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Original Article

Comparison of ultrasound-guided laser ablation and radiofrequency ablation in the treatment of small hepatocellular carcinoma

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Abstract: Objective: To investigate the clinical effects of ultrasound-guided laser ablation and radiofrequency ablation in the treatment of small hepatocellular carcinoma. Methods: From October 2013 to March 2016, 74 patients with small hepatocellular carcinoma were treated by ablation and divided into laser ablation group (group LA, 35 cases) and radiofrequency ablation group (group RFA, 39 cases). After three-month ablation, the levels of alphafetoprotein (AFP) and carcinoembryonic antigen (CEA) were compared. Postoperative adverse reactions and postoperative satisfaction of two groups were recorded. Results: There were no statistically significant differences between AFP (P=0.658) and CEA (P=0.323) in the ablation effects (P=0.583), and neither were adverse reactions (P=0.583): fever (P=0.855), nausea (P=0.990), vomiting (P=0.836), diarrhea (P=0.522), abdominal pain (P=0.994), skin rash (P=0.687); however, because of the simple operation and less trauma, patients' postoperative satisfaction of LA was higher (P=0.022). Conclusion: LA and RFA guided by ultrasound are effective methods in the treatment of small hepatocellular carcinoma; while compared with RFA, simple operation, stronger repeatability, and high patient satisfaction of LA make it more advantageous in the treatment of small hepatocellular carcinoma.

Keywords: Ultrasound-guided, laser ablation, radiofrequency ablation, small hepatocellular carcinoma

Introduction

Small hepatocellular carcinoma refers to diameter of single liver cancer nodule or the sum of diameters of two adjacent liver cancer nodules is less than 3 cm. Its early diagnosis and treatment are the key to improving patient's quality of life and reduce mortality rate [1]. With the advance of diagnosis and therapy technology, early diagnosis rate of small hepatocellular carcinoma becomes higher. In situ ablation of liver cancer has been the first choice to treat small hepatocellular carcinoma gradually [2, 3]. In situ ablation of liver cancer consists mainly of thermal ablation and chemical ablation. The former mainly includes laser ablation (LA), radiofrequency ablation (RFA), microwave ablation, cryoablation, etc. By comparison, LA and RFA in the treatment of small hepatocellular carcinoma are efficacious, safe and reliable, which can protect normal liver parenchyma and shorten hospital stays to the maximum extent.

RFA is a common method in the treatment of local ablation. Clinical studies have demonstrated that the treatment of RFA is superior to intratumoral microwave coagulation and ethanol injection in the required treatment times and complete ablation rate [4]. RFA can control the whole ablation treatment process by impedance regulation and temperature monitoring to ensure safety and effectiveness [5]. While LA can use heat energy transformed by light energy to damage tissues. When biological tissues radiated by laser, LA can not only heat the tissues and generate heat loss, but also make the tissues gasify, melt, inject and pyroly, and then solidify or cut the target tissues [6]. Also there are many clinical studies have investigated its advantages in the treatment of small hepatocellular carcinoma [7-9]. However, the comparisons of therapeutic effects, safety and recovery quality between RFA and LA are still rare.

This study intends to compare the effects of ultrasound-guided laser ablation and radiofrequency ablation in the treatment of small hepatocellular carcinoma, the differences of postoperative complications and patients' satisfaction and then to provide reference for the clinical treatment of small hepatocellular carcinoma.

Materials and methods

Selection of clinical data

This study was approved by Medical Ethics Committee of Jiangyin Hospital Affiliated to Southeast University and patients and their families have signed informed consent for treatment. From October 2013 to March 2016, 74 patients with small hepatocellular carcinoma came from Jiangyin People's Hospital were engaged in the study. Inclusion criteria: 1. Hepatocellular carcinoma patients with increased AFP were confirmed by punch biopsy or imaging examination (CT and/or MRI). 2. Diameter of single tumor foci, or the sum of diameters of two adjacent tumor foci was less than 3 cm, without infiltration of blood vessels and bile ducts, abdominal lymph nodes, distant transfer, etc. 3. Patients chose LA or RFA as the first treatment and had no previous treatment history. 4. Child-Pugh of liver function was A and B level.

Exclusion criteria: 1. Diameter of single tumor foci or the sum of diameters of two adjacent tumor foci was more than 3 cm. 2. There was infiltration of blood vessels and bile ducts, abdominal lymph nodes, distant transfer, etc. 3. Child-Pugh of liver function was C level. 4. Severe organ failure in heart, lung, kidney, and liver. 5. Active gastrointestinal bleeding, intractable abdominal ascites, severe bleeding and coagulation disorders, active infection, etc. 6. Patients dropped out of the treatment or were loss to follow-up.

