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INTERVENTIONAL RADIOLOGY

ORIGINAL ARTICLE

Palliative local treatment of bone metastases by ^{125}I seed brachytherapy under DynaCT guidance: single-center experience

Yuan Yao
Zhaonan Li
Dechao Jiao
Xueliang Zhou
Jing Li
Xinwei Han

PURPOSE
We aimed to evaluate the clinical benefit of ^{125}I seed brachytherapy under DynaCT guidance for palliative local treatment of bone metastases.

METHODS
From December 2014 to September 2017, 82 patients with painful bone metastases, who experienced treatment failure using standard strategies or rejected treatment were enrolled in this retrospective study. All patients underwent ^{125}I seed brachytherapy under DynaCT guidance. Technical success, visual analogue scale (VAS), numerical rating scale (NRS), verbal rating scale (VRS), Karnofsky performance status (KPS) and complications were analyzed.

RESULTS
The success rate of ^{125}I seed implantation was 100%. The VAS and NRS scores for the most severe pain were 7.0 (5.0–9.0) and 8.0 (6.0–9.0) before brachytherapy. The pain scores assessed every 2 hours gradually decreased within 12 hours ($p < 0.001$). A comparison of KPS scores showed that patients had significantly better quality of life on weeks 1, 4, and 8 than on week 0 ($p < 0.001$). The associated complications were mild subcutaneous hemorrhage 25.6% (21/82), fever 7.3% (6/82), minor displacement of radioactive seeds 5.0% (4/82), pathologic fracture 2.4% (2/82), and local skin reaction 2.4% (2/82). After symptomatic treatment, all complications were relieved. Minor displacement of radioactive seeds did not cause damage to adjacent tissues. No serious life-threatening complications occurred in the study group.

CONCLUSION
DynaCT-guided ^{125}I seed implantation is a safe and effective method for palliation of painful bone metastases from cancer after failure or rejection of conventional treatments.

Bone metastasis is a common problem in patients with advanced cancer, which is detrimental to their quality of life (1, 2). The incidence of bone metastasis and metastatic sites varies significantly depending on the primary tumor (3). It is estimated that about 50% or more cancer patients will have bone metastasis (4, 5). In fact, patients with bone metastases still suffer from poorly controlled pain during the treatment or progression of the disease, which can seriously affect diet, sleep, emotion, and daily activities (6). Therefore, the most important task of advanced cancer treatment is not only to improve survival rate, but also to relieve pain and improve the quality of life.

Palliative radiation therapy combined with analgesia is the standard treatment of painful bone metastasis (7, 8). Although external beam radiotherapy (EBRT) is an important method to relieve bone pain, it remains ineffective in 30% of patients, while nearly 50% of patients have recurrent pain after EBRT (9–11). Furthermore, due to previous EBRT treatment, patients with bone metastases (particularly spine metastases) may have reached the value of dose tolerance, limiting their treatment options. As an alternative to EBRT, percutaneous iodine-125 (^{125}I) seed brachytherapy may resolve this issue by providing a high dose of radiation straight to the tumor target, while reducing the effects on adjacent normal tissues (12). This study focused on the safety and efficacy of DynaCT-guided ^{125}I seed brachytherapy for bone metastases at different sites.

From the Department of Interventional Radiology (X.H. ✉ *13592583911@163.com*), First Affiliated Hospital of Zhengzhou University, Zhengzhou, China.

*Yuan Yao and Zhaonan Li contributed equally to this work.

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Methods

Patients

The characteristics of patients were delineated in Table 1. We retrospectively reviewed 82 patients who were treated in our institution between December 2014 and September 2017. A majority of patients received EBRT or chemotherapy prior to treatment, which did not relieve pain prior to enrollment in the study. The total number of seeds implanted was 2629, with an average of 32.0±20 per lesion. The heart, liver, kidney and blood function indicators of all patients were in the normal range with no signs of infection. This study was approved by the local institutional review board. The patients enrolled in this retrospective study met the following criteria: histologically or cytologically confirmed bone metastasis of the tumor; pain scores ≥4 in the past 24 hours according to visual analogue scale; conventional treatment failure or rejection of treatment (radiation therapy, chemotherapy, surgical resection and/or painkillers); expected survival time ≥3 months; ability to tolerate ^{125}I brachytherapy.

