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Efficacy and safety of iodine-125 particle implantation for treatment of bone metastatic tumor pain: a retrospective analysis

Y. FEI, B. HUANG, L.-S. XU, M. YAO

Department of Anesthesiology and Pain Medicine, The Affiliated Hospital of Jiaxing University, Jiaxing, China

Abstract. – OBJECTIVE: Patients with advanced tumors often suffer from spinal metastatic tumor pain. The current drugs are less effective and have side effects. The objective was to explore the efficacy of iodine-125 particle implantation in the treatment of bone metastatic tumor pain.

PATIENTS AND METHODS: In a retrospective study, a total of 27 patients with bone metastatic tumors who could not receive surgery or radiotherapy and chemotherapy were analyzed. All patients received conventional treatment, with the visual analog scale (VAS) of >3 points, and the daily onset pain of >3 times. All patients received CT-guided iodine-125 particle implantation to treat local painful lesions. VAS scores were recorded before treatment (T0) and 1 day (T1), 7 days (T2), 30 days (T3), 90 days (T4), and 180 days (T5) after treatment. Kaplan-Meier analytical method was used to calculate the local control rate (LCR) and survival rate (SR).

RESULTS: All patients successfully completed the CT-guided iodine-125 particle implantation. There was no significant difference in VAS scores before and 1 day after surgery. However, compared with pre-operation, the VAS scores decreased at 7, 30, 90, and 180 days after surgery. The postoperative follow-up was 6-38 months, with a median of 16 months; the LCR at 1, 2, and 3 years after the follow-up were 87%, 51%, and 21%, respectively, and the SR was 84%, 43%, and 16%, respectively. Moreover, no serious adverse reactions were observed.

CONCLUSIONS: Iodine-125 particle implantation was effective in the treatment of bone metastatic tumor pain without serious complications, and hence, can be used clinically.

Key Words:
Iodine-125 particle, Implantation, Cancer pain, Retrospective analysis.

Introduction

Malignant tumors are a major threat to human health. Advanced cancer pain is a common symptom in these patients, and it is also a critical factor affecting their quality of life (QOL) and physical and mental health[1,2]. As one of the effects of advanced cancer, the incidence of bone metastases is increasing annually with the increase in the incidence of primary tumors. The underlying pathogenesis is that the tumor causes bone instability and compression. Presently, the three-step conventional therapies are less effective, and the administration of high dose of opioids can cause side effects such as nausea, vomiting, urinary retention, and constipation, which greatly reduce the QOL of patients[3,4]. Therefore, developing new technologies for the treatment of bone metastatic tumor pain is imminent.

^{125}I particles are widely used in the treatment of malignant tumors and cancer pain because of their precise positioning, optimal tumor shape, high local target dose, low extra-tumor dose, long duration of action, fewer complications, and good patient tolerance and have achieved satisfactory therapeutic effect[5-7]. Whether iodine-125 (^{125}I) particle implantation can effectively alleviate the cancer pain of patients with bone metastasis has not been reported. Thus, this study aimed to investigate the effectiveness and safety of ^{125}I particle implantation in the treatment of bone metastatic tumor pain, and to provide a reference for clinical practice.

Patients and Methods

This study was approved by the Ethics Committee of the First Hospital of Jiaxing, and it was conducted in accordance with the Declaration of Helsinki. All patients signed written informed consent. Twenty-seven patients with bone metastases who were unable to undergo excision or radiotherapy and chemotherapy in the Pain Department of the First Hospital of Jiaxing from March 2015 to November 2017 were selected as the research objects in this study. The patient's visual analog scale (VAS) was ≥7 points on admission. The cohort consisted of 18 males and 9 females aged 44-83

Corresponding Authors: Longsheng Xu, MD; e-mail: xlsh2468@163.com; Ming Yao, MD; e-mail: jxyaoming666@163.com

Table I. The tumor characteristics of all patients.

