Prediction of microvascular invasion of hepatocellular carcinoma: usefulness of peritumoral hypointensity seen on gadoxetate disodium-enhanced hepatobiliary phase images

Kyung Ah Kim

Department of Medicine

The Graduate School, Yonsei University

Prediction of microvascular invasion of hepatocellular carcinoma: usefulness of peritumoral hypointensity seen on gadoxetate disodium-enhanced hepatobiliary phase images

Kyung Ah Kim

Department of Medicine

The Graduate School, Yonsei University

Prediction of microvascular invasion of hepatocellular carcinoma: usefulness of peritumoral hypointensity seen on gadoxetate disodium-enhanced hepatobiliary phase images

Directed by Professor Myeong-Jin Kim

The Doctoral Dissertation
submitted to the Department of Medicine
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Doctor of Philosophy

Kyung Ah Kim

December 2011

This certifies that the Doctoral Dissertation of Kyung Ah Kim is approved.

Thesis Supervisor : Myeong-Jin Kim

Thesis Committee Member#1 : Jin-Sub Choi

Thesis Committee Member#2 : Kyung Sik Kim

Thesis Committee Member#3 : Sang Hoon Ahn

Thesis Committee Member#4 : Soon Joo Cha

The Graduate School
Yonsei University

December 2011

ACKNOWLEDGEMENTS

I am pleased to acknowledge a lot of people who have enabled me to complete this thesis successfully. First of all, I would like to give special thanks to my thesis director, Prof. Myeong-Jin Kim, who always encouraged me and supported me to complete this thesis. He helped me with endless patience, and extensive knowledge through my doctoral course. Whenever I met difficulties through doctoral course, he always gave me useful comments to overcome them and solve problems. Without his support and careful guidance, it would be impossible to complete this work. Moreover he helped me to build up the qualification as an abdominal radiologist. It is not enough to say a few words to thank him for his kindness.

I would like to thank readers as supervisory committee of this thesis, Prof. Jin-Sub Choi, Prof. Kyung Sik Kim, and Prof. Sang Hoon Ahn and Prof. Soon Joo Cha who reviewed my thesis proposal, and offered advices. I also want to express my gratitude to Hyae Min Jeon who reviewed pathologic slides and took pictures of pathologic slides. I am grateful to Prof. Ki Whang Kim, Prof. Mi-Suk Park, Prof. Joon Seok Lim, Prof. Jin Young Choi, Prof Young Eun Chung who always inspired me and gave useful comments. And I want to extend my thanks to all the people in the Department of Radiology in Yonsei University College of medicine.

I thank my parents, and parents-in-law. My parents and parents-in-law have

always supported not only for materials but also for spiritual encouragement. Finally, I thank my husband, Byung Keun Park and my daughters, Su-Min and Su-In who make me smile with endless love. With all my heart, I never forget all love and kindness from all of you.

December, 2011

Kyung Ah Kim

<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

<ABSTRACT>

Prediction of microvascular invasion of hepatocellular carcinoma: usefulness of peritumoral hypointensity seen on gadoxetate disodium-enhanced hepatobiliary phase images

Kyung Ah Kim

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Myeong-Jin Kim)

PURPOSE: To determine whether peritumoral hypointensity seen on hepatobiliary phase images of preoperative gadoxetate disodium-enhanced magnetic resonance imaging (EOB-MRI) is useful for predicting microvascular invasion of hepatocellular carcinoma (HCC).

METHOD AND MATERIALS: This study was approved by the institutional review board. One hundred and four HCC masses in 104 patients who had undergone EOB-MRI and liver surgery within one month after EOB-MRI were evaluated. Two radiologists independently recorded the presence of a peritumoral hypointensity on hepatobiliary phase. Interobserver agreement was assessed, and consensus records were used. Tumor size was measured. Chi-square test and independent *t*-tests were used for univariate analysis. Multiple logistic regression was performed to determine factors for predicting microvascular invasion. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of peritumoral hypointensity were calculated.

RESULTS: Sixty HCCs had microvascular invasion and 44 did not. Interobserver agreement in determining peritumoral hypointensity was excellent

(κ = 0.83). By univariate analysis, peritumoral hypointensity and tumor size were significant for predicting microvascular invasion of HCC. On multiple logistic regression analysis, only peritumoral hypointensity was significant in predicting microvascular invasion of HCC (p=0.013). The sensitivity, specificity, PPV, and NPV of peritumoral hypointensity were 38.3%, 93.2%, 88.5%, and 52.6%.

CONCLUSION: Peritumoral hypointensity on the hepatobiliary phase of EOB-MRI is not sensitive but has high specificity for predicting microvascular invasion of HCC.

