules into dysplastic nodules and small HCCs. Neoangiogenesis is also important for the sustained growth of an HCC.

**MRI appearance of HCC (Fig. 9 on page 14):** On *T1-weighted MR images* HCC is most often hypointense relative to the liver, although areas of hyperintensity within hypointense lesions may be seen. These hyperintense regions within the HCC reflect the presence of fat, copper, protein, or blood secondary to intralesional hemorrhage. So, although T1 hyperintensity within a cirrhotic nodule is more typical of dysplastic nodules, it can also be seen in HCCs. On *T2-weighted sequences*, hepatocellular carcinomas typically demonstrate mild to moderate increased signal intensity (5).

The absence of **restricted diffusion** in a hepatic mass that otherwise demonstrates MR imaging features of hepatoma should not sway the diagnosis away from HCC. It should also be noted that the background cirrhotic liver also has restricted diffusion and is reported to demonstrate a reduced ADC relative to non fibrotic livers (7).

The characteristic **arterial enhancement** of HCC emphasizes the importance of optimizing techniques to image in the arterial phase. If imaged too early in the arterial phase when the aorta is initially opacified, the images may be optimal to obtain an MR angiogram but there may not be sufficient opacification of the liver. As a result, HCCs will not appear hypervascular and may not be detected easily. Consequently, arterial-phase images should be obtained during the late arterial phase or portal venous inflow phase. About 10 to 20% of HCCs may be hypovascular to the parenchyma on the immediate contrast-enhanced images. This may be related to lack of arterialization of the tumor (5).

Hypointensity relative to the surrounding parenchyma on the portal venous and delayed contrast-enhanced phases is called "washout" and is highly suggestive of HCC. The lack of washout does not exclude malignancy.

**Role of subtraction in diagnosis of HCC:**

1. **Suppression of the background parenchyma:** enhancement may be faint and difficult to be detected from the mildly enhancing parenchyma in the early arterial phase. By subtraction technique, background liver parenchyma is suppressed and the enhancement is more evident (Fig. 10 on page 15).

2. **Detection of fat containing (and less commonly hemorrhagic) HCC** (Fig. 11 on page 16): HCCs may sometimes contain fat, the tumors may appear iso-to hyperintense on T1-weighted imaging. HCCs contain intracellular lipid more often than macroscopic fat, which results in loss of
signal intensity on the opposed phase GRE T1-weighted images. Other processes such as hemorrhage, melanin, and copper or glycoprotein accumulation can also lead to hyperintense T1 signal. Although a fat-containing HCC may appear otherwise relatively nonspecific on MRI, and may not show the typical arterial phase hypervascularity or capsular enhancement, all lesions in the cirrhotic liver with signal intensity drop-off on the opposed phase images should be considered suspicious for HCC \(^{(5)}\).

3. **Nodule within nodule sign:** When foci of HCC develop within a preexisting dysplastic nodule. The appearance on T1-weighted imaging may be of a T1 hypointense HCC within a T1 hyperintense dysplastic/regeneration nodule. The subtracted images will suppress the signal of the dysplastic nodule and show the distinct enhancement of the neoplastic foci within Fig. 12 on page 17. The typical appearance of a high T2 signal intensity nodule within a low T2 signal intensity nodule is termed a "nodule within nodule" appearance.

4. **Diagnosis of malignant portal vein thrombosis** (Fig. 13 on page 17): Contrast enhancement of portal vein thrombi helps distinguish malignant portal vein thrombosis from bland (non enhancing) thrombosis in the cirrhotic liver. Increased conspicuity of contrast enhancement is seen on subtraction images, which also assists in determining the extent of tumor thrombi as distinguished from bland thrombus \(^{(3)}\).

**Role of dynamic subtraction in post interventional assessment of hepatic malignancies:**

The European Association for the Study of the Liver (EASL) recommended the use of lesion enhancement on contrast-enhanced CT as the standard modality to determine the treatment response of HCC after locoregional therapy \(^{(8)}\).

