Comparison of pre-implant treatment planning and post-implant dosimetry in I-125 spinal metastases brachytherapy

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Abstract. I-125 seed therapy has been developed and used for the treatment of numerous types of malignancies. It has been suggested that post-implant dosimetry deviates from pre-implant treatment planning; however, to the best of our knowledge, very few studies to date have investigated this discrepancy. In the present study, 11 patients with metastatic spinal tumors, who were treated with I-125 seed brachytherapy, were assessed. Pre- and post-implant dosimetry were compared by assessing: Tumor volume, dose distributions and dose volume histograms. The average doses delivered to 90% of the target volume (D90) in the pre-implant planning images of the spine was 119.07 Gy compared with 94.15 Gy in the post-implant dosimetry ($P<0.05$). The average V100 in the pre-implant planning images of the spine was 97.85% (range, 96.50-99.80%), compared with 84.46% (range, 66.40-96.70%) in the post-implant dosimetry, of the prescribed doses ($P<0.05$). Furthermore, both the number of needles and the Dmax of the cord differed between the two groups. Nevertheless, the mean gross tumor volume, the number of seeds, and the V150 and V200 were similar between the two groups. The results of the present study suggest that metastatic spinal tumors of the bone received a lower dose than the pre-implant planned dose coverage in I-125 seed brachytherapy.

Introduction

The bone is a popular site of metastases within the general population (1), along with the liver and the lung. In bone metastases, the spine is most commonly affected. Studies have suggested that spinal metastasis (SM) accounts for up to 40% of patients suffering from metastasis during the course of their disease (2-4). The most common symptoms of SM include, radicular and back pain and sensory disorder that leads to degradation of the patients' quality of life (5-8). The treatment strategy for spinal metastases depends on a number of factors, including: Histology, the site of disease, the extent of metastases and the neurologic status (9,10). Open surgery is one of the traditional treatment options used for spinal metastases (11); however, this approach often results in considerable trauma and severe side effects. Furthermore, prolonged hospitalization may delay the treatment of the primary disease (12,13). Given the complications associated with surgery, external beam radiotherapy (EBRT) has become an alternative option for the treatment and management of spinal metastases (14). Nevertheless, the conventional EBRT technique has a limited capability for dose escalation when treating spinal cord bone metastases, due to the dose limit of the organ-at-risk (OAR). For example, in order to avoid the risk of radiation-induced myelitis, the OAR dose of the spinal cord is kept below 45 Gy (3,15). Furthermore, both surgery or EBRT may not be appropriate for patients with medical problems or those unwilling to accept the complication risks of surgery (16).

Radioactive iodine-125 (I-125) seed implantation emits a low energy γ-ray and transfers steep dose gradients between target volumes and the adjacent OAR (17). Satisfactory clinical outcomes have been reported in the treatment of primary and secondary malignant tumors with I-125 brachytherapy (18-21). The steep dose gradients are particularly desirable for osteosarcoma or vertebral column metastases where tumors abut sensitive critical normal tissues, such as the spinal cord, and poor dose control can result in myelitis and vertebral body fracture, which would be catastrophic (3). Pre-implant treatment planning is crucial to brachytherapy; however, it has been suggested that the post-implant dosimetry may deviate from the pre-implant treatment planning (22). To the best of our knowledge, there have been limited studies that investigate this discrepancy. The present study retrospectively examined patients with metastatic spinal tumors who were treated with I-125 permanent interstitial implantation. The dosimetric differences between the pre- and post-implant treatment plans, with I-125 spinal metastases brachytherapy, were compared.

Materials and methods

Patients. The retrospective analysis in the present study was approved by the Ethics Committee of Shandong Provincial

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Hospital (Jinan, China). A total of 11 patients with metastatic spinal tumors, who were treated with I-125 permanent interstitial implantation from September 2014 to January 2016, were included in the present study. The following inclusion criteria were met by all patients: i) Pathological or cytological confirmation of primary malignant tumor; ii) Karnofsky performance score ≥60 (KPS; for functional impairment); iii) adequate general health and functions (hematological, hepatic, renal and cardiac); iv) ability to maintain the prone position for at least 1 h; v) vertebral destruction dominated by osteolytic lesions; vi) expected survival time ≥3 months; vii) the patient underwent seed implantation, while no surgery nor EBRT were conducted; viii) the patient was not in a period of ulceration; ix) no other distant metastases besides bone were observed and x) tumor identification via CT was performed prior to I-125 seed implantation. The exclusion criteria were as follows: i) Poor coagulation function or implantation could not be performed; ii) no proper needle path and iii) rejection of brachytherapy.