^{125}I seeds

The ^{125}I seeds (Said Biopharmaceutical Co. Ltd.) were configured in a cylindrical brachytherapy source encapsulated by titanium. The size of each titanium capsule was 0.8×4.5 mm. The measured emissions were low energy (35.5 keV γ) with a half-life of 59.6 days. The measured radioactivity of each seed was 0.72–0.81 mCi. The ^{125}I seeds have the most effective anti-tumor activity at a radius of 1.7 cm.

Main points

- Palliative radiation therapy combined with analgesia is the standard for the treatment of painful bone metastasis.
- As an alternative to external beam radiotherapy, percutaneous iodine-125 (^{125}I) seed brachytherapy may provide a high dose of radiation straight to the tumor target, minimizing the effects on adjacent normal tissues.
- The DynaCT workstation interface was used to adjust the width and location of the window to clearly display the lesion.
- DynaCT-guided ^{125}I seeds brachytherapy is an effective way to treat bone metastases. CT guidance may help expand the use of this therapy in primary bone tumors.

^{125}I-seed implant brachytherapy

Prior to ^{125}I seed brachytherapy, all patients obtained a tomographic image (C-arm CT guidance) of the corresponding layer of the tumor and measured the volume. Then, the Brachytherapy Treatment Planning System (TPS) (Beijing Atomic & High-Tech Industry Co., Ltd.) was used to design the implant. The target volume of the prescribed dose of the lesion is covered with a safety margin of 0.5–1 cm. Finally, in order to verify the position and intensity of the ^{125}I seeds, the last scanned image was reviewed according to TPS. If the lesion exhibited insufficient radioactivity, the process was repeated for implantation of additional ^{125}I seeds. (Figs. 1–3). Treatment information of bone metastasis in different parts was noted.

Patient evaluation after treatment

For each patient, the actuarial D90 (90% of the planned target volume) was greater than the prescribed dose, ranging from 101 to 145 Gy (mean, 126 Gy). Each patient's V100 (percentage of planned target volume receiving at least 100% of the prescribed dose) was more than 95%. Patients were assessed for pain severity using visual analogue scale (VAS: 0–3, mild pain; 4–6, moderate pain; 7–10 severe pain), numerical rating scale (NRS: scoring criteria similar to VAS), and verbal rating scale (VRS: level 1, mild pain; level 2, moderate pain; level 3, severe pain). Pain scores were recorded every 2 hours within 12 hours of treatment, and the quality of life was assessed by Karnofsky performance status (KPS) score before and 1 week, 4 weeks, 8 weeks after the procedure. Contrast-enhanced CT and laboratory tests (coagulation profile, platelet count, s-hemoglobin, WBC, RBC) were performed every two weeks for the first two months, and monthly afterwards.

Statistical analysis

The statistical package SPSS version 20.0 was used for statistical analysis. The effectiveness of brachytherapy was assessed by comparing VAS, NRS, and VRS within 12 hours of treatment and recent quality of life (KPS score) within 2 months. The percentage of recent complications after treatment was evaluated. Comparison of before and after treatment VAS and NRS scores were performed by nonparametric test (Wilcoxon test). KPS scores between baseline and other times were analyzed by paired t test, Kruskal-Wallis was used for the comparison of VRS (categorical data). $p < 0.05$ was considered statistically significant.

