were diagnosed as well-differentiated HCC and the remaining 10 nodules were diagnosed as dysplastic nodules on pathologic examination.

Table 1 compares the preoperative characteristics of the study patients. No differences were found in patient age and sex, etiology, liver function, and tumor progression as evaluated by preoperative imaging examinations and by post-operative pathologic examinations. Multiple HCC nodules were resected in 6 patients (10.2%) of hypointense nodule (-) group and 3 patients (16.7%) of hypointense nodule (+) group, without the difference in proportions. No difference was observed in the length of follow-up period.

Recurrence Rate after Hepatectomy According to the Presence of Non-hypervascular Hypointense NodulesDetected during Preoperative Gadolinium-Ethoxybenzyl-Diethylenetriamine Pentaacetic Acid-enhanced MRI

We determined the recurrence rate in patients after hepatectomy with curative intent based on the presence of non-hypervascular hypointense hepatic nodules identified during the hepatobiliary phase of

Gd-EOB-DTPA-enhanced MRI (Figure 1). The recurrence rate was significantly higher in patients in the hypointense nodule (+) group than the hypointense nodule (-) group (p<0.0001). In the univariate analysis, HCC differentiation and portal vein invasion were identified as factors associated with the rate of recurrence after hepatectomy along with preoperative non-hypervascular hypointense nodules by Gd-EOB-DTPA-enhanced MRI. In the multivariate analysis, these factors were confirmed to be independently associated with the rate of recurrence (Table 2). Among 18 patients with hypointense nodule (+) group, recurrence was observed in 7 of 11 patients with one non-hypervascular hypointense nodule, whereas recurrence was observed in all 7 patients with multiple non-hypovascular hypointense nodules.

Patterns of Recurrence after Hepatectomy According to the Presence of Non-hypervascular Hypointense Nodules Detected during Preoperative Gadolinium-Ethoxybenzyl-Diethylenetriamine Pentaacetic Acid-enhanced MRI

In 30 patients with HCC recurrence after hepatectomy, 16 patients

(53.3%) had intrahepatic metastasis recurrence and 14 patients (46.7%) had multicentric recurrence. There was no difference in the rate of intrahepatic metastasis recurrence between patients in the hypointense nodule (+) group and the hypointense nodule (-) group (p=0.8852). In contrast, patients in the hypointense nodule (+) group had a significantly higher rate of multicentric recurrence than patients in the hypointense nodule (-) group (p<0.0001, Figure 2). Univariate and multivariate analyses revealed that portal vein invasion was independently associated with intrahepatic metastasis recurrence but not preoperative non-hypervascular hypointense nodules detected by Gd-EOB-DTPA-enhanced MRI (Table 3). The presence of preoperative non-hypervascular hypointense nodules detected by Gd-EOB-DTPA-enhanced MRI was the only factor associated with multicentric recurrence in univariate and multivariate analyses (Table 4). Among 8 HCCs that recurred multicentrically in the hypointense nodule (+) group, 6 nodules (75.0%) had existed as non-hypervascular hypointense hepatic nodules on Gd-EOB-DTPA-enhanced MRI before hepatectomy and progressed to hypervascular HCC tumors (Figure 3), while the other 2 nodules (25.0%) newly occurred as multicentric recurrence after

hepatectomy.

Discussion

Although one study reported that dysplastic nodules and early, well-differentiated HCC can be differentiated based on findings on Gd-EOB-DTPA uptake [26], differentiation of early, non-hypervascular HCC from dysplastic nodules within hypointense nodules is not actually feasible and controversial [27]. In addition, it is nearly impossible to characterize these hepatic nodules specifically using US or MDCT. Therefore, a histological diagnosis should be obtained with percutaneous liver biopsy under US guidance. However, this is not always possible due to the need for multiple samples and its invasive nature. Therefore, we did not resect these hepatic nodules during hepatectomy, except for nodules located within the hepatectomy field.

