Focal Lesions in Cirrhotic Liver: Comparing MR Imaging During Arterial Portography with Gd-Enhanced Dynamic MR Imaging

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Abstract

The purpose of this study was to document the additional value of MR imaging during arterial portography (MRAP) in patients examined with intravenous contrast-enhanced dynamic MR imaging for the assessment of focal lesions in patients with cirrhosis or chronic viral hepatitis. The MR images of 24 patients with 39 hepatocellular carcinomas and 18 benign hepatocellular nodules examined with dynamic MR imaging and MRAP within a 14-day interval were retrospectively reviewed. For 39 hepatocellular carcinomas, MRAP revealed 37 perfusion defects (95%) while dynamic MR imaging demonstrated 35 occurrences of nodular contrast-enhancement (90%) on arterial dominant phases. Among the 11 benign nodules misinterpreted as hepatocellular carcinoma due to their high signal intensities on arterial-dominant phases of dynamic MR imaging, eight (73%) showed intratumoral portal venous perfusion on MRAP and were regarded as benign nodules. As a result of its high sensitivity and its potential ability to enable differentiation of benign and malignant hepatocellular nodules, MRAP can be added to dynamic MR imaging for planning future management in patients with equivocal hepatocellular nodules in the cirrhotic liver.

Key Words: Liver neoplasms, diagnosis; liver neoplasms, MR, comparative studies; portography

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver and it develops with underlying chronic liver disease, including cirrhosis or viral hepatitis in most patients.\(^1\) For imaging studies of a chronically-damaged liver, however, the regenerating nodules or dysplastic nodules should be differentiated from HCC, a malignant condition, for proper therapeutic planning or predicting the prognosis of patients. MR imaging during arterial portography (MRAP) was based on the same principle as CT arterial portography, allowing pure portal venous enhancement of the liver without arterial enhancement.\(^2\) Some recent reports have suggested that MRAP can also be used for the assessment of focal liver lesions with more homogenous parenchymal enhancement and higher sensitivity in the detection of liver tumors compared to CTAP.\(^3\)\(^-\)\(^6\) Meanwhile, intravenous contrast-enhanced dynamic MR imaging is highly sensitive and provides detailed study for hypervascular tumors including HCC.\(^7\)\(^-\)\(^11\) To our best knowledge, there has so far been no report regarding the usefulness of MRAP compared with dynamic MR imaging. We expected that we could determine more information for differential diagnosis of hepatocellular nodules related to chronic liver damages if MRAP was added to dynamic MR imaging. The purpose of this study was to document the additional value of MRAP for the assessment of hepatocellular nodules complicated with liver cirrhosis or chronic viral hepatitis by comparing the efficacy of MRAP to dynamic MR imaging in terms of lesion detection and characterization.

MATERIALS AND METHODS

Patients

Twenty-four patients (20 men and four women, 32–62 years old, mean age 50 years old) with he-
patocellular nodules examined with dynamic MR imaging underwent hepatic arteriography and subsequent MRAP during the same session. Hepatic angiography was performed for further study including preoperative evaluation or for chemoeembolization of malignant tumors. All patients had preexisting liver cirrhosis (n=17) or chronic viral hepatitis (n=7) verified by percutaneous needle biopsy (n=8) or serologic tests as well as imaging findings. The Child-Pugh classification of disease was A in 16 patients, B in six and C in two. There was no extrahepatic malignancy in any patients. Among the 24 patients, a total of 39 HCCs in 22 patients had been diagnosed by histology (n=8), by sustaining nodular uptake of iodized-oil on CT scans at 3-week or more intervals (n=26), or by growth of the tumor during subsequent follow-up periods (n=5). There were no nodules finally diagnosed as HCC in other two patients. Eighteen benign hepatocellular nodules were diagnosed in seven patients by histology (n=2), by no iodized-oil uptake (n=11) and/or by no size increase during 12–28 months follow-up imaging studies (n=16). Incidentally, five simple cysts were also diagnosed by surgery (n=1) and typical imaging findings (n=4), and one inflammatory granuloma was confirmed by surgery.

