Role of Dynamic Contrast-Enhanced MRI in Follow-Up of Patients with Hepatocellular Carcinoma after Trans-Catheter Arterial Chemoembolization

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Abstract

Background: MRI with its functional imaging techniques including dynamic study is a powerful tool in detection of tumor viability and complications after trans-catheter arterial chemoembolization of hepatocellular carcinoma. This study found that dynamic study is the gold standard in detection of the recurrent lesions. Well defined nodular enhancement, thick irregular marginal enhancement or gross enlargement of the lesion with arterial phase enhancement and contrast wash out were considered positive for malignancy, while ill-defined persistent enhancement or well defined rim marginal enhancement are considered as benign post interventional changes.

Objective: The purpose of this study is to emphasis the role of dynamic contrast enhanced MRI in follow-up of patients with hepatocellular carcinoma after trans-catheter arterial chemoembolization.

Patients and Methods: Twenty five patients with HCC underwent chemoembolization were included in this study. Follow-up by dynamic MRI and diffusion imaging was done at different time intervals. We classified the patients into resolved “benign” group and unresolved “malignant” group. We assessed and classified our patients according to morphological changes (size and signal intensity at T1, T2 and diffusion weighted images), quantitative diffusion analysis (ADC measurement), enhancement pattern in the dynamic study and the presence of complications.

Results: Dynamic MRI study had a sensitivity of 90.5%, a specificity of 96.6%, a positive predictive value of 95%, a negative predictive value of 93.3% and an overall agreement of 94%.

Conclusion: MRI is a powerful tool in detection of tumor viability and complications after trans-catheter arterial chemoembolization of hepatocellular carcinoma. Imaging protocol should include dynamic study combined with diffusion imaging with post processing of the images to obtain subtracted images, color mapping and ADC measurements for better tissue characterization and should be performed at regular time intervals.

Key Words: MRI – Hepatocellular carcinoma – Trans-catheter arterial chemoembolization.

Introduction

HEPATOCELLULAR Carcinoma (HCC) is the most common primary liver cancer, the fifth most common cancer and the third most common global cause of cancer-related deaths. In 2000, there were 564,000 new cases and 549,000 deaths from HCC worldwide, indicating the devastating prognosis of this tumor [1].

Unlike other forms of cancer, the diagnosis of HCC does not always require histological confirmation and HCC is usually diagnosed by tumor marker and triphasic CT or MRI study [2].

Current effective treatments for HCC include liver resection, transplantation, various local ablative and trans-arterial therapies. Surgical resection and liver transplantation are the main curative treatments. Unfortunately, only around 20% patients, mostly diagnosed by regular screening, may benefit from these surgical therapies [3].

Transarterial Chemoembolization (TACE) is the most commonly used treatment for HCC that cannot be submitted to surgery. It is based on the objective of tumor devascularization, in which the oxygen and nutrient supply to the tumor is blocked, resulting in tumor necrosis [4].

Also TACE affects the tumor to the maximum impact of chemotherapy by selective or super-selective injection of tumor vessels by chemotherapeutic agents and reducing the tumoral blood flow by the embolization of particles resulting in prolonged contact of the tumor with the chemotherapeutic agents [8].

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CT is still the examination of choice to follow-up patients being performed immediately after the TACE procedure to ensure the retention of lipidol by the tumor. It is repeated 1 month later for the detection of any tumoral residue or recurrence [5].

A diagnostic dilemma due to defective accumulation of lipidol either due to necrotic areas or residual tumor is still faced by radiologists. Also the hyperattenuating retained lipidol causes hardening artifact which degrades the interpretation of images [6].

Magnetic Resonance Imaging (MRI) of the liver is slowly transitioning from a problem solving imaging modality to a first line imaging modality for many diseases of the liver. The well established advantages of MRI over other cross sectional imaging modalities may be the basis for this transition. Technological advancements in MRI that focus on producing high quality images and fast imaging, increasing diagnostic accuracy and developing newer function-specific contrast agents are essential in ensuring that MRI succeeds as a first line imaging modality [7].

