

The value of 64-slice spiral CT perfusion imaging in the treatment of liver cancer with argon-helium cryoablation

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Abstract. We analyzed the effectiveness of using 64-slice spiral computed tomography (CT) and perfusion imaging to guide argon-helium cryoablation treatment of liver cancer. In total, 60 cases of advanced hepatocellular carcinoma before surgery treated with argon-helium cryoablation were included in the present study. Retrospective summary of the 60 cases of metaphase and advanced liver cancer were used as the control group. The control group were treated using cryoablation with argon-helium knife. We used enhanced scanning with 64-slice spiral CT to define the extent of their lesions and prepared a plan of percutaneous cryoablation for the treatment. Intraoperatively, we used the dynamics of CT perfusion imaging to observe the frozen ablation range and decreased the rate of complications. After surgery, the patients were followed-up regularly by 64-slice CT. We used conventional X-ray, CT and magnetic resonance imaging (MRI) for pre-operative lateralization. Intraoperative X-ray or ultrasound guidance and follow-up with CT or MTI were added to determine the clinical effectiveness and prognosis. The results showed that the total effective rate was improved significantly and incidence rate of overall complications decreased markedly in the observation group. Following treatment, AFP decreased significantly while the total freezing area and time were reduced significantly. The median survival time was increased significantly in the observation group. The numeric values of hepatic arterial perfusion, portal vein perfusion and **hepatic arterial perfusion index were all markedly** lowered after treatment. Differences were statistically

significant ($P < 0.05$). In conclusion, the use of 64-slice spiral CT perfusion imaging may considerably improve the effects of liver cancer treatment using the argon-helium cryoablation. It extended the survival time and reduced complications.

Introduction

There are two types of minimally invasive treatment for liver cancer: i) Vascular treatment such as hepatic arterial infusion chemotherapy, hepatic artery embolism and transcatheter hepatic arterial chemoembolization; and ii) non-vascular treatment such as percutaneous chemical ablation and percutaneous physical ablation. Percutaneous physical ablation includes cryotherapy using argon-helium superconductive operation system, radiofrequency ablation, microwave coagulation, laser-induced interstitial thermotherapy and high intensive focused ultrasound (1,2).

Argon-helium cryoablation is an extremely important minimally invasive freezing technique that combines two technologies: the ultralow temperature-programmed and temperature-programmed methods. The method has produced better effects compared to freeze and heat treatment alone (3); however, it is affected by many factors such as the classification of liver function in patients, superconducting knife diameter, tumor location, length of the elimination times and the extent (4). To decrease spontaneous rupture and hemorrhage, in the puncture approach, the use of necessary needle hemostasis technique and the decrease of the extent of freeze-thaw area should be considered (5,6).

In the present study, we analyzed the effectiveness of using 64-slice spiral computed tomography (CT) and perfusion imaging to guide argon-helium cryoablation treatment of liver cancer in 120 subjects.

Materials and methods

Data. From June 2014 to June 2015, we enrolled 60 patients with advanced hepatocellular carcinoma before surgery. They were placed in the observation group and were treated with argon-helium cryoablation. In the observation group, there were 42 males and 18 females aged, 52-76 years (average, 65.6 ± 14.2 years). According to the Barcelona BCLC staging (7), there were 45 cases of metaphase liver cancer and

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15 cases of advanced liver cancer. The maximum diameter of the tumor ranged from 2.5 to 4.6 cm (average, 3.4 ± 1.1 cm) and the number of tumors ranged from 1 to 4 (average, 2.2 ± 0.8). There were 52 cases of positive HBsAg, and AFP ranged from 56 to 732 ng/ml (average, 348.3 ± 72.6 ng/ml). A retrospective summary of the 60 cases of metaphase and advanced liver cancer were used as the control group. They had matching gender, age, tumor characteristics, and HBsAg-positive rates with AFP levels at 1:1.

