



## Research Paper

# Analysis of curative effect of I<sup>125</sup> implantation combined with radiofrequency ablation in treating bone metastases

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## ABSTRACT

The aims of this study were to investigate the clinical effects of I<sup>125</sup> implantation combined with radiofrequency ablation in treating bone metastases (BM) and analyze its clinical application so as to provide better treatment protocols for the treatment of BM. A total of 63 BM patients were randomly divided into the I<sup>125</sup> implantation group (CON, treated with I<sup>125</sup> seeds alone, 33 patients) and the combination group (I<sup>125</sup>-MA, 30 patients) to compare the clinical efficacy and adverse effects. After treatment, the clinical efficacy of Group I<sup>125</sup>-MA was significantly better than Group CON, and the quality of life was improved significantly ( $P < 0.05$ ). I<sup>125</sup>-MA has relatively better clinical efficacy in treating BM, which can not only significantly improve patients' life quality but also cause no serious adverse reaction. The therapy of I<sup>125</sup> implantation combined with radiofrequency ablation provides a new idea for treating bone metastases. Compare Group I<sup>125</sup>-MA and Group CON, remission rates of bone pain were 76.7% vs 42.4% ( $P < 0.05$ ); movement ability: 73.3% vs 39.4% ( $P < 0.05$ ); quality of life: improvement rates: 70% vs 42.4% ( $P < 0.05$ ), the median initial time of relieve pain: 3.5 days vs 7.6 days ( $P < 0.05$ ).

## 1. Introduction

Clinical studies have shown that most patients with tumors, especially those with advanced tumors, are often accompanied by distant metastases, among which bone is one of the common metastatic sites of malignant tumors [1]. Bone metastases (BM) is a common complication of advanced malignant tumors characterized by such clinical manifestations as severe pain, pathological fractures, or secondary neurological insufficiency or dysfunction, so it seriously affects the patients' quality of life [2,3]. Clinically, local radiotherapy, chemotherapy, and surgery are the main treatment methods, aiming to improve the patients' quality of life and prolong their lives. However, BM in early stages often has no obvious clinical manifestation and is difficult to be found, and the stage when discovered is often more serious, so that the above treatment methods may have poor efficacy. Studies have shown that I<sup>125</sup> particles have the features of short action range and strong biological effects, so the ray by the implanted I<sup>125</sup> seeds can directly kill tumor cells, thus playing the best therapeutic effects while minimizing the killing effects against normal cells at the same time. Tumor ablation

technology refers to applying chemical drugs or hyperthermia directly to the tumor area, thus achieving the effects of killing the tumor cells or realizing general necrosis of the tumor [4]. It has been clinically applied for more than 100 years; Jiao applied I<sup>125</sup> particles to treat BM-induced pain and achieved good effects. Although the effective time against cancer pain is slower than radiofrequency (RF) ablation, the pain control conditions between the two groups after 3-week treatment showed no significant difference [5]. When radiofrequency ablation is applied to the tissue, the high frequency AC channel at the tip of the electrode passes through the tissue to the back electrode, the current causes the direction and arrangement of the ion in the tissue to change with the direction of the current. Since the movement causes friction and generates heat, the temperature of the local area usually is higher than 100 °C, which also destroys the microenvironment and leads to local vascular thrombosis. While with the increase of the distance of the surrounding tissue from the electrode, the temperature drops rapidly [6]. During killing tumors, the mechanical and biological functions of the diseased limbs can be reserved, and the inactivated tumor segment can be fully used for reconstruction, thus reducing the complications in

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traditional surgical treatments. Over the past 20 years, cryoablation, radiofrequency ablation, and radioactive particle implantation have made great progresses in treating BM [7–11]. Goetz, reports the radiofrequency ablation treatment of cancerous pain patients with bone metastases, can relieve pain and improve the quality of life, the worst pain in 95% of patients can alleviate at least two points [12]. Gong etc. under computed tomography (CT) guidance in 20 patients with malignant metastatic tumors of bone application of radiofrequency ablation treatment technology, after 6 months follow-up results showed that all the survival patients after treatment and effective pain relief [13]. However, most researchers only studied the effects of  $I^{125}$  or radiofrequency ablation alone against M-caused pain, while did not mention how to improve BM patients' quality of life and prolong their survival. So how to alleviate BM pain together with improving BM patients' quality of life at the same time has become a hot research spot. In order to investigate the clinical efficacy of  $I^{125}$  implantation combined with radiofrequency ablation in treating BM, a total of 63 BM patients treated in our department from July 2014 to June 2016 (30 patients with  $I^{125}$  implantation combined with radiofrequency ablation, and 33 patients with  $I^{125}$  implantation alone) were enrolled and compare the clinical treatment efficacy.