Results

There were 43 males and 39 females (age range, 34–75 years, mean age, 57.2±18.6 years). Primary tumors were mainly in the lung (30.5%, 25/82), prostate (25.6%, 21/82), liver (15.9%, 13/82), breast (13.4%, 11/82), colon/rectum (6.1%, 5/82), kidney (2.4%, 2/82), and others (6.1%, 5/82). The main sites of tumor metastasis were ver-

Table 1. Characteristics of patients

Characteristics	Value
Patients (female/male)	39/43
Age (years), mean±SD	57.2±18.6
KPS score, mean±SD	69±4.3
Previous treatment	
EBRT	45 (54.9)
Chemotherapy	67 (81.7)
EBRT and chemotherapy	39 (47.6)
Opioid analgesics	22 (26.8)
Primary cancer site	
Lung	25 (30.5)
Prostate	21 (25.6)
Liver	13 (15.9)
Breast	11 (13.4)
Colon/rectum	5 (6.1)
Kidney	2 (2.4)
Other	5 (6.1)
Sites of painful bone lesion	
Vertebrae	43 (52.4)
Rib/sternum	39 (47.6)
Pelvis	21 (25.6)
Sacrum	17 (20.7)
Scapula	12 (14.6)
Extremity	11 (13.4)
Clavicle	6 (7.3)
Type of bone metastases	
Osteolytic	35 (42.7)
Osteoplastic	29 (35.3)
Mixed	18 (22.0)
Total number of ^{125}I seed implantation	2629
Mean±SD	32.0±20

Data are presented as frequency (percentage) or mean ± SD.
SD, standard deviation; KPS, Karnofsky performance status; EBRT, external beam radiation therapy.

