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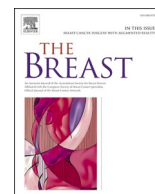
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The role of percutaneous vertebral augmentation in patients with metastatic breast cancer: Literature review including report of two cases

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ABSTRACT

Patients with metastatic breast cancer are at high risk for developing vertebral compression fractures due to underlying bone metastases and bone density loss. Vertebral augmentation techniques including percutaneous vertebroplasty and percutaneous balloon kyphoplasty are techniques used to stabilize compression fractures and improve pain. However, rare complications from these interventions have been observed, including spinal cord compression, nerve root compression, venous cement embolism, and pulmonary cement embolism. These complications pose unique potential challenges for patients with cancer who may already have decreased lung function and potential for venous thromboembolism. In this review, we first describe the role of percutaneous vertebral augmentations in patients with metastatic cancer, with a particular focus on patients with breast cancer. Then, we describe complications of vertebral augmentation in two patients with metastatic breast cancer including long-term symptomatic and radiographic follow-up.

1. Introduction

Spinal metastases are the most common type of metastatic tumors involving bone and cause severe impact on the quality of life of patients with cancer. The thoracic vertebra is the most common site of involvement, followed by the lumbar and cervical vertebra. About 5–10% of patients with advanced cancer develop metastases to the spine, most commonly from a primary lesion in the breast, lung, prostate, or kidney [1–3]. These metastases can be osteoblastic, osteolytic, or mixed depending on the cancer type. Spinal metastases can cause severe pain, vertebral fractures and spinal cord compression. Therefore, palliative treatment and preservation of neurological function are the main goals of the management. Locoregional treatments may improve pain and reduce complications, including surgery, percutaneous vertebroplasty (PVP), percutaneous balloon kyphoplasty (PKP), and radiation therapy (RT). Surgical management is generally considered for patients with unstable fractures or those at risk of significant neurological compromise [4]. Open surgery poses higher morbidity and mortality (20–40%) and is not the preferred management approach for most patients [5].

Instead, RT is preferred to reduce pain and provide durable local tumor burden control in most patients. However, RT is less useful when the spine is unstable or there are fractured vertebrae [6]. In those cases, vertebral augmentation techniques including PVP and PKP are used to help maintain spinal stability and provide pain relief [7].

PVP and PKP are minimally invasive radiologically guided procedures that involve injection of polymethylmethacrylate (PMMA) bone cement into the vertebral body with the objective of achieving pain relief and preventing further loss of vertebral body height [8,9]. One potential complication of these procedures is the development of pulmonary cement emboli (PCE), which can occur if bone cement dislodges and enters the pulmonary vasculature. Similarly, bone cement can deposit in other locations, such as the renal vasculature. There are case reports of patients with metastatic malignancy who experienced cement emboli after PVP or PKP, but few reports provide long-term follow-up [10–17]. This review discusses the goals of percutaneous vertebral augmentation in patients with cancer, including indications, contraindications, techniques and potential complications. Then, we provide case reports of two patients with metastatic breast cancer that developed

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complications from these procedures, including a case of PCE and renal vein cement embolism after PKP and a case of PCE after a PVP procedure.

1.1. Vertebral body metastasis and breast cancer

Breast cancer is the most common cancer affecting women worldwide, and bone metastases are the most common site of metastatic disease recurrence. The incidence of bone metastases in metastatic breast cancer is 60–75% in most studies, with a higher incidence in luminal subtypes [18,19]. While multiple cancer types metastasize to the bone, breast cancer is the most common cause of bone metastases given its high prevalence and the predilection for metastasis to the bone. In a study that included 382,733 patients with bone metastases identified via a search of the Oncology Services Comprehensive Electronic Records (including data from 52 United States cancer centers), breast cancer was the most common cause of bone metastases (36%), followed by lung cancer (16%) and colorectal cancer (12%) [20]. When breast cancer metastasizes to the bone, it interrupts the normal bone modelling process and causes bone degradation. Most breast cancer metastases to bone result in osteolytic lesions, which are mediated by osteoblast production of receptor activator for NF- κ B ligand (RANKL) and several osteoclastogenic cytokines. Osteoblasts also produce osteoprotegerin, a decoy receptor to RANKL that curtails osteoclast activation [21].

