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Clinical Study

CT-Guided ^{125}I Seed Interstitial Brachytherapy as a Salvage Treatment for Recurrent Spinal Metastases after External Beam Radiotherapy

Lihong Yao,[1] Qianqian Cao,[2] Junjie Wang,[1] Jiwen Yang,[3] Na Meng,[1] Fuxin Guo,[1] Yuliang Jiang,[1] Suqing Tian,[1] and Haitao Sun[1]

[1]*Department of Radiation Oncology, Peking University Third Hospital, Hua-Yuan North Road No. 49, Beijing 100191, China*
[2]*Cancer Center, The Second Hospital of Shandong University, Jinan, Shandong 250033, China*
[3]*Department of Nuclear Medicine, The First Affiliated Hospital of Wannan Medical College, No. 2 Zhe Shan Xi Road, Jinghu District, Wuhu 241001, China*

Correspondence should be addressed to Junjie Wang; junjiewang_edu@sina.cn

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The aim of this study is to evaluate the feasibility, safety, and clinical efficacy of CT-guided ^{125}I seed interstitial brachytherapy in patients with recurrent spinal metastases after external beam radiotherapy (EBRT). Between August 2003 and September 2015, 26 spinal metastatic lesions (24 patients) were reirradiated by this salvage therapy modality. Treatment for all patients was preplanned using a three-dimensional treatment planning system 3–5 days before ^{125}I seed interstitial brachytherapy; dosimetry verification was performed immediately after seed implantation. Median actual D_{90} was 99 Gy (range, 90–176), and spinal cord median D_{max} was 39 Gy (range, 6–110). Median local control (LC) was 12 months (95% CI: 7.0–17.0). The 6- and 12-month LC rates were 52% and 40%, respectively. Median overall survival (OS) was 11 months (95% CI: 7.7–14.3); 6-month and 1-, 2-, and 3-year OS rates were 65%, 37%, 14%, and 9%, respectively. Pain-free survival ranged from 2 to 42 months (median, 6; 95% CI: 4.6–7.4). Treatment was well-tolerated, with no radiation-induced vertebral compression fractures or myelopathy reported. Reirradiation with CT-guided ^{125}I seed interstitial brachytherapy appears to be feasible, safe, and effective as pain relief or salvage treatment for patients with recurrent spinal metastases after EBRT.

1. Introduction

Due to developments in cancer treatments, cancer patients are experiencing an increased life expectancy [1]. Bone metastases are a growing problem among patients who are living longer, with the spine being the most commonly affected site [2, 3]. Although external beam radiotherapy (EBRT) has long been the main form of treatment for spinal metastases [4–7], local recurrence in previously irradiated spinal segments has been reported in more than one-third of long-term survivors with malignancy [8]. Since EBRT was failure for the first time, reirradiation of spinal metastases presents a particular therapeutic challenge in radiation oncology.

When a second course of EBRT is given using conventional techniques, one must weigh the clinical benefits against the risks of radiation myelopathy, although there remains a relative lack of understanding of reirradiation spinal cord tolerance in the literature [9–13]. The spinal cord's sensitivity to radiation generally precludes high doses to the spine or reirradiation with conventional EBRT techniques [14, 15]. Following the advent of sophisticated treatment planning and image-guided technologies, various techniques have emerged that allow more accurate dose delivery. Among the techniques, spine stereotactic body radiotherapy (SBRT) in the reirradiation setting has been extensively investigated in terms of its feasibility, safety, and efficacy [16–18]. Higher, focused doses of radiation may be delivered for retreatment;

however, controversy concerning optimal doses and fraction numbers, planning constraints for SBRT of spinal metastases, and patient selection criteria for the choice of treatment still exists in the literature for SBRT. Furthermore, the cumulative spinal cord dose limits for its use in this setting are unknown.

^{125}I seeds interstitial brachytherapy has been used to treat tumors for over a century and has been developed more extensively during the past 20 years. Radioactive ^{125}I seed is the most widely used source for interstitial brachytherapy, with its long half-life, low energy, and 1.7 cm tissue half-value layer. Compared with EBRT, permanent ^{125}I seed interstitial brachytherapy produces high doses of radiation in the target area at a continuous lower dose rate, while sparing the surrounding normal tissues due to the unique physical properties of ^{125}I radionuclides.

