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RESEARCH

Comparison of the Effectiveness and Safety of Ultrasound- and CT-Guided Percutaneous Radiofrequency Ablation of Non-Operation Hepatocellular Carcinoma

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Abstract To retrospectively compare the effectiveness and safety of ultrasound (US)- and computer tomography (CT)-guided percutaneous radiofrequency ablation (PRFA) in treating patients with non-operation hepatocellular carcinoma (HCC). Forty patients with non-operation HCC who were treated with US-guided PRFA (20 patients with 24 HCC lesions) or CT-guided PRFA (20 patients with 27 HCC lesions) were enrolled in this study. Follow-up was performed with US and CT/MRI. Complete ablation rate, local recurrence rate, and overall survival rate were used to evaluate the efficacy of the two therapeutic choices. The PRFA-related complications including hilar bile duct injury, sepsis, liver failure, renal dysfunction, peritoneal hemorrhage, and skin burn were assessed. The operation time of CT-guided group was significantly longer than that of the US-guided group ($P<0.05$). The single ablation times for tumors with similar size showed no significant difference between the two groups ($P>0.05$). The differences in complete ablation rate (79.2 vs. 88.9 %, $P>0.05$) and local recurrence rate (16.7 vs. 14.8 %, $P>0.05$) between US- and CT-guided groups were not statistically significant. In the US-guided group, the 1-, 2-, and 3-year overall survival rates were 85, 74, and 68 %, respectively, while they were 84, 72, and 58 % in the CT-guided group. The differences were not statistically significant ($P>0.05$). No severe complications were found in the two groups. Both US- and CT-guided PRFA are safe and effective therapies for patients with HCC when surgical options are precluded.

Keywords US guidance · CT guidance · Radiofrequency ablation · Hepatocellular carcinoma

Highlights • Image guided PRFA is a minimally invasive therapy option in the treatment of primary and metastatic hepatic malignancies.
• CT and ultrasound, as the modalities of imaging guidance, have their own advantages and disadvantages.
• The decision about a certain modality of image guidance has to consider the individual situation like tumor size and location, as well as possible contraindications for a particular imaging modality.

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Introduction

Hepatocellular carcinoma (HCC) is the 5th most common cancer worldwide, and it is also the 3rd most common cause of mortality among all the cancers [1]. More than 70 % HCC patients cannot receive operation therapy due to liver cirrhosis or advanced stage of cancer [2]. Percutaneous radiofrequency ablation (PRFA) under image guidance, such as computed tomography (CT) or ultrasound (US), is a local tumor therapy to treat primary and secondary HCC, leading to clinical cure of patients [3]. US has the advantages of real-time monitoring, short operation time, and lack of radiation, and CT has a high accuracy of puncture and a high resolution of image [4]. However, these two approaches of image guidance also have limitations. To our knowledge, there have been limited published data regarding a comparison between US- and CT-guided PRFA for HCC patients to date. In this study, we aimed to retrospectively compare the technical effectiveness and safety of US- and CT-guided PRFA in treating HCC and provide reference to choose suitable way of image guidance.

Methods

Patients

Between April 1, 2007 and May 31, 2012, 40 patients who admitted to Department of oncology, The Third Hospital, Nantong University and received PRFA under CT or US guidance were enrolled in this study. Among them, 20 patients (17 males; aged 52.32±8.13 years) with 24 HCC lesions (15 lesions were no larger than 3 cm in diameter; 7 lesions had a diameter between 3 and 5 cm; 2 lesions had a diameter over 5 cm) received PRFA under US guidance. Twenty patients (15 males; aged 59.41±10.32 years) received PRFA under CT guidance. A total of 27 HCC lesions were determined among these patients, including 17 lesions no larger than 3 cm in diameter, 7 lesions with a diameter between 3 and 5 cm, and 2 lesions larger than 5 cm in diameter. Ethical approval for PRFA treatment was obtained from the research ethics committee of The Third Hospital, Nantong University. Informed consent was obtained from each patient.