MR imaging

MR images were obtained with a 1.5-T whole body imager (Magnetom Vision; Siemens, Erlangen, Germany). After obtaining T2-weighted turbo spin-echo images (TR/TE, 3,540–4,000/138; echo train length, 29) and unenhanced T1-weighted fast low-angle shot (FLASH) images (TR/TE=113–130/4.1, flip angle=80 degree), dynamic MR imaging was performed at 10, 35, 60 seconds and 5 minutes after a bolus injection of 0.1 mmol/kg gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) through the FLASH technique with the same parameters. Contrast agent was manually injected and the speed of injection was approximately 3–4 mL/sec. A four-element phased-array multi-coil was used to improve the signal-to-noise ratio, and all images were obtained in the axial plane. Automated shimming was performed in each examination to maximize magnetic-field homogeneity. A total of 12–15 sections were acquired with an 8 mm or 10 mm section thickness and a 1.6 mm or 2.0 mm intersection gap, so that the liver could be imaged in all patients with a single acquisition during each breath-holding period. Duration of signal acquisition was 16–18 sec in each phase.

For MRAP, the nature of the procedure was explained and informed consent was obtained from all patients and their family members. The time interval between the dynamic MR imaging and MRAP was 1 to 14 days (mean, 9.4 days). After performing hepatic arteriography, an angiographic catheter (5-French, 75 cm) was placed in the superior mesenteric artery (n=8) or splenic artery (n=16) and connected to a 100-cm-long tube to avoid changing the patient’s position during the MR study. MRAP was performed using the same sequence and same parameters as the previously-performed dynamic MR imaging. The contrast solution of 0.1 mmol/kg gadopentetate dimeglumine was diluted with normal saline in a syringe to make a total volume of 20 ml. Injection was performed manually, continuing for 25–30 sec, followed by flushing with normal saline in all cases. With the start of contrast injection into the angiographic catheter as the zero point, three sets of MRAP images were obtained serially at 20, 45, and 70 sec.

Image analysis

Determination of the number of focal hepatic lesions and the differential diagnosis of each lesion were made in conference by two observers who were unaware of the findings of other imaging data. A set of dynamic MR images with static T1- and T2-weighted images was evaluated for each patient during the first reading session, while the location, number and signal characteristics of the lesions were documented. The purpose of comparing static T1- and T2-weighted images was for the determination of benign nodules including hepatic cysts and hemangioma, and for the exclusion of pseudolesions. One criterion used for the detection of HCC on dynamic MR imaging was the high, nodular signal intensity distinguished from the surrounding liver parenchyma during the arterial dominant phases (Fig. 1). The location and number of enhancing nodules were recorded. After 7 days, another set of MRAP with static T1- and T2-weighted images was evaluated during the second reading session. We determined that a lesion existed if a nodular, wedge- or ring-
shaped perfusion defect was revealed on the image with the best enhancement of liver parenchyma among the three phases of MRAP (Fig. 1 and 2). The location and number of perfusion defects were also measured. Finally, the pathologic findings of the surgical specimens (n=6) combined with intraoperative sonography, hepatic angiography and follow-up studies, including iodized-oil CT of nonsurgical cases (n=18), were compared with the dynamic MR imaging and MRAP images for lesion-by-lesion analysis in a joint reading session seven days after the second reading session.

The focal lesion on dynamic MR imaging or MRAP was regarded as a true hepatocellular carcinoma only if it corresponded in location to a lesion found on the pathologic specimen, focus of iodized-oil uptake, or a growing tumor on the follow-up imaging studies. We also measured the maximum perpendicular diameter
of perfusion defects on MRAP and enhancing nodules on arterial-dominant phase of dynamic MR imaging for the lesions simultaneously detected by both techniques using electronic calipers. If there had been no abnormal signals on the corresponding areas of static T1 and T2-weighted images and no evidence of focal lesions on follow-up imaging studies, an area of transient perfusion defect on MRAP or transient contrast enhancement on dynamic MR imaging was regarded as a pseudolesion from a focal perfusional variation.

Statistical analysis

The McNemar test for paired data was used for statistical analysis of the detection rate of hepatocellular carcinoma in the two imaging techniques. The paired t-test was used to compare the size of the enhancing nodules on dynamic MR imaging with that of the perfusion defects on MRAP. A p value of less
than .05 was considered to indicate a statistically significant difference.

RESULTS

Compared to the surrounding liver parenchyma, the signal intensities of 39 HCCs on static T1-weighted MR imaging were as follows; low, n=21; iso, n=8; high, n=10. T2-weighted images showed high signal intensity for 23 HCCs, iso for 14 and low for two. A thin, circumferential marginal enhancement suggesting the fibrotic pseudocapsule was visualized in 13 tumors (33%) on 5-minute delay images after intravenous contrast injection.

