Transformation of Non-hypervascular Hepatobiliary Phase Hypointense Hepatic Nodules into Hypervascular Hepatocellular Carcinomas: regular MR follow-up results

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Background: Non-hypervascular hepatic nodules showing hypointensity onhepatobiliary phase imaging (HBPI) in cirrhotic patientsare known to be premalignant.

Purpose: The risk oftransformation of non-hypervascular MR hepatobiliary phase imaging (HBPI) hypointense nodules into hypervascular hepatocellular carcinomas (HCCs) were evaluated.

Materials and Methods: Cirrhotic patients with non-hypervascular HBPI hypointense nodules were retrospectively analyzed if they were diagnosed as HCC and MR followed up longer than one year during the period starting from January 2010 to October 2016 with regular intervals of 3-6 months. Risk factors for the transformation into hypervascular HCCs were analyzed using the Cox proportional hazard model.

Results: Among the 103 nonhypervascular HBPI hypointense nodules meeting the inclusion criteria, transformation into hypervascular HCCs occurred in 44 tumors (42.7%). Median follow-up period was 24 months. Multivariate analysis revealed that hyperintensity on T2-weighted images (T2WI) or diffusion-weighted images (DWI) were the two independent predictors of transformation into hypervascular HCCs (*P*= 0.036 and 0.041, respectively). All 14 tumors with hyperintensity on T2WI or DWI were transformed into hypervascular HCCs, and the 1- and 2-year transformation rates were 64.3% and 92.9%, respectively. For the other 89 nodules without initial hyperintensity on T2WI or DWI, the 1-, 2-, and 3-year transformation rates were 9.0%, 26.0%, and 39.1%, respectively. During follow-up, 21 of 29 (72.4%) showing a new change on T2WI, DWI, or dynamic phases were transformed into hypervascular HCCs.

Conclusion: The transformation rates of HBPI hypointense nodules into hypervascular HCCs could be predicted according to the initial or serial MRI findings. It is not definite whether most HBPI hypointense nodules without initial hyperintensity on T2WI or DWI will be ultimately transformed into hypervascular HCCs.

Index Words: Liver Tumor, MR, Hepatocellular carcinoma, Malignant Transformation,

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide, and commonly occurs in patients at high risk for this disease, especially cirrhosis. As is well known, HCCs usually develop through the multistep process of hepatocarcinogenesis. In particular, high grade dysplastic nodules and pathologically early stage HCCs are known to be precursors of progressed HCCs, and can be regarded as borderline malignant nodules. In contrast to progressed HCCs, vascular invasion or intrahepatic metastasis is not likely to occur in these borderline malignant hepatic nodules. Therefore, detection of these hepatic nodules may play a role in reducing the possibility of tumor spread in cirrhotic patients.

A recent study showed that hepatobiliary phase images (HBPI) of gadoxetic acid-enhanced MRI was superior to MDCT or dynamic gadoxetic acid enhanced MRI in the detection of borderline malignant hepatic nodules. These nodules frequently appear as non-hypervascular hypointense nodules on HBPI owing to the decrease in or lack of uptake of gadoxetic acid, which is liver-specific MR contrast agent. Many of these precursor nodules are transformed into hypervascular HCCs during follow-up, and hyperintensity on T2 weighted or diffusion weighted MR imaging is known as a potent risk factor for the subsequent transformation. However, previous studies did not tell whether each non-hypervascular HBPI hypointense nodule will be eventually transformed into hypervascular HCCs, how fast the nodules will be transformed into hypervascular HCC, or whether additional survival benefits can be expected from the early treatment of non-hypervascular HBPI hypointense nodules. In this study, regular MR follow-up were made for these non-hypervascular HBPI hypointense hepatic nodules to evaluate the risk of transformation into hypervascular HCC nodules.

Materials and Methods

Patients

Our Institutional Review Board approved this study and the requirement for written informed consent was waived. The inclusion criteria for this study were as follows: a) cirrhotic patients who were diagnosed as HCC with Barcelona Clinic Liver Cancer (BCLC) stage A; b) those who underwent RFA or surgical resection as an initial treatment for the HCC nodules; c) patients with one or multiple non-hypervascular HBPI hypointense nodules up to five in number; d) those who underwent repetitive gadoxetic acid-enhanced liver MRI with regular intervals of six months or less; e) Patients were included in the analysis if initial MR work-up was done during the period from January 2010 to July 2015; and f) the overall MR follow-up period was longer than one year. Those patients with six or more hypovascular HBPI hypointense nodules were excluded from the analysis to minimize the effect of clustering on statistical tests.

The detailed indications for RFA or surgical resection of HCC at our institute are as follows: When the patients had a single nodular HCC or multiple nodules up to three, each less than or equal to 3cm, hepatic resection was considered as the first-line treatment modality. However, when surgical resection candidates showed clinically significant portal hypertension (i.e., presence of varices or splenomegaly associated with thrombocytopenia), we recommended RFA as an alternative treatment modality instead of hepatic resection. In addition, RFA was also performed based on the preference of patients against the strong recommendations for surgery by the clinicians. After May 2012, we considered RFA as the first-line treatment modality in patients with a single nodular HCC less than 2 cm in diameter according to the current practice guidelines.

