JBUON 2019; 24(4): 1414-1419
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Observation of therapeutic effect of ^{125}I seed implantation combined with chemotherapy and antiviral therapy on HBV-related liver cancer

Yunjian Zeng, Yingmin Mao, Zili Shi, Yuqi Zhou, Lingfang Zhang

Department of Interventional Therapy, Tongde Hospital of Zhejiang Province, Hangzhou, China.

Summary

Purpose: *To investigate the therapeutic effect of ^{125}I seed implantation combined with chemotherapy and antiviral therapy on hepatitis B virus (HBV)-related liver cancer.*

Methods: *A total of 126 patients with HBV-related liver cancer were selected and divided into observation group (n=63) and control group (n=63). The patients in the control group were treated with transcatheter arterial chemoembolization (TACE) and antiviral therapy, while those in the observation group were treated with ^{125}I seed implantation combined with TACE and antiviral therapy. The therapeutic effect, liver function, serum HBV DNA and tumor marker levels, and changes in Child-Pugh score and Karnofsky performance status (KPS) score before and after treatment were compared between the two groups.*

Results: *After treatment in the observation group, the serum alanine aminotransferase (ALT), HBV DNA, alpha fetoprotein (AFP) levels and Child-Pugh score were lower than those in the control group, while the KPS score was significantly higher than in the control group ($p<0.05$). There was no statistically significant difference in the control rate of liver cancer after treatment between the two groups ($p>0.05$). The remission rate in the observation group was obviously higher than in the control group ($p<0.05$).*

Conclusion: *^{125}I seed implantation combined with chemotherapy and antiviral therapy can effectively eliminate HBV DNA, improve liver function, increase quality of life and enhance the therapeutic effect in patients with HBV-related liver cancer, so it is worthy of clinical popularization.*

Key words: *^{125}I seed implantation, chemotherapy, antiviral, HBV-related liver cancer*

Introduction

Liver cancer is formed via cancerization of intrahepatic bile duct cells or liver cells, and is one of the most common malignant tumors in the clinic [1]. In recent years, the understanding of liver cancer has been increasingly deepened with the continuous improvement in medical technology, and it is believed that its pathogenesis is closely related to genetic susceptibility, tobacco and alcohol use, contaminated drinking water, aflatoxin and viral hepatitis B and C [2]. According to a survey, liver cancer has become the third major malignant tumor following esophageal cancer and gastric cancer. The morbidity and mortality rates of liver cancer are increasing, and there are about 700,000 new cases every year. The number of deaths of liver cancer in China accounts for more than 50% of the total around the world [3]. Hepatitis B virus (HBV)-related liver cancer accounts almost for 85% of primary liver cancer, and it is mostly diagnosed in advanced stage. As a result, practically operative treatment cannot be performed, and non-operative treatments, such as biological therapy, chemother-

Corresponding author: Yunjian Zeng, BM. Department of Interventional Therapy, Tongde Hospital of Zhejiang Province, 234 Gucui Rd, Xihu District, Hangzhou, Zhejiang 310012, China.
Tel: +86 013867461373, Email: yjzeng@tom.com
Received: 11/12/2018; Accepted: 04/01/2019

apy, radiotherapy and transcatheter arterial chemoembolization (TACE), are often adopted [4]. Clinical treatment needs to be performed for several times, while metastasis and recurrence rates are high, turning the long-term efficacy poor [5]. Therefore, it is of great significance to search therapeutic methods for HBV-related liver cancer. ^{125}I seed implantation is a newly-developed radiotherapy technique for tumors, achieving better results in the treatment of liver cancer [6]. Therefore, the therapeutic effect of ^{125}I seed implantation combined with chemotherapy and antiviral therapy in HBV-related liver cancer patients was explored in this paper, so as to provide references for the clinical treatment of patients with HBV-related liver cancer.

Methods

General data

A total of 126 patients with HBV-related liver cancer treated in our hospital from March 2016 to January 2018 were selected and randomly divided into the observation group (n=63) and the control group (n=63). There were no significant differences in the age, gender, maximum tumor diameter, proportion of solitary tumor and Edmondson pathological grade between the two groups (p>0.05) (Table 1).

Diagnostic criteria for HBV-related liver cancer

The HBV-related liver cancer was diagnosed based on the diagnostic criteria in the *Clinical Diagnosis and Staging Criteria for Primary Liver Cancer* and *Prevention and Control Solution for Toxic Hepatitis* [7].

