Review

DOI: 10.5582/ddt.2015.01049

Extra vascular interventional treatment of liver cancer, present and future

Wenjing Hou[1], Xiaolin Zhu[2,*]

[1] Ultrasound Department, Tianjin Central Hospital of Gynecology and Obstetrics, Tianjin, China;
[2] Department of Hepatobiliary Surgery, Tianjin Medical University Cancer Institute & Hospital, Tianjin, China.

Summary **Interventional therapy for liver cancer is a new type of treatment, and its progress has been influenced by the development of the large scale imaging instrument and various therapeutic apparatus. This article, from these two aspects, discusses the status and progress of interventional treatment of liver cancer.**

Keywords: Functional magnetic resonance imaging, contrast-enhanced computed tomography, contrast-enhanced ultrasound, image fusion technology, radiofrequency tumor ablation, microwave ablation, cryoablation, percutaneous ethanol ablation, laser ablation, Nano-knife treatment

1. Introduction

The current treatment of liver cancer includes surgical resection, liver transplantation, interventional therapy, radiation therapy, and chemotherapy. Interventional treatment includes both extravascular and endovascular treatment. For liver cancer, the extravascular interventional treatment is addressed as precision to inactivate in-situ treatment of a tumor using energy generated by high-tech physics (*e.g.* radio frequency, microwave, argon, helium freezing, laser, high intensity focused ultrasound, Nano-knife, photodynamic *etc*.) and chemicals (*e.g*. ethanol, acetic acid, dilute hydrochloric acid, *etc*.). Advanced imaging equipment and technical guidance of ultrasound are used, digital subtraction angigraphy (DSA), computed tomography (CT), and magnetic resonance imaging (MRI), have advantages of positioning accuracy, less trauma, bearable pain and curative treatment. Nowadays, it can be a trend to build a hybrid high-tech operating room, equipped with ultrasound, DSA, CT, MRI and other medical imaging equipment in large hospitals at home and abroad. Radiologists, interventional radiologists, and surgeons break discipline restrictions, and work in close coordination and cooperation with each other, to achieve minimal trauma for patients, truly people-centered in accordance with evidence-based medical principles.

*Address correspondence to:
Dr. Xiaolin Zhu, Department of Hepatobiliary Surgery, Tianjin Medical University Cancer Institute & Hospital, Huanhu Road, Tianjin 300060, China.
E-mail: cherryzhu19@yahoo.com

2. Imaging and extra vascular interventional treatment of liver cancer

As far as increasing requirements in people's quality of life as well as the great development of medical imaging technology, digital technology, computer technology, biotechnology, molecular biology and cell immunity, therapeutic strategies are undergoing profound changes. How to use minimally invasive or non-invasive methods to inactivate and kill tumors in-situ while maximizing protection of the surrounding normal tissue, has become a hot spot and most urgent pursuit for tumor therapy physicians. Non-vascular interventional treatment, as the representatives of radiofrequency tumor ablation, microwave ablation, cryoablation, ethanol ablation, laser ablation, Nano-knife treatment, guided by MR, CT, ultrasound and other imaging examinations, has become an important part of clinical treatment. Imaging technology used in tumor treatment plays an important role in two aspects, one to locate the lesion, early diagnosis and postoperative follow-up, on the other hand, to guide treatment instrument arriving at target areas. Two imaging diagnoses plus elevated serological index can be diagnosed as liver cancer, which can be proof for extra vascular interventional treatment. Imaging detection of liver lesions is particularly important.