The number of perfusion defects on MRAP and high signal intensity lesions on early phases of dynamic MR imaging are listed in Table 1. Thirty-five (90%) out of a total 39 HCCs were demonstrated as high signal intensity nodules at the arterial dominant phase of dynamic MR imaging. MRAP demonstrated 37 HCCs (95%) as a perfusion defect distinguished from surrounding liver parenchyma (Fig. 1 and 2). MRAP was superior to dynamic MR imaging in the ability of HCC detection, however, no statistically significant difference existed (\(p > .05\)).

For 34 HCCs synchronously detected by dynamic MR imaging and MRAP, the maximum diameter measured by electronic calipers was a mean 2.49 cm (range, 1.0–4.5 cm) on MRAP and 2.23 cm (range, 0.8–4.1 cm) on dynamic MR imaging. The size of perfusion defect on MRAP was larger than the area of contrast-enhancement on dynamic MR imaging (\(p < .0001\)) and the difference was 0.26±0.14 cm. Regarding HCCs with a fibrotic pseudocapsule (n=13), the maximum diameter was 2.92 cm on MRAP and 3.33±0.11 cm larger than 2.59 cm on dynamic MR imaging. The mean maximum diameter of HCCs without a pseudocapsule was 2.23 cm on MRAP and 2.01 cm on dynamic MR imaging with a 0.22±0.14 cm size discrepancy (\(p < .0001\)).

Eighteen nodules with high signal intensity on static T1-weighted images associated with iso or low signal intensity on T2-weighted images did not show any evidence of HCC on histology (n=2) and/or follow-up imaging studies (n=18). Eleven (61%) of the 18 nodules were demonstrated as high signal intensity nodules on the arterial dominant phase of dynamic MR imaging and were suggested as HCCs.

| Table 1. The Number of Perfusion Defects on MRAP and High Signal Intensity Lesions on Early Phases of Dynamic MR Imaging |
|--------------------------------------------------|-----------------|-----------------|
| Hepatocellular carcinoma (n=39)                 | 37              | 35              |
| Benign hepatocellular nodules (n=18)            | 3               | 11              |
| Simple cysts (n=5)                              | 5               | –               |
| Inflammatory granuloma (n=1)                    | 1               | –               |
| Pseudolesions from Focal Perfusion variation     | 11              | 6               |

Among these 11 nodules that were falsely interpreted as HCCs on dynamic MR imaging, eight nodules (73%) were totally perfused by portal flow on MRAP and the possibility of malignancy could be excluded (Fig. 3). Three (17%) of 18 benign nodules showed decreased perfusion on MRAP, and were suggested as HCC even in the combined interpretation of both imaging techniques (Fig. 4). Two of the three nodules were histologically confirmed as dysplastic nodules after percutaneous gun-needle biopsies. There was no discrepancy between the size measured on MRAP and the size on dynamic MR imaging for these three nodules (1.3–2.6 cm; mean, 2.0 cm).

Incidentally, five simple cysts were found in two patients with characteristic MR imaging findings, including very high signal intensity on T2-weighted imaging and no intratumoral vascular perfusion. One surgically-confirmed inflammatory granuloma was manifested as a perfusion defect on MRAP and enhancement on delayed contrast-enhanced MR imaging. There was no definite enhancement on the arterial dominant phase of dynamic MR imaging for this inflammatory mass. Five simple cysts and one inflammatory granuloma were demonstrated as perfusion defects on MRAP.

Eleven non-tumorous perfusion defects were found additionally on MRAP. There were no abnormal signals distinguished from surrounding liver parenchyma on static MR images and follow-up imaging studies on the corresponding region for perfusion defects and regarded as pseudolesions. Among them, four were found in the posterior aspect of the quadrate lobe and three of those corresponded to the contrast-enhanced portions on the arterial dominant phase of dynamic MR imaging (Fig. 1). Five perfusion...
Defects were correlated to the non-tumorous arterial-portal venous shunt found on hepatic arteriography, and three of them corresponded with the areas of contrast-enhancement on dynamic MR imaging. One perfusion defect adjacent to the gallbladder and one subcapsular perfusion defect on the posterior aspect of the porta hepatis were also revealed on MRAP without any abnormal contrast-enhancement on dynamic MR imaging.

