Int J Clin Exp Med 2018;11(3):2551-2558
www.ijcem.com /ISSN:1940-5901/IJCEM0063072

Original Article

Comparison of gadoxetic acid disodium-enhanced MRI and biphasic spiral CT in detection of hepatocellular carcinoma in patients meeting the Milan criteria

Wenjie Tang*, Jie Qin*, Bing Hu, Lina Zhang, Ruomi Guo, Jin Wang

*Department of Radiology, The Third Affiliated Hospital, Sun Yat-sen University, Guangzhou, China. *Equal contributors.*

Received August 5, 2017; Accepted November 23, 2017; Epub March 15, 2018; Published March 30, 2018

Abstract: *Objective:* To prospectively compare gadoxetate disodium-enhanced MRI with biphasic spiral CT in the detection of HCC in patients within the Milan criteria. *Methods:* The study was designed as a prospective, open-label, within-patient with a corresponding blinded reading. AUCs were also applied to compare for the comparison of combined unenhanced and gadoxetic acid disodium-enhanced MRI versus biphasic spiral CT using the Hanleyand McNeil method. *Results:* For all liver lesions meeting Milan criteria, the diagnostic accuracy across the three readers was significantly greater with Gadoxetic acid disodium-enhanced MR imaging than with biphasic spiral CT. The AUC of GAD enhanced MRI were 0.873 with 95% CI = 0.801-0.925, 0.928 with 95% CI = 0.869-0.967 and 0.854 with 95% CI = 0.780-0.911 respectively in Reader 1, 2, and 3. The AUC of biphasic spiral CT were 0.724 with 95% CI = 0.638-0.800, 0.705 with 95% CI = 0.617-0.783 and 0.669 with 95% CI = 0.580-0.751 respectively in Reader 1, 2, and 3. The sensitivity across the three readers was significantly greater with Gadoxetic acid disodium-enhanced MR imaging than with biphasic spiral CT. Average across Readers were 0.851 with 95% CI = 0.745-0.962 *vs.* 0.692 with 95% CI = 0.596-0.793, respectively. *Conclusion:* Compared with biphasic spiral CT, Gadoxetic acid disodium-enhanced MRI yields significantly higher diagnostic accuracy and sensitivity in the detection of HCC in patients within Milan criteria.

Keywords: Magnetic resonance imaging, computed tomography, HCC, Milan criteria

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy cancer worldwide and the second most common cause of cancer-related mortality [1, 2]. It was estimated 78-2,000 new cases of HCC were diagnosed in 2012, of which 83% occurred in the developing areas, especially China [3, 4]. Liver transplantation is considered to be the most effective therapeutic option for patients with HCC, with the best long-term outcome occurring when it is performed in patients with localized tumors meeting the Milan criteria (a single lesion measuring 5 cm or 3 lesions measuring 3 cm in largest diameter and the absence of vascular invasion or extrahepatic disease) [5-7]. Moreover, many treatment options including hepatic resection (HR), transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA) are also applied for patients with Milan criteria [8, 9].

Imaging modalities could provide an exact diagnosis to enable optimal medical management for each patient. With the improvement of diagnostic modalities for HCC meeting the Milan criteria, the relevance ratio and detection of early-stage HCC have improved significantly [10]. Accurate identification of the number, size, location, and differential diagnosis of hepatic lesions is required for the final therapeutic decision. Contrast-enhanced ultrasound, computed tomography during arterial portography (CTAP), contrast-enhanced biphasic spiral computed tomography (CT), and magnetic resonance imaging (MRI), have been successfully used for the planning of a therapeutic strategy [11-13]. Despite of the improvements in the spatial and temporal resolution of both CT and MRI, neither technique is entirely satisfactory for the accurate assessment of HCC in patients with early HCC (tumor size <2 cm in diameter) [14].