Common radiological interventions used for treatment of liver malignancies include **endovascular** (transarterial chemoembolization, transarterial radioembolization) and **percutaneous** techniques (thermal ablation including radiofrequency, microwave, Laser and cryoablation) or (chemical ablation e.g. ethanol injection).

Almost all the previously mentioned methods (apart from cryoablation) induce high T1 signal necrotic areas, and hence raising the role of dynamic subtraction technique in detection of recurrent or residual disease.

We will describe the role of subtraction technique in the assessment of tumour necrosis after interventional therapy for hepatic tumours in the following images Fig. 14 on page 18, Fig. 15 on page 19, Fig. 16 on page 19, Fig. 17 on page 20, Fig. 18 on page 20.
Images for this section:

(A) Precontrast T1 image showed two adjacent nodules of high T1 signal (arrows). (B) Subtracted arterial phase image showed no enhancement within any of the nodules.

**Fig. 5:** Patient with liver cirrhosis showing regeneration nodules
Fig. 6: Regeneration nodule in patient with liver cirrhosis.

(A) Precontrast T1 image showed a small nodule of high T1 signal (arrow). (B) arterial phase of the dynamic study shows high signal of the nodule ? enhancement. (C) delayed phase shows low signal of the nodule (D) Subtracted arterial phase image shows drop of signal of the nodule proving that the high signal in the arterial phase is relative to the hypoenhancing liver parenchyma (not true enhancement) and the low signal in the delayed phase in not wash out but relative signal drop of the nodule due to progressively enhancing parenchyma.

(A) Precontrast T1 image showed a small nodule of high T1 signal (arrow). (B) arterial phase of the dynamic study shows enhancement within the nodule. (C) Subtracted arterial phase image proved the enhancement of the nodule (pathologically proven high grade dysplastic nodule).
Fig. 7: Patient with HCV related liver cirrhosis showing right hepatic lobe high grade dysplastic nodule

![Diagram showing progression from RN to DN to HCC focus to Small HCC to Large HCC (>2cm)](image)

Fig. 8: Drawing illustrates the concept of stepwise carcinogenesis of HCC in cirrhosis. According to this concept, a regenerative nodule (RN) increases in size and cellularity with changes of atypia and is transformed into a dysplastic nodule (DN). A focus of HCC may develop within a dysplastic nodule; this focus can progress to a small HCC and then to a large (>2-cm) HCC. Simultaneously, the nodule develops its own neovascularity, which is necessary to support the rapid growth of the nodule into HCC. Differences in color indicate subnODULES.
**Fig. 9**: Typical hepatocellular carcinoma. (A) Axial T2W image shows a lesion in the right hepatic lobe with mild increased signal intensity (arrow). (B) Axial unenhanced T1W GRE image shows low signal intensity within the lesion (arrow). (C) Axial gadolinium-enhanced arterial-phase T1FS GRE image shows hypervascularity typical of HCC (arrow). (D) Axial delayed gadolinium-enhanced T1FS GRE image shows washout of lesion with capsular enhancement (arrow). (E) Axial DWI (b500) shows lesion is increased signal intensity owing to restricted diffusion (arrow). (F) Axial ADC map shows lesion (arrow) is decreased in signal intensity proving that the high signal intensity on DWI is not from T2 shine-through, but from truly restricted diffusion.
A) unenhanced T1 image shows segment VIII focal lesion eliciting low T1 signal. B) arterial phase image shows faint enhancement of the lesion. C) Subtracted arterial phase image (B – A) shows that the enhancement is more evident due to suppression of the background parenchyma. D) delayed phase shows contrast wash out.

**Fig. 10:** Role of subtraction of in detection of faintly enhancing lesions due to suppression of the background parenchyma.

**Fig. 11:** Male patient with liver cirrhosis on top of chronic viral hepatitis. small well defined lesion is seen within the left lobe eliciting high signal in the (in phase) T1 image with drop of signal in the out of phase sequence denoting the presence of intracellular fat. small
nodular enhancement noted in the subtracted arterial phase image (arrow) that was not evident in the arterial phase. Note the high T2 signal and the free diffusion pattern of the lesion. This is a case of fat containing hypovascular HCC.

