Percutaneous Vertebroplasty in Vertebral Metastases from Breast Cancer: Interest in Terms of Pain Relief and Quality of Life

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Summary

Percutaneous vertebroplasty (PV) is a therapeutic option in patients with vertebral metastases (VM). However its efficacy in pain relief, improvement in quality of life and safety in patients with VM from breast cancer has not been reported. We present a longitudinal retrospective study of 31 consecutively treated female patients with VM from breast cancer where 88 vertebrae were treated in 44 sessions of PV, in which osteolytic, osteoblastic and mixed lesions were recorded. The visual analogue pain scale (VAS) was used to evaluate pain pre-PV, at one, three, six and 12 months post-PV. The Eastern Cooperative Group (ECOG) performance status scale was used at the same time intervals to measure quality of life: 90.3% pain relief was identified with a VAS reduction from 5.7 ± 2.0 pre-PV to 2.9 ± 2.2 post-PV at one-month follow-up ($p < 0.001$) and 0.6 ± 1.0 at 12-month follow-up ($p < 0.001$). In our series 48.4% of patients were classified as having an ECOG grade 0 and 1 pre-PV, which increased to 80.8% at the 12-month follow-up. While 22.6% of the patients were classified at ECOG grades 3 and 4 pre-PV, this improved to 0% at 12 months follow-up. The morbidity rate for this procedure was 12.9% immediately and only 3.2% at 30 days post-PV with all complications being resolved medically

or with CT-guided infiltration. PV is a safe procedure with a high efficacy in pain relief, and improvement of quality of life in patients with diverse types of VM from breast cancer.

Introduction

The spine is the third most common metastatic site, only the lung and the liver are more frequently affected¹. Vertebral metastases (VM) are found in up to 30-90% of autopsies from cancer patients. Up to 30% of VM are symptomatic. As a whole, VM occur in 40% of cancer patients of which 50% require treatment². Current treatment algorithms for VM include chemotherapy or radiotherapy (depending on tumour sensitivity), surgical debulking or fixation, and vertebroplasty^{3,4}. Breast cancer is the most common cancer in women, comprising 10.9% of all cancers; nonetheless it is also the first cause of symptomatic VM⁵. Therefore, VM from primary breast cancer is a public health problem in cancer survivors because of the need for rapid access to analgesic treatment to obtain pain relief and spinal stability and to improve their quality of life. Percutaneous vertebroplasty (PV) is a minimally invasive procedure guided by fluoroscopy or computed tomography that consists in the injection of polymethylmeth-

Figure 1 A) Sagittal short-Tau inversion recovery (STIR) image of thoracic spine. B) Sagittal T1 without contrast of lumbar spine in a 57-year-old woman showing multiple osteolytic lesions with vertebral compression fractures at thoracic T8, T9, T10, T11, and T12 vertebral bodies. C) Sagittal multiplanar reconstruction CT post-PV of the thoracolumbar spine showing vertebral filling obtained in two different sessions of PV at T10, T11, T12, L1 and L2 vertebral bodies. Despite the low volume of cement injected, the patient experienced a 50% pain relief at 1-month post-PV in the two different PV sessions and persisted asymptomatic (VAS 0/10) at the 12-month follow-up. She passed from ECOG grade 1 to ECOG 0 at the 1-month follow-up and remained in this grade at the 12-month follow-up.

Figure 2 A) Axial CT scan post-PV at T11 vertebra. B) Sagittal multiplanar reconstruction CT post-PV at T11 vertebra. A 41-year-old woman with a single blastic metastasis. Vertebral filling cement codified at 60%, venous leakage into the right and left anterolateral paravertebral plexuses (arrows). The patient obtained a 50% pain relief at the 1-month follow-up, asymptomatic (VAS 0/10) at the 3, 6 and 12 month follow-ups. ECOG grade 1 at the 1, 3, and 6-month follow-ups, ECOG grade 0 at the 12-month follow-up.

acrylate (PMMA) cement into the vertebral body. PV was developed in France by Galibert and Deramond in 1987 for the treatment of vertebral hemangioma⁶, and currently is also indicated in vertebral compression from osteoporosis and VM, and rarely for traumatic fractures⁷.

