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To explore the curative effect of CT-guided Iodine-125 radioactive seed implantation in the treatment of stage ⅠVprimary hepatocellular carcinoma

Fuqiang Zhang [a], Lin Zheng [b,*], Deyu Li [a], Hui Yang [a]

[a] Department of Nuclear Medicine, The Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, 450003, China
[b] Department of Minimally Invasive & Interventional, The Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, 450003, China

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ABSTRACT

Objectives: To explore the clinical efficacy and survival of CT-guided Iodine-125 radioactive seed implantation in the treatment of stage Ⅳ primary hepatocellular carcinoma.

Methods: A retrospective study of 62 patients with primary hepatocellular carcinoma in our hospital from January 2017 to December 2018 [60 males, 2 females, age (52.76 ± 10.82) years old], All patients were implanted with Iodine-125 radioactive seeds under CT guidance, followed up regularly after operation to observe the clinical efficacy, including comparison of changes in cancer size before and after treatment, tumor marker AFP, and improvement in complications such as abdominal pain and ascites. Follow-up 3–36 months to assess patient survival.

Results: Among the 62 patients, 3 months after Iodine-125 radioactive seed implantation, 5 cases (8.1%) had complete remission of cancer, 33 cases (53.2%) had partial remission, 12 cases (19.4%) had stable lesions, and 12 cases (19.4%) had disease progression. The effective rate was 61.3%. The tumor volume (31.44 ± 14.51cm3) was significantly smaller than before (50.96 ± 30.13cm3) ($t = 5.303$, $p < 0.05$). The tumor marker AFP (69.28 ± 50.99) ug/L of 3 months after implantation was significantly lower than that before treatment (90.63 ± 68.58) ug/L ($t = 3.702$, $P < 0.05$). The average survival time of Iodine-125 seed implantation for stageⅣhepatocellular carcinoma is 11.47 ± 0.85 months, and the median survival time is 9 months. The survival time of the group with better pathological differentiation (gradeⅠ+Ⅱ) was significantly better than that of the group with poor differentiation (grade Ⅲ+Ⅳ) ($x2 = 6.869$ $p < 0.05$). Among the 38 patients with different degrees of abdominal pain, 22 patients improved better than before; 15 of 28 patients with different degrees of ascites were better than before. All patients had no serious complications related to treatment.

Conclusions: Iodine-125 radioactive seed implantation therapy can safely and effectively treat hepatocellular carcinoma, and relieve the clinical symptoms of abdominal pain and ascites.

1. Introduction

Hepatocellular carcinoma (HCC) is a highly malignant digestive system tumor, and its morbidity and mortality are at the forefront of malignant tumors and increase each year.[1] HCC is the sixth most common malignancy and the third leading cause of death worldwide.[2] Due to the high degree of malignancy and rapid progression of HCC, the rich blood supply of the liver, and the possibility of distant metastasis, the patient does not develop specific clinical symptoms. Most patients are usually diagnosed at an advanced stage, and they lose the opportunity to undergo surgery. HCC does not respond to chemotherapy; molecularly targeted drugs (such as sorafenib) have been recently used in the treatment of HCC.[3,4] A previous phase III randomized control trial showed that the median OS of HCC increased to 6.5 months.[5] The conventional application of molecularly targeted drugs in China is restricted primarily because many patients cannot afford to buy these medications as the price is too high. In addition, some patients have poor tolerance to sorafenib, they stop taking the drug or reduce the dose, and the treatment effect is not satisfactory. Higher rates of adverse events have been reported with a shutdown rate of 15% to 38%.[5,6]

At present, a few clinical treatments have been used in patients with advanced HCC in the liver. Transarterial chemoembolization (TACE) is the primary method for treating unresectable HCC. However, TACE is often affected by the location of the lesion, blood supply, and other

* Corresponding author.
E-mail address: 86581830@qq.com (L. Zheng).

