A preliminary comparative clinical study of vertebroplasty with multineedle or single-needle interstitial implantation of $^{125}$I seeds in the treatment of osteolytic metastatic vertebral tumors

Clinical article

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Object. Percutaneous vertebroplasty (PVP) combined with brachytherapy using the interstitial implantation of $^{125}$I seeds has previously yielded encouraging clinical results in the treatment of metastatic vertebral tumors. However, the bone cement injection volume is very small due to the osteolytic damage to the metastatic vertebrae, and the ideal spatial distribution of the $^{125}$I seeds is difficult to achieve. In the current study, the authors present a clinical method for puncture needle insertion to achieve a greater bone cement injection volume and a more ideal spatial distribution of the $^{125}$I seeds.

Methods. Twenty-nine patients with osteolytic metastatic vertebral tumors were divided into 2 groups and were treated with either PVP combined with multineedle interstitial implantation of $^{125}$I seeds, or PVP combined with single-needle interstitial implantation of $^{125}$I seeds. Clinical efficacy was evaluated according to a visual analog scale (VAS) of pain, the Karnofsky Performance Scale (KPS), and the Response Evaluation Criteria In Solid Tumors (RECIST).

Results. Back pain was significantly alleviated in all patients after surgery. Compared with the preoperative scores, the VAS scores were significantly decreased in both groups at 1 week and 3 months postoperatively ($p < 0.05$), but there were no significant intergroup differences ($p > 0.05$). The postoperative quality of life was improved in both groups; the KPS scores increased significantly compared with the preoperative scores ($p < 0.05$), and the postoperative KPS scores were significantly different between the 2 groups ($p < 0.05$). No intergroup differences were observed in pain alleviation, but the bone cement injection volume was significantly greater in the multineedle group than in the single-needle group ($p < 0.05$). The clinical benefit rate and disease control rate at 3 months after the operation were both significantly better for the multineedle group ($p < 0.05$).

Conclusions. The outcomes of PVP combined with multineedle interstitial implantation of $^{125}$I seeds in patients with osteolytic metastatic vertebral tumors appeared to be better than the outcomes of PVP combined with single-needle interstitial implantation of $^{125}$I seeds. These better outcomes may be the result of the greater bone cement injection volume and the more ideal spatial distribution of the $^{125}$I seeds.

Key Words • spinal metastasis • percutaneous vertebroplasty • iodine 125 • brachytherapy • multineedle puncture • oncology

Spinal metastases are common complications of malignant tumors, and the most frequent metastatic sites are the thoracic and lumbar vertebrae.10,15 The tumors most likely to result in spinal metastasis include those of the breast, lung, and prostate.21 The incidence of spinal metastasis has gradually increased in recent years along with the increased incidence of each type of tumor, the improvements in diagnostic techniques, and the prolongation of life in patients with cancer.19 With the damage from metastasis aggravating the spine, the spinal cord may be affected (constricted, compressed), which could induce sensory and motor dysfunction or even paralysis in serious cases. Furthermore, osteolytic metastatic tumors can destroy the vertebral bone structure, impair spinal...
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stability, or even induce pathological vertebral fractures, thus seriously affecting the quality of life of patients.\textsuperscript{2,3} The traditional surgical treatments for spinal metastasis have many disadvantages, such as major trauma, a high incidence of complications, and a long recovery time. Percutaneous vertebroplasty (PVP) is an effective treatment for spinal metastases.\textsuperscript{12} $^{125}$I is a synthetic low-energy radioisotope of iodine that emits $\gamma$-rays and x-rays, and this isotope has often been used for brachytherapy.\textsuperscript{21} Percutaneous vertebroplasty combined with the implantation of $^{125}$I seeds not only restores spinal stability but also has local antitumor effects.\textsuperscript{23} However, traditional PVP, in which 1 needle punctures the vertebral body at each pedicle, does not allow for ideal $^{125}$I seed distribution or a large bone cement injection volume, especially in osteolytic vertebrae. In this study, we used either multiple or single needles to implant the seeds and cement, and we assessed the differences between the implantation methods. To date, few comparative clinical studies concerning the implantation of $^{125}$I seeds have been performed. In Zibo Central Hospital from November 2010 to June 2012, 16 patients with osteolytic spinal metastases were treated with PVP combined with single-needle interstitial implantation of $^{125}$I seeds, and 13 patients with osteolytic spinal metastases were treated with PVP combined with multineedle interstitial implantation of $^{125}$I seeds, both with significant clinical efficacy. In this paper, we report the details of our preliminary study.