Key words: hepatocellular carcinoma, pathology, diagnosis, microvascular invasion, gadoxetate disodium, magnetic resonance imaging

Prediction of microvascular invasion of hepatocellular carcinoma: usefulness of peritumoral hypointensity seen on gadoxetate disodium-enhanced hepatobiliary phase images

Kyung Ah Kim

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Myeong-Jin Kim)

I. INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver [1]. Without treatment, the prognosis for patients with HCC is known to be very poor with a median survival of 6 to 9 months [2]. Surgery is regarded as the curative treatment of choice for eligible patients [3]. The size, number, and nuclear grade of the tumors, presence of vascular invasion, and severity of liver disease are all regarded as important predictors of postoperative recurrence and survival [4, 5]. Of these, the presence of vascular invasion is considered an independent prognostic factor for tumor invasiveness that could result in metastasis [6-8]. Therefore, preoperative identification of vascular invasion is important when determining the best candidates for surgical resection or liver transplantation and predicting postoperative outcome. Vascular invasion can be classified as macrovascular invasion, which involves major (first or second branches) portal or hepatic veins, and microvascular invasion, which involves

third branches or microscopic vessels [9]. Myata et al reported that microvascular and major vascular invasions of HCC were related with a 4.4- and 15-fold increased risk of tumor recurrence, respectively [10]. Malignant portal vein thrombus in major portal branches can be identified on Doppler ultrasound (US) or contrast enhanced US [11, 12]. Enhancing expansile portal vein thrombus on computed tomography (CT) or magnetic resonance imaging (MRI) is highly suggestive of malignant thrombus caused by HCC [13, 14]. However, microvascular invasion resulting from HCC is difficult to detect on preoperative imaging. Although invasion of major branches of the portal or hepatic vein can be accurately identified with sensitivities of 81 – 95% on preoperative imaging [9, 15], it is still difficult to detect microvascular invasion caused by HCC [16].

Gadoxetate disodium, a recently introduced hepatobiliary contrast agent, is widely used to improve detection and characterization of HCC [17-21]. In clinical practice, we have observed areas of hypointensity around some HCCs on hepatobiliary phase images of gadoxetate disodium-enhanced MRI (EOB-MRI). These HCCs turned out to be associated with microvascular invasion upon pathological examination. We hypothesized that this peritumoral hypointensity may be an indicator of microvascular invasion of HCC. The purpose of this study was to determine whether peritumoral hypointensity seen on hepatobiliary phase images of EOB-MRI could be useful for predicting microvascular invasion of HCC.

II. MATERIALS AND METHODS

1. Patients

This retrospective study was approved by the institutional review board at our institution and the requirement for informed consent was waived. MRI using gadoxetate disodium was performed in 2159 consecutive patients between March 2008 and June 2009. Patients who were diagnosed with HCC and underwent liver resection or transplantation within one month after undergoing MRI were selected. None of the patients underwent any locoregional treatment of HCC during the period between MRI and surgery. Patients who underwent preoperative MRI more than one month before the surgery or who had previously received any treatment for HCC, were excluded. A total of 104 patients were finally included in the study (80 males and 24 females; mean age, 55 years; range, 28 – 76 years). The main tumor mass in each patient was evaluated and any other lesion that might represent a satellite tumor or intrahepatic metastasis was excluded. Thus, 104 HCC lesions were assessed in 104 patients. The presence of microvascular tumor invasion from HCC was evaluated from pathological reports of surgical specimens. At our institution, presence or absence of microvascular invasion is always described in the postoperative pathologic reports of HCC. Microvascular invasion was defined as a tumor within the vascular space lined by endothelium that was visible only on microscopy [8].

2. Image acquisition

MRI examinations were performed with a 3.0 T magnetic resonance (MR) system (Magnetom Tim Trio; Siemens Medical Solutions, Erlangen, Germany). In-phase and opposed-phase T1 weighted images (TR 140; TE 1.23; slice thickness, 5.5 mm; flip angle, 65°; matrix, 256 × 192; Echo train length (ETL), 1) and T2-weighted images (TR 3,765; TE 88; slice thickness, 5 mm; flip angle, 150°; ETL, 30; matrix, 256 × 192) were obtained. Precontrast images were acquired with a fat-suppressed T1-weighted gradient echo (GRE) sequence (TR 2.54; TE 0.92; slice thickness, 2 mm; flip angle, 12.8606°; ETL, 1; matrix, 256 × 192). A test bolus timing image was acquired by using 1.0 ml of gadoxetate disodium (Primovist, Bayer Schering Pharma, Berlin, Germany) at a flow rate of 2.0 ml/s. After the test bolus, gadoxetate disodium at a dose of 0.025 mmoL/kg was injected intravenously at a flow rate of 2.0 ml/s, followed by a 20 ml saline flush. Dynamic imaging was carried out in four phases (arterial, portal, hepatic and equilibrium) using the same sequences used for precontrast images. Hepatobiliary phase (HBP) images were acquired 10 – 20 minutes after gadoxetate disodium injection.