Previously, we have reported the possibility of ^{125}I seed interstitial brachytherapy for the salvage treatment of recurrent lymph node metastases [19, 20], rectal carcinoma [21], pancreatic carcinoma [22], soft tissue sarcoma [23], and primary spinal tumors [24]; yet, there have rarely been reports on its use for spinal metastases after EBRT. Therefore, the aim of this study was to review our preliminary experience with this salvage therapy in patients with recurrent spinal metastases after EBRT in the reirradiation setting and to evaluate the feasibility, safety, and clinical efficacy of this technology.

2. Methods and Materials

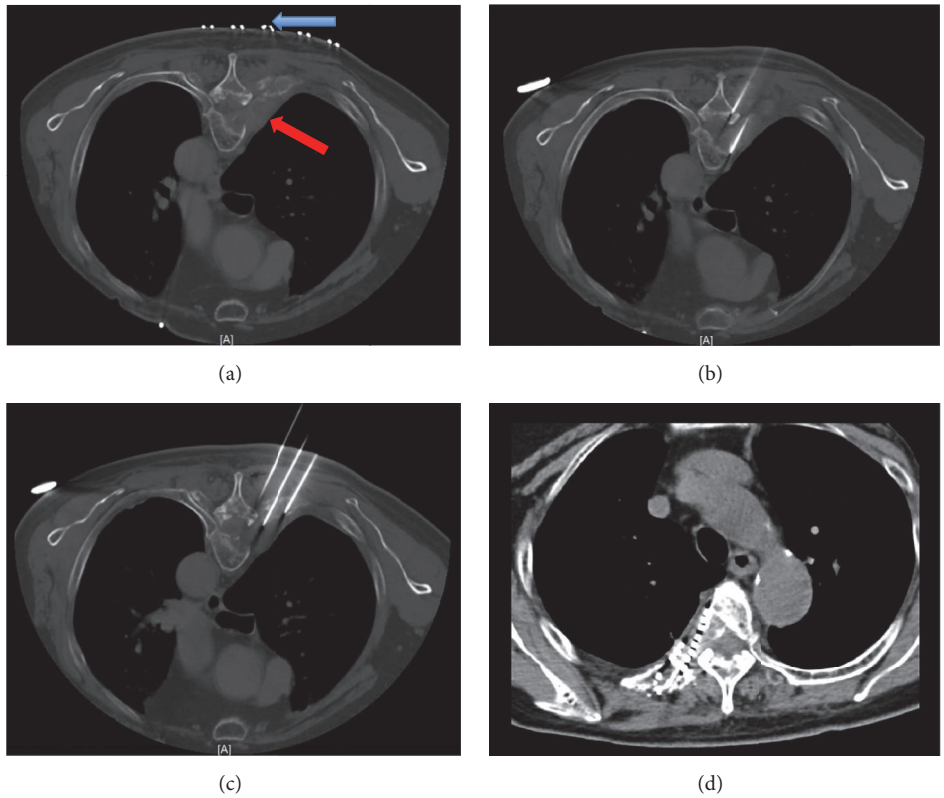
2.1. Patient Selection. Between August 2003 and September 2015 at Peking University Third Hospital, 26 spinal metastatic lesions (24 patients) were reirradiated with ^{125}I seed interstitial brachytherapy under CT guidance as a salvage treatment for local failure after EBRT. The eligibility criteria were as follows: histologically and radiologically proven recurrent spinal metastases after EBRT; Karnofsky patient performance status of 60 or higher; absence of systemic metastasis, or less than three oligometastases stable after treatment; expected survival more than 3 months; and no major renal, hepatic, or bone marrow dysfunction. All of the patients had been interviewed by surgeons and radiation oncologists and were considered unsuitable for salvage surgery or EBRT or had refused surgery or EBRT.

