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Retrospective Study

Risk Factors for Local Bone Destruction Progression in Palliative Percutaneous Vertebroplasty for Vertebral Metastases and the Significance of Bone Cement Filling Rates

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Background: For palliative percutaneous vertebroplasty (PVP) for vertebral metastases, local bone destruction progression (LBDP) commonly occurs in the previously treated vertebrae. There were no studies regarding LBDP and its risk factors in previous reports, and there was no uniform evaluation method for the distribution of bone cement in the vertebrae.

Objectives: We aimed to investigate the risk factors for LBDP after PVP for palliative treatments in patients with vertebral metastases. We also proposed that filling rates could be used as a simple evaluation method to detect vertebral metastases and explored its clinical significance.

Study Design: This was a retrospective study.

Setting: A university hospital.

Methods: A total of 48 patients and 54 vertebrae that had received PVP as a palliative treatment for vertebral metastases were recruited between October 2012 to October 2019 from the Shengjing Hospital of the China Medical University. We collected and evaluated the data including age, gender, cement filled completely or not, cement dose used, the cement distribution score, time of LBDP, and so on, and the filing rate we proposed was also included.

Results: This retrospective study divided 48 patients and 54 vertebrae into group A for those with an LBDP of less than 6 months (n = 41), and group B for those with an LBDP of 6 or more months (n = 13). The complete filling of bone cement and bone cement dose in group B was much higher than that in group A (2.85 ± 0.97 vs. 4.12 ± 1.77; $P = 0.027$), and the time of recurrent pain in group B was significantly higher compared with that in group A (8.46 ± 2.73 vs. 3.39 ± 1.63; $P < 0.0001$). There was a statistical difference in the Saliou score and filling rate between the 2 groups (11.77 ± 3.17 vs. 9.34 ± 3.28, $P = 0.023$; 0.752 ± 0.227 vs. 0.489 ± 0.161, $P < 0.0001$). Univariate logistic analysis showed that complete filling of cement, the cement dose, Saliou score, and filling rate were statistically significant predictors of LBDP occurring in less than 6 months. Multivariate logistic analysis showed that the filling rate was an independent predictor of patients with vertebral metastases developing LBDP in less than 6 months (odds ratio, < 0.001; 95% confidence interval, < 0.001–0.006; $P = 0.0007$). The cutoff value for the filling rate calculated from the receiver operating characteristic (ROC) curve analysis was 0.646, which could identify patients who had LBDP in less than 6 months of PVP with a sensitivity of 85.4% and specificity of 84.6%. The 6-month LBDP in the 0.646 or less ROC curve group was higher than that in the greater than 0.646 ROC curve group (97.22% vs. 55.56%, $P < 0.0001$).

Limitations: The retrospective nature and small sample size were significant. Variation in the time and state of bone cement injected during all PVP procedures was a bias. There was no pathological diagnosis of all vertebral metastases.

Conclusions: The cement dose, complete filling of cement, Saliou score, and filling rate were factors negatively related to LBDP occurring in less than 6 months. Patients with lower filling rates are maybe more likely to have early LBDP compared with those with higher filling rates.

Key words: Bone cement, distribution of bone cement, local bone destruction progression, percutaneous vertebroplasty, palliative treatment, vertebral metastases

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Thirty-three percent of patients with cancer have vertebral metastases, and 83% to 95% suffer pain (1,2). Since the introduction of percutaneous vertebroplasty (PVP) in the late 1980s, it has been used effectively in the treatment of a painful vertebral lesion, including osteolytic metastasis, myeloma, painful or aggressive hemangioma, and osteoporotic vertebral collapse (3). PVP has been shown to effectively relieve pain caused by vertebral metastases, improving the quality of life of these patients (4,5).

The increasing application of PVP for vertebral metastasis treatments has been accompanied by increased reports of complications (6-8). Clinical practice has given much attention to the complex complications affecting the clinical efficacies and life-threatening complications, such as root cord compression, bone refracturing, and pulmonary embolism (7,9,10). Among the complications, local bone destruction progression (LBDP) commonly occurs in vertebrae previously treated for metastatic disease and that show incomplete filling of cement, which is different from new fractures and is easily overlooked. There have been only a few studies looking at the risk factors of LBDP. In addition, the distribution of bone cement in vertebral bodies as an effective evaluation method has not been rigorously demonstrated in clinical situations. Saliou et al (11) reported this evaluation method and designated the Saliou score, which has been favored by some clinicians. However, few reports regarding the association of cement distribution scores with complications have been published. A recent retrospective study on cement distribution patterns in vertebral metastases analyzed the relationship between cement distribution patterns, cement leakage, and adjacent vertebral fractures (12), but did not analyze these factors in relation to LBDP.