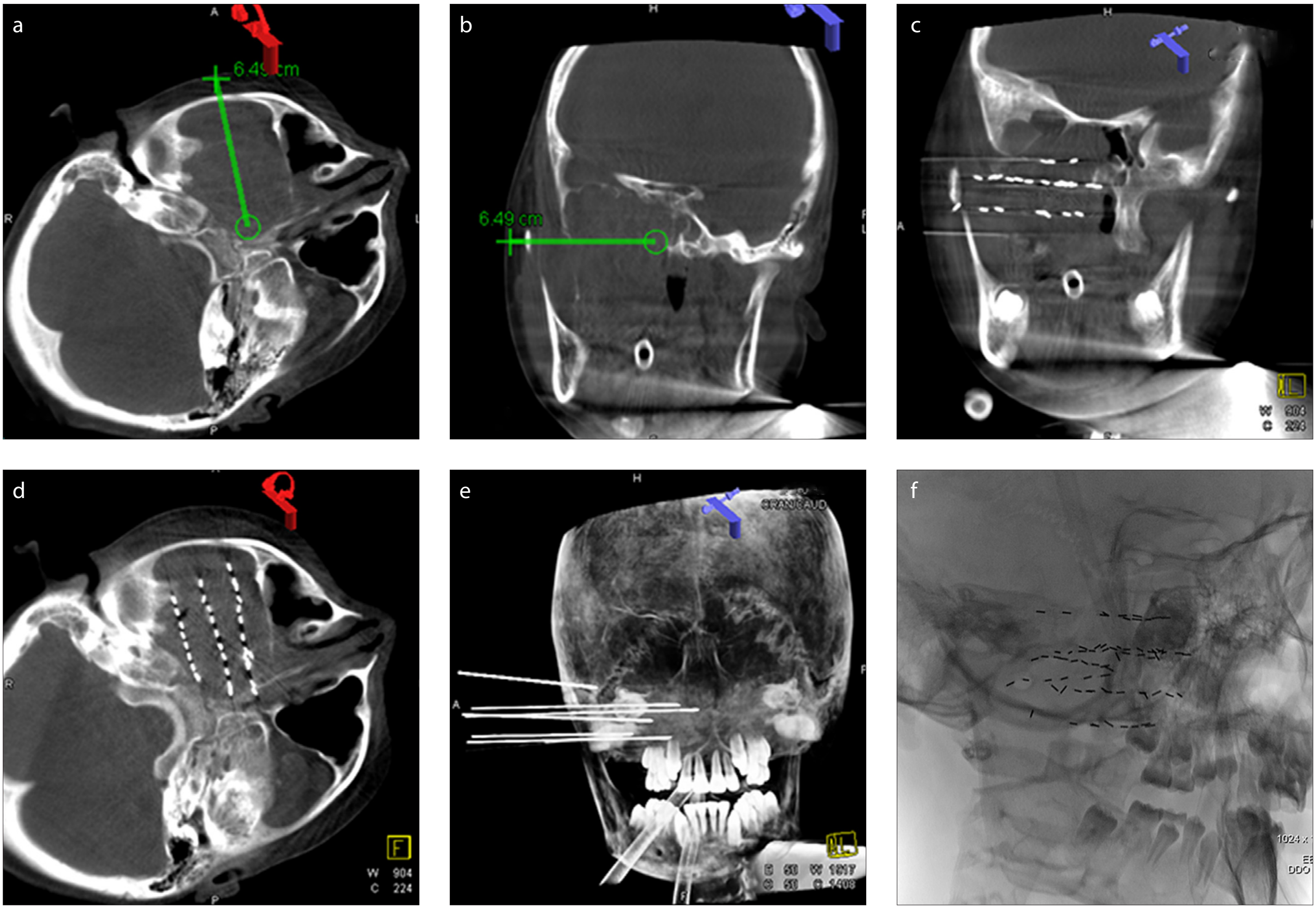

Figure 1. a–f. Axial **(a)** and sagittal **(b)** DynaCT images show a 54-year-old male lung cancer patient presenting with skull metastasis. The treatment was carried out under general anesthesia. After brachytherapy treatment planning system (TPS) was used to formulate the treatment plan, implantation of the ^{125}I seeds **(c–e)** was completed based on the prepuncture path provided by DynaCT. Digital radiography **(f)** image confirms that the ^{125}I seeds have been successfully placed at the specified location. The visual analogue scale (VAS) pain scores of patients before and 12 hours after ^{125}I seed brachytherapy were 8 points and 3 points respectively, and the pain was significantly relieved.

tebrae (52.4%, 43/82), rib/sternum (47.6%, 39/82), pelvis (25.6%, 21/82), sacrum (20.7%, 17/82), scapula (14.6%, 12/82), extremity (13.4%, 11/82), and clavicle (7.3%, 6/82). The types of bone metastases were osteolytic in 35 patients (42.7%), osteoplastic in 29 (35.3%), and mixed in 18 (22.0%), respectively. The success rate of the treatment was 100%.

No patients were lost to follow-up during treatment. A total of 2629 ^{125}I seeds were implanted (mean±SD, 32.0±20). Fig. 4a summarizes the effectiveness of pain relief. Analysis of the results of VAS and NRS showed significant differences between pain scores at different times ($p < 0.001$). The VAS score for the most severe pain was 7.0 (5.0–9.0) before brachytherapy. At 2, 4, 6, 8, 10, and 12 hours after the procedure the VAS scores decreased to 6.0 (4.0–9.0), 4.5 (2.0–8.0), 4.0 (2.0–7.0), 4.0 (2.0–7.0), 3.0 (2.0–6.0) and 3.0 (1.0–6.0), respectively. Similarly, The NRS score for the most severe pain was 8 (6.0–9.0) before brachytherapy. At 2, 4, 6, 8, 10, and 12 hours after the procedure the NRS scores decreased to 7.0 (5.0–9.0), 6.0 (4.0–7.0), 5 (3.0–8.0), 4.0 (3.0–6.0), 4.0 (3.0–6.0) and 4.0 (2.0–5.0), respectively. Similarly, the pain level measured with VRS gradually decreased compared with the condition before treatment ($p < 0.001$) (Fig. 4b).

KPS scores revealed that patients had significantly better quality of life at 1, 4, and 8 weeks after the procedure compared with pretreatment ($p < 0.001$) (Fig. 4c). The KPS scores on weeks 0, 1, 4, and 8 were 69.0±4.3, 74.9±4.7, 77±5.8, and 79.0±3.7, respectively.