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factors; hence, its clinical application is limited, and the curative effect is insufficient.[7] In recent years, Iodine-125 radioactive seed implantation has achieved good results in the treatment of solid tumors. It provides continuous brachytherapy, has high local dose rate, and allows rapid peripheral attenuation. It has good local control and few side effects. Its application in the clinical setting has been gradually recognized.[8,9] This retrospective study aimed to analyze the data of 62 patients in our hospital who were undergoing computer tomography (CT)-guided Iodine-125 seed implantation for advanced HCC due to their inability to undergo surgical resection as well as to discuss its efficacy and complication rate.

2. Materials and methods

2.1. Clinical data

The study was approved by the ethics committee of The Affiliated Cancer Hospital of Zhengzhou University. All clinical practices and observations were conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from each patient before the study was conducted. Patients who were admitted in our hospital for Iodine-125 seed implantation from January 2017 to December 2018 were eligible for the study. Patients with clear results on biopsy, with clinical stage IV disease, with advanced liver cancer who underwent radioactive seed implantation as the primary treatment method, who did not receive other antitumor treatments, and with complete follow-up data were included in the study. A total of 62 patients were screened according to the above criteria, including 60 men and 2 women, aged 29–75 years (average: 52.76 ± 10.82 years). HCC was divided into four grades according to the degree of differentiation: 13 patients had grade I, 19 had grade II, 18 had grade III, and 12 had grade IV. Among these patients, 37 had lung metastasis, 21 had bone metastasis, 8 had brain metastasis, 12 had retroperitoneal lymph node metastasis, and 3 had adrenal metastasis. The indications for Iodine-125 seed implantation were as follows: patients who were not suitable for surgery or interventional arterial embolization after undergoing a multidisciplinary consultation in the Department of Oncology and Intervention; ② patients who were poor and cannot tolerate surgery or TACE, or those who were not willing to undergo surgery or TACE; and ③ patients whose preoperative multiple imaging assessments revealed a tumor diameter of $\leq$7 cm, a KPS score of $>$60, and an estimated survival time of $>$3 months. This treatment was not indicated for patients with active bleeding in the tumor area, ② a coagulation disorder, ③ contraindications to anesthesia, and ④ severely low levels of different blood cell types (WBC$<3.0 \times 10^9$/L; PLT$<80 \times 10^9$/L).

2.2. Instruments and equipment

A 64-row CT scanner configured by American GE was used in this study. Iodine-125 seed implantation device: A 15–20 cm × 18 G puncture needle produced by Yaguang Corporation of Japan was utilized. The implant gun and push guide were produced by Zhejiang Xiangshan Jinheng Machinery Manufacturing Co., Ltd. The radioactive seed treatment plan system (TPS) was developed by Beijing Feitian Zhaoye Technology Co., Ltd. The Iodine-125 seed source was produced by Beijing Atomic Science and Technology Co. Ltd. Each Iodine-125 seed has a diameter of 4.5 mm and a length of 0.8 mm, is fully enclosed in a titanium shell, has an activity of 14.8–25.9 MBq, and has a half-life of 59.4 d; a high temperature and high-pressure steam sterilization method is used to sterilize the seeds.

2.3. Preoperative preparation

The CT image is transmitted to the TPS treatment planning system, and the gross tumor volume (GTV) and planning target volume (PTV) are accurately delineated according to the scanned image. The prescribed dose of 100–150 Gy is entered into the aforementioned system. In order to determine the percentage of prescription dose (PD) delivered to 90% of the GTV (D90), the Iodine-125 seed number required for matching peripheral dose, particle spatial distribution, and other parameters are calculated, and the dose-volume histogram (DVH) is drawn. Before the operation, routine blood collection and blood tests are performed to assess the liver function, blood type, coagulation function, presence of any infectious disease, etc.; the patients are also instructed to fast for 4–6 h prior to the operation.