Staging criteria

The Edmondson pathological grading criteria [8] are adopted as follows: Grade I: The cancer cells are arranged in a thin beam shape, with good differentiation; Grade II: the cancer cells have with abundant eosinophilic cytoplasm dark stained and large nucleus; Grade III: tumor giant cells with darker stained nucleus; Grade IV: the cancer cells have less intercellular junctions and cytoplasm with poor differentiation and obvious dark stained nucleus.

Inclusion and exclusion criteria

Inclusion criteria: 1) patients who met the above diagnostic and staging criteria; 2) those with non-diffuse lesions and no more than 5 lesions; 3) those without undergoing antiviral therapy, chemotherapy and radiotherapy; and 4) patients who agreed and actively cooperated in this study and signed the informed consent. *Exclusion criteria:* 1) patients with a history of severe cardiovascular diseases, or diseases of the brain or kidney; 2) those with severe ascites, complete embolization of main portal vein or severe jaundice; 3) those with a tumor diameter > 1 cm; 4) those complicated with other hepatitis-related virus infection; 5) those with cancer due to alcohol, drug, autoimmune liver diseases or fatty liver; 6) those who did not cooperate well or who had incomplete imaging data due to scanning techniques; and 7) those who had poor compliance or quit halfway.

Control group

Patients in the control group were treated with TACE and antiviral therapy as follows: 1) Antiviral therapy: All patients took orally lamivudine (NMPN H20030581, GSK, Suzhou, China, specification: 100 mg) once a day. The patients whose serum HBV DNA became positive again after being negative were treated combined with entecavir (NMPN H20052237, Bristol-Myers Squibb, Shanghai, China, specification: 50 mg) once a day. 2) TACE: The femoral artery was punctured using the modified Seldinger technique, and a 5F catheter was gradually inserted into proper hepatic artery for selective catheterization. At the same time, the following chemotherapeutic drugs were injected into the blood vessels with abundant blood supply according to the radiography technique: 12 mg mitomycin for injection (NMPN H33020786, Pfizer, Shanghai, China), 20 mg pirarubicin hydrochloride for injection (NMPN H10930105, Shenzhen Wanle Pharmaceutical Co., Ltd., Shenzhen, China), 500 mg 5-fluorouracil injection (NMPN H20051627, Hainan Zhonghualianhe Pharmaceutical Co., Ltd., Haikou. China). The iodized oil was used as the embolization agent.

Observation group

Based on the above treatment, ^{125}I seed implantation was performed as follows: The number of seed needles and the number and activity of seed were determined using the seed implantation system. The seed radioac-

Table 1. Comparisons of baseline data between the two groups (n=63)

Group	*Age (years)*	*Mean age (years)*	*Male/female (n)*	*Mean maximum diameter of tumor (cm)*	*Proportion of solitary tumor, n (%)*	*Edmondson pathological grade*		
						I n (%)	*II* n (%)	*III* n (%)
Control group	35-74	50.26±6.74	41/22	5.32±1.05	56 (88.89)	18 (28.57)	20 (31.75)	25(39.68)
Observation group	36-75	50.32±6.81	39/24	5.41±1.02	53 (84.13)	16 (25.40)	21 (33.33)	26(41.27)
t/x^2		0.025	0.137	0.488	0.612		0.162	
p		0.490	0.711	0.313	0.434		0.922	

tive source (^{125}I closed type, source activity: 0.5-2.8 millicurie) was manufactured by Seed-Med, Tianjin. Under the guidance of CT, the entry scope and direction were determined to avoid the surrounding great vessels and organs. The seed needle was inserted 0.5 cm away from the deep edge of tumor. Then, the seeds were implanted using the implantation gun at an interval of 1 cm, and the needle was pushed gradually till the anterior edge of tumor. After operation, conventional treatments, such as nutritional support, hemostasis and anti-infection, were performed. After 1 month, the patients were re-examined, and the seeds were supplemented according to the new and residual tumors until there were no new lesions and residual tumors, or patients with poor liver function failed to bear the implantation of extra seeds.