This study demonstrates a higher rate of recurrence of HCC in patients in whom non-hypervascular hypointense hepatic nodules were identified during the hepatobiliary phase of preoperative Gd-EOB-DTPA-enhanced MRI. This large difference in the recurrence

rates indicated that the presence of non-hypervascular hypointense nodules detected during the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI is a risk factor for recurrence of HCC after hepatectomy. Although we did not find differences in the rate of intrahepatic metastasis recurrence according to non-hypervascular hypointense hepatic nodule status, we found a significantly higher rate of multicentric recurrence in patients with preoperative concurrent non-hypervascular hypointense hepatic nodules. In addition, the majority of multicentric recurrences involved the hypervascularization of non-hypervascular hypointense hepatic nodules observed preoperatively with Gd-EOB-DTPA-enhanced MRI. It is controversial whether all non-hypervascular hypointense nodules detected during the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI have the potential to progress to typical, hypervascular HCC. However, 26.5% of non-hypervascular hypointense nodules showed hypervascular spots with a long-term follow-up in our previous study [28]. In addition to the likelihood of non-hypervascular hypointense nodules progressing to HCC, the results of the present study suggest that the presence of non-hypervascular hypointense nodules detected during the hepatobiliary

phase of preoperative Gd-EOB-DTPA-enhanced MRI may indicate a high risk of multicentric recurrence of HCC after hepatectomy. Interestingly, multicentric recurrence was observed in all patients with multiple preoperative non-hypervascular hypointense nodules. Whereas intrahepatic metastasis recurrence is considered as a occurrence of metastasis of the HCC that had been resected, multicentric recurrence is considered as new development of HCC that is not related to the resected HCC. Therefore, the presence of non-hypervascular hypointense nodules, especially multiple nodules, may indicate enhanced hepatocarcinogenesis even when the nodule itself does not progress to HCC.

There are several limitations to this study. The sample size was not large and the observation period was relatively short because Gd-EOB-DTPA has been in clinical use since February 2008 in Japan. In addition, the impact of the presence of non-hypervascular hypointense hepatic nodules on survival after hepatectomy was not analyzed because there were no patient deaths during the study period. However, we believe that our data should be shared with clinicians because of the markedly high rates of recurrence after hepatectomy in patients with preoperative

non-hypervascular hypointense hepatic nodules. Further studies with more patients and a longer observation period are needed to confirm this observation. Furthermore, measures to suppress multicentric recurrence in patients with preoperative concurrent non-hypervascular hypointense hepatic nodules should be investigated in the future.

In conclusion, patients with preoperative concurrent non-hypervascular hypointense hepatic nodules on the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI are at higher risk of HCC recurrence after hepatectomy. Clinicians should take this into consideration when determining of treatment modalities.

References

[1] Parkin DM, Bray F, Ferlay J, Pisani P. Global Cancer Statistics, 2002. CA Cancer J Clin 2005; 55:74-108.

[2] Befeler AS, DiBisceglie AM. Hepatocellular carcinoma: diagnosis and treatment. Gastroenterology 2002; 122:1609-1619.

[3] Umemura T, Kiyosawa K. Epidemiology of hepatocellular carcinoma in Japan. Hepatol Res 2007; 37:S95-100.

[4] Kawata S, Murakami T, Kim T, Hori M, Federle MP, Kumano S, et al. Multidetector CT: diagnostic impact of slice thickness on detection of hypervascular hepatocellular carcinoma. Am J Roentgenol 2002; 179: 61-66.

[5] Ichikawa T, Erturk SM, Araki T. Multiphasic contrast-enhanced multidetector-row CT of liver: contrast-enhancement theory and practical scan protocol with a combination of fixed injection duration and patients' body-weight-tailored dose of contrast material. Eur J Radiol 2006; 58: 165-176.

[6] Oka H, Kurioka N, Kim K, Kanno T, Kuroki T, Mizoguchi Y, et al. Prospective study of early detection of hepatocellular carcinoma in patients

with cirrhosis. Hepatology 1990; 12: 680-687.

[7] Hamm B, Staks T, Muhler A, Bollow M, Taupitz M, Frenzel T, et al. Phase I clinical evaluation of Gd-EOB-DTPA as a hepatobiliary MR contrast agent: safety, pharmacokinetics, and MR imaging. Radiology 1995; 195:785–792.

[8] Vogl TJ, Kummel S, Hammerstingl R, Schellenbeck M, Schumacher G, Balzer T, et al. Liver tumors: comparison of MR imaging with Gd-EOB-DTPA and Gd-DTPA. Radiology 1996; 200: 59–67.

