Oncology and Translational Medicine
DOI 10.1007/s10330-021-0477-7

August 2021, Vol. 7, No. 4, P172–P176

ORIGINAL ARTICLE

The clinical efficacy of percutaneous ethanol-lipiodol injection (PEI) combined with high-intensity focused ultrasound (HIFU) for small hepatocellularcarcinoma in special or high-risk locations*

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Abstract

Objective The objective of this study was to explore the short-term effects and postoperative complications of ultrasound-guided percutaneous ethanol-lipiodol injection (PEI) combined with high-intensity focused ultrasound (HIFU) for the treatment of small hepatocellular carcinoma in a special or high-risk location.
Methods Forty patients with small liver cancer in a special or high-risk location were randomly divided into two groups: 20 patients were treated with PEI combined with HIFU (P + H group), and 20 patients were treated with HIFU alone (H group). There were no significant differences in average age, liver function, tumor location, tumor number, or tumor size between the two groups ($P > 0.05$).
Results Significant differences were observed in ablation parameters between the two groups ($P < 0.05$). Under the same power, ablation rates of the P + H group were significantly higher than those in the H group, and postoperative complications in the P + H group were significantly lower than those in the H group ($P < 0.05$).
Conclusion The combination of PEI and HIFU has better clinical value than HIFU alone for small-cell liver cancer in special or high-risk locations.
Key words: hepatocellular carcinoma; special location; high-intensity focused ultrasound (HIFU); percutaneous ethanol-lipiodol injection (PEI); ethanol; lipiodol

Received: 8 January 2021
Revised: 21 February 2021
Accepted: 21 May 2021

Cancer can occur in any part of the liver, and 23.4%–34.7% of hepatocellular carcinoma is located in a special or high-risk location (caudate lobe, adjacent to the top of the diaphragm, gallbladder fossa, hepatic portal, main blood vessels, heart, gastrointestinal organs, etc.) [1–2]. Due to the specificity of its location, it is difficult to operate on small liver cancer in high-risk locations, and radiofrequency and microwave ablation in clinical practice have serious postoperative complications that are regarded as refractory disease or taboo by many scholars [3]. In recent years, with the rapid development of ultrasound therapy, high-intensity focused ultrasound (HIFU) has played an important role in the treatment of *in situ* ablation of hepatocellular carcinoma, especially for small liver cancer in special or high-risk areas. However, due to the influence of tumor structure, location, and "thermal toxicity", the effect of HIFU on tumors with rich blood supplies or in special areas is not ideal. To improve the effects of HIFU, we used an ethanol-lipiodol injection combined with HIFU in the treatment of small liver cancer in special or high-risk areas, and compared the results to using to HIFU alone. We observed the short-term efficacy and evaluated the safety of this method.

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* Supported by the research grant from Dalian Health and Family Planning Commission of China (No. 1611020).

Clinical records and methods

General data

This was a prospective study carried out in a single tertiary referral center. Ethical approval was obtained from the local ethics committee. Forty patients who presented with pathologically and clinically confirmed small liver cancer in special or high-risk areas (the maximum diameter of a single lesion or the sum of the diameters of multiple lesions ≤ 5.0 cm [4]) were randomly selected (50 lesions included) and divided into two groups: the HIFU group (H group) and the percutaneous ethanol-lipiodol injection (PEI) combined with HIFU group (P + H group). Each group consisted of 20 patients of various ages and sexes. Twenty-one cases were not treated with other methods [Transcatheter arterial chemoembolization (TACE) was not effective and the operation was refused], eight cases recurred, and eleven cases metastasized. According to the Child-Pugh classification, the numerical scores of all the cases were Child-B or Child-A, without contraindications.

The main reagents used were anhydrous alcohol injection (Tianjin Kemiou Chemical Reagent Co., China), ethanol content ≥ 99.7%, and iodinated oil injection.

Instruments and equipment

Instruments and equipment used included: (1) PEIT needles with three holes, diameter of 21G and length of 200 mm, and 1 cm calibrations (HAKKO Medical, Japan); (2) Acuson S2000 Diagnostic Ultrasound Systemprobe with a frequency of 3.5 MHz anda guide frame (Siemens Medical Solutions, USA); (3) Model JC focused ultrasound tumor therapeutic system (Chongqing HIFU Medical Technology Co., Ltd, China), which was mainly composed of a treatment table (high-frequency generator, integrated transducer and six-dimension motion devices), therapeutic control part, ultrasound monitoring device, water handling system, and a safety protecting device. The therapeutic transducer had a diameter of 200 mm, a therapeutic frequency of 0.8 MHz, and a focal length of 170 mm.

Methods

Preoperative preparation

Routine blood, urine, stool, liver and renal function, electrolyte, blood glucose, blood group, and alpha fetoprotein tests, as well as coagulogram, electrocardiogram, echocardiography, upper abdominal ultrasound, chest CT, plain scan, and contrast-enhanced MRI of the upper abdomen were performed for all patients to ensure the location, size, shape, blood supply, and adjacent organs of the tumors, and the bowel and skin were prepared. No history of alcohol allergy or negative iodine test results were shown for the patients in the P + H group. Informed consent was obtained from all patients before the operations.