**DISCUSSION**

MR imaging has been used to improve the identification and characterization of focal hepatic lesions in the chronically-damaged liver, and rapidly advancing technology has expanded its use. Previous studies related to static MR imaging findings, however, have shown that there are many overlaps between small HCCs and dysplastic nodules depending on their cellular differentiation. Since the introduction of high resolution, fast T1-weighted imaging technique, dynamic contrast-enhanced imaging has become possible, resulting in higher detection rates and easier tumor characterization. Generally speaking, in high-risk patients (such as liver cirrhosis or chronic hepatitis) for hepatocellular carcinomas, hepatocellular nodules with contrast enhancement
during the arterial phase of dynamic MR imaging that have also been detected in unenhanced T1 or T2-weighted images are regarded as hepatocellular carcinomas and actively managed by operation or local therapy. However, there are many lesions that cannot be definitely determined whether the nodule is truly contrast-enhanced or not during dynamic studies. Particularly for high signal intensity nodules on unenhanced T1-weighted images, there is difficulty in determining subtle contrast enhancement during the arterial dominant phases of dynamic MR imaging due to their inherently higher signal intensity distinguished from the surrounding hepatic parenchyma. In those cases, we hesitate to determine the future management schedule for nodular lesions. Sometimes we can obtain the percutaneous biopsy specimen, however, there can be a risk of sampling error and the diagnosis for borderline lesions is not always easy, even in the core biopsy.

Regarding the process of multistep development of hepatocellular carcinomas, we know about the stage of decreased hepatic arterial and portal venous branches in the nodule before the profound development of tumor vessels, e.g., unpaired arteries. With reference to previous studies including ours, MRAP can detect the decrease of portal venous flow.
in the nodule more sensitively than CTAP can.\textsuperscript{5,6} During that stage, there would be no contrast enhancement on the dynamic MR imaging while the nodules are manifested as a perfusion defect during MRAP. MRAP can perform a role by disclosing the decreased portal flow in the malignant or potentially-malignant nodules. In some benign nodules with high signal intensities on dynamic MR imaging, however, the intralocal portal flow was decreased and could not be differentiated from HCC.

Kanematsu et al reported that the size of a malignant focal lesion of the liver was overestimated on CTAP, and the major mechanism was explained and verified as compromised portal venous flow in the compressed peritumoral liver parenchyma from expansile tumor growth.\textsuperscript{19,20} For HCCs synchronously found by both imaging techniques, the size of perfusion defects on MRAP were significantly greater than the size of high signal intensity on dynamic MR imaging, whether the nodules had fibrotic pseudocapsules or not. For cases of inherently high signal intensity nodules on unenhanced T1-weighted images, the ring-shaped peritumoral perfusion defect resulted in overestimation of the tumor size and was helpful for characterization of HCCs despite the weak of lesion-to-liver contrast during MRAP (Fig. 2). On the contrary, there was no size discrepancy between MRAP and dynamic MR imaging for the few benign hepatocellular nodules that had not been distinguished from HCCs by two imaging techniques.

Regarding the non-tumorous hepatic perfusion abnormalities on contrast enhanced CT or MR imaging, the mechanism of these pseudolesions have been verified and speculated upon by many investigators.\textsuperscript{21-25} In this study, the number of pseudolesions manifested as perfusion defects on MRAP was greater than that of the enhancing pseudolesions on dynamic MR imaging. Even for pseudolesions, MRAP was more sensitive than CTAP, and the cause of the lower sensitivity of dynamic MR imaging may possibly be explained by its missing the narrow, variable time windows for optimal timing to make a contrast. Contrast agents are introduced selectively for the hepatic artery during arteriography and for the splenic or superior mesenteric artery during MRAP. Basically, the hepatic artery is not perfused during MRAP and the portal vein is not perfused during hepatic arteriography. On dynamic MR imaging, there may be a chance to mask the contrast between the area of arterial hyperperfusion and surrounding liver by subsequent portal venous inflow of the surrounding liver parenchyma.