Although contrast-enhanced CT is the most widely used imaging technique for the detection and characterization of liver lesions [15, 16], MRI is an attractive alternative. In MRI, a variety of quantitative and qualitative determinants, such as signal intensity characteristics, lesion morphology, and contrast uptake patterns, have been proposed for lesion characterization [17]. Gadolinium ethoxybenzyl diethylenetriaminepenta-acetic acid (gadoxetic acid disodium or Gd-EOB-DTPA) is a novel dual-acting but tissue-specific MR contrast agent targeted to liver imaging [18, 19]. It is given as a bolus and dynamic imaging is thus possible. After intravenous bolus injection, gadoxetic acid disodium is partially taken up by functioning hepatocytes and excreted without biotransformation through the biliary system [20]. Such a pharmacokinetic profile enables the acquisition in a single examination of a standard dynamic MR study of the liver.

Several studies have compared gadoxetic acid disodium-enhanced MRI with multiphasic contrast CT in the detection of patients with HCC [21, 22] and indicated that gadoxetic acid disodium-enhanced MRI yields significantly higher diagnostic accuracy and sensitivity in the detection of HCC in patients. To our knowledge no study had focused on detection of early HCC (meeting the Milan criteria). The purpose of this study was to prospectively compare gadoxetate disodium-enhanced MRI with biphasic single-slice spiral CT in the detection of HCC in the patients with early HCC.

Materials and methods

The study was designed as a prospective, open-label, within-patient comparison of the diagnostic performance of gadoxetic acid-enhanced MRI and CT in terms of the detection and differential diagnosis of focal liver lesions with a corresponding blinded reading. The study was approved by the ethics committee of Sun Yat-sen University. All patients gave their written informed consent.

Patients

Patients with age of at least 18 years, known or suspected focal liver lesions, who had been scheduled for CT, and liver surgery were included in the study. Exclusion criteria were previous injection of gadoxetic acid, any other investigational product (within 30 days prior to study entry), other contrast material within 24 h prior to or after administration of the study medication, and injection of any liver-specific agent within 2 weeks prior to the study. Pregnant or lactating women, clinically unstable patients, patients scheduled for biopsy or liver surgery within 24 h post-administration of the study medication or patients with a known anaphylactoid or anaphylactic reaction to any other drug were also excluded.

MR and CT imaging

MR imaging was performed with a 1.5-T unit (OPTIMA MR360 General Electric Company) with a 8-radiofrequency channel system, which provided a maximum gradient strength of 45 mT/m and a peak slew rate of 200 mT/m/msec. All patients underwent unenhanced, single-breath-hold, T2-weighted two- dimensional turbo spin-echo and T1-weighted two-dimensional dual gradient recalled echo (GRE) MR imaging. After unenhanced imaging, patients received the full dose (0.025 mmol per kilogram of body weight) of gadoxetate disodium (Primovist, Bayer Schering Pharma; 0.1 mL per kilogram of body weight) at a rate of 2 mL/sec through a 20-gauge intravenous catheter placed into a peripheral vein. Contrast medium administration was followed by a 20-mL saline flush at a rate of 2 mL/sec. T1-weighted three-dimensional spoiled GRE volumetric interpolated breath-hold (VIBE) images were obtained at 20-40, 60, and 180 seconds after contrast medium injection, during the hepatic arterial, hepatic venous, and delayed phases, respectively, as well as during the liver-specific hepatobiliary phase (20 minutes after contrast medium administration). The optimal imaging delay for the hepatic arterial phase was determined by using a test bolus imaging technique [23]. Detailed MR imaging parameters are provided in **Table 1**.

Biphasic single-slice spiral CT was acquired within 6 weeks before or after MRI and it was performed during the arterial (25-35 sec after injection) and portovenous (45-70 sec) phases. One hundred to two hundred milliliters of non-ionic iodinated contrast material (CM) were

Table 1. Imaging parameters used in the MR imaging

Imaging Time Points	Pulse Sequence	TR/TE (msec)†	Flip Angle	Section Thickness (mm)	Matrix Size	Bandwidth (Hz/pixel)	Field of View (cm)	Acquisition Time (sec)
Preinjection	T2-weighted 2D TSE	4000/76	150°	5-7	192 256	260	30-50	36‡
	T1-weighted 2D dual GRE	140/2.2-4.4	90°	5-7	192 256	260	30-50	36‡
Dynamic imaging	T1-weighted 2D dual GRE	Parameters for T1-GRE above were to be required but without FS and the shortest possible TE in phase						
Hepatocyte phase	T1-GRE T2 TSE	Parameters for T1-GRE and T2 as for preinjection with fat suppression						