Aim of the work:
The purpose of this study is to emphasis the role of dynamic contrast enhanced MRI in follow-up of patients with hepatocellular carcinoma after trans-catheter arterial chemoembolization.

Patients and Methods
Twenty five patients with hepatocellular carcinoma and underwent TACE were included in this study. The study was performed between May 2014 and November 2014. The study was conducted in the National Cancer Institute and a private Radiology Center.

Inclusion criteria:
Patient known to have hepatocellular carcinoma lesions underwent TACE.

Exclusion criteria:
Contraindications to MRI, e.g. claustrophobia, cardiac pacemakers.
Tumors other than hepatocellular carcinoma.

The patients were subjected to the following:
Full clinical assessment including age, sex and clinical presentation.
Laboratory investigations (liver biochemical profile, alpha fetoprotein).

Abdominal MRI (dynamic post contrast study and diffusion weighted imaging).

MRI examination:
Conventional MRI, post Gd-DTPA dynamic and diffusion MR imaging were performed. First blind characterization and detection of embolized focal lesions was performed, second the diffusion images with ADC values were reviewed. Then characterizing the enhancement pattern of the focal lesions was detected. MR imaging was performed on high field system (1.5 Tesla) magnet units (Achieva) using a phased array coil to cover the whole liver.

A- Pre-contrast imaging included:
T1 weighted (T1W) images: Repetition time (TR)=10msec, echo time (TE)=4.58msec, matrix 179/320, slice thickness 7-8mm, slice gap 1-2mm, and FOV: 355mm.

T2 weighted (T2W) images (single shot free breathing): TR $445ms, TE=26-28msec, matrix 180-200 X 240 with a field of view: 365mm, slice thickness 7-8mm, slice gap 1-2mm.

T2 SPAIR (Spectral Attenuated Inversion Recovery) fat suppression sequence: TR $400msec, TE=80msec, matrix 204 X 384 with a field of view: 365mm, slice thickness 7-8mm, slice gap 1-2mm.

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In-phase and out-phase gradient echo sequence (Dual/FFE): TR=75-100msec, TE=4.6msec for in phase and 2.3msec for out phase, matrix 143 X 240 with a field of view: 345mm, slice thickness 7-8mm, slice gap 0mm.

Heavy T2 weighted images: TR=520msec, TE=200msec, matrix 235/384 with a field of view: 375mm, slice thickness 7-8mm, slice gap 1-2mm.

B- Dynamic study:
Dynamic study was performed after bolus injection of 0.1 mmol/kg body weight of Gd-DTPA at a rate of 2ml/s, flushed with 20ml of sterile 0.9% saline solution from the antecubital vein. The injection of contrast media and saline solution was performed manually. Dynamic imaging using T1 THRIVE (High Resolution Isotropic Volume Examination) technique was performed in triphasic way [arterial phase (16-20 sec.), porto-venous phase (45-60sec.) and delayed equilibrium phase (3-5min.)] after administration of contrast media.

C- Diffusion study:
Respiratory-triggered fat-suppressed single-shot echoplanar DW imaging was performed in
the transverse plane with tri-directional diffusion gradients by using $b$-values 0, 500 & 1000 sec/mm$^2$ to increase sensitivity to cellular packing. Parallel imaging with Generalized Auto-calibrating Partially Parallel Acquisition (GRAPPA) with an acceleration factor of two was applied to improve image quality. The other parameters were as follows: Repetition time (TR) ≥ 1880 msec, echo time (TE) = 70 msec, number of excitations (NEX)=3, matrix 256 X 256 with a field of view as small as possible with 52% rectangular field of view, slice thickness 7-8 mm, slice gap 1-2 mm, scan time 3-4 min.

**Analysis of the MR images:**

Images were sent to the workstation for further image processing. The morphological features of each lesion were recorded including size, border and signal intensity at T1, T2, and SPAIR images. Assessment for the presence of complications, residual or recurrent tumor viability.

**Dynamic study analysis:**

We perform arterial and portal phase subtraction which is automated process available on the workstation.

Color coded perfusion mapping is then performed which includes relative enhancement and maximum relative enhancement.

