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Evaluation of Early-Stage Hepatocellular Carcinoma by Magnetic Resonance Imaging With Gadoxetic Acid Detects Additional Lesions and Increases Overall Survival

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See editorial on page 1274.

BACKGROUND & AIMS: Hepatocellular carcinoma (HCC) has a high rate of intrahepatic recurrence after curative treatment, possibly because metastases are not always identified before treatment. Magnetic resonance (MR) imaging with a liver-specific contrast agent, gadoxetic acid, can detect small HCCs with high levels of sensitivity. We investigated whether MR imaging with gadoxetic acid increases overall and recurrence-free survival of patients initially assessed by computed tomography (CT). **METHODS:** We performed a retrospective study of data from 700 patients diagnosed with a single-nodular HCC by dynamic 4-phase CT in Seoul, Korea, from January 2009 through December 2010. Of these patients, 323 underwent additional evaluation with gadoxetic acid–enhanced MR imaging (CT+MR group). The 377 patients who did not undergo MR imaging analysis are referred to as the CT group. **RESULTS:** The CT and CT+MR groups were comparable in most baseline characteristics (Child–Pugh class A, 93.1% vs 94.7%; and median size of the primary HCCs, 2.8 vs 2.6 cm, respectively). Seventy-four additional HCC nodules were detected in 53 (16.4%) of the patients who underwent MR evaluation after CT (CT+MR group). These detections increased the Barcelona Clinic Liver Cancer stages for 43 patients (13.3%) and modified their treatment plans. On multivariable analyses, the CT+MR group had a significantly lower rate of HCC recurrence (hazard ratio [HR], 0.72; 95% confidence interval [CI], 0.54–0.96) and lower overall mortality (HR, 0.65; 95% CI, 0.44–0.96) than the CT group. In an analysis of 285 pairs of patients matched on the basis of the propensity score, the CT+MR group had significantly lower overall mortality (HR, 0.66; 95% CI, 0.44−0.99). **CONCLUSIONS:** Among patients who underwent dynamic CT analysis of a single-nodular HCC, additional evaluation by MR imaging with gadoxetic acid led to the detection of additional HCC nodules in 16% of patients, reduced the risk of disease recurrence, and decreased overall mortality.

Keywords: BCLC; Gadoxetic Acid; Liver Cancer; Combined Image Analyses.

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Hepatocellular carcinoma (HCC) is the sixth most common cancer and the second largest cause of cancer mortality in the world.[1,2] The incidence of HCC has increased rapidly in Western countries[3] and is expected to increase further in the next decade.[4,5] The implementation of surveillance programs for the early detection of HCC in high-risk populations and improvements in treatment modalities have increased the likelihood of curative treatment.[6–8] However, the prognosis still is poor, even after curative treatment, mainly because of the high rate of intrahepatic recurrence.[9,10]

Early intrahepatic recurrence of HCC after curative treatment may represent metastasis of the primary tumor that was undetected before the primary treatment.[9–11] Thus, accurate assessment of tumor extent before treatment is critical for reducing recurrence as well as for defining the HCC stage and treatment strategy. A standard intrahepatic work-up before treatment of HCC includes dynamic 4-phase computed tomography (CT) and/or magnetic resonance (MR) imaging using extracellular contrast agents.[12–14] However, the sensitivity of these imaging techniques are only approximately 60% for nodules 2 cm or smaller.[15–18]

Gadolinium ethoxybenzyl dimeglumine (gadoxetic acid) is a liver-specific contrast agent for MR imaging that has combined perfusion- and hepatocyte-specific properties. Its high hepatocytic uptake improves lesion detection by increasing liver-to-lesion conspicuity in hepatobiliary phase images.[19–21] Gadoxetic acid–enhanced MR imaging generally

Abbreviations used in this paper: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CT, computed tomography; HCC, hepatocellular carcinoma; HR, hazard ratio; IPTW, inverse probability treatment weighting; MR, magnetic resonance; PH, proportional hazard.

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is superior to dynamic CT or MR imaging enhanced by other types of contrast agents for the detection and characterization of liver lesions.[22–31] When compared with dynamic CT, gadoxetic acid–enhanced MR imaging shows an approximately 15% to 25% increase in sensitivity for the detection of HCC lesions.[21,32–34] Thus, gadoxetic acid–enhanced MR images may be useful for the accurate assessment of patients who are being evaluated for curative-intent HCC treatment.[32] However, whether evaluation of early HCC with gadoxetic acid–enhanced MR imaging would improve the clinical outcome of patients compared with that of a conventional evaluation with dynamic CT or MR images is unknown.

In this cohort study, we aimed to determine whether additional evaluations with MR imaging using a liver-specific contrast agent, gadoxetic acid, would improve the overall and recurrence-free survival of patients who initially were assessed to have a single-nodular HCC by dynamic 4-phase CT imaging.