†TE = echo time, TR = repetition time. Parameters are for both opposed-phase and in-phase imaging. ‡Two breath-hold acquisitions were performed and concatenated for the image reconstruction of the upper abdomen.

administered via an antecubital vein with a mechanical injector and with a flow velocity of 3-5 mL/sec. CECT examinations were performed with tube voltage of 120 kV and 80 mA tube current.

Safety evaluation

Patients were observed for adverse events (AE) from inclusion until 72 hours after injection. Vital signs (blood pressure, heart rate, respiratory rate, and temperature) were monitored and 12-lead ECGs recorded at various time points. Clinical laboratory tests (hematological, coagulation, clinical chemistry tests, and urinalysis) were also performed and evaluated. Clinical investigators in each center classified the drug relationship of any AE into not, unlikely, possible, probable or definite relation to the contrast agent.

Efficacy evaluation

The primary efficacy parameter, lesion detection included the number, size, and segmental localization of lesions in the liver. Gadoxetic acid disodium-enhanced MRI, and CT were evaluated separately. In the overall evaluation, Gadoxetic acid disodium-enhanced MRI was compared with CT.

Image evaluation was performed as an on-site assessment by one clinical investigator in our center. Separately an off-site assessment by three experienced and independent abdominal radiologists, who were not involved in the clinical investigation and fully blinded to all patient-related information, was obtained. The blinded reading was performed in a core lab for digital image management.

Standard of reference (SOR)

The SOR was defined as the combination of histopathology for the resected part of the liver and intraoperative (IO) US for the non-resected segments. Surgical specimens were clearly marked at their borders by the surgeon at the time of the operation to enable an overview of the anatomical details and segmental distribution for pathologic evaluation. The resected specimens were sectioned by the pathologist in the same orientation (axial) and in the same slice thickness as for MRI and CT (5-8 mm). In rare cases for which IOUS was not available for non-resected liver segments, an additional diagnostic procedure (CT, MRI, US) was carried out within the 3-month review period and was accepted as the SOR.

Correlation of imaging with the SOR

The on-site investigators, the three blinded readers, the surgeons and the pathologists documented all lesions according to Couinaud's system of liver anatomy by drawing liver maps [24]. These maps consisted of eight transverse sections representing the cross-sectional anatomy of the entire liver. Each lesion was documented as accurately as possible according to size and segmental localization using one section of the liver map. For each individual lesion the imaging maps were compared with the map of the SOR by an independent radiologist to verify the same location of the lesion in all the modalities (i.e., lesion tracking).

Statistical analysis

Because some patients had multiple lesions detected and verified by the SOR, an adjustment of the 2-sided McNemar test proposed by Eliasziw and Donner [25] was used with a 5% significance level. The diagnostic performance for the gadoxetic acid disodium-enhanced MRI and biphasic spiral CT was measured using the area under ROC curve (AUC). AUCs were also applied to compare for the comparison of combined unenhanced and gadoxetic acid disodium-enhanced MRI versus biphasic spiral CT

Table 2. General information of the patients

Variable	All patients (n = 124)
Age in yrs. (median range)	50.6±10.6 (31-78)
Gender	
Male	108 (87.1%)
Female	16 (12.9%)
HBsAg	
Positive	106 (86.2%)
Negative	18 (13.8%)
HBeAg	
Positive	52 (42%)
Negative	72 (58%)
TBL (μmol/l)	19.1±12.6
ALB (g/dl)	40.5±5.3
ALT (U/L)	51.3±34.6
PT (S)	12.8±1.2
PLT (*10^9/L)	123±61
AFP (ng/ml)	
>400	60 (48.6%)
≤400	64 (51.4%)
Blood transfusion	
Yes	21 (16.8%)
No	103 (83.2%)
Edmondson-Steiner grade	
III or IV	80 (64.6%)
I or II	44 (35.4%)
Cirrhosis	
Yes	84 (68%)
No	40 (32%)
Tumor encapsulation	
No (no or part)	64 (51.4%)
Yes (complete)	60 (48.6%)
Tumor diameter (<5 cm)	
Median diameter	2.932±1.240 (0.5-5.0)
>2 cm	83 (66.9%)
≤2 cm	41 (33.1%)
Tumor number	
Multiple	46 (37.4%)
Solitary	78 (62.6%)