2.4. Iodine-125 seed implantation[10]

The patient is placed in a supine or lateral position, and an extracorporeal positioning grating is placed on the area of the skin that corresponds to that of the lesion. According to the patient's previous image data, an accurate CT scan bed position is selected. According to the preoperative TPS system, the number and position of the implanted Iodine-125 seed at each level and position are determined. The skin needle insertion point and best needle insertion path on the first layer are identified. The marked puncture point and the surrounding area were routinely disinfected, a sterile hole towel was laid, and local infiltration anesthesia (with a mass fraction of 2% lidocaine) was applied to the puncture point area. Multi-point puncture three-dimensional implantation with particle spacing of 0.5–1.0 cm and line spacing of 1.0 cm was performed. If bleeding occurs on the puncture site during the operation, a compressed gelatin sponge strip is inserted through the puncture needle, and the Iodine-125 seed is implanted after hemostasis is achieved. During the operation, vital signs were closely monitored and internal bleeding, subcapsular hematoma, and other complications were closely monitored. After the operation, bandage and local pressure were applied to prevent bleeding at the puncture site. Antibiotics were routinely used for 2–3 days to prevent infection. The patients were observed for 48 h after surgery and were instructed to stay on bed rest and avoid performing strenuous exercise; preventive hemostasis was performed.

2.5. Postoperative verification and efficacy evaluation

The patients were closely monitored for postoperative complications such as bleeding, subhepatic hematoma, pleural reaction, and seeds displacement. When the implantation under CT guidance was completed, the CT image was re-transmitted to the TPS implantation system for postoperative verification. Three months after treatment, CT and MRI were performed to assess the status of the lesions, and venous blood was drawn to screen for liver function and tumor marker AFP biochemical indicators. The patient was followed up once every 3 months within 1 year and every 6 months after 1 year. The efficacy evaluation was performed according to the World Health Organization's criteria for efficacy evaluation: (1) complete remission (CR): all visible lesions disappeared completely, which was maintained at least 4 w or more; (2) partial remission (PR): the sum of the product of the two largest vertical diameters of the tumors was reduced by more than 50%, this reduction was maintained for more than 4 weeks, there was absence of lesion progression, and no new lesions appeared; (3) stabilization of disease (SD): tumor shrinkage or enlargement was less than 25%, no new lesions appeared; and (4) PD: the volume of the lesion was $\geq$25% or new lesions appeared. The efficacy was calculated using the following equation: total effective rate = (CR + PR)/total number of cases × 100%. The patients were observed for presence of and improvement in complications such as abdominal pain and ascites.

2.6. Statistical processing

SPSS 26.0 statistical software was used to analyze various data. The measurement data were subjected to normality analysis and variance homogeneity test, while the measurement data with a normal distribution were expressed as $x \pm s$. Two doctors with a deputy senior position or

higher were selected to measure the size of the cancerous lesions before and after Iodine-125 seed implantation. The paired t-test was performed using a statistical software. Before and after treatment, the AFP value of tumor markers was measured using a paired t-test. The Kaplan-Meier method was used for survival analysis, while the log-rank test was used to compare the differences in survival curves. All statistical methods were significantly different ($P < 0.05$).

3. Results

3.1. Overall situation of Iodine-125 seed implantation

A total of 1446 Iodine-125 seeds were implanted in 62 patients, and 10–50 seeds were implanted in each patient (average: 23.3 ± 10.47). The seeds were evenly distributed in the tumor and implanted 0.5–1.0 cm from the edge of the surrounding large blood vessels, nerves, and mesentery. No seeds were detached from the tumor, and the success rate of permanent seed implantation was 100% (1446/1446). A total of 103 tumor lesions were implanted, including 69 in the right lobe of the liver and 34 in the left lobe of the liver, with an average of 14 (1446/103) implanted seeds per lesion.