2.1. *Functional magnetic resonance imaging (fMRI)*

fMRI is a physiological function of the organizational structure, based on the image displayed in its state imaging technology. It appears to provide a minimally invasive way for liver cancer preoperative diagnosis and postoperative evaluation. fMRI includes a variety of methods, T1WI diffusion tensor and T2WI combine diffusion weighted imaging (DWI), perfusion weighted imaging (PWI), magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI) and blood oxygen level dependent functional magnetic resonance imaging (BOLD-fMRI), and contrast enhanced MRI after injection of the new hepatocyte-specific MRI contrast agent, Cypriot disodium (gadolinium ethoxybenzyl diethylenetdamine pentaacetic acid, Gd-EOB.DTPA). No other investigations can exceed MRI in the diagnostic value of small hepatocellular carcinoma (*1,2*). The use of all kinds of contrast agents should however be used with caution in patients with renal failure given the risk of nephrogenic systemic fibrosis which is a rare disorder associated with fibrosis of the skin, joints, eyes, as well as internal viscera (*3*). The other disadvantage to MRI is the relatively long time it takes to complete the study which may be a challenge for critically ill transplant candidates who need more detailed imaging before listing for transplant.

2.2. *CT and contrast-enhanced CT*

Contrast-enhanced CT has already become the most common and important method used in cancer diagnosis, but it is still highly restricted to smaller diameter tumor detection proportions. Multi-detector computed tomography (CT) scanning remains a very useful tool in the diagnosis of HCC. Advances over the last 10 years have seen CT scanners become considerably faster while attempting to limit the radiation dose. The sensitivity of multidetector CT (MDCT) is reported at 81% as compared to 91% with MRI in a meta-analysis of 15 comparative studies between MRI and MDCT. The specificity of MDCT was 93% compared to 95% in the MRI group. CT scans do afford the ability to perform three-dimensional reconstructions that may help with operative planning which is an advantage over MRI (*4*). Although a rare event, this mode of imaging does however place patients at risk for contrast induced nephropathy (*5*).

Although not included in standard diagnostic guidelines, modern advances show that perfusion CT scanning may offer more information regarding liver hemodynamics and blood flow directed toward tumors in the liver (*6*). This may become more useful as transarterial chemoembolization (TACE) is an evolving therapy for HCC. It also may aid in treatment monitoring. Current perfusion CT does, however, deliver a higher radiation dose as well as lower resolution (*7*).

2.3. *Ultrasound and contrast enhanced ultrasound (CEUS)*

CEUS is one of the representatives of these new technologies, and the use of contrast agents significantly improves the resolution of ultrasound diagnostic sensitivity and specificity. It has been widely used in clinical diagnosis of liver diseases, and in particular has an irreplaceable role in the diagnosis of liver tumors. Real-time CEUS dynamically reveals hepatic tumor hemodynamics by enhanced mode and enhanced phase. First, CEUS can early detect nodules in a liver cirrhosis background, and make a differential diagnosis; its diagnostic accuracy is at a high rate compared with enhanced CT and MRI. Ryu *et al*. (*8*) reported an analysis of 48 patients and a total of 50 liver tumors and found the use of a suitable acoustic window; CEUS had a similar diagnostic value compared with CT/MRI examination. Zhu *et al*. (*9*) studied 45 patients who had lesions in liver with cirrhosis that underwent both contrast-enhanced MRI examination and CEUS examination before surgery, and found that the diagnostic accuracy was 77.3% and 62.7%, respectively. Zheng *et al*. considered when evaluating response to therapy after HCC, although compared with the contrast-enhanced CT/MRI examination, CEUS showed great superiority. At the same time CEUS can make up CT/MRI deficiencies, such as CEUS offers real-time dynamic imaging, on the very early or very late phase to observe a lesion which may not appear on CT, and MRI image enhancement mode is extremely useful. Second, unique structure of micro bubble intravascular contrast agents favor depiction of the hemodynamic characteristics of HCC in CEUS examination, and will not cause the phenomenon of false-enhancement in delay phase in enhanced CT or MRI due to contrast agent leaks to tumor gaps. Third, CEUS allows multiple injections of contrast agent, for the quick clearance of contrast agent from blood, so as to observe enhanced mode repeatedly. Last, as a safe agent excluded by respiration, patients with heart and kidney failure can also tolerate the treatment.