[9] Kim SH, Kim SH, Lee J, Kim MJ, Jeon YH, Park Y, et al. Gadoxetic acid-enhanced MRI versus triple-phase MDCT for the preoperative detection of hepatocellular carcinoma. Am J Roentgenol 2009; 192: 1675-1681.

[10] Van Beers BE, Pastor CM, Hussain HK. Primovist, Eovist: What to expect? J Hepatol 2012; 57: 421-429.

[11] Reimer P, Rummeny EJ, Shamsi K, Balzer T, Daldrup HE, Tombach B, et al. Phase II clinical evaluation of Gd-EOB-DTPA: dose, safety aspects, and pulse sequence. Radiology 1996; 199: 177-183.

[12] Bruix J, Sherman M. Management of hepatocellular carcinoma.

Hepatology 2005; 42: 1208-1236.

[13] Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020-1022.

[14] Kokudo N, Makuuchi M. Evidence-based clinical practice guidelines for hepatocellular carcinoma in Japan: J-HCC guidelines. J Gastroenterol 2009; 44: S119-S121.

[15] Liver Cancer Study of Japan. Intrahepatic metastasis and multicentric occurrence. General rules for the clinical and pathological study of primary liver cancer. Third English edition. Tokyo: Kanehara & Co. Ltd., 2011: 54-55.

[16] Kumada T, Nakano S, Takeda I, Sugiyama K, Osada T, Kiriyama S, et al. Patterns of recurrence after initial treatment in patients with small hepatocellular carcinoma. Hepatology 1997; 25: 87-92.

[17] Tsuda H, Hirohashi S, Shimosato Y, Terada M, Hasegawa H. Clonal origin of atypical adenomatous hyperplasia of the liver and clonal identify with hepatocellular carcinoma. Gastroenterology 1988; 95: 1664-1666.

[18] Takenaka K, Adachi E, Nishizaki T, Hiroshige K, Ikeda T, Tsuneyoshi M, et al. Possible multicentric occurrence of hepatocellular carcinoma: a

clinicopathological study. Hepatology 1994; 19: 889-894.

[19] Frericks BB, Loddenkemper C, Huppertz A, Valdeig S, Stroux A, Seja M, et al. Qualitative and quantitative evaluation of hepatocellular carcinoma and cirrhotic liver enhancement using Gd-EOB-DTPA. Am J Roentgenol 2009; 193: 1053-1060.

[20] Matsui O, Kadoya M, Kameyama T, Yoshikawa J, Takashima T, Nakanuma Y, et al. Benign and malignant nodules in cirrhotic livers: distinction based on blood supply. Radiology 1991; 178: 493-497.

[21] Takayasu K, Muramatsu Y, Furukawa H, Wakao F, Moriyama N, Takayama T, et al. Early hepatocellular carcinoma: appearance at CT during arterial portography and CT arteriography with pathologic correlation. Radiology 1995; 194:101-105.

[22] Hayashi M, Matsui O, Ueda K, Kawamori Y, Gabata T, Kadoya M. Progression to hypervascular hepatocellular carcinoma: correlation with intranodular blood supply evaluated with CT during intraarterial injection of contrast material. Radiology 2002; 225: 143-149.

[23] Kaplan EL, Meier P. Non parametric estimation for incomplete observation. J Am Stat Assoc 1958; 53: 457-481.

[24] Petro R, Pike MC. Conservation of the aproximation (0-E2)/E in the log rank test for survival data on tumor incidence data. Biometrics 1973; 29: 579-584.

[25] Cox D. Regression models and life tables. J R Stat Soc 1972; 34: 187-220.

[26] Sano K, Ichikawa T, Motosugi U, Sou H, Muhi AM, Matsuda M, et al. Imaging study of early hepatocellular carcinoma: usefulness of gadoxetic acid-enhanced MR imaging. Radiology 2011; 261: 834-844.

[27] Kogita S, Imai Y, Okada M, Kim T, Onishi H, Takamura M, et al. Gd-EOB-DTPA-enhanced magnetic resonance images of hepatocellular carcinoma: correlation with histological grading and portal blood flow. Eur Radiol 2010; 20: 2405-2413.