The aim of this work is to present the efficacy in pain relief, improvement in quality of life, and the safety of PV in patients with VM from breast cancer previously treated or not with spinal radiotherapy.

Methods

We present our experience regarding 31 female patients with breast cancer who developed VM. This is a retrospective series of consecutively treated patients referred by the Institut Curie to the Department of Interventional Neuroradiology of Pitié-Salpêtrière Hospital between February 2000 and November 2005. Patients were selected to be treated by PV procedure after a consensus meeting that included their attending clinician, oncologist, pain relief specialist, radiotherapist and interventional neuroradiologist for the treatment of VM. Patients had to meet the following inclusion criteria: a) patients who suffered from breast cancer; b) age between 18 and 80 years; c) clinical and imaging evidence (MRI or CT) of VM in the cervical, thoracic, lumbar or sacral segments; d) osteolytic, osteoblastic or mixed appearance of VM; e) excruciating pain corresponding with

VM levels despite pharmacological treatment, or adverse effects related to opioids (constipation, urinary retention, and/or confusion), or opioid tolerance developed in patients with controlled pain; f) patients treated with spine radiotherapy or waiting to receive radiotherapy sessions; g) expected survival time ≥ 3 months; and h) vertebral fractures with posterior wall disruption but no epidural involvement, or fractures with posterior wall disruption and mild epidural involvement but no contact with the spinal cord or nerve root (Schimony groups 1 and 2)⁸. All patients were treated following a pragmatic clinical practice situation in which radiotherapy was or was not available due to scheduling overload in the radiotherapy unit. Since 1992, PV has become a routine procedure in our institution. Our institutional review board approved our study but did not require approval for the retrospective review of their records and images because their anonymity was preserved. However all patients gave their informed consent to undergo PV.

Exclusion criteria included patients with: a) clinical signs of spinal cord compression or cauda equina syndrome; b) fractures with epidural involvement and contact with spinal cord or nerve roots; c) complete vertebral destruction; d) posterior arch involvement; and e) local infection at the puncture site or septicemia. Relative contraindications included transient chemotherapy-induced haematologic anomalies such as: a) leucopenia ($<2.5 \times 10^3/\mu\text{L}$); b) thrombocytopenia ($<100.0 \times 10^3/\mu\text{L}$); and c)

Figure 3 A) Axial CT scan pre-PV at T7 showing an osteolytic lesion in the right hemivertebra (dotted arrow); there is a blastic lesion in the left hemivertebra (dashed arrow), representing mixed metastases. The 55-year-old woman also had mixed vertebral metastases at L1 and L2 previously treated with radiotherapy. B) Postero-anterior X-ray film showing adequate cement distribution in L2, up to 80% of cement filling; with poor distribution in L1 with less than 30% of cement filling and discal L1-L2 leakage. C) Axial CT acquisition post-PV showing a heterogeneous distribution of cement more with affinity to fill up the osteolytic portion of the treated vertebrae with asymptomatic left anterolateral paravertebral venous plexus leakage (arrowhead) and epidural venous plexus leakage (arrow). D) Multiplanar CT sagittal reconstruction post-PV showing asymptomatic epidural venous leakage (arrowhead), anterolateral plexus leakage (arrow) and asymptomatic discal L1-L2 leakage (asterisk). The patient experienced 50% pain relief at 1-month post-PV follow-up, and continued at the 3-month follow-up, with a regression to VAS 8/10 post-PV. She progressed from ECOG grade 3 at the pre-PV to grade 2 at the 1-month follow-up, to grade 1 at the 3 month-follow-up. Unfortunately she died from cancer progression that included circumferential epidural involvement with spinal cord compression at the 12-month follow-up.

elevated international normalized ratio >1.5 . Only those patients whose abnormalities had resolved underwent PV.

All patients had a clinical work-up that included clinical evaluation, CT or MRI of the

spine, and pre-operative evaluation by an anaesthesiologist. We obtained clinical information through electronic medical records, and procedure; while imaging was obtained from the PACS. CT or MR images were evaluated by

Figure 4 VAS box plot graph showing evolution over time per patient treated by PV at different time cut-offs during follow-up. VAS: visual analogue scale of pain.