However, limitations as well exist in CEUS examination, in such situations as physical obesity, gas interference in intestine, deep location in ultrasonic far field, or close to the top of the diaphragm or corners, the lesions can not be clearly displayed in two-dimensional ultrasound, let alone in CEUS. Time for each angiography contrast agent through the lesion is shorter, only no more than two lesions can be checked, so it can not observe the whole liver each time. For AFP increased patients with multiple small intra-hepatic nodules or abnormal situations, only conventional ultrasound examination repeatedly performed is needed (*11-14*).

Application of CEUS in clinic is later than enhanced CT and MRI, and there is examination with many similarities among them, but the enhanced mode is not the same. Ultrasound guided extra vascular interventional treatment of liver cancer is widely used compared to MRI and CT for its convenience, because it is less time-consuming, and gives a real-time and non-invasive examination.

2.4. *CEUS combined with CT and MRI*

At present, it has been reported that a new imaging method, navigated by image fusion technology by CT/MRI-ultrasound, pinpoint the location of the original tumor. This method is able to integrate the advantages of CT/MRI, three-dimensional or three-dimensional CEUS imaging and other kinds of ultrasound, make a good collection of CT/MRI static volumetric imaging and real-time ultrasound imaging technology, the CT/MRI good spatial resolution and real-time ultrasound good operation, simplicity complementary. Truly perfect "eye" (CT/MRI) and "hand" (ultrasound operation) combination. It will be the size of the tumor before surgery, location fusion superimposed and displayed on the ablation lesions, based on the joint use of three-dimensional ultrasound contrast can be more comprehensive and an objective assessment of ablation forecast and secure borders through images, CT/MRI an ultrasound navigation image fusion image is expected to become liver cancer diagnosis, guide treatment and postoperative evaluation of the most accurate method, and the accuracy of vascular interventional treatment of hepatocellular carcinoma has important clinical significance (*15-20*).

2.5. *Tumor ablation and image guidance*

Tumor ablation can be performed by percutaneous, laparoscopic surgery and surgery. Percutaneous tumor ablation guided by ultrasound, CT, MRI and other imaging methods has an advantage of less trauma, shorter hospitalization time, is less costly with faster recovery and retains the body's normal tumor tissues and organ function to the maximum, compared to laparoscopic and open surgical approach, but it cannot completely replace the other two ways in some instances. For example, for tumors near the bowel and diaphragm, the laparoscopic approach is a priority for bowel and diaphragm protection. When the main tumor is excised, other satellite lesions can be ablated at the same time.

Ultrasound, CT, MRI and other imaging that are used to guide tumor ablation also have their own advantages. As well as making good use of these examinations can help disease diagnosis and treatment better. Real-time ultrasound imaging, as a multi-angle detection, is safe and the cheapest imaging examination, is the priority method for guided ablation; contrast enhanced ultrasound helps to confirm the size and shape of the tumor, which can define the scope of tumor invasion, atypical small HCC detection and satellite lesions, as well as provide a more reliable reference for tumor ablation. Contrast-enhanced ultrasound can be performed for follow-up in case of local tumor progression or new lesions early. However, ultrasound has poor spatial resolution for deep lesions, especially in obesity. Sonic energy is badly absorbed or reflected by lungs, bones, intestine, ribs and so on, which make tumor there unrecognized. Besides, the former larger ablation lesions can produce steam after ablation; these mimic bubble artifacts and will obviously interfere with the subsequent puncturing and treatment.

CT with high spatial resolution and intensity resolution can be widely used in whole body. Nowadays, as well as three-dimensional reconstruction technology employed, CT can more clearly show size, accurate location, quantity and relationship with organs nearby, which can provide reasonable proposal for ablation. CT examination also can evaluate the efficacy after ablation and follow up. The biggest disadvantage is radiation restriction.