All 24 patients (14 males, 10 females; median age, 59 years, age range, 31–77 years) were included in our analyses. The primary tumor sites among the patients were lung cancer in 6 (25.0%), liver in 5 (20.8%), renal in 4 (16.7%), colorectal in 2 (8.3%), and other sites in 7 (29.2%). The thoracic spine was the most common location for the 26 spinal segments treated (46.2%). Most of our patients presented with *good performance status* prior to ^{125}I seed brachytherapy (median Karnofsky performance status 80). The burden of disease in patients at the time of brachytherapy was (1) a single spine lesion in 10 (41.7%), (2) multiple osseous lesions without visceral metastases in 5 (20.8%), and (3) spine and visceral metastases in 9 (37.5%). All of the 26 seed implantation sites had received prior EBRT, with a median dose of 40 Gy (range, 30–60). Median time from end of EBRT to ^{125}I seed interstitial brachytherapy was 6 months (range, 6–36). Table 1 summarizes the cohort.

Table 1: Patient (n = 24) and tumor (n = 26) characteristics.

Parameter	Number of patients (%)
Gender	
Male	14 (58.3%)
Female	10 (41.6%)
Median age (range)	59 (31–77)
Primary tumor	
Lung cancer	6 (25.0%)
Liver carcinoma	5 (20.8%)
Renal carcinoma	4 (16.7%)
Colorectal cancer	2 (8.3%)
Others	7 (29.2%)
Level of spinal involvement[*]	
Cervical	3 (11.5%)
Thoracic	12 (46.2%)
Lumbar	10 (38.5%)
Sacral	1 (3.8%)
Number of spine metastases	
1	22 (91.7%)
2	2 (8.3%)
NRS pain score	
1–3	8 (33.3%)
4–6	12 (50.0%)
7–10	4 (16.7%)
Neurologic symptoms	
Yes	9 (37.5%)
No	15 (62.5%)
KPS	
Median (range)	80 (60–90)
Preseed implant therapy[*]	
Surgery + EBRT + CTx	9 (34.6%)
Surgery + EBRT	4 (15.4%)
EBRT + CTx	6 (23.1%)
EBRT	7 (26.9%)
Time between EBRT and ^{125}I implant (months)	
Median (range)	6 (6–36)
Prior EBRT total dose/number of fractions	
30 Gy/10 fraction	5 (20.8%)
38 Gy/19 fraction	2 (8.3%)
40–48 Gy/12–21 fraction	8 (33.3%)
50–54 Gy/20–30 fraction	5 (20.8%)
60 Gy/20 fraction	3 (12.5%)
60 Gy/25 fraction	1 (4.2%)
Prior D_{max} of spinal cord (Gy)	
Median (range)	35 (11.6–45.7)

NRS = numeric rating scale; KPS = Karnofsky performance score; EBRT = external beam radiotherapy; CTx = chemotherapy.
[*]Number of treatment lesions.



(a) (b) (c) (d)

Figure 1: Representative CT scans of a patient during ^{125}I brachytherapy. (a) Spine metastases recurrence (arrow: red) from breast cancer after surgery, EBRT (40 Gy/20 f), and chemotherapy. Clips (arrow: blue) attached to the skin to determine the needle entry point. (b-c) An applicator accurately inserted into the metastases to implant ^{125}I seeds. (d) Immediate postoperative CT scan images showing uniform distribution of ^{125}I seeds within the tumor.

The primary treatment of the 26 spinal metastatic lesions was (1) surgery, EBRT, and chemotherapy (9 lesions, 34.6%); (2) surgery combined with EBRT (4 lesions, 15.4%); (3) EBRT combined with chemotherapy (6 lesions, 23.1%), and (4) EBRT (7 lesions, 26.9%). Patient signs and symptoms before salvage seed implantation included varying degrees of pain in all 24 (100%), neurological dysfunction in 9 (37.5%), and ambulatory dysfunction in 18 (75%).