Primary tumor	n	Metastasis site	n	Pathologically	n
lung cancer	9	chest wall and rib	9	adenocarcinoma	14
liver cancer	8	atlas shift	7	squamous cell carcinoma	3
prostate cancer	3	lumbar spine metastasis	3	hepatocellular carcinoma	8
rectal cancer	3	cervical spine	3	clear cell carcinoma	2
renal cancer	2	humeral	5		
thyroid cancer	1				
breast cancer	1				

(mean age 69±10) years old. The tumor characteristics of all patients are listed in Table I. Of these, 17 patients displayed the status after resection of the primary tumors, 24 patients had previously received systemic chemotherapy, and 22 patients were receiving external radiotherapy. All patients had bone metastases after surgery and/or after radiotherapy and chemotherapy, which were not suitable for reoperation or radiotherapy and chemotherapy as assessed by the orthopedists, surgeons, and oncologists. The pain was mainly limited to bone metastases, and the estimated survival time of all patients in this group was > 6 months.

After admission, all patients received standardized titration treatment for cancer pain. The main drugs included morphine hydrochloride sustained-release tablets, oxycodone hydrochloride sustained-release tablets, morphine sulfate sustained-release tablets, morphine hydrochloride injection, or fentanyl transdermal patches, supplemented by combination drugs, including non-steroidal anti-inflammatory analgesics, weak opioids, and amitriptyline hydrochloride. Furthermore, medications such as metoclopramide and Cistanche oral liquid were given to symptomatically treat adverse reactions. The method and standard of the titration treatment were as described previously[8]. All patients in this group did not meet the criteria for the standardized titration treatment for cancer pain, and the number of daily pain episodes was more than 3 times and the VAS was more than 3 points. After assessing the degree of tolerance and determining that there was no contraindication to puncture, the patient was subjected to computer tomography-guided (CT-guided) ^{125}I particle implantation. Before operation, CT scan was performed on the puncture target area. The scanning parameters of the single-slice CT machine were slice thickness 2 mm, tube voltage 110 kV, and tube current 200 mA. The information of the scanned image was transmitted into the treatment planning system (Beijing Feitian Zhaoye Ltd, China) where the radioactive particle source implantation was performed. Subsequently, preoperative planning of the responsible lesions was carried out to delimit the clinical target volume (CTV) and planning target volume (PTV) of the tumor; PTV was the 0.5-1.0 cm of the CTV external expansion. The matched dose around the tumor was 90-120 Gy. According to the preoperative plan and the actual situation during the operation, as well as the shape and adjacent structures of the tumor, the parallel or fan-shaped needle arranging method was used. In addition, a 15-cm-length and 18G particle puncture needle (Japan HAKKO Co., Ltd) was used to puncture along the axis of the tumor. The space was 1 cm, and the spacing of each row of particles (Seeds Biological Pharmacy, Tianjin, China) was 1 cm and the activity was 0.6-0.7 mCi. The particle implantation gun and push rod (Beijing Feitian Zhaoye Ltd, Beijing, China) were used for implantation. The distance between particles and the organ sensitive to the radiotherapy was >1 cm. CT scanned the target lesions immediately after the operation, and images were transmitted into the treatment planning system (TPS) of radioactive particle source implantation for quality verification. If there was a cold dose area, re-implantation was appropriate.

Pain Management Evaluation

According to the VAS score, the evaluation and comparative analysis were conducted regarding the pain intensity before operation (T0) and 1 (T1), 7 (T2), 30 (T3), 90 (T4), and 180 days (T5) after the operation. Efficacy evaluation: According to the WHO evaluation criteria in solid tumors, the efficacy was divided into complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). The local effective rate was estimated based on the proportion of CR and PR. According to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC), the complications after ^{125}I particle implantation were evaluated.