Magnetic resonance imaging (MRI) is the gold-standard diagnostic modality in the imaging of metastatic spinal tumors, which can evaluate the extent of epidural extension, degree of spinal cord compression, presence of surrounding edema, and presence of spinal root impingement. Metastases to the spine can lead to significant morbidity due to pathologic fractures, hypercalcemia, spinal cord compression, and pain [22]. The management of symptomatic spinal metastases is palliative in most cases and does not prolong survival. Local and systemic treatment approaches can reduce pain and help improve and maintain level of function [23]. Current treatment strategies include analgesics, bisphosphonates, RT, open surgery, and minimally invasive percutaneous interventional procedures such as vertebral augmentation. Surgical treatments allow spinal cord decompression and tumor resection which may restore and preserve neurological functions, but have a greater risk of complications and thus are appropriate for only select patients [24]. PVP and PKP are less invasive techniques which can provide pain relief, improve quality of life, and provide mechanical stabilization [4]. Among patients with metastatic breast cancer, vertebral augmentation is the preferred intervention for the management of severe mechanical pain without symptoms of spinal cord compression [25].

1.2. Vertebral cement augmentation strategies: definitions of PVP and PKP

Vertebral augmentation is the umbrella term that describes any minimally invasive procedure that involves the percutaneous injection of bone cement into a fractured vertebra to help alleviate pain caused by a compression fracture and provide stability to the vertebra to prevent further vertebral collapse [26,27]. Two types of vertebral augmentation include PVP and PKP, which are percutaneous vertebral augmentation techniques used to stabilize and repair vertebral compression fractures using a cement such as PMMA [7].

PVP is a minimally invasive procedure in which bone cement is injected percutaneously into the target vertebral body. PVP was first performed by Galibert and Deramond et al. in France in 1987 for the treatment of painful aggressive vertebral hemangiomas [26] and subsequently described in the United States in 1993 [28]. This procedure is typically performed under fluoroscopic guidance using a single-plane fluoroscopy unit with a C-arm or biplane fluoroscopy, although CT-guided procedures are performed in some cases. The patient is placed in the prone position, local anesthetic is administered, and then PMMA

cement is injected under continuous fluoroscopic control. Of note, vertebral augmentation can also be used before or during an open surgery as needed. The amount of cement injected varies between 2 and 4 ml per pedicle depending on the location of the vertebral body and the severity of vertebral collapse [29].

PKP is a newer vertebral augmentation technique that was first described in 2001 [28]. During this procedure, an inflatable balloon is utilized to create a cavity for the cement and then cement is injected into this space to restore height, correct the spinal deformity, reduce kyphosis, relieve pain, and improve function [30,31]. As a general approach, PVP may be preferred for treatment of vertebral metastases where the vertebral collapse is mild or the collapsed vertebral body is less likely to restore the height, whereas PKP may be a better choice for patients with severe kyphosis and multiple wedge fractures [32].

1.3. Indications and contraindications for vertebral augmentation

Vertebral augmentation can be used for benign or malignant conditions. Indications for vertebral augmentation for benign conditions include for osteoporosis and hemangiomas. Indications and contraindications for vertebral augmentation for spinal metastases are shown in Table 1. In general, it is important to consider the goals of the procedure for each patient to determine whether vertebral augmentation can help achieve that goal. Due to limited anti-neoplastic effect of percutaneous vertebral augmentation, RT or interstitial RT can be combined with PVP and PKP to prevent tumor progression. Radiofrequency ablation can also be performed in combination with PVP to provide antineoplastic activity [25].

2. Evaluating the safety and efficacy of PVP and PKP for the management of vertebral metastasis

Previous studies have demonstrated that percutaneous vertebral augmentation is effective to provide pain relief, improve quality of life, and improve performance status in patients with vertebral metastases. In most studies, pain was measured using the visual analog scale (VAS) which is scored 0–10, with 10 being the worst pain. Many studies also evaluated quality of life using the Oswestry Disability Index (ODI) and/or performance status using the Karnofsky performance scale (KPS).

