

Therapeutic Effect Evaluation of ^{125}I Seed Implantation for Treating Refractory Hepatocellular Carcinoma

Du L¹, Tang Z^{2*}, Liu J³, Tian J³ and Shao C^{3*}

¹Department of Radiology, Shanghai Anda Hospital, Shanghai 201204, China

²Department of Radiology, Southern Branch of the Sixth People's Hospital of Shanghai Jiaotong University, Shanghai 201400, China

³Department of Radiology, Changhai Hospital, Shanghai, China

Abstract

Background: This study evaluated the clinical application of CT guided ^{125}I iodine implantation in patients with intractable hepatocellular carcinoma (HCC).

Methods: According to the treatment planning system (TPS), CT-guided ^{125}I iodine seed therapies were performed on 34 lesions in 29 HCC patients with the prescription dose of 120~150 Gy, Imaging changes and liver function of patients before and after the therapeutic modality were observed.

Results: After a follow-up of 6 months, of 34 lesions, 4 lesions were Complete Remission (CR) (11.8%), 23 lesions were Partial Remission (PR) (67.6%), 6 lesions were No Change (NC) (17.6%), and 1 lesion was Progress Disease (PD) (2.9%), and the total response rate (CR + PR) was 79.4%. Liver function dropped to level B from level A in 8 cases, dropped to level C from level B in 3 cases, liver function was unchanged in 18 cases.

Conclusion: CT-guided ^{125}I iodine seed implantation brachytherapy is effective and safe for most intractable HCC.

Keywords: Carcinoma; Hepatocellular; Iodine isotopes; Brachytherapy

Introduction

Hepatocellular Carcinoma (HCC) is one of the common malignant tumors with high incidence and lethality rate. Due to absence of effective early diagnosis methods, the mortality rate is almost near the incidence (the survival rate of patients with HCC is between 3% and 5% in America and the developing countries according to literature) [1]. Surgery has long been considered the preferred method for HCC treatment, but only 10% to 15% of the patients who are diagnosed accurately with HCC are possibly be cured through surgery, the remaining majority is just too late for surgery [2,3]. With the development of medical technology, various non-surgery measures are playing an increasingly important role in cross-discipline treatment of HCC. The refractory hepatocellular carcinoma is refractory to systemic and intra-arterial therapy. The radioactive nuclide therapy, especially radioactive ^{125}I and ^{103}Pd interstitial brachytherapy which has shown an encouraging therapeutic effect, is an early, extensively adopted and rapid-progressing way to treat malignant tumors [4]. We performed the CT-guided percutaneous ^{125}I seed implantation brachytherapy on 29 patients with primary liver cancer. The purpose of the present is to explore the efficacy and safety of CT guided ^{125}I implantation in patients with refractory hepatocellular carcinoma. The details are reported as below.

Materials and Method

Materials

Clinical data: The patients with primary HCC in our hospitals during the period from January 2009 to December 2010 were included in our research as long as they met the following conditions:

- clinically confirmed HCC (according to medical history, HBV or HCV, AFP, B-mode ultrasonography, CT, MR or pathology)
- one or more tumors with clear boundaries shown on CT image
- still residual activity after the transcatheter arterial

chemoembolization (TACE) treatment

- Child-Pugh A or B
- no metastases

Any above patients who met the following conditions were excluded:

- the hepatic cirrhosis classification is C
- vague tumor boundary on CT image
- other combined disease(s) that may fail the treatment plan

In our research group, there were 29 patients with 34 focuses, who comprised 22 males and 7 females at age ranging from 38 to 66 years old, and median age 49 years old. 15 patients were confirmed to have HCC through the CT-guided fine-needle liver biopsy or post-operative pathological evidence, and suffered a relapse after the imaging diagnosis; the remaining 14 patients were clinically diagnosed to have HCC according to their comprehensive medical histories, physical signs, serum AFPs and imaging findings. Before the seed implantation, all patients showed focuses with residual active regions after the TACE treatment. 5 out of 29 patients had multiple focuses with their livers. According to the Child-Pugh grading criteria, 20 patients belonged to grade A and 9 patients were grade B. All patients received the CT-