## 2. Materials and methods

### 2.1. General information

The 63 BM patients admitted to our department from July 2014 to June 2016 were randomly divided into Group  $I^{125}$ -MA (30 cases) and Group CON (33 patients). Inclusion criteria: (1) with a history of malignancy, and confirmed as malignant bone metastases by bone lesion imaging (X-ray, magnetic resonance imaging (MRI), computed tomography (CT), or PET-CT); or without a history of malignant tumor, but diagnosed as malignant bone metastases by bone biopsy or cytology; (2) more than 3-month expected survival period; (3) with general conditions, can accept surgery and anesthesia; (4) with pathological fractures or the risk of potential pathological fractures (Mirels score > 8); (5) cannot accept extensive resection or need long period for the recovery after extensive resection. Group  $I^{125}$ -MA included 16 males and 14 females, aging 35–76 years, with the median age as 62 years. Classified according to the primary lesions, Group  $I^{125}$ -MA contained 12 cases of lung cancer, 4 cases of gastric cancer, 5 cases of intestinal cancer, 7 cases of breast cancer, 1 case of renal cancer, and 1 case of thyroid cancer. Group CON included 17 males and 16 females, aging 28–78 years, with the median age as 65.5 years, and contained 13 cases of lung cancer, 3 cases of gastric cancer, 7 cases of intestinal cancer, 7 cases of breast cancer, 2 cases of renal cancer, and 1 case of thyroid cancer. There was no significant difference in the age, sex, primary lesion, pathologic type, and BM site between the two groups ( $P > 0.05$ ). This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Guangdong TCM-Integrated Hospital. Written informed consent was obtained from all participants.

### 2.2. Treatment

Local radiofrequency ablation treatment group patients first kill local tumor cells, radiofrequency ablation under intravenous anesthesia, intravenous diazepam before anesthesia 0.25 0.05 mg/kg + pethidine 0.51 mg/kg, the treatment process of giving oxygen, ecg monitoring, intraoperative monitoring heart rate, blood pressure, blood oxygen saturation and other vital signs. Radiofrequency electrode (HGCF zhuhaihokai medical instruments co-3000) on the patients with ham, two temperature monitoring electrodes placed on the ends of the earth on the front edge of melting (near location). Electrode is exposed to air, continuous monitoring of subcutaneous temperature. CT location scan according to the size of the lesions, place choose proper rf needle

electrodes and the puncture point. Local disinfection preparation, the marked place the needle electrode into skin, make the rf needle electrode tip percutaneous puncture to the part of soft tissue lesions, according to CT scan images of the adjust direction and depth of the rf needle electrodes, left in the position of the needle destruction of bone tissue 1 cm. After ablation, pull out the rf needle electrodes. After that, certain number of  $I^{125}$  particles (China Isotope & Radiation Co., Ltd.) were implanted under CT guidance, the particle number and distribution of which were determined by the TPS planning system so as to achieve the dose within the target zone (namely D90, dose applied in 90% target area) > prescription dose. The mean peripheral dose should be equal to PD, the dose uniformity index should be kept within 100–150% of PD, and the dose heterogeneity rate should be < 20% of PD. The  $I^{125}$  particles should completely distribute in the tumor cells while not in normal cells under the guidance of CT. Group CON was only performed CT-guided  $I^{125}$  particle implantation using the same method as Group  $I^{125}$ -MA. Group  $I^{125}$ -MA was totally implanted 12–56  $I^{125}$  seeds, with the median number of implanted particles as 35. Group CON was totally implanted 10–55  $I^{125}$  seeds, with the median number of implanted particles as 34. The patients in the two groups were closely monitored electrocardiogram (ECG), blood pressure, respiration, and other vital signs within postoperative 24 h, as well as performing conventional symptomatic treatment such as hemostasis and anti-inflammation (Fig. 1).

