European Radiology (2019) 29:3122–3131
https://doi.org/10.1007/s00330-018-5941-x

HEPATOBILIARY-PANCREAS

Non-hypervascular hepatobiliary phase hypointense nodules on gadoxetic acid-enhanced MR can help determine the treatment method for HCC

Dong Ho Lee[1] · Jeong Min Lee[1,2] · Mi Hye Yu[3] · Bo Yun Hur[4] · Nam-Joon Yi[5] · Kwang-Woong Lee[5] · Kyung-Suk Suh[5] · Jung-Hwan Yoon[6] · Yoon Jun Kim[6] · Jeong-Hoon Lee[6] · Su Jong Yu[6] · Joon Koo Han[1,2]

Received: 24 July 2018 / Revised: 25 October 2018 / Accepted: 30 November 2018 / Published online: 14 January 2019

Abstract

Objective This study was conducted in order to evaluate whether the presence of nonhypervascular hepatobiliary phase (HBP) hypointense nodules can help determine the treatment method for single nodular hepatocellular carcinoma (HCC) ≤ 3 cm.

Methods This study was approved by the institutional review board. A total of 345 patients with single nodular HCC ≤ 3 cm underwent pretreatment gadoxetic acid-enhanced MR followed by hepatic resection ($n = 123$) or radiofrequency ablation (RFA) ($n = 222$). We retrospectively analyzed the results of tumor recurrence according to the presence of nonhypervascular HBP hypointense nodules at each treatment method.

Results Nonhypervascular HBP hypointense nodules were found in 18 of 123 patients treated by hepatic resection and in 63 of 222 patients who underwent RFA. The presence of nonhypervascular HBP hypointense nodules was a significant affecting factor for recurrence-free survival (RFS) after both hepatic resection ($p = 0.004$, hazard ratio [HR] = 2.75 [1.38–5.51]) and RFA ($p = 0.004$, HR = 1.78 [1.20–2.63]). In patients with nonhypervascular HBP hypointense nodules, 5-year RFS was 34.0% after hepatic resection, which was not significantly different from the 28.0% after RFA ($p = 0.618$). However, in patients without nonhypervascular HBP hypointense nodules, 5-year RFS was 65.0% after hepatic resection, which was significantly better than the 51.0% after RFA ($p = 0.042$), owing to significantly lower cumulative incidence of local tumor progression after hepatic resection ($p < 0.001$).

Conclusions While the presence of nonhypervascular HBP hypointense nodules on gadoxetic acid-enhanced MR taken prior to treatment was a significant predictive factor of tumor recurrence after both hepatic resection and RFA, in patients without nonhypervascular HBP hypointense nodules, hepatic resection can provide significantly better RFS than RFA.

Key Points

- *The presence of nonhypervascular hepatobiliary phase (HBP) hypointense nodules was a significant risk factor for tumor recurrence after either hepatectomy or radiofrequency ablation (RFA).*
- *Hepatectomy provided significantly better recurrence-free survival than RFA in patients without nonhypervascular HBP hypointense nodules.*
- *In patients with nonhypervascular HBP hypointense nodules, recurrence-free survival after RFA was comparable to hepatectomy.*

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00330-018-5941-x) contains supplementary material, which is available to authorized users.

✉ Jeong Min Lee
jmsh@snu.ac.kr

[1] Department of Radiology, Seoul National University Hospital, 101 Daehangno, Jongno-gu, Seoul 03080, South Korea

[2] Department of Radiology, Seoul National University College of Medicine, Seoul, South Korea

[3] Department of Radiology, Konkuk University School of Medicine, Seoul, South Korea

[4] Department of Radiology, Healthcare System Gangnam Center, Seoul National University Hospital, Seoul, South Korea

[5] Department of Surgery, Seoul National University Hospital, Seoul, South Korea

[6] Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea

Keywords Hepatocellular carcinoma · Ablation technique · Hepatectomy · Magnetic resonance imaging

Abbreviations

AFP	Alpha-fetoprotein
CI	Confidence interval
EM	Extrahepatic metastasis
HBP	Hepatobiliary phase
HCC	Hepatocellular carcinoma
HR	Hazard ratio
IDR	Intrahepatic distant recurrence
LTP	Local tumor progression
MR	Magnetic resonance
RFA	Radiofrequency ablation
RFS	Recurrence-free survival
SD	Standard deviation

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignant tumor and the third leading cause of cancer-related deaths worldwide [1]. Among its various treatment options, hepatic resection has been considered the most effective curative option, particularly in patients with early stage HCCs and well-preserved liver function [2–5]. Radiofrequency ablation (RFA) has also emerged as another curative local treatment method which can provide comparable overall survival to hepatic resection, particularly for small HCCs equal to or less than 3 cm in size [6–8]. Moreover, RFA is less invasive than hepatic resection, with significantly lower complication rates and hospital stay durations after RFA of HCC than hepatic resection. Therefore, considering the comparable overall survival after treatment as well as its less invasiveness, RFA is now recommended as the first-line treatment modality for very early stage HCCs [9]. However, with recent advances in surgical techniques such as in laparoscopic surgery as well as in postoperative care, the clinical outcome of hepatic resection for HCC has also improved [10–12], and thus, controversy regarding the choice of the most appropriate treatment modality between hepatic resection and RFA in patients with small HCCs still remains. Therefore, ascertaining which patient group may most benefit from a certain treatment method over another would be an important step in the management of patients with HCCs.

Recently, gadoxetic acid (Gd-EOB-DTPA, Primovist or Eovist, Bayer Healthcare), which is a hepatocyte-specific contrast agent, has been increasingly used for the evaluation of HCCs as it can provide both the dynamic and hepatobiliary phases (HBP) in a single examination. Owing to the excellent liver-to-lesion contrast obtained from the HBP, gadoxetic acid-enhanced liver magnetic resonance (MR) imaging could provide significantly better diagnostic performance in detecting both HCCs and liver metastasis than dynamic CT or dynamic MR imaging using extracellular contrast agents [13–15]. Furthermore, gadoxetic acid-enhanced liver MR can also provide pertinent prognostic information of HCC patients as the presence of nonhypervascular HBP hypointense nodules has been reported to be a significant risk factor of tumor recurrence after curative treatment of HCC through either hepatic resection or RFA [16, 17]. However, whether the presence of nonhypervascular HBP hypointense nodules observed on gadoxetic acid-enhanced liver MR taken prior to treatment can help determine the treatment method for HCC patients has not yet been investigated. If gadoxetic acid-enhanced liver MR can indeed provide information which may be useful in selecting the treatment method, it would be of great utility in the management of patients with HCC.