3. Image analysis

Imaging analysis was done using the picture archiving and communication

system (Centricity RA1000; GE Healthcare, Milwaukee, Wis). The largest tumor mass -in each patient was evaluated through review of imaging. Two radiologists with 18 and 3 years of experience in abdominal imaging, respectively, were blinded to the pathologic results of microvascular invasion of HCC and independently reviewed peritumoral hypointensity in the dynamic four phases (arterial, portal, hepatic and equilibrium) and HBP MR images. Peritumoral hypointensity was defined as an irregular, wedge-shaped or flame-like hypointense area of liver parenchyma located outside of the tumor margin. The hypointense areas were relatively hypointense to the surrounding parenchyma, but less hypointense than the tumor itself in most cases. In a few cases of hyperintense HCCs, the areas were more hypointense than the hyperintese area of the tumor, but were less hypointense than the hypointense rim that was usually depicted in those hyperintense HCCs. When the two radiologists differed in their interpretation of images, a conclusion was reached by consensus. Tumor size defined by the maximum diameter was measured by a radiologist at a workstation with picture acquisition and communication system.

4. Statistics

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, version 17.0; SPSS, Chicago, IL). Interobserver agreement for peritumoral low SI on HBP images were assessed as kappa value:

0-0.20, slight agreement; 0.21-0.40, fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, substantial agreement; and 0.81-1.00, almost perfect agreement [22]. The diagnostic accuracy of variables (tumor size and peritumoral hypointensity on HBP imaging) for predicting microvascular invasion of HCC was measured using the area under the receiver operating characteristic curve (AUC). A chi-square test was used for univariate analysis of the relationship between microvascular invasion of HCC and peritumoral hypointensity on HBP imaging. An independent *t*-test was used for univariate analysis to determine the existence of a relationship between microvascular invasion of HCC and tumor size. Logistic regression analysis for the two imaging factors was performed to evaluate the usefulness of tumor size and peritumoral hypointensity on HBP images for predicting microvascular invasion of HCC. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for peritumoral hypointensity on HBP images. A p-value less than 0.05 was considered statistically significant.

III. RESULTS

Microvascular invasion was found in 60 (57.7%) of the 104 HCCs upon histopathological examination. Tumor size ranged from 1.4 to 15.5 cm (mean, 3.6 cm) with 15 tumors < 2 cm, 68 tumors of 2 to < 5 cm, and 21 tumors ≥ 5 cm in diameter. The mean diameter of the tumor showing microvascular invasion (4.10 cm ± 2.31) was significantly greater than that of HCCs without microvascular invasion (2.92 cm ± 1.24, p = 0.001) (Table 1). At a cut-off value of tumor size > 2.2 cm, the AUC was 0.673 (95% CI: 0.574 to 0.762) for predicting microvascular invasion with 86.6% (95% CI: 75.4 - 94.0) sensitivity, 38.6% (95% CI: 24.4 - 54.5) specificity, a PPV of 65.8% (95% CI; 54.29 - 76.13), and a NPV of 68% (95% CI: 46.50 - 85.01). Tumor size was not a statistically significant predictor of microvascular invasion of HCC upon multiple logistic regression analysis (p = 0.071).

Table 1. Univariate analysis of peritumoral hypointensity on hepatobiliary phase imaging and tumor size for prediction of microvascular invasion of hepatocellular carcinoma.

Imaging findings		MVI (-) (n=44)	MVI (+) (n=60)	Subtotal	P-value
Peritumoral hypointensity					<0.001
	Yes	3 (2.9 %)	23 (22.1 %)	26 (25 %)	
	No	41 (39.4 %)	37 (35.6 %)	78 (75 %)	
	Subtotal	44 (42.3 %)	60 (57.7 %)	104 (100 %)	
Tumor size					0.001
	< 2 cm	10 (9.6 %)	5 (4.8 %)	15 (14.4 %)	
	2 - 5 cm	31 (29.8 %)	39 (37.5 %)	70 (67.3 %)	
	> 5 cm	3 (2.9 %)	16 (15.4 %)	19 (18.3 %)	
	Subtotal	44 (42.3 %)	60 (57.7 %)	104 (100 %)	