***Corresponding authors:** Zhen T, Department of Radiology, Southern Branch of the Sixth People's Hospital of Shanghai Jiaotong University, Shanghai, China, Tel: +86-13816490856; Fax: +86-21-57412830; E-mail: T-zhen@126.com

Chengwei Shao, Department of Radiology, Changhai Hospital, Shanghai, China, Tel: +86-13386274178; E-mail: cwshao@sina.com

Received April 12, 2014; Accepted June 16, 2014; Published June 23, 2014

Citation: Du L, Tang Z, Liu J, Tian J, Shao C (2014) Therapeutic Effect Evaluation of ^{125}I Seed Implantation for Treating Refractory Hepatocellular Carcinoma. OMICS J Radiol 3: 165. doi:10.4172/2167-7964.1000165

Copyright: © 2014 Du L, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

guided percutaneous ¹²⁵I seed implantation brachytherapy. The study was conducted in accordance with the guidelines of the Regional Ethics Committee for conducting research involving humans. Each subject or his/her relative/caregiver provided signed consent to participate in the treatment.

Method

Materials: The materials required by the ¹²⁵I radioactive seed implantation included 18G seed implantation needle, implantation gun and ¹²⁵I radioactive seed, all provided by Ningbo Junan Pharmaceutical Technology Co., Ltd.

¹²⁵I seed has a half-life of 59.6d, an energy of 27.4~31.4 Kev (X ray) and 35.5 Kev (γ ray), and an activity of 0.6~0.8 mCi per seed. The matched peripheral dose is 120~150 Gy. The seeds were sterilized with high pressure for later use. The pre-operative plan was performed according to the CT and MR images and the radioactive seed implantation treatment planning system (TPS 2.3) to determine gross target volume dosage as well as seeds' quantity and spatial arrangement. The radiation oncologist outlined the planning target volume (PTV) on each transverse image. The D90 (the doses delivered to 90% of the target volume defined by CT using dose-volume histograms) of irradiation was determined. The total activity and the number of ¹²⁵I seeds to be implanted in the target were obtained using the three dimensional radiation Therapy Planning System (3D-TPS, Beijing Fei Tian Industries Inc., Beijing, China). After performance of local anesthesia, 18G implantation needle was guided by CT to puncture into the tumor before the seed was implanted backward by the seed gun at an interval of 1.0 cm. The seeds were appropriately placed to tumor and 1.0 cm outside tumor according to the tumor shape. After the completion of implantation, the needle was removed and the bleeding was arrested by compression. Afterwards, the CT scan was performed for the purpose of post-operative verification of even distribution. If the spatial distribution was uneven, additional seeds might be implanted to correct and cure the cold points. Postoperative dosimetry was routinely performed of all patients. The implant dose was determined using three-dimensional seed identification and a 5 mm thickness CT scan immediately after seed implantation. The images and sources were entered into computerized treatment planning system. The median number of ¹²⁵I was 75 (range, 15 to 229). The activity of the ¹²⁵I seeds ranged from 0.6~0.8 mCi per seed. The operation lasted 30 to 120 minutes and went successfully on all patients. The liver maintenance measure, mainly drugs intended to protect and restore liver functions, were taken before and after the operation. The liver function examinations were also performed on a regular basis after the operation.

Therapeutic evaluation: The imaging evaluation was performed according to the therapeutic evaluation of solid tumor issued by WHO (the World Health Organization) [5].

The three maximum diameters that are perpendicular to each other in imaging of tumors before and after treatment were compared.

The criteria for therapeutic evaluation included:

- complete remission (CR): the tumor completely disappears and the imaging examination shows no or centralized metallic seeds
- partial remission (PR): the tumor in image shrinks, and the product decreases by $\geq 50\%$ compared to that before treatment, or by $<50\%$ but the activity reinforcement is significantly abated

- no change (NC): the product decreases by $<50\%$ compared to that before treatment, and the active area reinforcement shows no significant abatement, or the product increases by $<25\%$
- progress disease (PD): the product increases by $\geq 25\%$ compared to that before treatment, and the active area reinforcement scope expands, and new active areas appear in periphery [3]

All patients received the follow-up visits lasting a period ranging from 2 to 12 months and their liver functions were assessed before and after operation according to Child-Pugh grading criteria. After that, we continue our telephone follow-up. The median telephone follow-up was 48 months (range, 36-60 months).

