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Original Article

Comparison of ultrasound guided versus CT guided radiofrequency ablation on liver function, serum PIVKA-II, AFP levels and recurrence in patients with primary hepatocellular carcinoma

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Abstract: Objective: This study aimed to compare the effects of ultrasound and CT-guided radiofrequency ablation (RFA) on liver function, serum antagonist-II (PIVKA-II), alpha-fetoprotein (AFP) levels, and disease recurrence in patients with primary hepatocellular carcinoma (PHC). Methods: Ninety-eight patients with PHC were enrolled and treated with RFA. They were grouped as the ultrasound-guided group (n=51) and the CT-guided group (n=47) according to the specific guidance methods. The clinical efficacy, recurrence and survival after treatment, as well as the changes of liver function, serum PIVKA-II and AFP levels before and after treatment were compared between the two groups. Results: The total effective rate of the CT-guided group (87.23%) was significantly higher than that of the ultrasound-guided group (62.75%) ($P < 0.05$). Total bilirubin (TBIL), direct bilirubin (DBIL), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were reduced in both groups after treatment ($P < 0.05$) and were lower in the CT-guided group than in the ultrasound-guided group ($P < 0.05$). Albumin (ALB) levels were elevated in both groups after treatment ($P < 0.05$) and were higher in the CT-guided group than in the ultrasound-guided group ($P < 0.05$). PIVKA-II and AFP levels decreased in both groups after treatment ($P < 0.05$) and were significantly lower in the CT-guided group than in the ultrasound-guided group ($P < 0.05$). The 2-year and 3-year recurrence rates in the CT-guided group were 4.26% and 8.51%, respectively, significantly lower than 17.65% and 27.45% in the ultrasound-guided group ($P < 0.05$), and the 2-year and 3-year survival rates in the CT-guided group were 89.36% and 72.34%, respectively, significantly higher than 72.55% and 50.98% in the ultrasound-guided group ($P < 0.05$). Conclusion: Compared with ultrasound guidance, CT-guided RFA can more effectively improve liver function, reduce serum IVKA-II and AFP levels, reduce recurrence rate, and improve survival time in the treatment of PHC.

Keywords: Ultrasound-guided, CT-guided, radiofrequency ablation, liver function, PIVKA-II, methemoglobin, recurrence

Introduction

Primary hepatocellular carcinoma (PHC) is caused by the carcinogenesis of stem cells or intrahepatic bile duct cells and has a high morbidity and mortality, with the clinical manifestations of weakness, abdominal distension, ascites, and pain in the liver area. PHC has an insidious process, characterized by high malignancy and rapid progression. Most patients are already at a locally advanced stage when diagnosed, missing the best treatment window. Studies have shown that the occurrence of PHC is related to contaminated drinking water, viral hepatitis, genetics, tobacco, alcohol consumption, *etc*., and the mortality of PHC in China accounts for about 1/2 of the global cases, which seriously threatens the lives of patients [1, 2].

There are different treatment options for different stages of PHC, including surgical resection, radiotherapy, chemotherapy, hepatic artery chemoembolization, and radiofrequency ablation (RFA). Liver metastasis and liver transplantation are the preferred options for the clinical treatment of PHC. However, since the early symptoms of PHC are subtle, early tumors may

show multicentric, disseminated, metastatic characteristics and are accompanied by cirrhosis as well as inadequate liver function, making surgery more difficult. A study has shown that the success rate of radical resection in patients with PHC is only about 30% [3]. In contrast, only 20% to 30% of patients with PHC are suitable for surgery depending on the tumor location, size, and number, while 30% to 70% of patients experience recurrence after surgery [4, 5]. Hepatic artery chemoembolization is commonly used clinically to treat patients with PHC who cannot undergo surgical resection. However, studies have shown that the tumor blood supply arteries in patients with PHC are very complex, and although hepatic artery chemoembolization shows efficacy in the short term, the long-term outcomes and prognosis are poor because hepatic artery chemoembolization cannot completely block the tumor blood supply, and patients with larger tumors are prone to recurrence after treatment [6, 7].