A total of six men and five women (median age, 52 years; range, 41-69 years) were enrolled in the present study, including six cases of lung cancer, three cases of breast cancer and two cases of kidney cancer. Metastases involving the vertebral arch and the vertebral body accounted for 63.6% of all patients, while 36.4% of the patients presented with metastasis in the vertebral body alone. The degree of pre-implant pain in each patient was assessed using the numerical rating scale (NRS) graded from 1 to 10. One case (9.1%) had no pain (NRS=0), six patients (54.5%) had moderate pain (NRS=4-6) and four patients (36.4%) had severe pain (NRS=7-10). None of these patients received spinal treatment prior to the I-125 interstitial brachytherapy. The patients' characteristics are presented in Table I.

Table I. Patient characteristics (n=11).

Characteristic	No. of patients	Percentage, %
Sex		
Male	6	54.5
Female	5	45.5
Primary tumor		
Lung	6	54.5
Breast	3	27.3
Kidney	2	18.2
Location of spine metastasis		
Thoracic	7	63.6
Lumbar	4	36.4
NRS score		
0	1	9.1
1-3	0	0.0
4-6	6	54.5
7-10	4	36.4
KPS median (range)	60 (70-80)	

NRS, numerical rating scale. KPS, Karnofsky performance status.

Radioactive source and instruments. Radioactive I-125 seeds (HAT Co., Ltd.) were shaped as a cylindrical titanium package body with a length of 4.5 mm, a diameter of 0.8 mm and an activity range from 0.30-0.80 mCi. I-125 produces γ-rays (5% of 35 keV; 95% of 28 keV) with a half-life of 59.4 days, a half-value thickness of 0.025 mm lead and an incipient rate of 7 cGy/h, at a distance of 1.7 cm (23).

CT (Light Speed 16, GE Healthcare Sciences) of the spine was performed using the following settings: 120 kV, 275 mA and a 5 mm width. Prior to the I-125 seed implantation, dose distribution was calculated using Beihang Treatment Planning System (TPS; standard version; Beijing ASTRO Technology Development Co., Ltd.) based on the American Association of Physicists in Medicine TG43 brachytherapy formalism.

Pre-treatment planning. Pre-treatment planning was performed 1-2 weeks before the seed implantation. Axial images (at 5 mm intervals) of the abdomen were obtained for all patients prior to the seed implantation and were transferred to the TPS. Contouring was performed in every CT slice. The prescription dose for the planned target volume (PTV) was 90-110 Gy. The PTV was a 0.5-1.0 cm expansion of the gross tumor volume (GTV). Needle locations were drawn based on the lesion size and its association with the surrounding tissues. There was a 0.5-1.0 cm spacing between adjacent needles. The seeds were distributed in the needle passage by the TPS, followed by modification according to the isodose curve and dose-volume histogram (DVH). Pre-planning dosimetry aimed for the majority of the target volume (>90%) to receive 100% of the prescription dose (V100>90%) and <50% of the target volume to receive 200% of the prescription dose (V200<50%).

Implant procedure. CT guided transperineal insertion of the permanent seed implantation was performed according to the treatment plan, under local anesthesia. The seeds were implanted and positioned against its deepest margin using an 18-gauge needle with a turntable gun (Beijing Atom High Tech). The I-125 seeds were spaced 0.5-1.0 cm from each other. Dose-sparing was ensured by implanting the seeds 1.0 cm away from the spinal cord.

Post-implant dosimetry. CT scans were performed immediately following the implantation. Images were captured at 5 mm intervals, without a gap. Seeds were located on the CT images. Contouring was performed by the same physician who performed the pre-implant contouring. DVHs of the target and surrounding normal tissue structures were generated from the pre- and post-implant scans. Parameters including V100, V150, V200, the doses delivered to 90% of the target volume (D90) and Dmax of the spinal cord were evaluated.

Follow-up schedule. Clinical and radiographical evaluation of the tumor response was performed 1 month after implantation. Follow-ups were scheduled every 2 months for the first year post-implantation and every 3-6 months thereafter. The therapeutic outcome was assessed according to the response evaluation criteria in solid tumors (RECIST) standard (24), which includes: Complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Local tumor control referred to the absence of tumor progression on CT (SD + PR + CR).

