Results of Treating Vertebral Metastases by Percutaneous Vertebroplasty Combined with Interventional Chemotherapy

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OBJECTIVE Vertebral metastases are a common manifestation in patients with advanced cancer and treatment is often ineffective. This study was conducted to explore the efficacy of treating vertebral metastases by percutaneous vertebroplasty (PVP) combined with interventional chemotherapy.

METHODS Seventy-five patients with vertebral metastases (42 men, 33 women; ages 31~76 years) were divided into 2 groups: 39 cases were treated by PVP combined with chemotherapy (VPCC group), and 36 cases were treated by PVP alone (VP group). All procedures were guided by computed tomography (CT) scanning. The results and complications were evaluated by a questionnaire regarding pain and routine follow-up.

RESULTS The response rate was significantly higher in the VPCC group than in the VP group (93.0% *vs* 74.4%, P<0.05); total response rates for the VPCC and VP groups were 25.6% and 10.3% respectively. A common complication related to VPCC was transient aggravating pain.

CONCLUSION PVP may ameliorate pain, and consolidate the vertebrae of patients with vertebral metastases. Its short-term effect may be enhanced by adding drugs into the bone cement.

KEYWORDS: vertebral metastases, vertebroplasty, radiology, interventional, tomography, X-ray computed.

Percutaneous vertebroplasty (PVP) consists of injection, usually under fluoroscopic guidance, of polymethylmethacrylate (PMMA) through a needle into a weakened vertebral body to treat vertebral collapse due to osteoporosis, vertebral metastasis or to obtain analgesia and spinal stabilization. The original technique of percutaneous vertebroplasty involved placement of polymethylmethacrlylate (PMMA) or autologous bone graft via an open-operation. This procedure has been used in the past for the management of neoplastic compression fractures. The first percutaneous vertebroplasty of which we are aware was performed in France by Galibert et al.[1] in 1984 and reported in the literature in 1987. A patient with a cervical vertebra angioma underwent the procedure to obtain analgesia and spinal stabilization. Over the past few years, the technique of percutaneous vertebroplasty has been developed for the treatment of osteolytic metastases, myeloma, hemangioma, and osteoporosis.[2-5]

Metastases at a distant place are a common manifestation seen in pa-

tients with advanced cancer. Vertebral collapse due to metastases frequently causes persistent and often excruciating pain which significantly impairs mobility and the quality of life. The purpose of this study was to determine the efficacy of vertebroplasty combined with chemotherapy as a means to treat vertebral metastases.

MATERIALS AND METHODS

Clinical data

Patient data

A prospective study was carried out in the Department of Radiology, Gansu Province Tumor Hospital from May 2002 to June 2004. Seventy-five patients with vertebral metastases (42 men, 33 women; ages 31~76 years, median 52 years) were divided into 2 groups: 39 cases were treated by percutaneous vertebroplasty combined with chemotherapy (VPCC group), and 36 cases were treated by percutaneous vertebroplasty alone (VP group). All procedures were guided by computed tomography (CT) scanning. Altogether 79 vertebrae had a lesion. Thirty-seven metastatic foci were at the thoracic vertebrae, 42 at the lumbar vertebrae, and 3 at the sacral vertebrae. Eligible patients were treated for disabling back pain and/or impaired mobility secondary to vertebral collapse from varying etiology. All were refractory to conservative therapy. The clinical characteristics of patients who received percutaneous vertebroplasty (PVP) alone or PVP combined with chemotherapy are described in Table1.

There were no apparent significant differences between the 2 groups in their clinical characteristics. Radiography and CT were performed before vertebroplasty to assess the extent of the lytic lesions. All CT scans were obtained in the axial plane, unenhanced 5-mm-thick contiguous sections, with a Siemens AR Star. After injection, CT scans were performed to assess the disposition, appearance and leakage of the bone cement. Fourty-eight cases (VPCC 27 and VP 21) were re-examined by a second CT scan, 9 cases (VPCC 4 and VP 5) were re-examined by a third CT scan and 18 cas-

Table 1. Patient characteristics.

