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*Review*

# Dosimetry for $^{125}$I radioactive seed implantation therapy for hepatocellular carcinoma

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## Abstract

Hepatocellular carcinoma (HCC) is an aggressive malignancy. Early lesions respond well to hepatic resection or liver transplantation. However, only a few of HCC patients are suitable for surgical intervention. External beam radiation and chemotherapy is poorly efficacious. In the last 20 years, HCCs belonging to the radiosensitive tumor group has been confirmed. Along with the development of new radiotherapy technology and facilities, the research about brachytherapy(especially $^{125}$I seed implantation therapy) has provoked more interests in the world. Radioactive seed implantation therapy is a form of interstitial brachytherapy, with the property of local "conformal radiotherapy" and the advantages of minimal invasion, convenience, high performance, and minimal adverse effects. It is a promising therapy for HCC, however the dosimetry hasn't yet been identified and lacks verification in prospective research. This report aims to further explore the best prescription dose and radioactivity for $^{125}$I interstitial implantation brachytherapy for HCC.

*Key words*: carcinoma, hepatocellular/radiotherapy; brachytherapy; radioactive seeds; $^{125}$I

## INTRODUCTION

Hepatocellular carcinoma(HCC) is the third most common cause of cancer death worldwide, giving rise to >590,000 deaths per year[1]. Although early lesions respond well to hepatic resection, liver transplantation, and some to percutaneous ablation or chemoembolization[2], most patients with HCC still present with advanced disease, with only 10% to 20% of patients suitable for surgical intervention. External beam radiation is not useful for HCC as the sensitivity of the normal liver limits the dose that can be delivered, and chemotherapy is poorly efficacious[3]. The median survival of inoperable patients remains about 3 months in places where the disease is endemic[4]. In the last 20 years, it has been confirmed that HCC is the radiosensitive tumor. Along with the development of the new radiotherapy technology and facility, the research about brachyhtherapy, (especially $^{125}$I seed implantation therapy) has provoked more interest in the world, however its dosimetry remains to be further studied. This review pays attention to this related dosimetry.

## RADIOACTIVE SEED IMPLANTATION THERAPY

Radioactive seed implantation therapy belongs to the interstitial brachytherapy family. With the property of local "conformal radiotherapy", it has the potential advantage of delivering the maximum radioactivity to the tumor, with sharp dose fall-off to surrounding normal structures, thus side effects can be limited. It is believed that delivery of high doses of radiation in such a localized setting will lead to significant tumor response, with minimal toxicity and collateral acute radiation damage to other tissues. That is whether the source of radiation remains locked *in situ* with minimal systemic distribution. Radioactive seed implantation therapy has a history of about one hundred years, and the earliest recorded in the beginning of the 1890s. The early radioactive seed used in clinical practices was of high energy radionuclide, like Cobalt -60($^{60}$Co), the Radium -226($^{226}$Ra) and so on. With the releasing of the gamma

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beam, protection was difficult to ensure, so the serious damage to the patient was created, and the practice in clinics was restricted. However, a new low energy radionuclide, like $^{125}I$, $^{103}Pd$, etc., have been developed one after another successfully in the recent 20 years, which has expanded the application of radioactive seeds. $^{125}I$ seed has been used for the treatment of many kinds of malignancies, such as pancreatic cancer, pulmonary carcinoma, oral and maxillofacial malignancy, head and neck malignant tumor, and so on[5-9]. Especially, in the field of prostate carcinoma, its clinical effect has been elucidated as success in related references[10-14]. Due to availability, the reports cited are relatively more concerned with $^{125}I$ seed implantation therapy for liver metastasis of colon cancer, and more specifically related reports on sample therapy for HCC are fewer.