RFA is a thermal coagulation therapy, which kills tumorigenic cells through thermal effects, and it is a minimally invasive technique that is inexpensive, safe and reliable, reproducible, and less invasive, providing radical treatment for PHC patients who are intolerant of surgical treatment [8]. RFA is an important method for the treatment of mid- to advanced-stage PHC, and its effectiveness for early PHC is comparable to that of surgery [9]. RFA can not only kill tumor cells, but also inhibit tumor angiogenesis, so as to improve the anti-tumor immunity of patients, and reduce the damage to the liver, which has become the key option of minimally invasive treatment for PHC [10, 11]. Initially, RFA was mainly guided by ultrasound, and CT guidance was gradually adopted with more and more extensive application of RFA. It has been pointed out that CT guidance can compensate some of the shortcomings of ultrasound guidance and is more advantageous in some aspects [12]. However, it has also been shown that CT guidance cannot adjust the position of puncture needle in real time, and CT-guided RFA procedures have a longer treatment time, which leads to many problems [13]. Serum abnormal prothrombin (PIVKA-II) is synthesized by the liver, and alpha-fetoprotein (AFP) is secreted in large amounts when hepatocytes are not differentiated. Therefore, PIVKA-II and AFP levels will change during the treatment of PHC patients. In this study, the effects of ultrasound guided and CT-guided RFA were compared in PHC. The liver function, serum antagonist-II (PIVKA-II), alpha-fetoprotein (AFP) levels and recurrence of patients were also analyzed, providing an auxiliary reference for the clinical treatment of PHC.

Materials and methods

General data

Ninety-eight patients with PHC admitted to our hospital were included, and they were divided into the ultrasound-guided group (n=51) and the CT-guided group (n=47) according to the specific guidance methods. Inclusion criteria: (1) PHC diagnosed by imaging and pathology; (2) tumor diameter < 6 cm; (3) expected survival time > 6 months. Exclusion criteria: (1) those with cancerous thrombosis of the inferior vena cava, hepatic vein or portal vein; (2) those with abnormalities of the hematological system and immune system; (3) those with cancerous lesions caused by drugs, alcohol, autoimmune issues, *etc*.; (4) those with contraindications to radiofrequency ablation; (5) those with coagulation dysfunction; (6) those with distant lymph node metastases and extrahepatic metastases; and (7) those who withdrew from the study midway. This study was approved by the Ethics Committee of The First People's Hospital of Fuyang Hangzhou. The research subjects and their families were informed and signed a fully-informed consent form.

Methods

All patients underwent preoperative systemic evaluation of liver and kidney function, routine blood work, blood biochemistry, and electrocardiogram, and hepatic magnetic resonance imaging (MRI) or contrast-enhanced CT scan using a GY-8100 radiofrequency ablation therapy instrument (Shanghai Hanfei Medical Equipment Co., Ltd.). (1) The CT-guided group received CT-guided RFA. The size, location, and number of tumors were determined by CT scan. Based on the surface markers, the location of the puncture point and the path of the needle into the tumor were planned. The guide needle was first used for rough positioning, followed by performing puncture. CT scans were repeated to adjust the angle and depth of the needle, so that the needle could accurately advance into

the tumor. The power was adjusted 60-200 W, and the ablation time was 6-12 min/time. After the tumor was completely ablated, the puncture needle was withdrawn and the path is closed. (2) In the ultrasound-guided group, ultrasound was used to determine the size, location, and number of the tumors, and the RF needle was inserted into the tumor under the guidance of ultrasound with a power adjustment range of 60-200 W. The ablation time was 6-12 min/time, and after the tumor was completely ablated, the puncture needle was withdrawn and the needle path was closed. The effect of ablation was reviewed using enhanced MRI or CT after one month.