**Methods**

**Patient Selection**

Twenty-nine patients were included in this study (18 men and 11 women); the patients ranged in age from 28 to 70 years (mean 49.2 years). The indications for study inclusion were: having an estimated survival of more than 3 months according to orthopedic and oncology specialists; a lack of complete paralysis; having fewer than 3 damaged vertebrae; having no metastatic disease in other organ systems; being in poor health, resulting in ineligibility for open surgery; and the inability to tolerate long cycles of chemotherapy and radiation therapy. To observe the effects of PVP and brachytherapy, the patients who were strong enough for open surgery, chemotherapy, and conventional external beam radiation therapy (EBRT), and those who could not lie prone for more than 1 hour, were excluded from this study. The primary tumors included 13 cases of lung cancer, 6 cases of breast cancer, 3 cases of thyroid cancer, 2 cases each of gastric cancer, rectal cancer, and prostate cancer, and 1 case of kidney cancer. In total, 47 vertebrae were involved, including 31 thoracic vertebrae and 16 lumbar vertebrae. The vertebral metastases primarily manifested as osteolytic destruction, including obvious damage to the posterior margin of 11 vertebrae, combined destruction in the pedicles and transverse processes of 8 vertebrae, and 5 cases of paraspinal metastasis that formed paraspinal masses. One patient had incomplete paralysis prior to surgery.

All the patients were diagnosed via aspiration biopsy or had undergone surgical excision of their primary tumors, which were verified by pathological examination. Furthermore, all patients had significant low-back pain and corresponding imaging examination results. The 29 patients were randomly divided into 2 groups, in which 16 patients (26 vertebrae) underwent PVP combined with single-needle interstitial implantation of $^{125}$I seeds, and 13 patients (21 vertebrae) underwent PVP combined with multineedle interstitial implantation of $^{125}$I seeds. The patients and their families were well-informed of the details and signed informed consent forms prior to participating in the study. This study was approved by the Medical Ethics Committee of Zibo Central Hospital.

**Instruments and Radioactive Source**

Flat panel detector digital subtraction angiography (GE) was used for intraoperative image monitoring. The radioactive $^{125}$I seeds were purchased from Beijing Atom Hi-Tech Co., Ltd., at a size of 0.8 mm $\times$ 0.45 mm and an activity range of 0.5–0.9 mCi. The complete set of Model 201 vertebroplasty instruments was obtained from Shandong Guanlong Medical Supplies Co., Ltd. The polymethylmethacrylate (PMMA) bone cement used in our study was Osteopal V (Heraeus Medical GmbH).

**Three-Dimensional Treatment Planning System**

The tumor target regions were outlined preoperatively with a treatment planning system (Nuclear Industry Corp., Beijing Kelinzhong Medical Technology Institute);\textsuperscript{11} spatial patterns of the seed distribution were created for each patient, and the minimum peripheral dose range was preliminarily defined as 90–140 Gy.