Observation indexes

1) Determination of liver function indexes: 5 mL fasting venous blood was drawn from patients at 8:00 in the morning before treatment and at 1 month, 2 months and 3 months after treatment, and centrifuged at 3000 rpm and 4°C for 10 min (centrifugal radius: 10.5 cm) using the centrifuge [Ortho BioVue, Johnson & Johnson (Shanghai, China) Medical Equipment Co., Ltd.] to separate the plasma and serum. The plasma and serum were stored in a refrigerator at -75°C for later experiments. The level of alanine aminotransferase (ALT) was detected via enzyme-linked immunosorbent assay (ELISA). 2) The serum HBV DNA level [9] was detected via quantitative real-time polymerase chain reaction (qRT-PCR) (LightCycler). 3) Determination of tumor marker levels: The level of alpha fetoprotein (AFP) was detected using the AU5800 full-automatic biochemical analysis system (Beckman Coulter, Miami, FL, USA). 4) Child-Pugh score [10]: It was estimated based on the scoring criteria for liver reserve capacity established by Child-Pugh. 5) KPS score [11]: death (0 point), critical disease and life-threatening risk at any moment (10 points), critical disease and must be hospitalized (20 points), completely bedridden and need to be hospitalized, but no life risk (30 points), nursing and help needed in most of daily activities (40 points), nursing and help often needed (50 points), self-care ability in most of daily activities, and nursing and help occasionally needed (60 points), complete self-care ability in life, but cannot work (70 points), self-care ability with slight difficulty in life (80 points), mild conditions but can move normally (90 points), no any symptoms (100 points). The 10-20 points indicate critical disease, 30-50 points indicate poor recovery, 60-100 points indicate good recovery, and 0 point indicates death.

Evaluation criteria for therapeutic effect [2]

The clinical efficacy in all patients was evaluated 3 months after treatment, as follows: Progressive disease (PD): The tumor necrosis was increased by no less than 25% compared with that before treatment, or there were new lesions. No changes (NC): The tumor necrosis was reduced by no more than 50%, or increased by no less than 20% compared with that before treatment. Partial remission (PR): The tumor necrosis was reduced by no less than 50% compared with that before treatment. Complete remission (CR): The imaging showed that the tumor was affected in a strip shape or disappeared, or there was complete necrosis. Control rate = (NC + PR + CR)/total cases × 100%, remission rate = (PR + CR)/total cases × 100%.

Statistics

SPSS 19.0 software (SPSS Inc., Chicago, IL, USA) was used for data processing. Measurement data were expressed as mean±standard deviation, and t-test was used for quantitative data. Data were expressed as rate, and x^2 test was used for percent data. P<0.05 suggested that the difference was statistically significant.

Results

Comparison of serum ALT level between the two groups

The serum ALT level was significantly lower in the observation group than in the control group at each time point after treatment (p<0.05), and it gradually decreased with time in both groups (Table 2).

Table 2. Comparison of mean serum ALT level between the two groups (units per litre)

	Before treatment	*1 month after treatment*	*2 months after treatment*	*3 months after treatment*
Control group	72.31±24.63	68.25±23.12	65.23±22.52	61.09±20.53
Observation group	71.38±24.71	61.32±21.09	53.62±16.56	48.15±15.38
t	0.212	1.757	2.967	4.004
p	0.416	0.040	0.001	<0.001

Table 3. Comparison of mean serum HBV DNA level between the two groups

	Before treatment	*1 month after treatment*	*2 months after treatment*	*3 months after treatment*
Control group	5.92±1.21	5.43±1.15	5.02±1.02	4.68±0.97
Observation group	5.98±1.22	4.51±0.96	3.68±0.85	3.01±0.56
t	0.277	4.875	8.011	11.835
p	0.391	<0.001	<0.001	<0.001

Comparison of serum HBV DNA level between the two groups

The serum HBV DNA level was significantly lower in the observation group than that in the control group at each time point after treatment (p<0.05), and gradually decreased with time in both groups (Table 3).

Comparison of serum AFP level between the two groups

The serum AFP level was significantly lower in the observation group than in the control group at each time point after treatment (p<0.05), and gradually declined with time in both groups (Table 4).

Comparison of Child-Pugh score between the two groups

The Child-Pugh score was significantly lower in the observation group than in the control group at each time point after treatment (p<0.05), and it increased with time in both groups (Table 5).

Comparison of KPS score between the two groups

The KPS score was significantly higher in the observation group than in the control group at each time point after treatment (p<0.05), and it was gradually increased with time in both groups (Table 6).

Comparison of therapeutic effect between the two groups

The control rate of liver cancer after treatment had no statistically significant difference between the two groups (p>0.05). The remission rate in the observation group (80.95%) was significantly higher than that in control group (58.73%), and the difference was statistically significant (p<0.05) (Table 7).