Therefore, the purpose of this study was to retrospectively evaluate whether the presence of nonhypervascular HBP hypointense nodules on gadoxetic acid-enhanced liver MR can inform the decision-making between hepatic resection and RFA in patients with single nodular HCC equal to or less than 3 cm in size.

Patients and methods

Patients

Our Institutional Review Board approved this retrospective study with waiver of the requirement for written informed consent. From January 2009 to December 2014, 519 consecutive patients with a single nodular HCC equal to or less than 3 cm in size without a previous history of HCC treatment underwent either hepatic resection ($n = 194$) or RFA ($n = 325$) at our institution for HCC. The inclusion criteria were (a) well-compensated Child–Pugh class A liver function, (b) those who underwent gadoxetic acid-enhanced MR within 30 days prior to HCC treatment, and (c) no concomitant serious medical illness other than liver disease. The exclusion criteria for this study were (a) patients who underwent liver transplantation during the follow-up period and (b) patients without available medical record and/or imaging study after treatment for HCC. Among the 519 patients, 174 patients were excluded according to the inclusion and exclusion criteria: (a) absence of pretreatment gadoxetic acid-enhanced MR taken within 30 days prior to HCC treatment ($n = 116$); (b) Child–Pugh class B liver function ($n = 27$); (c) concomitant medical illness ($n = 9$; history of stomach cancer in 5, breast cancer in 3, and lymphoma in 1); (d) undergoing liver transplantation during the follow-up period after HCC treatment ($n = 17$); and (e) immediate follow-up loss after treatment ($n = 5$). Therefore, the remaining 345 patients (hepatic resection, $n = 123$, and RFA, $n = 222$) finally comprised our study population (Fig. 1).

Acquisition and evaluation of gadoxetic acid-enhanced liver MR

All enrolled patients underwent gadoxetic acid-enhanced liver MR prior to HCC treatment, with the mean interval of 10.0 days (range, 0–30 days; median, 8 days). The detailed MR imaging protocol are given in the Electronic supplementary material. Two abdominal radiologists (M.H.Y and B.Y.H with 11 and 8 years of experience in liver MR, respectively) independently evaluated gadoxetic acid-enhanced liver MR. Both radiologists were aware that the patients had undergone either hepatic resection or RFA for curative HCC treatment, but were blinded to their clinical outcomes. Presence of nonhypervascular HBP hypointense nodules was defined as solid nodules showing hypointensity on the HBP which do not show higher signal intensity than the spleen on heavily T2-weighted images [16, 17]. To assess the presence of nonhypervascular HBP hypointense nodules, both radiologists carefully evaluated all HBP images including axial and coronal images to detect hypointense nodules in the liver. Thereafter, both radiologists decided whether arterial enhancement was present or not within the hypointense nodules detected on HBP images, and both precontrast T1-weighted image and arterial phase image were carefully evaluated for the assessment of presence of arterial hyperenhancement. We also routinely used subtraction imaging obtained from precontrast T1-weighted image and arterial phase image to decide the presence of arterial hyperenhancement, especially for nodules showing hyperintensity on precontrast T1-weighted image. The readers excluded hemangiomas or hepatic cysts determined based on their classic enhancement patterns or nonenhancement on dynamic phase images and hyperintensity on T2-weighted MR imaging, respectively [16]. In cases of discrepancy between the two readers as to the presence of nonhypervascular HBP hypointense nodules on gadoxetic acid-enhanced MR, consensus was reached through discussion with a third experienced radiologist (J.M.L with 25 years of experience).

Procedure and follow-up after treatment

One of the three experienced hepatic surgeons (25, 20, and 14 years of experience) performed the hepatic resections, and RFA was performed by one of the four specialized physicians with 20, 18, 16, and 11 years of experience in thermal ablation, percutaneously, under real-time ultrasound CT/MR fusion imaging guidance with conscious sedation [18]. Development of complications related to the treatment and duration of the hospital stay of each patient was also searched and recorded.

One month after treatment, imaging studies and biochemical tests including the liver function test and serum alpha-fetoprotein (AFP) were obtained in all patients. If there was no residual tumor on 1 month follow-up imaging, follow-up examinations were performed every 3 months during the first year and every 3 to 6 months during the second year. Thereafter, if there was no tumor recurrence, the follow-up schedule was maintained at the same frequency as that of the surveillance program for liver cirrhosis (i.e., ultrasound at 6-month intervals).

We classified tumor recurrence which developed during the follow-up period into three categories: local tumor progression

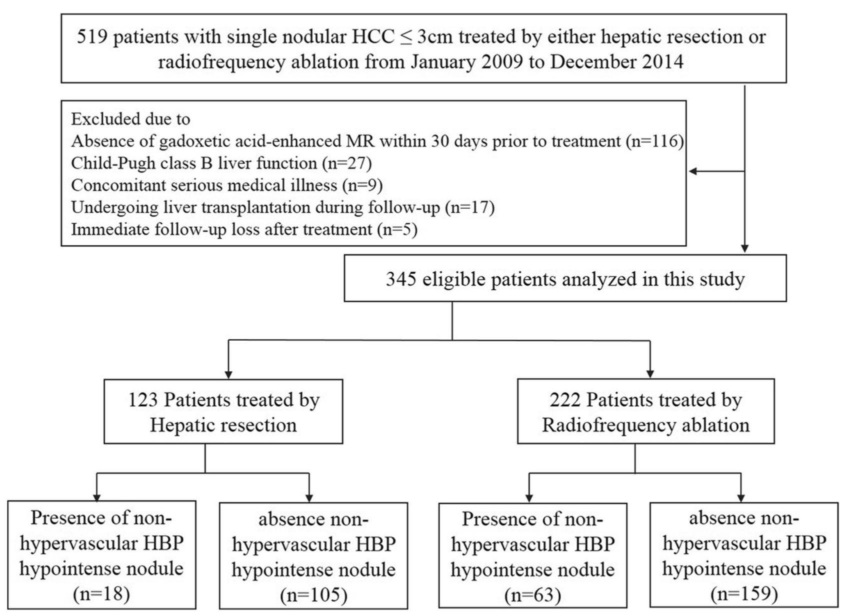

Fig. 1 Flow diagram summarizing the patient enrollment process of this study. HBP = hepatobiliary phase of gadoxetic acid-enhanced liver MR imaging