In this study, we performed a retrospective analysis of patients who had received PVP due to vertebral metastases between October 2012 and October 2019 to determine risk factors for LBDP within 6 months of treatment. We investigated the relationship between LBDP and age, gender, whether the bone cement was filled completely or not, the amount of bone cement used, the cement distribution score, and lesion characteristics combined with other treatments. We proposed a simple ratio to evaluate bone cement distributions in the treatment of vertebral metastases using PVP, and the clinical significance of a simple ratio was also analyzed.

Methods

This retrospective study was approved by our institutional review board with a waiver of informed consent. A total of 48 patients and 54 vertebrae receiving vertebroplasty for palliative treatment of metastatic vertebral bodies were enrolled in the study from October 2012 to October 2019. The study population consisted of 20 men and 28 women, with a mean age of 62.6 years (range, 42–85 years). All patients with a history of primary cancer had undergone computed tomography (CT) or magnetic resonance (MR) examination before surgery. Destruction of the vertebral body by metastases from primary cancers was a reason for pain and disability. Patients with other vertebral compression fracture etiologies, such as osteoporosis or myeloma, patients with other curative or palliative tumor treatments such as standard chemotherapy or radiotherapy, and patients without integrated data or loss to follow-up were excluded from this study. The flowchart of the study is shown in Fig. 1.

The clinical data were reviewed, including gender, age, combined treatments (radiotherapy, radiofrequency ablation), lesion characteristics (osteolytic, osteoblastic, and mixed destruction, degrees of compression), and whether the bone cement completely filled or not was judged by the operators via CT or MR, LBDP, the Visual Analog Scale (VAS) before and after an operation, cement dose used, overall survival (OS), and the revised Tokuhashi score (13). The distribution of bone cement was evaluated, and the scores of each vertebral body were calculated according to Saliou et al (11). The authors of this study also created a simple algorithm to describe the filling rate, that is, the length of bone cement in the maximum range of bone destruction divided by the length of the maximum range of bone destruction (Fig. 2). Both were included in the calculation.

The PVP Procedure

The PVP procedure was performed under the guidance of digital subtraction angiography (AXIOM Artis-dTA; Siemens, Munich, Germany) or 128-slice spiral CT (IngenuityCore, Philips Medical Systems, Suzhou, China). The operated vertebrae ranged from the fourth thoracic vertebra to the first sacral vertebra. The patient was placed in a prone position, 1% lidocaine was administered subcutaneously with a 10-mL syringe and a 22-gauge needle. Under fluoroscopic or CT guidance, a cementoplasty trocar (13-gauge, Medtronic, CA, USA) was inserted into a vertebral pedicle and introduced into the anterior one-third of the vertebral body. If radiofrequency ablation (a bipolar radiofrequency probe, OLYMPUS-CELON, Teltow, Germany) was also used, CT or Dyna CT (reconstructed by digital subtraction angiography) showed precise needle placement. If necessary, the needle tip had to exceed the midline of the vertebral body during a unilateral approach or both needles passed through a bipedicular approach to achieve a uniform distribution of bone cement. The stylet was then removed, and a polymethylmethacrylate-based bone cement (OSTEOPALV, Heraeus Medical GmbH, Wehrheim, Germany) was injected slowly into the vertebral body when it became a doughy and viscous state under continuous fluoroscopic control or intermittent CT scanning. If cement leakage was observed, the cement injection was stopped or paused. After the procedure was completed, the trocar was removed, and local compression was needed for hemostasis.