MRI image examination is a very suitable guidance and monitoring equipment for ablation. It has the following advantages: first, it has good resolution of tissue and anatomical structures that can highly proceed other examination, so it can clearly show the tumor and relationship with adjacent structures. Its fast imaging technique makes it efficient for real-time monitoring the whole procedure; second, its unique black blood or white blood technique provides a method to recognize blood vessels without a contrast agent administrated, which greatly reduces unnecessary iatrogenic injury; third, with multiple parameter imaging techniques, some blurred lesion on CT can be displayed clearly; fourth, with multi-planar imaging capability, we can select the plane and show puncture path of the lobe; fifth, with no ionizing radiation, MRI can be the best image examination helping interventional treatment; and last, it is the only imaging technology with real-time temperature monitoring, being highly sensitive to the temperature and amount of water molecule, which is important to control the scope and efficiency of ablation. The ultimate aim of minimally invasive tumor ablation is to achieve inactivation of tumor in situ and keep live function at a maximum, MRI can clearly distinguish the damaged area and normal tissue ablation without enhancement, an animal experiment showed that the actual ablation scope measured in pathology after ablation is close to that evaluated by MRI during ablation, no more than 2 mm. MRI has a more sensitive and accurate evaluation efficacy than any other image examination. It is the best option to determine whether the tumor has complete ablation. However, MRI and ablation relative equipment is expensive; patients with pacemakers and metal implants should not be guided by MRI treatment; non-magnetic compatibility rescue and monitoring equipment cannot enter the MRI operating room and so on, which greatly restrains its application. Expected because of development of industries, MRI guidance will become popular in clinical settings.

Currently, the preoperative ultrasound CT/MRI image fusion is used to locate the tumor ablation, and navigation and real-time evaluation of the efficacy has gained great attention. Real-time ultrasound, CT or MRI fusion imaging can better guide and monitor ablation, equipped with a virtual navigation system not only helps to determine the scope of tumor invasion, develop and simulate puncture route, but also to predict ablation volume.

3. Ablation and treatment evaluation

Italian scholars Rossi *et al*. raised the possibility of percutaneous radiofrequency ablation of liver tumors in 1990 (*21*), and first published this in 1993 (*22*). In recent years, under the guidance of imaging technology, ablation plays an important role in the treatment of liver cancer. Among them, radiofrequency ablation (RFA) and microwave ablation (MWA) are better represented. Due to less invasion, and ease of operation, they can effectively inactivate tumor by coagulation. This brings a breakthrough for tumor treatment (*23,24*).

3.1. *Radiofrequency ablation (RFA)*

The principle of radiofrequency ablation is tissue coagulation caused by electromagnetic waves (usually 375-500 kHz). Electromagnetic waves in the needle electrode produce an alternating magnetic field, alternating magnetic field excited alternating current and collision, friction heat, heat deposition exceeds the tolerable level of tumor and causes necrosis; the small blood vessels around the tumor are occluded due to heat damage and thereby block tumor blood supply, in addition to the thermal effect of RFA it can enhance immune function, inhibit residual tumor cell growth and enhance tumor sensitivity to radiotherapy and chemotherapy. A cohort study (*25*), success rate of complete ablation in lesions less than 2 cm is over 90%, with local recurrence rate of less than 1%. A recent comparison of percutaneous RFA and liver resection of small liver cancer meta-analysis shows that, overall survival rates were similar in patients with small HCC by either percutaneous RFA or surgical resection, for compliance with standards of Milan and suitable for surgery or percutaneous RFA. The later would have little invasion, low incidence of complications and so on. Patients unwilling to accept surgery can be recommended to select percutaneous RFA (*26*).

Compared with microwave ablation, for a diameter > 3 cm tumor, the rate of local recurrence and complications, like biloma, is high. It is believed that with accumulated experience, medical technology update, and equipment advances, RFA treatment of liver cancer will be used wider and wider (*27*).