3.2. Comparison of the size of HCC lesions before and after treatment

Among the 62 patients, 3 months after Iodine-125 radioactive seed implantation, 5 patients (8.1%) had complete remission (Fig. 1), 33 (53.2%) had partial remission, 12 (19.4%) had stable lesions, and 12 (19.4%) had disease progression. The treatment had an effectivity rate of 61.3%. The tumor volume (31.44 ± 14.51 cm^3) was significantly smaller than that prior to treatment (50.96 ± 30.13 cm^3) ($t = 5.303$, $P < 0.05$). The tumor marker AFP value (69.28 ± 50.99 μg/L) at 3 months after implantation was significantly lower than that before treatment (90.63 ± 68.58 g/L) ($t = 3.702$, $P < 0.05$) (see Table 1).

3.3. Evaluation of survival time of patients who underwent Iodine-125 seed implantation after a follow-up of 3–36 months

The Kaplan-Meier test was used to analyze the survival time, and the survival curve was plotted (Fig. 2). The average survival period of patients after Iodine-125 seed implantation for advanced HCC is 11.47 ± 0.85 months, and the median survival time is 9 months. The well-differentiated group (grade I + II; 32 cases) showed an average survival time of 13.78 ± 1.19 months and a median survival time of 14 months; the poorly differentiated group (grade III + IV; 30 cases) had an average survival time of 8.92 ± 0.98 months and a median survival time of 6 months. The survival time of the well-differentiated group was significantly better than that of the poorly differentiated group ($x^2 = 6.869$ $P = 0.009$).