Discussion

The pathogenic factors of HBV-related liver cancer are mainly virus-based, and there is a certain degree of immunosuppression, so it is hard to

Table 4. Comparison of mean serum AFP level between the two groups (μg/mL)

	Before treatment	*1 month after treatment*	*2 months after treatment*	*3 months after treatment*
Control group	182.35±83.26	170.36±78.51	160.39±67.62	142.39±49.53
Observation group	181.69±83.19	149.16±72.35	132.69±62.51	87.63±41.25
t	0.045	2.11	2.386	6.743
p	0.482	0.016	0.009	<0.001

Table 5. Comparison of mean Child-Pugh score between the two groups

	Before treatment	*1 month after treatment*	*2 months after treatment*	*3 months after treatment*
Control group	7.25±1.23	7.82±1.25	9.83±1.57	10.62±1.63
Observation group	7.21±1.19	7.32±1.02	7.65±1.39	7.98±1.52
t	0.186	2.460	8.252	9.402
p	0.427	0.008	<0.001	<0.001

Table 6. Comparison of mean KPS score between the two groups

	Before treatment	*1 month after treatment*	*2 months after treatment*	*3 months after treatment*
Control group	70.25±3.84	73.54±3.69	76.23±3.98	79.68±4.01
Observation group	69.87±3.74	76.22±3.86	80.32±4.06	86.32±3.85
t	0.563	3.983	5.710	9.466
p	0.287	<0.001	<0.001	<0.001

Table 7. Comparison of mean KPS score between the two groups

	PD	*NC*	*PR*	*CR*	*Control rate*	*Remission rate*
Control group	7 (11.11)	19 (30.16)	15 (23.81)	22 (34.92)	56 (88.89)	37 (58.73)
Observation group	4 (6.35)	8 (12.70)	20 (31.75)	31 (49.21)	59 (93.65)	51 (80.95)
x^2					0.896	7.385
p					0.344	0.007

completely eliminate HBV in the body [12]. However, HBV DNA will continue to replicate in the body, further damaging the liver cells and leading to complications such as upper gastrointestinal hemorrhage and liver failure, ultimately causing death in patients [13]. Lamivudine used in this paper is nucleotide analog, which mainly binds to the HBV DNA polymerase region via replacement, thereby terminating the strand replication process in HBV, reducing the HBV DNA level in the blood and alleviating or delaying the liver dysfunction [14]. In addition, the lipiodol anti-cancer drug vector complex was used in the TACE in the treatment of HBV-related liver cancer in this paper, which could embolize hepatic artery, thereby blocking the tumor blood supply to a certain degree and affecting the growth of tumor cells. Moreover, TACE can also selectively kill tumor cells, thus gradually reducing the size of the liver cancer and affecting less the blood supply of normal liver tissues, so it can obtain a certain effect in the treatment of HBV-related liver cancer [5]. However, in the clinical treatment it was found that the tumor size, tissue type, dual blood supply, parasitic blood supply, variant blood supply, collateral circulation, polygenetic feeding artery in liver cancer, incomplete embolization of hepatic artery and arteriovenous shunt in HBV-related liver cancer will affect the deposition of iodized oil in the tumor, so that there is incomplete necrosis of liver cancer cells, potentially leading to liver cancer relapses easily [16]. The long-term application of the potent antiviral drug entecavir used in this paper will also produce certain drug resistance and lower the therapeutic effect, so the clinical remission rate of patients receiving chemotherapy combined with antiviral therapy is low.

The therapeutic effect of ^{125}I seed implantation in prostate cancer has been confirmed clinically, but there is still a lack of clinical data about its therapeutic effect on HBV-related liver cancer [17]. The tolerance of normal liver tissues to radioactive agents is relatively poor, so their dose is limited, thus leading to poor therapeutic effect. The ^{125}I seed is an energy radionuclide with a diameter of 0.8 mm and a length of 4.5 mm, whose latter half-life and former half-life are 180 days and 59.6 days. Its radiation radius can be up to 17 mm in tissues, and it can emit γ-rays and X-rays, and be used in the brachytherapy of cancer, with characteristics of local conformal radiotherapy, realizing the maximum radioactive radiation at the tumor site. At the same time, the dose in normal tissues affected can decline in a short time, there are few adverse reactions and it is not affected by breathing and body movement during radiation, greatly reducing the probability of tumor volume loss [6]. In this paper, the HBV DNA clearance, liver function, quality of life and therapeutic effect were better in patients treated with ^{125}I seed implantation. The possible reason is that the γ-rays emitted in ^{125}I seed implantation can kill cycle sensitive cells, and the low-dose radiation also has a certain effect on the changes in cycle distribution of tumor cell, arrests the cycle in G2-M phase, increases the sensitivity of liver cancer cells to chemotherapeutic drugs and improves the long-term efficacy. After TACE, the lesions of liver cancer are relatively reduced, and most of them are in a hypoxic state and have a low ability to resist radioactive rays. The radioactive rays emitted by ^{125}I seed can damage the vascular endothelial cells of liver cancer to a certain extent, thereby reducing the expression of vascular endothelial growth factors and the microvascular formation, inhibiting tumor angiogenesis and killing tumor cells [18].