The complications were scored using the Radiation Therapy Oncology Group (PTOG)/European Organization for Research and Treatment of Cancer (EORTC) late radiation morbidity score [6].

The survival time was calculated from the date of implantation to the last date of follow-up or date of death. In these calculations, deaths due to any reason were scored as events. Local control was defined as lack of tumor progression either in or adjacent to the implanted volume. The overall local control and survival times were determined using the Kaplan-Meier method by using SPSS12.0 for Windows (SPSS, Chicago, IL).

Results

Imaging evaluation

In our research group, 26 patients survived in 3 months after seeds implantation; the CT or MRI examination performed on them showed that 26 patients had 31 focuses, of which 3 reached CR, 21 PR, 5 NC and 2 PD; according to the 3-month follow-up visit assessment, 1 focus appeared to be progressive, which reached PR in 3 months after implantation of additional seeds (Figure 1).

3 patients out of the group were not re-examined in 3 months after seeds implantation but re-examined in 6 months; the CT or MRI examination performed on them showed that they had 3 focuses, of which 1 reached CR, 1 PR, 1 NC and 0 PD.

As a result, the 29 patients of the group had 34 focuses and the imaging evaluation performed on them in 6 months after operation showed that 4 focuses reached CR (11.8%), 23 PR (67.6%), 6 NC (17.6%) and 1 PD (2.9%), and that the total effective rate (CR+PR) reached 79.4%. According to the focus size, the 34 focuses were divided into 3 grades for respective assessment of therapeutic effect. The assessment results were as shown in Table 1. The above patients showed no significant migration of radioactive seeds.

Liver functions before and after operation 29 patients were assessed before and after operation according to Child-Pugh grading criteria. Before the operation, 16 patients belonged to grade A, 13 grade B and 0 grade C; after the operation, the conventional liver protection treatment was performed, and 26 patients were assessed once again in terms of liver functions in 3 months after operation. The assessment result

Therapeutic effect	CR	PR	NC	PD
Focus size				
T \leq 3cm	3	4	1	0
3cm < T \leq 5cm	1	8	2	0
T > 5cm	0	11	3	1
total	4 (11.8%)	23 (67.6%)	6 (17.6)	1 (2.9%)

Table 1: Imaging-based Assessment of Therapeutic Effect of Focuses in Various Sizes in 6 Months after Seeds Implantation.

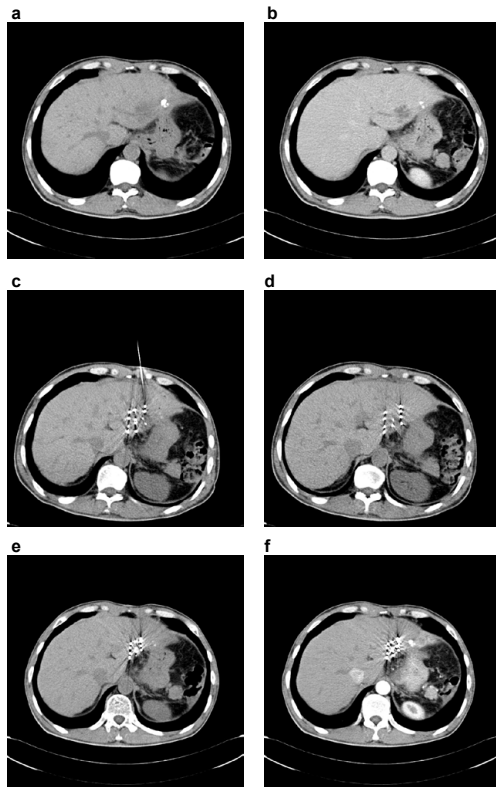


Figure 1: The CT pictures of a 45-year-old male with hepatocellular carcinoma (A, CT plain scan after Transcatheter Arterial Chemoembolization (TACE) for 3 months: a 3 cm×4 cm low density cancer lesion is showed in the third section of liver and there is a lesion with iodine oil deposition around it; B, CT enhanced scan: Lesions are more clearly; C, CT plain scan during ¹²⁵I radioactive seed implantation: The seeds were appropriately placed to tumor and 1.0 cm outside tumor; D, CT plain scan after ¹²⁵I radioactive seed implantation: The seeds are showed clearly; E and F, CT plain scan and enhanced scan after ¹²⁵I radioactive seed implantation for 5 months: The lesion is shrink and seeds spacing are significantly narrowed).