According to response evaluation criteria in solid tumors (RECIST), all patients were stable on CT or PET-CT imaging after 2 months of ^{125}I seed brachytherapy, and the range of tumor necrosis gradually increased during follow-up. At 2-month follow-up, no case of complete response was seen, while 70 had partial response (85.4%), 12 stable disease (14.6%), and 0 progressive disease (0%), with a clinical benefit rate of 100%. Several procedure-related complications occurred during or after brachytherapy, namely, mild subcutaneous hemorrhage (25.6%, 21/82), fever (7.3%, 6/82), minor displacement of radioactive seeds (5.0%, 4/82), pathologic fracture (2.4%, 2/82), and local skin reaction (2.4%, 2/82) (Table 2). After symptomatic treatment, all complications were relieved. Follow-up images showed that 4 patients (5.0%) had minor displacement of radioactive seeds, but the displacement did not cause damage to adjacent tissues. No serious life-threatening complications were found throughout the study group.

Discussion

Bone metastasis is the most common source of cancer-related pain, which greatly affects the quality of life of patients with

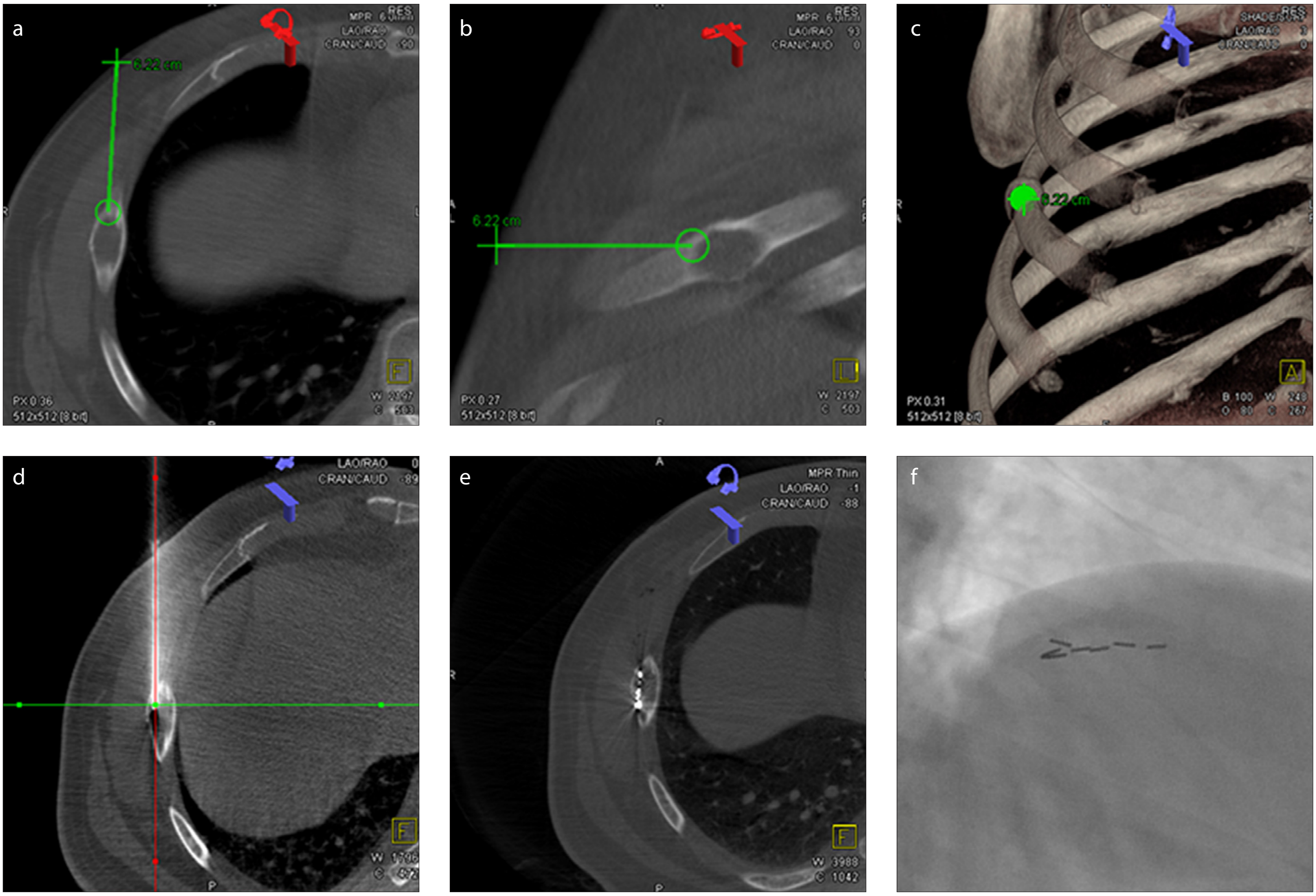

Figure 2. a–f. Axial (**a**) and coronal (**b**) DynaCT images show rib transfer in a 67-year-old male prostate cancer patient. According to the TPS plan, pre-puncture path was selected and implantation of ^{125}I seeds was completed based on the selected path (**c–e**). Digital radiography (**f**) image confirms that the ^{125}I seeds have been successfully placed at the specified location. After implantation of ^{125}I seeds, the patient's VAS pain score was reduced from 7 points to 4 points, and the pain was significantly relieved.

Table 2. Complications of ^{125}I brachytherapy

Complications	n (%)
Mild subcutaneous hemorrhage	21 (25.6)