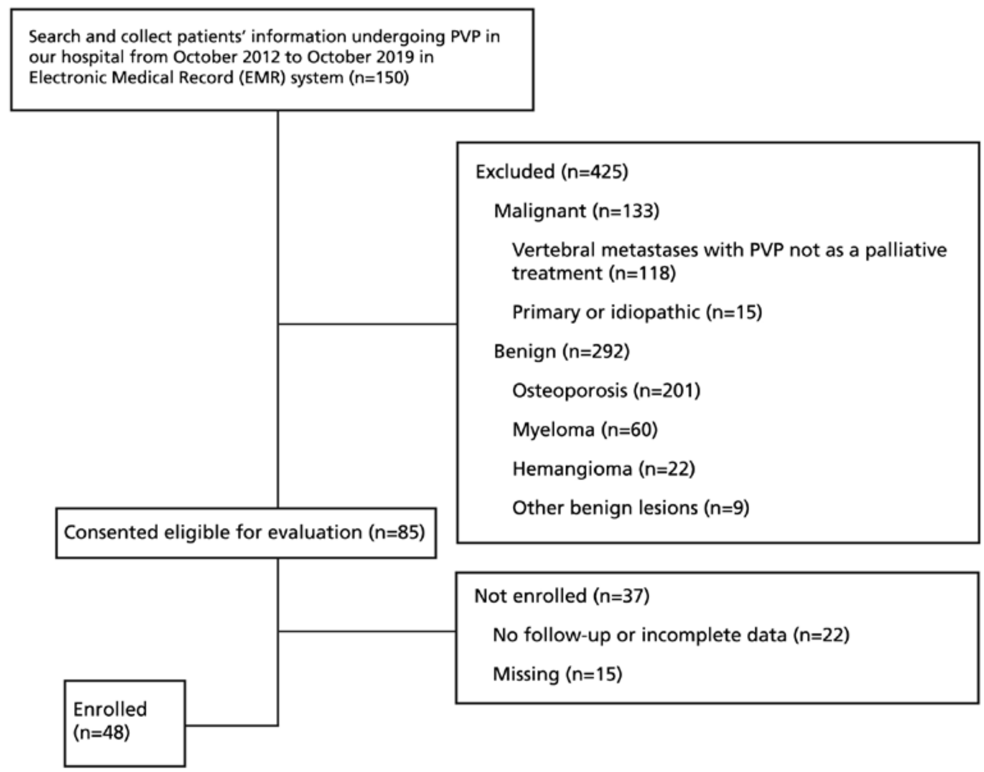

Fig. 1. *Flow chart of patients through the study.*

Fig. 2. *The filling rate of the bone cement after PVP equals the distance of the arrow line divided by the distance of the arrow line plus that of the straight-line distance.*

Patient Follow-Up

The patients received a first follow-up evaluation 1 month after surgery, and then were re-evaluated at 3-month intervals or according to changes in a condition. CT and/or MR imaging were performed to determine the distribution of the cement and lesions (shown in Fig. 3A–D). If a patient could not be admitted to the hospital, evaluations were conducted by telephone, which addressed the following issues: the general