(LTP), intrahepatic distant recurrence (IDR), and extrahepatic metastasis (EM). LTP was defined as the appearance of any arterial enhancing tumor tissue showing washout on the portal venous and/or delayed phase adjacent to the local treated area (i.e., resection margin in the case of hepatic resection and the ablation zone in the case of RFA), and IDR as the development of one or more HCCs not adjacent to the treated site [19].

Statistical analysis

To compare the baseline patient characteristics between hepatic resection and RFA, chi-square or Fisher's exact test was used for categorical variables and the Mann–Whitney *U* test for continuous variables. Overall survival was defined as the interval between curative HCC treatment and death or the date of the last follow-up visit before March 31, 2018. Recurrence-free survival (RFS) rate was defined as the interval between curative HCC treatment either hepatic resection or RFA and the first date of any type of HCC recurrence (either local and/or distant) or the last follow-up date if there was no recurrence during the follow-up period. Patients who underwent liver transplantation during the follow-up period after curative HCC treatment were censored from the study at the date of their transplantation. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. In addition, a univariate Cox proportional hazards model was fitted to each clinical, biochemical, and imaging feature. All variables with a p value < 0.05 at univariate analysis were then included for multivariate analysis using a stepwise Cox hazards regression model to evaluate their value as independent predictors. After the initial analysis, in order to reduce any potential bias caused by the differences in the baseline patient characteristics of the two treatment methods, propensity score analysis was done, and the results after propensity score matching are given in the Electronic supplementary material. All statistical analyses were performed using SPSS version 21 (SPSS).

Results

Baseline patient characteristics of the two treatment methods

Baseline characteristics of the study population according to their treatment methods are summarized in Table 1. Mean age, gender distribution, serum albumin level, prothrombin activity, platelet count, and tumor size were significantly different between the hepatic resection group and the RFA group. The prevalence of nonhypervascular HBP hypointense nodules

Table 1 Baseline characteristics

Parameters	Hepatic resection ($n = 123$)	RFA ($n = 222$)	p value†
Age (years)	58 (51–63)	60.5 (54–67)	0.003
Gender (*n*, %)			0.003
Male	103 (83.7%)	153 (68.9%)	
Female	20 (16.3%)	69 (31.1%)	
Etiology (*n*, %)			0.432
HBV-related	97 (78.9%)	167 (75.2%)	
HCV-related	11 (8.9%)	28 (12.6%)	
Alcoholic	6 (4.9%)	12 (5.4%)	
Others	9 (7.3%)	15 (6.8%)	
Albumin (mg/dL)	4.2 (3.9–4.4)	4.0 (3.7–4.2)	< 0.001
Total bilirubin (mg/dL)	0.8 (0.6–1.0)	0.7 (0.6–1.0)	0.190
Prothrombin activity (INR)	1.05 (1.01–1.09)	1.08 (1.02–1.15)	0.008
AFP (ng/mL)	7.5 (3.0–156.0)	7.5 (3.8–28.1)	0.534
Platelet count (K/m^3)	147 (121–187)	120 (89–157)	< 0.001
Tumor size (cm)	2.2 (1.8–2.8)	1.7 (1.3–2.1)	< 0.001
Nonhypervascular HBP hypointense nodule (*n*, %)			0.004
Presence	18 (14.6%)	63 (28.4%)	
Absence	105 (85.4%)	159 (71.6%)	

Continuous variables are presented as median (interquartile range)

RFA, radiofrequency ablation; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *INR*, international normalized ratio, *AFP*, alpha-fetoprotein; *HBP*, hepatobiliary phase of gadoxetic acid-enhanced liver MR

† p values were determined using the Mann–Whitney test for continuous values and the Fisher's exact test for categorical values

was also significantly different between the two treatment modalities.

Survival and complication outcomes of each treatment modality

The mean and median follow-up periods in 345 patients were 45.6 ± 24.0 (standard deviation, SD) months and 42.0 months. The estimated 1-, 3-, and 5-year overall survival rates of the 123 patients with single nodular HCCs ≤ 3 cm who underwent hepatic resection were 98.3, 96.6, and 91.5%, respectively. The estimated 1-, 3-, and 5-year overall survival rates of the 222 patients who underwent RFA were 99.5, 97.0, and 89.6%, respectively. There were no significant differences in overall survival between the hepatic resection and RFA groups ($p = 0.899$).

Among the 123 patients treated by hepatic resection, eight patients experienced major complications (6.5%), namely bile leakage ($n = 3$), postoperative hemorrhage requiring surgical evacuation ($n = 1$), care for posthepatectomy liver failure ($n = 2$), and fever with fluid collection requiring drainage ($n = 2$). Among the 222 patients who underwent RFA, major complications developed in five patients (2.3%) including bleeding requiring angiographic embolization ($n = 3$), right pleural effusion due to infused artificial ascites during RFA requiring drainage ($n = 1$), and fever with abscess formation ($n = 1$). The major complication rate was significantly lower in the RFA group than in the hepatic resection group (2.3 vs. 6.5%, $p = 0.047$). Mean and median hospital stays were 11.7 ± 8.4 (SD) days (range, 6 to 96 days) and 10 days, respectively, after hepatic resection in 123 patients, and 3.1 ± 1.8 (SD) days (range, 1 to 10 days) and 2 days, respectively, after RFA in 222 patients; this difference was statistically significant ($p < 0.001$).

