Natural history of nonenhancing lesions incidentally detected during the diagnosis of hepatocellular carcinoma

Kiyoko Ebisawa, MD,[a] Yutaka Midorikawa, MD, PhD,[a] Tokio Higaki, MD,[a] Hisashi Nakayama, MD, PhD,[a] Shingo Tsuji, PhD,[b] Haruna Nishimaki, MD,[c] Hiroki Haradome, MD, PhD,[d] Osamu Abe, MD, PhD,[d] Masahiko Sugitani, MD, PhD,[c] Mitsuhiko Moriyama, MD, PhD,[e] *and* **Tadatoshi Takayama, MD, PhD,[a]** *Tokyo, Japan*

Background. *Incidental detection of nonenhancing tumors during imaging studies for patients with classical hepatocellular carcinoma is not unusual. These tumors are considered to have a high potential of malignant transformation. The aim of this study was to clarify the natural history of such tumors.*
Methods. *In 93 patients who underwent liver resection for hepatocellular carcinoma, 138 nonenhancing or enhancing nodules without washout were detected during dynamic computed tomography and observed without further treatments. We subsequently compared the cumulative occurrence of new hepatocellular carcinomas to that of the malignant transformation of these lesions. We additionally compared the appearance of new hepatocellular carcinomas between the patients with (n = 93) and without (n = 782) nonenhancing lesions or enhancing lesions without washout.*
Results. *After a median follow-up period of 0.7 years (range, 0.2–6.8), the median intervals from resection to the appearance of new classical hepatocellular carcinoma and malignant transformation of nonenhancing lesions or enhancing lesions without washout were 1.6 years (95% confidence interval, 1.2–1.9) and 2.3 years (1.9–6.8 years; P = .002), respectively. On the other hand, the median intervals from resection to the appearance of new lesions in patients with and without nonenhancing lesions or enhancing lesions without washout were 1.6 years (95% confidence interval, 1.2–1.9) and 2.1 years (1.9–2.1 years; P = .031), respectively.*
Conclusion. *During the natural history of nonenhancing lesions and enhancing lesions without washout that coexist with hepatocellular carcinoma, new lesions often develop prior to the malignant transformation of these lesions. This should be considered a risk factor for the appearance of new hepatocellular carcinoma. (Surgery 2016;160:654-60.)*

From the Departments of Digestive Surgery,[a] Pathology,[c] Radiology,[d] and Gastroenterology,[e] Nihon University School of Medicine and Genome Science Division,[b] Research Center for Advanced Science and Technologies, University of Tokyo, Tokyo, Japan

Diagnosis of hepatocellular carcinoma (HCC) is usually based on the appearance of the contrasted medium pattern that is seen during a radiologic examination.[1] Nonenhancing nodules that do not show any intake of contrasted medium in the arterial phase or enhancing nodules without washout in the portal phase are considered to indicate premalignant lesions.[2-4] Recently, nonenhancing lesions and enhancing lesions without washout in the liver that do not exhibit any typical radiologic features of classical HCC are being seen more frequently due to the development of gadolinium ethoxybenzyl diethylene triamine pentaacetic acid-enhanced magnetic resonance imaging (EOB-MRI) and contrast-enhanced ultrasonography.[5-7]

However, immediate treatment of nonenhancing lesions and enhancing lesions without washout remains controversial. Researchers have reported that patients with these premalignant lesions are good candidates for liver resection, as the tumor can be radically removed.[8-10] It also has been shown that relapses rarely occur due to less malignant biologic characteristics that accompany these

Supported by a Grant-in-Aid for Scientific Research (C) 15K10152 from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Accepted for publication April 13, 2016.

Reprint requests: Yutaka Midorikawa, MD, PhD, Department of Digestive Surgery, Nihon University School of Medicine, 30-1 Oyaguchikami-machi, Itabashi-ku, Tokyo 173-8610, Japan. E-mail: mido-tky@umin.ac.jp.