Diagnosis of HCC

All patients initially underwent imaging studies, including gadoxetic acid-enhanced liver MRI and/or dynamic CT. The diagnosis of HCC was made using the noninvasive criteria defined by the American Association for the Study of Liver Disease (AASLD) recommendations, consisting of arterial hyper-enhancement with washout on portal or delayed phase images. In patients who did not meet the noninvasive diagnostic criteria, HCC diagnoses were made through liver biopsies with pathologic confirmation.

Acquisition of Gadoxetic Acid-enhanced Liver MR Imaging

Gadoxetic acid (Primovist®; Bayer Healthcare, Berlin, Germany) enhanced liver MRI was performed for the diagnosis and staging of HCCs in all patients. MR scans were performed by using a 1.5T (SignaHdxt, GE Medical Systems, Milwaukee, WI, USA) or a 3.0T (Skyra, Siemens Medical Solutions, Erlangen, Germany) superconducting system with an 8-channel (SignaHdxt) or a 32-channel (Skyra) phased-array coil. Our gadoxetic acid-enhanced liver MRI protocol consisted of a breath-hold T1-weighted dual-echo (in-phase and opposed-phase) gradient-echo (GRE) sequence, dynamic 3D fat-saturated T1-weighted GRE sequences, a breath-hold fat-saturated T2-weighted fast spin echo or turbo spin echo sequence (T2WI), a heavily T2-weighted single shot fast spin echo or single shot turbo spin echo sequence, and free-breathing diffusion weighted imaging (DWI) using a single shot echo planar imaging sequence. Dynamic 3D fat-saturated T1-weightedGRE sequences were performed both before and after administration of gadoxetic acid, which is a liver specific contrast media.

All patients received a rapid bolus of 1 ml/10 kg body weight (0.025 mmol/kg) of gadoxetic acid at a rate of 1.0 ml/s, immediately followed by a 25 ml saline flushing through an antecubital venous catheter using a power injector. Scanning delay times for arterial phase imaging after contrast administration was determined with real-time MR fluoroscopic monitoring. The arterial phase (AP) was scanned seven seconds after the contrast media had arrived at the distal thoracic aorta. And then, portal venous phase (PVP), early venous phase (EVP), late venous phase (LDP), and hepatobiliary phase (HBP) were subsequently scanned 50 seconds, 80 seconds, 2 minutes, and 20 minutes after starting the administration of contrast media, respectively. In order to evaluate the enhancement pattern of nodules on AP images, subtraction images were obtained by subtracting precontrast images from AP images. The slice thickness of the 3D-GRE sequence for postcontrast T1-weighted imaging at our institute was 3 mm.

Evaluation of MR images

All MR images were retrospectively and independently reviewed on a picture archiving and communication system workstation (Marosis, Marotech, Seoul, Korea) by two radiologists (HJC and YKC, with 10 and 5 years of experience in liver MRI, respectively). Both radiologists were blinded to the pathologic or clinical details. Non-hypervascular HBPI hypointense nodules were defined as solid nodules with low signal intensity on HBPI, which do not show higher signal intensity than that of the spleen on heavily T2-weighted images. Only HBPI hypointense nodules with the maximal diameter greater than or equal to 5mm were included in this study. This was based on a previous study that none of those nodules with the diameter less than 5 mm showed malignant transformation during the follow-up.² Hemangiomas or hepatic cysts were excluded from the study, which were determined based on their classic enhancement pattern or non-enhancement on dynamic phase images and hyperintensity on T2- and heavily T2-weighted MR images, respectively. To detect nonhypervascular HBPI hypointense nodules from the liver, reviewers evaluated the HBPI first, and then the AP images. When discordance in the imaging assessment was present between the two radiologists, consensus was made through discussion.

Statistical Analysis

Risk factors for the transformation into hypervascular HCCs were analyzed using univariate and multivariate Cox proportional hazard model. Potential risk factors included patient's age and sex, tumor size, hyperintensity on T2WI or DWI, multiplicity of HBPI hypointense nodules, baseline serum level of AFP, initial treatment modality for HCC, history of local therapy of hypervasucelar HCC nodules, Child-Pugh class, etiology of cirrhosis, and the existence of portal hypertension. *P*-values less than 0.05 were regarded as statistically

Results

Patients and Tumors

During the period from January 2010 to October 2016, 345 consecutive patients with HCC took repetitive MR examinations three or more times over one year. Among them, 103 non-hypervascular HB hypointense nodules in 60 patients were finally included in the study (Figure 1). The baseline patient and tumor characteristics are described in Table 1. The diagnosis of HCC was obtained based on the radiological findings in 33 patients, and by the pathological confirmation in the remaining patients. As an initial treatment, partial hepatectomy and RFA was performed in 27 and 33 patients, respectively. Major and minor resections were performed in 15 and 12 patients, respectively. The number of non-hypervascular hypointense hepatocellular nodules were one in 39 patients, two in nine patients; three in seven patients, four in three patients, and five in two patients. The mean and median size of a total of 103 non-hypervascular hypointense nodules were 8.5 ± 3.0 mm (range:5.0–17.0 mm) and 8.0 mm, respectively.