MVI = microvascular invasion

Peritumoral hypointensity was seen in 26 (25.0%) of 104 HCCs on HBP images of EOB-MRI (Table 1), and 23 (88.5%) of them showed microvascular invasion upon histopathological examination (Fig. 1, 2). None of the patients showed similar hypointensity on precontrast, arterial, or portal phase images. In nine of 26 patients, peritumoral hypointensity were noted on hepatic or equilibrium phase images, but they were less distinct than the peritumoral hypointensity seen on HBP images. Peritumoral hypointensity was statistically significant for predicting microvascular invasion of HCC in both univariate analysis ($p < 0.001$) and multiple logistic regression ($p = 0.013$). The sensitivity, specificity, PPV, and NPV for predicting microvascular invasion by the presence of peritumoral hypointensity were 38.3%, 93.2%, 88.5%, and 52.6%, respectively. The AUC for predicting microvascular invasion by the presence of peritumoral hypointensity was 0.658 (95% CI: 0.558 – 0.748). The kappa value for interobserver agreement between the two radiologists in determining the presence of peritumoral hypointensity was 0.83, indicating almost perfect agreement.

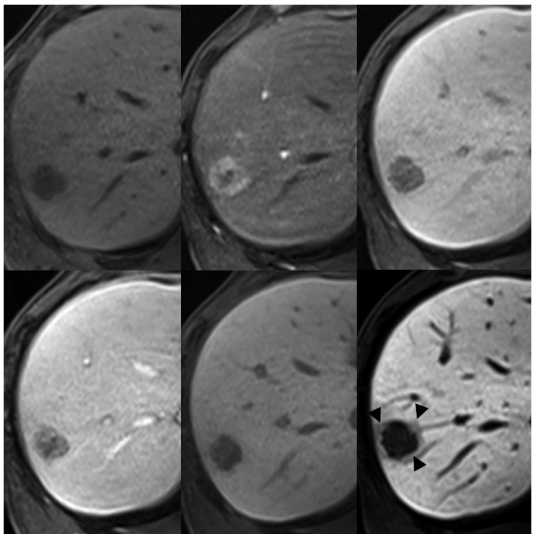
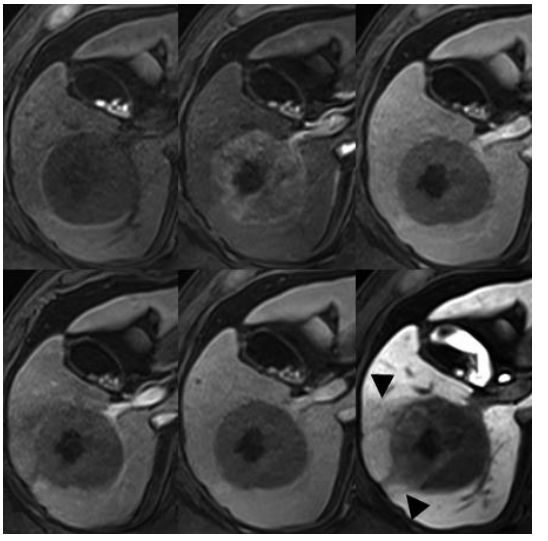
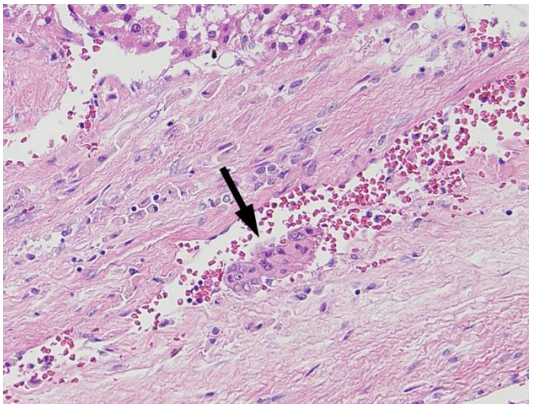


Figure 1. A 66-year-old man. Precontrast image, arterial phase, portal phase, hepatic phase, equilibrium phase, and hepatobiliary phase of gadoxetic acid-enhanced MRI are arranged in order. HCC (size 2.3 cm) in the right lobe of the liver shows typical arterial enhancement and delayed washout. Peritumoral low signal intensity (three arrow heads) is noted around the tumor in the hepatobiliary phase image.