2.2. Pretreatment Planning. In order to study tumor location and volume, each patient underwent a CT scan 3–5 days before brachytherapy. CT transverse images of spinal metastases were obtained using 5 mm slice thickness and spacing. Gross tumor volume (GTV) and organs at risk were contoured on each transverse image by an experienced radiation oncologist. Clinical target volume (CTV) included the GTV and a 0.3–0.5 cm area of peripheral tissue. The dose was prescribed as D_{90} (dose delivered to 90% of the target volume defined by CT using a dose volume histogram) that would encompass the CTV. The D_{90}, total number, and activity of ^{125}I seeds were calculated by a three-dimensional radiation therapy planning system (3D-TPS; Beijing Fei Tian Industries Inc., Beijing, China).

2.3. CT-Guided Brachytherapy Protocol. Under adequate local anesthesia, patients were immobilized in the prone position to facilitate CT guidance during the brachytherapy procedure. After the target volume had been determined, 18-gauge needles were implanted into the mass and spaced at a distance of 1.0 cm in a parallel array, extending at least 0.3–0.5 cm beyond the margins of the tumor (Figure 1). A multiangle nonplanar puncture technique was used to keep the needles at least 1.0 cm away from large blood vessels and the spinal cord. ^{125}I seeds (Model 6711; t1/2, 59.4 days; energy, 27.4–31.4 keV; half-value layer of lead, 0.0025 cm; half-value layer of tissue, 2.0 cm; Beijing Atom and High Technique Industries Inc., Beijing, China) were implanted using a Mick applicator (Mick Radio-Nuclear Instruments Inc., Mount Vernon, NY, USA), in a linear arrangement, with spaces between seeds (center to center) of approximately 1.0 cm. Once the seeds were correctly distributed, the needles were removed. All patients received prophylactic perioperative antibiotics.

2.4. Postimplantation Dosimetry. Immediately after seed implantation, a CT scan was routinely obtained for all the patients to confirm the location of the seeds and to perform the postimplant dosimetry in case a need for supplementary implantation arose. Actual isodose distributions for each slice (Figure 2) and dose volume histograms for the target were generated.

2.5. Pain and Functional Evaluation. According to a numeric rating scale (NRS) for chronic pain, pain intensity at the

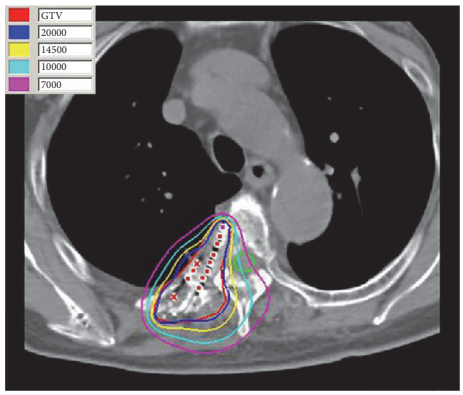


Figure 2: Dose distribution curves of a representative patient: female; 71 years old; breast cancer; D_{90}, 158.3 Gy.

treated vertebral level was evaluated and graded as follows: 0, no pain; 1–3, mild pain; 4–6, moderate pain; and 7–10, severe pain [25]. American Spinal Injury Association (ASIA) International Standards for Classification of Spinal Cord Injury was used for neurological assessment [26]. Based on ambulatory capacity and any requirement for assistance, an ambulatory function score was assigned to each patient [27].

2.6. Follow-Up and Statistical Analyses. All outcome measurements were measured from the date the seed brachytherapy was performed to the time of the event. Clinical follow-up assessments were performed during periodic clinic visits. Nursing follow-up was performed by telephone within 1 week of treatment, and electronic notes were reviewed. Follow-up evaluation consisted of CT, MRI, and clinical exam between two and three months posttreatment and then repeated every six months for two years. Local tumor response was initially evaluated clinically and radiologically, one month after seed brachytherapy according to the Response Evaluation Criteria in Solid Tumors version 1.1 [28]. Local failure was defined as progressive tumor growth within the treated segment of spine on CT, MRI, or positron emission tomography scan. Complications were scored using the Radiation Therapy Oncology Group-European Organisation for Research and Treatment of Cancer Late Radiation Morbidity Score Criteria [29]. Death from any cause was scored as an event for survival rate calculations. Patients were censored at the date of the last follow-up visit or death. Tumor local control (LC), overall survival (OS), and pain-free survival (PFS) rates after seed brachytherapy were analyzed with SPSS version 20.0 (Chicago, USA) using the Kaplan-Meier method. We used the paired t-test to analyze the NRS score to classify pain. A two-tailed P value < 0.05 was considered statistically significant.