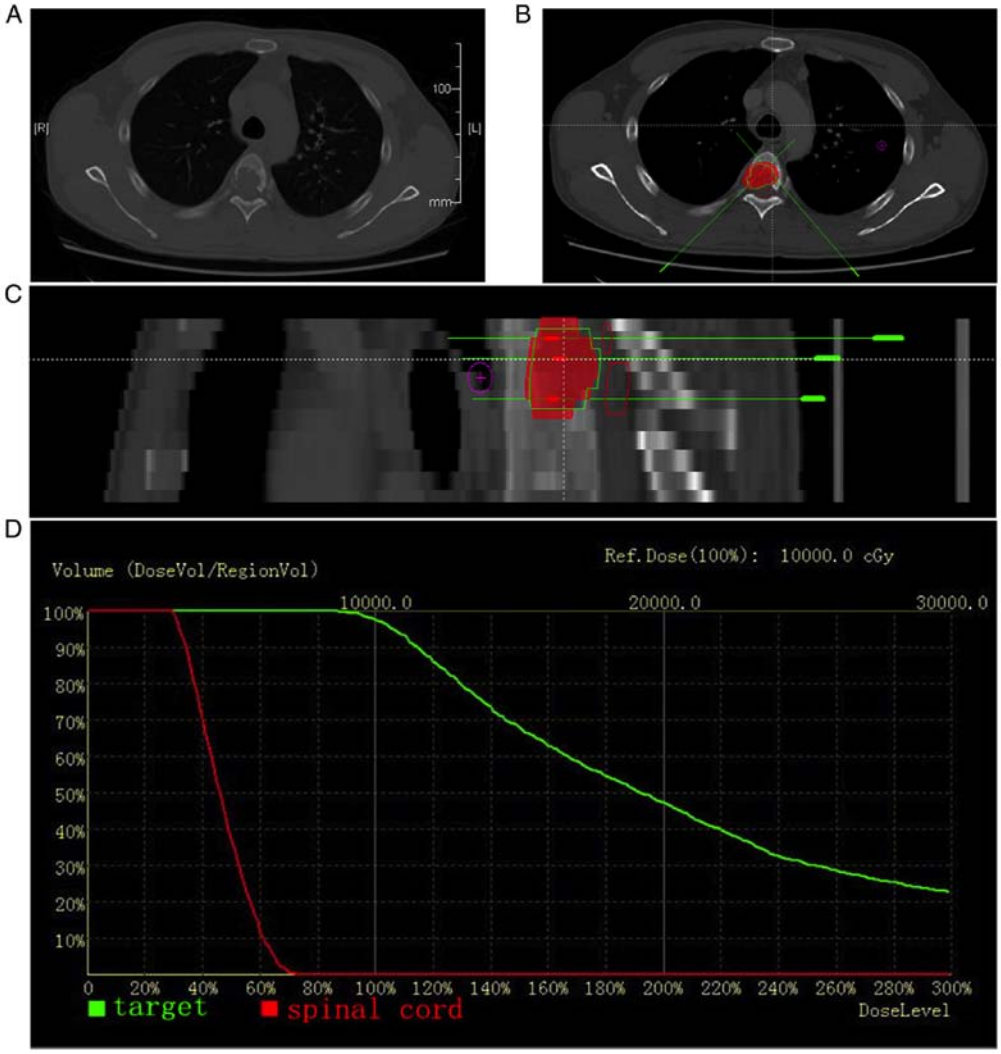

Figure 1. Pre-implant planning of I-125 brachytherapy. (A) T5 metastasis of lung cancer, (B and C) Axial and sagittal images of pre-implant treatment planning that shows the seeds distribution and isodose curve, (D) Dose-volume histogram of the target tumor (green) and spinal cord (red).

Statistical analysis. Dosimetry parameters were reported as the means ± standard deviation. Statistical analysis was performed using SPSS 20.0 software (IBM Corp.). Paired t-tests were performed to compare the difference in dosimetric parameters between the pre- and post-implant conditions. The data in the text are consistent with a normal distribution. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Pre-implant dosimetric characteristics. The V100 was between 96.50-99.80% (mean; 97.80%) and the V200 was between 35.20-49.50% (mean; 43.97%). The Dmax was between 18.17 and 74.32 Gy (mean, 63.54 Gy). The D90 was between 113.20 and 128.86 Gy (mean; 119.07 Gy) and the number of seeds per patient ranged from 8-44 (median, 30; Fig. 1A-D). The pre-implant dosimetric characteristics are presented in Table II.