Figure 5 Kaplan-Meier graph showing time cut-offs at which the patients achieved 50% reduction in pain, compared with the VAS pre-PV.

Figure 6 Time series graph showing the positive slope in ECOG grade 0 due to an increase in the total number of asymptomatic patients; negative slope in ECOG grades 1, 2, 3 and 4 related to a decrease in the number of patients in these groups. Positive slope in ECOG grade 5 due to the deaths recorded in this study.

one neuroradiologist and data was recorded in a database. We recorded age at diagnosis of vertebral metastases, date of the procedure, modality of associated radiotherapy, appearance of vertebral metastases, number of ses-

sions of PV, vertebral level treated, and number of vertebra treated per PV session, volume of cement injected, percentage of vertebral cement filling, technical incidents as well as complications within 30 days post-PV, patients who

received bisphosphonates, patients who did not complete follow-up, as well as causes related to their drop from follow-up. The visual analogue pain scale (VAS) was used to evaluate pain intensity before PV procedures, and at the one, three, six and 12 months post-PV. The VAS assesses pain level on a scale of 0-10, with 0 being no pain and 10 indicating the worst pain⁹. This evaluation was obtained by the pain relief specialist during consultations and was reported in this study. Concerning quality of life we used the Eastern Cooperative Group (ECOG) Performance Status scale, which has the following grades: 0) Fully active, able to carry on all pre-disease performance without restriction; 1) Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work; 2) Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours; 3) Capable of only limited self-care, confined to bed or chair more than 50% of waking hours; 4) Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair; 5) Dead¹⁰. ECOG gradings were recorded by the attending oncologist before PV procedures at one, three, six and 12 months post-PV. These grades were also obtained by the pain relief specialist and recorded in the electronic medical record of Institut Curie, and allowed an assessment of how the disease affects the daily living activities of the patient in addition to disease progression¹⁰.

All PV procedures were performed by the senior neuroradiologist with more than ten years' experience in the PV procedure, always using a digital subtraction angiography unit with a C-arm (Angiostar, Siemens, Erlangen, Germany). The patient was under conscious sedation in combination with local anaesthesia with lidocaine 1% at pedicle levels (transpedicular approach) or in the middle portion of the vertebral body (posterolateral approach) administered by fluoroscopic guidance. General anaesthesia with orotracheal intubation was used when treating the cervical spine or first two thoracic levels, as well as when the anaesthesiologist considered it necessary.

The technique of PV has been described elsewhere^{7,11}. At the end of the procedure we recorded the presence of cement leakage to the vertebral disk, anterolateral, lateral, foraminal and epidural veins, paravertebral plexus, vena cava, intercostal arteries, soft tissue or spinal

canal. We also quantified the total volume of cement injected as well as the total percentage of opacified volume of the vertebral body, using the visual evaluation in anteroposterior and lateral view films obtained at the end of the PV procedure. All complications were recorded in the database, including haematoma, radicular pain and pulmonary embolism due to cement migration and lodgement in the pulmonary vasculature that was confirmed by CT in all suspicious cases.

We performed a descriptive statistical analysis for the variables included. VAS was evaluated pre-PV and post-PV at one, three, six and 12 months with the Mann-Whitney U test. We considered statistical significance when P value <0.05 , and we also reported confidence intervals at 95%. A Kaplan-Meier analysis was also performed to evaluate the moment at which patients obtained pain relief $\geq 50\%$ compared to the pre-PV status. Quality of life was evaluated with a time series graph to show the trend of different grades of ECOG performance status in the studied population. All statistical analyses were performed using the SPSS version 20 software (IBM, Somers, NY, USA).