## $^{125}I$ SEED AND HCC

### Property of $^{125}I$ seeds

$^{125}I$ seed comes close to being the ideal sealed therapeutic radionuclide. With single activity 0.3~1.0mCi, the half-life of $^{125}I$ seed is 60.2d and its energy is 27. 4~31. 4 Kev X beams and 35.5 Kev γ beams. The maximum emission range in tissue is about 1.7cm. They are easy to be preserved and protected, and simultaneously there is less damage to the patient and the medical staff. Therefore, it is gradually well received in practices of radioactive seed interstitial implantation brachytherapy.

### Dosimetry of $^{125}I$ seeds

At present, the issue can be classified as either "systematic" or "stochastic" in terms of their impact on large groups or individual patients, respectively. Systematic changes affecting large numbers of patients occur infrequently and include changes in source dosimetric parameters, prescribing practice, dose calculation formalism, and improvements in calculation algorithms. The operator must be aware of how incipient changes accord with previous experience. Stochastic issues involve procedures that are applied to each patient individually[15]. In fact, that is now the state of dosimetry, for $^{125}I$ implantation therapy for HCC.

$^{125}I$ is given in a low dose rate radionuclide(of 0.05~0.10Gy/h generally) with an initial dose rate of 0.0013 Gy/min. The interstitial implantation also belongs to the irradiation of extremely low dose rate. As the energy of gamma beam is low and decays very rapidly, the change of the dose distribution is very complicated. If the real dose distribution needs to be measured, the detector should be satisfied with the following conditions: enough precision and sensitivity and enough small volume. But this is very difficult according to the present conditions. So its dose distribution mainly depends on the calculation, but not measurement. According to the formula: $D_{(T)}=D_{(0)}\times T_{1/2}\times 1.443\times[1-e^{-T\times 0.693/T_{1/2}}]$ and $D_{(r)}=S_k\wedge 1/r^2 g_{(r)}\Phi_{an}$, it can be calculated, where the absorbed dose in some point after T hours and the dose rate within 1~9 cm range around the seeds[10]. Generally, the $^{125}I$ seed clinical total activity is calculated by the following methods:① Dimension-averaging method; the most classically manual algorithm, [A(total activity), mCi = tumor median diameter(d),cm × K],[d=(Length +Width+Height)/3,K=5]; ② Power Law squared method, [A, mCi = 2.15 × $d^2$]; ③ Treatment Planning System(TPS). It is worthy of the remark, that the mentioned are all designed according to prostate carcinoma. However, the biological behavior and radiosensitivity of HCC are incompletely consistent with prostate carcinoma. At present, some TPS and related instruments(including $^{125}I$ seed) have been designed to be adapted to the permanent implantation brachytherapy for many kinds of stereo-tumors.

In March 2004, the recommendations of the American Association of Physicists in Medicine(AAPM) on the interstitial brachytherapy dosimetry using $^{125}I$ and $^{103}Pd$ were reported in Medical Physics[16]. This update was pursued primarily due to the marked increase in permanent implantation of low-energy photon-emitting brachytherapy sources over the past decade, and clinical need for accurate dosimetry in the implementation of interstitial brachytherapy. Additionally, there were substantial improvements in the brachytherapy dosimetry form, accuracy of related parameters and methods for determining these parameters[17]. These recommendations included some minor changes in the dose-calculation form and a major update of the dosimetry parameters for eight widely used interstitial brachytherapy sources. A full implementation of these recommendations could result in unintended changes in delivered dose without corresponding revisions to the prescribed dose. For $^{125}I$ implants using Model 6711 seeds(most published clinical experience with permanent brachytherapy is based upon widely used source model), there are no significant changes(less than 2%)[18,19].