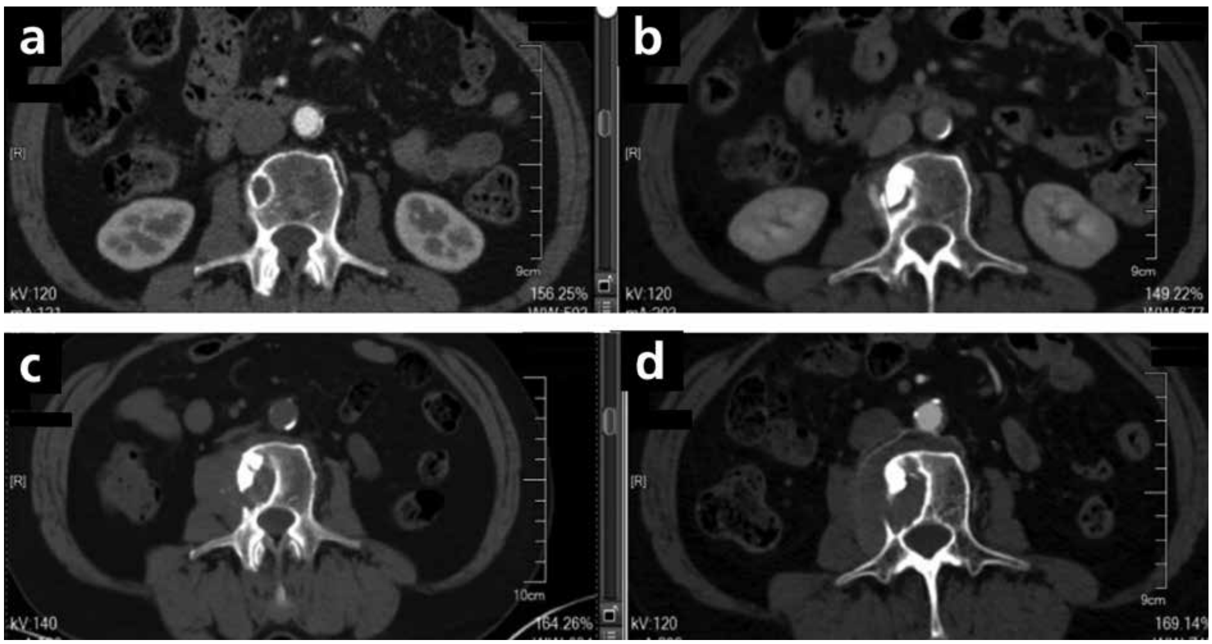

Fig. 3. *A 65-year-old woman with a previous history of endometrial cancer had vertebral metastases and felt pain in the corresponding location. (A) The CT scan suggested that the right half of the local vetebral body was damaged. (B) The CT scan 4 months after PVP suggested that the original vertebral cement filling was incomplete; however, the pain was alleviated very well. (C) Eight months after PVP, the damage of the local vertebral body increased compared with earlier times, and there was a local paravertebral metastasis. At this time, the pain had recurred for 1 m onth. (D) Eleven months after PVP, the patient had severe pain that could not be alleviated with oral analgesics. The scope of local vertebral bone damage expanded, and the local paravertebral soft tissue metastasis worsened.*

condition of the patient, survival/mortality, the direct cause of death, subsequent therapy (radiotherapy, chemotherapy, diphosphonate treatment), recurrent pain, interval periods, and other specific conditions. The follow-up endpoint was death.

Statistical Analyses

All analyses were performed using the Statistical Analysis System 9.3 edition for Windows (SAS Institute Inc., Cary, NC). All *P* values were 2-tailed, and differences with *P* values < 0.05 were considered statistically significant. The mean with standard deviation (SD) was used for continuous variables, absolute frequencies, and percentages for categorical variables. The independent sample Student t test was used to compare continuous variables, and the χ^2 test or the Fisher exact test was used to assess statistically significant differences for the categorical data. Univariate logistic regression analysis was used to identify the potential predictors for LBDP, and variables with *P* values < 0.05 were entered into a multivariate logistic regression analysis to test for independence. The results of the regression analysis were presented as the odds ratio (OR) and 95% confidence interval (CI). A receiver operating characteristic (ROC) curve analysis was used to identify the cutoff value of filling rate to predict 6-month LBDP. A 2-sided $P < 0.05$ was considered significant.

Results

The PVP procedure was successful in all patients without severe complications. The patients were grouped by time of postoperative LBDP. Patients in group A had an LBDP of less than 6 months, and those in group B had an LBDP of 6 or more months. There was a statistically significant difference between the 2 groups about cement completely filled, with greater filling in group B compared with that in group A (5 [38.46%] vs. 1 [2.44%]; $P = 0.002$), and the bone cement dose used in group B was much higher (2.85 ± 0.97 vs. 4.12 ± 1.77; $P = 0.027$) compared with that in group A.

The time of pain recurrence in group B was significantly greater compared with that in group A (8.46 ± 2.73 vs. 3.39 ± 1.63; $P < 0.0001$). A statistical difference in the Saliou scores was also found between the groups with a higher score in group B versus group A (11.77 ± 3.17 vs. 9.34 ± 3.28, $P = 0.023$). The filling rate between the 2 groups was also significant, with a higher filling rate in group B versus group A (0.752 ± 0.227 vs. 0.489 ± 0.161; $P < 0.0001$). The other baseline characteristics were not statistically different, as shown in Table 1.

Univariate logistic analysis showed that complete cement filling, the cement dose, Saliou score, and filling rates were statistically significant predictors of 6-month LBDP. Univariate and multivariate logistic analyses showed that the filling rate was an independent predictor of 6-month LBDP in patients with vertebral metastases (OR, < 0.001; 95% CI, < 0.001–0.006, $P = 0.0007$; Table 2).