TBL: total bilirubin; ALB: albumin; ALT: alanine aminotransferase; PT: prothrombin time; PLT: blood platelet; AFP: alpha-fetoprotein.

using the Hanleyand McNeil method [26]. Statistical analysis were conducted with the SPSS for Windows version 18.0 release (SPSS, Inc., Chicago, IL) and ROC curve analysis were computed using MedCalcV.11.0.3.0 (MedCalc software, Mariakerke, Belgium). A value of $P<0.05$ was considered significant in all the analysis. The definition of true positives (TP), false positives (FP), true negatives (TN), and false negatives (FN) were defined as follows: TP = malignant in the imaging procedure and in SOR, TN = benign or no lesion in the imaging procedure and in SOR, FP = malignant or not assessable in the imaging procedure but benign or no lesion in SOR and FN = benign, no lesion or not assessable in the imaging procedure but malignant in SOR.

Results

General information of the patients

A total of 184 patients received gadoxetic acid MRI and biphasic spiral CT. according to the Standard of reference (SOR), all lesions were meeting the Milan criteria. Of these patients, 44 were excluded from the efficacy analysis due to a missing valid SOR for the whole liver (16 patients) and major protocol deviations (five patients). Thus, the data from the remaining 124 patients (108 males and 16 females; with a mean age of 50.6 years, range 31-78 years, and a mean weight of 75 kg) were available for efficacy and included in the MRI evaluation and the CT evaluation. The patients' characteristics were showed in **Table 2**.

Safety of gadoxetic acid disodium

Gadoxetic acid disodium was well tolerated. No clinically relevant changes in hemodynamic or laboratory parameters, in ECG or vital signs attributable to the contrast agent were detected. One patient discontinued the study due to anxiety and dyspnea due to claustrophobia. During gadoxetic acid disodium injection or thereafter, 10 patients out of 124 (8.1%) reported a total of 30 adverse events. They were assessed as follows: 18 not, 4 unlikely, 5 possibly, 2 probably (paresthesia = feeling warmth, vomiting), and 1 definitely related (paresthesia = feeling warmth) to the CM. The most frequently reported symptoms of definitely, possibly or probably related to AEs were paresthesia, headache, vomiting, tremor, pruritus, chills, and asthenia.

Diagnostic accuracy

For all liver lesions meeting Milan criteria, the diagnostic accuracy across the three readers was significantly greater with Gadoxetic acid

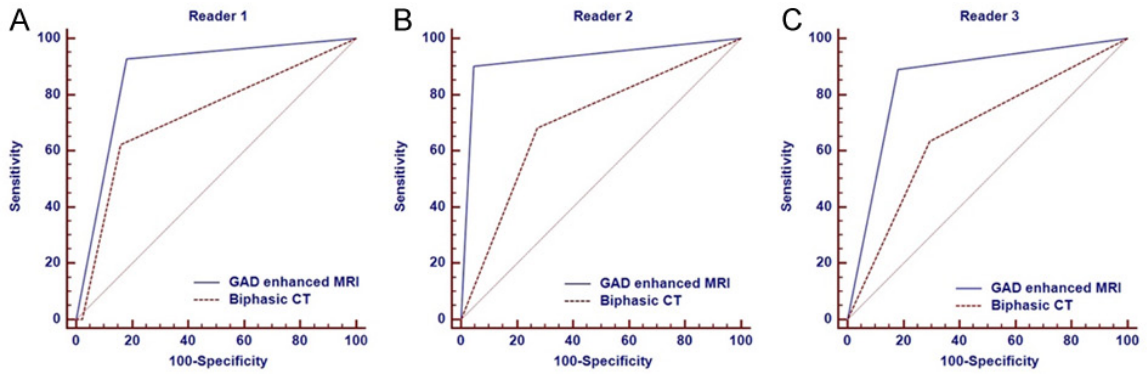

Figure 1. ROC curves of Gadoxetic acid disodium-enhanced MRI in predicting diagnosis of HCC with Milan criteria compared with biphasic spiral CT in Reader 1 (A), 2 (B), 3 (C).