**Operative Techniques**

The surgery was performed in an interventional operating room under the guidance of a flat panel detector digital subtraction angiography instrument. A single experienced doctor administered the local anesthesia and the preoperative and intraoperative analgesic treatments while the patient was prone. The puncture approaches included the transpedicular and extrapedicular approaches.\textsuperscript{9} All patients were given bilateral punctures; the patients in the single-needle group were given regular single-needle punctures on each side. According to the tumor position and size, patients in the multineedle group were given 1 or 2 additional needle punctures, which were no less than 1 cm away from the posterior wall of the vertebral body, to ensure that the needle tips were 3-dimensionally distributed within the tumor (Fig. 1). A sufficient number of $^{125}$I seeds were implanted according to the treatment planning system after the successful puncture. The PMMA bone cement was prepared on site and was drawn into the syringe after seed implantation. The cement was not injected until the polymerization process of the PMMA was in the waiting phase, and lateral floroscopy was used to closely monitor the injection process to prevent leakage of bone cement from the vertebral bodies. The number of implanted $^{125}$I seeds was calculated according to the treatment planning system. The seeds were distributed densely in the single-needle group, and the spatial pattern was significantly different from the planned spa-
Efficacy Evaluation

Computed tomography scans were obtained 3 months after seed implantation. According to the Response Evaluation Criteria In Solid Tumors (RECIST), a complete response is the disappearance of all target lesions for more than 4 weeks; a partial response occurs when all the target lesions decrease by more than 50% for more than 4 weeks; progressive disease occurs when all the target lesions increase by more than 25%; and stable disease is the index between a partial response and progressive disease, that is, all the target lesions increase by less than 25% or decrease by less than 50%. The response rate and disease control rate are commonly used clinical indices: the response rate = (complete response + partial response)/total cases × 100%; the disease control rate = (complete response + partial response + stable disease)/total cases × 100%.

Pain was scored according to a visual analog scale (VAS), and improvement in the quality of life was analyzed with the Karnofsky Performance Scale (KPS) score. The data were obtained before treatment, and 1 week and 3 months after surgery.

Statistical Analysis

Statistical analyses were performed using SPSS version 16.0 (SPSS Inc.). The data were expressed as means ± SDs; the measurement data were analyzed with the Student t-test, and p < 0.05 was regarded as statistically significant.

Results

All patients underwent successful surgical operations. There was no metastatic disease in other vertebrae or in other organ systems. All patients completed the 3 months of follow-up, but 4 patients in the single-needle group and 3 patients in the multineedle group died 6 months after surgery. The outcomes at 3 months after the operation in the single-needle group were as follows: complete response, 0 vertebrae; partial response, 19 vertebrae; stable disease, 6 vertebrae; progressive disease, 1 vertebrae; response rate 73.1%; and disease control rate 96.2% (Table 1). The outcomes in the multineedle group at 3 months after the operation were as follows: complete response, 0 vertebrae; partial response, 18 vertebrae; stable disease, 3 vertebrae; progressive disease, 0 vertebrae; response rate 85.7%; and disease control rate 100% (Table 1). Overall, 8–30 radioactive $^{125}$I seeds were implanted into each vertebra.

### Table 1: Response rate and disease control rate comparison between the single-needle and multineedle groups

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>3 Mos Postop (%)</th>
<th>$\chi^2$</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>response rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>single-needle group</td>
<td>73.1</td>
<td>5.116</td>
<td>0.024</td>
</tr>
<tr>
<td>multineedle group</td>
<td>85.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>disease control rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>single-needle group</td>
<td>96.2</td>
<td>4.519</td>
<td>0.034</td>
</tr>
<tr>
<td>multineedle group</td>
<td>100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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vertebral body (mean 18.5 seeds/segment); the number of seeds implanted into the appendix and the paraspinal metastasis lesion sites was 4–10 seeds/segment. No significant difference between the 2 groups was observed in the number of seeds implanted into each vertebral body. The volumes of bone cement injected into the thoracic vertebrae and lumbar vertebrae were 1.5–4.5 ml/segment and 1.5–7.5 ml/segment, respectively. The average volume of injection was 2.3 ± 0.5 ml/segment in the single-needle group and 3.9 ± 1.4 ml/segment in the multineedle group, a significant difference (p < 0.05). No postoperative complications, including infections, blood vessel and spinal cord injuries, or pulmonary emboli, were observed in either group. There were 3 cases of bone cement leakage, including 1 case of intervertebral space leakage and 2 cases of paravertebral vein leakage. No cases of leakage were accompanied by any clinical symptoms.

