ORIGINAL ARTICLE

Gut and Liver, Vol. 6, No. 3, July 2012, pp. 362-367

Comparative Study of Shear Wave Velocities Using Acoustic Radiation Force Impulse Technology in Hepatocellular Carcinoma: The Extent of Radiofrequency Ablation

Jiyoung Kang*, Heejin Kwon*, Jinhan Cho*, Jongyoung Oh*, Kyungjin Nam*, Seongkuk Yoon*, Myongjin Kang*, Sungwook Lee†, and Sangyeong Han†

*Departments of *Radiology and †Internal Medicine, Dong-A Medical Center, Dong-A University College of Medicine, Busan, Korea*

Background/Aims: The purpose of this study was to assess the value of acoustic radiation force impulse (ARFI) for predicting the extent of radiofrequency ablation (RFA) in hepatocellular carcinoma (HCC) by correlating the elasticity of HCC and peritumoral parenchyma (as measured by ARFI) with the extent of ablation determined by computed tomography (CT). **Methods:** From September 2009 to June 2011, 158 patients underwent RFA ablation for HCC (single, ≤3 cm). We evaluated the data of a total of 38 prospectively enrolled patients who underwent both ARFI imaging and contrast-enhanced CT after one session of 12 minutes of RFA without a change in needle position. The ARFI imaging indices, including the mean shear wave velocity (SWV) of HCC, mean SWV of the peritumoral parenchyma and tumor size, were evaluated to determine the statistical correlation with RFA extent after one session of 12 minutes of RFA. **Results:** A stiffer liver parenchyma in patients with cirrhosis results in a smaller ablation zone. **Conclusions:** SWV of ARFI in liver parenchyma was well correlated with RFA extent. After evaluating the correlation between ARFI and RFA extent, we suggest that the SWV in liver parenchyma might be a noninvasive supplementary tool for predicting the extent of RFA. **(Gut Liver 2012;6:362-367)**

Key Words: Elasticity imaging techniques; Hepatocellular carcinoma; Radiofrequency ablation

INTRODUCTION

Radiofrequency ablation (RFA) induces localized coagulation necrosis by creating resistive ionic heating (50°C to 100°C) through one or more electrodes, which are directly inserted into the tumor, delivering high-frequency alternating currents.[1,2] A potential eradicative RFA should include the entire tumor plus a 5-10 mm peritumoral safety margin in an ideal sphere of necrosis, whereas an area of coagulation smaller than expected may lead to local recurrence.[3,4] In clinical practice, many factors (i.e., probe gauge, tip length, temperature achieved, heating duration, heat-sink effect of nearby blood vessels, incomplete fusion of RFA lesions between prongs of expandable electrodes or surgical clips near the tumor) may alter this ideal geometrical shape producing an irregularly sized, distorted or incomplete area of necrosis.[5-8] Until now, there are no studies that have evaluated the influence of objective stiffness value in tumor or parenchyma on the ablation extent.

Acoustic radiation force impulse (ARFI) has the advantage of enabling a "real-time" evaluation of liver fibrosis and is free of adverse effects; it is comfortable for the patient and examiner and needs no external compression, and this makes evaluation of deep tissue feasible.[9] ARFI imaging is able to noninvasively evaluate the stiffness of hepatic tissues, characterize focal hepatic lesions, and guide the placement of interventional devices.[10,11]

This study aimed to assess the stiffness liver by using an ARFI imaging technique and to identify the correlation between not only the severity of hepatic parenchymal fibrosis and RFA extent of hepatocellular carcinoma (HCC) but also the HCC stiffness and RFA extent respectively in patients with HCC and underlying liver cirrhosis.