Table 3. Sensitivity for the detection of HCC

Lesion Group and Imaging Modality All lesions (*n* = 124)	Reader 1	Reader 2	Reader 3	Average across Readers
Biphasic spiral CT	0.66 (0.53, 0.78)	0.70 (0.60, 0.80)	0.71 (0.59, 0.83)	0.69 (0.59, 0.79)
Gadoxetic acid-enhanced MR imaging	0.82 (0.69, 0.94)	0.91 (0.81, 1.00)	0.83 (0.69, 0.97)	0.85 (0.74, 0.96)
Difference between MR imaging and CT	0.16 (0.03, 0.29)	0.21 (0.11, 0.30)	0.11 (0.02, 0.21)	0.16 (0.07, 0.25)
P value	0.0289	0.0017	0.0274	0.0004

Table 4. Analysis regarding lesion size in the blinded reading

Examination	Number of lesions	Reader 1		Reader 2		Reader 3	
		<1 cm	≥1 cm	<1 cm	≥1 cm	<1 cm	≥1 cm
MRI	Matched	36	120	42	122	37	117
	Not matched	21	24	15	22	20	27
Biphasic spiral CT	Matched	25	115	30	124	21	117
	Not matched	26	23	21	14	30	21

disodium-enhanced MR imaging than with biphasic spiral CT. The AUC of GAD enhanced MRI were 0.873 (95% CI = 0.801-0.925), 0.928 (95% CI = 0.869-0.967) and 0.854 (95% CI = 0.780-0.911) in Reader 1, 2, and 3, respectively. The AUC of biphasic spiral CT were 0.724 (95% CI = 0.638-0.800), 0.705 (95% CI = 0.617-0.783) and 0.669 (95% CI = 0.580-0.751) in Reader 1, 2, and 3, respectively (*P*<005, **Figure 1**).

Efficacy in the imaging evaluation

For all liver lesions meeting Milan criteria, the sensitivity across the three readers was significantly greater with Gadoxetic acid disodium-enhanced MR imaging than with biphasic spiral CT. Average across Readers were 0.851 (95% CI = 0.745-0.962) *vs*. 0.692 (95% CI = 0.596-0.793), respectively (*P*<0.001, **Table 3**).

When individual lesions were evaluated, for correct detection of lesions smaller than 1 cm, Gadoxetic acid disodium-enhanced MR imaging (42/57 lesions) was clearly superior to biphasic spiral CT (25/51 lesions). A greater number of small lesions were detected in Gadoxetic acid disodium-enhanced MR imaging than in CT (**Table 4**).

Discussion

Milan criteria were firstly established by Mazzaferro *et al.* in 1996 [27]. The overall actuarial survival at 4 years was 75% and the recurrence-free survival was 83% in this landmark study. They further justified their criteria by publishing a meta-analysis in 2011 that comprehensively validated the Milan criteria's ability to capture tumour with favorable biology and hence improved survival [28]. From this per-

spective, Milan criteria could be identified as criteria for early HCC. The development of imaging technology promotes the early detection of HCC. However, which strategy is more accurate is still controversial.

The optimum imaging strategy prior to any therapy should ideally provide diagnostic information with high sensitivity but also with a low false-positive rate. Lesion characterization is particularly important because of the high prevalence of benign liver lesions [29]. Our data was consistent with a recent study by Kim *et al*. [21], which showed a trend, although not statistically significant, toward improved diagnostic accuracy with gadoxetate disodium-enhanced MR imaging compared with multidetector CT for the detection of HCC in patients with cirrhosis, particularly for smaller lesions (<2 cm). This finding has important clinical implications. The superior tumor detection with gadoxetate disodium-enhanced MR imaging could enable the diagnosis of HCCs within Milan criteria. This offers the possibility of clinical interventions when liver function is still preserved, and potential curative therapies can be performed, including transplantation, hepatic resection, and percutaneous tumor ablation techniques [30-32].