Patients and Methods

Study Subjects

The study population was obtained from a historical cohort of 2647 consecutive patients who were diagnosed with HCC by dynamic CT imaging at Asan Medical Center, a 2700-bed academic tertiary referral hospital in Seoul, Korea, between January 2009 and December 2010 (Supplementary Figure 1). Of these, 1136 patients were assessed to have a single-nodular HCC by dynamic CT. Patients were excluded if they had any of the following criteria: age younger than 20 years or older than 80 years, Eastern Cooperative Oncology Group performance status scale higher than 2, Child–Turcotte–Pugh class C liver function, non–4-phase CT, findings not typical for HCC on dynamic CT images, or an interval between diagnosis and treatment that was longer than 4 weeks.

Gadoxetic acid first was introduced to our institution in July 2008, and gradually was incorporated into the MR imaging evaluation of HCC. In our institution, it was the general practice to check dynamic CT scans first for the initial diagnosis of HCC. For patients who were assumed to have a single-nodular HCC on CT images, our abdominal radiologists first began to recommend an additional check using gadoxetic acid–enhanced MR imaging before treatment. The strategy gradually was adopted by physicians and surgeons. Thus, the decision to check MR imaging before treatment was not based on patient characteristics but was a matter of protocol adoption. Since 2009, gadoxetic acid was virtually the only contrast agent used for MR imaging evaluations of HCC at our institution. During the study period, there was no change in the modality or method of management for HCC at our institution.

This study was approved by the Institutional Review Board of Asan Medical Center, and the requirement for informed consent from patients was waived.

Acquisition of CT and MR Images

The 4-phase dynamic CT images were taken as contiguous slices of 5-mm thickness with a multidetector spiral scanner using a dedicated liver protocol as described in our previous study.[35] CT scans were obtained with 64-multidetector CT scanners (GE Light Speed VCTXT; General Electric Medical Systems, Milwaukee, WI) in the unenhanced, arterial, portal, and delayed venous contrast-enhanced phases. Patients were given 2 mL/kg of iodine contrast intravenously at a rate of 4 mL/s via the antecubital vein. Arterial phase images were obtained using a bolus tracking technique with a trigger enhancement threshold at the upper abdominal aorta of 100 Hounsfield units with a diagnostic delay time of 25 seconds. Portal and delayed phase images were obtained at 72 and 180 seconds, respectively, after contrast injection. There has been no change in CT techniques or instrumentation since January 2009.

MR imaging was performed with a 1.5-T scanner (Magnetom Avanto; Siemens, Erlangen, Germany) with a 6-element, phased-array body coil. Gadoxetic acid (Primovist or Eovist; Bayer, Berlin, Germany) was administered using a power injector as a bolus at a dose of 0.025 mmol/kg (0.1 mL/kg) with a rate of 1 mL/s, followed by a 20-mL saline flush at the same flow rate. The peak time of the time-density curve to determine image acquisition timing was achieved using a test-bolus technique in which 1 mL of gadoxetic acid was injected with a saline flush, and the abdominal aorta was scanned once per second. Axial T1-weighted images of the arterial, portal, equilibrium, and hepatobiliary phases were obtained with a 4-mm slice thickness at 5 seconds, 60–70 seconds, 3 minutes, and 20 minutes after the peak time, respectively, after contrast injection.

Image Analysis and Diagnostic Criteria

All CT and MR images were interpreted as part of the routine clinical practice by board-certified abdominal radiologists with more than 5 years' experience in liver imaging using a picture archiving and communication system. Although the final diagnostic decision was left to the radiologist's judgment, they generally used the following predefined criteria of our institution, which have not changed since January 2009. The initial diagnosis of HCC was based on findings from dynamic 4-phase CT showing typical features of HCC (ie, a nodule >1 cm with arterial hypervascularity and portal- or delayed-phase washout).[12] Patients who had a secondary lesion showing typical features of HCC on CT images were excluded, whereas those with secondary indeterminate lesions were included. Most secondary indeterminate lesions were classified as selective arterial enhancement or selective portal or delayed washout.

The nodules additionally detected by gadoxetic acid–enhanced MR imaging were classified for the probability of being HCC. A definite HCC was defined as a nodule larger than 1 cm showing arterial enhancement and hypointensity in the portal or equilibrium phase. A probable HCC was defined as follows[28,36–38]: a nodule 1 cm or larger showing arterial enhancement and hypointensity in the hepatobiliary phase, a nodule 1 cm or larger showing arterial isointensity and hypointensity in both portal and hepatobiliary phases, a nodule 1 cm or larger showing arterial enhancement and T2 hyperintensity, a nodule 1 cm or larger showing T2 hyperintensity and hypointensity in both portal and hepatobiliary phases, or a nodule smaller than 1 cm showing arterial enhancement and hypointensity in both portal and hepatobiliary phases.

Outcomes and Follow-up Evaluation

The primary outcome measure of this study was all-cause mortality. The secondary outcome was recurrence of HCC after curative-intent treatments. The index date or zero-time was