A



B

Figure 2. (A) A 63-year-old man. Precontrast image, arterial phase, portal phase, hepatic phase, equilibrium phase, and hepatobiliary phase of gadoxetic acid-enhanced MRI are arranged in order. A large HCC (8.5 cm) in the right lobe of the liver shows typical arterial enhancement and delayed washout. Peritumoral low signal intensity (two arrow heads) is noted around the tumor in

the equilibrium phase and hepatobiliary phase images. (B) Microscopic evaluation reveals a tumor thrombus (black arrow) within the small vessel. (Hematoxylin-eosin stain,100 x magnification)

IV. DISCUSSION

Our study showed that peritumoral hypointensity seen on HBP images of EOB-MRI can be useful for predicting microvascular invasion of HCC preoperatively. The presence of peritumoral hypointensity showed high specificity (93.2%) and a positive predictive value of 88.5%. This relationship may be explained by decreased uptake of gadoxetate disodium by hepatocytes due to obstruction of minute portal branches by tumor thrombi, resulting in hemodynamic changes. Similar findings around hepatic tumors have been reported for superparamagnetic iron oxide (SPIO)-enhanced MRI [10, 23, 24]. Scharf et al. [23] and Mori et al. [24] showed that when portal perfusion decreases around a tumor, uptake of SPIO also decreases in the liver parenchyma surrounding the tumor. If the intrahepatic portal vein is occluded and hepatic arterial flow is insufficiently compensated, the liver parenchyma is injured, causing edema, hepatocytic depletion, and fibrosis [25]. The cause of peritumoral hypointensity on HBP images of EOB-MRI may be similar to that of impaired uptake of SPIO. Perfusion changes by microvascular invasion of HCC may affect not only Kupffer cells but also the organic anion transporting peptides (OATPs) or the canalicular transporter multidrug resistance-associated protein 2 (MRP2) within hepatocytes, which are known to be responsible for the uptake of gadoxetate disodium [26-28].

Although our study showed that peritumoral hypointensity was highly

specific (93.2%) for the diagnosis of microvascular invasion of HCC, this type of finding was not common (25% of overall HCC) and its sensitivity was low (38%). In our study, peritumoral hypointensity, if present around the tumor, was usually seen on HBP images or, less frequently, on late dynamic phase images. Peritumoral hypointensity was not seen on precontrast or early phase images in dynamic studies. This may be explained by the biphasic enhancement characteristics of gadoxetate disodium, which enable two separate imaging acquisition sessions for early dynamic and delayed hepatobiliary phase imaging [29]. During early dynamic phase imaging, gadoxetic acid acts as an extracellular MR contrast material that reflects early hemodynamic changes. However, during the delayed phase images, it acts as a hepatocyte-specific agent reflecting hepatocyte function. Our finding that peritumoral hypointensity was seen on HBP images but not on early dynamic phase images suggests that peritumoral hypointensity reflects the alteration of hepatic function around tumors with microvascular invasion. Therefore, the relatively low sensitivity of peritumoral hypointensity for the detection of microvascular invasion in our study may be explained by the lack of change in peritumoral hepatocyte function in some tumors, despite the presence of microvascular invasion.

In our study, tumor size was not an independent predictor for microvascular invasion, even though it was a significant factor in univariate analysis. Tumor size has long been considered an important predictor for the

presence of microvascular invasion, postoperative recurrence, or prognosis [10, 30-32], but has not always been confirmed as an independent predictor [33, 34]. One possible reason for our finding that tumor size was not an independent predictor for microvascular invasion of HCC is the fact that only surgically eligible cases were included in our study and all lesions were 1.4 cm or larger. Therefore, it is possible that, if smaller lesions had been included, tumor size might have a closer relationship with the presence of microvascular invasion. We found that a cut-off value of 2.2 cm yielded the greatest AUC value for the prediction of microvascular invasion, with a sensitivity of 86.7%, but that specificity was as low at 38.6%. The recommended cut-off value for tumor size as a predictor of microvascular invasion varies from 3 to 7 cm [30, 35, 36].

One of the limitations of our study is that we did not compare the relative accuracy between peritumoral hypointensity and other imaging findings that have been described in previous studies [10, 33, 34, 37]. Nishie et al. [37] and Shirabe et al. [33] showed that the areas of peritumoral hemodynamic change or perfusion defects seen on CT during arterioportography (CTAP) or hepatic arteriography (CTHA) were larger in HCCs with minute portal invasion. Miyata et al. [10] also showed that distortion of corona and tumorous arterioportal (AP) shunt as determined by SPIO-enhanced MRI and CTHA were useful predictors of microvascular invasion. However, we could not compare our results with their findings because CTAP and CTHA are invasive techniques that are not

widely performed. In a study by Kim et al. [34], gadobenate dimeglumine - enhanced multi-arterial phase dynamic MRI was used to demonstrate that irregular circumferential peritumoral enhancement was helpful in predicting microvascular invasion. However, multi-arterial phase dynamic imaging is not currently available, and gadobenate dimeglumine was not used in our study because it requires a relatively long (60 – 90 minutes) scan delay time for the acquisition of HBP images.