Inclusion criteria for the study were: i) No liver surgery, no radiotherapy and chemotherapy, no trauma, no particle implantation; ii) tumor diameter was <5 cm, the number of lesion ≤ 3 and, the number of primary liver cancer was ≤ 5 ; iii) no severe liver and renal insufficiency and stable vital signs; iv) liver function Child-Pugh grade A or grade B; and v) no arteriovenous fistula formation and no contrast agent allergy history with security needle path. Exclusion criterias: i) Low quality computed tomography (CT) image; ii) the convergence part of liver cancer near the intrahepatic bile duct and other parts leading to ablation difficulties; iii) incomplete or lost follow-up records; and iv) patients who died during the follow-up period for any reason other than liver cancer. This study obtained the informed consents and approval from the Ethics Committee of the Affiliated Hospital of Hebei University of Engineering (Hebei, China).

Study method. We used GE 64-slice spiral CT to enhance three phases scanning preoperatively and determined the extent of lesions and the blood supply situation to optimize the formulation of the argon-helium knife treatment. We observed and controlled the freezing-melting range by dynamic CT perfusion imaging to minimize the complications. Postoperative curative effects and prognosis was evaluated using 64-slice CT during the follow-up examinations. In the control group we verified the clinical effects as well as prognosis for routine X-ray, CT, magnetic resonance imaging (MRI) or ultrasound.

Patients in the observation group were prepared in routine time for plain scan and enhanced upper abdominal. We used Stellant dual tube high pressure syringe in Medrad (Medrad, Pittsburgh, PA, USA), and non-ionic contrast agent (350 mg I/ml). Scanning parameters were as follows: Tube voltage was 80 kV, tube current was 80 mAs, detector was set at 16 cm, layer thickness was 0.5 mm, layer spacing was 0.5 mm, matrix was 512×512 and scanning speed was 0.5 sec/cycle. Perfusion scan process began scanning after 8 sec when contrast agent was injected and scanned once from 8 to 28 sec every 2 and 3 sec from 34 to 52 sec, and every 5 sec from 59 to 69 sec. This created a total of 21 dynamic volume data and each volume data contained 320 images, thus 6,720 images were obtained in total. The original images were handled in the workstation after transmitted to Aquilion ONE and processed through slope method. The correction of the respiratory motion position was carried out under the body correction software in the body perfusion software. Consequently the corrected data package was introduced into the body perfusion software and the double input mode was selected to carry out the analysis. The abdominal aorta and the portal vein were selected as feeding artery and draining vein. The region of interest was respectively arranged corresponding to aorta abdominalis, portal vein, liver and spleen to

generate the TDC curve. The perfusion parameters of pseudo color pictures (red for high perfusion, blue low perfusion and the remaining colors between them) of TDC hepatic arterial perfusion (HAP), portal vein perfusion (PVP) volume and hepatic arterial perfusion index (HAPI) could be obtained in the lines of TDC curve. Three axial, coronal and sagittal ROI perfusion parameters were obtained randomly. Preoperative and postoperative ROI selection was kept as consistent as possible. ROI selection was done by two radiologists at deputy director level and each value was repeatedly measured every 4 weeks and the average values were calculated. Four to six weeks after operation, patients were examined using the same method for post-processing imaging and analyses. After the first examination, they were re-examined once every 3 months.

For preoperative CT imaging, we chose the correct position, supine, prone position or lateral position. We then determined the surface puncture, puncture path, measuring needle's angle and depth and the required number of cryotherapy probes to develop the correct arrangement and sequences. Using CT images, argon-helium superconductive operation system (Endocare, Irvine, CA, USA) entered the tumor target with argon-helium knife special puncture needle (the probe in 2 or 3 mm and the tip in 1.5 mm) along the proposed puncture points. Subsequently, we went back from the needle core and the expansion tube, leaving in the catheter sheath, and accurately embedded argon-helium knife in the sheath (sheath was withdrawn 3-5 cm). The ultra-low temperature operation system initiated after CT imaging confirmed the correct position of the argon-helium knife. The treatment mode was as follows: The argon was frozen for 10-15 min then helium rewarmed for 3 min (this was considered a cycle). Probe could be affected by the local anatomical structure, in the cases of larger tumors, tumors that are very close to adjacent tissue structure and tumors already invading other tissues. During a single cycle we melted up to 70-90% of the tumor, however, it was difficult to melt the entire tumor in one attempt. Residual tumor was treated during the second cycle. During the cryoablation process, patients were monitored closely and were asked to advise the investigators should there be any discomfort during the process. CT scanning of the ablation zone was performed periodically to better monitor the ice ball formation and to avoid freezing injuries to adjacent vital structures. After the operation, the patients were monitored closely to verify whether there were any adverse reactions, such as fever and pain in order to treat them properly.