Results

A total of 31 patients were recorded in 44 sessions of PV, accounting for 88 treated vertebrae. The mean age of patients treated with PV was 55.1 years ($SD \pm 10.1$, range 38.0-75.8). Metastases by vertebral level were osteolytic lesions in 34/88 vertebrae (38.6%) (Figure 1), osteoblastic 6/88 (6.8%) (Figure 2), and mixed in 48/88 (54.5%) (Figure 3). Epidural involvement was identified in 6/88 (6.8%) of the vertebrae, depicted by MRI in 42/44 (95.5%) and by CT in 2/44 (4.5%). A total of 4/31 patients (12.9%) received 8 Gy monosession radiotherapy and 27/31 patients (87.1%) received standard 30 Gy radiotherapy. Indications for PV were pain relief in 42/44 sessions (95.5%) and spine stabilization in 2/44 (4.5%). PV was employed as a first line therapy in 7/31 patients (22.6%) because of lack of availability in scheduling radiotherapy, but all of them subsequently received their radiotherapy treatment; 24/31 patients (77.4%) received the radiotherapy first and then the PV. A total of 21/31 PV-treated patients (67.7%) previously received bisphosphonates.

In 19/44 (43.2%) sessions of PV only one

vertebral level was treated; in 15/44 (34.1%) of the sessions two vertebral levels were treated; in 4/44 (9.1%) of the sessions three vertebral levels were treated; in 3/44 (6.8%) sessions four vertebral levels were treated, while in 3/44 (6.8%) sessions five vertebral levels were treated. The thoracic region accounted for 49/88 (55.7%) treated vertebral bodies, followed by the lumbar region with 33/88 (37.5%) and the cervical region with 5/88 (5.7%), while the sacrum accounted for only one level 1/88 (1.1%); thus the thoracolumbar region accounted for 82/88 (93.2%) treated vertebral bodies. In most of the treated vertebral levels we used a bilateral transpedicular approach, which accounted for 64/88 (72.7%) of treated vertebrae, while unilateral approach was used in 24/88 (27.3%) vertebrae. Mean volume of cement used per vertebral body was 4.4 ml, while the mean percentage of volume filling per vertebral body, calculated upon visual evaluation, was 57.5%.

We reported a total of 45 technical incidents in 44 sessions of PV, none of them were symptomatic: vascular leakages accounted for 24/45 (53.3%), of which 16/45 (35.6%) were venous paravertebral leakages, 5/45 (11.1%) were epidural venous leakages, and 3/45 (6.7%) were intercostal arterial leakages. Soft tissue leakages accounted for 21/45 (46.7%) of the leakages, of which discal leakages in 8/45 (17.8%), soft paravertebral soft tissue leakage in 13/45 (28.9%). Despite the presence of 4/31 patients (12.9%) with epidural involvement up to group 2 of Schimony scale, patients treated with PV in this series did not develop neurological deficit. In this series a total of four complications were identified (4/31, 12.9%), three cases of radicular pain, two of them related to a soft tissue foraminal leakage, while the third was not related to any leakage; one case resolved with non-steroidal anti-inflammatory drugs (NSAID), another case with NSAID and steroids, and the third required CT-guided foraminal infiltration with lidocaine and steroids guided by CT, neither of the patients who developed the radicular pain related to soft tissue foraminal leakage require surgical debulking of the cement. We identified a case of pulmonary embolism that was not related to any leakage, thus the pulmonary embolism was related to a thrombus formation within a segmentary pulmonary artery, and for that reason the patient received anticoagulation therapy with warfarin; the patient completed three months of follow-up because she was recruited late in this series (Table 1).

These data allow us to report a perioperative morbidity at 30 days post-PV of 4/31 (12.9%) patients. The patient with the pulmonary embolism (3.2%) had symptoms lasting more than 30 days, while the other 3/31 cases of radicular pain resolved within two weeks with the treatment previously described. We did not identify deaths related to the PV procedure within 30 days post-PV, thus our mortality rate was 0.0%.