**Quantitative diffusion analysis (ADC measurement):**

ADC maps were generated on the workstation. Calculation of the ADC value is an automated process available on the workstation.

The ROI included the embolized focal lesion area.

Another area of 2 cm diameter in the surrounding cirrhotic liver parenchyma was also measured in each case.

In case of focal hyperintensity within or at the margins of the embolized lesion; its ADC value was calculated.

The ADC was measured three times and the three measurements were averaged.

**Interpretation of the MR image:**

- Signal of the embolized lesion at T1, T2, SPAIR and DWIs was classified as: High, low or heterogeneous.
- Dynamic study interpretation:
  1. Arterial phase enhancement: That should be confirmed by the subtraction images and color map (to prove that the high signal in the arterial phase is due to enhancement and not due to the original precontrast high T1 signal).

2. Contrast wash-out: Decrease in the enhancement on delayed phase imaging compared with early phase imaging.

3. Presence of ill-defined peri-lesional parenchymal enhancement: Post interventional reactive changes: This is defined as early phase enhancement beyond the embolized lesion on the surrounding liver parenchyma that persists in the delayed phase.

4. Well defined enhancement at the margin of the embolized lesion which may be either: Granulation tissue rim: Persistent or delayed phase enhancement.

Nodular or hallow enhancement: That suggest tumor recurrence.

**We categorize the patients into two groups:**

- Resolved group: No MRI signs of residual or recurrent viability (regardless the presence of newly developed lesions).
- Unresolved group: If there's evidence of residual or recurrent tumor.

**Standard of reference:**

It was difficult to obtain pathologic confirmation in patients who underwent chemoembolization because most of these patients do not undergo surgery. In addition, biopsy may result in sampling error as recurrent lesions are mostly small nodules.

So, the standard of reference was:

Benign findings (resolved lesions) are considered if:

- Focal area at the margin of the embolized lesion that shows early or late arterial phase enhancement that must be proved by the subtraction and color map images.
- Contrast wash out: The lesion becomes hypointense relative to the liver parenchyma in the delayed phase.
- Diffusion hyperintensity (restriction) and low ADC value (<1.05 X 10$^{-3}$ mm$^2$/s).
- Increased serum AFP levels in the follow-up laboratory studies.

Residual/recurrent HCC (unresolved lesions) is considered if:

- Focal area at the margin of the embolized lesion that shows early or late arterial phase enhancement
that must be proved by the subtraction and color map images.

Contrast wash out: The lesion becomes hypointense relative to the liver parenchyma in the delayed phase.

Diffusion hyperintensity (restriction) and low ADC value (≤1.05 × 10⁻³ mm²/s).

Increased serum AFP levels in the follow-up laboratory studies.

Results

Twenty-five patients were included in this study, 23 males (92%) and 2 females (8%). The patients’ age was ranging from 48 to 68 years with the mean age of 57.7 years. 22 patients (88%) were above or equal 50 years while only 3 patients (12%) were below 50 years old.

There were 15 patients (60%) with a single embolized lesion and 10 patients (40%) with multiple embolized lesions. 48% of the embolized lesions were above or equal 4cm, while 52% were below 4cm.

76% of the embolized lesions were eliciting bright T1 signal intensity while 24% were eliciting dark T1 signal intensity, while 44% were eliciting bright T2 signal intensity and 56% were eliciting dark T2 signal intensity.

52% of the embolized lesions showed enhancing areas within in the arterial phase (residual/recurrence), 28% were not enhanced while 20% showed delayed marginal enhancement.

MRI reading reveals that 52% of the embolized lesions were unresolved lesions (residual/recurrence). This was supported by elevated serum AFP level.

MRI reading shows 48% were resolved (well embolized). This was supported by decrease serum AFP level as well as absence of further progression in size or development of pathological enhancement on follow-up MRI studies after 3 months.

Apart from the embolized lesions, 56% of cases (14 patients) showed newly developed lesions while 44% (11 patients) didn’t.

In 18 cases (72%) the portal vein was patent while it was thrombosed in 7 cases (28%). 5 cases of the thrombosed portal vein were malignant thrombosis.