Observation index. Differences in tumor treatment effects, AFP changes, total frozen area, freezing time, complication, median survival time and perfusion parameters were compared. The effects of tumor treatment was in accordance with RECIST standards, which was divided into complete remission (CR), partial remission (PR), stable disease (SD) and disease progression (PD). The total efficiency was calculated as: $CR+PR+SD/\text{total number of the cases} \times 100\%$.

Statistical analysis. SPSS 19.0 statistical software (Chicago, IL, USA) was used for data analysis. Quantitative data were expressed as mean + standard deviation and qualitative data were expressed as the number of cases or percentage (%). Comparison

Table I. Comparison of the effects of tumor therapy and the occurrence of complications.

Group types	Case	CR	PR	SD	PD	Total effective rate	Fever	Pain	Skin frostbite	Nausea and vomiting	Abdominal bleeding	Bile duct fistula and hepatic abscess	Others	Total incidence rate
Observation	60	12	16	20	12	48 (80.0)	4	3	1	3	2	3	2	18 (30.0)
Control	60	8	14	15	23	37 (61.7)	5	4	2	4	5	6	3	29 (48.3)
χ^2						4.881								4.232
P-value						0.027								0.040

CR, complete remission; PR, partial remission; SD, stable disease; PD, disease progression.

Table II. Comparison of AFP changes, total freezing area and freezing time.

Groups	AFP (ng/ml)	Total freezing area (cm ²)	Freezing time (min)
Observation	124.5±42.6	7.2±1.5	20.7±4.2
Control	206.3±51.7	9.6±1.7	34.9±4.8
t-test	6.325	10.624	8.452
P-value	<0.001	<0.001	<0.001

Table III. Comparison of perfusion parameters in the observation group before and after treatment.

Item	HAP (ml/min · 100 ml)	PVP (ml/min · 100 ml)	HAPI (%)
Before treatment	124.6±33.2	82.7±24.3	69.4±18.5
After treatment	45.5±10.6	63.2±16.9	30.5±8.2
t-test	15.624	9.328	7.826
P-value	<0.001	<0.001	<0.001

HAP, hepatic arterial perfusion; PVP, portal vein perfusion; HAPI, hepatic arterial perfusion index.

in the two groups was tested using the independent samples t-test. The paired t-test was used for same group comparisons and the comparison of two groups was tested using the χ^2 test. Median survival was analyzed by Kaplan-Meier. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Comparison between the effects of tumor therapy and the occurrence of complications. The total effective rate for the observation group was significantly higher than that in the control group and the total incidence of complications in the observation group was significantly lower than that of the control group. Differences were statistically significant ($P < 0.05$) (Table I).

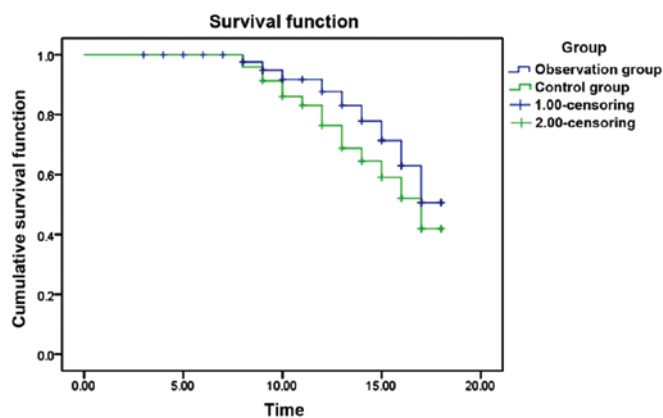


Figure 1. Analysis of Kaplan-Meier in median survival time.