The inclusion criteria of the patients were as follows: 1) patients with a single liver tumor smaller than or equal to 7 cm in diameter; or patients with less than 4 tumors with a diameter smaller than or equal to 3 cm; 2) no extrahepatic metastases and no imaging evidence of tumor invasion into the blood vessel or bile vessel; 3) liver cirrhosis classified as Child-Pugh class A or B; 4) blood platelet count $>50\times10^9$/L, Hemoglobin ≥90 g/L or total serum bilirubin <3 mg/dL; 5) patients with normal activated partial thromboplastin time and prothrombin time, and fibrinogen activity was over 50 %; 6) loss of operation chance due to one of the following reasons: the tumor located in the center of hepatic parenchyma trauma or cross the two pulmonary lobes; the distance between the tumor and large vessels or hepatic portal was less than 5 mm; tumor relapse within 1 year after operation; 7) without severe heart disease, pulmonary disease, or diabetes.

PRFA Technique

The RF generator (RF2000™, Talon CO, USA), which provided a maximum power-output of 200 W, was used to perform PRFA treatment. Multipolar special needles with stylet (LeVeen™3512 (15 g) and LeVeen™3515 (15 g)) were used. For US-guided PRFA, the vendor offered a color Doppler ultrasonograply (CDU) (Logiq-S6, GE CO, USA) with a frequency of 3.5 MHz. For CT-guided PRFA, light speed 16 row spiral CT (GE CO, USA) was used to fix the position or review.

US-Guided PRFA

Patients lay in a supine or left lateral position to expose the operation site. A pair of diffusion electrodes was affixed on the patients' back to prevent burns. US scanning was performed to determine the size and location of tumors. After the placement scheme and the entry point were determined, ultrasound guided needle was opened to determine the path direction, which should avoid the important blood vessels and bile duct. After regular disinfection, the operation towel was paved, and anesthesia was done by 2 % lidocaine to hepatic subcapsular. The skin incision (2 cm in diameter) was made in the puncture point. The multi or mono electrode radiofrequency needle was put into the distal shelf of the tumor along the ultrasonic probe, and was spread out like the umbrella, and started treating.

CT-Guided PRFA

Patients lay in a supine position to expose the operation site. A pair of diffusion electrodes was affixed on the patients' back to prevent burns. Positioning film was also affixed to the body surface of the patients. CT scanning was conducted to determine the size and location of the tumor. After choosing the largest diameter as the puncture plane, position line was opened to determine the entry point, path direction, puncture angle, and depth of needle. Avoid the important blood vessels and bile duct. PRFA was performed similar as the PRFA under US guidance when the operation started until the needle was put into the distal shelf of the tumor. Then, play the CT scan again to insure the needle's position, spread out the electrode like the umbrella, and started treating.

Evaluation of Curative Effect

Assessment of treatment response was based on the combination of CT/MRI imaging, color doppler ultrasound (CDU), or biopsy 1 month after the operation. Complete response (CR) means no enhancement in arterial phase by CT scanning, echo enhancement, and vanishment of the tumor blood signal by CDU. Incomplete response (ICR) means partial enhancement in arterial phase by CT scanning, part echo enhancement, and few tumor blood signals by CDU.

Follow-Up

The blood routine, liver function (ALT and AST), renal function (BUN and Cr), coagulation time, and US and CT/MRI of the patients were retested in 1–2 weeks after the operation. The liver function and CDU was detected once a month and CT/MRI was played once every 3–6 months. The follow-up data were obtained from the record of patients' reexamination until October 31, 2012.

Statistical Analyses

Statistical analyses were done by SPSS 17.0 for Windows (SPSS). The x^2 test and Student's t test were used for comparison between groups. Cumulative survival time was calculated by the Kaplan–Meier method and analyzed by the log-rank test. A $P<0.05$ was considered statistically significant.

Results

Comparisons of Ablation Time and Operation Time Between US- and CT-Guided PRFA

In the US-guided PRFA group, a total of 15 HCC lesions had a diameter ≤3 cm. Among them, 11 received ablation once and 4 (2 in Hepatic diaphragm dome, one in hepatic subcapsular, and one in portal vein side) received ablation twice. A total of 9 HCC lesions had a diameter larger than 3 cm in the US-guided PRFA group. Among them, 4 received ablation once and 5 received ablation more than once. In the CT-guided PRFA group, 17 HCC lesions had a diameter ≤3 cm. Among them, 14 received ablation once and 3 (one in hepatic subcapsular, one in caudate lobe inferior vena cava and one under hepatic subcapsular) received ablation twice. Among the 10 lesions with a diameter larger than 3 cm, 7 (3–5 cm in diameter) received ablation once and 3 (over 5 cm in diameter) received ablation more than once. There was no significant difference in the ablation time between the two groups ($P>0.05$) (Table 1).