In this series the mean follow-up time was 9.7 months, SD $\pm$ 3.7 (range 1 to 12 months). Ten patients did not complete the 12 months of follow-up: one because she was recruited late in the study and only completed six months of follow-up, while another developed pulmonary embolism related to the PV procedure that required complete anticoagulation, and completed three months of follow-up because she was recruited late in the study. Eight patients died: one from refractory heart and acute renal failures after completing one month of follow-up; six patients developed cancer progression: one with brain metastases and a six-month follow-up; two with meningeal carcinomatosis, one completed a three-month follow-up, the other completed a six-month follow-up; three developed epidural involvement, the first required radiotherapy and laminectomy and completed six months of follow-up, while the second developed pneumonia that impeded laminectomy, and completed a one-month follow-up, the third also developed fractures at L1 and L2 levels and spinal cord compression, and completed a six-month follow-up. Finally one patient developed sepsis unrelated to the PV procedure, that was related to immunosuppressive state in a patient with cancer and systemic therapy who completed a three-month follow-up.

We observed a progressive pain relief over the follow-up period in 28/31 patients (90.3%). On the other hand, three patients (3/31, 9.7%) developed a worsening of pain, two of them corresponded to cancer progression and developed the worsening pain at the three-month follow-up. In one patient it was not possible to control the pain during the complete 12-month follow-up despite changes in medications, the other patient controlled pain with a change in medication at the 12-month follow-up, while the third patient developed a sciatica secondary to a disk herniation at three months of follow-up, and it resolved with analgesics and physiotherapy. The mean and standard deviation of pain measured with the VAS were as follows: pre-PV value was 5.7 ± 2.0 ; one month post-PV 2.9 ± 2.2 ; three

months post-PV 1.8 ± 2.2 ; six months post-PV 1.5 ± 2.4 ; and 12 months post-PV 0.6 ± 1.0 . The Mann-Whitney U test showed a significant pain reduction when comparing pre-PV VAS with: one month post-PV, $p < 0.001$ (Confidence interval 95%: 2.12, 3.76); three months post-PV $p < 0.001$ (CI 95%: 0.96, 2.63); six months post-PV $p < 0.000$ (CI 95%: 0.57, 2.50); 12 months post-PV $p < 0.001$ (CI 95%: 0.10, 1.04). As we can see a significant reduction in pain level was achieved compared with the pre-PV during the study (Table 2). The box-plot graph of the VAS showed a decrease of pain intensity at six and 12 month of follow-ups under the 25th percentile value of pre-PV level (Figure 4). But if we analyze the mean values of VAS, at one-month follow-up 70% of the patients achieved a pain reduction of 50%, compared with the pre-PV VAS; while at three months, 95% of the patients had achieved 50% of pain reduction; finally at six months, 100% of the patient had 50% of pain reduction. Reported data are for surviving patients and those who accomplished the different cut-off points of the follow-up. These results were easily confirmed with the Kaplan-Meier graph (Figure 5) in which we could identify the percentage of the patients achieving a 50% of pain reduction at the different selected time cut-offs. As shown in this schematic representation, 100% of the patients evaluated with the Kaplan-Meier method achieved a 50% pain reduction measured by the VAS. Furthermore, neither of the two PV sessions performed for spinal stabilization developed fracture at the

treated level either in the adjacent superior or inferior vertebrae.

Results of the quality of life measured by the ECOG performance status showed in a time series analysis that at time cut-off we can identify a positive slope in grade 0 of ECOG performance status graph, in which at pre-PV accounted for one patient and 13 patients at 12-month follow-up, reflecting a significant number of patients that changed from different grades of ECOG performance status to an asymptomatic status; 14 patients accounted for ECOG grade 1 at pre-PV, while at the 12-month follow-up eight patients were identified in this grade; nine patients accounted for ECOG grade 2 at pre-PV, while at the 12-month follow-up no patient was in this grade; seven patients accounted for ECOG grade 3 at pre-PV, but at the 12-month follow-up no patient remained in this grade; no patient accounted for ECOG grade 4 at pre-PV, and no patients were classified in this grade at the 12-month follow-up; finally no patient accounted for ECOG grade 5 at pre-PV, while four patients were recorded in this grade at the 12-month follow-up, with another two patients that died at three and two more at six months of follow-up. This graph also showed a positive slope due to the patients' deaths. For ECOG grades 1 to 4 the graph showed a negative slope due to a change in patients in ECOG grade. It is also important to note that we had two patients who did not complete the follow-up for the reason stated above.