Another limitation of our study is that we didn't perform quantitative analysis of hypointensity in our study. Peritumoral hypointensity was usually seen as an irregular wedge-shaped or flame-like appearance, and was clearly defined from the tumor or peritumoral parenchyma. Therefore, quantification of the signal intensity was deemed not to be realistic in clinical practice. Another limitation is that we did not evaluate interobserver agreement between the radiologists or pathologists. In addition, test-retest immediate reproducibility was not assessed. However, we did not experience a remarkable discrepancy between radiologists regarding the identification of peritumoral hypointensity. For the histologic analysis, presence of microvascular invasion was prospectively determined by a liver pathologist based on obvious identification of microscopic tumor thrombi. Therefore, we believe that the results should be reproducible. Finally, in our study, the extent of peritumoral intensity and the amount of microvascular invasion were not quantitatively correlated with each

other. Peritumoral hypointensity was usually present in a substantial area of the tumor boundary, but whether microvascular invasion was present in many or few vessels, or whether the invasion was only present close to the main tumor or extended to far from the tumor were not assessed. Further studies to define the relationship between imaging findings and the degree of microvascular invasion are warranted.

V. CONCLUSION

In conclusion, the presence of peritumoral hypointensity on HBP images was found to be specific for the diagnosis of microvascular invasion of HCC on preoperative gadoxetate disodium-enhanced MRI, although the sensitivity was low. Radiologists should be aware of this potentially helpful finding when planning surgical resection in patients with HCC.

REFERENCES

1. Yang JD, Roberts LR. Epidemiology and management of hepatocellular carcinoma. Infect Dis Clin North Am 2010;24:899-919, viii.
2. Barbara L, Benzi G, Gaiani S, Fusconi F, Zironi G, Siringo S, et al. Natural history of small untreated hepatocellular carcinoma in cirrhosis: a multivariate analysis of prognostic factors of tumor growth rate and patient survival. Hepatology 1992;16:132-7.
3. Hao K, Luk JM, Lee NP, Mao M, Zhang C, Ferguson MD, et al. Predicting prognosis in hepatocellular carcinoma after curative surgery with common clinicopathologic parameters. BMC Cancer 2009;9:389.
4. Vauthey JN, Klimstra D, Franceschi D, Tao Y, Fortner J, Blumgart L, et al. Factors affecting long-term outcome after hepatic resection for hepatocellular carcinoma. Am J Surg 1995;169:28-34; discussion -5.
5. Wayne JD, Lauwers GY, Ikai I, Doherty DA, Belghiti J, Yamaoka Y, et al. Preoperative predictors of survival after resection of small hepatocellular carcinomas. Ann Surg 2002;235:722-30; discussion 30-1.
6. Hemming AW, Cattral MS, Reed AI, Van Der Werf WJ, Greig PD, Howard RJ. Liver transplantation for hepatocellular carcinoma. Ann Surg 2001;233:652-9.
7. Imamura H, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Miyagawa S, et al. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. J Hepatol 2003;38:200-7.
8. Roayaie S, Blume IN, Thung SN, Guido M, Fiel MI, Hiotis S, et al. A system of classifying microvascular invasion to predict outcome after resection in patients with hepatocellular carcinoma. Gastroenterology 2009;137:850-5.
9. Eguchi S, Takatsuki M, Hidaka M, Soyama A, Tomonaga T, Muraoka I, et al. Predictor for histological microvascular invasion of hepatocellular carcinoma: a lesson from 229 consecutive cases of curative liver resection. World J Surg 2010;34:1034-8.
10. Miyata R, Tanimoto A, Wakabayashi G, Shimazu M, Nakatsuka S, Mukai M, et al. Accuracy of preoperative prediction of microinvasion of portal vein in hepatocellular carcinoma using superparamagnetic iron oxide-enhanced magnetic resonance