Items	VP group	VPCC group
Number of cases	36	39
Median age (years)	50(37-75)	52(31-76)
Gender (male/female)	19/17	23/16
Primary Cancer (cases)		
Lung	18	17
Breast	14	15
Stomach	2	4
Liver	1	2
Thyriod	-	1
Nasopharygeal	1	-
Involved vertebrae/cases	T8/3, T10/1, T11/6, T12/8, L1/6, L2/1, L3/5, L4/6, L5/2, S1/1	T8/1, T9/3, T10/4, T11/3, T12/8, L1/6, L2/4, L3/7, L4/2, L5/3, S1/2
Clinical pre-operative indication	Pain and/or stabilization	Pain and/or stabilization
Local post-operative complication	One case leaked toward disk without clinical symptoms, three cases leaked toward adjacent soft tissue without clinical symptoms	One case leaked toward epidural fat without clinical symptoms, one case leaked toward adjacent soft tissue without clinical symptoms,two cases leaked toward a disk without clinical symptoms
Chemotherapeutics		Five cases with EADM 10 cases with MTX, 24 cases with MMC

EADM:Epirubicin; MTX:Methotrexate; MMC:Mitomycin.

es were re-examined by radiography.

Instruments and drugs

The bone cement employed was Osteobond copolymer (Zimmer, Warsaw, IN., USA) which consisted of liquid methyl methacrylate (MMA), powdered polymethylmethacrylate (PMMA) and 10% barium sulfate. The chemotherapeutic agents were Epirubicin (EADM), Methotrexate (MTX) and Mitomycin (MMC). The copolymer was administered using 18 G epidural puncture needles and 1 ml plastic syringes.

Methods

Operative process

Prothrombin and partial prothrombin times were tested in all patients prior to vertebroplasty. The patients were placed in a prone or lateral position on the CT scanning table based on the position of the vertebral lesions. The injection point was determined by a self-made calibration scale, the injection pathway was planned, and the injection depth and angle were calculated using the CT monitor. Aseptic procedures and local anesthesia with 2% xylocaine were used on the overlying skin and tissues in the area of the injection. The injection depth and angle were gradually adjusted and the needle tip finally placed into the middle of the vertebral lesions using CT guidance.

The chemotherapeutic agents which were aimed at the primary malignant tumor, included EADM (10~20 mg), MTX (5~10 mg), and MMC (2~4 mg). The chemotherapeutic agents were homogeneously mixed with PMMA (10 g) and MMA (5 ml). Then the mixture was taken up into a 1 ml plastic syringe and injected slowly into the vertebral lesions. The doses injected were as follows: for the thoracic vertebrae 2.0~5.0 ml (mean 3.5 ml) and for the lumbar vertebrae 3.5~5.5 ml (mean 4.5 ml). Upon completing the injection, and removal of the needle, the puncture point was assessed for its appearance and leakage of bone cement. The patient was then placed in a supine position for 3 h for symptomatic treatment of pain, bleeding and inflammation.

Evaluation of therapeutic effect

The pain was scaled using a verbal rating scale (VRS) and visual analogue scale (VAS)[6]: The grades of preoperative pain were 0(no pain); I(slight pain); II (moderate pain): the pain was apparent and intense, the first echelon analgesics were required and sleep was disturbed; III (severe pain): the pain was unbearable and the second echelon analgesics were required; IV (excruciating pain): the pain was intense and the third echelon analgesics were required. The grade of postopera tive pain was 0, no relief; I, pain relief < 25%; II, pain relief < 26%~50%, analgesics were reduced; III, pain relief <51%~75%, analgesics were reduced 1 echelon; IV, pain relief < 76%~90%, analgesics were reduced 2 echelons or discontinued; V, pain relief <91%~100%, discontinued analgesics. The effect of spinal stabiliza tion and strengthening of the vertebrae were assessed based on CT scans and radiographs to determine if the vertebral fractures were still manifest.

Statistical analysis

The grade of preoperative and postoperative pain of patients in the VP and VPCC groups was assessed by the Wilcoxon Test, and the relief rate of pain of patients in the 2 groups determined by using a chi-square test by SPLM software.