3.2. *Microwave ablation (MWA)*

MWA uses frequency > 900 MHz (usually 900-2,500 MHz) electromagnetic waves, the microwave heating effect causes biological tissue tumor tissue degeneration and coagulation necrosis. Not only heating by "ionic heating" like RFA, but also by "dipole heating", and the later works as well. Two electromagnetic wave frequency ranges, 915 MHz and 2,450 MHz are applied in clinics. The later is more commonly used. Theoretically, under the same energy output, ablation with 915 MHz can penetrate deeper, gaining a broader ablation range. In addition to possessing all the advantages of RFA MWA still has its some advantage: no limit to current poor conduction, fast temperature rise , a small subsidence effect caused by organized carbonization, a larger ablated range for single-needle, shorter ablation time, less pain and no need of grounding negative plates. In addition, compared to a simple "ionic heating", MWA mainly produces heat by water-based "dipole heat", and therefore it is suitable for the treatment of cystic tumors. The RFA effective tissue heating zone is limited to a few millimeters from the needle tip center, and the rest of the ablation zone is by thermal conduction, while microwaves have good transmission characteristics, and it can heat effectively all tissue as set up by the antenna (*28,30*).

Another scholar advised improving the efficacy of radiofrequency ablation and reduce medical risks by adjusting the output power, the application of digital technology and combined intravenous anesthesia reconstruction techniques.

3.3. *Cryoablation*

Cryotherapy is based on the argon helium frozen ablation technique, argon rapid expands quickly so that tissue temperature drops below zero rapidly. Cold causes cell necrosis by formation of ice crystals, then helium makes a rapid heating release causing ice hockey swell thawing, rupture, and further damage to tissue cell structure collapse, ultimately leading to cell necrosis. Permopongkosol S *et al*. (*31*) reported that cryoablation greatly reduced pain during treatment, unaffected by vasoactive effect "thermal sinking". Cryoablation is superior to RFA for a tumor near large vessels. However, there are many complications: including freezing without concerning the edges, when there is a hockey burst, tumor cells may break into the surrounding tissue, inadequate refrigeration may cause bleeding after treatment or even "freeze shock (cryoshock)", which is the main reason for death. Although most scholars agree that cryoablation efficiency can be equal to RFA treatment of liver cancer. Since local recurrence rate is lower when comparing RFA to cryoablation, there is a tendency to choose RFA as treatment for cancer, which needs further randomized verified trials.

3.4. *Percutaneous ethanol infusion (PEI)*

PEI is another commonly used interventional extravascular treatment. Coagulating inactivation produced by alcohol induces cell dehydration, protein denaturation, chemical embolization of tumor blood vessels and other small pathways and leads to cell coagulation necrosis. Lencioni RA *et al*. reported that PEI was more effective than RFA for an enveloped tumor or that with adjacent large blood vessels, or vital organs (*32*). However, PEI treatment has a high lesion recurrence rate, for tumors less than 3 cm recurrence rate was 33%, lesion when larger than 3 cm recurrence rate of over 43%. This may be due because alcohol cannot evenly distribute throughout the tumor, especially for lesions including septum. This kind of treatment is just like "irrigation", and does not designate a valid "security border". It had little effect on tumors with satellite nodules (*33*).

On the contrary, RFA can outline a "security border" and have lower local recurrence rate. Randomized clinical trials (*32,34*) confirmed that RFA helped keep local treatment area stable for a clear "security border".

3.5. *Laser ablation (LA)*

LA uses thin, flexible optical fibers (diameter 300-600 μm) or optical fiber specially designed water-cooled in center to insert inside tumor under image guidance, tumor generates heat through absorption of laser and produces thermal effects, pressure effects, photochemical effects and electromagnetic effects, thus achieving the purpose of killing tumor by degeneration, coagulation, and vaporization (*35*).

Laser has characteristics of deep penetration, easily absorbed by water, output power is adjustable, flexible operation, uniform energy distribution, and it is better for tumor treatment. A large randomized multicenter study has not yet been developed, there is a lack of long-term follow-up studies after treatment, and currently there is no treatment-related international consensus standards and guidelines. Laser ablation effects in combination with other treatments need further study (*36*).