3. Results

3.1. Salvage Brachytherapy Characteristics. ^{125}I seed interstitial brachytherapy was performed successfully for all 26 lesions, and a second procedure was repeated in 4 patients (16.7%) with a larger tumor volume after three months. Treatment details for the four patients receiving a second brachytherapy are summarized in Table 2. Postoperative dosimetry verification showed that ^{125}I seed distributions were consistent with preimplantation plans. No seed migration was observed in any of the patients. ^{125}I seed interstitial brachytherapy characteristics are shown in Table 3. The median GTV volume was 41.0 cc (range, 3.8–121.4). The median ^{125}I seed activity was 0.68 mCi per seed (range, 0.45–0.84 mCi). The number of ^{125}I seeds implanted ranged 10–103 (median, 50). Postplanning evaluation showed that the actual D_{90} was 90.3–176.0 Gy (median, 99.0). The median maximum dose of spinal cord was 39.2 Gy (range, 6.1–110.5); for cauda equina, the median maximum dose was 20.5 Gy (range 5.0–70.2 Gy); values for other organs at risk were all within the respective tissue dose constraints.

3.2. Local Control and Survival. At the time of analysis, the median patient follow-up was 9.5 months (range, 3–42), and no patients were lost to follow-up. The patients were evaluated radiographically for all of the brachytherapy procedures. Of the 26 tumors, complete response (CR) occurred in one, and partial response (PR) and stable disease (SD) both occurred in 11 lesions. This gave an overall response rate (CR + PR) of 46.2% (12/26). Following repeat procedure for the four patients, all lesions were SD after the second ^{125}I seed brachytherapy. Median LC was 12 months (95% CI: 7.0–17.0). The actuarial LC rates at 6 and 12 months were 51.7%, and 40.2%, respectively.

During follow-up, 20 patients (83.3%) had developed distant metastases and subsequently died. Four patients (16.7%) are alive with distant metastases but no evidence of local recurrence. Median OS was 11 months (95% CI: 7.7–14.3); the 6-month and 1-, 2-, and 3-year OS rates were 65%, 37.4%, 14.0%, and 9.4%, respectively.

3.3. Pain Relief. Prior to salvage ^{125}I seed interstitial brachytherapy, pain was the main symptom which was reported by all the patients. After the procedure, many patients experienced different degrees of relief from pain after 1 to 3 weeks; the rate of pain relief was 91.7% (22/24). NRS pain scores before and after brachytherapy were 5.0 ± 1.8 and 2.6 ± 1.9, respectively ($t = 8.3$, $P < 0.001$). A comparison of reported levels of pain before and after brachytherapy during our first time follow-up is shown in Table 4. PFS ranged from 2 to 42 months (median: 6 months; 95% CI: 4.6–7.4).

3.4. Functional Improvement. On preseed brachytherapy neurological assessment, 9 of the 24 patients showed neurologic symptoms, with an ASIA grade C in 1 (4.2%) and D in 8 (33.3%). The sensory function of the grade C patient was preserved, but his motor function was impaired such that he could not walk. Postseed brachytherapy assessment revealed that the neurologic symptoms of 50% (4 of 8) grade D patients improved to grade E. Overall neurological function recovery or retention rate was 79.2% (19/24).

The preoperative ambulatory function score was I in 6/24 patients (25%, able to ambulate normally), II in 10 (41.7%), and III in 8 (33.3%), and no patients were unable to ambulate. All patients who were able to ambulate with or without

Table 2: Treatment details for the four patients receiving a second brachytherapy.