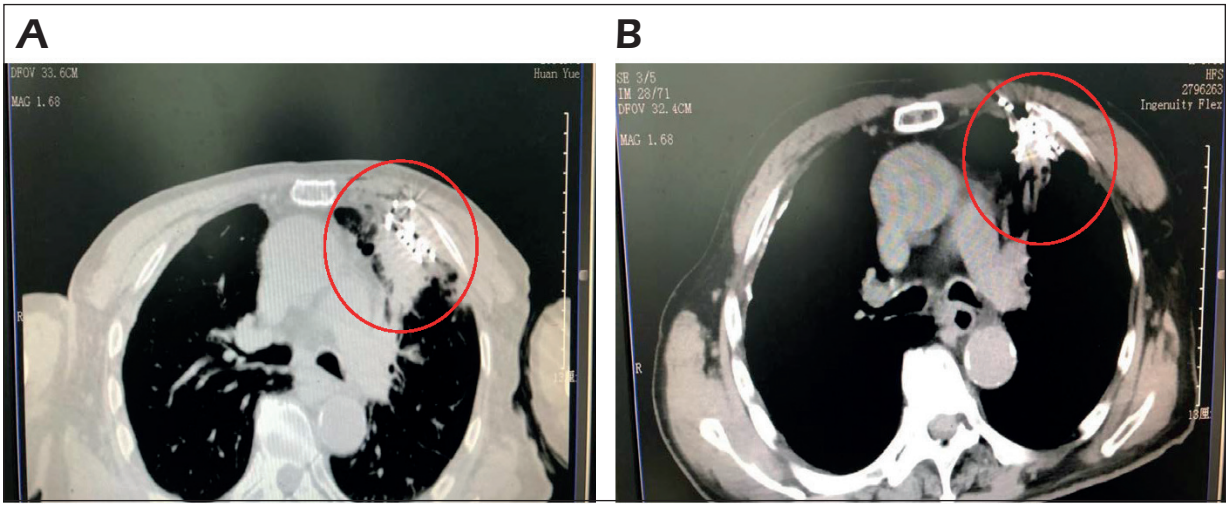

Figure 1. Results showed an elderly male patient with lung cancer showing rib metastasis. **A**, Implantation of ^{125}I seeds. **B**, Three months after ^{125}I particle implantation, the tumor was significantly reduced, and the pain was effectively controlled. The red circles indicated the location of the tumor.

Statistical Analysis

Statistical analyses were performed using SPSS software, version 19.0 (IBM, Armonk, NY, USA). The Kaplan-Meier analytical method was used to calculate local control rate (LCR) and Survival rate (SR). LCR = sum of CR and PR/the total cases × 100%. SR is the percentage of patients who survived during follow-up. VAS scores were expressed as the means ± standard error of mean and were analyzed using one-way analysis of variance (ANOVA). A *p*-value of <0.05 was considered statistically significant.

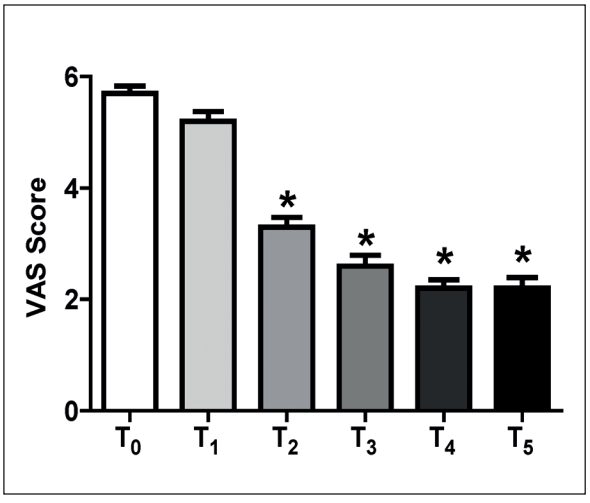

Figure 2. VAS score was tested before operation (T0) and on days 1 (T1), 7 (T2), 30 (T3), 90 (T4), and 180 (T5) after the operation. All data are expressed as mean ± standard error of the mean. n=27, * p <0.05 compared to the T0 group.

Results

All patients successfully completed the particle implantation, and the particles were evenly distributed along the long axis of the tumor. The CT image showed a significant reduction in tumors after 3 months (Figure 1). The number of implanted ^{125}I particles was 27-119 (median, 53), the particle spacing was 0.5-1.0 cm, the range of particle activity was 0.6-0.7 mCi, and the range of minimum peripheral dose (MPD) verified after the operation was 90-145 (median, 120) Gy.