Recurrence outcomes

Recurrence-free survival for each treatment modality The estimated 1-, 3-, and 5-year RFS rates were 90.8, 68.8, and 60.0%, respectively, in the 123 patients after hepatic resection, which were significantly higher than the RFS rates of 86.7, 59.9, and 43.7% in the 222 patients after RFA ($p = 0.046$). The estimated 1-, 3-, and 5-year cumulative incidences of LTP were 0.8, 3.5, and 5.3%, respectively, after hepatic resection versus 5.1, 12.4, and 17.3% after RFA; this difference was statistically significant ($p = 0.003$). However, the cumulative incidences of IDR ($p = 0.525$) and EM ($p = 0.197$) were not significantly different between the hepatic resection and RFA groups.

Predictive factors of recurrence-free survival after hepatic resection Significant predictive factors of RFS after hepatic resection are summarized in Table 2. Tumor size was significantly associated with the development of tumor recurrence. In addition, the presence of nonhypervascular HBP hypointense nodules was another significant affecting factor for RFS after hepatic resection ($p = 0.004$, HR = 2.75, 95% CI = 1.38–5.51): The estimated 1-, 3-, and 5-year RFS rates after hepatic resection were 88.9, 34.0, and 34.0% in the 18 patients with nonhypervascular HBP hypointense nodules, which were significantly lower than the 91.2, 75.9, and 65.0% in the 105 patients without nonhypervascular HBP hypointense nodules (Figs. 2a and 3). The 5-year cumulative incidence of IDR in the 18 patients with nonhypervascular HBP hypointense nodules was 56.9%, which was significantly higher than the 32.9% in the 105 patients without nonhypervascular HBP hypointense nodules ($p = 0.004$) (Fig. 2b). However, there were no significant differences in either the cumulative incidences of LTP ($p = 0.092$) or EM

Table 2 Cox survival analysis of the predictors of recurrence-free survival in 123 patients with single nodular HCCs ≤ 3 cm after hepatic resection

Characteristic	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Gender (male)	0.88	0.37–2.11	0.777			
Age (per 1 year)	1.01	0.98–1.04	0.549			
Tumor size (cm)	2.40	1.30–4.42	0.005	2.24	1.20–4.19	0.012
Serum AFP (ng/mL)	1.00	0.99–1.01	0.628			
Serum albumin (g/L)	0.66	0.25–1.74	0.401			
Total bilirubin (mg/dL)	1.02	0.88–1.17	0.821			
Prothrombin activity (INR)	2.67	0.26–1.27.6	0.411			
Platelet count (K)	1.00	0.99–1.01	0.839			
Nonhypervascular HBP hypointense nodule	3.14	1.58–6.25	0.001	2.75	1.38–5.51	0.004

HCC, hepatocellular carcinoma; *HR*, hazard ratio; *CI*; confidence interval; *AFP*, alpha-fetoprotein (per 100 units); *INR*, international normalized ratio; *HBP*, hepatobiliary phase of gadoxetic acid-enhanced liver MR imaging