RESULTS

Therapeutic effect

The grades of preoperative and postoperative pain of patients in the VP and VPCC groups are described in Table 2. The grade of patient preoperative pain between the VP and VPCC groups showed no significant difference ($P>0.05$), while the grade of patient postoperative pain relief between the VP and VPCC groups did show a significant difference ($P<0.01$). Considering 0 and I as not effective, the effective rate and relief rate of the VP group were 74.4% and 10.3%, while the effective rate and relief rate of the VPCC group were 93.0% and 25.6%. Using the chi-square test, 2 groups showed significant differences ($P<0.05$). The clinical response to the procedure was achieved immediately after the procedure and after 7 days, best response was obtained after 1~2 weeks, and lasted 1~6 weeks. The majority of

the patients achieved significant pain relief and im proved mobility after the bone cement injection.

Table 2. Grade of preoperative and postoperative pain of patients in the VP and VPCC groups

	Preoperation		Postoperation	
Grade	VP	VPCC	VP	VPCC
0	0	0	3	1*
I	0	0	7	2*
II	5	4	6	3*
III	21	23	14	9*
IV	13	16	5	17*
V	0	0	4	11*

*$P<0.01$, *vs* VP group.

Complications

Thirty-three patients (VP 7 and VPCC 26) had intense pain just after injection of the bone cement, 16 (7 with MTX, 6 with EADM, 3 with MMC) patients from the VPCC group had more intense pain than those from the VP group. One patient with MTX and 2 patients with EADM had bilateral intercostal radiating neuralgia, as well as abdominal muscle tonus, which was relieved after 30 min and eliminated after 2 h. In 8 vertebrae bone cement migration was observed after the procedure as follows: 3 cases leaked toward a disk, 4 cases leaked into adjacent soft tissue and 1 leaked into the vertebral canal and paravertebral soft tissue (Fig.1) without clinical symptoms. None of the patients in this study experienced radiculopathy compressive myelopathy, bleeding and infection, cardiovascular dysfunction or pulmonary embolism. No patients from the VPCC group had an adverse reaction relating to the chemotherapeutics such as leukopenia, sicchasia or emesis.

Follow-up

CT scans were performed immediately after the procedure was completed. The bone cement distributed as spots (Fig.2) in 13.2% of the cases, as plaques (Fig.3) with a lesion filling of more than 50% in 62.5% of the cases and as flakes (Fig.4) with a lesion filling of more than 90% in 24.3%. of the cases. Of 5 cases (VP 2 and VPCC 3) there was no follow-up. The others were followed-up until the patients died or the study was finished. The mean time for follow-up was 6.8 months. Thirty-two patients died from causes unrelated to PVP such as respiratory failure (RF) or multiple system organ failure (MSOF). None of patients developed complications due to PVP in the follow-up period, and there were no serious vertebral fractures. The shape of the bone cement, as seen on CT images during the period of follow-up, did not change. In 10.9% (9/82) of the vertebrae with PVP density increased and 6.1% (5/82) vertebrae with PVP developed a sclerotics border around the vertebral lesion. No recurrence of pain was noted during a mean follow-up of 3 months. However during a mean follow-up of 4~6 months, 18 patients (VP 11 and VPCC 7) at 18 sites of vertebral lesions reported a recurrence of pain, 9 (VP 6 and VPCC 3) developed further vertebral lesions, 4 (VP 2 and VPCC 2) showed an adjacent vertebral lesion, and 5 (VP 2 and VPCC 3) had no further vertebral lesions but recurrence of pain. In 11 patients, 14 vertebrae develped pain during a mean follow-up period of 7~12 months. Of the VP patients, 74.4% (29/30) and of the VPCC patients 79.1% (34/43) survived more than 6 months. Eleven patients (15 lesions) of 17 patients (23 lesions) survived more than 1 year and were still without pain.