Conclusions

In conclusion, ^{125}I seed implantation combined with chemotherapy and antiviral therapy can effectively eliminate HBV DNA, improve liver function, increase quality of life and enhance the therapeutic effects in patients with HBV-related liver cancer, so this approach is worthy of clinical popularization.

Conflict of interests

The authors declare no conflict of interests.

References

1. Wang M, Wang Y, Feng X et al. Contribution of hepatitis B virus and hepatitis C virus to liver cancer in China north areas: Experience of the Chinese National Cancer Center. Int J Infect Dis 2017;65:15-21.
2. Chen J, Zhang Y, Cai H, Yang Y, Fei DY. Comparison of the effects of postoperative prophylactic transcatheter arterial chemoembolization (TACE) and transhepatic arterial infusion (TAI) after hepatectomy for primary liver cancer. JBUON 2018;23:629-34.
3. Petrick JL, Braunlin M, Laversanne M, Valery PC, Bray

F, McGlynn KA. International trends in liver cancer incidence, overall and by histologic subtype, 1978-2007. Int J Cancer 2016;139:1534-45.

4. Park SH, Lee SM, Kim YJ, Kim S. ChARM: Discovery of combinatorial chromatin modification patterns in hepatitis B virus X-transformed mouse liver cancer using association rule mining. BMC Bioinformatics 2016;17:452.
5. Chen T, Qian G, Fan C et al. Qidong hepatitis B virus infection cohort: a 25-year prospective study in high risk area of primary liver cancer. Hepatoma Res 2018;4 (PMID:29479565).
6. Zhang J, Wu N, Lian Z et al. The Combined Antitumor Effects of (125)I Radioactive Particle Implantation and Cytokine-Induced Killer Cell Therapy on Xenograft Hepatocellular Carcinoma in a Mouse Model. Technol Cancer Res Treat 2017;16:1083-91.
7. Vucenik I, Zhang ZS, Shamsuddin AM. IP6 in treatment of liver cancer. II. Intra-tumoral injection of IP6 regresses pre-existing human liver cancer xenotransplanted in nude mice. Anticancer Res 1998;18:4091-6.
8. Eder-Czembirek C, Erlacher B, Thurnher D, Erovic BM, Selzer E, Formanek M. Comparative Analysis of Clinical and Pathological Lymph Node Staging Data in Head and Neck Squamous Cell Carcinoma Patients Treated at the General Hospital Vienna. Radiol Oncol 2018;52:173-80.
9. Yang N, Feng J, Zhou T et al. Relationship between serum quantitative HBsAg and HBV DNA levels in chronic hepatitis B patients. J Med Virol 2018;90:1240-5.
10. Chan AW, Kumada T, Toyoda H et al. Integration of albumin-bilirubin (ALBI) score into Barcelona Clinic Liver Cancer (BCLC) system for hepatocellular carcinoma. J Gastroenterol Hepatol 2016;31:1300-6.
11. Lu Z, Xiao Z, Liu F et al. Long non-coding RNA HULC promotes tumor angiogenesis in liver cancer by up-regulating sphingosine kinase 1 (SPHK1). Oncotarget 2016;7:241-54.
12. Yamashita T, Nault JC. Stemness of liver cancer: From hepatitis B virus to Wnt activation. J Hepatol 2016;65:873-5.
13. Liu S, Li X, Li H et al. Is the Hong Kong Liver Cancer staging system the best guide for hepatitis B virus-related hepatocellular carcinoma patients with multiple tumors? Oncotarget 2016;7:51598-607.
14. Jiang E, Shangguan AJ, Chen S, Tang L, Zhao S, Yu Z. The progress and prospects of routine prophylactic antiviral treatment in hepatitis B-related hepatocellular carcinoma. Cancer Lett 2016;379:262-7.
15. Su TH, Kao JH. Response to Four-year entecavir therapy reduces hepatocellular carcinoma, cirrhotic events and mortality in chronic hepatitis B patients. Liver Int 2017;37:310-1.
16. Choi J, Han S, Kim N, Lim YS. Increasing burden of liver cancer despite extensive use of antiviral agents in a hepatitis B virus-endemic population. Hepatology 2017;66:1454-63.
17. Cheng J, Ma S, Yang G, Wang L, Hou W. The Mechanism of Computed Tomography-Guided 125I Particle in Treating Lung Cancer. Med Sci Monit 2017;23:292-9.
18. Liu Y, Liu R, Wang P, Li S, Shen H. Percutaneous implantation of (125)iodine seeds for treatment of portal vein tumor thrombosis in hepatocellular carcinoma. Med Oncol 2015;32:214.