These data show that as we can see in Table

Table 1 **Technical incidents and complications.**

Variables	N= 44 percutaneous vertebroplasty sessions	N= 31 patients treated by percutaneous vertebroplasty
Technical incidents		
Venous leakage	16 (35.6%)	
Soft tissue leakage	13 (28.9%)	
Discal leakage	8 (17.8%)	
Epidural venous leakage	5 (11.1%)	
Arterial leakage	3 (6.7%)	
Total	45 (100.0%)	
Complications		
Radicular pain		3/31 (9.7%)
Pulmonary embolism		1/31 (3.2%)
Total		4/31 (12.9%)

Table 2 Pain measured with Visual Analogue Scale.

Variable	31 patients $\mu \pm SD$ (N)	p value (CI 95%)
VAS		
Pre	5.7 $\pm$ 2.0 (31)	
1 m	2.9 $\pm$ 2.2 (31)	0.001 (2.12, 3.76)
3 m	1.8 $\pm$ 2.2 (29)	0.001 (0.96, 2.63)
6 m	1.5 $\pm$ 2.4 (26)	0.001 (0.57, 2.50)
12 m	0.6 $\pm$ 1.0 (21)	0.001 (0.10, 1.04)
VAS: visual analogue scale; μ : mean; SD: standard deviation; N: number; CI: confidence interval.		

3 and Figure 6 most treated patients improved their quality of life. Unfortunately eight patients died for reasons related to their poor clinical condition as well as the short life expectancy in patients with VM.

Discussion

Pain relief

Among the possibilities for the treatment of VM, PV has been used by different centers around the world alone or in association with radiotherapy, chemotherapy or surgery¹²⁻¹⁶. Initial studies used PV to treat different primary cancer, but recently some research groups have included only one type of cancer. In relation to pain relief, our study is in line with the results of other authors. A retrospective study by Trumm et al. included only osteolytic VM of patients with breast cancer with a total of 53 patients of

whom 78.6% patients experienced pain relief. Their VAS score changed from 6.4 pre-PV to 5.1 at 24 hours post-PV ($p>0.05$), and to 3.4 at the six-month follow-up ($p<0.05$)¹⁵. In another study Jha et al. included 147 patients with VM compression fractures whose lesions were from different primary cancers: a total of 25 (17%) patients with breast cancer and the overall rate of responders (patients with improved or resolved pain) was 88.5%, independent of the primary cancer. However in their multivariate analysis they found that only patients with lung cancer or multiple myeloma had decreased odds of pain resolution¹⁷. In a prospective study, Chew et al. included 128 patients with PV in patients with VM and myeloma of which 22 had VM from breast cancer, finding a change in VAS pre-PV from 7.57 $\pm$ 1.88 to six weeks post-PV 4.77 $\pm$ 2.67 ($p<0.001$)¹⁸. Mikami et al., in a retrospective study, included only 69 patients with VM from different primary cancers, but only 12 patients with breast cancer. Overall, VAS pre-PV changed from 7.3 to 1.9 post-PV ($p<0.001$), the group with VAS score of 0-2.5 pre-PV had a rate of 4%, while in the post-PV group it was 65%¹⁹. In relation to the type of VM, Calmels et al. reported a series that included 52 patients with osteoblastic and mixed metastases from different primary cancers, and an analgesic efficacy rate of 92% at the six-month follow-up²⁰.

Our study we recorded 31 patients with VM from breast cancer that presented not only osteolytic lesions but also osteoblastic and mixed lesions, as their clinical presentation, and we identified pain relief in 90.3% of the patients. VAS scores improved from 5.7 $\pm$ 2.0 pre-PV to 2.9 $\pm$ 2.2 post-PV at one-month follow-up

Table 3 Quality of life measured through the ECOG performance status at different time cut offs.