### 2.3. Observation index

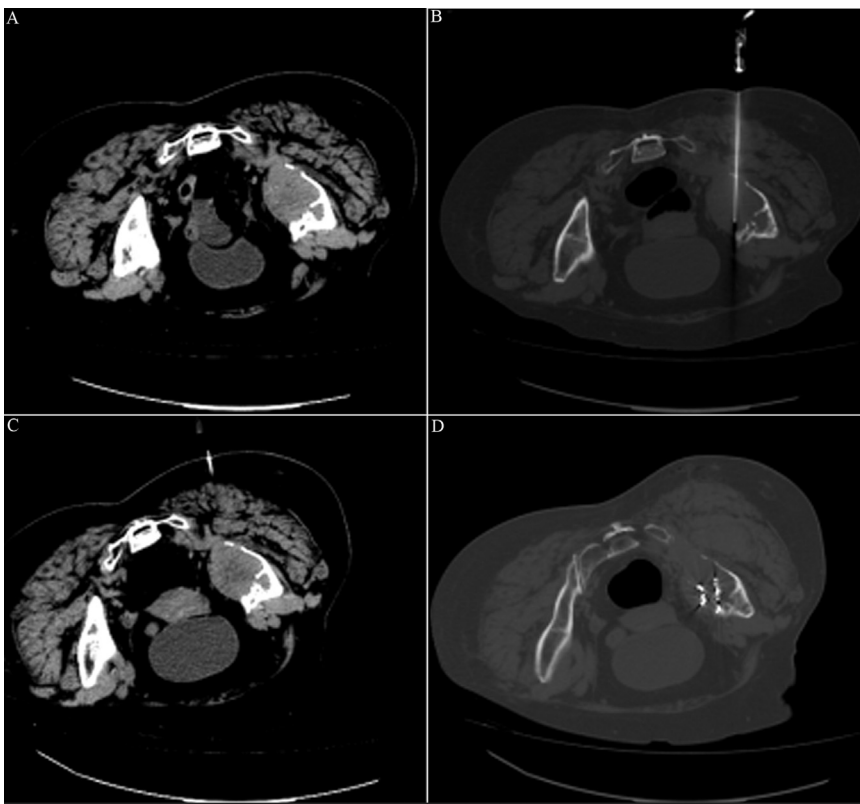
All the patients should be carefully observed postoperative adverse reactions and complications. Each group was also scored the pain every day after treatment, including the pain degree and onset time. CT/MRI was performed 1 week before treatment, as well as 2 weeks and 3 months after treatment; meanwhile, the patients' mobility, quality of life, and side effects were also evaluated.

### 2.4. Criteria of efficacy determination

① Bone pain: the patients' pain was divided into 4 grades according to the verbal rating scale (VRS) issued by WHO. Standards of pain relief: significantly effective, the pain was relieved by 2 grades or more; effective, the pain was relieved by 1 grade or more; invalid, the pain was reduced while restored to the original level in the treatment course, or the pain was not alleviated or aggravated. Significant effective + effective was calculated as the effective rate. ② Locomotor activity: grade 0: the patient can move freely; grade II: the patient's activity was limited; grade III: the treatment was completely inactive; evaluation criteria: significantly effective: the mobility was improved by 2 grades or more; effective: the mobility was improved by 1 grade or more; invalid: the mobility did not increase or decrease. ③ Quality of life: the patient was scored according to the Karnofsky rating criteria, significantly improved: the score was improved by 20 points; improved: the score was improved by 10 points; stable: the score was improved or reduced by less than 10 points; invalid: the mobility did not increase or decrease. ④ Side effects: the patient was assessed according to the toxicity grading standards issued by WHO. In addition, the conditions of such symptoms as particle displacement or edema/compression surrounding the implantation site were also observed and recorded.

### 2.5. Statistical analysis

SPSS17.0 software was used for the data processing. The comparison of the rate used the *t*-test, with  $P < 0.05$  considered statistical significance.



**Fig. 1.** It showed a female patients with lung cancer presenting with bone metastasis. (1) Pretreatment; (2) Radiofrequency ablation; (3) After radiofrequency ablation; (4) Implantation of  $I^{125}$  seeds.

### 3. Results

#### 3.1. Bone pain

① Group  $I^{125}$ -MA had 13 significantly effective cases, 10 effective cases, and 7 invalid cases, and the effective rate was 76.7%; Group CON had 7 significantly effective cases, 7 effective cases, and 19 invalid cases, and the effective rate was 42.4%. There was significant difference in the effective rate between the two groups ( $P < 0.05$ ). ② Locomotor activity: Group  $I^{125}$ -MA had 10 significantly effective cases, 12 effective cases, and 8 invalid cases, and the effective rate was 73.3%; Group CON had 6 significantly effective cases, 7 effective cases, and 20 invalid cases, and the effective rate was 39.4%. There was significant difference in the locomotor activity between the two groups ( $P < 0.05$ ). ③ Quality of life: Group  $I^{125}$ -MA had 11 significantly improved cases, 10 improved cases, 8 stable cases, and 1 invalid case, and the improvement rate was 70%; Group CON had 6 significantly improved cases, 8 improved cases, 11 stable cases, and 8 invalid cases, and the improvement rate was 42.4%. There was significant difference in the improvement rate between the two groups ( $P < 0.05$ ). ④ Onset time of analgesic effects: the median onset time of analgesia in Group  $I^{125}$ -MA was 3.5 days and 7.6 days in Group CON, and the difference was statistically significant ( $P < 0.05$ ).

#### 3.2. Side effects

The two groups both showed significant adverse reactions.