Number	GTV volume (cc)	Seed activity (mCi)	Number of seeds/D_{90} (Gy)	GTV: V_{90}/V_{100} (%)	D_{max} of spinal cord (Gy)	Therapy after seed implant	RR	LR (m)	Pain-free survival (m)	Cause of death	OS (m)
1	72.5	0.7	74/93.2	90.2/89.3	35.7	No	PD	6	6	MM	24
	60.3	0.8	73/121.5	93.2/90.1	25.6		SD	18			
2	61.3	0.6	57/92.2	83.5/81.9	35.6	No	SD	3	3	MM	12
	61.3	0.8	51/93.5	85.8/82.1	6.0		SD	9			
3	59.3	0.8	75/158.3	96.3/94.9	38.4	No	PR	3	3	MM	14
	48.5	0.7	46/91.8	85.6/81.6	30.6		SD	3			
4	121.4	0.7	88/92.2	85.5/82.2	61.1	No	SD	3	3	MM	6
	17.9	0.8	23/139.3	97.8/95.6	25.0		SD	6			

RR = response rate; PR = partial response; SD = stable disease; PD = progressive disease; LR = local recurrence; m = months; MM = multiple metastasis; SS = survival; OS = overall survival after seed implantation.

Table 3: ^{125}I seed interstitial brachytherapy parameters in 24 patients.

Parameter	Median	Range
GTV volume (cc)	41.0	3.8–121.4
Number of seeds	50	10–103
Seed activity (mCi)	0.7	0.5–0.8
Total seed activity (mCi)	33.8	6.0–62.5
D_{90} (Gy)	99.0	90.3–176.0
GTV: V_{90} (%)	91.2	83.5–98.1
GTV: V_{100} (%)	90.3	80.3–97.6
D_{max} of spinal cord (Gy)	39.2	6.1–110.5
D_{max} of cauda equina (Gy)	20.5	5.0–70.2

D_{90}, dose delivered to 90% of the target volume; V_{90} and V_{100}, the percentage of the target volume receiving at least 90% and 100% of the prescription dose.

Table 4: Comparison of the NRS pain scores before and after brachytherapy*.

Pain score	Before brachytherapy	After brachytherapy
No pain	0.0	16.7 (4/24)
Mild pain	33.3 (8/24)	54.2 (13/24)
Moderate pain	41.7 (10/24)	25.0 (6/24)
Severe pain	25.0 (6/24)	4.2 (1/24)

*All values given as % (cases).

assistance remained ambulatory after treatment. 75% (6 of 8) of patients who had score III were improved to II, and 20% (2 of 10) of patients who had score II were improved to I.

3.5. Toxicity and Complications. Treatments were well-tolerated; no mortality or morbidity was attributable to the brachytherapy itself. Even with the relatively high doses of radiation, no radiation-induced vertebral compression fractures, adverse neurologic sequelae, or myelopathy occurred; nor were there complications greater that grade 3 observed (scored according to the Radiation Therapy Oncology Group). Three patients developed vertebral compression fractures, one at 3 months and two at 6 months after brachytherapy, with no evidence of tumor progression. These were de novo fractures. Another patient developed lower limb paraplegia 2 months after the procedure due to compression fracture caused by tumor progression. Treatment details of four patients who developed fractures are provided in Table 5.

4. Discussion

Recently, ^{125}I seed interstitial brachytherapy has usually been investigated in combination with surgery for the treatment of spinal metastases [27, 30, 31]. We are the first to report the treatment of patients with metastatic spinal tumors with ^{125}I seed interstitial brachytherapy alone in a reirradiation setting. The reasons for performing ^{125}I seed interstitial brachytherapy in cases with prior EBRT failures in this series were to achieve LC, alleviate pain, preserve or improve neurologic function, achieve mechanical stability, and improve quality of life; these are all aims of using salvage ^{125}I seed interstitial brachytherapy.

After comprehensive analysis, Prasad and Schiff [2] reported that the longer the survival time, the higher the risk of local recurrence. 50% patients relapsed in 2 years and, of the patients who survived for three years, almost all experienced recurrence. Over time, clinical benefits reported in the literature have varied for the different treatment modalities used for vertebral body and paraspinal tumors.