However, the average operation time of CT-guided PRFA group was significantly longer than that of the US-guided PRFA group (t=−2.651, 85.56±33.78 vs. 63.33±24.64 min, $P=0.011$).

The Relationship Between the Imaging Change and Ablation Degree After PRFA Treatment

One months after operation, the echo enhanced and internal flow signal disappeared in the 19 CR lesions guided by US (Fig. 1A); the echo enhanced partly with blood flow signal reduced in another 3 ICR cases; 2 ICR showed no blood flow signal by color doppler flow iImaging (CDFI) and the edge nodular was enhanced by CT scanning. Twenty-two CR cases in CT-guided group showed no enhancement in arterial phase (Fig. 1B), and three ICR cases showed nodular enhancement at arterial phase. Two ICR cases showed a low density area around the lesions, which had no progression followed up for 3 months, thus they were considered as edema inflammatory lesion surrounding the post-PRFA lesion.

Comparisons of Complete Tumor Ablation Rate and Local Recurrence Rate After the PRFA Treatment

In the US-guided group, the complete ablation rate in patients with tumor diameter smaller than 3.0 cm was significantly higher than that with tumor diameter larger than 3.0 cm ($P=0.027$), while the local recurrence rate was not statistically significant ($P>0.05$). In the CT-guided PRFA group, complete ablation rate in patients with tumor diameter smaller than 3.0 cm was significantly higher than that with tumor diameter larger than 3.0 cm ($P=0.044$), while the local recurrence rates were not statistically significant ($P>0.05$).

By comparing between the two groups, the complete ablation rate is higher and the local recurrence rate was lower in the CT-guided group, but there was no significant differences ($P>0.05$) (Table 2).

Comparison of the Adverse Reaction and Complication Rate of PRFA Between Two Groups

The postoperative adverse reaction and complications after the US-guided PRFA therapy included: 14 cases of fever (70 %), 6 cases of pain (30 %), 3 cases of nausea and vomiting (15 %), and 2 cases of the electrode plate skin burns (10 %). Postoperative adverse reaction and complications after the CT-guided PRFA treatment included: 16 cases of fever (80 %), 8 cases of pain (40 %), 3 cases (15 %), nausea and vomiting. The adverse reaction and complication rates between the two groups had no significant difference ($P>0.05$).

Table 1 The ablation times in different size tumors

Diameter (cm)	Ablation times	US-guided group		CT-guided group		X^2 value	P value
		Number	Rate	Number	Rate		
≤3.0	1	11	45.8 %	14	51.9 %	0.035	0.851
	2	4	16.7 %	3	11.1 %		
>3.0	1	4	16.7 %	7	25.9 %	0.437	0.508
	2-3	5	20.8 %	3	11.1 %		

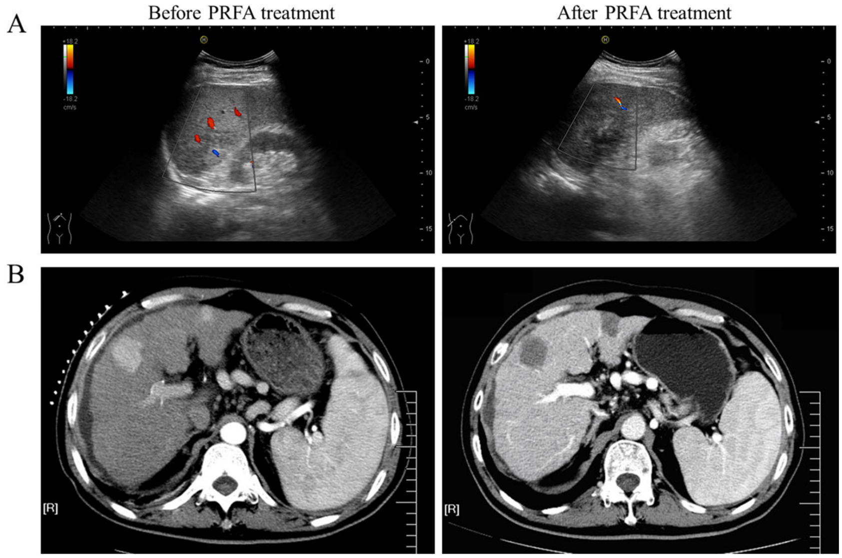

Fig. 1 Image change of the complete response (*CR*) cases after PRFA treatment. The increased echogenicity and disappeared blood flow signals could be found by US (**A**) 1 month after PRFA treatment and low density in the lesion and no enhancement could be found in arterial phase by enhanced CT (**B**)