Correspondence to: Heejin Kwon
Department of Radiology, Dong-A Medical Center, Dong-A University College of Medicine, 26 Daesingongwon-ro, Seo-gu, Busan 602-715, Korea
Tel: +82-51-240-5367, Fax: +82-51-253-4931, E-mail: risual@dau.ac.kr

Received on September 22, 2011. Revised on December 14, 2011. Accepted on December 26, 2011. Published online on May 2, 2012.
pISSN 1976-2283 eISSN 2005-1212 http://dx.doi.org/10.5009/gnl.2012.6.3.362

MATERIALS AND METHODS

1. Patients

The subjects were drawn from a consecutive series of 158 patients with HCC and who treated by RFA between September 2009 and June 2011.

Of the 158 prospective patients, 38 were enrolled in the study, based on the inclusion and exclusion criteria. Inclusion criteria were adult patients with a single primary HCC smaller than 3 cm (0.8 to 3 cm) in diameter, visible HCC on ultrasonography, no eligibility for surgical resection or refusal of surgery, and an acceptable and safe path through intercostal approach between the lesion and the skin as observed on ultrasonography. All patients had underlying liver cirrhosis. Exclusion criteria were HCC located in left lobe, recurred HCC after RFA or transarterial chemoembolization, multiple HCCs, incomplete ablation of HCC after, shear wave velocities (SWV) is uncheckable or unreliable by high variability (>1 m/sec) and presence of extrahepatic metastasis or vascular invasion.

B-mode ultrasound (US) pre-RFA image and Real-time elastography on an Acuson S2000™ system (Siemens, Mountain View, CA, USA) were performed on the 38 patients for evaluation of the HCC and peritumoral parenchyma before performing RFA. Then RFA was performed to treat HCC.

Of the 38 patients (16 women, 22 men; mean age, 62.3 years; range, 40 to 78 years), 10 have HCC in segment 5, 11 in segment 6, 4 in segment 7, and 13 in segment 8.

On CT images before performing RFA, the longitudinal diameter of HCC ranged from 0.8 to 2.5 cm with a mean value of 1.68±0.57 cm. On elastographic images, the region of interest (ROI) box depth ranged from 30 to 80 mm with a mean depth of 45.97±0.2 mm.

The diagnosis of HCC was made based on the guidelines proposed by the Korea Liver Cancer Study Group and the National Cancer Center. According to these criteria, a patient is considered positive for HCC if the patient has one or more risk factors (HBV infection, hepatitis C virus infection or cirrhosis) and one of the following: a serum α-fetoprotein (AFP) level of >400 ng/mL and a positive finding with at least one of three typical imaging studies (spiral computed tomography [CT], contrast enhanced dynamic magnetic resonance imaging [MRI] or hepatic angiography), or a serum AFP level of <400 ng/mL and positive findings with at least two of the three imaging studies. A positive finding for typical HCC with dynamic CT or MRI is indicative of arterial enhancement, followed by venous washout in the delayed portal/venous phase.[12]

2. Pre-RFA image acquisition

In the case of all the patients, Acuson S2000™ US system (Siemens) with a curved array 4-1 MHz was used. Before performing RFA, longest diameter of HCC on CT scan was measured, and SWV of both HCC and peritumoral parenchyma was analyzed by ARFI imaging by one operator. Tumor location was described according to the Couinaud segmental anatomic clas-