ECOG at cutoff time/grade	ECOG PRE N (%)	ECOG 1 m N (%)	ECOG 3 m N (%)	ECOG 6 m N (%)	ECOG 12 m N (%)
0	1 (3.2)	10 (32.3)	10 (32.3)	12 (41.4)	13 (50.0)
1	14 (45.2)	12 (38.7)	13 (41.9)	11 (37.9)	8 (30.8)
2	9 (29.0)	4 (12.9)	6 (19.4)	2 (6.9)	0 (0.0)
3	7 (22.6)	4 (12.9)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	1 (3.2)	0 (0.0)	1 (3.4)	0 (0.0)
5	0 (0.0)	0 (0.0)	2 (6.5)	2 (6.9)	4 (15.4)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	1 (3.8)
Total	31 (100.0)	31 (100.0)	31 (100.0)	29 (100.0)	26 (100.0)
ECOG OMS. 0= asymptomatic; 1= symptomatic but still performing ambulatory activities; 2= bedridden <50% of the day; 3= bedridden $\geq$ 50% of the day; 4= bedridden permanently, needs helps for quotidian activities; 5= dead.					

($p < 0.001$), and continued decreasing to 0.6 ± 1.0 post-PV at 12-month follow-up ($p < 0.001$). This study identified three patients (9.7%) that developed worsening of pain despite the PV, in two of them it was related to cancer progression and in the other to sciatica from a disk herniation. To our knowledge this is the first study to include all types of VM (i.e., osteolytic, osteoblastic and mixed) in patients with breast cancer, including VM with epidural involvement up to Shimony groups 1 and 2. The results presented in this series of consecutively treated patients is important because patients with VM from breast cancer develop all types of VM with or without epidural involvement who could require palliation therapy that could be obtained with PV. Furthermore, the Kaplan-Meier graph in our study demonstrates that 70% of the patients achieved 50% of pain relief post-PV at one-month follow-up, and that at six months follow-up 100% of patients achieved 50% of pain relief. These data are confirmed by the box plot graph that shows a progressive analgesic effect of PV which is more evident when we compare the VAS percentile. The pre-PV VAS 25th percentile was superior to the post-PV six month follow-up VAS 100th percentile, and this trend continued decreasing up to the 12 month follow-up.

Quality of life

Chew et al. evaluated quality of life through the Roland-Morris Questionnaire (RMQ), which measures the degree of disability associated with back pain. It is a scale ranging from 0-23 with higher scores indicating increased degrees of disability. They reported a fall in RMQ score from $18.55 (\pm 4.79)$ pre-PV to $13.5 (\pm 6.95)$, $p < 0.001$ at six weeks post-PV¹⁸. None of the aforementioned studies evaluated quality of life^{15,17,19}. Our study evaluated quality of life through ECOG performance status, a grading system that allows assessment of the patient's disease progression but also interpretation of how the diseases affects the daily living activities of the patients with cancer. In our series 15/31 patients (48.4%) were classified as ECOG performance status grades 0 and 1 at pre-PV status, while at the 12-month post-PV follow-up 21/26 patients (80.8%) were classified in ECOG performance status grades 0 and 1, autonomous in their daily life activities, that represents a relative increase of 32.4% of patients. On the other hand, 7/31 patients (22.6%) were classified ECOG grades

3 and 4 at pre-PV status, while at the 12-month post-PV follow-up they were 0/26 patients (0%), this represents a relative decrease of 22.6% of patients that were bedridden more than 50% of the time or permanently. During the study 8/31 (25.8%) patients died, none of them from complications of the PV procedure. The causes of death were cancer progression 6/8 (75%), poor clinical condition 1/8 (12.5%), and sepsis in an immunocompromised cancer patient 1/8 (12.5%). These results show that PV improves quality of life in patients with different types of VM from breast cancer, who had previously received or not received radiotherapy, at least for a period of 12 months.