imaging and computed tomography during hepatic angiography. J Gastroenterol 2006;41:987-95.
11. Sorrentino P, D'Angelo S, Tarantino L, Ferbo U, Bracigliano A, Vecchione R. Contrast-enhanced sonography versus biopsy for the differential diagnosis of thrombosis in hepatocellular carcinoma patients. World J Gastroenterol 2009;15:2245-51.
12. Tarantino L, Francica G, Sordelli I, Esposito F, Giorgio A, Sorrentino P, et al. Diagnosis of benign and malignant portal vein thrombosis in cirrhotic patients with hepatocellular carcinoma: color Doppler US, contrast-enhanced US, and fine-needle biopsy. Abdom Imaging 2006;31:537-44.
13. Shah ZK, McKernan MG, Hahn PF, Sahani DV. Enhancing and expansile portal vein thrombosis: value in the diagnosis of hepatocellular carcinoma in patients with multiple hepatic lesions. AJR Am J Roentgenol 2007;188:1320-3.
14. Tublin ME, Dodd GD, 3rd, Baron RL. Benign and malignant portal vein thrombosis: differentiation by CT characteristics. AJR Am J Roentgenol 1997;168:719-23.
15. Shirabe K, Kajiyama K, Harimoto N, Masumoto H, Fukuya T, Ooya M, et al. Prognosis of hepatocellular carcinoma accompanied by microscopic portal vein invasion. World J Gastroenterol 2009;15:2632-7.
16. Cucchetti A, Piscaglia F, Grigioni AD, Ravaioli M, Cescon M, Zanello M, et al. Preoperative prediction of hepatocellular carcinoma tumour grade and micro-vascular invasion by means of artificial neural network: a pilot study. Journal of hepatology 2010;52:880-8.
17. Kim SH, Lee J, Kim MJ, Jeon YH, Park Y, Choi D, et al. Gadoxetic acid-enhanced MRI versus triple-phase MDCT for the preoperative detection of hepatocellular carcinoma. AJR Am J Roentgenol 2009;192:1675-81.
18. Ahn SS, Kim MJ, Lim JS, Hong HS, Chung YE, Choi JY. Added value of gadoxetic acid-enhanced hepatobiliary phase MR imaging in the diagnosis of hepatocellular carcinoma. Radiology 2010;255:459-66.
19. Di Martino M, Marin D, Guerrisi A, Baski M, Galati F, Rossi M, et al. Intraindividual Comparison of Gadoxetate Disodium-enhanced MR Imaging and 64-Section Multidetector CT in the Detection of Hepatocellular Carcinoma in Patients with Cirrhosis. Radiology 2010;256:806-16.
20. Akai H, Kiryu S, Matsuda I, Satou J, Takao H, Tajima T, et al.

Detection of hepatocellular carcinoma by Gd-EOB-DTPA-enhanced liver MRI: Comparison with triple phase 64 detector row helical CT. Eur J Radiol 2010.
21. 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;20:2405-13.
22. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159-74.
23. Scharf J, Hoffmann V, Lehnert T, Anselm H, Richter GM, Kauffmann GW. Pseudolesions at T1-weighted gradient-echo imaging after administration of superparamagnetic iron oxide: comparison with portal perfusion abnormalities at CT during arterial portography. Radiology 1998;207:67-72.
24. Mori K, Yoshioka H, Itai Y, Okamoto Y, Mori H, Takahashi N, et al. Arterioportal shunts in cirrhotic patients: evaluation of the difference between tumorous and nontumorous arterioportal shunts on MR imaging with superparamagnetic iron oxide. AJR Am J Roentgenol 2000;175:1659-64.
25. Choi BI, Lee KH, Han JK, Lee JM. Hepatic arterioportal shunts: dynamic CT and MR features. Korean J Radiol 2002;3:1-15.
26. Tsuda N, Matsui O. Cirrhotic rat liver: reference to transporter activity and morphologic changes in bile canaliculi--gadoxetic acid-enhanced MR imaging. Radiology 2010;256:767-73.
27. Tsuboyama T, Onishi H, Kim T, Akita H, Hori M, Tatsumi M, et al. Hepatocellular Carcinoma: Hepatocyte-selective Enhancement at Gadoxetic Acid-enhanced MR Imaging--Correlation with Expression of Sinusoidal and Canalicular Transporters and Bile Accumulation. Radiology 2010;255:824-33.
28. Kitao A, Zen Y, Matsui O, Gabata T, Kobayashi S, Koda W, et al. Hepatocellular Carcinoma: Signal Intensity at Gadoxetic Acid-enhanced MR Imaging--Correlation with Molecular Transporters and Histopathologic Features. Radiology 2010;256:817-26.
29. Kim YK, Kwak HS, Kim CS, Han YM. Detection and characterization of focal hepatic tumors: a comparison of T2-weighted MR images before and after the administration of gadoxectic acid. J Magn Reson Imaging 2009;30:437-43.
30. Kaibori M, Ishizaki M, Matsui K, Kwon AH. Predictors of microvascular invasion before hepatectomy for hepatocellular carcinoma. J Surg Oncol 2010;102:462-8.