Percutaneous ethanol-lipiodol injection

Via local anesthesia with 2% lidocaine, the patients in the P + H group were placed in the treatment position, disinfected, and paved with a sterile sheet 30 min before HIFU. In order to avoid major blood vessels and bile ducts under ultrasound guidance, 21G PEIT needles were inserted into the lesions, and the margins between treated and untreated tissue could be as narrow was 0.5–1.0 cm. An injection of 1.5 mL of amixture of anhydrous alcohol and iodinated oil (proportion of 8:1) was administered slowly due to the size of the tumor, and the needle body was rotated to disperse it evenly. The needle was quickly removed after the operation.

High-intensity focused ultrasound

Surgeries on both the H and P+H groups were performed under general anesthesia. The gastric tube was placed prior to the operation (although no gastric tube was placed when the tumor was far from the gastrointestinal site). When the lesion was on the top of the diaphragm, "artificial pleural effusion" was required prior to the operation [5]. Combined with preoperative MRI and intraoperative ultrasound localization, the injection trace in the target area of the patients in the P + H group could be clearly displayed (hyperechoic reflection); accordingly, the therapeutic effect of HIFU was evaluated based on the gray scale of the target tissue during the treatment. When hyperechoic changes in the target area or overall gray scale increased, the treatment was considered to be effective [6].

Observed contents

(1) Efficacy index: Contrast-enhanced MRI was performed one month after the HIFU operation to evaluate ablation volume and rate of the tumors. Ablation volume (cm^3) = $4/3\pi \times R1 (cm) \times R2 (cm) \times R3 (cm)$ (R1 = longest diameter/2; R2 = shortest diameter/2; R3 = height/2); ablation rate = ablation volume/target volume × 100%. (2) Safety index: Complications were statistically analyzed according to the classification developed by the Society of Interventional Radiology [7].

Statistical analysis

All data were expressed as $\bar{\chi} \pm s$ and compared with a t-test or chi-square test using the SPSS 20.0 software package (SPSS Inc., New York, USA). Statistical significance was defined as a two-tailed P-value < 0.05.

Results

Comparison of general condition

No significant difference was observed in average age, liver function, tumor size, tumor number, or tumor location between the H and P + H groups ($P > 0.05$), which showed that the treatment conditions between

Table 1 The comparison of general condition between H and P + H groups ($\overline{\chi} \pm s$)

Groups	Cases	Sex		Average age (years)	Child-Pugh grades			Average volume of tumor (cm³)
		Male	Female		Grade A	Grade B	Grade C	
H group	20	16	4	63.50 ± 8.96	15	5	0	28.90 ± 19.31
P + H group	20	17	3	62.85 ± 9.89	17	3	0	26.73 ± 16.23

Table 2 The comparison of the location of the lesions between H and P + H groups (*n*)

Groups	Lesion numbers	Location						
		Diaphragm top	Main blood vessels	Gallbladder fossa	Hepatic portal organs	Heart	Gastrointestinal	Caudate lobe
H group	23	3	8	3	3	2	3	1
P + H group	27	4	7	4	4	2	4	2

Table 4 The comparison of the complications between H and P + H groups [*n* (%)]

Groups	Fever (°C)		Liver function	Skin injury			Postoperative local pain			
	≥ 38	< 38	ALT/AST slight increase	I°	II°	III°	Grade 0	Grade I	Grade II	Grade III
H group	1 (5)	2 (10)	6 (30)	14 (70)	2 (10)	2 (10)	0	2 (10)	14 (70)	4 (20)
P + H group	2 (10)*	3 (15)*	8 (40)*	13 (65)	0*	0*	3 (15)*	5 (25)*	11 (55)*	1 (5)*

Note: Postoperative pain was classified by verbal rating scale (VRS) of World Health Organization (WHO): Grade 0 (no pain), Grade I (mild pain), Grade II (moderate pain), Grade III (severe pain). *, Comparison between H and P + H groups, $P < 0.05$. ALT/AST: Alanine aminotransferase/Aspartate aminotransferase

the two groups were consistent and could be compared (Tables 1 and 2).

Comparison of ablation parameters in HIFU

Significant differences in ablation parameters between the H and P + H groups ($P < 0.05$) were observed, which showed that under the same power, ablation rates of the P + H group were significantly greater than those in the H group (Table 3).

Table 3 The comparison of ablation parameters between H and P + H groups ($\overline{\chi} \pm s$)

Groups	Ablation volume (cm³)	Ablation rate (%)
H group	11.66 ± 7.26	40.35
P + H group	18.46 ± 13.12	69.01*

Note: *, Comparison between H and P + H groups, $P < 0.05$

Comparison of postoperative complications

No treatment-related deaths, intestinal perforation, bile leakage, liver failure, tumor implantation, ormetastasis were observed in either group. Slight differences existed in fever and liver function damage when the condition returned to normal within one week ($P < 0.05$). No significant difference was observed in skin injury I° (local swelling and erythema) between the two groups ($P > 0.05$). However, in the H group, two patients had blisters and two had skin necrosis. Postoperative local pain in the H group was more severe than that in the P + H group ($P < 0.05$; Table 4).