Comparison of the Survival Rate of the Patients Between Two Groups

Patients were followed up till October 31, 2012, with a median follow-up time of 38 months (ranged 5–67 months). In the US-guided group, one case was lost during the follow-up period, and the dropout rate was 5 % (1/20). Ten people still alive, while seven died of cancer and complications, and two people died of other diseases. The 1-, 2-, and 3- year survival rates were 85, 74, 68 %. The median survival time was 39.0 month. In the CT guided group, no case was lost in the follow-up period. Nine patients still alive, while eight died of liver cancer, and three people died of other diseases. The 1-, 2-, and 3- year survival rates were 84, 72 and 58 %. The median survival time was 43 month. There's no significant difference (P>0.05) of the 1-, 2-, and 3- year survival rates between two groups (Fig. 2).

Discussion

Image guided PRFA is a minimally invasive therapy option in the treatment of primary and metastatic hepatic malignancies [5]. Especially in the treatment of HCC, PRFA is already an accepted part of the therapy concept. Because of the limited damage, simple operation, good repeatability, recent curative effect, and low cost of PRFA, it has been widely used in clinical, and changes the treatment of liver cancer model in a certain extent [6, 7]. Modalities of imaging guidance during ablation therapy are CT, US, or magnetic resonance (MR) [8]. US guidance offers a real-time multiplanar imaging and enables a fast applicator placement. Its disadvantages are limited capability to visualize tumor tissue and monitor thermal effects due to air bubbles produced by vaporization. CT imaging has a high image resolution [9], and is not affected by the air in the lung and intestinal [10]. It also has obvious advantages in discovering small liver cancer, cancer under diaphragm, and liver cirrhosis. It has a high accuracy and won't be interrupted by the air bubbles because of the three-dimensional positioning. But the CT-guided PRFA treatment also has some limitations: repeated scan is needed to confirm the exact location of RF needle, time-consuming, and the puncture accuracy is easily influenced by the patient's respiratory motion. In addition, CT guidance cannot offer the real-time image monitoring during the puncture process; when the tumor adjacent to major vessels or organs, it is easy to cause serious complications. In this study, we compared the clinical efficacy and safety of US- and CT-guided PRFA treatment in liver cancer, in order to provide a reference to choose the better way of image

Table 2 Complete tumor ablation rate and local recurrence rate of the tumor after PRFA

	Diameter (cm)	Complete tumor ablation rate	X^2 value	P value	Local recurrence rate	X^2 value	P value
US-guided group	≤3.0	93.3 % (14/15)	4.867	0.027	6.7 %(1/15)	2.880	0.089
	> 3.0	55.6 % (5/9)			33.3 %(3/9)		
CT-guided group	≤3.0	100 % (17/17)	4.034	0.044	5.9 %(1/17)	1.306	0.253
	> 3.0	70.0 % (7/10)			30.0 %(3/10)		

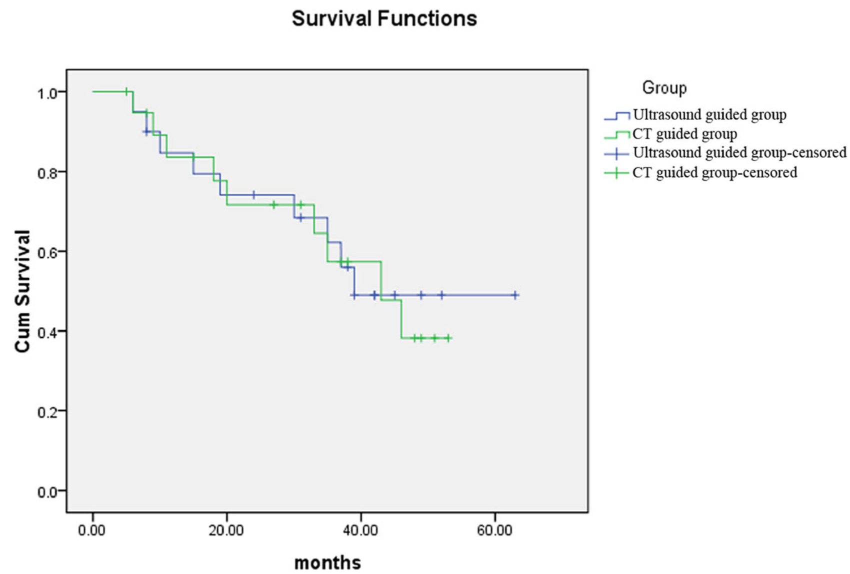

Fig. 2 Kaplan-Meier survival curves of US-guided PRFA group and CT-guided PRFA group. There's no difference of overall survival rate between the two groups

guidance which can improve the positioning accuracy, increases the complete tumor ablation rate, and reduce the occurrence of complications after operation.