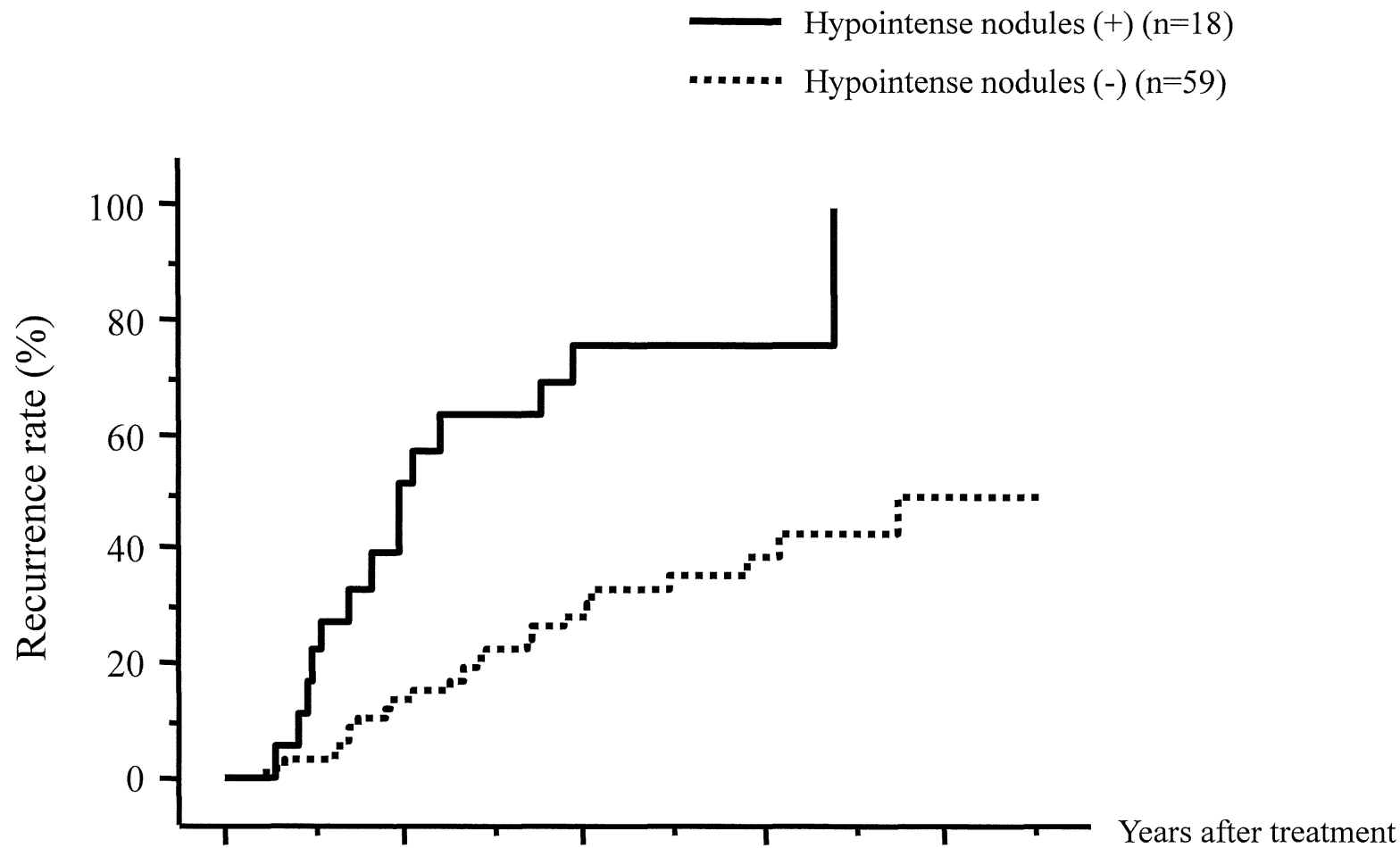
[28] Kumada T, Toyoda H, Tada T, Sone Y, Fujimori M, Ogawa S, et al. Evolution of hypointense hepatocellular nodules observed only in the hepatobiliary phase using Gd-EOB-DTPA enhanced magnetic resonance imaging. Am J Roentogenol 2011; 197: 58-63.