showed that 4 patients who had belonged to grade A now belonged to B and 1 who had belonged to grade B now belonged to grade C. 29 patients were assessed once again in terms of liver functions in 6 months after operation. Compared with the data gained in 3 months after operation, 4 patients who had belonged to grade A now belonged to B, and 2 who had belonged to grade B now belonged to grade C. Among those who belonged to grade C, 1 patient had a single focus ≤ 3 cm but many sub-foci inside it; 2 patients had focuses >5 cm, one having progressive focus according to imaging evaluation, the other one having many sub-foci in other parts of liver. The remaining patients basically belonged to grade A or B.

Time-based variance in focus size 26 out of 29 patients received continuous follow-up visits in 2 to 6 months after operation. The follow-up visit results showed that 25 of 31 focuses reached CR or PR according to the imaging assessment results, and that their focuses shrank with time. Specifically, in 2 to 3 months after operation, 3 focuses reached CR and 3 PR; in 3 to 4 months after operation, 1 out of the remaining focuses reached CR and 15 PR; in 4 to 5 months after operation, 4 focuses, each with a size >5 cm, shrank significantly.

So far, 15 patients had died. The median overall survival time was 23. 14.8 months for all patients, and the 1, 2 and 3-year survival rate was 85.4%.

Complications

Two patients had grade 1 skin reaction, one experienced grade 1 mucosal reaction. We did not observe blood vessel damage and neuropathy in the patients.

Discussions

Hepatic Carcinoma (HCC) is a severely malignant tumor of which the cells proliferate rapidly in their short life. A normal liver is a radiosensitive organ. Studies have shown that 75% patients show hepatic insufficiency if external exposure is >30 grays (Gy). External beam irradiation therapy for HCC has been used infrequently in part because of the limited tolerance of the entire liver (30 Gy), which is insufficient to control macroscopic disease [7]. The external radiation therapy for hepatic carcinoma has been reported to lead to some serious complications such as radiation hepatitis, radiation pneumonia, pulmonary embolism, pulmonary fibrosis, gastroduodenal ulcer and arrest of bone marrow. The application of chemotherapy drugs decreases the radiation tolerance of liver, and more than 80% patients with primary hepatic carcinoma have a significantly lowered hepatic radiation tolerance due to their combination with cirrhosis at various degrees. This is also one of the reasons why the conventional radiotherapy has a poor therapeutic effect [8-12]. The CT-guided percutaneous permanent radioactive seed implantation as a supplement to operation, chemotherapy and radiotherapy is increasingly valued in treatment of hepatic malignant tumor. The radioactive seeds that are implanted in tumor can continuously emit γ ray which multiplies the radiation effect of tumor cells and so continuously radiate and destroy the DNA double strands of tumor karyon to lead to loss of reproductive ability of tumor cells; in addition, unlike external radiation, the radioactive seed implantation therapy doesn't cause systemic complications and therefore influences the liver functions to a lighter extent. Among the patients in our research during the follow-up visit, most kept their liver function Child-Pugh grade at B or above, and the only 3 whose grade descended to C showed systemic poor conditions caused by tumor metastases. It is thus clear that the operation itself had insignificant