Comparison of AFP changes, total freezing area and freezing time. Following treatment, AFP was significantly lower in the observation group. Total freezing area and freezing time were significantly lower than those in the control group. Differences were statistically significant ($P < 0.05$) (Table II).

Comparison of median survival time. The two groups were followed up for an average of 14 months. In the observation group, 18 cases (30.0%) succumbed while in the control group the number of deaths was 29 (48.3%). The mortality rate in the observation group decreased significantly. Differences were statistically significant ($\chi^2 = 4.232, P = 0.040$). In the observation group, the median survival time was > 17 months and median survival time in the control group was 17 months. Differences were statistically significant (log-rank test $\chi^2 = 10.744, P = 0.001$) (Fig. 1).

Comparison of perfusion parameters in the observation group. Following treatment, HAP, PVP and HAPI levels were significantly lower than those before treatment. Differences were statistically significant ($P < 0.05$) (Table III and Fig. 2).

Discussion

The principle of argon-helium cryoablation is as follows: i) High pressure normal temperature argon gas (cold medium) and high pressure normal temperature helium (heat medium) are introduced sequentially; ii) argon expands rapidly at the point of the knife and the temperature in lesion tissue

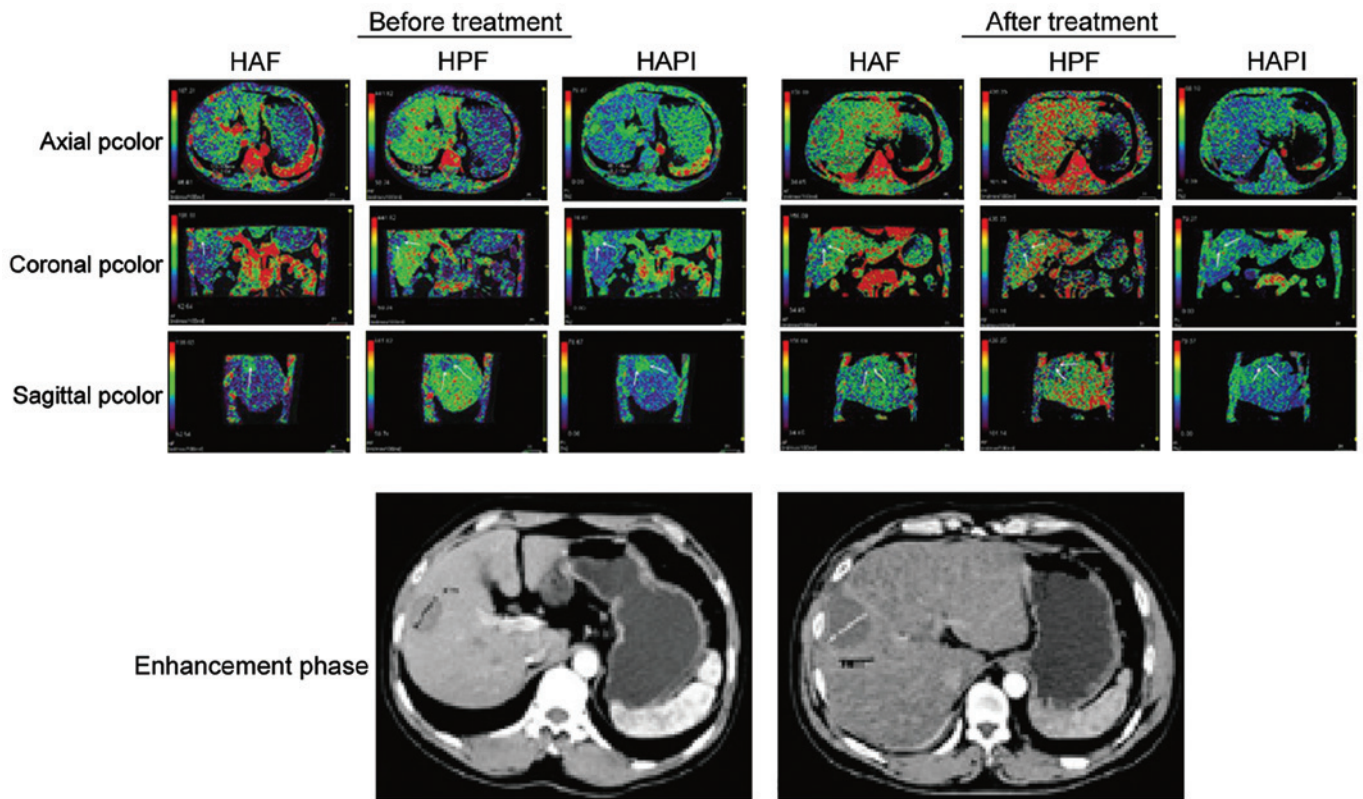


Figure 2. The increase and perfusion of CT (red for high perfusion zone and blue for low perfusion zone). All changes in parameter of axial, coronary and sagittal pseudo color are in agreement. Tumors show high HAF, low HPE and high HAPI. Before treatment and in the increasing stage, there was sufficient blood that rapidly strengthened in the tumor. Ablation range expressed in arterial phase increased markedly after the treatment, tumors were all in low density and there was no consolidation. HAPI, hepatic arterial perfusion index; HAP, hepatic arterial perfusion.

reaches -140°C within 60 sec; and iii) helium expands rapidly at the point of the knife and thaws the ice ball rapidly by elevating the temperature up to $40-45^{\circ}\text{C}$. Thermocouple installed at the point of the knife constantly monitors the temperature. Basic studies on cryoablation revealed that intracellular ice had the tendency to induce cell death (8). The sudden formation of ice crystals in cells rapidly destroys the fluidity and osmotic pressure balance of the cell membrane. By increasing the freezing speed, the number of dead cells were markedly elevated. Owing to the recrystallization of ice crystals, keeping cells frozen for an extended period can further increase