The cutoff value of the filling rate, calculated from the ROC curve analysis, was 0.646 for the determination of 6-month LBDP. The area under the ROC curve was 0.846 (95% CI, 0.6786–1). The sensitivity and specificity were 85.4% and 84.6%, respectively (Fig. 4). There was a statistical significance between the 0.646 or less and greater than 0.646 groups with respect to complete cement filling, cement dose, distant metastases, OS, and Saliou scores. The 6-month LBDP was the most significant factor measured between the 0.646 or less and greater than 0.646 groups, which showed higher 6-month LBDP in the 0.646 or less group compared with that in the greater than 0.646 group (97.22% vs. 55.56%, $P < 0.0001$, Table 3). No significant difference was found in the baseline characteristics between the 2 groups.

Table 1. *Baseline characteristics of the enrolled patients.*

	LBDP < 6 m (n = 41) Group A	LBDP ≥ 6 m (n = 13) Group B	*P* value
Age, years (mean ± SD)	64.80 ± 10.5124	61.69 ± 11.18	0.364
Gender (M/F), n	18/23	9/4	0.202
Combined with radiotherapy (%)	4 (9.76)	1 (7.69)	1
Combined with RFA (%)	25 (60.98)	7 (53.85)	0.75
Combined with diphosphonate (%)	24 (58.54)	9 (69.23)	0.536
Cement completely filled (%)	1 (2.44)	5 (38.46)	0.002
Lesion characters			0.079
Osteoblastic	3 (7.32)	3 (23.08)	
Osteolytic	29 (70.73)	10 (76.92)	
Mixed	9 (21.95)	0 (0)	
Vertebral compression degree			0.189
Collapse > 50%	10 (24.39)	6 (46.15)	
Collapse < 50%	12 (29.27)	1 (7.69)	
No collapse, but 50% involved	19 (46.34)	6 (46.15)	
Paravertebral soft tissue invasion and metastasis	16 (39.02)	4 (30.77)	0. 746
Distant metastasis	16 (39.02)	6 (46.15)	0.75
OS	9.76 ± 7.69	8.92 ± 3.55	0.594
The revised Tokuhashi score	6.3415 ± 2.9800	5.8462 ± 1.4051	0.4189
Cement dose (mean ± SD)	2.85 ± 0.97	4.12 ± 1.77	0.027
Preoperative VAS (mean ± SD)	7.29 ± 1.58	7.31 ± 1.11	0.975
Postoperative VAS (mean ± SD)	2.41 ± 1.4	2.15 ± 1.28	0.553
Time of pain recurrence (mean ± SD)	3.39 ± 1.63	8.46 ± 2.73	< 0.0001
Saliou score (mean ± SD)	9.34 ± 3.28	11.77 ± 3.17	0.023
Filling rate (mean ± SD)	0.489 ± 0.161	0.752 ± 0.227	< 0.0001

Abbreviations: RFA, radiofrequency ablation.

Discussion

It is well accepted that PVP is effective for the rapid palliation of pain in cases of vertebral metastases (3,14,15). The antitumor effect of bone cement is still controversial (16,17). Without other effective treatment for tumor, different degrees of tumor progress would occur at the local metastasis sites (18). In this retrospective study, the pain scores of all patients were relieved after palliative PVP, but LBDP, which could be a sign of osteolysis due to residual tumor after palliative PVP, also occurred at different times post PVP. Besides the factors that primary foci influence, we believe that bone cement injection might affect LBDP. Therefore we felt it was of great significance to analyze the risk factors affecting LBDP, and the results of our study identified the cement dose used, complete filling of cement, the Saliou score, and the filling rate as significant risk factors for LBDP of less than 6 months.

Table 2. *Logistic regression analysis for predicting 6-month long-term progression.*

Variables	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Gender	0.348	0.092-1.315	0.1195			
Age	1.029	0.968-1.095	0.3585			
Cement completely filled	25	2.564-243.75	0.0056			
Paravertebral soft tissue invasion and metastasis	0.694	0.183-2.638	0.5923			
Cement dose	0.485	0.282-0.833	0.0088			
Time to distant metastasis	1.045	0.824-1.325	0.7143	0.664	0.430-1.026	0.0653
Preoperative VAS (mean ± SD)	0.993	0.648-1.522	0.9742			
Postoperative VAS (mean ± SD)	1.159	0.719-1.868	0.5452			
OS	1.021	0.919-1.134	0.7042			
Saliou score (mean ± SD)	0.794	0.645-0.977	0.0296			
Filling rate (mean ± SD)	< 0.001	<0.001-0.028	0.009	< 0.001	< 0.001-0.006	0.0007

Abbreviations: RFA, radiofrequency ablation.