Fever	6 (7.3)
Minor displacement of radioactive seeds	4 (5.0)
Pathologic fracture	2 (2.4)
Local skin reaction	2 (2.4)
Massive bleeding	0
Hydropneumothorax	0
Radiation pneumonia	0
Granulocytopenia	0

end-stage cancer (13, 14). Furthermore, nearly 75% of patients with advanced cancer experience bone pain caused by metastasis (15). The etiology of bone metastasis is multifactorial, including osteoclast-mediated bone remodeling, mechanically sensitive fiber deformation after normal mechanical stress (decreased bone tensile strength due to cancer), and nerve stimulation by tumor-derived products (16–18).

Conventional therapies for the treatment of painful bone metastases include systemic chemotherapy, topical interventions, and analgesic treatments (19, 20). Currently, the most accepted topical treatment for patients is external beam radiation therapy (EBRT), which is used in 60% of patients for pain relief (21–23). Although EBRT has achieved some success, there have been some limitations. First, once adjuvant radiation therapy is applied for primary tumors of a tumor patient, the use of EBRT in bone metastasis is limited to some extent. Second, the EBRT exposure area is greater than that of ^{125}I seed brachytherapy, which inevitably results in severe radiation damage to surrounding normal tissue. Moreover, due to the presence of nearby vital organs (with bone metastasis close to the spinal cord or nerves), the external beam radiation cannot reach the dose that kills the bone tumor. When the limited dose of EBRT fails to kill the tumor cells completely, especially in case of radiation insensitive tumor cells, sublethally damaged tumor cells self-repair and proliferate thereafter (24–26).

^{125}I seed implantation is a major internal radiation therapy. The tumor cells are killed by long-term continuous irradiation, which has