Randomized grouping: patients were randomly divided into group LA (35 cases) and group RFA (39 cases) by Random allocation table.

Main instructions and equipment

Instructions and equipment for LA: EchoLaser X4 laser ablation system (ESAOTE S.P.A, Italy). MyLab Twice ultrasonic instrument, with CA541 and LA522E (two probes) (ESAOTE S.P.A, Italy).

Instructions and equipment for RFA: Radiofrequency therapeutic apparatus, and Ultrasonic instrument Siemens s2000 (Ultrasonic instrument Siemens) which had SIEMENS 4v1 probe and puncture frame were applied.

Methods

Before and after undergoing LA or RFA through ultrasound-guided percutaneous puncture, all patients were examined by contrast-enhanced ultrasound (CEUS). The way of ablation therapy was chosen according to the results of CEUS.

Group LA: The results of CEUS were used to confirm the location of cancer, insertion region, direction and placement of needles, and choose a proper position for adequate operative field exposure. Diameter of cancer lesions ≤2 cm required one optical fiber, 2 cm < diameter of cancer lesions <3 cm required 2-3 optical fibers with 1.0 cm of spacing. Under the guidance of color ultrasound, 21 G puncture needle was inserted at intercostal space or under the diaphragm. Then needle core was removed, laser fiber inserted. Parameters of LA: 5 W of output power of each fiber, 1800 J of output energy, time of one ablation (seconds) = output energy/output power. After starting the laser control panel, laser ablation was performed under the constant monitoring of color ultrasound, and the ablation area was 5 mm larger than foci nodules.

Group RFA: Patients were chosen and remarked the puncture point in their proper positions. The electrode needle was inserted to the bottom of the cancer for single point ablation through the best needle path under the guidance of color ultrasound. The puncture procedure should avoid the bile vessels and the great vessels of liver. When it came to important organs, artificial pleural effusion was used to assist RFA. As for the comparatively large tumor, 2 celon cold circulation double electrodes were inserted in accordance with tumor morphology. If maximum diameter of the punctured tumor was 30 mm, T40 celon cold circulation double electrodes was used to make the distance between two electrode needles less than 2.5 cm. If the shape of tumor was irregular, three T40 celon electrode needles were placed in the reg-

Table 1. Comparison of clinical data between group LA and group RFA

	Age (years)	Gender		The location of liver cancer		The amount of tumor foci		The diameter of tumor foci (cm)	Liver function (Child-Pugh classification)	
		Male	Female	Left lobe	Right lobe	Single lesion	Double lesion		A level	B level
Group LA (n=35)	55.6±10.8	28	7	12	23	33	2	2.0±0.3	30	5
Group RFA (n=39)	56.8±9.6	30	9	13	26	36	3	1.9±0.5	33	6
t/χ^2	-0.506	0.103		0.007		0.115		1.028	0.018	
P value	0.614	0.748		0.931		0.735		0.307	0.894	

Table 2. Comparison of therapeutic effects in group LA and group RFA adopting different ways of ablation

Group	CR (case)	PR (case)	NOR (case)	PRO (case)
Group LA (n=35)	31 (88.6%)	4 (11.4%)	0	0
Group RFA (n=39)	36 (92.3%)	3 (7.7%)	0	0
χ^2 value		0.301		
P value		0.583		

ular triangle in parallel to make the distance between each needle less than 2.5 cm. After the completion of needle arrangement, RFA was carried out.

Outcome measure

The ablation effects and AFP and CEA levels of plasma were compared between the two groups after three months. Ablation effects referred to mRECIST standard: complete remission (CR): no enhancement in angiography; partial remission (PR): the area of no enhancement in angiography >70%; no remission (NOR): the area of no enhancement in angiography <10%; progression remission (PRO): the enhancement area > the area before the treatment. Postoperative adverse reactions were recorded such as fever (axillary temperature >37°C), nausea (upper abdominal discomfort and the urge to vomit), vomiting (forcible ejection of the stomach contents from the mouth), diarrhea (daily stool >3 times), abdominal pain (the feeling of abdominal pain subjectively), skin rash (visible skin damaged). After 3 days' surgery, patients' degree of satisfaction was investigated by using self-made satisfaction questionnaire containing intraoperative discomfort, postoperative therapy effects, adverse reactions, physical recovery, etc. Maximum score of 100 for the questionnaire, 81-100 represented that patients were with great satisfaction about this ablation, 61-80 with general satisfaction, less than 60 with dissatisfaction. Patients' degree of satisfaction = (cases of great satisfaction + cases of general satisfaction)/total cases *100%.