We performed a systematic literature search of Pubmed for studies of vertebral augmentation for cancer-related vertebral metastases that included patients with metastatic breast cancer published from January 2000 to October 2021. We screened and included retrospective and prospective studies that evaluated the safety and efficacy of PVP and PKP in patients with spinal metastases that included a breast cancer subgroup. We used the search terms “breast cancer” and “vertebral augmentation”, and also reviewed the studies cited in those references. Retrospective studies that evaluated the safety and efficacy of PVP and

Table 1
Indications and contraindications for vertebral augmentation.

Indications ^a	Contraindications
<ul style="list-style-type: none"> ○Patients with severe pain due to spinal metastases that are refractory to medical therapy [I] ○Patients with spinal instability or potential instability caused by spinal metastases, vertebral bodies weakened by neoplasm [I] ○Patients who have contraindications to open spinal surgery or who decline open spinal surgery [II] ○Vertebral augmentation may be used prior to or during open surgery and internal fixation to prepare for surgery or complete surgical techniques [I] 	<ul style="list-style-type: none"> ○Patients with asymptomatic lesions or pain that improves with medical therapy [I] ○Ongoing local or systemic infection or septicemia/sepsis [I] ○Retropulsed bone fragment or epidural tumor causing myelopathy [II] ○Spinal canal compromise due to the tumor, resulting in myelopathy [I] ○Uncorrectable coagulopathy [I] ○Allergy to bone cement or opacification agent [I]

^a Level of evidence for each recommendation is shown in brackets.

PKP in the treatment of spinal metastases are summarized in Table 2. These studies included patients with multiple myeloma and solid cancers including breast cancer [33–41]. For example, in one retrospective study, PVP was performed in 39 consecutive patients with painful osteoblastic metastatic spinal lesions to evaluate the safety and efficacy of fluoroscopy-guided PVP [42]. Pain was measured using VAS, quality of life using ODI, and performance status using KPS. In this study, the procedural intervention resulted in clear improvement in pain control, with a significant decline in the VAS score post-procedure ($p < 0.001$). The ODI and KPS scores significantly improved compared to baseline ($p < 0.001$). In terms of safety, extraosseous cement leakage was seen in 15 cases, but it did not cause any clinical complications. In another study, Trumm et al. evaluated the safety and efficacy of PVP for the treatment of osteolytic metastases in 53 patients with metastatic breast cancer [34]. In this study, pain improved with a reduction in VAS score from 6.4 to 3.4 ($p < 0.05$, mean follow-up 9.2 months). Local cement leakage was identified in 69.8% of patients without major complications [34].

There are also prospective studies that evaluated the safety and efficacy of PVP and PKP in patients with spinal metastases, which are summarized in Table 3. These studies reported that PVP and PKP are both safe and effective in providing pain relief with spinal metastases [43–47]. For example, in one study, 52 patients who underwent 59 vertebroplasty procedures for 103 painful vertebral metastases were enrolled in a study to evaluate the analgesic efficacy of percutaneous

vertebroplasty [43]. Analgesic efficacy was classified as excellent, good, fair and poor. In this study, the analgesic efficacy rate was 86% at 1 month and 92% at 6 months. They reported cement leakage in 52 of the 103 treated vertebrae (50.5%), most of which were asymptomatic. Two patients experienced PCE due to a cement leak. In another prospective study, Chew et al. evaluated the outcomes of 128 patients (including 22 patients with breast cancer) who underwent percutaneous vertebroplasty [45]. VAS scores reduced 7.75 ± 1.88 pre-vertebroplasty to 4.77 ± 2.69 post-vertebroplasty ($p = 0.0001$). Back-specific functional status was measured by the Roland-Morris disability questionnaire (RDQ) score, which uses a scale of 0–23 with a higher score indicating a higher disability. RMQ scores improved from 18.5 ± 4.79 pre-intervention to 13.5 ± 6.96 post-intervention ($p = 0.001$). Complications included cement extension to the vena cava ($n = 1$), local hematoma ($n = 1$), and loss of sensation over the T1 dermatome ($n = 1$). Another phase I/II clinical trial, JIVROSG-0202, was designed to evaluate the role of PVP as palliation for painful malignant vertebral compression fractures [44]. The response rate was 70% at week 1 after PVP and increased to 83% at week 4. No major adverse events were reported in this study.