Gadoxetic acid disodium is a novel gadolinium-based MR contrast agent for liver imaging with the unique property of acting as both extracellular and hepatocyte targeted compound. Good tolerance with limited side effects similar to those of extracellular Gd-based contrast media at doses likely to be diagnostically useful has been assessed [18]. A recent multicenter trial showed improvement in lesion detection for gadoxetic acid disodium-enhanced liver MRI when compared to unenhanced MRI [33]. Sensitivity was higher and fewer false positive lesions resulted with gadoxetic acid disodium-enhanced MRI when compared to spiral CT, especially when lesions less than 1 cm in diameter were considered. In this study, for all liver lesions meeting Milan criteria, the diagnostic accuracy across the three readers was significantly greater with Gadoxetic acid disodium-enhanced MR imaging than with biphasic spiral CT. The AUC of GAD enhanced MRI were 0.873 (95% CI = 0.801-0.925), 0.928 (95% CI = 0.869-0.967) and 0.854 (95% CI = 0.780-0.911) in Reader 1, 2, and 3, respectively. The AUC of biphasic spiral CT were 0.724 (95% CI = 0.638-0.800), 0.705 (95% CI = 0.617-0.783) and 0.669 (95% CI = 0.580-0.751), respectively.

Our prospective multicenter investigation has limitations. First, we should have focused more on the delayed imaging. Therefore, the precise knowledge on the benefit of delayed or parenchymal phase of imaging at 10 or 20 minutes after contrast injection remains. However, our assumption after reviewing the images is that the impact of delayed imaging on the characterization of a liver lesion is limited. Nonetheless, it may in some special circumstances be crucial. Second, at present the dose of gadoxetic acid disodium is rather small. Therefore, the dynamic effect may be less than that seen with gadoxetic acid disodium with higher doses. However, the dosage may change in the future as seen with gadoxetic acid disodium. With increasing the amount of contrast agent, the potential of gadoxetic acid disodium in both lesion detection and characterization may be augmented. Third, recent evidence indicates that contrast medium uptake and biliary excretion may be delayed in patients with cirrhosis [24]. Future studies are warranted to determine the interval that maximizes the conspicuity of HCC at gadoxetate disodium-enhanced MR imaging during the hepatobiliary phase.

In conclusion, compared with biphasic spiral CT, Gadoxetic acid disodium-enhanced MRI yields significantly higher diagnostic accuracy and sensitivity in the detection of HCC in patients within Milan criteria.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jin Wang, Department of Radiology, The Third Affiliated Hospital, Sun Yat-sen University, 600 Tianhei Road, Guangzhou 510630, China. E-mail: wangjehbh@163.com

References

[1] El-Serag HB and Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007; 132: 2557-2576.

[2] Dyer Z, Peltekian K and van Zanten SV. Review article: the changing epidemiology of hepatocellular carcinoma in Canada. Aliment Pharmacol Ther 2005; 22: 17-22.

[3] Flores A and Marrero JA. Emerging trends in hepatocellular carcinoma: focus on diagnosis