Statistical analysis

SPSS19.0 was adopted to process and analyze related data. Count and ranked data were expressed in rate (%). Measurement data was analyzed by $\overline{X}\pm S$. Comparison of age and diameter of cancer was conducted by using independent samples T-test. χ^2 test was used to compare the differences of other count and grade data between the two groups, such as gender, the distribution of liver cancer, the amount of tumor foci, liver functionclassification, adverse reactions after treatment, therapeutic effects, satisfaction of patients, etc. Repeated measures analysis of variance was applied to compare the changes of postoperative AFP and CEA concentration between the two groups. After that, Bonferroni was used to test the concentration differences at different time in the same group and the same time points in different groups. And statistical difference was defined as P<0.05 (two-sided test).

Results

Basic situation

There were 58 males and 16 females in 74 patients; aged 37 to 76 years old; the location of liver cancer: 49 cases of right lobe liver cancer, 25 cases of left lobe liver cancer; the amount of tumor foci: 69 cases of single lesion, 5 cases of double lesions;the diameter of the tumor was 1.3~2.9 cm; liver function (Child-Pugh): 63 cases of A and 11 cases of B.

Table 3. Comparison of AFP and CEA levels in group LA and group RFA before the treatment and after 3 months' treatment ($\bar{x}\pm S$)

	AFP (μg/L)		CEA (U/L)	
	Group LA	Group RFA	Group LA	Group RFA
Before the treatment	973.67±117.96	983.78±107.11	289.81±16.49	282.10±17.23
After 3 months' treatment	770.36±160.69**	781.52±131.87**	182.68±12.83**	180.65±10.30**

Note: Compared with before the treatment, **P<0.001.

Table 4. Comparison of adverse reactions between group LA and group RFA (case)

Group	Fever	Nausea	Vomiting	Diarrhea	Abdominal pain	Skin rash
Group LA (n=35)	4 (11.4%)	17 (48.6%)	10 (28.6%)	1 (2.9%)	26 (74.3%)	1 (2.9%)
Group RFA (n=39)	5 (12.8%)	19 (48.7%)	12 (30.8%)	1 (2.6%)	29 (74.4%)	3 (7.7%)
χ^2 value	0.033	0.0002	0.043	0.41	0.0001	0.163
P value	0.855	0.990	0.836	0.522	0.994	0.687

Table 5. Comparison of postoperative satisfaction of two groups

Groups	Great satisfaction	General satisfaction	Dissatisfaction	Satisfaction degree
Group LA (n=35)	30	3	2	94.3%
Group RFA (n=39)	25	2	12	69.2%
χ^2 value				7.603
P value				0.022

There was no significant difference between the two groups in the basic data, see **Table 1**.

Comparison of ablation effects between group LA and group RFA

After 3 months' treatment, the patients in group LA (31 cases of CR, 4 cases of PR) and group RFA (36 cases of CR, 3 cases of PR) were all relieved after ablation, and the differences of treatment effects were not statistically significant (P=0.583, **Table 2**).

Comparison of plasma AFP and CEA levels between group LA and group RFA

Repeated measures analysis of variance showed that there was no significant difference between the two groups in the treatment of plasma AFP (F=0.230, P=0.633); there were some differences in the changes of plasma CEA, but no statistical significance (F=3.831, P=0.054). After 3 months' treatment, AFP, CEA levels of two groups were lower than those of before the treatment (for all comparisons, P<0.001), but there was no significant difference between the AFP and CEA concentration of two groups at each time point (**Table 3**).

Comparison of adverse reactions between group LA and group RFA

LA group and RFA group both had adverse reactions, such as fever, nausea, vomiting, diarrhea, abdominal pain and skin rash, but there was no significant difference in the cases of adverse reactions between the two groups (P>0.05). See **Table 4**.

Comparison of postoperative satisfaction between group LA and group RFA

The satisfaction of the patients was investigated and analyzed. In the group LA, there were 30 cases of great satisfaction, 3 of general satisfaction and 2 of dissatisfaction. The satisfaction rate of the patients was 94.3%. Compared with the group REA (69.2%), the difference was statistically significant (P=0.022). See **Table 5**.