Vertebral augmentation has also been compared to non-surgical management in a randomized multicenter study. Specifically, Berenson et al. assessed the safety and efficacy of PKP compared with nonsurgical management in 134 patients with cancer who had painful

Table 2

Summary of retrospective studies evaluating the efficacy and safety of PVP and PKP in patients with spinal metastases.

Reference	Study recruitment period	n	Primary malignancy (n)	PVA type	Efficacy	Complications
Fourney et al., 2003	Oct 2000 to Feb 2002	56	MM (21), BC (9), LC (6), lymphoma (6), others (14)	PVP, PKP, PVP&PKP	Reduction in VAS score ($p = 0.02$) Reduction in analgesic consumption ($p = 0.03$) Vertebral height gain ($p = 0.01$) Reduction in VAS score ($p < 0.05$)	Asymptomatic cement leakage (9.2%) after PVP
Trumm et al., 2008	Jan 2003 to Jan 2007	53	All BC (53)	PVP	Reduction in VAS score ($p < 0.05$)	Local cement leak (69.8%) without major complications
Lee et al., 2009	2004 to 2008	19	BC (8), PC (4), others (7)	PVP	Symptomatic improvements in 84% of patients	Local complication (5.3%)
Lim et al., 2009	2001 to 2007	102	BC (24), MM (19), LC (16), liver (10), others (33)	PVP	Reduction in VAS score ($p = 0.001$) Improvement in vertebral body compression ratio Correction of kyphotic angle ($p < 0.05$)	Leakage of cement (17%) without any clinical or neurological symptoms
Mikami et al., 2011	2002 to 2008	69	BC (12), LC (8), PC (7), CRC (7), others (38)	PVP	Reduction in VAS score 7.3 to 1.9 with a mean improvement rate of 73.3%	Local cement leakage (49%)
Trumm et al., 2012	Dec 2001 to June 2009	202	BC (68), MM (40), LC (22), RCC (10), PC (8), others (54)	PVP	Significant reduction in VAS score ($p < 0.05$)	Local PMMA leakage rate was 58.6% Pulmonary cement embolism (7.8%)
Zhi et al., 2014	Jan 2003 to Jan 2008	80	BC (16), LC (9), PC (6), GC (6), others (5)	PVP vs. PKP	Significant reduction in VAS score ($p < 0.001$) in both PVP and PKP groups. The difference in VAS score between these two groups was insignificant.	Cement leakage was significantly higher in PVP group (30.3%) compared to PKP group (16.9%) $p < 0.05$ - None of them symptomatic
Tian et al., 2016	Mar 2010 to Feb 2015	39	LC (15), PC (11), BC (9), others (4)	PVP	Reduction in VAS scores ($p < 0.001$) ODI scores and KPS scores improved ($p < 0.001$)	Extraosseous leakage ($n = 15$) without any clinical complications
Zhang et al., 2017	July 2008 to June 2012	153	LC (79), BC (31), GC (15), sarcoma (7), others (21)	PVP Group A vs. Group B ^a	Both groups experienced significant pain relief and QoL improvement after the intervention ($p < 0.001$).	Cement leakage rate; - Group A: 23.6% - Group B: 26.1% PCE ($n = 1$) in Group B PCE ($n = 13$) 5 of them symptomatic and treated with LMWH
Mansour et al., 2018	NA	102 ^b	MM (37), BC (25), lymphoma (13), others (27)	PVP	NA	

Abbreviations: BC, breast cancer; CRC, colorectal cancer; GC, gastric cancer; LC, lung cancer; LMWH, low molecular weight heparin; KPS, Karnofsky Performance Status; MM, multiple myeloma; n, number of patients; NA, not available; QoL, quality of life; PVA, percutaneous vertebral augmentation; PC, prostate cancer; PCE, pulmonary cement embolism; PKP, percutaneous kyphoplasty; PVP, percutaneous vertebroplasty; pts, patients; RCC, renal cell carcinoma; RDQ, Roland-Morris Disability Questionnaire; VAS, visual analog scale; vs, versus.