Post-implant dosimetric characteristics. The number of I-125 seeds that were implanted ranged from 10-58 (median, 30; Fig. 2A-D). The specific activity of the I-125 seeds ranged from 0.3-0.8 mCi per seed (median; 0.6 mCi). The V100 was between 66.40 and 96.70% (mean, 84.46%) and the V200 was between 21.10 and 67.90%) (mean, 45.73%). The D90 ranged from 62.31-128.39 Gy (mean, 94.15 Gy). The Dmax ranged from 16.07-274.30 Gy (mean, 112.78 Gy), for the cauda equina. The post-implant dosimetirc characteristics are presented in Table III.

Pre- and post-implant dosimetric comparisons. The pre- and post-implanting plan-associated parameters are presented in Table IV. A greater number of needles were used in the pre-implant treatment planning (mean, 9) compared with the implantation (mean, 4). However, the mean GTV, number of seeds and the activity per seed were revealed to be similar between the two groups.

The pre- and post-implant dosimetric comparisons are presented in Table V and Fig. 3. The mean D90 value in the pre-implant planning images of the spine was greater than the post-implant dosimetry (119.07 vs. 94.15 Gy; $P<0.05$). Similarly, the mean pre-implant V100 was greater than the mean post-implant V100 (97.80 vs. 84.46%; $P<0.05$), of the prescribed doses. These differences may be due to variations

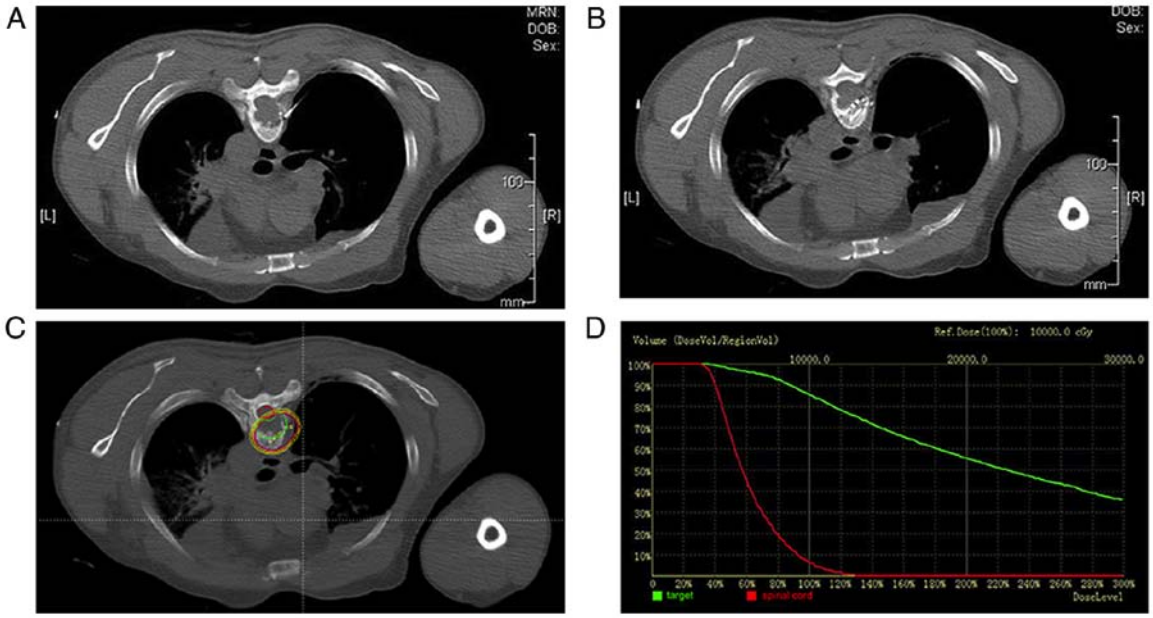

Figure 2. Post-implant CT scans following I-125 seed implantation. (A) The piercing process: An 18-gauge needle was inserted into the tumor to implant I-125 seeds, (B and C) Seed distributions and isodose curves of I-125 seed implantation, (D) Dose-volume histogram of the target tumor (green) and spinal cord (red).

in the shape, puncture path, position of critical organs, such as the spinal cord, and bone obstruction. Therefore, it is difficult to precisely implant the seeds according to the pre-implant plan. The mean Dmax of the spinal cord in post-implant dosimetry was higher compared with pre-implant planning (112.78 vs. 63.54; $P<0.05$). However, the V150 and V200 were revealed to be similar between the two groups.