Figure legends

Figure 1. Overall recurrence rate after hepatectomy in patients with or without concurrent non-hypervascular hypointense hepatic nodules detected during the hepatobiliary phase of preoperative gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging.

Figure 2. (A) Rates of intrahepatic metastasis recurrence after hepatectomy in patients with or without concurrent non-hypervascular hypointense hepatic nodules detected during the hepatobiliary phase of preoperative gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging. (B) Rates of multicentric recurrence after hepatectomy in patients with or without concurrent non-hypervascular hypointense hepatic nodules detected during the hepatobiliary phase of preoperative gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging, among 59 patients excluding 16 patients with intrahepatic metastasis recurrence.

Figure 3. (A) Hepatobiliary phase of gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (Gd-EOB-DTPA-enhanced MRI, left panel) and computed tomography during hepatic arteriography (CTHA, right panel) before hepatectomy for hepatocellular carcinoma (HCC). In addition to the typical HCC located in segment VIII, hypointense hepatic nodule was detected in segment VI during the heratobiliary phase of Gd-EOB-DTPA-enhanced MRI (arrow). No hypervascular nodule was detected at this site by CTHA (arrow). (B) Hepatobiliary phase of gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (Gd-EOB-DTPA-enhanced MRI, left panel) and computed tomography during hepatic arteriography (CTHA, right panel) 10 months after hepatectomy for hepatocellular carcinoma (HCC). The nodule detected during the heratobiliary phase of Gd-EOB-DTPA-enhanced MRI showed minute growth in size with clearer margin comparing preoperative image (arrow). The hypervascularity of this nodule was identified by CTHA (arrow). This nodule was detected by re-hepatectomy and was diagnosed as HCC pathologically.