The pain improvement of patients is shown in Figure 2. Moreover, the VAS scores before and one day after surgery were not statistically significant (p >0.05). Compared to the pre-operation, VAS scores decreased significantly at 7, 30, 90, and 180 days after surgery (all p <0.05).

The postoperative follow-up period was 6-38 (median, 16) months. No case was lost to follow-up, 6 cases of CR, 8 cases of PR, 9 cases of SD, and 4 cases of PD. The local effective rate was 52%. The cohort included 9 survivors and 18 deaths, of these, 10 died of multiple organ failure, 7 died of cachexia, and 1 died of sepsis. Kaplan-Meier analysis was used to calculate the LCR at 1, 2, and 3 years after follow-up, which was 87%, 51%, and 21%, respectively, and SR was 84%, 43%, and 16%, respectively (Figure 3).

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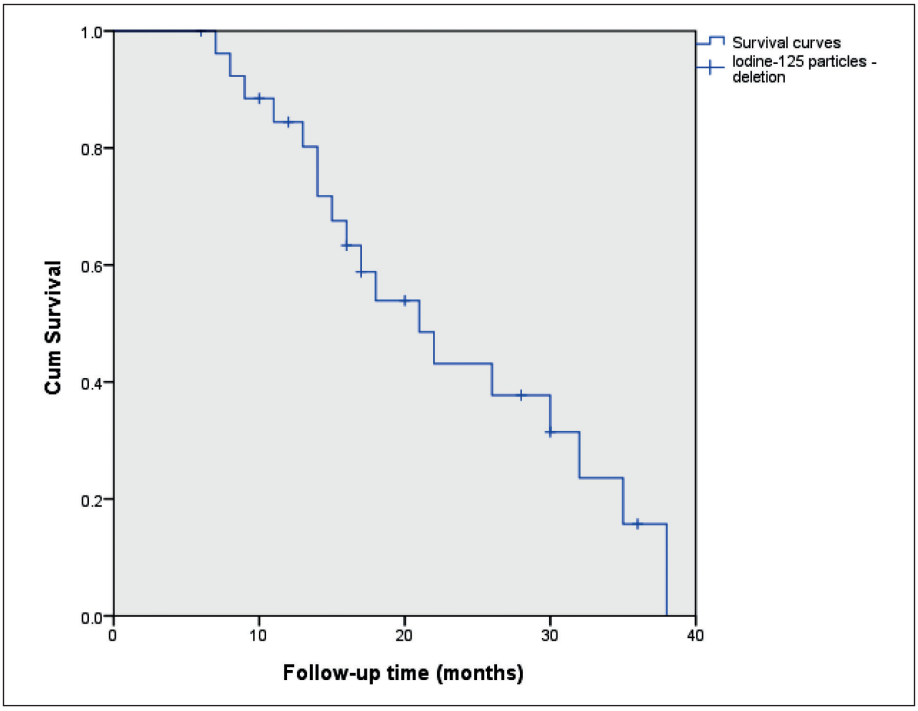

Figure 3. The survival curve of patients undergoing ^{125}I particle implantation. LCR for patients 1, 2, and 3 years after the operation was 87%, 51%, and 21%, respectively, and the survival rate (SR) at 1, 2, and 3 years after operation was 84%, 43%, and 16%, respectively.

late LCR 1, 2, and 3 years after follow-up, which were 87%, 51%, and 21%, respectively, and SR was 84%, 43%, and 16%, respectively (Figure 3).

In addition, blood pneumothorax, large vascular rupture, embolism, osteonecrosis of radiation, myelitis, and severe bone marrow suppression were not observed in the 27 patients treated in this study. Three patients developed fever on the first day after surgery, which improved after symptomatic treatment, and one patient developed advanced radiation pneumonia, which was also improved.