Local control and survival. The mean time between the implantation and the follow-up was 5.45 months (range, 2-17 months). All patients survived until the end of the follow-up. No cases of CR were observed in the combined-treatment group, while one case of PR (9.1%), 10 cases of SD (90.9%) and no cases of PD (0.0%) were observed, with a local control rate of 100.0%.

Discussion

I-125 brachytherapy has served as a tumor treatment strategy for a number of years. Several studies have demonstrated that I-125 brachytherapy provides satisfactory local control of solid tumors, including prostate carcinoma, lung cancer, lung metastasis and pancreatic cancer (25-27). I-125 seeds are permanently implanted into the tumor and low energy γ-rays are continuously emitted. Due to the low penetration of low energy γ-rays, dose deposition to tissue decreases rapidly with distance from the radioactive source (23). The radiobiological advantages of interstitial I-125 seed implants include decreased treatment time, a high radiation dose conformity to the tumor and the sparing of surrounding normal tissues (17). These traits are particularly desirable for the treatment of spinal tumors, because poor dose control can result in myelitis and vertebral body fracture, which would be catastrophic.

Pre-implant treatment planning assesses the dose distribution and seed arrangement based on volumes recorded in CT images, which are acquired several days or weeks prior to implantation. Accurate dose distribution increases the efficacy of I-125 brachytherapy (28). Although seeds are implanted into patients according to a predetermined arrangement, studies have suggested that the post-implant dosimetry is usually different from the pre-implant planning in prostate brachytherapy (29-31). The potential reasons for such discrepancies between the pre- and post-implant dosimetry include, post-operative prostatic inflammation and edema (32,33), difficulty to precisely implant the seeds according to the pre-implant plan (34,35), measures taken by the implanting physician to spare the surrounding normal tissues (36,37) and post-operative seed displacement (36-38). However, to the best of our knowledge, very few studies have directly investigated this issue in spinal metastases brachytherapy.

The present study compared the pre- and post-implant dosimetry in I-125 spinal metastases brachytherapy. The results revealed a difference in the mean V100 and D90 between the two groups. In all 11 cases, the post-implant V100 was lower compared with the pre-implant treatment plans, whereas there was only one case in which the post-implant D90 was greater than that of the pre-implant. In this case, osteolytic destruction was serious and both needle puncture and seed implantation were easy. It has been suggested that the stiffness and shape of the bone are vital to the implantation procedure, enabling the correct implantation of the seeds and protection of the OAR, particularly the spinal cord (39). Similarly, the average number of needles used in the implantation was lower than the pre-implant treatment planning. Despite a difference in the V100 and D90 between the two groups, the local control rate remained at 100%. This may indicate that V100 <90% is effective in controlling bone metastatic diseases.

The prostate volume changes that were observed during and after the seed implantation were primarily due to prostatic inflammation and edema (40). In the spinal cases, the present data revealed little difference in the GTV both before and after implantation. This may be due to the fact that the spine is not

Table II. Pre-implant treatment planning characteristics.

Patient no.	Location of spine metastasis	GTV, cc	Seed activity, mCi	No. of needles, n	No. of seeds, n	D90, Gy	GTV: V100, %	GTV: V150,%	GTV: V200, %	Dmax of spinal cord, Gy
1	T10	30.5	0.8	10	30	117.08	97.00	72.40	49.20	74.17
2	L2	8.2	0.8	7	11	115.95	98.00	64.60	38.20	69.38
3	T2	4.9	0.8	5	8	128.86	99.80	75.00	49.50	60.33
4	L4	51.2	0.8	15	44	114.00	96.50	71.40	48.70	74.11
5	T5	8.3	0.6	9	15	114.54	97.60	68.10	47.30	72.62
6	T7	14.4	0.6	12	23	116.92	97.20	69.00	40.20	73.26
7	T12	5.0	0.6	4	11	127.64	99.00	78.00	45.60	18.17
8	T11	34.5	0.6	8	39	118.40	97.00	73.30	49.30	74.32
9	L2	32.3	0.6	11	37	123.95	98.70	70.30	37.60	46.16
10	L4	42.0	0.8	12	37	113.20	97.30	69.10	42.90	72.94
11	T7	8.8	0.3	9	30	119.25	97.70	64.40	35.20	63.48

GTV, gross tumor volume; D90, dose delivered to 90% of the target volume.