Nowadays, the related dosage data of $^{125}I$ seed interstitial brachytherapy for HCC is mostly derived from clinical experience. For the same reason as the mentioned, the best prescription dosage and the best radioactivity of seed still need to be explored. Ricke J, *et al*[20-22]noticed that the mean minimal dose inside the liver tumor margin amounted to 17~18Gy(range, 10~25Gy); Zhang FJ, *et al.*[23] described that $^{125}I$ seeds of the radioactivity of 30 MBq, the matched peripheral dose(MPD) was 100 to approximately 150 Gy, and the number of radioactive seeds for one patient ranged from 10 to approximately 100. With referrence to the literature, it is thought to be reliable that the dose of $^{125}I$

single seed generally contains 0.6 mCi ,and it is safer to control at the volume dose of 20~25 mCi. Meantime, the key in $^{125}$I seeds interstitial brachytherapy for HCC is the reasonable MPD, i.e.,80~100 Gy is rationa; it does not only display the advantages of minimally invasive, high performance and minimal adverse effect and so on but also reduces the damage to normal liver cells as far as possible.

### Curative effect and adverse effect

Referring to reports of Zhang FJ, *et al.*[23]; among the 45 lesions, 17 obtained complete remission(CR), 20 partial remission(PR), 7 no change(NC), and 1 progression of disease(PD). The response rate was 82.2%. Side effects occurred during the procedure, including pneumothorax in 1 cases with the lung compression of less than 30 percent, bleeding in 3 cases, and blood in sputum and fervescence in 5 cases. Seeds migration 2 months after the operation occurred in 2 cases. WBC decreased slightly in 2 cases 2 weeks after the operation, with the WBC count $\geqslant 3 \times 10^9$/L. No other severe complications, such as massive hemorrhage, bile fistulae, and pancreatic fistula were seen. Luo KY, *et al.*[24] reported the encouraging results for $^{125}$I seeds implantation therapy for liver cancer. Survival rates at 12, 24, 36 month were found as 91.7%, 86.7%, 75.0%, respectively. No severe adverse effects were seen. Although the related experience is limited, outcomes following $^{125}$I seeds versus other methods of delivering radiotherapy, such as three-dimensional conformal radiation therapy (3DCRT) and stereotactic body radiotherapy(SBRT), need be described briefly. Whatever 3DCRT or SBRT, the tumor immobilization(to account for respiratory related organ motion[25]) must be considered thoroughly, however, this problem has no impact on $^{125}$I seed implantation for HCC. The University of Michigan has conducted numerous trials of conformal RT in liver cancer patients over the past 15 years. From April 1996 to April 2003, 128 patients were treated with conformal hyperfractionated RT delivered with concurrent continuous infusion hepatic arterial FUdR. Thirty-eight patients(30%) developed three to four grade toxicity, and five cases(4%) of radiation-induced liver disease(RILD) were observed. The median survival of 35 HCC patients was 15.2 months[26,27]. Mendez Romero *et al.* [28]treated 8 patients with 11 HCCs of Child-Pugh class A or B. For the HCC patients, the crude local control rate was reported 82%, and the one- and two-year actuarial OS rates was 75 and 40%, respectively. In the HCC group, one patient(Child-Pugh class B) developed 5 grade toxicity due to liver failure and infection, demonstrating that patients with Child B cirrhosis need to be treated with caution. Whatever, the datum compared with 3DCRT and SBRT yet shall be further studied in the randomized controlled trial(RTC).

## PROSPECT

Modern brachytherapy has led to effective treatments through the establishment of broadly applicable dosimetric thresholds for maximizing survival with minimal morbidity. Proper implementation of recent dosimetric consensus statements and quality assurance procedures is necessary to maintain the established level of safety and efficacy.

$^{125}$I seed implantation therapy for HCC can enhance the exposure dose of target area and reduce the irradiated scope of the surrounding normal tissue, and it might enhance the rate of local control of the tumor and the survival rate of the patient. It provides an effective treatment and a new direction, however its dosimetry has not as yet reached a consensus in the world. Now the state of the related data is still based on the clinical experience, without verification in prospective large samples multicentric randomized research. So, further study on the mentioned problem and formulating the precise and scientific dosimetric standard of $^{125}$I seed implantation therapy for HCC, is our focus in the future. Along with the further studies, this promising therapy will be more standard, more applicable, and more systematical.

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