Early on, Wright et al. [32] reviewed their experience in 37 patients with re-EBRT of recurrent paraspinal tumors using image-guided intensity modulated radiotherapy (IG-IMRT). A median dose of 2000 cGy was delivered to the PTV, and the most common radiation schedule was 2000 cGy in 5 fractions. The observed LC rate was 60% at a median follow-up of 8 months; OS rate was 72% at a median follow-up of 12 months, and the median OS time was 18 months. The numbers of patients reporting stable or improved pain and function status after salvage irradiation were 91% and 70%, respectively. Toxicity seen in the patients in this study was very mild, and the clinical outcomes were encouraging, similar to ours. However, many of their patients underwent surgery at the first time of failure prior to radiation, and this may have caused a smaller overall tumor volume of their cohort when compared with that of our patients.

Recently, a more aggressive therapy was delivered by SBRT that is based on various techniques specific to the re-EBRT setting including Cyberknife [9, 17] and linear accelerator-based IG-IMRT with hypofractionated [14, 18] and single fraction regimens [12, 15, 33]. SBRT has several theoretical advantages over conventional EBRT. A steep dose gradient allows for protection of the spinal cord and surrounding radiosensitive structures (cancer-free tissues). Furthermore, higher doses are delivered over fewer treatment days, making it more convenient. SBRT is more widely used in small-to-medium-sized extracranial tumors, and, now, many investigators have reported experience with salvage SBRT for patients with spinal or paraspinal metastases [9, 14, 16–18, 33]. Thibault et al. [18] reported their results with salvage SBRT for spinal metastases after in-field failure of initial SBRT. The second (salvage) SBRT dose was 30 Gy (median total dose) given in 4 fractions. The median OS was 10.0 months, and the 1-year OS and LC were 48% and 81%, respectively. They observed that bulk paraspinal disease was the only significant predictive factor for LC on multivariate analysis, which may reflect the difficulty in controlling tumor bulk by this therapy schedule. A spine SBRT program requires a significant investment to ensure safe treatment and to define patient selection criteria for the choice of treatment.

^{125}I seed interstitial brachytherapy, a form of low-dose-rate brachytherapy, is the permanent placement of radioactive ^{125}I seeds inside or next to the treatment locus. Today, ^{125}I seed interstitial implantation is performed under image guidance—using CT, MRI, or ultrasound—which improves the accuracy of seeds location in a known tumor volume compared with traditional intraoperative seed implantation. With its high-resolution images, CT is particularly suitable for precise guidance and localization in the skeletal system.

Table 5: Treatment details of four patients who developed fractures.

Number/gender/age	Diagnosis	Location	Prior therapies (except primary)	*Recurrent time (months)	GTV volume (cc)	Number of seeds/D_{90} (Gy)	GTV: V_{90}/V_{100} (%)	D_{max} of spinal cord delivered by EBRT/brachytherapy (Gy)	Therapy after seed implant	**Fracture time (months)
1/M/68	Liver cancer	T11	S + EBRT 40 Gy + CTx	6	61.7	88/141.9	94.8/93.1	25.3/74.1	No	6
2/F/56	Endometrial carcinoma	L4-S1	S + EBRT 50 Gy + CTx	6	61.3 61.3	57/92.2 51/93.5	83.5/81.9 85.8/82.1	38.2/35.6 6.1	No	6
3/F/59	Renal carcinoma	C3-4	S + EBRT 38 Gy	36	24.4	27/102.1	91.7/90.0	35/49.3	No	3
4/F/68	Lung cancer	T7-8	EBRT 40 Gy	10	41.8	45/93.3	89.3/88.1	38.5/46.3	CTx	2

M = male; F = female; S = surgery.

*Recurrent time is the time interval between EBRT and ^{125}I seed interstitial brachytherapy.

**Fracture time is calculated from ^{125}I seed implantation performed to fracture developed.

Other abbreviations as in Tables 1, 2, and 3.