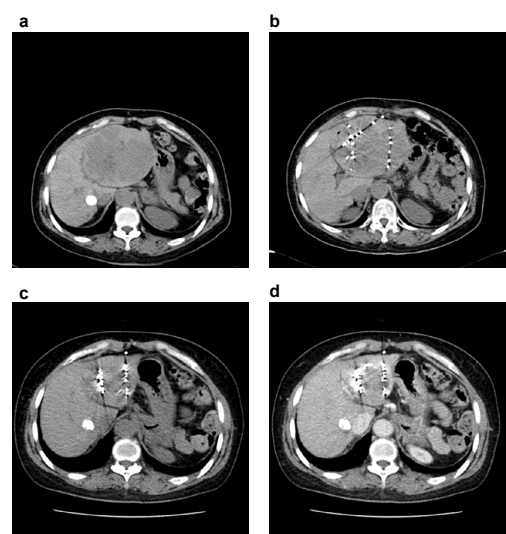


Figure 2: The CT pictures of a 55-year-old female with hepatocellular carcinoma (A, CT plain scan after TACE for 4 months: a 8 cm×10 cm low density cancer lesion is showed in the left hepatic lobe and there is a lesion with iodine oil deposition in right hepatic lobe; B, CT plain scan after ¹²⁵I radioactive seed implantation: The seeds are showed clearly; C and D, CT plain scan and enhanced scan after ¹²⁵I radioactive seed implantation for 7 months: The lesion is shrink and seeds spacing are significantly narrowed).

impact on the liver functions.

Compared with the three-dimensional conformal radiotherapy, the solution in our research has a better therapeutic effect and lighter adverse reaction. Through analysis, the reasons include:

- The sensitivity of tumor cells to rays differs in time phase; the DNA post-synthetic phase and the karyokinesis phase are the sensitive phase in which a few rays can destroy the reproductive ability of tumor. The sensitivity is poor in other time phases, especially in the stationary phase in which the cells are insensitive to rays [13,14]. The *in-vitro* short-term radiotherapy can only kill the tumor cells of sometime phases. ¹²⁵I radioactive seed implantation brachytherapy can continuously act on tumor cells and kill or hurt tumor stem cells. Enough doses and enough half-life of seeds can make all tumor cells lose their reproductive ability so as to heal patients [15].
- The three-dimensional conformal radiotherapy does not only kill and wound tumor through the focusing effect of rays, but also hurts the peripheral tissues. The effective damaging radius of radioactive seed is small, ranging from 0.5 to 1.0 cm, consequently causing less damage to peripheral normal tissues.

Through the therapeutic effect observation given to tumors in various sizes, we found that a focus can reach CR or be very likely to reach PR when it is ≤ 5 cm, and that the majority of the focuses which are >5 cm may reach PR. In general, most patients reached PR. Even if the radioactive seeds were arranged to surround the tumor and the target volume dose based on the calculation by TPS met the requirement of therapeutic dose, the therapeutic effect still varied due to the following reasons:

- different pathological types of tumors had different sensitivities to radiotherapy, which may be the main reason
- unexpected factors appeared during operation influenced the arrangement of seeds in a way against the plan
- big tumor constantly shrank in the course of operation, but different shrinkage of each part of it led to a changed target volume and a less even dose distribution

Moreover, according to the imaging-based evaluation of therapeutic effect, we found that there were continuous enhancement zones at various degrees around the seeds of most patients, instead of apparent fast-in-fast-out symptoms (Figure 2). We believe that this was closely related to radioactive damage. After a liver is radiated, its endothelial cells are first damaged; subsequently, the liver will suffer central vein occlusion, then local hepatic dropsy and finally hepatic fibrosis. Usually 1 to 4 months are required to observe such hepatic variations caused by the radioactive damages after the liver is radiated, which is consistent with the follow-up visit time spent by us.

According to our observation given to time-based variations in tumor size, we found that the tumors of those patients who reached CR or PR shrank significantly in 3 or 4 months after treatment. The reasons are analyzed as follows: the half-life of ¹²⁵I is 59.6 d, γ ray energy 35.5 keV, the initial dose rate 7.7 cGy/h, the release in 240 d about 94%, and the Relative Biological Effectiveness (RBE) 1.4. It is thus clear that in about 120 days, the exposure dose of seed still remained a high level; for the tumor cells having undergone a long-term continuous exposure, the necrosis and survival rates already reversed, consequently 3 or 4 months are the period with a good therapeutic effect.