Discussion

The treatment methods for bone metastases mainly include surgery, chemotherapy, and external radiotherapy[9]. However, for bone metastatic tumors, surgery is often inappropriate, and patients cannot withstand such major surgery, which may lead to poor efficacy[10]. In addition, due to the low tolerance of the spinal cord to radiation doses, an increase in the dose of external radiotherapy may lead to serious complications, such as radiation myelitis[11]. Therefore, the application of external radiotherapy in spinal metastatic tumors is limited[12]. ^{125}I particle implantation to treat tumors is to kill tumors by brachytherapy. The principle of "high dose in local target area and low dose in outside tumor" is applied to the treatment of spinal metastases, and satisfactory therapeutic effects have been achieved. Wang et al[13] reported that 19 patients with spinal metastatic tumors underwent ^{125}I particle implantation. The LCR of the patients at 1, 2, 3, and 5 years after the operation was 63%, 47%, 31%, and 3%, and the SR was 74%, 56%, 43%, and 43%, respectively. The 27 patients treated in this study had LCRs of 87%, 51%, and 21, respectively, and SRs of 84%, 43%, and 16%, respectively, at 1, 2, and 3 years after surgery. In this study, the precise puncture guided by CT ensured the conformal distribution of particles in the tumor. Preoperative TPS design and immediate postoperative dose verification can avoid the cold dose area, thereby improving the efficacy.

The current study results did not show a significant difference in VAS scores before and after 24 h of the operation, which may be related to the swelling and pain of the puncture site after surgery. The VAS scores at 7, 30, 90, and 180 days after surgery were lower than those before surgery, indicating that the ^{125}I particle internal irradiation

rapid treatment of bone metastatic tumor pain has a fast and long-lasting effect. These results were consistent with the findings of Song et al[14]. One patient developed advanced radiation pneumonia (Grade I) 3 months after the operation, accompanied by an irritable dry cough. No fever was seen, and the patient was recovered after 6 weeks of adrenal cortical hormone treatment. There was no acute or chronic radiation pneumonia (above Grade I). Surprisingly, 3 patients developed fever after the operation with a body temperature of <38.5°C, which improved after symptomatic treatment. Furthermore, none of the 27 patients in this group had hemopneumothorax, large vascular rupture, embolism, osteoradionecrosis, radiation myelitis, and severe myelosuppression, suggesting that CT-guided ^{125}I particle implantation is conducive to an accurate target puncture with high safety, effectively avoiding severe complications during surgery.

The subjects of this study were patients with bone metastatic tumor pain who were in poor general conditions and could not tolerate surgery, chemotherapy, and external radiotherapy. Moreover, they experienced severe pain, poor efficacy after long-term oral administration of high dose of opioids and severe gastrointestinal side effects caused by the drugs. Therefore, this study proposed the indications for ^{125}I particle to treat bone metastatic tumor pain as follows: (1) Patients with distant metastases of malignant tumors, who had severe symptoms due to local lesions. (2) Patients whose poor general condition was poor and cannot tolerate surgery, chemotherapy, and external radiotherapy. (3) Patients with severe pain, poor analgesic effect after oral opioids, and intolerable adverse reactions such as nausea, vomiting, and excretion dysfunction. (4) Patients with expected survival time > 6 months.

Since the follow-up time of the current small-sample study is 6-38 months, a large sample study and long-term follow-up are needed to confirm the efficacy of ^{125}I particle in the treatment of bone metastatic tumor pain. Owing to different shape and location of the tumor, the precise puncture guided by CT cannot exclude the cold dose area. Thus, when conditions permit, non-coplanar template 3D printing technology can effectively reduce the occurrence of the cold dose area and improve the efficacy, and effectively avoiding errors[15]. In addition, the half-life of ^{125}I particle is 59 days, and the duration of its efficacy is about 1 year. Nevertheless, radiological protection should be manifested as required during implantation and this process[16].

Conclusions

The current results indicated that ^{125}I particle implantation can effectively alleviate the pain of patients, improve the quality of life of patients, and enable them to live with more dignity for the rest of the time, which will undoubtedly bring social benefits.

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Data Availability

The data used to support the findings of this study are included in the article. For other data-related requests, please contact the author.

Author Contributions

All authors contributed toward data analysis, drafting, and critically revising the paper, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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