Discussion

HIFU is a non-invasive local therapy technique that has been widely used in the treatment of solid tumors, such as those in liver and pancreatic cancers. Compared with traditional techniques, such as surgery, radiofrequency therapy, microwave therapy, and intervention therapy, HIFU has more advantages, such as a more accurate curative effect, less trauma and pain, faster recovery, and repeatability of treatment [8]. HIFU is also a safer and more effective non-invasivetreatment for small liver cancer in special or high-risk areas. However, due to the differences in tumor shape, location, and "thermal toxicity", in our study, the energy subsidence of HIFU in the focal region was reduced, and the risk of comlications increased. At the cost of reducing acoustic power and prolonging treatment time, the ablation rate was reduced, and the chances of tumor residual and recurrence and complications increased.

The safe and effective improvement of the energy deposition and therapeutic effect of HIFU for liver cancer in special or high-risk regions is an important topic worldwide. Both physical and chemical methods can be used to change the acoustic properties and environment of target tissues (AET) [9], such as intratumoral injection of anhydrous alcohol or TACE, before HIFU. This method affects the mechanism that controls the coagulation and denaturation of tissue protein and vascular embolism, and can improve thermal toxicity and accelerate irreversible coagulative necrosis. Since anhydrous alcohol disperses poorly and has a limited solidification range, iodinated oil is used because of its high acoustic impedance, which can easily stimulate an increase in temperature [10], as well as act as an anti-proliferative cytotoxin. Intratumoral injection [11–12] of iodinated oil can block material exchange between tumor cells and tissue fluid, especially the acquisition of oxygen, which directly leads to the necrosis of tumor cells. The higher the percentage of iodinated oil deposition, the higher the necrosis rate of the tumor and the better the therapeutic effect. One study reported [13] that when anhydrous alcohol and iodinated oil are mixed, they can strengthen each other and reduce the threshold power of the cavitation effect. In other words, the cavitation effect can occur easily under low acoustic power with ethanol-lipiodol injection during HIFU, which causes the temperature at the focal regionto rise, and also increases the volume of coagulative necrosis covering the entire tumor; thus, the chance of tumor recurrence is reduced. This may be an important rationale for the use of PEI prior to HIFU in the treatment of liver cancer. In addition, iodinated oil also has "tracing" characteristics which make it easier to determine the treatment region and evaluate the postoperative effect of HIFU.

Our study showed that, under the same acoustic power, the ablation rates in the P + H group were significantly higher than those in the H group, which indicated that the intratumoral ethanol-lipiodol injection had significantly changed the AET, which improved the therapeutic effect of HIFU.

Due to the even dispersion of anhydrous alcohol and iodinated oil, which form a "sound beam barrier" that increases the acoustic impedance and local heat deposition, it becomes easier and faster to form a conglomerate gray scale change. When sound waves are reflected into the necrotic zone to reduce the energy deposition in the ectopic area, they effectively protect the normal tissue around the tumor, thus reducing the complications of HIFU for small liver cancer in high-risk or special regions. This was consistent with the results in the P + H group in this study. No serious complications, such as gastrointestinal perforation orbile leakage, were observed in this study, although minor ones, such as transient fever and liver function damage, were slightly more severe in the P + H group. However, these were considered to be reversible and related to the toxic absorption effect of anhydrous alcohol and iodinated oil. The skin damage in the P + H group was mostly seen as local mild swelling, while in the H group some individual patients had blisters, and two patients had skin injuries classified as III°. The classified scores of postoperative pain in P + H group were significantly lower compared to the H group.

Because of the abundant blood supply of hepatocellular carcinoma, the injection speed should be slow in order to prevent the drugs from becoming diluted, entering the blood vessels orbiliary tract, or returning to the abdominal cavity. For lesions in special or high-risk locations, it is extremely challenging for ultrasound-guided puncture to ensure one-time success when the patients are holding their breath. Core needle puncture, while tracking the tip of the needle, is recommended to ensure that the tip can reach the deep part of the tumor and that the drug evenly diffuses. Therefore, it is necessary to push and rotate the needle body during the injection process. At the same time, early injection prior to HIFU reduces the coagulation range for tumor tissues, thus reducing the synergistic effect of the drug during HIFU. Therefore, ethanol-lipiodol injection 1 h before HIFU plays a synergistic role and is beneficial for intraoperative localization.

The ethanol-lipiodol injection has both a direct chemical effect on the tumor and a synergistic effect on HIFU in the treatment of hepatocellular carcinoma, which can improve the efficacy of HIFU in clinical therapy.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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DOI 10.1007/s10330-021-0477-7
Cite this article as: Zou XL, Zhao CZ, Wang T, *et al*. The clinical efficacy of percutaneous ethanol-lipiodol injection (PEI) combined with high-intensity focused ultrasound (HIFU) for small hepatocellularcarcinoma in special or high-risk locations. Oncol Transl Med, 2021, 7: 172–176.