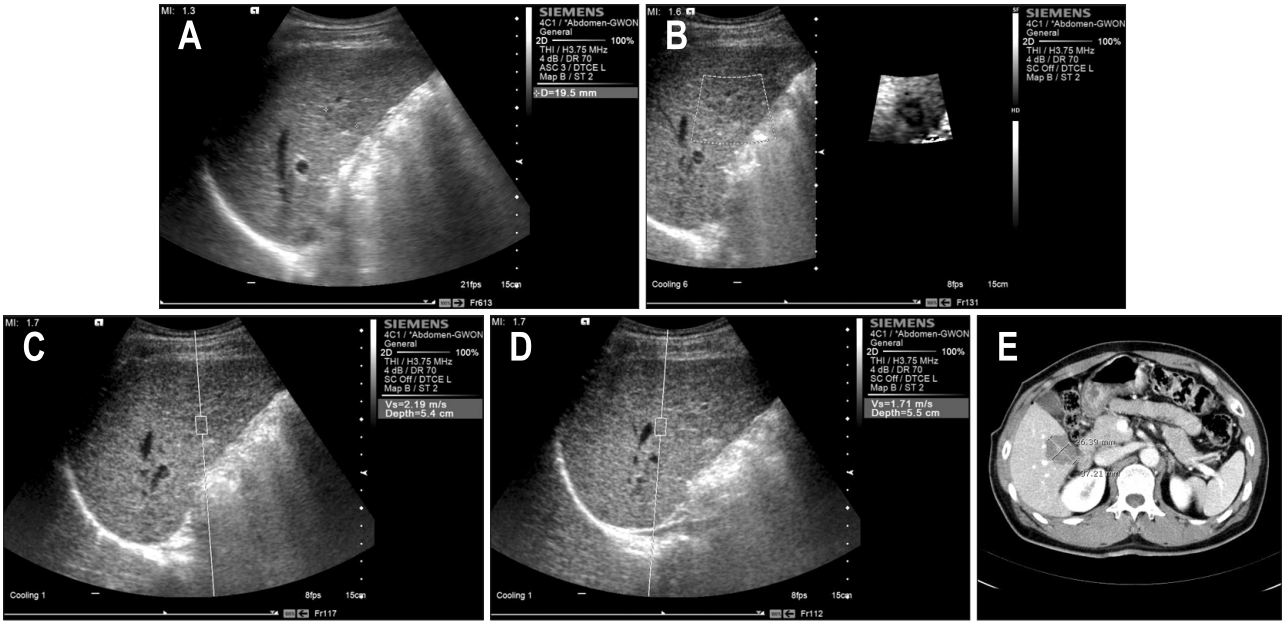

Fig. 1. Hepatocellular carcinoma (HCC) and underlying LC in S5 in the liver of a 56-year-old man. HCC and underlying liver cirrhosis in S5 of liver in a 56-year-old man. (A, B) On a B-mode image obtained using a 4-MHz curved array, the HCC appears as a well-defined, hypoechoic mass approximately 19.5 mm in size, located in the S5 segment of the liver. The HCC appears as dark coloration on real-time acoustic radiation force impulse imaging. (C, D) Measurement of shear wave velocity of the HCC and hepatic parenchyma at similar region of interest depths (5.4 and 5.5 cm below the skin) reveals that stiffer tumors display greater velocity (2.19 m/sec) than cirrhotic parenchyma (1.71 m/sec). (E) Post-radiofrequency ablation computed tomography scan in the arterial phase displays an oval, well-ablated and necrotic alteration in the HCC, which was (3.7×2.6×π)/4 cm^2 in size.

sification.

HCCs were classified into 3 types based on the results of grayscale maps of tissue stiffness by two independent operators. Discrepancies between the two reviewers were resolved through consensus. The tumors were categorized as stiffer (darker), equally stiff (of the same color), or softer (brighter), based on the brightness of the lesion relative to that of the liver on the ARFI images.[11]

Table 1. Comparative Measurement Values according to the Mean Values of ARFI and Computed Tomography