and therapeutics. Clin Med Insights Oncol 2014; 8: 71-76.
[4] Poon D, Anderson BO, Chen LT, Tanaka K, Lau WY, Van Cutsem E, Singh H, Chow WC, Ooi LL, Chow P, Khin MW and Koo WH. Management of hepatocellular carcinoma in Asia: consensus statement from the Asian Oncology Summit 2009. Lancet Oncol 2009; 10: 1111-1118.
[5] Bruix J, Gores GJ and Mazzaferro V. Hepatocellular carcinoma: clinical frontiers and perspectives. Gut 2014; 63: 844-855.
[6] Azzam AZ. Liver transplantation as a management of hepatocellular carcinoma. World J Hepatol 2015; 7: 1347-1354.
[7] Zhou J, Wang Z, Qiu SJ, Huang XW, Sun J, Gu W and Fan J. Surgical treatment for early hepatocellular carcinoma: comparison of resection and liver transplantation. J Cancer Res Clin Oncol 2010; 136: 1453-1460.
[8] Benson AB 3rd, Abrams TA, Ben-Josef E, Bloomston PM, Botha JF, Clary BM, Covey A, Curley SA, D'Angelica MI, Davila R, Ensminger WD, Gibbs JF, Laheru D, Malafa MP, Marrero J, Meranze SG, Mulvihill SJ, Park JO, Posey JA, Sachdev J, Salem R, Sigurdson ER, Sofocleous C, Vauthey JN, Venook AP, Goff LW, Yen Y and Zhu AX. NCCN clinical practice guidelines in oncology: hepatobiliary cancers. J Natl Compr Canc Netw 2009; 7: 350-391.
[9] Merchant N, David CS and Cunningham SC. Early hepatocellular carcinoma: transplantation versus resection: the case for liver resection. Int J Hepatol 2011; 2011: 142085.
[10] Ke M, Xu T, Li N, Ren Y, Shi A, Lv Y and He H. Prognostic nutritional index predicts short-term outcomes after liver resection for hepatocellular carcinoma within the Milan criteria. Oncotarget 2016; 7: 81611-81620.
[11] Kuszyk BS, Bluemke DA, Urban BA, Choti MA, Hruban RH, Sitzmann JV and Fishman EK. Portal-phase contrast-enhanced helical CT for the detection of malignant hepatic tumors: sensitivity based on comparison with intraoperative and pathologic findings. AJR Am J Roentgenol 1996; 166: 91-95.
[12] Pawluk RS, Tummala S, Brown JJ and Borrello JA. A retrospective analysis of the accuracy of T2-weighted images and dynamic gadolinium-enhanced sequences in the detection and characterization of focal hepatic lesions. J Magn Reson Imaging 1999; 9: 266-273.
[13] Kim YK, Lee JM, Kim CS, Chung GH, Kim CY and Kim IH. Detection of liver metastases: gadobenate dimeglumine-enhanced three-dimensional dynamic phases and one-hour delayed phase MR imaging versus superparamagnetic iron oxide-enhanced MR imaging. Eur Radiol 2005; 15: 220-228.
[14] Jang HY, Choi JI, Lee YJ, Park MY, Yeo DM, Rha SE, Jung ES, You YK, Kim DG and Byun JY. Performance of gadoxetic acid-enhanced liver magnetic resonance imaging for predicting patient eligibility for liver transplantation based on the Milan criteria. J Comput Assist Tomogr 2017; 41: 25-31.
[15] Kamel IR, Choti MA, Horton KM, Braga HJ, Birnbaum BA, Fishman EK, Thompson RE and Bluemke DA. Surgically staged focal liver lesions: accuracy and reproducibility of dual-phase helical CT for detection and characterization. Radiology 2003; 227: 752-757.
[16] Yaqoob J, Bari V, Usman MU, Munir K, Mosharaf F and Akhtar W. The evaluation of hepatocellular carcinoma with biphasic contrast enhanced helical CT scan. J Pak Med Assoc 2004; 54: 123-127.
[17] Tang Y, Yamashita Y, Namimoto T and Takahashi M. Characterization of focal liver lesions with half-fourier acquisition single-shot turbo-spin-echo (HASTE) and inversion recovery (IR)-HASTE sequences. J Magn Reson Imaging 1998; 8: 438-445.
[18] Hamm B, Staks T, Muhler A, Bollow M, Taupitz M, Frenzel T, Wolf KJ, Weinmann HJ and Lange L. Phase I clinical evaluation of Gd-EOB-DTPA as a hepatobiliary MR contrast agent: safety, pharmacokinetics, and MR imaging. Radiology 1995; 195: 785-792.
[19] Reimer P, Rummeny EJ, Shamsi K, Balzer T, Daldrup HE, Tombach B, Hesse T, Berns T and Peters PE. Phase II clinical evaluation of Gd-EOB-DTPA: dose, safety aspects, and pulse sequence. Radiology 1996; 199: 177-183.
[20] Tirkes T, Mehta P, Aisen AM, Lall C and Akisik F. Comparison of dynamic phase enhancement of hepatocellular carcinoma using gadoxetate disodium vs gadobenate dimeglumine. J Comput Assist Tomogr 2015; 39: 479-482.
[21] Kim SH, Kim SH, Lee J, Kim MJ, Jeon YH, Park Y, Choi D, Lee WJ and Lim HK. Gadoxetic acid-enhanced MRI versus triple-phase MDCT for the preoperative detection of hepatocellular carcinoma. AJR Am J Roentgenol 2009; 192: 1675-1681.
[22] Halavaara J, Breuer J, Ayuso C, Balzer T, Bellin MF, Blomqvist L, Carter R, Grazioli L, Hammerstingl R, Huppertz A, Jung G, Krause D, Laghi A, Leen E, Lupatelli L, Marsili L, Martin J, Pretorius ES, Reinhold C, Stiskal M and Stolpen AH. Liver tumor characterization: comparison between liver-specific gadoxetic acid disodium-enhanced MRI and biphasic CT--a multicenter trial. J Comput Assist Tomogr 2006; 30: 345-354.
[23] Kanematsu M, Semelka RC, Matsuo M, Kondo H, Enya M, Goshima S, Moriyama N and Hoshi H. Gadolinium-enhanced MR imaging of the liver: optimizing imaging delay for hepatic arte-