Complications

Our study reported technical incidents related to cement leakages but otherwise asymptomatic in the immediate and follow-up post-PV, similar to those reported by other authors. Barragán-Campos et al., in a retrospective series of 117 patients with VM from different primary cancer²¹, reported that in the 304 vertebrae they treated, a total of 423 leakages occurred, of which 78.5% were vascular (epidural veins, paravertebral plexus, anterolateral paravertebral plexus, lateral paravertebral plexus, and foraminal veins) and 21.5% were non-vascular (puncture trajectory, paravertebral soft tissue, and into the disk). From all these technical incidents they detected only eight complications, hence a morbidity rate of 6.8% at 30 days of follow-up. Six (5.1%) complications were local and included: two (1.7%) puncture site soft-tissue haematomas and four cases of radicular pain (3.4%), two of them related to foraminal venous leakage. All complications were resolved medically within two weeks. Two (1.7%) cases of pulmonary embolism, only one of them symptomatic, were codified as systemic complications. The symptomatic patient received anticoagulation therapy but perished despite the treatment eight days post-PV, thus having a mortality rate of 0.85% at 30 days of follow-up. In the same study a univariate analysis discarded the association between foraminal venous leakage and radicular pain. On the other hand, it established an association between cement leakage through the vena cava and pulmonary embolism. Trumm et al. documented 69.8% leakages in 86 vertebrae: 31.3% were discal leakages, intraspinal in 26.9%, paravertebral in 26.9%, posterolateral in 14.9%. They reported only four complications,

all of them minor: one case of sudden sickness at the time of needle insertion, and three patients with exacerbation of pain, two during needle insertion, and one during cement injection; no patients died during the procedure or in the six-month follow-up. Thus they had immediate morbidity of 7.5%, and a mortality of 0% at 30 days of follow-up¹⁵.

In our study among the 44 PV sessions we identified 45 cement leakages, representing 1.02 episodes of technical incidents per session, not related to any symptoms. The high number of cement leakages could be explained by one or more of the following factors: a) careful monitoring of cement distribution during the PV procedure; b) use of CT imaging for post-PV control; c) treatment of two or more vertebral levels in 56.8% of the PV sessions; d) inclusion of mixed and osteoblastic lesions in 61.3% of cases, which are more prone to leakages²⁰; e) relatively high volume of cement injected per vertebral body.

We recorded a relatively high rate of complications, 4/31 (12.9%), but most of them were immediate complications: 3/31 patients (9.6%) developed a minor complication, radicular pain; three of which resolved within two weeks, two of them with oral medication and the other with CT-guided infiltration of lidocaine and steroids. But at 30 days post-PV we recorded only one complication, non-cement related pulmonary embolism, giving us a morbidity rate of 1/31 patients (3.2%). No mortality episodes were recorded during this study. These data show that PV is safe in patients with different types of VM from breast cancer.

Strengths and weakness

The strengths of this study include the following: a) pain and quality of life were measured by a pain relief specialist, and an oncologist not involved in the PV procedure, thus there is no bias in the measured outcome; b) clinical decision between first line therapy, i.e. PV procedure or radiotherapy, which reflect a pragmatic approach in the clinical setting; c) inclusion of patients with more than one VM; d) inclusion of patients previously treated with radiotherapy, thereby obviating a second session of radiotherapy which reduces the early and late toxicity as well as the possibility of radiation myelitis; e) inclusion of patients with spinal instability, in which the PV procedure avoided a more complex surgical fixation in

patients with a short life expectancy. We also identified the following weakness in our study: a) retrospective observational study with its inherent observation bias; b) absence of a control group with which to compare the results to eliminate a placebo effect; c) small sample size; d) mid-term follow-up (12 months); and e) absence of analysis of use prescription analgesic medication.

Conclusion

This retrospective series showed that PV is a safe procedure, having a high efficacy in pain relief, but also improving quality of life, allowing patients with different types of VM from breast cancer to improve their quality of life and to continue their daily life activities. These results are very promising because the PV procedure itself is a minimally invasive technique and could be performed in patients with poor clinical status, having one or multiple VM in the spine, or those patients with a short life expectancy. Another advantage is that the PV procedure could be used as a first line therapy in cases in which there is no immediate availability of radiotherapy or in which the patient needs fast pain relief just because of adverse effects or tolerance to opioids.

The mechanism for pain relief is not well known. Several hypotheses attempt to explain this phenomenon: local anaesthesia effect, stabilization of the fractured vertebra, exothermic reaction on the nerve tissue, and chemical toxicity²², but none have been conclusive.

In the follow up very few patients had local recurrence suggesting a possible carcinolytic effect of cement, suggesting further studies to evaluating.

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