Table 3. *A comparison of the clinical characteristics of 54 vertebrae grouped by filling rates.*

	Filling rate ≤ 0.646 (n = 36)	Filling rate > 0.646 (n = 18)	*P* Value
Age, years (mean ± SD)	65.86 ± 11.11	60.44 ± 8.89	0.0780
Gender	15/21	12/6	0.1480
Cement completely filled	0 (0)	6 (33.33)	0.0007
Paravertebral soft tissue invasion and metastasis	16 (44.44)	4 (22.22)	0.1422
Cement dose	2.72 ± 0.91	4.03 ± 1.56	0.0032
Time to distant metastasis	5.90 ± 2.70	3.67 ± 1.91	0.0028
Preoperative VAS (mean ± SD)	7.14 ± 1.40	7.61 ± 1.61	0.2714
Postoperative VAS (mean ± SD)	2.36 ± 1.40	2.33 ± 1.33	0.9445
OS	10.92 ± 7.78	6.83 ± 3.47	0.0103
Saliou score (mean ± SD)	8.78 ± 3.13	12.22 ± 2.69	0.0002
6-Month LBDP	35 (97.22%)	10 (55.56%)	< 0.0001

Abbreviations: RFA, radiofrequency ablation.

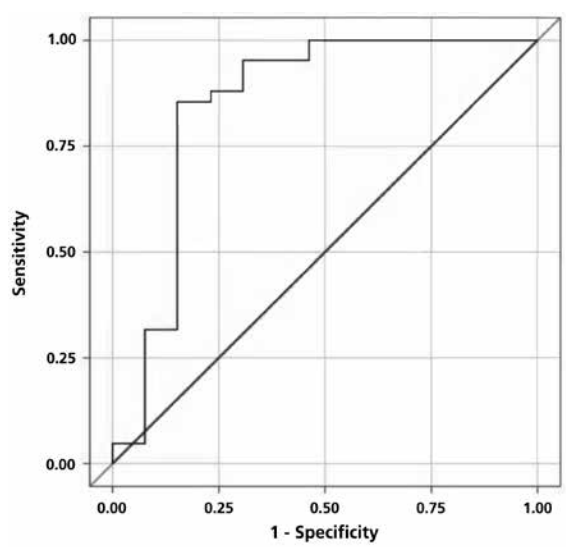

Fig. 4. *ROC curve showing the predictive cutoff value of the filling rate (0.646) for 6-month long-term progression. The area under the ROC curve was 0.846, and the sensitivity and specificity were 85.4% and 84.6%, respectively.*

For the purpose of just relieving pain due to vertebral metastases, our results suggested that the higher the cement dose used, the less likely that LBDP occurred in less than 6 months. Some previous studies have shown that bone cement kills tumor cells by the heat generated in the process of polymerization, and as the amount of bone cement injected increased, the temperature reaches a higher level (19,20). In other words, the more bone cement used, the greater the effect of local tumor killing, and the longer the interval to LBDP. Cotten et al (21) reported on the average amounts of bone cement needed to fill each spinal segment, for instance, 2.5 mL of bone cement should be used in the cervical spine, 5.5 mL should be used in the thoracic spine, and 7.0 mL should be used in the lumbar spine. However, in this study, the amount of bone cement injected was significantly less than what was used in that study, which was especially seen in the dose used in group A (LBDP < 6 months, 2.85 ± 0.97 mL). Unfortunately, as the amount of bone cement used increases, the incidence of cement leakage and other complications also increases. Therefore we cannot blindly pursue the dose of bone cement injected. In the previous studies, interventional tumor removal or radiofrequency ablation have been used to reduce tumor volume and then to increase the dose of cement injected safely (22-24).