DISCUSSION

Metastases are a common complication with malignant spinal osteolytic tumors, often causing intense back pain, vertebral collapse and even paraplegia depriving the patient of his/her mobility. Surgical decompression and placement of autologous bone grafts have been used somewhat in the past for the management of neoplastic compression fractures. However the operation is not often used because it usually causes extension of metastases and the patient to develop a poor condition. Radiotherapy can relieve pain in more than 80% of the patients, but it takes about 10~20 days before a definite effect takes place. Also, this approach does not reinforce the steadiness of the affected vertebral body, where a compression fracture can take place. Chemotherapy is not effective for metastases, so at present only symptomatic treatment of pain is the usual therapy employed.

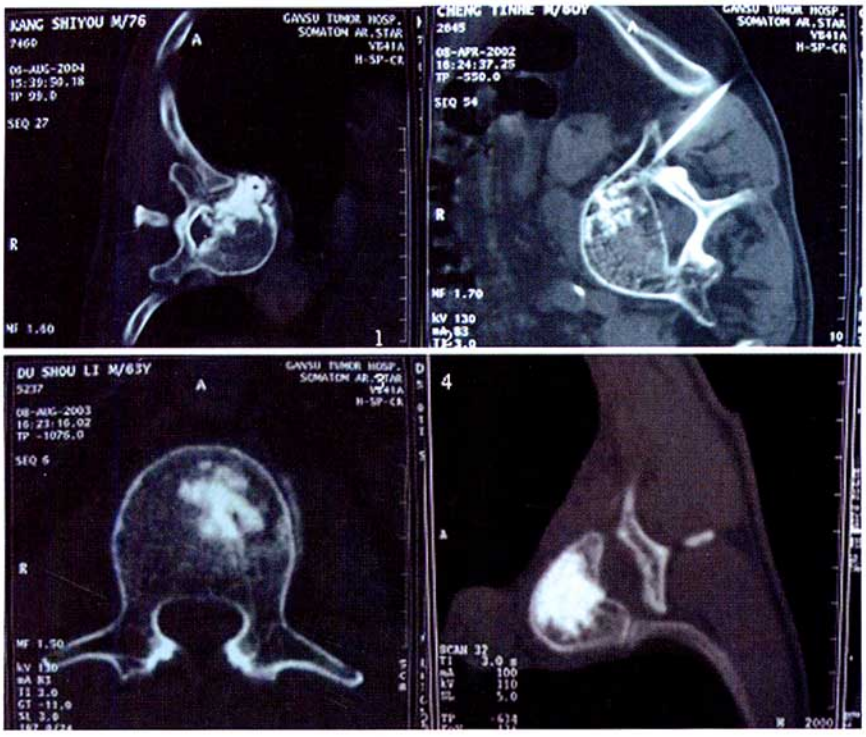

Fig.1. Metastatic lung cancer in vertebrae T10 observed by CT imaging. Bone cement leak into the vertebral canal and paravertebral soft tissue after injection of 5ml of bone cement. The patient shows no symptoms.

Fig.2. Metastatic breast cancer in vertebrae L5 observed by CT imaging. Bone cement distribute as spot after 2.5ml of bone cement.

Fig.3. Metastatic lung cancer in vertebrae L1 observed by CT imaging. Bone cement distribute as lump with lesion filling rate of more than 85%.

Fig.4. Metastatic kidney cancer in vertebrae T10 observed by CT imaging. Bone cement distributes as a flake with a lesion filling rate of more than 90%.

The pain from vertebral metastases caused by the focus was correlated with the stimulation by the fracture or tumor at the nerve endings of the osteal tissues. The mechanism of pain relief after PVP is variable. The bone cement, as a type of hardener, was injected into the focus for the reformation or transplantation of new bone or prosthesis to internally reinforce steadiness in the region and to relieve pain.[7] The polymerization of the PMMA and MMA can generate heat up to 52℃ ~ 93℃ ,[5] resulting in thermal destruction of the nerve endings around the tissue. Tohmeh et al. [8] suggested that the chemical toxicity of PMMA would kill the tumor and nerve endings. Sun et al.[9] indicated, from their experiments, that EDAM could be released from the bone cement mixture and thus destroy the tumors and also relieve pain from the chemical toxicity.