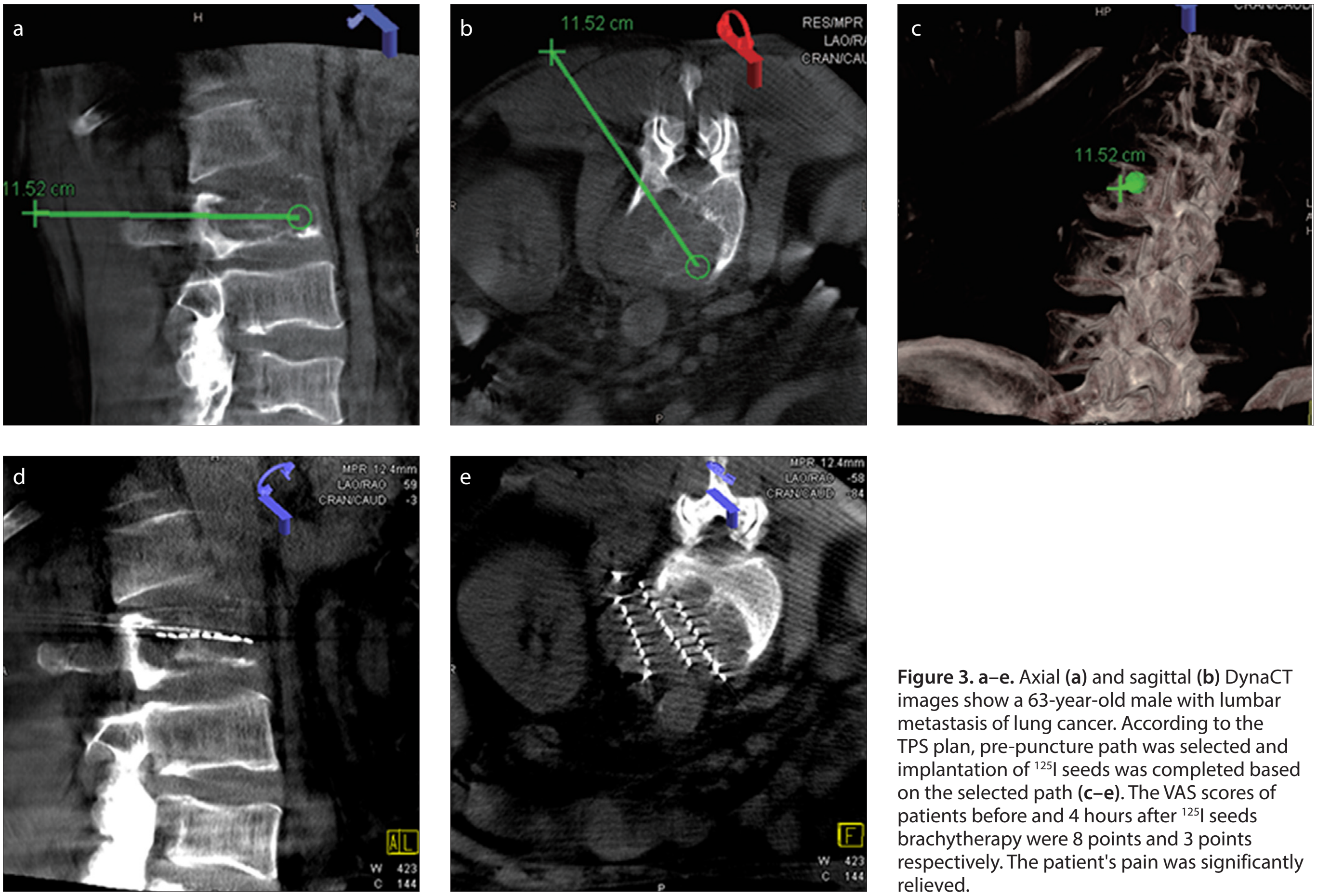

Figure 3. a–e. Axial **(a)** and sagittal **(b)** DynaCT images show a 63-year-old male with lumbar metastasis of lung cancer. According to the TPS plan, pre-puncture path was selected and implantation of ^{125}I seeds was completed based on the selected path **(c–e)**. The VAS scores of patients before and 4 hours after ^{125}I seeds brachytherapy were 8 points and 3 points respectively. The patient's pain was significantly relieved.