Outcome measurements

(1) Clinical efficacy was assessed according to the World Health Organization criteria related to solid tumors. Patients whose tumors completely disappeared for 1 month were considered to have complete remission (CR); patients whose tumors shrank by more than 50% but still had tumors were considered to have partial remission (PR); patients whose tumors shrank by less than 50% or increased by less than 25% were stable disease (SD); Patients with tumor enlargement of 25% and above were classified as progressive disease (PD). (2) Five mL of fasting venous blood was drawn from patients in the early morning before and 1 month after treatment, centrifuged at 3000 rpm for 10 min using a centrifuge. The supernatant was taken for measurement. An AU5800 automatic biochemical analyzer (Beckman Coulter, USA) was used to detect liver function indicators, including total bilirubin (TBIL), direct bilirubin (DBIL), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and albumin (ALB) levels. ELISA kit (Shanghai Enzyme-Linked Biotechnology Co., Ltd) was used to detect PIVKA-II levels; UniCel DxI800 electrochemiluminescence immunoassay Analyzer (Beckman Coulter, USA) was used to detect AFP level. (3) Patients were followed up for 3 years and recurrence as well as survival was recorded.

Statistical methods

All data were processed by SPSS 22.0. Count data were expressed as [n (%)] and examined by χ^2 test. Measurement data were expressed as ($\overline{x}$ ± s) analyzed with independent samples t-test for comparison between groups and paired t-test for comparison within the same group. Survival curves were analyzed using Kaplan-Meier analysis. Figure illustrations were created by GraphPad Prism 8. Statistically significant differences were indicated with $P < 0.05$.

Results

Baseline data

The ultrasound-guided group had 41 males and 10 females, aged 34 to 72 years, with a mean age of (51.69±7.26) years. The CT-guided group had 34 males and 13 females, aged 35 to 69 years, with a mean age (50.96±7.45) years. The baseline data showed no significant difference between the two groups ($P > 0.05$) (**Table 1**).

Clinical efficacy

After treatment, the CT-guided group had 29 cases (61.70%) of CR, 12 cases (25.53%) of PR, 5 cases (10.64%) of SD, and 1 case (2.13%) of PD, with a total effective rate of 87.23%; while the ultrasound-guided group had 18 cases (35.29%) of CR, 14 cases (27.45%) of PR, 13 cases (25.49%) of SD, and 6 cases (11.76%) of PD, with a total effective rate of 62.75%. After treatment, the clinical efficacy in the CT-guided group was better than that in the ultrasound-guided group (Z=3.306, $P < 0.05$), and the total effective rate of treatment in the CT-guided group was significantly higher than that in the ultrasound-guided group ($P < 0.05$) (**Table 2**).

Liver function indicators

There was no significant difference in TBIL, DBIL, AST, ALT, ALB levels between the two groups before treatment ($P > 0.05$). After treatment, TBIL, DBIL, AST and ALT levels were decreased in both groups ($P < 0.05$) and were significantly lower in the CT-guided group [(30.24±5.38) μmol/L, (11.24±3.57) μmol/L, (31.67±9.67) U/L, (26.46±6.64) U/L] than in the ultrasound-guided group [(37.27±5.75) μmol/L, (18.96±5.26) μmol/L, (42.58±10.24) U/L, (36.92±7.96) U/L] ($P < 0.05$), while ALB levels were increased in both groups ($P < 0.05$) and were significantly higher in the CT-guided group [(40.48±4.71) g/L] than in the ultrasound-guided group [(35.58±4.94) g/L] ($P < 0.05$) (**Table 3**).

Table 1. Comparison of baseline data for both groups [n (%)]

Group	Number of cases	Age	Gender		Tumor Diameter	Number of tumors		Liver Function Child-Pugh Classification		
			Male	Female		Single	Multiple	Grade A	Grade B	Grade C
CT-guided group	47	50.96±7.45	34 (72.34)	13 (27.66)	4.12±0.67	32 (68.09)	15 (31.91)	28 (59.57)	16 (34.04)	3 (6.38)
Ultrasound-guided group	51	51.69±7.26	41 (80.39)	10 (19.61)	4.11±0.71	33 (64.71)	18 (35.29)	32 (62.75)	15 (29.41)	4 (7.84)
t		0.385	0.883		0.072	0.125		0.068		
P		0.701	0.347		0.943	0.724		0.794		

Table 2. Comparison of clinical outcomes after treatment between the two groups [n (%)]