Discussion

In recent years, minimally invasive medicine has developed rapidly, which has an obvious clinical advantage in the application of hepatobiliary surgery, and local ablation technology is an important part of minimally invasive medicine. RFA and LA are the commonly used ablation technology in the treatment of small hepatocellular carcinoma. Studies have shown that in the treatment of small hepatocellular carcinoma, the therapeutic effects are not much difference between intervention means assisted with RFA and surgical resection [10, 11]. As a minimally invasive thermotherapy, LA can lead to the death of cancer cells through the thermal effects of the lesion tissues; besides, it has stable ablation range, small tissue damage and reliable curative effects [12, 13].

RFA is to put the electrode into the tumor foci, through increasing the temperature of the cancer tissue by electromagnetic wave motion, to kill cancer cells; the blood supply to cancer cells can be cut off after the coagulation of foci around the tissues and blood vessels, so as to prevent intrahepatic transfer [14]; RFA establishes thermal effects on closed loop that directly causes the apoptosis of cancer cells. A large number of studies have shown that there was no significant difference from RFA treatment and surgical treatment as for treating small hepatocellular carcinoma. Besides, RFA has advantages of short operation time, mild trauma, quick rehabilitation and so on [15-17]. Despite these, RFA still has some limitations. About 10% to 25% of high-risk areas of liver cancer patients cannot be treated with RFA. If they were forced to undergo the RFA operation, it was easy to cause serious complications or poor ablation. LA is a kind of local thermal ablation therapy, which can lead to the increase of tissue temperature, evaporation of water and coagulation necrosis by the thermal effects of monochromatic light. It has been used in the treatment of small hepatocellular carcinoma, and achieves satisfactory results [18]. The effects of LA are good, whose mechanisms are: (1) hyperthermia directly kills cancer cells [19]; (2) hyperthermia indirectly kills cancer cells [20]; (3) according to the location and size of the foci, the power and time of LA can be changed, so that the necrotic area is relatively stable and can cover the entire foci, to completely remove the lesion, minimize the damage of normal liver tissue, and reduce postoperative complications.

This study showed that after 3 months' ablation, there was no statistically significant difference in ablation effects, AFP and CEA levels of LA, RFA, which proved that both LA and RFA had good clinical and curative effects for small hepatocellular carcinoma. Jiao LR et al. found that the specificity, sensitivity and accuracy of small hepatocellular carcinoma detected by AFP combined with CEA were high, which was a sensitive indicator to reflect liver minimally invasive surgery; however, the levels of AFP and CEA in the group LA and group RFA were significantly lower than those before the treatment, which indicated that LA and RFA had effects on small hepatocellular carcinoma [21]. At the same time, Caspani B et al. believed that ultrasound-guided LA treatment of high-risk areas of small hepatocellular carcinoma had the same ablation effects with other non-high-risk areas and less complications [22]. The main reason was that LA was not affected by tissue impedance like RFA. The range of LA was stable, generally caused no damage to important organs. As for postoperative adverse reactions, although studies showed that LA reduced situ ablation significantly, such as abdominal pain, bradycardia, fervescence, subcapsular hematoma, mild liver injury, pleural effusion and other complications, 4 cases of fever, 17 cases of nausea, 10 cases of vomiting, 1 case of diarrhea, 26 cases of abdominal pain, 1 case of rash were found in this study; it may be caused by the operation methods and the use of contrast media in CEUS [23]. There was no statistically significant difference between the adverse reactions of the LA group and the RFA group, which was different from the literature mentioned above, and the reason might be related to the small sample size of this study, or the different personal habits of operators. Although there was no significant difference in the number of complications, the satisfaction rate of patients in LA group was significantly higher than that in the RFA group. The thinner puncture needle, more stable ablation range, no damage to vital organs, and less potential complications of LA (complications not included in the study area) were the possible explanations.

In summary, LA and RFA both are the effective ways of minimally invasive treatment of small hepatocellular carcinoma, while with simpler and more convenient operation, thinner puncture needle, as well as higher satisfaction of postoperative patients, ultrasound-guided LA has advantages to become a reliable method for clinical treatment of small hepatocellular carcinoma. However, future studies are needed badly to perfect the research, because the sample size of this article is small, the follow-up time is short, and the long-term quality of life and survival rate of the patients are not observed.

Disclosure of conflict of interest

None.

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