Table III. Post-implant dosimetric characteristics.

Patient no.	Location of spine metastasis	GTV, cc	Seed activity, mCi	No. of needles, n	No. of seeds, n	D90, Gy	GTV: V100, %	GTV: V150, %	GTV: V200,%	Dmax of spinal cord, Gy
1	T10	30.6	0.8	5	25	64.72	73.20	54.40	40.60	123.32
2	L2	8.3	0.8	4	12	79.18	75.00	58.00	40.70	92.61
3	T2	4.9	0.8	3	11	102.53	90.70	71.90	54.60	38.31
4	L4	51.2	0.8	5	42	103.72	91.70	66.00	47.60	119.87
5	T5	8.3	0.6	3	22	88.13	85.80	68.50	55.60	129.73
6	T7	14.4	0.6	6	37	128.39	96.70	83.30	65.30	274.30
7	T12	5.1	0.6	2	10	101.01	90.30	65.10	29.70	16.07
8	T11	34.6	0.6	2	34	62.31	66.40	38.90	21.10	159.30
9	L2	32.4	0.6	9	58	113.17	93.40	79.90	67.90	77.64
10	L4	41.9	0.8	9	52	107.88	92.10	74.90	56.40	110.85
11	T7	8.8	0.3	3	22	84.61	73.80	33.00	23.50	98.54

GTV, gross tumor volume; D90, dose delivered to 90% of the target volume.

Table IV. Plan-associated parameters for pre-planning and post implantation.

Parameter	Pre-planning	Post-implanting	P-value
GTV, mean (range) cc	21.83 (4.9-51.2)	21.87 (4.9-51.2)	0.104
Number of needles, median (range)	9 (4-15)	4 (2-9)	<0.001
Number of seeds, median (range)	30 (8-44)	30 (10-58)	0.231
Activity per seed, median (range)	0.6 (0.3-0.8)	0.6 (0.3-0.8)	1

Table V. Pre- and post-implant dosimetric comparisons.

Parameter	Pre-implant	Post-implant	P-value
D90, mean (range), Gy	19.07 (113.20-128.86)	94.15 (62.31-128.39)	0.002
V100, mean (range), %	97.80 (96.50-99.80)	84.46 (66.40-96.70)	0.001
V150, mean (range), %	70.51 (64.40-78.00)	63.08 (33.00-83.30)	0.148
V200, mean (range), %	43.97 (35.20-49.50)	45.73 (21.10-67.90)	0.746
Dmax of cord, mean (range), Gy	63.54 (18.17-74.32)	112.78 (16.78-274.30)	0.018