Back pain was significantly alleviated in all patients after surgery. The VAS scores were significantly decreased in both groups at 1 week and 3 months after the operation compared with the preoperative scores (p < 0.05; Table 2), but no intergroup differences were observed (p > 0.05). The postoperative quality of life was improved in both groups: the KPS scores significantly increased compared with the preoperative scores (p < 0.05), and the postoperative KPS scores were significantly higher in the multineedle group than in the single-needle group (p < 0.05). No intergroup differences were observed in pain alleviation, but as previously noted, the bone cement injection volume was significantly different between the groups (p < 0.05). The clinical response rate and disease control rate at 3 months after the operation were significantly different between the 2 groups (p < 0.05), with the multineedle technique shown to be more effective than the single-needle technique (Table 1).

**Discussion**

Spinal metastases usually induce severe pain or even pathological fractures that may compress the spinal cord and result in limb sensory and motor disorders. All of these factors not only seriously affect the quality of life of cancer patients but also hasten death. The treatment principles include bone pain management, improvement in the quality of life, the prevention of complications, and improvement in the prognosis. Traditional surgical methods are associated with major trauma, a high incidence of complications, and long periods of bed rest that are difficult for patients with metastatic spinal tumors to tolerate, and multivertebral body damage cannot be eliminated with traditional surgery. Traditional chemotherapy also has many disadvantages, such as long cycles and significant adverse effects, which might not be tolerable in unfit patients (such as the weak, elderly, those with poor performance status, and others).

Radiation therapy is accepted as the first-line choice for most patients with metastatic spinal tumors. Brachytherapy was introduced in radiation therapy for the treatment of prostate cancer in 1965. Brachytherapy is the permanent placement of radioactive sources inside or next to the tumor. Radioactive $^{125}$I seeds persistently kill all tumor cells in the growth cycle. Therefore, brachytherapy with $^{125}$I seeds has more effective results than those obtained with the repeated short-term doses of radiation used in conventional EBRT. To cover the entire tumor and marginal subclinical area effectively, the placement of $^{125}$I seeds must be guided with a 3D treatment planning system to achieve an ideal $^{125}$I seed spatial pattern. The treatment planning system digitally processes the imaging data of the patients, constructs a 3D digital model of the target region, and designs an ideal seed distribution pattern according to the tumor boundaries, the location of key tissues, and the prescribed radiation dose; therefore, the radioactive seeds can be distributed more precisely and comprehensively. However, the 3D distribution of radioactive $^{125}$I seeds is difficult to achieve in a traditional one-needle-through-each-vertebral-pedicle PVP operation; thus, we revised the single-needle puncture method to a multineedle puncture method. In this manner, we were able to ensure that the radioactive seeds were distributed as much as possible according to the ideal pattern preoperatively determined by the treatment planning system.

Since Galibert et al. successfully treated 1 patient with a cervical vertebral hemangioma using PVP in 1984, this method has become an important approach in the treatment of vertebral tumor metastases because of the minimal trauma, minor complications, and good efficacy of PVP. This method can stabilize collapsed vertebral bodies, destroy cancer cells and pain receptors, and block the vessels of tumors. However, as a type of local treatment measure, PVP can kill only the tumor cells that surround the PMMA, the active time is quite short, and the tumor cells cannot be killed persistently. To enhance the efficacy of PVP, some authors combined it with the interstitial implantation of $^{125}$I seeds. It has even been reported that PVP with $^{125}$I brachytherapy reduces the incidence ratio of myelopathy in clinical settings. In our study, there were no cases of myelopathy, either in the multineedle puncture group or in the single-needle puncture group. Because of the immediate efficacy of PMMA in the treatment of vertebral tumor metastases, it is difficult to determine the difference in early outcomes of PVP and PVP combined with interstitial implantation of ra-