cell damage. On termination of the freezing period, the thawing period is initiated. Ice crystals expand when helium rapidly increases the temperature, which induces the explosion of ice balls formed during the freezing period and this explosion destroys the tumor. After the heating period there is another round of freezing to attack any tumor cells that escaped the initial freezing round. After 2 cycles of freezing and thawing, lesion tissues can be destroyed completely (9).

Argon-helium cryoablation treatment can cause hepatic failure, myoglobinuria, cold shock and other complications. The extent of freeze thaw area is an important factor (10) and the total acreage of freeze thaw can be an independent predictor of whether postoperative complications would increase. Results showed that the total treatment efficiency in the observing group significantly increased and the total incidence of complications was significantly reduced. Values of HAP, PVP and HAPI were significantly lower compared with before treatment. We believe that the application of 64-slice

CT helped the planning process of percutaneous cryoablation. Intraoperative argon-helium knife in combination with 64-slice CT to control the freezing and thawing acreage, can expand the scope of the damage, reduce recurrence and reduce complications (11).

In the present study, for the first time we used a 1.64-slice spiral CT to plan treatment using an argon-helium knife. The application of the CT perfusion analysis software package in preoperative blood supply and staging of liver cancer and tumor range evaluation made the argon-helium targeting cryoablation more accurate and reliable (12). The application of 64-slice spiral CT with the z-axis coverage of up to 4 cm, was useful in gaining a more comprehensive analysis of the hemodynamic characteristics of liver cancer and we applied the perfusion pattern to evaluate the flow pattern of the liver cancer (13). In order to guide the surgical approach and expand or reduce the scope of freezing and thawing, the 64-slice CT 3D reconstruction technique was used in this study (14). The study had a few defects: i) Success of the scan was dependent on the patients' respiratory training; ii) time scan range of breath holding scan was different, thus the choice of time period needed to be repeated; iii) there was no uniform standard in result assessment and time of freezing for argon-helium cryoablation.

We concluded that the use of 64-slice spiral CT perfusion imaging in the treatment of liver cancer can significantly improve the treatment efficiency of argon-helium cryoablation. This method can extend the survival time and reduce the complications.

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