The cases with unresolved lesions show areas of diffusion restriction. 5 false positive cases were misdiagnosed on diffusion weighted imaging and when we reviewed the corresponding pattern of diffusion restriction we found that the true positive cases showed focal peripheral nodular restriction, while the false positive cases showed intralesional heterogeneous restriction. So, we considered that the increase in false positive findings in our study is likely originating from intralesional hemorrhage or liquefactive necrosis that causes diffusion restriction.

The probability of presence of residual or recurrent lesions after chemoembolization increases with the increase in the size of the embolized lesions, as shown in the graph below.

Dynamic MRI study had a sensitivity of 90.5%, a specificity of 96.6%, a positive predictive value of 95%, a negative predictive value of 93.3% and an overall agreement of 94%.
Cases:

Fig. (1): (A-B) T1 and T2 sequences showing the embolized lesion at segment IVa with high signal intensity, (C) Arterial subtraction phase showing the lesion with no enhancement, (D) Delayed phase showing the lesion with marginal enhancement (representing reactive tissue changes).
Fig. (2): (A-B) The embolized lesion at segment VIII is eliciting bright T1 and iso-intense T2 signal intensity respectively, (C-D) The lesion is showing contrast uptake in the arterial phase with gradual partial washout in the delayed phase, (E) The lesion shows bright signal on DWI.
Fig. (3): (A-D) T1, T2, arterial, and delayed phases showing the embolized lesion at segment III with high T1, Low T2 with no contrast uptake in arterial or delayed phases. (E-F-G-H-I) T1, T2, arterial phase, delayed phase, and DWIs showing the smaller embolized lesion at segment VII/VIII with small component along its anterior aspect that shows contrast uptake in the arterial phase that washed out in the delayed phase and showed diffusion restriction in the diffusion sequence (arrows).
Role of Dynamic Contrast-Enhanced MRI in Follow-Up of Patients with HCC

Discussion

Correct detection, classification, and characterization of hepatic focal lesions are of paramount importance as they may significantly affect the choice of therapeutic approach in many cases [8].

Monitoring tumor response to loco-regional therapy is an increasingly important task in oncologic imaging. Early favorable response generally indicates effectiveness of therapy, and may result in significant survival benefit. Early identification of treatment failure is also critical in patient management, since a repeat treatment cycle can be performed if liver function is maintained, before disease progression occurs [9].

Authors stated that the successful tumoral treatment after TACE results in diminished blood supply with subsequent diminished tissue fluid. Thus the typical post treatment appearance is high signal intensity on T1-weighted images and low signal intensity on T2-weighted images [10].

In this study, 15 patients (60%) were having single embolized lesion while 10 patients (40%) were having multiple embolized lesions. 48% of the embolized lesions were above or equal 4cm, while 52% were below 4cm. The study found that (48%) of the patients (resolved group) showed no MRI evidence of residual or recurrent viability at the embolized lesions while (52%) of them (unresolved group) showed evidence of residual or recurrent viability compared to (50%) complete tumor ablation and (50%) local recurrence that Satoh et al., reported in 2008 [11].

The signal intensity of the embolized lesion in the non-enhanced T1 and in the T2 weighted images was studied and we found that 76% of the embolized lesions were eliciting bright T1 signal intensity while 24% were eliciting dark T1 signal intensity, while 44% were eliciting bright T2 signal intensity and 56% were eliciting dark T2 signal intensity. [12] found in a corresponding similar study that HCC lesions eliciting bright T1 signal intensity post chemoembolization were 74.2% while only 33% were eliciting bright T2 signal intensity.

The study found that almost all of the embolized lesions in the unresolved group of patients (residual/recurrence) showed enhancing areas within in the arterial phase. The study also found that 58% of the embolized lesions in the resolved group of patients (complete tumor ablation) were not enhanced at all while 42% of them showed delayed marginal enhancement. This is more or less similar to what [13] reported in 2009 where residual tumor showed homogeneous or heterogeneous rapid enhancement on the arterial phase images while the necrotic tumoral area following TACE did not show enhancement on contrast-enhanced series and that was conclusive that enhancing portions of the tumor are presumed to be viable. In addition, an enhancing rim that reflects either viable tumor or reactive tissue can appear on contrast-enhanced images. And because of this hyperintense ring appearing in the late phases of dynamic series, it can be difficult to detect small residual areas located in the capsule, and this explains the 42% of the embolized lesions in the resolved group of patients in this study that showed delayed marginal enhancement; hence the importance of complementing the dynamic contrast enhanced study with the arterial subtraction phases and also with the diffusion weighted sequences.