### 4. Discussion

The incidence of BM is 35–40 times than that of primary malignant bone tumors. Survey data have shown that among advanced cancer patients, about 70% will occur bone metastases, and about 1.6 million patients globally occur BM each year. BM is one of the main causes of cancer pain, can cause pathologic fracture, spinal cord compression,

hypercalcemia, or bone marrow failure, and accelerate disease development, thus seriously affecting patients' quality of life. Treating BM has exhibited exact effects in relieving cancer pain, improving quality of life, or even extending the survival period. However, early diagnosis of BM is difficult, and most patients can only be clinically confirmed in late stages when the pain is unbearable; however, they will lose the best time of surgical treatment, so how to improve the therapeutic effects of BM and patients' quality of life has become an important issue in clinical medicine. BM severely affects cancer patients' quality of life [14], increases the cost of medical care, and shortens patients' survival period [2,3,15]. Radiation therapy is the standard treatment for BM pain, with a pain response rate as over 60% [16–19]. Although the analgesic effects of radiotherapy are better, it can not significantly improve patients' survival and quality of life, or other aspects [20]. Common radiotherapy uses external irradiation, which often increases patients' pain, such as causing pathological fractures or local edema, due to frequently moving patients. As an independent treatment, the implantation of  $I^{125}$  radioactive particles in patients has been widely used in prostate cancer. In recent years, the CT-guided one-time  $I^{125}$  radioactive particle implantation can be accurately directed into tumor lesions, so that patients can benefit with one one-time implantation. Our department innovatively applied radiofrequency ablation combined with  $I^{125}$  implantation in the treatment of BM, and no similar report has been found in domestic and international research recently.

In this study,  $I^{125}$  radioactive particle implantation combined with radiofrequency ablation was applied to treat BM, and the results showed that the analgesic effective rate was 76.7%. Furthermore, the patients' mobility and quality of life were significantly improved, exhibiting statistical difference than group CON, consistent with the clinical treatment results of Rosenthal and Xiang [7,10] who applied  $I^{125}$  particle implantation alone to treat BM and reduce the patients' pain caused by invasive surgery. The median onset time of analgesia was 3.5 days, significantly earlier than Group CON. No serious adverse reaction occurred in Group  $I^{125}$ -MA during the treatment course, so the treatment was not affected. Tumor tissue contains more liquid, so it can

**Table 1**  
General Information [n(%)].

Items	Total	Group CON	Group I <sup>125</sup> -MA
Gender			
Male	37(58.7)	17(51.5)	16(53.3)
Female	26(41.3)	16(48.5)	14(46.7)
Age			
< 50ys	20(31.7)	11(33.3)	9(30.0)
> 50ys	43(68.3)	22(66.7)	21(70.0)
Primary tumor			
Lung cancer	25(39.7)	13(39.4)	12(40.0)
Gastric cancer	7(11.1)	3(9.1)	4(13.4)
Colon cancer	12(19.0)	7(21.2)	5(16.7)
Breast cancer	14(22.2)	7(21.2)	7(23.3)
Renal carcinoma	3(4.8)	2(6.1)	1(3.3)
Thyroid carcinoma	2(3.2)	1(3.0)	1(3.3)
Focal distribution			
Lung cancer	40(42.1)	19(38.0)	21(46.7)
Gastric cancer	9(9.5)	5(10.0)	4(8.9)
Colon cancer	14(14.7)	8(16.0)	6(13.3)
Breast cancer	24(25.3)	13(26.0)	11(24.5)
Renal carcinoma	5(5.3)	3(6.0)	2(4.4)
Thyroid carcinoma	3(3.1)	2(4.0)	1(2.2)

be heated to 60–100 °C in a short time, thus resulting in coagulation and necrosis of tumor cells. Although the radiation energy caused by the subsequently implanted I<sup>125</sup> radioactive particles is not large, it can continue to act on tumor cells and damage the tumor stem cells continuously; therefore, after sufficient dose and half-life, all tumor cells will lose their reproductivity, so that bone pain can be relieved, bone substances can be slowly reconstructed, and the patients' activity and quality of life can be improved.

In summary, I<sup>125</sup> particle implantation combined with radiofrequency ablation against bone metastases can significantly reduce patients' pain, prevent the occurrence of bone pain and fracture, and improve patients' quality of life with rapid onset and less toxic side effects, so it's worthy of further clinical promotions.

However, there still exist shortcomings in our study: the case size is small, and the follow-up time is short, so we need to further extend the sample size and prolong the follow-up time. Whether I<sup>125</sup> implantation combined with radiofrequency ablation can significantly prolong patients' survival still needs further confirmation (Table 1).

## Conflicts of interest

The authors declare no conflict of interest.

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