Group	Number of cases	CR	PR	SD	PD	Total effective
CT-guided group	47	29 (61.7)	12 (25.53)	5 (10.64)	1 (2.13)	41 (87.23)
Ultrasound-guided group	51	18 (35.29)	14 (27.45)	13 (25.49)	6 (11.76)	32 (62.75)
Z/χ^2		3.036				7.719
P		0.002				0.005

Table 3. Comparison of liver function indices before and after treatment ($\bar{x} \pm s$)

Group	Time point	TBIL (μmol/L)	DBIL (μmol/L)	AST (U/L)	ALT (U/L)	ALB (g/L)
CT-guided group (n=47)	Before treatment	45.29±8.24	35.24±6.19	74.07±15.84	65.27±13.66	30.64±6.62
	After treatment	30.24±5.38	11.24±3.57	31.67±9.67	26.46±6.64	40.48±4.71
t_a		10.485	23.026	15.663	17.518	8.303
P_a		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Ultrasound-guided group (n=51)	Before treatment	44.68±8.57	35.72±6.45	76.06±15.64	64.94±13.81	30.68±6.16
	After treatment	37.27±5.75	18.96±5.26	42.58±10.24	36.92±7.96	35.58±4.94
t_a		5.128	14.381	12.79	12.554	4.432
P_a		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
T_b		0.359	0.375	0.625	0.119	0.031
P_b		0.721	0.708	0.533	0.906	0.975
t_c		6.235	8.429	5.411	7.031	5.016
P_c		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Note: t_a, P_a indicate within-group comparisons, t_b, P_b indicate pre-treatment comparisons, and t_c, P_c indicate post-treatment comparisons.

Serum PIVKA-II, AFP levels

The pre-treatment PIVKA-II and AFP levels in the CT-guided group were (1562.49±129.19) mAU/mL and (132.56±17.29) ng/mL, respectively, which were not significantly different from (1535.72±126.37) mAU/mL and (136.05±15.65) ng/mL in the ultrasound-guided group ($P > 0.05$). After treatment, both groups exhibited decreased PIVKA-II and AFP levels ($P < 0.05$). PIVKA-II and AFP levels were (567.33±59.89) mAU/mL and (86.88±10.31) ng/mL in the CT-guided group, respectively, significantly lower than (788.95±85.23) mAU/mL and (102.56±11.23) ng/mL in the ultrasound-guided group ($P < 0.05$) (**Table 4**; **Figure 1**).

Comparison of recurrence rate

The 1-year recurrence and survival rates in the CT-guided group were 4.26% and 93.62%, respectively, which had no significant difference from 5.88% and 90.20% in the ultrasound-guided group ($P > 0.05$). The 2-year and 3-year recurrence rates were 4.26% and 8.51%, respectively, in the CT-guided group, significantly lower than 17.65% and 27.45% in the ultrasound-guided group ($P < 0.05$). The 2- and 3-year survival rates were 89.36% and 72.34%, respectively, in the CT-guided group, significantly higher than 72.55% and 50.98% in the ultrasound-guided group ($P < 0.05$) (**Table 5**; **Figure 2**).

Table 4. Comparison of PIVKA-II, AFP levels before and after treatment ($\bar{x} \pm s$)

Group	Number of cases	PIVKA-II (mAU/mL)		*t*	*P*	AFP (ng/mL)		*t*	*P*
		Before treatment	After treatment			Before treatment	After treatment		
CT-guided group	47	1562.49±129.19	567.33±59.89	47.912	< 0.001	132.56±17.29	86.88±10.31	15.557	< 0.001
Ultrasound-guided group	51	1535.72±126.37	788.95±85.23	34.988	< 0.001	136.05±15.65	102.56±11.23	12.416	< 0.001
t		1.037	14.776			1.049	7.181		
P		0.303	< 0.001			0.297	< 0.001		