In our study, we found that the complete tumor ablation rate of people with smaller diameter tumors (≤3.0 cm) is 93.3 %, while the complete tumor ablation rate was 55.6 % in people with larger diameter tumor (>3.0 cm) by enhanced CT examination 1 month after US-guided PRFA, which suggested that low complete tumor ablation rate connected with bigger tumor size. Four tumors had the local recurrence showed by enhanced CT examination. It may be because that there are differences between the three-dimensional structures of tumor and two-dimensional of ultrasound imaging, so it is difficult to guarantee the complete coverage of 3D structure of a larger tumor by ultrasound. In addition, air bubbles produced by vaporization during the treatment may blur the contours of the tumor, which makes the position more difficult [11]. In 27 HCC lesions guided by CT during PRFA, the complete tumor ablation rate of people with smaller diameter tumor (≤3.0 cm) is 100 %, while the complete tumor ablation rate was 70 % in people with larger diameter tumor (>3.0 cm) by enhanced CT examination 1 month after the operation. There were also 4 tumors which had the local recurrence, which confirmed the results reported by Park BJ and Laspas F [12, 13]. There's no significant difference of complete tumor ablation rate and local recurrence rate between the groups with ultrasound guidance and CT guidance.

In this study, 3 tumors at the top of diaphragm were complete ablated once by CT guiding while 2 tumor at the top of diaphragm were ablated twice by ultrasound guiding. It is because that CT image is not affected by the impact of gas. Tumor near diaphragm can be shown clear, and leading an accurate puncture with the bottom-up slant paracentesis. As the plate electrode was not well affixed to patients caused by sweating during operation, two patients had deep second skin burn (about 2 cm in diameter) but were cured after local treatment. No serious complications, such as diaphragm perforation and pneumothorax, occurred. At present, CT-guided PRFA is always used in cases with difficulty of US guidance [14, 15]. If necessary, TACE can be played 2 weeks before surgery, which can improve the puncture accuracy and safety according to tumor lipiodol deposition.

In our study, the operation process time in US-guided group was significantly shorter than that in the CT group; this was mainly due to the real-time multiplanar imaging which enabled a fast applicator placement. In CT-guided PRFA, CT scanning should be done 3 to 4 times when the needle punctured into the liver in a distance, the needle was in the pre positioning point, and open the needle electrode. The whole process was relatively complicated and increased the radiation exposure time. The real-time multiplanar imaging of US played a great advantage in PRFA to avoid the damage to the surrounding structures, especially the perivascular. But US could be easily affected by the ribs and the gas, which affected the display of tumor and the puncture needle. In this point, it is more safety to choose CT-guided PRFA.

There's no significant difference in the 1-, 2-, and 3- year cumulative survival rates between US- and CT-guided groups. The long-term results were satisfactory. Tumor size and position were the most significant factors influencing the curative effect. In our study, the larger the tumors were, the lower the complete ablation rate was. It might because that when the tumor volume is too large, it couldn't achieve complete ablation, thereby affecting the survival rate of patients. Even by repeated ablation or enlargement of the ablation range cannot compensate this defect. On the other hand, track implantation of cancer cell might occur during the repeated ablation. In addition, except for 3 diaphragm cases guided by CT received complete ablation, 2 cases under diaphragm, two subcapsular tumors, and 1 near the blood were not completely ablated once. One of these cases had a rapid progress and only survived for 6 months. All of the 5 cases were guided by ultrasound. The possible reason might be the incompletely ablation considering the surrounding important structures.

In conclusion, image guided PRFA is a minimally invasive therapy option in the treatment of primary and metastatic hepatic malignancies. CT and US, as the modalities of imaging guidance, have their advantages and disadvantages. Therefore, the decision about a certain modality of image guidance has to consider the individual situation like tumor size and location, as well as possible contraindications for a particular imaging modality.

Conflict of Interest The authors have declared that no competing interests exist.

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