The curative effect of PVP combined with chemotherapy is better and more effective than PVP alone. To our knowledge, however, there are no reports in the literature to indicate whether the bone cement may enhance the effect by increasing the chemical toxicity of the chemotherapeutic agent. The choice of drugs should be considered based on their made of action, rate of delivery and the effect on the primary tumor. We found that the long-term curative effect of the 2 groups was similar, indicating that the chemotherapeutic drug is insufficient in restraining the tumor. There were no obvious bad reactions related to the chemotherapeutic drugs carried in the bone cement such as leukopenia, nausea, emesis, etc. This may indicate that a single drug is insufficient or that there was limited release from the bone cement.

Since there was no further vertebral collapse during follow-up after PVP treatment, it indicated that the dosage of the injected bone cement ensured vertebral reinforcement and maintenance of function. Cotton et al.[10] suggested a mean injected dose of 2.5 ml for the cervical vertebrae, 5.5 ml for the thoracic vertebrae and

7.0 ml for the lumbar vertebrae for best results. We injected less than Cotton (mean T 3.5 ml and L 4.5 ml), perhaps related only to the single entity, smaller lesions, the use of chemotherapeutic drugs, and the patients themselves. We agree with Bascoulergue et al.[10,11] that pain relief was not proportional to the degree of the lesion filled with PMMA. The effect of spinal stabilization between the VP and VPCC groups showed no significant differences, but we should determine if the agents influenced the strength and hardness of the bone cement after they were mixed.

The influence of PMMA on a tumor is correlated with its effection pain: the more the tumor is suppressed, the more the pain is relieved; if the tumor redevelops, the pain will recur.

Currently scholars perform these procedures under a C-arm angiographic unit. Gangi et al.[12] have completed punctures under a combination of CT and fluoroscopic monitoring. We performed the procedures under intermittent CT scanning, compared to conventional fluoroscopy alone. CT scanning shows a clear T-section anatomic structure to observe the position of the needle. Because of a time lag, is difficult to identify with real-time transverse CT during the operation. To avoid leakage of the bone cement, one should carefully assess the degree of lesion and collapse, the range of breakdown of a given vertebra though preoperative fluoroscopy and a CT scan, and strictly control the indications. To conduct the procedure, one should push the needle through the cortex, traverse the center of the pedicle, and be directed into the lesion of the vertebral body, maintaining the integrity of the medial wall of the pedicle and the posterior wall of vertebral body. Ideally, the needle tip should be placed at the junction of the anterior third of the vertebral body close to the midline. The pressure of injection should be increased slowly. The injection volume of the PMMA should increase or be reduced based on the range and position of the lesion. Relatively more may be injected if the range of the lesion is big and the posterior wall of the vertebral body is not destroyed. To our knowledge the amount of cement required for a good clinical outcome has never been systematically studied. Testing of cadaveric spines suggests that up to 8 ml of cement is required to achieve biomechanical integrity.[13] However, the risk of extra-osseous extravasation of cement increases with an increasing volume of cement injected. To minimize the risk for such extravasation, we tend to place relatively small amounts of cement into a given vertebral body.

The complications following PVP were few. Chiras et al.[14] reported that the incidence of osteoporosis was 1.3%, vertebral hemangioma was 2.5% and vertebral metastases was 10%. In our study, the patients developed transient pain after the injection of PMMA combined with the chemotherapeutic drugs, an effect that may be related to stimulation by the drugs. The MMA gave better results than the EADM and MTX. The principal radiographic complication with PMMA leakage was epidural and foraminal extravasation. Any resultant spinal cord or nerve root damage may require emergency surgical decompression. In our group, PMMA leakage occurred in 8 (9.8%) of the cases, seven leaked toward the disc, epidural fat or perivertebral soft tissue, and one leaked into the spinal canal because of the posterior wall of the vertebral body was destroyed, without clinical symptoms in any of these cases. The puncture needle (18 G epidural puncture needle) we used had a beveled distal end that may allow one to direct cement in a given direction, and thus avoid leakage.

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