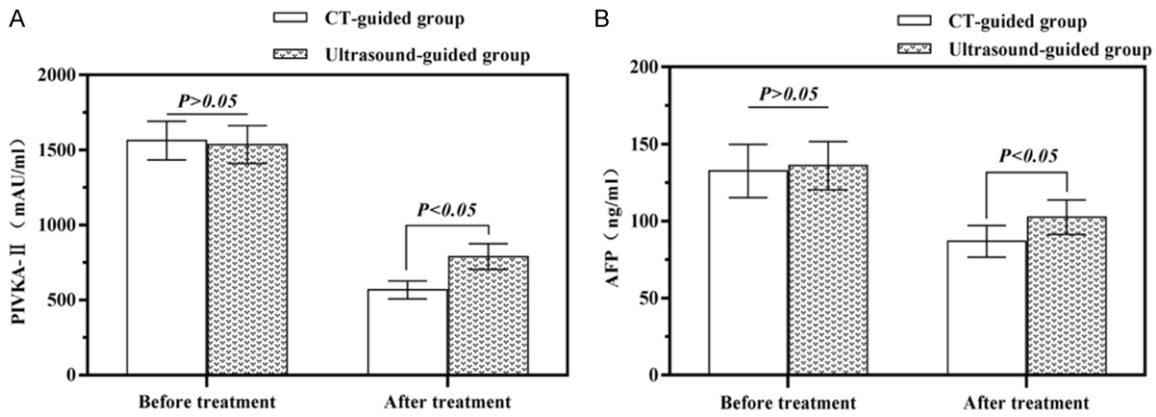

Figure 1. Comparison of PIVKA-II and AFP levels before and after treatment between the two groups. There was no significant difference in PIVKA-II and AFP levels between the two groups before treatment ($P > 0.05$). After treatment, PIVKA-II and AFP levels were reduced in both groups, and the levels in the CT-guided group were lower than those in the ultrasound-guided group ($P < 0.05$).

Table 5. Comparison of recurrence rates as well as survival rates [*n* (%)]

Group	Number of cases	Recurrence rate			Survival rate		
		1 year	2 years	3 years	1 years	2 years	3 years
CT-guided group	47	2 (4.26)	2 (4.26)	4 (8.51)	44 (93.62)	42 (89.36)	34 (72.34)
Ultrasound-guided group	51	3 (5.88)	9 (17.65)	14 (27.45)	46 (90.20)	37 (72.55)	26 (50.98)
χ^2		0.134	4.402	5.852	0.382	4.424	4.701
P		0.715	0.036	0.016	0.537	0.035	0.030

Discussion

CT guidance and ultrasound guidance are the most common guidance methods for RFA in clinical practice. Ultrasound guidance is flexible and relatively easy to operate, and can determine the puncture route by real-time multidimensional scans. Therefore, the puncture needle technique can advance into the tumor avoiding ligamentous structures, bile ducts, and large vessels with high safety [14, 15]. CT-guided images are clearer and can ensure the best optimal position of the puncture needle into the lesion with more accurate localization [16]. Meanwhile, CT guidance can combine with liver-enhanced MRI at special sites, such as lesions at the paramedian duct, the top of the diaphragm, and even lesions that cannot be clearly shown under ultrasound guidance; thus showing the location of the tumor more precisely, and the echogenic changes during RFA treatment do not affect the judgment resulting from CT guidance [17]. In RFA, the results regarding the effects of ultrasound guidance and CT guidance are different. This study compared the effects of the two guidance methods.

Evidence has shown that the occurrence and the development of PHC are related to the dysregulation of immune function [18]. Patients with PHC have impaired immune function and