0039-6060/$ - see front matter

http://dx.doi.org/10.1016/j.surg.2016.04.019

lesions.[11] Along with other researchers, we have advocated that the survival benefit achieved by treating such lesions is marginal due to the substantial risk of developing classic HCC in other sites.[12-14]

Although only a few reports have been published, some of these studies have examined how such premalignant lesions need to be treated when they coexist with a classical HCC.[7] For example, it has been suggested that nonenhancing lesions and enhancing lesions without washout might be able to be removed easily in conjunction with the resection of classical HCC, as this would improve the patients' prognosis. On the other hand, the presence of nonenhancing nodules at the time of the resection for hypervascular HCC is a risk factor for postoperative recurrence. This has been mainly ascribed to multicentric hepatocarcinogenesis,[15,16] with new classical HCC next to the nonenhancing lesion appearing prior to the vascularization.

In the current study, we followed the natural clinical course of the nonenhancing lesions and enhancing lesions without washout that were diagnosed in patients during their primary operation for HCC. We then compared the period of the malignant transformation with the appearance of new malignant lesions to clarify whether there is justification for the treatment of these nonenhancing lesions and enhancing lesions without washout.

METHODS

Patients. Patients who underwent liver resection for HCC between 2003 and 2014 in hospitals affiliated with Nihon University were included in this study. Among these patients, nonenhancing lesions or enhancing lesions without washout other than the classical HCC that was the target of the resection (as described later) were observed closely during each of the outpatients' office visits. None of the patients received any additional treatment until there was an observation of vascularization or washout in the portal phase or until the appearance of other new classical HCC.

Diagnosis. All patients underwent preoperative, multiphase, contrast-enhanced computed tomography (CT) scans with/without gadoxetate-disodium–enhanced MRI. A 4-channel multidetector CT scanner was used, and examinations were performed with 5 mm of collimation. After the patient underwent precontrast CT scans, 2 sets of contrast-enhanced CT scans were obtained, with one performed during the arterial phase and the other during the portal phase. The standard protocol for contrast-enhanced CT required 120–150 mL of nonionic intravenous contrast materials (370 mg/mL) administered by a power injector at a rate of 3 mL/second, with delays of 35 seconds for the arterial phase and 65 seconds for the portal phase. MRI was performed using gadoxetate disodium administered intravenously at a rate of 2 mL/second, with delay times for the arterial and portal phases of 20 and 60 seconds, respectively.

Results of the imaging modalities, which included CT and MRI, demonstrated that the enhancing nodules in the arterial phase with washout in the portal phase of the contrasted CT were diagnosed as classical HCC. When observations of the nonenhancing lesions in the arterial phase and the enhancing lesions without washout in the portal phase found these lesions to be distinguishable from cysts or hemangiomas, they were defined as marginal lesions (Supplementary Fig 1, online only version). Diagnoses of classical HCC, nonenhancing tumors, and enhancing tumors without washout were made during a central review of the imaging by specialized radiologists.

Liver resection. Curative resection was performed for classical HCC in accordance with the liver function of each patient.[17] Only when intraoperative ultrasonography indicated that the nonenhancing lesions or enhancing lesions without washout had an unclear boundary, thin halo, or posterior echo enhancement, which strongly suggests tumors are malignant, was a core needle biopsy performed for the purpose of decision-making for additional treatment (Supplementary Fig 2, online only version). Pathologic evaluations of biopsy samples were performed by pathologists with >10 years' experience in the field of liver pathology. The criteria required to be defined as pathologic included low-grade dysplastic nodule showing minimal nuclear atypia, slightly increased nucleocytoplasmic ratio, and no mitotic figures. On the other hand, a high-grade dysplastic nodule that showed cytologic and/or architectural atypia and occasional mitotic figures was considered insufficient for a diagnosis of malignancy. HCC was defined by an increase in cellularity with both an increased nucleocytoplasmic ratio and eosinophilic staining.

When preoperative CT findings and intraoperative ultrasonography findings with/without core needle biopsy proved the lesions were not malignant, patients were placed under observation.

Follow-up after liver resection. Patient follow-up was performed using several imaging studies, including ultrasonography, contrasted CT, and EOB-MRI. In addition, serum tumor markers were examined once every 3 months for the purpose of determining the appearance of any