Sex	Age	Tumor location	Tumor size, cm	ARFI color	HCC SWV average, m/sec	Parenchymal SWV average, m/sec	RFA longest diameter, cm	RFA extent, cm^2	ROI depth, mm
M	62	S8	1.7	Bright	3.65	1.2	3.92	9.8	47
F	72	S5	2.5	Bright	2.19	3.25	2.7	4.05	55
M	50	S5	2.36	Bright	1.28	2.41	4.2	13.86	52
M	72	S8	1	Bright	2.24	1.48	3.7	8.14	34
M	55	S6	1.66	Bright	2.21	2.8	2.5	5.25	38
M	74	S8	2.04	Bright	0.96	2.4	3.5	8.75	80
F	64	S5	2.5	Bright	1.02	1.73	4.3	15.05	48
F	73	S8	1.7	Bright	1.4	2.72	2.4	5.76	61
M	65	S8	2.8	Bright	1.26	1.63	3.4	13.12	41
F	71	S5	1.2	Bright	2.16	2.73	3.7	5.04	30
M	60	S8	2.1	Bright	1.96	2.5	2.9	5.28	23
M	61	S8	2.5	Bright	1.5	2.2	3.4	8.37	63
F	59	S6	1.8	Bright	1.8	2.6	2.5	11.47	32
M	54	S6	1.2	Bright	2.8	3.27	3.4	4.68	31
F	72	S6	1.8	Bright	2.7	3.36	3	5.5	30
F	65	S5	1.4	Bright	2.7	3.36	2.4	6.21	35
M	69	S6	1.5	Bright	2.6	3.25	3.2	8.75	52
F	48	S8	0.8	Bright	2.5	3.6	4.1	5.72	32
F	63	S7	1.2	Bright	1.8	2.83	3	6.9	55
M	70	S6	1.89	Dark	2	1.76	2.7	7.48	41
M	76	S6	1.5	Dark	2.6	1.74	2.4	9.52	30
M	50	S5	1.2	Dark	2.3	1.57	2.4	5.94	54
F	59	S7	2	Dark	2.4	1.97	3.2	10.36	64
F	58	S8	2.01	Dark	3.4	2.73	3.1	5.6	44
M	40	S8	1.6	Dark	2.5	1.9	3.5	12.09	37
F	77	S6	2.5	Dark	2.6	2.1	3.7	10.26	41
M	78	S6	1.4	Dark	3.6	3.3	3.7	3.96	47
M	54	S7	2	Dark	2.4	1.8	2.6	8.32	58
M	56	S5	1.9	Dark	2.19	1.61	2.5	9.62	55
F	73	S5	1	Iso	1.83	1.86	2.9	4.64	55
M	46	S8	1.9	Iso	1.3	1.4	2.8	9.86	70
M	73	S8	1.6	Iso	3.97	3.97	2.7	5.75	46
M	54	S6	1	Iso	2.87	2.94	3.9	5.52	65
F	71	S6	1.7	Iso	2.72	2.67	3.8	9	30
M	61	S5	2	Iso	2.87	3.1	2.2	4.84	57
M	54	S5	1.1	Iso	2.9	2.8	3.5	4.64	39
F	53	S7	1	Iso	2.5	2.6	2.6	6.38	37
F	55	S8	1	Iso	2.1	2.7	2.9	13.2	38

ARFI, acoustic radiation force impulse; HCC, hepatocellular carcinoma; SWV, shear wave velocity; RFA, radiofrequency ablation; ROI, region of interest; M, male; F, female.

According to a previous study, the intercostal approach had the highest rate of success (97.2%), and left liver lobe measurement yielded significantly high ARFI SWV and value variance (p=0.0016 and p=0.0198) owing to cardiac motion, when compared with the intercostal approach in the right liver lobe.[13] Therefore, ARFI imaging was performed in the right lobe of the liver through the intercostal space after deep expiration to avoid breathing motion with minimal scanning pressure applied by the operation.

The patients were examined in left lateral decubitus position with the right arm in maximum abduction. A measurement depth of 2 cm below the liver capsule was chosen to standardize the examination,[14] and the depth ranged between 30 and 80 mm. According to studies by Fahey *et al*.,[15] they showed the presence of a significant difference in the SWV between just below the liver capsule and the portion of the liver deeper than 10 to 12 cm.

Measurements in the surrounding parenchyma were also performed with the ROI within 2 to 3 cm of the focal lesion. Five successful acquisitions in both HCC and hepatic parenchyma were performed in each patient. The highest and lowest values were excluded, and the mean value was obtained with the other 3 numerical values.