3.6. *High intensity focused ultrasound (HIFU)*

The sonic frequency HIFU used is significantly higher than the applied ultrasonic diagnostic ultrasound (frequency 0.8-3.2 MHz, time-averaged intensity of the focus area is 100-10,000 W/cm^2, peak voltage and peak sparse concentrated pressure do not wind, 30 MPa and 10 MPa). The principle of HIFU is to gather low energy density beam convergence to target the body, sound propagation in body, and to transfer orderly ultrasonic vibrational energy into disorderly molecules energy, local tumor temperature soars to 65 (0.1 to 0.5 seconds -100°C), and causes tumor tissue coagulation necrosis, and achieves the purpose of non-invasive tumor inactivation without damage to the upper tumor tissue and adjacent normal tissue. HIFU can involve three-dimensional tumor structure as a scanning motion, this administrates tumor treatment with different shapes and size. As a kind of ultrasound, HIFU also has acoustic shadow, reflection, and refraction. HIFU has little effect on deep lesions, intestines or ribs nearby and may damage normal tissue due to refraction (*37*).

3.7. *Irreversible electroporation (IRE)*

Electroporation is a kind of physical phenomena with nanoscale pores in the cell membrane. Nanoscale pores are produced by potential instability due to a high-voltage field effect in the form of microsecond and millisecond pulsars in the phospholipid bilayer membrane (*38*). According to pulse amplitude and time applied to the cell membrane, nonporous membrane can be divided into temporary or permanent, to reverse electroporation (RE) and in reverse electroporation. In RE conditions, cells can be fully restored and survive, and IRE leads to cell death. IRE has a special pattern of non-thermal ablation of cells, without affecting the collagen support structure that allows regeneration of healthy tissue ablated in the tissue area, there is no scarring and other important characteristics, which has caused great attention (*39*) in the clinical treatment of cancer. This kind of reverse electroporation is also called "Nano knife".

IRE technology has ability to inactivate selected tumor only, there is no thermal conductivity effect, no sharp edges around the ablation zone, no neighboring tissue impairment like arteries, veins, peripheral nerves, urethra or intrahepatic bile duct, *etc*. IRE technology still has many shortcomings, such as electrical pulse induced arrhythmias and strong muscle contractions (and thus should be under general anesthesia treatment), the electrode needle placement has pneumothorax and bleeding risk, and this needs to be further studied and solved. A large standard randomized multi-center clinical study and long-term follow-up study needs be performed.

4. Conclusion

Extra vascular interventional treatment of liver cancer is safe, minimally invasive, repeatable and effective, *etc*. It is widely used in the treatment of solid tumors in the liver, plays an important role in tumor resolution and is minimally invasive. Selecting the appropriate therapeutic indication to give a comprehensive treatment is key to reduce complications and lower recurrence rate, which is a major challenge of extravascular interventional treatment of liver cancer in the future.

References

1. Lee JM, Zech CJ, Bolondi L, Jonas E, Kim MJ, Matsui O, Merkle EM, Sakamoto M, Choi BI. Consensus report of the 4th International Forum for Gadolinium-