Other factors affecting LBDP were complete filling of cement, the Saliou score, and the filling rate. We believed that these factors reflected the filling state and distribution of bone cement; in other words, the quality of bone cement injection. With regard to the bone cement distribution, previous studies have focused on vertebral compression fractures caused by osteoporosis (25,26). A previous retrospective study about vertebral metastasis by Delpla et al (27) showed that the Saliou score, the rate of vertebrae cement filling (0%; < 50% and > 50%), the presence of disc leakage, and the contact of cement with both vertebral endplates was associated with the quality of cement injections. However, we did not evaluate the cement contact with both endplates because it is more suitable for osteoporotic vertebral fractures (28). The data of our study showed that the occurrence of LBDP could be prolonged in patients who received better quality cement injections. Another study showed that when vertebral tumors were treated with PVP, the residual tumor tissues were mainly peripherally distributed around the bone cement core, between the nuclear area of the bone and the normal bone cement (29). Therefore we believe that vertebrae should be completely filled with bone cement, and that the cement should make full contact with the tumor tissues to be entirely efficacious as an antitumor agent with maximal residual tumor-killing leading to the prolongation of LBDP.

Evaluation of the Bone Cement Distribution

To date, there has been no unified standard for bone cement filling image evaluation for vertebral metastases. The Saliou score (11) has been accepted by some clinicians as an evaluation method. This score divides each vertebra into 9 equal sections of the same size in both front and lateral views. Each section represents 1 point, with a full score of 18 points; greater than 12 points is considered satisfactory. Cement filling was considered to be complete when the cement was present in each section on both views. When this was not the case, cement filling was considered to be incomplete, however, this method had some limitations. If the lesion was confined to the right part of the vertebral body, and not across the midline, even if the bone cement was completely filled in the area of the bone destroyed by a tumor, the cement was not seen on each section in frontal views. Therefore this method does not apply in all cases. Moreover, even if each section scored 1 point, the cement filling could also be incomplete, with only a small amount of cement being used. The complication of calculus and strong subjectivity in assessments are also drawbacks of this evaluation method.

In this study, to our knowledge, we are the first to propose cement filling rates as a simple evaluation method. This method uses a ratio of the longest diameter of measurable bone destruction and the maximum diameter of bone cement measured on CT or MR. Note that both are measured in the same line on the axial view. We proposed this method for the following reasons: first, it conforms to the operational process, in which the puncture needle is introduced from the back to forward direction during the PVP procedure, and therefore the cement is filled into the vertebral body from the anterior part of the vertebral body to the posterior part. Essentially, the bone cement is distributed gradually into the sagittal direction according to the coronal position, and the posterior part of the damaged vertebral body, near the spinal canal, is a common site of incomplete bone cement filling. Second, it conforms to the principle of avoiding complications. Because of the biologic behavior of tumors when invading the posterior vertebral body (30) and the distribution of the vertebral venous plexus, cement leakage can happen through posterior cortical vertebral deficiencies or the vertebral venous system (31). To avoid leakage, when injecting bone cement into this location, incomplete filling of the cement occurs easily, allowing residual tumor tissue to invade readily. Therefore measuring the maximal level of vertebral bone destruction and the distribution of cement on the CT or MR axial view can reflect the state of cement injections fairly accurately. Moreover, vertebral bone destruction in axial view measurements is also convenient and easy to obtain.

In the present study, the results of the univariate analysis showed that the higher the Saliou score, the lower the probability of having LBDP in less than 6 months, and we first found that the filling rate and

Saliou score were individual prediction factors for LBDP occurring in less than 6 months, and the filling rate was an independent factor influencing LBDP. In the present study, the filling rate was statistically significant in being able to predict that LBDP would occur in less than 6 months with the cutoff value of 0.646. These results showed that patients with decreasing filling rates were more likely to have LBDP in less than 6 months, the results of which merit further evaluation.

Our study has several limitations. First, it is retrospective, nonrandomized, from a single-center, and the sample size is small. The small sample size is a primary limitation and is mainly because a few cases met the screening criteria and the relatively integrated data. A well-designed study with larger sample sizes should be performed in future studies. Second, the time and state of bone cement injected during all PVP procedures was variable, which influences cement viscosity and dose and is a bias that cannot be ignored. Finally, no pathologic diagnoses of the vertebral metastases were performed, and therefore the influence of a primary tumor's invasiveness on local tumor progression could have affected LBDP.

Conclusions

In this retrospective study of PVP for the palliative treatment of vertebral metastases, we have identified that LBDP that occurred in less than 6 months was associated with bone cement filling rates, cement dose, the presence of complete cement filling, and the Saliou score; the filling rate was found to be an important risk factor. Patients with a filling rate less than 0.646 are tended to have earlier LBDP compared with those with higher filling rates. It is possible that performing another PVP to increase filling rate or adding local radiotherapy, including radioactive I125, could help to reduce the incidence of LBDP.

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