Pretreatment planning and postimplantation dosimetry verification using TPS are also obtained based on CT images, which solves the problem of radiation dose adjustment and conformity of dose distribution in the target volume. In addition, unlike the traditional radiotherapy, CT-guided ^{125}I seed interstitial brachytherapy is a onetime procedure that shortens the treatment period.

Feng et al. [34] analyzed 26 patients who underwent CT-guided ^{125}I seed interstitial brachytherapy for painful bone metastases after prior EBRT failure. They found highly significant reductions in pain scores and improvement in quality of life for the patients after ^{125}I seed interstitial brachytherapy. Risks of major complications were reported to be relatively low. Zhang et al. [35] explored the clinical efficacy of CT-guided ^{125}I seed interstitial brachytherapy of 20 consecutive patients with 24 advanced spinal metastases. The matched peripheral dose was 90–130 Gy. The pain relief rate was 95%. Median LC and OS were 12.5 months and 16 months, respectively; and the 1-year LC and OS rates were 60% and 78.81%, respectively. In our analysis, however, the 1-year LC and OS rates were 40.2% and 37.4%, respectively. Our pain relief rate (91.7%), however, was similar to that in their study (95%). The study of Zhang et al. [35] was prospective; the metastatic lesions of the patients had never been irradiated. The GTV (median 40.95 cc) of our patients were relatively larger, which may have been the reason their patients showed overall better outcomes.

Previously, we reported salvage ^{125}I seed interstitial brachytherapy results for recurrent spinal metastatic and primary tumors [24, 36]. The current study includes a larger sample size and a more homogeneous group of patients, which helps to validate the efficacy of reirradiation by ^{125}I seed interstitial brachytherapy as salvage therapy for spinal metastases. In our analysis, four patients suffered from an incomplete paraplegia caused by vertebral compression fractures at different times following brachytherapy. No matter delivered by EBRT or by brachytherapy, the maximum spinal cord doses of the four patients are not the highest in all of our patients. GTV volumes of patients 1 and 2 were very large and the vertebral metastatic tumors were osteolytic. For patient 3, tumor location and spinal stability might account for vertebral compression fractures. Patient 4 developed lower limb paraplegia 2 months after the procedure due to compression fracture caused by tumor progression. Currently, there is no large sample study involving the correlation between tumor size and treatment efficacy. The question of whether bulky tumors may benefit from ^{125}I seed interstitial brachytherapy remains controversial, and further research is needed to determine the answer. The possible disadvantages of this approach are as follows: (1) compared with EBRT, it is minimally invasive, (2) this is a very complex technology of personnel dependence, (3) in addition to prostate cancer, patients must be at their own expense in our country, and (4) like the spine SBRT program, there is a long learning curve for this technique.

Limitations of this study include the heterogeneity of the cohort of patients with respect to specific site and volume of the metastases, as well as the primary tumor type. Secondly, it was a retrospective study with a relatively small sample size patients. Furthermore, our study lacked a control group and had a relatively short follow-up time period. Therefore, a multicenter, randomized controlled trial with a long follow-up time is needed to verify our preliminary results regarding the clinical efficacy of ^{125}I seed interstitial brachytherapy for recurrent spinal metastases after EBRT failure.

5. Conclusions

Salvage reirradiation with permanent CT-guided ^{125}I seed interstitial brachytherapy for local failure spinal metastases after prior EBRT appears to be safe and effective. It can ease pain, improve or preserve neurological and ambulatory function, optimize local tumor control, and extend the survival time—all with endurable toxicity. It is a potential alternative salvage therapy for spinal metastases in a reirradiation setting; however, data from a larger, longer-term study of this promising procedure are needed to reach a definite conclusion.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

Junjie Wang conceived and designed the study; Lihong Yao carried out the data collection, prepared the figures, and drafted the manuscript; Qianqian Cao, Jiwen Yang, and Na Meng participated in the data collection; Fuxin Guo carried out the needle penetration; Yuliang Jiang and Suqing Tian performed seed implantation; Haitao Sun carried out the dose calculation of seed implantation. All authors read and approved the final version of the manuscript.

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