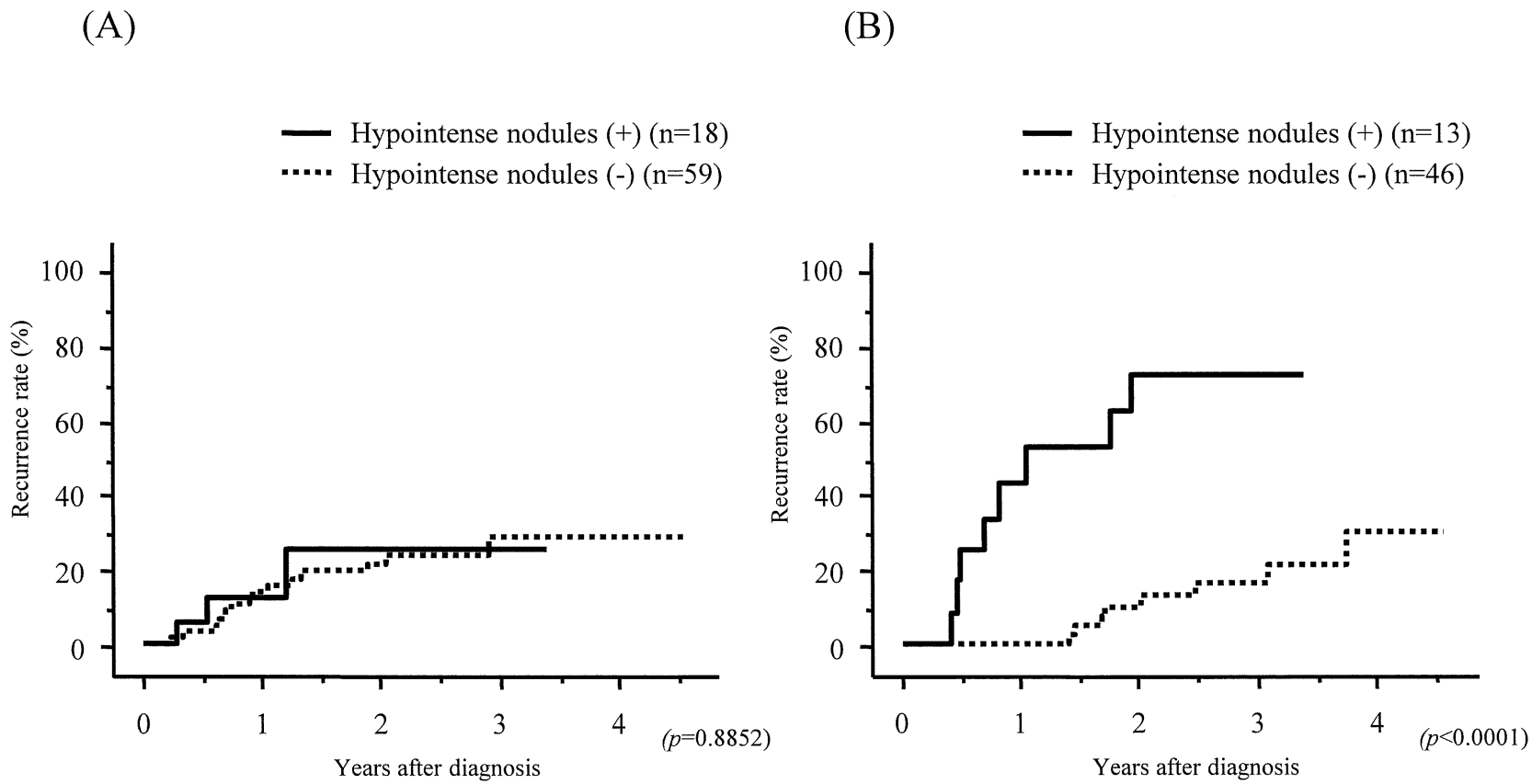


Patients at risk

Hypointense nodules (+)	18	17	14	7	2
Hypointense nodules (-)	59	58	47	29	16

($p<0.0001$)

Figure 1



Patients at risk

Hypointense nodules (+)	18	17	14	7	2
Hypointense nodules (-)	59	58	47	29	16

Hypointense nodules (+)	13	12	10	5	1
Hypointense nodules (-)	46	44	35	19	9

Figure 2

(A)

(B)

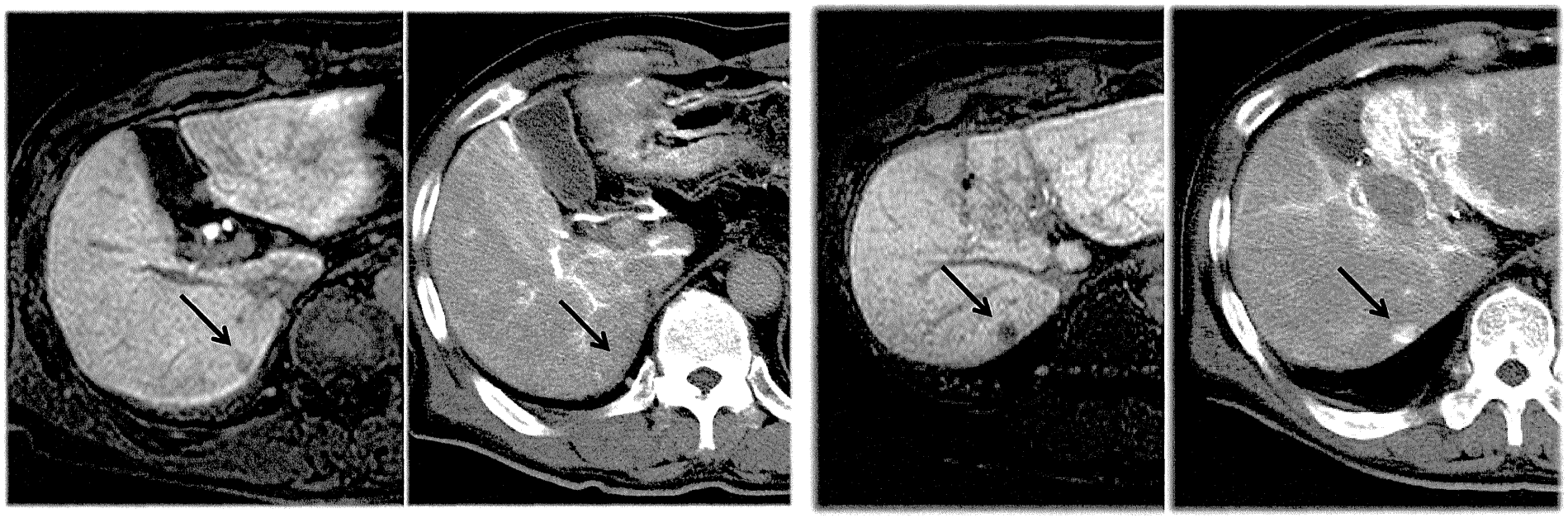


Figure 3

Table 1. Comparison of clinical characteristics of study patients based on the presence of non-hypervascular hypointense nodules detected during the hepatobiliary phase of gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (n = 77)