ARFI imaging involves the selection of an anatomic region to be interrogated for elastic properties with the use of an ROI cursor by placing a "measuring box" (10 mm long and 5 mm wide) while performing real-time B-mode imaging (Fig. 1). The ROI was included entirely within the lesion, excluding all vessels and biliary structures.

3. Overall RFA treatment procedure

All of the patients were treated by percutaneous RFA under real-time sonographic guidance (Eccocee SSA-340A Color Doppler Ultrasound [Toshiba, Tokyo, Japan], ATL HDI 5000 Color Doppler Ultrasound [Philips, Bothell, WA, USA]) with a 3.5-MHz curved probe by a single interventional radiologist who had 11 years of experience in interventional therapy.

A local anesthetic drug, 1% lidocaine, was injected from the insertion point on the skin to the peritoneum along the planned puncture track. The skin was incised with a small lancet, and the needle was advanced to the selected area. Conscious sedation with intravenous fentanyl or meperidine was maintained. The HCCs were treated with single internally cooled electrodes. RFA was performed with 20-cm-long, 15-gauge electrodes.

An RFA was performed with a 200 W generator (Radionics, Burlington, MA, USA) using single (with one 3.0 cm tip) internally cooled electrodes (Radionics) with impedence-controlled pulsed current. The active treatment time was 12 minutes, as per the manufacturer's recommendations. Overlapping ablation or repositioning the electrode to ablate the entire tumor was not performed.

After one 12-minute RFA session, ablation area extent (semi major axis×semi minor axis×π) was analyzed directly from CT.

4. Statistical analysis

Tumor location according to Couinaud segment, depth of ROI, tumor size, SWV of HCC, parenchymal SWV, and RFA extent were analyzed. Data were expressed as mean±standard deviation. The Spearman rank correlation coefficients were used to assess the relationships among RFA extent, SWV of tumor, and hepatic parenchymal SWV. All statistical tests were 2 sided, and a p-value of <0.01 was considered to indicate statistical significance. Statistical analyses were performed with the statistical package IBM SPSS for Windows version 19.0 (IBM, New York, NY, USA). ARFI imaging values were not normally distributed and were therefore expressed as mean values.

RESULTS

1. Subject characteristics

No patient had major complications after RFA. All patient informations including tumor size, ages, tumor location, sex, and RFA extent are presented in Table 1.

All patients were divided into 3 categories (brighter, same, darker groups) according to the grayscale image of the tumor compared with the surrounding hepatic parenchyma, indicating the stiffness difference.

The liver stiffness measurements of tumor and hepatic parenchyma, represented by SWV, were obtained.

Results derived from statistical comparisons between total mean values typical for each group of lesions are presented in Table 2.

The Spearman correlation coefficients of RFA extent and hepatic parenchymal SWV in all the patients were -0.590 (p=0.001). In the present study, highly significant negative correlations were found between hepatic parenchymal stiffness, represented as mean SWV on ARFI elastography, and RFA extents measured by CT. And also cut off value in parenchymal SWV is 2.41 that means in case of parenchymal SWV is over 2.41, 12 minutes

Table 2. Correlations between RFA Extent, Parenchymal SWV, and HCC SWV Determined by ARFI Imaging

	Parenchmal SWV, m/sec (n=38)	HCC SWV, m/sec (n=38)
RFA extent, cm		
Spearman correlation coefficient	0.590*	-0.304
p-value	0.001	0.064
HCC size		
Spearman correlation coefficient	0.283	-0.353
p-value	0.086	0.030

RFA, radiofrequency ablation; SWV, shear wave velocity; HCC, hepatocellular carcinoma; ARFI, acoustic radiation force impulse.

post RFA extent is significantly decreased.

These results could explain that the softer the hepatic parenchyma, the greater the RFA extent, and a strong inversed proportional relationship between the severity of liver cirrhosis and the RFA extent of HCC.