Our study had several limitations. Since the subjects were not considered for liver transplantation, the appropriate histological confirmation of all nodules was not possible. And there is no single “gold standard” to diagnose the nature of the lesions, and for the nodules with no histological proof, a combination of follow-up imaging studies and iodized-oil CT was used to determine the nature of the lesions. It is possible that those lesions diagnosed as HCC may be hepatocellular adenoma, focal nodular hyperplasia or hemangioma. Hepatocellular adenoma or focal nodular hyperplasia, however, is extremely rare in Korea, and hemangioma can be easily characterized on the static image. As well, there was no evidence of extrahepatic malignancy in any subjected patients during the period of this study. Meanwhile, Korea is one of the endemic areas for hepatitis B virus (HBV), a well known risk factor for HCC. With widespread employment of screening programs for high-risk patients, however, a great number of new cases are being identified at an earlier stage than in the past. During the period of screening studies for high-risk patients, newly-developed lesions on ultrasonography and/or on CT used to be subjected to MR imaging studies. Arterial enhancement and delayed washout on dynamic CT or MR imaging, tumor vasculature and tumor staining on hepatic arteriography, and nodular lipiodol-uptake on follow-up CT scans were generally regarded as highly-suggestive findings for newly-developed or newly-found HCCs in high-risk patients. A significantly elevated serum alpha FP level is also helpful.

Regarding the benign nodules which we suggested as regenerating or dysplastic nodules, we could also not get histologic specimens in many cases. Practically, without resecting the whole specimen, the histologic confirmation of benign or precancerous hepatocellular nodules is still controversial even for experienced pathologists. Sampling error during needle biopsy of small lesions can also be problematic. There were only two histologically-proven dysplastic nodules regarded as premalignant lesions. For 16 benign nodules, there was no size increase during a 12–28 months follow-up period, which suggested benign hepatocellular nodules accompanied with well-known static MR imaging findings of benign
nODULES AND NO NODULAR IODIZED-OIL UPTAKE AFTER CHEMOEMBOLIZATION FOR INVOLVED SEGMENT. REGARDING PSEUDOLESIONS, WE REFERRED TO CONVENTIONAL MR IMAGES, CT SCANS, SONOGRAMS, OR ANGI OGRAMS TO CONFIRM THE ABSENCE OF A TRUE LESION IN THE CORRESPONDING AREA.

FOR MEASUREMENT OF LESION SIZE, ERRORS ON MR IMAGES ARE INEVITABLE, EVEN THOUGH BOTH MRAP AND DYNAMIC MR IMAGES WERE OBTAINED WITHIN A SHORT INTERVAL OF UP TO 14 DAYS WITH THE SAME SCAN AND PARAMETERS. BECAUSE OF THE VARIABILITY OF SIGNAL INTENSITIES ON UNENHANCED T1-WEIGHTED IMAGES AND/OR POOR CONSPICUITY OF THE LESIONS ON FAST T2-WEIGHTED IMAGES, THE SIZE OF THE NODULES ON THE STATIC IMAGES WAS NOT READILY MEASURABLE, AND THE REAL SIZE OF THE LESION COULD NOT BE DETERMINED.

IN CONCLUSION, DESPITE LIMITATIONS IN THIS STUDY, MULTIPHASE MRAP READILY DETECTED HCC THROUGH THE HIGH SENSITIVITY FOR DECREASED PORTAL FLOW. ESPECIALLY FOR NODULES WITH HIGH SIGNAL INTENSITY ON STATIC T1-WEIGHTED IMAGING, WHICH CANNOT BE READILY ASSESSED BY DYNAMIC MR IMAGING, MRAP HAS THE POTENTIAL FOR CHARACTERIZATION OF NODULES THROUGH THE EVALUATION OF INTRASOLEAL PORTAL FLOWS. THE LARGER SIZE OF NODULES MEASURED ON MRAP COMPARED TO THE SIZE MEASURED ON DYNAMIC MR IMAGING CAN BE HELPFUL IN THE DIAGNOSIS OF MALIGNANCY. WE KNOW THAT ONE OF THE MAJOR PURPOSES OF CLOSE FOLLOW-UP FOR PATIENTS OF LIVER CIRRHOSIS OR CHRONIC HEPATITIS IS THE EARLY DETECTION OF NEWLY DEVELOPING MALIGNANCY. FOR THIS REASON, MRAP CAN BE AN ADDITIONAL METHOD FOR THE EARLY DETECTION OF HEPATOCELLULAR NODULES WITH HIGHLY MALIGNANT POTENTIAL.

REFERENCES