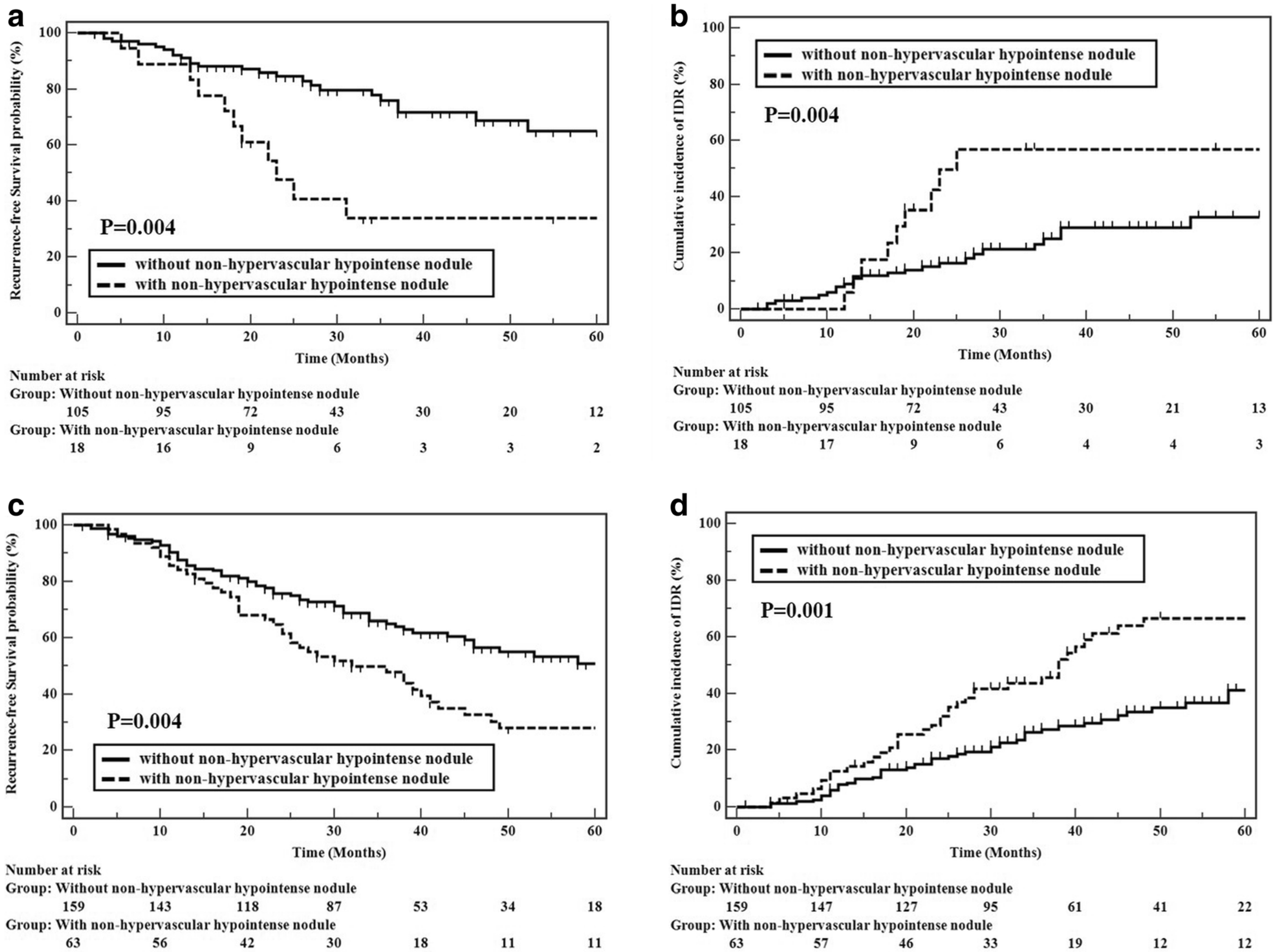

Fig. 2 Recurrence-free survival and cumulative incidence of intrahepatic distant recurrence after curative treatment of single nodular HCCs ≤ 3 cm. **a** Kaplan–Meier estimation of recurrence-free survival in 105 patients without nonhypervascular HBP hypointense nodules after hepatic resection compared with 18 patients with nonhypervascular HBP hypointense nodules. **b** Kaplan–Meier estimation of the cumulative incidence of intrahepatic distant recurrence (IDR) in 105 patients without nonhypervascular HBP hypointense nodules after hepatic resection compared with 18 patients with nonhypervascular HBP hypointense nodules. **c** Kaplan–Meier estimation of recurrence-free survival in 159 patients without nonhypervascular HBP hypointense nodules after RFA compared with 63 patients with nonhypervascular HBP hypointense nodules. **d** Kaplan–Meier estimation of the cumulative incidence of IDR in 159 patients without nonhypervascular HBP hypointense nodules after RFA compared with 63 patients with nonhypervascular HBP hypointense nodules

($p = 0.460$) between patients with nonhypervascular HBP hypointense nodules and patients without.

Predictive factors of recurrence-free survival after RFA Significant predictive factors for RFS after RFA in the 222 patients with single nodular HCCs ≤ 3 cm are summarized in Table 3. The presence of nonhypervascular HBP hypointense nodules was the only significant predictive factor for RFS after RFA on multivariate analysis ($p = 0.004$, HR = 1.78, 95% CI = 1.20–2.63): The estimated 1-, 3-, and 5-year RFS rates after RFA were 84.1, 48.0, and 28.0% in 63 patients with nonhypervascular HBP hypointense nodules, which were significantly lower than the 87.7, 65.0, and 51.0% in the 159 patients without (Fig. 2c). The 5-year cumulative incidence of IDR in the 63 patients with nonhypervascular HBP hypointense nodules was 66.5%, which was significantly higher than that of 41.1% in the 159 patients without nonhypervascular HBP hypointense nodules ($p = 0.001$) (Fig. 2d). However, there were no significant differences in the cumulative incidences of LTP ($p = 0.593$) and EM ($p = 0.709$) between patients with nonhypervascular HBP hypointense nodules and patients without.

Prevalence of nonhypervascular HBP hypointense nodules and follow-up results Gadoxetic acid-enhanced MR taken prior to treatment showed nonhypervascular HBP hypointense nodules in 81 out of 345 patients (23.5%, 81/345) (18 patients in the hepatic resection group [14.6%, 18/123] and 63 patients in the RFA group [28.4%, 63/222]): one nonhypervascular HBP hypointense nodule in 41 patients, two nodules in 12 patients,