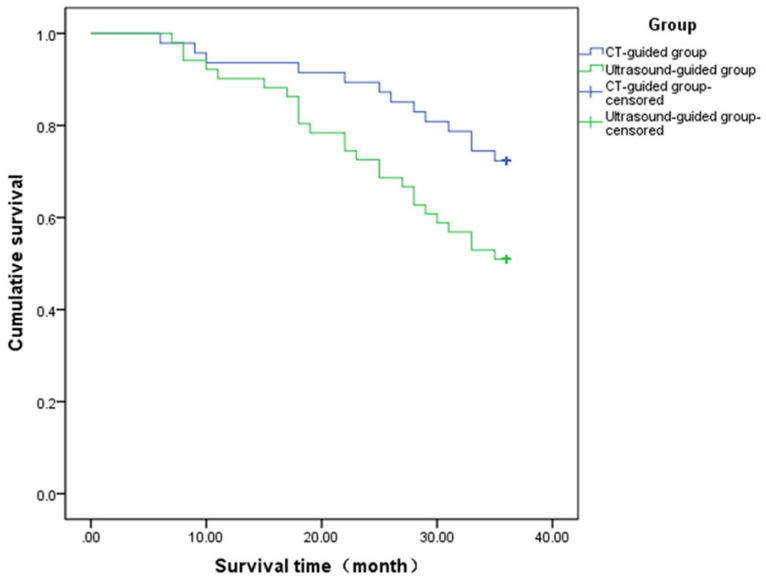

Figure 2. Comparison of 3-year survival curves between the two groups during the follow-up. The survival of the CT-guided group was superior to that of the ultrasound-guided group ($P < 0.05$).

thus relatively low immune function, and liver function indicators can reflect the degree of liver function injury in PHC patients [19]. Bilirubin includes TBIL and DBIL, whose levels are increased when hepatocytes are damaged [20, 21]. ALT is involved in the metabolism of proteins, and its levels will rise in the blood during liver inflammation [22]. AST is abundant in the heart muscle, followed by the liver, and serum AST concentrations increase in the presence of hepatocyte necrosis [23]. As the source of nutrition, ALB is a protein maintaining osmotic pressure of the body, which is mainly synthesized by the liver, and the decrease of its level can reflect the impairment of liver function [24]. TBIL, DBIL, AST, and ALT levels were decreased in both groups after treatment, and they were lower in the CT-guided group than in the ultrasound-guided group. ALB levels were increased in both groups and were higher in the CT-guided group than in the ultrasound-guided group. The results of the study showed that both modalities could improve liver function injury, but CT-guided RFA was more effective.

PIVKA-II is synthesized by the liver, and acts as an autologous growth factor during the growth of liver tumors. Serum PIVKA-II is highly expressed in PHC patients, and PIVKA-II can better reflect early liver tumors and hepatocellular carcinoma nodules [25]. AFP is a tumor marker and is sourced from embryonic hepatocytes, and fetuses secrete large amounts of AFP because their hepatocytes are not fully differentiated. Hepatocytes of PHC patients are undifferentiated and therefore their AFP levels are also highly expressed [26]. In this study, PIVKA-II and AFP levels were decreased in both groups after treatment, and were lower in the CT-guided group than in the ultrasound-guided group. The results of the study showed CT-guided RFA was more effective in improving serum PIVKA-II, AFP levels.

This study also showed that the overall treatment efficiency in the CT-guided group (87.23% vs. 62.75%) was significantly higher than that in the ultrasound-guided group. The 2-year recurrence rate (4.26% vs. 17.65%) and 3-year recurrence rate (8.51% vs. 27.45%) in the CT-guided group were significantly lower than those in the ultrasound-guided group; and the 2-year survival rate (89.36% vs. 72.55%) and 3-year survival rate (72.34% vs. 50.98%) in the CT-guided group were significantly higher than those in the ultrasound-guided group. The results of the study showed that CT-guided RFA was more effective in reducing recurrence rates and improving survival time for the treatment of PHC. The underlying reasons may be that the resolution of ultrasound is poorer compared to CT, and during RFA, the vaporization effect of ultrasound guidance will interfere with visualization, which makes it more difficult for the operator to judge the ablation effect and perform multiple ablations. If the two tumors are located close to each other, the vaporization effect produced by the first ablation will obstruct the field of view of the later ablation, so the treatment effect and survival time under ultrasound guidance are worse and the recurrence rate is higher compared to CT guidance [27, 28].

In conclusion, patients with PHC have liver function damage and high expression of serum IVKA-II and AFP levels. RFA can effectively

improve the liver function damage and reduce serum IVKA-II and AFP levels of patients. Compared with ultrasound guidance, CT-guided RFA was more effectively in treating PHC. However, this study is a retrospective analysis, and the guidance mode of RFA treatment is chosen by the operator, which may cause bias in the selection. Both CT guidance and ultrasound guidance were operated by surgeons. They are not as professional as sonographers in terms of operation, which may have a certain impact on the curative effect, and the study sample is relatively small, and further larger sample size studies are needed.

Disclosure of conflict of interest

None.

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