31. Sakata J, Shirai Y, Wakai T, Kaneko K, Nagahashi M, Hatakeyama K. Preoperative predictors of vascular invasion in hepatocellular carcinoma. Eur J Surg Oncol 2008;34:900-5.
32. Kim BK, Han KH, Park YN, Park MS, Kim KS, Choi JS, et al. Prediction of microvascular invasion before curative resection of hepatocellular carcinoma. J Surg Oncol 2008;97:246-52.
33. Shirabe K, Kajiyama K, Abe T, Sakamoto S, Fukuya T, Akazawa K, et al. Predictors of microscopic portal vein invasion by hepatocellular carcinoma: measurement of portal perfusion defect area ratio. J Gastroenterol Hepatol 2009;24:1431-6.
34. Kim H, Park MS, Choi JY, Park YN, Kim MJ, Kim KS, et al. Can microvessel invasion of hepatocellular carcinoma be predicted by pre-operative MRI? Eur Radiol 2009;19:1744-51.
35. Adachi E, Maeda T, Kajiyama K, Kinukawa N, Matsumata T, Sugimachi K, et al. Factors correlated with portal venous invasion by hepatocellular carcinoma: univariate and multivariate analyses of 232 resected cases without preoperative treatments. Cancer 1996;77:2022-31.
36. Esnaola NF, Lauwers GY, Mirza NQ, Nagorney DM, Doherty D, Ikai I, et al. Predictors of microvascular invasion in patients with hepatocellular carcinoma who are candidates for orthotopic liver transplantation. J Gastrointest Surg 2002;6:224-32; discussion 32.
37. Nishie A, Yoshimitsu K, Asayama Y, Irie H, Tajima T, Hirakawa M, et al. Radiologic Detectability of Minute Portal Venous Invasion in Hepatocellular Carcinoma. Am J Roentgenol 2008;190:81-7.

< ABSTRACT (IN KOREAN)>

간암의 미세혈관침범 예측: Gadoxetate disodium 조영 증강 후 얻은 자기공명영상상 지연기 종양 주변부 저음영의 유용성

<지도교수 김 명 진 >

연세대학교 대학원 의학과

김경아

연구목적: 수술 전 Gadoxetate disodium (EOB) 으로 조영 증강하여 얻은 자기공명영상 지연기에 보이는 종양 주변부의 저음영이 간암의 미세혈관 침범을 예측하는데 도움이 되는지 알아보고자 하였다.

연구대상 및 방법: 본 연구는 임상시험심사위원회의 승인을 받았다. 수술 전 EOB로 조영 증강하여 얻은 자기공명영상검사를 시행했고, 동검사 시행 후 한달 이내에 간 수술을 받은 104 명의 간암 환자에서 관찰된 104개의 간암 종괴를 대상으로 하였다. 두 명의 영상의학과 의사가 각각 독립적으로 자기공명영상을 분석하여 지연기 영상에서 종양 주변부의 저음영이 있는지 유무를 표시하였다. 독립적 영상 분석 후, 지연기 영상에서 종양 주변부의 저음영의 유무에 대한

관찰자간 의견 일치 정도를 살펴보고, 이에 대한 합의를 이루어 최종적으로 분석 결과를 얻었다. 그리고 종양의 크기를 측정하였다. 지연기 영상에서 종양 주변부의 저음영과 종양 크기에 따른 간암의 미세혈관 침범 여부를 예측하는 것에 대해 Chi-square test 와 independent *t*-tests을 이용하여 일변량 분석을 시행하였다. 간암의 미세혈관 침범을 예측하는데 도움이 되는 요인을 찾기 위해 다변량 분석법도 시행하였다. 그리고 지연기 영상에서 종양 주변부에서 보이는 저음영이 간암의 미세혈관 침범을 예측하는 것에 대한 민감도, 특이도, 양성예측도, 음성예측도를 구하였다.

연구결과: 60 개의 간암에서는 미세혈관 침범이 있었고, 44 개의 간암에서는 미세혈관 침범이 관찰되지 않았다. 지연기 영상에서 종양 주변부의 저음영 유무에 대한 관찰자간 일치도는 높았다. (κ = 0.83) 간암의 미세혈관 침범 예측력에 대한 일변량 분석 결과에서는 지연기 영상에서 보이는 종양 주변부의 저음영과 종양 크기 모두가 통계학적으로 의의가 있었다. 그러나 다변량 분석에서는 간암의 미세혈관 침범을 예측하는데, 지연기 영상에서 보이는 종양 주변부의 저음영만이 통계학적으로 의의가 있었다 (p = 0.013). 지연기 영상에서 보이는 종양 주변부의 저음영으로 간암의 미세혈관 침범을

예측하는데 대한 민감도, 특이도, 양성예측도, 음성예측도는 각각 38.3%, 93.2%, 88.5%, 52.6% 였다.

결론: EOB로 조영 증강하여 얻은 자기공명영상 지연기에 보이는 종양 주변부의 저음영은 간암의 미세혈관 침범을 예측하는데 민감도는 낮았지만 특이적인 소견이었다.

핵심되는 말 : 간암, 병리학, 진단, 미세혈관 침범, gadoxetate disodium, 자기공명영상