Fig. 12: Nodule within nodule sign.
**Fig. 13:** Dynamic subtraction in detection of malignant portal vein thrombosis.

- **A)** Axial arterial phase image shows ill defined right hepatic lobe enhancing focal lesion adjacent to the right portal vein. **B)** delayed phase image shows contrast wash out of the tumour mass. Note the thrombosed right portal vein with a suspicious small hypointense tumour thrombus within (arrow).
- **C)** Subtracted early arterial phase image shows distinct enhancement of the suspicious tumour thrombus within the right portal vein (arrow). **D)** Early portal phase subtracted image shows rapid wash out of the thrombus. The distal part of the right portal vein shows non enhancing filling defect (bland thrombus).

- **A)** unenhanced T1 image shows chemoembolized lesion within segment IVa with a small nodule of high T1 signal at its periphery (arrow). **B)** arterial phase image shows high signal of the small peripheral nodule. **C)** delayed phase shows hypointense signal of the nodule ? wash out ? relative drop of signal **D)** Subtracted arterial phase image (B – A) shows drop of signal of the nodule. Again this proves that the high signal in the arterial phase is not true enhancement and the low signal in the delayed phase in not wash out but relative signal drop of the nodule due to progressively enhancing parenchyma.
**Fig. 14:** Post chemoembolization of HCC showing the role of subtraction in characterization of the small nodule of high T1 signal.

**Fig. 15:** Patient with HCC on top of liver cirrhosis underwent Transarterial chemoembolization A) unenhanced T1 image shows chemoembolized lesion within segment III exhibiting high T1 signal. note the small area of low signal at its periphery (arrow). B) arterial phase image shows high signal of the embolized lesion and the small peripheral area. C) Subtracted arterial phase image (B - A) shows distinct enhancement of the peripheral low signal nodule yet with no enhancement of the larger embolized segment. D) delayed phase shows wash out of the enhancing lesion and relative drop of signal of the non enhancing component.
**Fig. 16:** Post chemoembolization of HCC showing small viable component.

- **A)** unenhanced T1 image shows hyperintense embolized right lobe focal lesion.
- **B)** arterial phase image shows suspicious enhancing nodule within the embolized lesion (arrow).
- **C)** Subtracted arterial phase image (B – A) shows distinct enhancement of the small nodule. The tumour viability is proved in the next session of transarterial chemoembolization.

**Fig. 17:** Role of subtraction in suppression of the high T1 signal of the ablation zone after RFA of small left lobe hepatocellular carcinoma.

- **A)** unenhanced T1 image shows hyperintense ablation zone within the left lobe.
- **B)** arterial phase image shows high signal of the ablation zone.
- **C)** Subtracted arterial phase image (B – A) shows complete drop of signal of the ablation zone denoting absence of viable tumour tissue.
Fig. 18: The same patient in figure 17 shows a small recurrent lesion at the margin of the ablation zone.
Conclusion

Dynamic subtraction MRI is a recent technique having several applications in MR imaging. It’s a technique whereby corresponding contrast-enhanced and unenhanced T1-weighted sequences are digitally subtracted using post-processing MRI software to remove the precontrast high T1 signal so the remaining high signal in the subtracted images is due to enhancement.

Several hepatic lesions present with high T1 signal intensity and detection of enhancement within such lesions is challenging. Subtraction technique provides a powerful tool for detection of enhancement areas within the high T1 signal lesions.

The most important pitfall in subtraction technique is the misregistration artifact which is not uncommon in abdominal MR imaging, however we described one of the solutions for this problem in our poster by manually choosing the images to be subtracted from each series.

Personal information

authors from department of diagnostic and interventional radiology.

Cairo university. Egypt

First authore-mail: bahaa.mahmoud@kasralainy.edu.eg

References