rial and portal venous phases--a prospective randomized study in patients with chronic liver damage. Radiology 2002; 225: 407-415.

[24] Hammerstingl R, Huppertz A, Breuer J, Balzer T, Blakeborough A, Carter R, Fuste LC, Heinz-Peer G, Judmaier W, Laniado M, Manfredi RM, Mathieu DG, Muller D, Mortele K, Reimer P, Reiser MF, Robinson PJ, Shamsi K, Strotzer M, Taupitz M, Tombach B, Valeri G, van Beers BE and Vogl TJ. Diagnostic efficacy of gadoxetic acid (Primovist)-enhanced MRI and spiral CT for a therapeutic strategy: comparison with intraoperative and histopathologic findings in focal liver lesions. Eur Radiol 2008; 18: 457-467.

[25] Eliasziw M and Donner A. Application of the McNemar test to non-independent matched pair data. Stat Med 1991; 10: 1981-1991.

[26] Hanley JA. Receiver operating characteristic (ROC) methodology: the state of the art. Crit Rev Diagn Imaging 1989; 29: 307-335.

[27] Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A and Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996; 334: 693-699.

[28] Mazzaferro V, Bhoori S, Sposito C, Bongini M, Langer M, Miceli R and Mariani L. Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience. Liver Transpl 2011; 17 Suppl 2: S44-57.

[29] Karhunen PJ. Benign hepatic tumours and tumour like conditions in men. J Clin Pathol 1986; 39: 183-188.

[30] Bigourdan JM, Jaeck D, Meyer N, Meyer C, Oussoultzoglou E, Bachellier P, Weber JC, Audet M, Doffoel M and Wolf P. Small hepatocellular carcinoma in Child A cirrhotic patients: hepatic resection versus transplantation. Liver Transpl 2003; 9: 513-520.

[31] Livraghi T, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C and Rossi S. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? Hepatology 2008; 47: 82-89.

[32] Figueras J, Jaurrieta E, Valls C, Ramos E, Serrano T, Rafecas A, Fabregat J and Torras J. Resection or transplantation for hepatocellular carcinoma in cirrhotic patients: outcomes based on indicated treatment strategy. J Am Coll Surg 2000; 190: 580-587.

[33] Huppertz A, Balzer T, Blakeborough A, Breuer J, Giovagnoni A, Heinz-Peer G, Laniado M, Manfredi RM, Mathieu DG, Mueller D, Reimer P, Robinson PJ, Strotzer M, Taupitz M and Vogl TJ. Improved detection of focal liver lesions at MR imaging: multicenter comparison of gadoxetic acid-enhanced MR images with intraoperative findings. Radiology 2004; 230: 266-275.