Malignant Transformation of HBPI Hypointense Hepatic Nodules

During a mean and median follow-up period of 27.9 ± 14.2 months and 23.5 months, 44 hypervascular HCCs (42.7%) developed in 27 patients among the 103 nonhypervascular hypointense hepatic nodules . The mean and median size of 44 nonhypervascular hypointense nodules that progressed into hypervascular HCC were 8.8 ± 3.2 mm (range: 5–16 mm) and 8.0 mm, respectively. For the other 59 non-hypervascular hypointense nodules that did not change into hypervascular HCC, the mean and median size were similar as 8.0 ± 2.8 mm (range: 5–17 mm) and 7.8 mm, respectively. The difference in the diameter between the nodules with or without malignant transformation was not statistically significant (*p* = 0.705). In addition, the mean and median size of the 44 hypervascular HCC transformed from pre-existing nonhypervascular hypointense nodules were 14.2 ± 3.6 mm and 13.3 mm, respectively. Median doubling time for the 44 tumors was 164.8 days during the last follow-up (range; 34- 507 days). Among the 23 tumors for which the median doubling times during the last follow-up were less than 180 days, 22 tumors (95.7%) were finally transformed into hypervascular HCC nodules.

Univariate and Multivariate Analysis of the Prognostic Factors for Transformation Univariate and multivariate analysis revealed that hyperintensity on T2WI or DWI were the two independently adverse predictors of transformation into hypervascular HCCs (*p*= 0.036 and 0.041, respectively). Other factors such as tumor size, initial treatment modality (resection or ablation) or the history of prior treatment of hypervascular HCC nodules were not statistically significant (Table 1). All 14 tumors with initial hyperintensity on T2WI and/or DWI were transformed into hypervascular HCCs during follow-up. For these 14 nodules, the 1- and 2-year transformation rates were 64.3% and 92.9%, respectively. The median times to the transformation into overt HCC were 8.0 months (95% CI; 3.1-12.9 months). As for the 89 nodules without initial hyperintensity on T2WI and/or DWI, the 1-, 2-, and 3-year transformation rates were 9.0%, 26.0%, and 39.1%, respectively. The median times to the transformation into overt HCC were 62.0 months (95% CI; 31.4-92.6 months). The difference in the transformation rates between the nodules with or without hyperintensity on T2WI and/or DWI was statistically significant (*p*< 0.001).

Serial Changes in the MRI findings during Follow-up

Among the 89 nodules without initial hyperintensity on T2WI or DWI, 12 tumors showed a new finding of hyperintensity on T2WI and/or DWI during regular MR follow-up. All the 12 tumors were transformed into hypervascular HCC, and the 1-year transformation rates after the appearance of such signal intensity changes was 91.7%. Median period was 8.0 months (95% CI; 6.6-9.4 months). During follow-up, 22 of the 89 nodules showed a new finding of hypointensity on PVI or EVP. Fourteen of the 22 nodules (63.6%) showed malignant transformation. Five of 14 nodules showed a new appearance of hyperintensity on T2WI and/or DWI before transformation into hypervascular HCCs. Among the 89 nodules, 18 nodules showed a new finding of hypointensity on EVP, and 11 of the 18 nodules showed malignant transformation. The 1-, 2-, and 3-year malignant transformation rates were 23.6%, 71.4%, and 71.4%, respectively. The median time to the transformation after the corresponding change was 19.3 months (95% CI; 17.4-20.6 months). During follow-up, eight of 87 nodules showed a new finding of hypointensity on PVP, and five of seven nodules showed malignant transformation 3, 6, 9, 20, and 21 months after the detection of corresponding signal intensity changes, respectively. The median time to the transformation after the corresponding change was 20.0 months (95% CI; 3.7-36.4 months). Sixty nodules without initial hyperintensity on T2WI and/or DWI did not show any MR signal intensity changes during follow-up. Only five of these 60 tumors showed malignant transformation. The 1-, 2-, and 3-year transformation rates in these tumors were 100%, 100%, and 87.5%, respectively. Overall, 35 of 44 (79.5%) transformation of non-hypervascular HB hypointense nodules into hypervascular HCC were associated with baseline or newly-appeared hyperintensity on T2WI and/or DWI, or with new signal intensity changes on PVP or EVP images.

Overall Survival and Recurrence After the Diagnosis of HCCs

During follow-up, 11 patients (18.3%) died owing to the following causes; liver failure (*n* = 4), progression of HCC (*n* = 6), and pneumonia (*n* = 1). For the 27 patients initially treated with surgical resection, the estimated 1-, 3-, and 5-year overall survival rates were 100%, 100%, and 87.5%, respectively. For the 33 patients initially treated with RFA, the estimated 1-, 3-, and 5-year overall survival rates were 100%, 87.2%, and 79.1%, respectively. The difference in the survival rates according o the initial treatment modalities was not statistically significant (*p*= 0.329). The percentage of patients with portal hypertension were 16.0% and 33.3% in patients initially treated by surgical resection or RFA, respectively (*p*= 0.127).

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