2. Reproducibility of ARFI

We evaluated the shear wave velocity (SWV) of 6 normal subjects the control group who underwent 5 trials per day, during 5 days to evaluate the reproducibility of ARFI elastography measurement. The coefficient variation value calculated as dividing the standard deviation by the mean and multiplying by 100 was 9.07±3.19 (range, 7.6 to 11.4). There was no statistical difference between the mean of SWV at the each trial.

DISCUSSION

Many studies have evaluated the role of ARFI in the assessment of liver fibrosis in chronic diffuse liver disease and hepatic tumors, but no data regarding the correlation between RFA and liver stiffness have yet been published.

The results presented in the previous section establish that noninvasive ARFI elastography can provide not only predictive information about tumor ablation extent after performance of RFA for treatment of HCC but also parenchymal cut off stiffness value.

The use of a combined sonography/ARFI imaging system is a new US-based technique that is designed to study the mechanical properties of tissues, especially in characterization of diffuse liver diseases and evaluation of liver stiffness and to monitor the results of RFA.[13,15,16]

SWV, also known as virtual touch tissue quantification, is generated by acoustic radiation force, depends on tissue elasticity, and is regarded as an objective method for evaluating mechanical tissue properties.[11]

ARFI elastography could change the liver US paradigm, because it provides information about liver stiffness during routine US examination of the liver without a need to move patients.[17]

In this study, the correlation between RFA extent and hepatic parenchymal mean SWV and mean SWV of HCC was evaluated. The results of statistical analysis showed a highly significant negative correlation (Spearman correlation coefficient -0.590, p=0.001) between parenchymal mean SWV and RFA extent. This suggests that the higher the parenchymal SWV, which indicates hepatic fibrosis, the smaller the RFA extent, which indicates to decrease RFA efficacy.

The present study also assessed the SWV and color elastomaps of HCC and the surrounding liver by ARFI elastography. The mean SWV values obtained were 2.31±0.71 m/sec in HCCs and 2.46±0.70 m/sec in parenchyma; HCC lesions were softer than the surrounding cirrhotic liver, but the difference was insignificant. This result is similar to that of a study by Gallotti *et al*.,[10] who revealed mean wave velocity values of 2.17±0.85 m/sec in HCCs and 2.99 m/sec in parenchyma. They considered that the lower wave velocity value observed in HCCs than in surrounding liver parenchyma were attributable to the presence of multiple cells in cords and small amounts of connective tissue in HCCs and the great abundance of fibrosis in the surrounding liver, which was almost always cirrhotic parenchyma.[10]

Comparison of the SWV between HCC and hepatic parenchyma showed no significant correlation, with the Pearson correlation coefficient of 0.335 (p=0.1). Cho *et al*.[11] also concluded that SWV values of liver nodules were independent of the status of the surrounding liver parenchyma. Furthermore, no association between SWV of HCC and tumor size was observed in the present study.

The major weak point of this study was that the measured stiffness on ARFI imaging was not correlated with real stiffness, histologic liver fibrosis stage, cellularity, or the amount of necrosis determined by pathological examination of the specimens. In addition, diagnoses of liver cirrhosis and HCC were based on clinical, radiologic, and laboratory findings but not on histopathologic findings. Therefore, the possibility that some patients were assigned to the wrong group cannot be excluded. Despite these study limitations, images obtained through ARFI elastography provided additional qualitative information regarding the stiffness of liver parenchyma and the extent of RFA.

Measurement of SWV made quantification of tumor and hepatic parenchymal stiffness possible and showed the potential to expect the extent of RFA.

In conclusion, in patients with HCC and underlying liver cirrhosis, severity of hepatic parenchymal fibrosis is of special interest, because the SWV measured by ARFI is an important parameter in the prediction of RFA treatment extent. Because the surrounding liver shows increased stiffness, RFA extent of HCC decreases, and because the surrounding liver is softer, RFA can be more easily performed which means the shortening of ablation time regardless of hepatic tumor stiffness. Also vice versa, if the peritumoral SWV is higher than the cutoff value 2.41, multiple session of RFA may be needed to ablate the tumor with free safe margin.