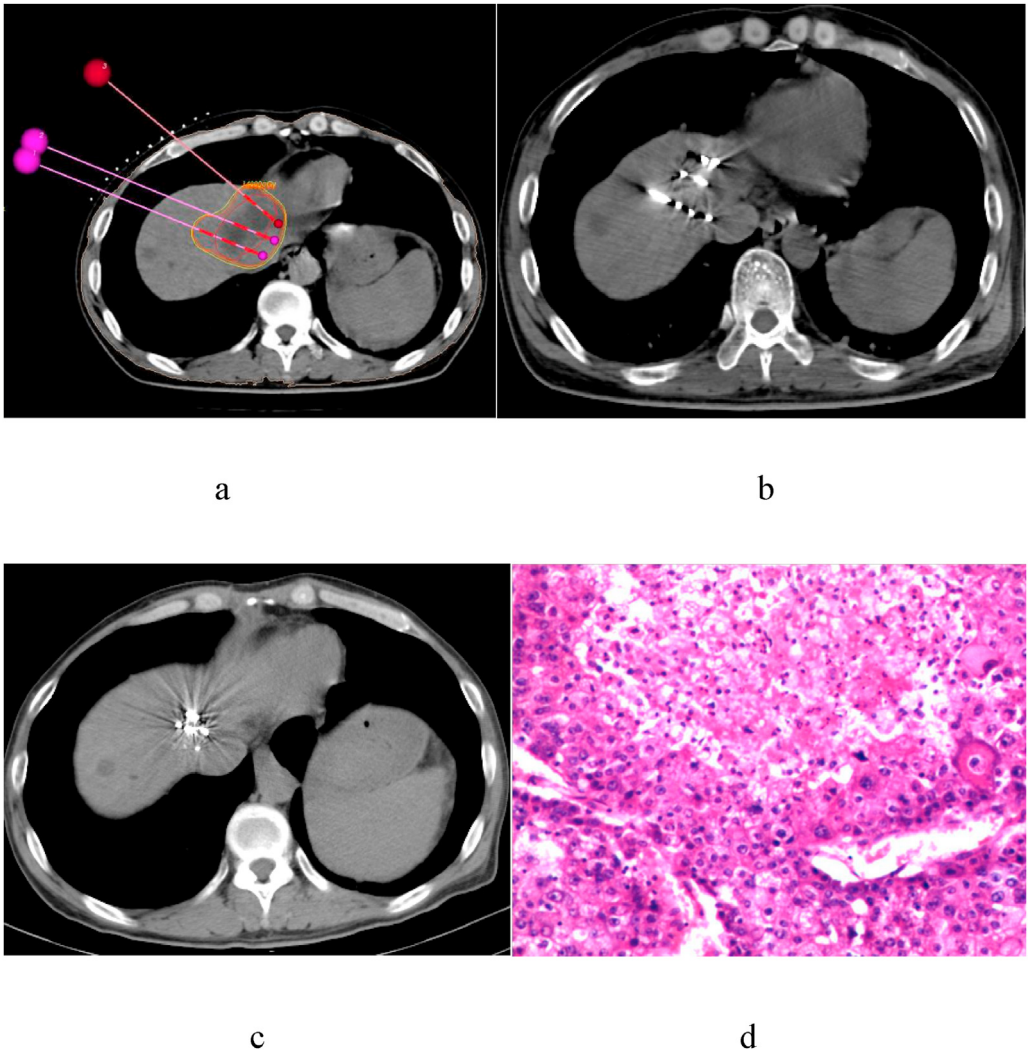

Fig. 1. Typical case of Iodine-125 seed implantation.

Table 1
Comparison of tumor volume and marker changes before and after Iodine-125 seed implantation.

	Preoperative	Postoperative	T value	P value
Tumor volume	50.96 ± 30.13	31.44 ± 14.51	5.303	0.000
AFP	90.63 ± 68.58	69.28 ± 50.99	3.702	0.000

Note:Paired T test was used for each value before and after treatment. The unit of tumor volume is cm^3 and the unit of AFP is μg/L.

3.4. Changes in related clinical symptoms caused by cancer before and after treatment

Among the 38 patients with varying degrees of abdominal pain symptoms, 6 experienced absence of pain symptoms after treatment, 16 experienced pain relief, 12 had no obvious symptom changes, and 4 experienced worse pain. The pain relief rate was reported to be 57.9%. Among the 28 patients who developed ascites prior to treatment, 3 showed absence of ascites symptoms, 12 experienced a reduction in the volume of ascites, 7 showed no obvious changes, and 5 experienced an increase in the severity of ascites symptoms at 3 months after treatment. There was no significant change in 23 patients with liver cirrhosis 3 months after treatment.

3.5. Adverse effects of Iodine-125 seed implantation therapy

No severe bleeding or hematoma occurred during the operation, and none of the patients developed vascular embolism or died. Twelve patients had high fever within 1 week after treatment, but their temperature returned to normal after receiving anti-inflammatory and symptomatic treatments. At the end of follow-up, results of patients' repeat blood routine and liver and kidney function tests showed absence of bone marrow suppression or severe liver and kidney function impairment.

4. Discussion

In recent years, radioactive Iodine-125 seed implantation has gradually received attention as the treatment of HCC. This technology has high conformity, easy operation, and few complications. Multiple studies have shown that Iodine-125 seed implantation has a high local tumor control rate. Moreover, it prolongs the survival time of postoperative patients.[11] It has excellent physical properties. First, it has a long first half-life (59.4d). The Iodine-125 seed is permanently implanted into the tumor under CT or ultrasound guidance, which can continue to produce low-dose gamma rays for a long time and close distance, blocking the entire cell cycle – especially the proliferation phase – and causing rapid tumor cell apoptosis.[12] Second, the radiation energy is low; the seed only emits 35.5 keV gamma rays during the implantation procedure, thus making it easy to protect the surrounding tissues; and the risk of radiation exposure to the patients' families after implantation is relatively low. Third, the radiation radius is short, the diameter is approximately 1.7 cm, the damage to the surrounding tissue is small, and the treatment only causes a few side effects. Based on the above characteristics, Iodine-125 seed implantation has been widely used clinically and has gradually become a research hotspot.