¹²⁵I radioactive seed implantation with CT guidance has some advantages:

- the implant technique is performed easily under local anesthesia without severe pain and discomfort during hospitalization and

- CT guidance reduces geometric miss, minimizes the radiation dose to the surrounding organs due to the sharp dose fall-off outside the implanted volume, and enhances sub lethal damage repair, thereby protecting healthy organs from late tissue damage

At the same time, we observed a very low rate of complications, one patient had grade 1 skin reaction, one experienced grade 1 mucosal reaction. No severe procedure-related complications occurred in any case, and no adverse events were attributable to seed implantation itself. We did not observe blood vessel damage and neuropathy in these group patients.

Conclusion

If the CT-guided percutaneous therapy is used to treat the refractory hepatocellular carcinoma, the focuses of most patients can reach PR with a good local control and a small impact on the liver functions. The therapy is therefore considered a safe and effect method. However, considering the small number of patients and the short follow-up period, a definite conclusion will require a larger number of patients and follow-up over a longer term.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. *CA Cancer J Clin* 55: 74-108.
2. El-Serag HB, Mason AC (1999) Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 340: 745-750.
3. Krishnan S, Dawson LA, Seong J, Akine Y, Beddar S, et al. (2008) Radiotherapy for hepatocellular carcinoma: an overview. *Ann Surg Oncol* 15: 1015-1024.
4. Jiang YL, Meng N, Wang JJ, Ran WQ, Yuan HS, et al. (2010) Percutaneous computed tomography ultrasonography-guided permanent iodine-125 implantation as salvage therapy for recurrent squamous cell cancers of head and neck. *Cancer Biol Therapy* 9: 959-966.
5. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. *Cancer* 47: 207-214.
6. Cox JD, Stetz J, Pajak TF (1995) Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) *Int J Radiat Oncol Biol Phys* 31: 1341-1346.
7. Mcintosh A, Hagspiel KD, Al-Osaimi AM, Northup P, Caldwell S, et al. (2009) Accelerated treatment using intensity-modulated radiation therapy plus concurrent capecitabine for unresectable hepatocellular carcinoma. *Cancer* 115: 5117-5125.
8. Mazon R, Bajard A, Montbarbon X, Gassa F, Malet C, et al. (2012) Permanent ¹²⁵I-seed prostate brachytherapy: early prostate specific antigen value as a predictor of PSA bounce occurrence. *Radiat Oncol* 7: 46.
9. Zhu L, Jiang Y, Wang J, Ran W, Yuan H, et al. (2013) An investigation of ¹²⁵I seed permanent implantation for recurrent carcinoma in the head and neck after surgery and external beam radiotherapy. *World J Surg Oncol* 11: 60.
10. Ebara S, Katayama N, Tanimoto R, Edamura K, Nose H, et al. (2008) Iodine-125 seed implantation (permanent brachytherapy) for clinically localized prostate cancer. *Acta Med Okayama* 62: 9-13.
11. Wang J, Jiang Y, Li J, Tian S, Ran W, et al. (2009) Intraoperative ultrasound-guided iodine-125 seed implantation for unresectable pancreatic carcinoma. *J Exp Clin Cancer Res* 28: 88.
12. Shi L, Wu C, Wu J, Zhou W, Ji M, et al. (2012) Computed tomography-guided permanent brachytherapy for locoregional recurrent gastric cancer. *Radiat Oncol* 7: 114.
13. Shirabe K, Shimada M, Tanaka S, Maeda T, Maehara Y (2002) [Current therapeutic strategy of hepatocellular carcinoma with extensive portal thrombus]. *Fukuoka Igaku Zasshi* 93: 197-203.
14. Fan J, Zhou J, Wu ZQ, Qiu SJ, Wang XY, et al. (2005) Efficacy of different treatment strategies for hepatocellular carcinoma with portal vein tumor thrombosis. *World J Gastroenterol* 11: 1215-1219.
15. Zhang FJ, Li CX, Jiao DC, Zhang NH, Wu PH, et al. (2008) CT guided ¹²⁵I seed implantation for portal vein tumor thrombus in primary hepatocellular carcinoma. *Chin Med J (Engl)* 121: 2410-2414.