Ethoxybenzyl-Diethylenetriamine Pentaacetic Acid Magnetic Resonance Imaging. Korean J Radiol. 2011; 12:403-415.
2. Kogita S, Imai Y, Okada M, Kim T, Onishi H, Takamura M, Fukuda K, Igura T, Sawai Y, Morimoto O. Gd-EOB-DTPA-enhanced magnetic resonance images of hepatocellular carcinoma: Correlation with histological grading and portal blood flow. Eur Radiol. 2010; 20:2405-2413.
3. Kaewlai R, Abujudeh H. Nephrogenic systemic fibrosis. AJR Am J Roentgenol. 2012; 199:W17-W23.
4. Chen L, Zhang L, Bao J, Zhang J, Li C, Xia Y, Huang X, Wang J. Comparison of MRI with liver-specific contrast agents and multidetector row CT for the detection of hepatocellular carcinoma: A meta-analysis of 15 direct comparative studies. Gut. 2013; 62:1520-1521.
5. Davenport MS, Khalatbari S, Cohan RH, Dillman JR, Myles JD, Ellis JH. Contrast material-induced nephrotoxicity and intravenous slow-osmolality iodinated contrast material: Risk stratification by using estimated glomerular filtration rate. Radiology. 2013; 268:719-728.
6. Ippolito D, Sironi S, Pozzi M, Antolini L, Invernizzi F, Ratti L, Leone EB, Fazio F. Perfusion CT in cirrhotic patients with early stage hepatocellular carcinoma: Assessment of tumor-related vascularization. Eur J Radiol. 2010; 73:148-152.
7. Okada M, Kim T, Murakami T. Hepatocellular nodules in liver cirrhosis: State of the art CT evaluation (perfusion CT/volume helical shuttle scan/dual-energy CT, *etc*.). Abdom Imaging. 2011; 36:273-281.
8. Ryu SW, Bok GH, Jang JY, Jeong SW, Ham NS, Kim JH, *et al*. Clinically useful diagnostic tool of contrast enhanced ultrasonography for focal liver masses: Comparison to computed tomography and magnetic resonance imaging. Gut Liver. 2014; 8:292-297.
9. Zhu XL, Hou WJ, LI Q, Zhang S, Xu Y, Du P. Early diagnosis of small hepatocellular carcinoma in patients with liver cirrhosis using ultrasound and contrast-enhanced magnetic reaonance. Chin J Ultrasonogr. 2010; 19:688-692.
10. Zheng SG, Xu HX, Liu LN. Management of hepatocellular carcinoma: The role of contrast-enhanced ultrasound. World J Radiol. 2014; 6:7-14.
11. Jang HJ, Yu H, Kim TK. Contrast-enhanced ultrasound in the detection and characterization of liver tumors. Cancer Imaging. 2009; 9:96-103.
12. Rimola J, Forner A, Tremosini S, Reig M, Vilana R, Bianchi L, *et al*. Non-invasive diagnosis of hepatocellular carcinoma ≤ 2 cm in cirrhosis. Diagnostic accuracy assessing fat, capsule and signal intensity at dynamic MRI. J Hepatol. 2012; 56:1317-1323.
13. Wei C, Shen E, Sun D, Zhang A, Sun J, Hu B. Assessment of alternated cooling and heating treatment by US combined CEUS in the VX2 rabbit liver tumor model. Chinese Science Bulletin. 2014; 59:865-873.
14. Martie A, Sporea I, Popescu A, *et al*. Contrast enhanced ultrasound for the chacterization of hepatocellular carcinoma. Med Ultrason. 2011; 13:108-113.
15. Minami Y, Chung H, Kudo M, Kitai S, Takahashi S, Inoue T, Ueshima K, Shiozaki H. Radio-frequency ablation for hepatocellular carcinoma: Usefulness of virtual CT sonography with magnetic navigation. Eur J Radiol. 2012; 81:277-280.
16. Goldberg SN, Charboneau JW, Dodd GD, *et al*. Image-guided tumor ablation: Proposal for standardization of terms and reporting criteria. Radiology. 2003; 228:335-345.
17. Mori K, Fukuda K, Asaoka H, Ueda T, Kunimatsu A, Okamoto Y, Nasu K, Fukunaga K, Morishita Y, Minami M. Radiofrequency ablation of the 1iver: Determination of ablative margin at MR imaging with impaired clearance of feruearbotran-feasibility study. Radiology. 2009; 251:557-565.
18. Kim YS, Lee WJ, Rhim H, *et al*. The minimal ablative margin of radiofrequency ablation of hepatocellular carcinoma (>2 and <5 cm) needed to prevent local tumor progression: 3D quantitative assessment using CT image fusion. Am J Roentgenol. 2010; 195:758-765.
19. Kim YS, Lee WJ, Rhim H, Lim HK, Choi D, Lee JY. Contrast-enhanced sonography with abdominal virtual sonography in monitoring radiofrequeney ablation of hepatocellular carcinoma. J Clin Ultrasound. 2010; 38:138-144.
20. Lee JY, Choi BI, ChungYE, Kim MW, Kim SH, Han JK. Clinical value of CT/MRI-US fusion imaging for radiofrequency ablation of hepatic nodules. Eur J Radiol. 2012; 81:2281-2289.
21. Rossi S, Fornari F, Pathies C, *et al*. Thermal lesions induced by 480 KHz localized current field in guinea pig and pig liver. Tumori. 1990; 76:54-57.
22. Rossi S. Percutaneous ultrasound-guided radiofrequency electrocautery for the treatment of small hepatocellular carcinoma. J Intervent Radiol. 1993; 8:97-103.
23. Nishikawa H, Kimura T, Kita R, *et al*. Radiofrequency-ablation for hepatocellular carcinoma. Int J Hypertherma. 2013; 29:558-568.
24. Chen MH, Dong JH. Ablation treatment of hepatocellular carcinoma: Current status, pitfalls and future. Chin J Hepatol. 2012; 20:241-244.
25. Livraghi T, Meloni F, Distasi M, *et al*. Sustained complete reponse 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.
26. Zhou DC, Geng XP, Zhu LX, Zhao HC, Liu FB, Zhao YJ. Percutaneous radiofrenquency ablation versus hepatic resection for hepatocellular carcinoma: A meta analysis. Zhonghua Wai Ke Za Zhi. 2011; 49:1132-1136.
27. Bruix J, Sherman M. Management of hepatocellular carcinoma: An update. J Hepatol. 2010, 53:1020-1022.
28. Sun Y, Wang Y, Ni X, *et al*. Comparison of ablation zone between 915 and 2,450 MHz cooled shaft microwave antenna: Results in in vivo porcine livers. AJR Am J Roentgenol. 2009; 192:511-514.
29. Shi W, Liang P, Zhu Q, Yu X, Shao Q, Lu T, Wang Y, Dong B. Microwave ablation: Results with double 915 MHz antennae in ex vivo bovine livers. Eur J Radiol. 2011; 79:214-217.
30. Liu FY, Yu XL, Liang P, et a1. Comparison of percutaneous 915 MHz microwave ablation and 2450 MHz microwave ablation in large hepatocellular carcinoma. Int J Hyperthermia. 2010; 26:448-455.
31. Permpongkosol S1, Nicol TL, Khurana H, Link RE, Zhai QJ, Kavoussi LR, Solomon SB. Thermal maps around two adjacent cryoprobes creating over lapping ablations in porcine liver, lung, and kidney. J Vasc Interv Radiol. 2007; 18:283-287.
32. Lencioni RA, Allgaier HP, cioni D, *et al*. Small hepatocellular carcinoma in cirrhosis: Randomized comparison of radio-frequency thermal ablation versus per