**TABLE 2: Comparison between preoperative and postoperative VAS and KPS scores**

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>VAS Score</th>
<th>KPS Score</th>
</tr>
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<tbody>
<tr>
<td>preop</td>
<td></td>
<td></td>
</tr>
<tr>
<td>single-needle group</td>
<td>7.7 ± 1.3</td>
<td>45.6 ± 4.3</td>
</tr>
<tr>
<td>multineedle group</td>
<td>8.0 ± 1.2</td>
<td>42.3 ± 5.8</td>
</tr>
<tr>
<td>1 wk postop</td>
<td></td>
<td></td>
</tr>
<tr>
<td>single-needle group</td>
<td>2.1 ± 0.8</td>
<td>81.6 ± 6.2</td>
</tr>
<tr>
<td>multineedle group</td>
<td>2.4 ± 1.1</td>
<td>87.4 ± 7.1</td>
</tr>
<tr>
<td>3 mos postop</td>
<td></td>
<td></td>
</tr>
<tr>
<td>single-needle group</td>
<td>2.6 ± 1.0</td>
<td>80.1 ± 7.3</td>
</tr>
<tr>
<td>multineedle group</td>
<td>2.2 ± 1.3</td>
<td>86.1 ± 6.4</td>
</tr>
</tbody>
</table>

* All values given as mean ± SD.
dioactive seeds. Furthermore, most of the patients in both groups refused to accept a late operation. Therefore, to provide the patients with a long-term tumor killing effect, we did not include a control group using PMMA only.

The primary complication of this combined treatment method was bone cement leakage induced by the PVP, although there were no clinical symptoms in either group. In the treatment of osteoporotic vertebral compression fractures, the unanimous consensus is that there is no significant correlation between bone cement injection volume and clinical pain alleviation, and 1.0–2.0 ml of PMMA injected into the thoracolumbar vertebrae produced good analgesic effects. Belkoff et al. reported that 2 ml of bone cement could restore vertebral strength; however, for spinal metastases, we recommend injecting more bone cement into the tumor tissue to increase the contact area between the bone cement and tumor tissue. By doing so, more tumor tissue can be destroyed by the bone cement. However, in many cases in this study, the CT scans revealed a large number of tumors that had invaded and destroyed the posterior wall of the vertebral body. This situation is common for osteolytic vertebral metastases. Mousavi et al. reported that cement extravasation occurred in 85.7% of patients with metastatic spinal tumors, although without significant clinical complications. Baroud et al. believed that the leakage rate of bone cement was positively correlated with the injection volume. The multineedle puncture method provides an opportunity to inject a greater volume of cement with the same injection volume via each needle.

Conclusions

Percutaneous vertebroplasty combined with the multineedle or single-needle interstitial implantation of 125I seeds showed good clinical efficacy in alleviating the pain of spinal metastases in this study. However, the multineedle puncture approach has many advantages, such as more reasonable seed distribution patterns, increased bone cement injection volumes, and less cement extravasation. Both the control of spinal metastases and the postoperative quality of life in the multineedle group were better than those in the single-needle group. However, this operation demands a high skill level of the surgeon. Serious surgical complications can occur if the surgeon does not have extensive experience in vertebral body punctures, especially upper thoracic punctures.

There were some limitations in this preliminary clinical trial. To observe the effects of PVP and brachytherapy and to exclude the effects of open surgery, chemotherapy, and EBRT, the patients in this study were in poorer health than typical patients with vertebral metastatic tumors, and they were only a small portion of all patients with vertebral metastatic tumors. The small patient population also prevented us from establishing a control group, specifically a group using only PMMA.

The VAS and KPS scores can be affected easily by many factors, especially when new metastatic disease occurs in additional vertebrae or in other organ systems. This is only a preliminary clinical study to compare the effects of multineedle or single-needle placement at delivering 125I and bone cement into metastatic spinal lesions. In the future, we will attempt to include a larger population of patients and a control group, as well as a longer follow-up period, to formulate more definitive conclusions regarding these methods.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: T Li. Acquisition of data: Z Wang, Liu, Han, P Wang. Analysis and interpretation of data: J Li, Liu, Han, P Wang. Drafting the article: T Li, Z Wang. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: T Li. Statistical analysis: J Li, Liu. Administrative/technical/material support: T Li, J Li, Liu. Study supervision: T Li.

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