ARFI technique is a new and promising noninvasive, sonography-based method for the assessment of liver fibrosis and is a good predictive method for assessing RFA extent in patients with liver cirrhosis and HCC.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

This study was supported by Dong-A University reserch fund.

REFERENCES

1. Ni Y, Mulier S, Miao Y, Michel L, Marchal G. A review of the general aspects of radiofrequency ablation. Abdom Imaging 2005;30:381-400.
2. Laeseke PF, Frey TM, Brace CL, et al. Multiple-electrode radiofrequency ablation of hepatic malignancies: initial clinical experience. AJR Am J Roentgenol 2007;188:1485-1494.
3. Minami Y, Kudo M. Radiofrequency ablation of hepatocellular carcinoma: current status. World J Radiol 2010;2:417-424.
4. Goyal N, Jain N, Rachapalli V, Cochlin DL, Robinson M. Non-invasive evaluation of liver cirrhosis using ultrasound. Clin Radiol 2009;64:1056-1066.
5. Mulier S, Ni Y, Miao Y, et al. Size and geometry of hepatic radiofrequency lesions. Eur J Surg Oncol 2003;29:867-878.
6. Stippel DL, Brochhagen HG, Arenja M, Hunkemöller J, Hölscher AH, Beckurts KT. Variability of size and shape of necrosis induced by radiofrequency ablation in human livers: a volumetric evaluation. Ann Surg Oncol 2004;11:420-425.
7. Montgomery RS, Rahal A, Dodd GD 3rd, Leyendecker JR, Hubbard LG. Radiofrequency ablation of hepatic tumors: variability of lesion size using a single ablation device. AJR Am J Roentgenol 2004;182:657-661.
8. Kim SK, Rhim H, Kim YS, et al. Radiofrequency thermal ablation of hepatic tumors: pitfalls and challenges. Abdom Imaging 2005;30:727-733.
9. Sporea I, Sirli R, Popescu A, Danilă M. Acoustic radiation force impulse (ARFI): a new modality for the evaluation of liver fibrosis. Med Ultrason 2010;12:26-31.
10. Gallotti A, D'Onofrio M, Romanini L, Cantisani V, Pozzi Mucelli R. Acoustic radiation force impulse (ARFI) ultrasound imaging of solid focal liver lesions. Eur J Radiol 2012;81:451-455.
11. Cho SH, Lee JY, Han JK, Choi BI. Acoustic radiation force impulse elastography for the evaluation of focal solid hepatic lesions: preliminary findings. Ultrasound Med Biol 2010;36:202-208.
12. Chun YH, Kim SU, Park JY, et al. Prognostic value of the 7th edition of the AJCC staging system as a clinical staging system in patients with hepatocellular carcinoma. Eur J Cancer 2011;47:2568-2575.
13. Popescu A, Sporea I, Sirli R, et al. The mean values of liver stiffness assessed by acoustic radiation force impulse elastography in normal subjects. Med Ultrason 2011;13:33-37.
14. Friedrich-Rust M, Wunder K, Kriener S, et al. Liver fibrosis in viral hepatitis: noninvasive assessment with acoustic radiation force impulse imaging versus transient elastography. Radiology 2009;252:595-604.
15. Fahey BJ, Nelson RC, Bradway DP, Hsu SJ, Dumont DM, Trahey GE. In vivo visualization of abdominal malignancies with acoustic radiation force elastography. Phys Med Biol 2008;53:279-293.
16. Kapoor A, Mahajan G, Sidhu BS, Lakhanpal VP. Real-time elastography in differentiating metastatic from nonmetastatic liver nodules. Ultrasound Med Biol 2011;37:207-213.
17. Kim JE, Lee JY, Kim YJ, et al. Acoustic radiation force impulse elastography for chronic liver disease: comparison with ultrasound-based scores of experienced radiologists, Child-Pugh scores and liver function tests. Ultrasound Med Biol 2010;36:1637-1643.