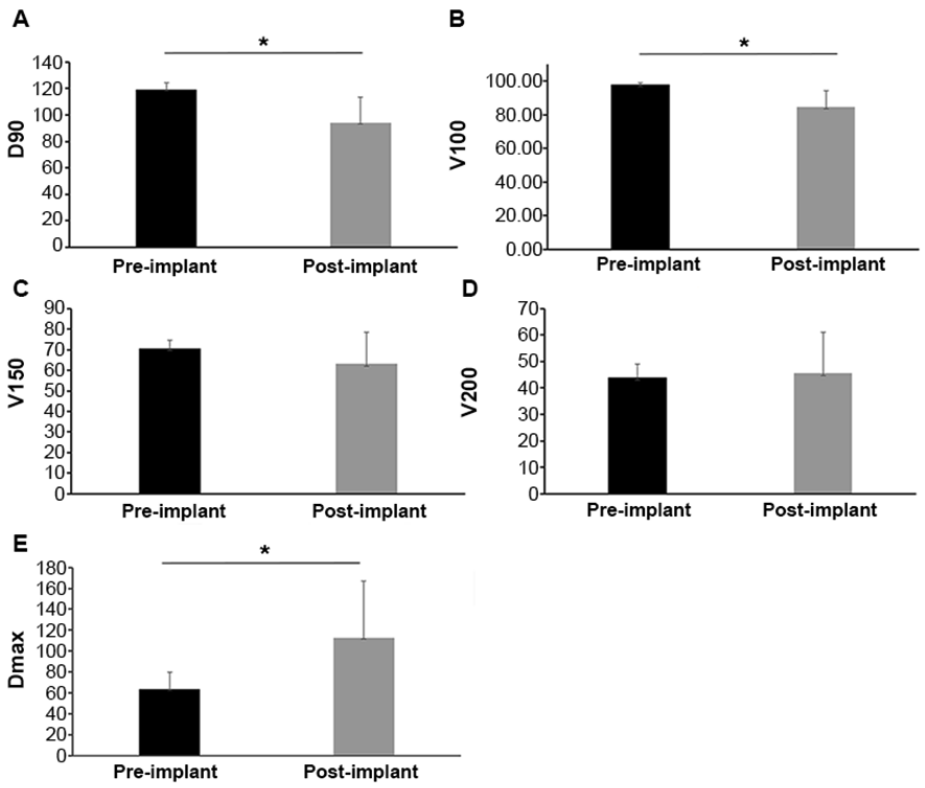

Figure 3. Comparison between dosimetric parameters in the pre-implant treatment plan (black) and the post-implant dosimetry (gray) for the 11 patients. (A) Pre-implant D90 was greater than the post-implant D90 (119.07±5.41 vs. 94.15±20.40 Gy), (B) Pre-implant V100 was greater than the post-implant V100 (97.80±0.99 vs. 84.46±10.35%), (C) Pre-implant V150 was similar to the post-implant V150 (70.51±4.13 vs. 63.08±15.94%), (D) Pre-implant V200 was similar to the post-implant V200 (43.97±5.37 vs. 45.73±16.05%). (E) Mean Dmax of the spinal cord in post-implant dosimetry was higher compared with pre-implant planning (112.78 vs. 63.54). Columns represent the means ± standard deviation for D90 (Gy), V100 (100%), V150 (100%), V200 (100%) and Dmax (Gy). *P<0.05 vs. control. D90, dose delivered to 90% of the target volume.

prone to edema upon surgery. The Dmax of the spinal cord in post-implant dosimetry was generally greater than in the pre-implant treatment plans. In two of the cases (no. 3 and no. 7), the Dmax in the spinal cord was lower following implantation, and the lesion was located away from the spinal cord. In one case, the Dmax of the spinal cord increased to 274.3 Gy without the occurrence of myelitis. Rogers *et al* (41) reported that radiation myelitis was not recorded despite the delivery of 167.3 Gy.

Similarly, Harrison *et al* (42) demonstrated that brachytherapy, using permanent or temporary implants, revealed no myelitis following 60 Gy in paraspinal tumors, pancoast carcinoma or other sarcoma treatment. Although the recommended clinical dose limit for the spinal cord is 45 Gy (41), no myelitis was observed. This may indicate that: i) CT used for these two plans had spinal cord coverage larger than the true spinal cord; ii) dose distribution was calculated using a TPS brachytherapy planning system based on the AAPM TG43 formalism that does not account for the complex internal environment in humans or iii) the 45 Gy for the spinal cord was obtained from previous data in the study of conventional radiotherapy and EBRT (3,43), and currently, there is no equivalent conversion. Future studies should continue to investigate the recommended clinical dose limit of spinal cord in brachytherapy. Furthermore, a longer follow-up period should be implemented for the evaluation of a suitable spinal cord dosage and the assessment of the clinical significance of suboptimal PTV dose coverage in patients who attain good dosimetry.

A high rate of tumor control and rapid pain relief was achieved with interstitial I-125 seed brachytherapy. The present study demonstrated that CT guided I-125 seed brachytherapy in the treatment of spinal metastases tumors is both safe and effective. However, the seed number and position in the post-implant dosimetry was observed to deviate from the pre-implant treatment planning. Thus, strict adherence to the pre-implant treatment plan remains crucial.

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Availability of data and materials

The datasets used and/or analyzed in the present study are available from the corresponding author on reasonable request.

Authors' contributions

GC analyzed and interpreted the data, and wrote the manuscript. MH designed the present study. All authors approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Shandong Provincial Hospital (approval no. 2015-011; Jinan, China). Written informed consent for publication was obtained from all patients.

Patient consent for publication

Not applicable.

Competing interests

The authors have declared that they have no competing interests.

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