	Non-hypervascular hypointense nodule (+) (n=18)	Non-hypervascular hypointense nodule (-) (n=59)	*p* value
Age (mean ± SD, years) (range)	65.8 ± 9.0 (46-76)	69.1 ± 7.0 (53-82)	0.2727
Sex (female/male)	3 (16.7)/ 15 (83.3)	18 (30.5)/ 41 (69.5)	0.3921
Etiology (HBV/ HCV/ non-HBV, non-HCV)	2 (11.1)/ 11 (61.1)/ 5 (27.8)	9 (15.3)/ 39 (66.1)/ 11 (18.6)	0.6796
Child-Pugh class (A/B)*	17 (94.4)/ 1 (5.6)	58 (98.3)/ 1 (1.7)	0.9474
Albumin (mean ± SD, g/dL)	3.91 ± 0.51	4.08 ± 0.32	0.1664
Total bilirubin (mean ± SD, mg/dL)	0.88 ± 0.36	0.84 ± 0.33	0.7296
15-minute ICG retention rate (%)	18.1 ± 5.4	16.0 ± 6.7	0.2405
Prothrombin (%)	95.3 ± 15.6	95.1 ± 11.2	0.9105
Platelet count (x1000/mL)	132 ± 47	152 ± 66	0.5433
Tumor size (mean ± SD, cm) (range)	2.52 ± 0.99 (1.3-4.7)	2.84 ± 1.54 (1.0-8.6)	0.6600
Number of tumors (single/multiple)	15 (83.3)/ 3 (16.7)	53 (89.8)/ 6 (10.2)	0.7358
Portal vein invasion (absent/present)**	17 (94.4)/ 1 (5.6)	50 (84.7)/ 9 (15.3)	0.4989
Differentiation (well-/moderately or poorly)**	7 (38.9)/ 11 (61.1)	21 (35.6)/ 38 (64.4)	0.9999
Growth pattern (expansive/ infiltrative)**	14 (77.8)/ 4 (22.2)	52 (88.1)/ 7 (11.9)	0.4718
Follow-up period (months) (median, range)	31.3 (9.4-53.9)	34.9 (8.5-55.4)	0.4200

Percentages were in parentheses. HBV, hepatitis B virus; HCV, hepatitis C virus; ICG, indocyanine green test.

*Child-Pugh class A includes patients without cirrhosis.

**Evaluated by pathologic examination based of resected specimens.

Table 2. Univariate and multivariate analyses of factors associated with post-operative recurrence in HCC patients (n=77)

Factor		Univariate analysis		Multivariate analysis	
		Risk ratio (95% C.I.)	*p* value	Risk ratio (95% C.I.)	*p* value
Age		0.9943 (0.9535-1.0396)	0.7974	-----	
Sex	Male	1			
	Female	1.0068 (0.6818-1.4290)	0.9711	-----	
Child-Pugh class*	A	1			
	B	0.0428 (0.0198-1.5669)	0.2068	-----	
Tumor size		0.9376 (0.7179-1.1700)	0.5935	-----	
Number of tumors	Single	1			
	Multiple	1.0419 (0.5669-1.6643)	0.8792	-----	
Differentiation**	Well-	1		1	
	Moderately/poorly	1.5871 (1.0958-2.4354)	0.0134	1.6536 (1.1381-2.5445)	0.0073
Growth pattern**	Expansive	1			
	Infiltrative	1.1101 (0.6798-1.6625)	0.6487	-----	
Portal vein invasion**	Absent	1		1	
	Present	1.5659 (1.0161-2.2813)	0.0428	1.7818 (1.1388-2.6597)	0.0134
Non-hypervascular	Absent	1		1	
hypointense nodules	Present	1.9396 (1.3615-2.7222)	0.0004	2.1767 (1.5089-3.1105)	0.0001