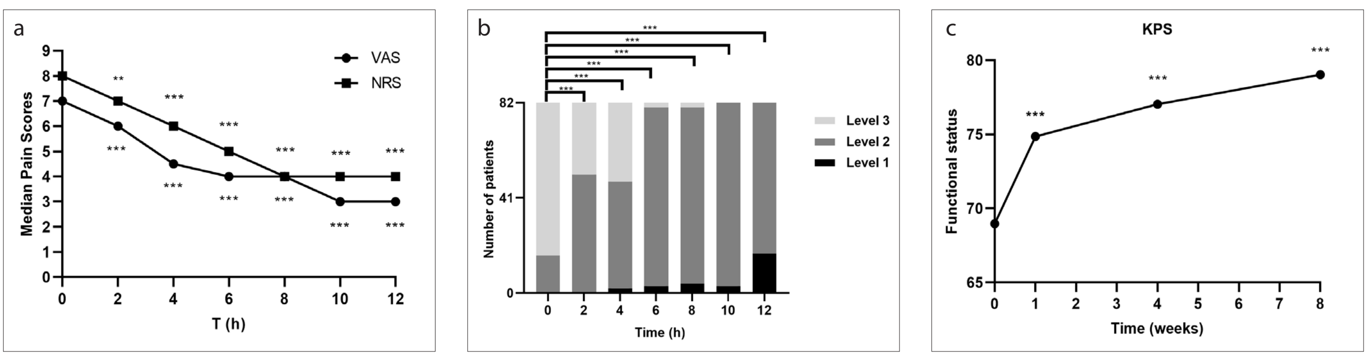

Figure 4. a–c. Summary of the effectiveness of pain relief. Panel **(a)** shows significant decrease in visual analogue scale (VAS) and numerical rating scale (NRS) within 12 hours of ^{125}I seed implantation. Panel **(b)** shows the number of patients with pain level 1–3 according to verbal rating scale (VRS) within 12 hours of the procedure. Panel **(c)** shows significant improvement in Karnofsky performance status (KPS) scores in post treatment weeks 1 through 8 compared with KPS score in pretreatment week 0. $^{**}p < 0.01$, $^{***}p < 0.001$.

the characteristics of targeted therapeutic effect, long duration, high local control rate, and low complication rate (27–29). A retrospective study of metastatic tumors of the spine showed 95% pain relief after CT-guided radioactive ^{125}I seed implantation with the median control time of 12.5 months in all patients, suggesting that brachytherapy is a possible alternative treatment for spinal metastasis (30). This conclusion is similar to the findings of Shi et al. (31). Another study found that ^{125}I brachytherapy is a safe and effective way to alleviate the pain related to bone metastasis after conventional treatment failure or rejection in lung cancer patients (24). These results further revealed that ^{125}I seed brachytherapy is effective and feasible for relieving painful bone metastases.

In our retrospective study, we used DynaCT for image acquisition and pre-processing. After the TPS program was completed, the DynaCT workstation interface was used to adjust the width and location of the window to clearly display the lesion. The iGuide mode was chosen and the lesion was positioned in the axial, sagittal and coronal planes using the cross. Under the guidance of DynaCT, the puncture was performed according to a predesigned procedure. Compared with traditional cylindrical CT guidance, this method can modify the needle track at any time under C-arm to avoid damage to adjacent blood vessels or organs, ensuring the safety and accuracy of ^{125}I seed implantation.

In this study, the preoperative VAS, NRS and KPS scores were significantly different from those after treatment, and there were no major complications. The quality of life of all patients was remarkably improved after the treatment. However, the main limitation of this study was the lack of control studies and short follow-up. Therefore, further comparison with EBRT or chemotherapy and longer follow-up is needed for analysis. Second, some patients lack understanding of the pain scores and KPS scoring system, and the content of the responses may be subjective and increase the bias of the results. Finally, many different types of tumors are included, which may cause bias in results due to differences in radiosensitivity.

In conclusion, we present the experience of DynaCT-guided ^{125}I seed implantation for the treatment of painful bone metastases after EBRT failure. The method is highly operable and can significantly improve local control and quality of life, indicating that DynaCT-guided ^{125}I seed brachytherapy is an effective way to treat bone metastases and its use may eventually be expanded to primary bone tumors.

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Conflict of interest disclosure

The authors declared no conflicts of interest.

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