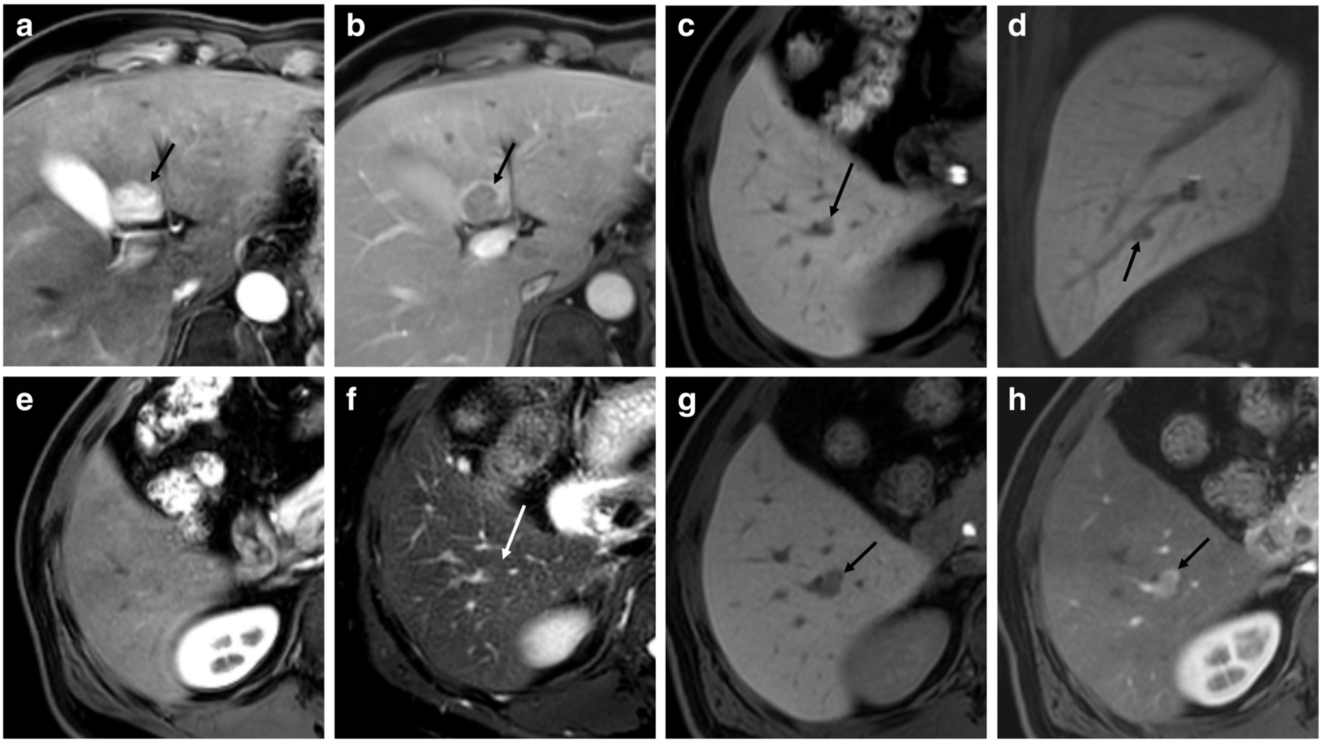

Fig. 3 Development of intrahepatic distant recurrence in a patient with a nonhypervascular HBP hypointense nodule. **a** Arterial phase gadoxetic acid-enhanced MR shows a 2.4-cm enhancing nodular lesion in segment IV of the liver (arrow). **b** On portal venous phase images, this nodule shows washout and the capsular appearance (arrow). **c**, **d** In addition to the HCC in segment IV, axial (**c**) and coronal (**d**) HBP images show a 9-mm hypointense nodule in segment VI (arrows in **c** and **d**). **e** On arterial phase MR image, this nodule shows no arterial hyperenhancement. **f** On axial T2-weighted image, this nodule shows iso-signal intensity to liver parenchyma (arrow). **g**, **h** On follow-up gadoxetic acid-enhanced MR taken 17 months after hepatic resection for a segment IV HCC, the size of the nodule in segment VI had increased from 9 to 12 mm with arterial enhancement (arrows in **g** and **h**), indicating the development of intrahepatic distant recurrence

three in eight patients, four in one patient, and more than five in 19 patients. We excluded 19 patients with more than five nonhypervascular HBP hypointense nodules from further analysis as exact lesion-by-lesion matching for such multiple nodules can hardly be possible. The mean and medium size of a total of 93 nonhypervascular HBP hypointense nodules in 62 patients with less than five nodules were 8.2 ± 2.3 mm (range, 5 to 15 mm) and 8 mm, respectively. Two nonhypervascular HBP hypointense nodules with 9 and 11 mm size, respectively, which were located in the same segment to the HCC lesion in two patients, were simultaneously resected during the hepatic resection, and histopathologic examination revealed low-grade

Table 3 Cox survival analysis of the predictors of recurrence-free survival in 222 patients with single nodular HCCs ≤ 3 cm after radiofrequency ablation

Characteristic	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Gender (male)	0.65	0.42–1.00	0.050	0.65	0.42–1.01	0.053
Age (per 1 year)	1.01	0.99–1.04	0.207			
Tumor size (cm)	1.33	0.97–1.83	0.078			
Serum AFP (ng/mL)	1.00	0.99–1.01	0.578			
Serum albumin (g/L)	1.05	0.64–1.74	0.839			
Total bilirubin (mg/dL)	1.22	0.72–2.06	0.458			
Prothrombin activity (INR)	5.02	0.80–31.5	0.086			
Platelet count (K)	1.00	0.99–1.01	0.237			
Nonhypervascular HBP hypointense nodule	1.79	1.21–2.64	0.004	1.78	1.20–2.63	0.004

HCC, hepatocellular carcinoma; *HR*, hazard ratio; *CI*, confidence interval; *AFP*, alpha-fetoprotein (per 100 units); *INR*, international normalized ratio; *HBP*, hepatobiliary phase of gadoxetic acid-enhanced liver MR imaging dysplastic nodule for the 9-mm-sized nodule and high-grade dysplastic nodule for the 11-mm-sized nodule. Therefore, follow-up examination to evaluate the development of typical hypervascular HCC from the pre-existing nonhypervascular HBP hypointense nodules was available for 91 nodules in 60 patients. During the mean and median follow-up period of 44.5 ± 24.6 and 41.0 months in these 60 patients, respectively, 25 hypervascular HCCs (25/91, 27.5%) developed in 23 patients within the 91 pre-existing nonhypervascular HBP hypointense nodules detected on pretreatment gadoxetic acid-enhanced MR. The mean and medium size of 25 nonhypervascular HBP hypointense nodule which progressed into typical hypervascular HCC were 9.6 ± 2.5 and 9 mm, respectively. However, the mean and medium size of 66 nonhypervascular HBP hypointense nodule which did not progress into typical hypervascular HCC were 7.3 ± 1.6 and 7 mm, respectively: This difference was statistically significant ($p < 0.001$). The estimated 1-, 3-, and 5-year cumulative incidences of progression into typical hypervascular HCC from pre-existing nonhypervascular HBP hypointense nodules were 7.4, 24.1, and 27.9%, respectively.

Recurrence-free survival according to the treatment method in regard to the presence of nonhypervascular HBP hypointense nodules

In our study, 264 patients did not have any nonhypervascular HBP hypointense nodules on gadoxetic acid-enhanced MR (hepatic resection, $n = 105$; RFA, $n = 159$). The estimated 1-, 3-, and 5-year RFS rates after hepatic resection in the 105 patients without nonhypervascular HBP hypointense nodules were 91.2, 75.9, and 65.0%, respectively, which were significantly higher than those of 87.7, 65.0, and 51.0% after RFA in 159 patients ($p = 0.042$) (Fig. 4a). The 5-year cumulative incidence of LTP was 3.2% in the 105 patients who underwent hepatic resection compared to 17.1% in the 159 patients who underwent RFA: This difference was statistically significant ($p = 0.001$). However, the cumulative incidences of IDR ($p = 0.658$) and EM ($p = 0.423$) were not significantly different between the hepatic resection and RFA groups in patients without nonhypervascular HBP hypointense nodules.

The remaining 81 patients had nonhypervascular HBP hypointense nodules on gadoxetic acid-enhanced MR (hepatic resection, $n = 18$; RFA, $n = 63$). The estimated 1-, 3-, and 5-year RFS rates after hepatic resection in the 18 patients with nonhypervascular HBP hypointense nodules were 88.9, 34.0, and 34.0%, respectively, which were not significantly different from the 4.1, 48.0, and 28.0% after RFA in 63 patients ($p = 0.618$) (Fig. 4b).