cutaneous ethanol injection. Radiology. 2003; 228:235-240.

33. Livraghi T, Goldberg SN, Lazzaroni S, *et al*. Small hepatocellular carcinoma: Treatment with radio-frequency ablation versus ethanol injection. Radiology. 1999; 210:655-661.
34. Shiina S, Teratani T, Obi S, *et al*. A randomized controlled trial of radio frequency ablation for small hepatocellular carcinoma. Gastroenterology. 2005; 129:122-130.
35. Liang P, Dong BW, Gu Y, Li JH, Yu XL, Li JL, Su L, Wang XD, Tang J, Zhang Y. Clinical study of US-guided percutaneous Nd-YAG laser in the treatment of liver cancer. Zhonghua Fang She Xue Za Zhi. 1995; 29:225-229.
36. Torzilling G, Liveraghi T, oliveari N. Interstitial percutaneous therapies in primary and second primary liver tumors. Ann Italchin. 1999; 70:185-194.
37. Gelat P, Ter Haar G, Saffari N. A comparison of methods for focusing the field of a HIFU array transducer through human ribs. Phys Med Biol. 2014; 59:3139-3171.
38. Neumann E, Schaefer-Ridder M, Wang Y, Hofschneider PH. Gene transfer into mouse lyoma cells by electroporation in high electric fields. EMBO J. 1982; 1:841-845.
39. Rubinsky B, Onik G, Mikus P. Irreversible electroporation: A new ablation modality-clinical implications. Technol Cancer Res Treat. 2007; 6:37-48.

(Received July 21, 2015; Revised August 11, 2015; Accepted August 21, 2015)