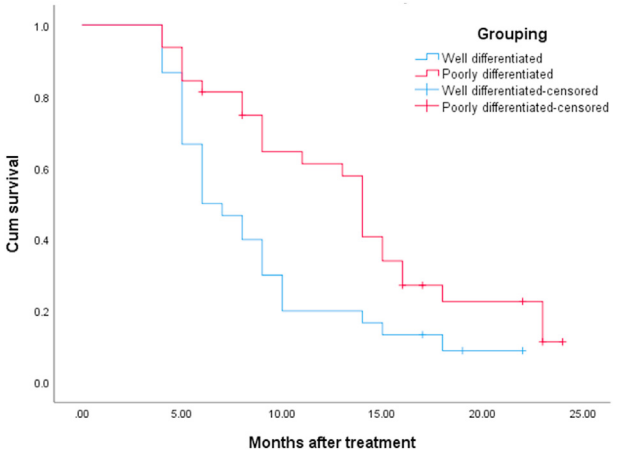

Fig. 2. Survival curve of Iodine-125 seeds implanted into hepatocellular carcinoma.

HCC is sensitive to radiation.[13] The γ-rays released by Iodine-125 seed can affect tumor DNA metabolism, destroy tumor blood vessels, and induce apoptosis through direct and indirect effects, to achieve the purpose of treating HCC. Many scholars have used different imaging methods during Iodine-125 seed implantation for the treatment of inoperable mid-advanced liver cancer lesions in order to achieve local control, thereby improving the prognosis of patients with advanced liver cancer. Li et al.[8] used Iodine-125 seed implantation to treat 80 patients with liver cancer. They reported an effective local control rate of 80% and a 3-year progression-free survival rate of 66.6%. Chen et al.[14] analyzed the survival status of Iodine-125 seed implantation in the treatment of HCC patients and found that the 1-, 3-, and 5-year survival rates (94.12%, 73.53%, and 55.88%, respectively) were higher than those of conservative treatments (88.24%, 52.94%, and 29.41%, respectively), all of which were statistically different (all $P < 0.05$). The conclusions of the above scholars are basically consistent with the results of this study. However, the abovementioned research did not specifically classify the pathology of liver cancer, but only discussed liver cancer in general. This article specifically focuses on HCC. It showed that Iodine-125 seed implantation therapy has a better objective response rate (61.3%) and prolonged the patient's survival time, with an average survival time of 11.47 ± 0.85 months and with a median production period of 9 months. Grouping the degree of differentiation, the survival of well-differentiated groups is significantly better than that of low-differentiated groups, also indicating that the degree of liver cancer differentiation is an important factor affecting the survival of patients with Iodine-125 seed implantation. The reason why Iodine-125 seed implantation relieves pain symptoms and prolongs the survival rate of patients is that it reduces the size of cancer lesions. This was verified by comparing the volume of cancer lesions before and after surgery in this study. The volume of cancer is significantly reduced, and the reduction of the primary focus decreases the incidence of local tumor recurrence and distant metastasis, avoids the development of lesions in the important organs of the body, and greatly increases the chance of patient survival. In addition, the reduction in cancer volume reduces the pressure of liver tissue in the surrounding capsule, effectively reducing the incidence of abdominal pain, ascites, and other complications. At the same time, AFP is an important indicator for evaluating the prognosis of patients with liver cancer.[15]. In this study, AFP, the most sensitive tumor marker for liver cancer, was also used as an observation indicator.

The incidence of adverse reactions to Iodine-125 seed implantation treatment is extremely low. A total of 62 patients in this study did not experience severe bleeding or hematoma during the operation, and no vascular embolism or death occurred. Twelve patients developed high fever within 1 week after surgery, which improved after receiving anti-inflammatory and symptomatic treatment. At the end of follow-up, the postoperative review of blood routine and liver and kidney function showed absence of bone marrow suppression or severe liver and kidney function impairment.

In summary, this study revealed the mechanism of Iodine-125 seed implantation to improve the survival rate of patients with advanced HCC by evaluating the recent lesion changes and long-term clinical effects. At the same time, Iodine-125 seed implantation for the treatment of primary HCC is safe, is effective, and has few complications. It provides a new, effective, and safe treatment method for patients with HCC who cannot undergo surgery, external radiation treatment, or chemotherapy.

Declaration of competing interest

The authors declare that they have no conflicts of interests to this work. We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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