In the experience of Kim et al., [14] image subtraction was helpful for the assessment of the therapeutic efficacy for HCC by TACE in HCCs, which makes the depiction of tumor enhancement difficult on post-contrast T1-weighted images. Accordingly, to accurately assess tumor enhancement, we used the image subtraction techniques as well as color mapping images.

Apart from the embolized lesions, 56% of cases (14 patients) showed newly developed lesions while 44% (11 patients) didn't.

Diffusion-weighted imaging gives an insight about water content within the tumor and the degree of its viability. The viable tumor cells have intact membranes that cause restricted diffusion whereas necrotic tumors have increased water diffusion due to disruption of the cell membrane [15,16].

Yu et al., [17] found that DWI increased the sensitivity for the detection of post TACE residual HCC with increased false positives. Thus, the decreased specificity compromised the increased sensitivity gained by DWI and decreased the overall diagnostic accuracy. They referred the increase in false positive findings to peri-lesional parenchymal insults. They demonstrated that hypercellularity intermingled with a fibrotic content in the inflammatory granulation tissue could cause restricted diffusion.

In our study, 5 false positive cases were misdiagnosed on diffusion weighted imaging. They exhibited intra lesional heterogeneous restriction and likely originating from intra lesional hemorrhage or liquefactive necrosis that causes diffusion restriction. In the studies of Holtas et al., Tung et al., Batra et al., [18-20] sterile liquefactive necrosis
and intracavitary microhaemorrhage are accepted to be the cause of hyperintensity in diffusion-weighted MR images of malignant necrotic lesions. Diffusion weighted MRI has some advantages compared to dynamic MRI. First, contrast medium administration is not required, and the examination is obtained in a relatively short time. Second, the technique is easy to be repeated, allowing close follow-up during and after tumor treatment. Also, image post-processing is less time-consuming compared to dynamic contrast-enhanced MR imaging. At last, diffusion-weighted MR imaging allows easy evaluation of the whole tumor. This is important because of the in homogeneity that may occur within tumors [21]. In addition, respiratory triggered diffusion weighted images compensated the false results by the dynamic MRI in our patients who could not hold their breath adequately.

Also vascular invasion into the portal vein was noticed in 7 cases (28%) while it was patent in 18 cases (72%) [22]. Reported that the incidence of malignant portal vein thrombosis in association with HCC ranges from 5% to 44% in which it demonstrates the same signal intensity and contrast enhancement pattern as the primary tumor.

So far MRI was found to be of great value in the follow-up of cases of HCC that underwent chemoembolization specially in diagnosing residual or recurrent tumor tissue in the embolized lesions and in detecting new developed lesions. This technique can be implemented simply and reliably. It offers the advantages of significantly shorter acquisition times, retrospective thin-or thick-section reconstruction from the same raw data, improved three-dimensional rendering, and high-quality liver imaging with high intrinsic soft-tissue contrast. It also provides a global overview of the abdomen. Its relative contraindications include renal impairment and sensitivity to IV contrast.

In our study, we had some diagnostic limitations. First relatively small number of patients, so future study with large number of patients would be recommended. Second, various time intervals between interventions and follow-up studies, which were determined by clinical practice and not the study design. Third, the lack of histologic proof in most cases, but this is also related to clinical practice where histology is not always indicated.

Conclusion:

MRI is a powerful tool in detection of tumor viability and complications after trans-catheter arterial chemoembolization of hepatocellular carcinoma. Imaging protocol should include dynamic study combined with diffusion imaging with post-processing of the images to obtain subtracted images, color mapping and ADC measurements for better tissue characterization and should be performed at regular time intervals.

References