Discussion

Our study results demonstrated that the presence of nonhypervascular HBP hypointense nodules on gadoxetic acid-enhanced MR was a significant predictive factor of tumor recurrence after both hepatic resection and RFA for a single nodular HCC ≤ 3 cm. Considering that nonhypervascular HBP hypointense nodules are thought to represent borderline hepatocellular nodules including high-grade dysplastic nodules or early HCCs which have the potential to progress into typical hypervascular HCCs during a patient's follow-up period [8, 20–23], this result may not be too surprising. We also found that the cumulative incidence of IDR was significantly higher in

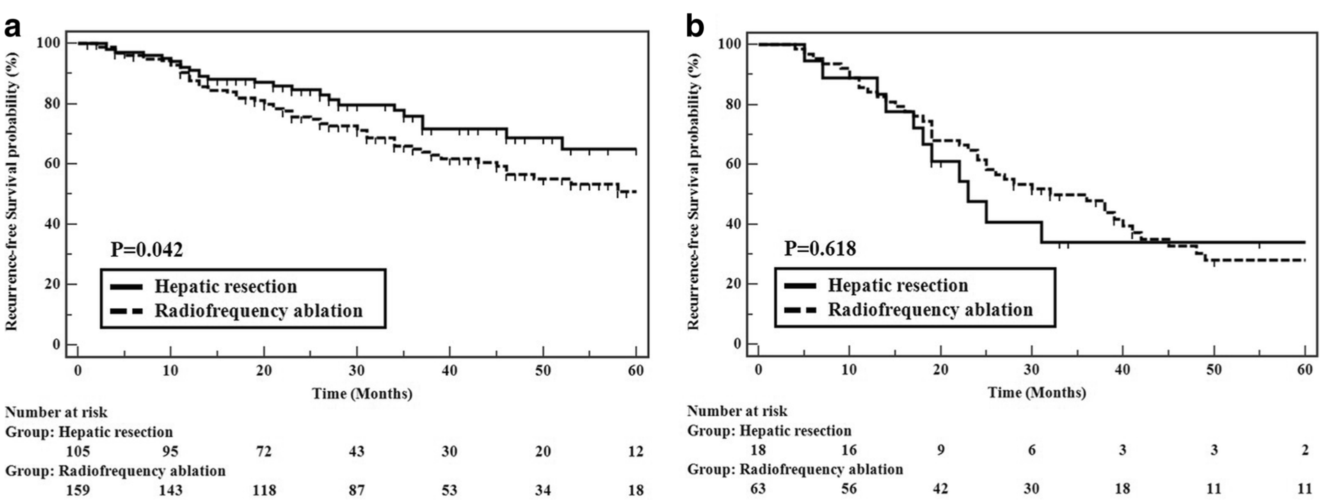

Fig. 4 Recurrence-free survival according to the presence of nonhypervascular HBP hypointense nodules. **a** Kaplan–Meier estimation of recurrence-free survival in 105 patients with nonhypervascular HBP hypointense nodules after hepatic resection compared with 159 patients with nonhypervascular HBP hypointense nodules after RFA. **b** Kaplan–Meier estimation of recurrence-free survival in 18 patients without nonhypervascular HBP hypointense nodules after hepatic resection compared with 63 patients without nonhypervascular HBP hypointense nodules after RFA

patients with nonhypervascular HBP hypointense nodules than in patients without, regardless of the treatment modality. As IDR can be considered an occurrence of a new HCC in another part of the liver apart from the pre-existing HCC, the presence of nonhypervascular HBP hypointense nodules may be a sign of the enhanced hepatocarcinogenesis of the background liver [17]. In our study, 27.5% (25/91) of pre-existing nonhypervascular HBP hypointense nodules progressed into typical hypervascular HCC during the follow-up period, and this result correlated well with the results of previous studies reporting the conversion rate of arterial hypervascularization of 26.5 to 35.0% from pre-existing nonhypervascular HBP hypointense nodules [20, 21, 24, 25]. In addition, the size of nonhypervascular HBP hypointense nodules progressed into typical hypervascular HCC was significantly larger than those which did not change into hypervascular HCC, and this result also correlated well with the recent meta-analysis result [25]. Therefore, considering the results of our previous studies, the presence of nonhypervascular HBP hypointense nodules on gadoxetic acid-enhanced liver MR would be a significant risk factor for tumor recurrence in patients with HCC after curative treatment.

As for the results of RFS according to the treatment method, a significant difference was revealed between patients with nonhypervascular HBP hypointense nodules and those without. In patients with nonhypervascular HBP hypointense nodules, 5-year RFS after hepatic resection was not significantly different from that after RFA; however, in patients without nonhypervascular HBP hypointense nodules, 5-year RFS after hepatic resection was significantly higher than that after RFA owing to the significantly lower cumulative incidence of LTP. This difference may be explained by the early occurrence of IDR in patients with nonhypervascular HBP hypointense nodules. In this study, the median time to develop IDR was 23 months in those who underwent hepatic resection and 36 months in those who received RFA in patients with nonhypervascular HBP hypointense nodules, and the earlier occurrence of IDR before 36 months in patients with nonhypervascular HBP hypointense nodules might have reduced the benefit of the significantly lower rate of LTP from hepatic resection. Therefore, RFS would not be significantly different between hepatic resection and RFA in patients with nonhypervascular HBP hypointense nodules. Our study results were consistent even after propensity score matching to reduce the potential bias arising from differences in baseline patient characteristics between hepatic resection and RFA. Until now, there are still controversies regarding the most preferred therapeutic option for single nodular HCCs ≤ 3 cm. The American Association for the Study of Liver (AASLD) recommends adults with Child–Pugh class A cirrhosis and resectable T1 or T2 stage HCC to undergo resection over RFA, whereas the European Association for the Study of the Liver (EASL) recommends that RFA should be adopted as the first-line therapy for small HCC < 2 cm (BCLC-0) in favorable locations even in surgical patients [26, 27]. In this regard, based on our study results, patients with single nodular HCCs ≤ 3 cm and Child–Pugh class A cirrhosis without nonhypervascular HBP hypointense nodules on gadoxetic acid-enhanced MR would potentially be the best candidates for hepatic resection. On the other hand, in patients with nonhypervascular HBP hypointense nodules, as both hepatic resection and RFA can provide similar RFS after treatment, RFA might be the better choice owing to its less invasiveness and shorter hospital stay.

There are several limitations in our study that should be mentioned. First, due to its retrospective design, there may have been the potential for selection bias, particularly in the 11.9% of patients (62/519) who were excluded from our analysis owing to the lack of pretreatment gadoxetic acid-enhanced MR. Second, we enrolled patients with small single nodular HCCs ≤ 3 cm so as to compare the clinical outcomes between hepatic resection and RFA, and therefore, generalization of our study results may be limited for patients with HCCs larger than 3 cm. In addition, further studies with multicenter design and large number of patients are warranted to externally validate our study results, especially in Western populations, as the causes of liver disease and/or HCC may be different from that in our study (i.e., hepatitis B viral infection in our study and hepatitis C viral infection or other alcohol-related disease in Western countries).

In conclusion, the presence of nonhypervascular HBP hypointense nodules on gadoxetic acid-enhanced MR taken prior to treatment was shown to be a significant predictive factor of tumor recurrence after both hepatic resection and RFA. However, in patients without nonhypervascular HBP hypointense nodules, hepatic resection may provide significantly better RFS than RFA.

Funding The authors state that there are no grants or funds supporting this study.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Jeong Min Lee.

Conflict of interest The authors declare that they have no conflict of interest.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- Retrospective
- Observational
- Performed at one institution

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P (2001) Estimating the world cancer burden: Globocan 2000. Int J Cancer 94:153–156
2. Mazzaferro V (2007) Results of liver transplantation: with or without Milan criteria? Liver Transpl 13:S44–S47
3. Bruix J, Sherman M, American American Association for the Study of Liver Diseases (2011) Management of hepatocellular carcinoma: an update. Hepatology 53:1020–1022
4. European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer (2012) EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 56:908–943
5. Yu SJ (2016) A concise review of updated guidelines regarding the management of hepatocellular carcinoma around the world: 2010-2016. Clin Mol Hepatol 22:7–17
6. Chen MS, Li JQ, Zheng Y et al (2006) A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg 243:321–328
7. N'Kontchou G, Mahamoudi A, Aout M et al (2009) Radiofrequency ablation of hepatocellular carcinoma: long-term results and prognostic factors in 235 Western patients with cirrhosis. Hepatology 50:1475–1483
8. Lee DH, Lee JM, Lee JY et al (2014) Radiofrequency ablation of hepatocellular carcinoma as first-line treatment: long-term results and prognostic factors in 162 patients with cirrhosis. Radiology 270:900–909
9. Forner A, Llovet JM, Bruix J (2012) Hepatocellular carcinoma. Lancet 379:1245–1255
10. Lai EC, Tang CN, Ha JP, Li MK (2009) Laparoscopic liver resection for hepatocellular carcinoma: ten-year experience in a single center. Arch Surg 144:143–147 discussion 148
11. Dagher I, Belli G, Fantini C et al (2010) Laparoscopic hepatectomy for hepatocellular carcinoma: a European experience. J Am Coll Surg 211:16–23
12. Guro H, Cho JY, Han HS, Yoon YS, Choi Y, Periyasamy M (2016) Current status of laparoscopic liver resection for hepatocellular carcinoma. Clin Mol Hepatol 22:212–218
13. Lee YJ, Lee JM, Lee JS et al (2015) Hepatocellular carcinoma: diagnostic performance of multidetector CT and MR imaging—a systematic review and meta-analysis. Radiology 275:97–109
14. Korean Society of Abdominal Radiology (2017) Diagnosis of Hepatocellular Carcinoma with Gadoxetic Acid-Enhanced MRI: 2016 Consensus Recommendations of the Korean Society of Abdominal Radiology. Korean J Radiol 18:427–443
15. Lee KH, Lee JM, Park JH et al (2013) MR imaging in patients with suspected liver metastases: value of liver-specific contrast agent gadoxetic acid. Korean J Radiol 14:894–904
16. Lee DH, Lee JM, Lee JY et al (2015) Non-hypervascular hepatobiliary phase hypointense nodules on gadoxetic acid-enhanced MRI: risk of HCC recurrence after radiofrequency ablation. J Hepatol 62:1122–1130
17. Toyoda H, Kumada T, Tada T et al (2013) Non-hypervascular hypointense nodules detected by Gd-EOB-DTPA-enhanced MRI are a risk factor for recurrence of HCC after hepatectomy. J Hepatol 58:1174–1180
18. Ahn SJ, Lee JM, Lee DH et al (2017) Real-time US-CT/MR fusion imaging for percutaneous radiofrequency ablation of hepatocellular carcinoma. J Hepatol 66:347–354
19. Goldberg SN, Grassi CJ, Cardella JF et al (2005) Image-guided tumor ablation: standardization of terminology and reporting criteria. Radiology 235:728–739
20. Kim YK, Lee WJ, Park MJ, Kim SH, Rhim H, Choi D (2012) Hypovascular hypointense nodules on hepatobiliary phase gadoxetic acid-enhanced MR images in patients with cirrhosis: potential of DW imaging in predicting progression to hypervascular HCC. Radiology 265:104–114
21. Hyodo T, Murakami T, Imai Y et al (2013) Hypovascular nodules in patients with chronic liver disease: risk factors for development of hypervascular hepatocellular carcinoma. Radiology 266:480–490
22. Yamamoto A, Ito K, Tamada T et al (2013) Newly developed hypervascular hepatocellular carcinoma during follow-up periods in patients with chronic liver disease: observation in serial gadoxetic acid-enhanced MRI. AJR Am J Roentgenol 200:1254–1260
23. Lee DH, Lee JM, Kang TW et al (2018) Clinical outcomes of radiofrequency ablation for early hypovascular HCC: a multicenter retrospective study. Radiology 286:338–349
24. Kumada T, Toyoda H, Tada T et al (2011) Evolution of hypointense hepatocellular nodules observed only in the hepatobiliary phase of gadoxetate disodium-enhanced MRI. AJR Am J Roentgenol 197:58–63
25. Suh CH, Kim KW, Pyo J, Lee J, Kim SY, Park SH (2017) Hypervascular transformation of hypovascular hypointense nodules in the hepatobiliary phase of gadoxetic acid-enhanced MRI: a systematic review and meta-analysis. AJR Am J Roentgenol 209:781–789
26. European Association for the Study of the Liver (2018) EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. https://doi.org/10.1016/j.jhep.2018.03.019
27. Heimbach JK, Kulik LM, Finn RS et al (2018) AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 67:358–380