^a Group A ($n = 93$) included patients who underwent PVP ≤ 3 vertebral levels per session. Group B ($n = 60$) included patients who underwent PVP > 3 vertebral levels per session.

^b Seventy-eight (76.5%) patients had malignant vertebral fractures, and 24 (23.5%) patients had osteoporotic fractures. All had a pathology-confirmed diagnosis of cancer.

Table 3

Summary of prospective studies evaluating the efficacy and safety of PVP and PKP in patients with spinal metastases.

Reference	Study type	Study recruitment period	n	Primary malignancy(n)	Procedure type	Efficacy	Complications
Calmels et al., 2007	Prospective	1996 to 2002	52	BC (40), PC (3), LC (3), others (6)	PVP	Analgesic efficacy rate 86%	Cement leak (50.5%), 5 (8.5%) cases were symptomatic
Kobayashi et al., 2009	Phase I/II	Feb 2003 to May 2006	36	BC (7), CRC (7), LC (7), others (12)	PVP	Response rate was 70% and increased to 83% at week 4. Reduction in VAS score (p = NA)	Local complications (8.5%) Local complication (3%) No cement leakage
Chew et al., 2011	Prospective	June 2001 to June 2010	128	MM (41), BC (22), LC (16), Lymphoma (11), others (38)	PVP	Reduction in VAS score (p = 0.001) Reduction in RDQ score (p = 0.001)	Cement leakage to vena cava (n = 1), local hematoma (n = 1), loss of sensation over T1 dermatome (n = 1)
Berenon et al., 2011	RCT	May 2005 to March 2008	134	MM (49), BC (28), LC (11), PC (8), others (33)	PKP (n = 70) Nonsurgical management ^a (n = 64)	RDQ score was −8.5 points in PKP arm (p < 0.0001) at 1 month	Back pain (n = 4 in PKP arm, n = 5 in control arm) Symptomatic vertebral fracture (n = 2 in PKP arm, n = 3 in control arm)
Chen et al., 2013	Prospective	May 2005 to Jan 2012	6	BC (2), LC (2), liver (1), PC (1)	PKP	Reduction in VAS score and ODI scores (p = NA)	Asymptomatic cement leakage into the anterior vertebral vein.

Abbreviations: BC, breast cancer; CRC, colorectal cancer; LC, lung cancer; MM, multiple myeloma; n, number of patients; NA, not available; ODI, Oswestry Disability Index; PVA, percutaneous vertebral augmentation; PC, prostate cancer; PKP, percutaneous kyphoplasty; PVP, percutaneous vertebroplasty; pts, patients; RCT, randomized controlled trial; RDQ, Roland-Morris Disability Questionnaire; VAS, visual analog scale.

^a Non-surgical management was control group.

Table 4

Case reports of cement leakage after PVP and PKP for the treatment of spinal metastases in patients with metastatic breast cancer.

Reference	Age	Procedure type	Procedure indication	Complications	Symptoms of Complications	Treatment of Complications
Ratliff et al., 2001	50	PVP at T1	T1 vertebra metastasis with collapse of the vertebral body but without cord compression.	Cement leakage into the C8 and T1 foramina and spinal canal	Radiculopathy and myelopathy developed	Surgical decompression
Amoretti et al., 2007	72	PVP at L3	Pathologic L3 compression fracture	Cement embolus in the aorta, along with the hook-shaped cement fragment in the lumbar artery.	No symptoms	No treatment
Leitman et al., 2011	81	PVP at L2 and L3	Vertebral body compression fractures of the L2 and L3 vertebrae	Cement within the vertebral venous plexus demonstrated after PVP PCE incidentally discovered after 10 years after COPD exacerbation.	No respiratory symptoms following PVP for 10 years.	Supportive treatment for COPD
Chick et al., 2012	37	PKP at L1 and L2	Anterior wedge compression deformities of the L1 and L2 vertebral bodies	PCE	One month later, patient had pleuritic chest pain, shortness of breath, tachycardia and generalized weakness	Anticoagulation with enoxaparin One month later symptoms resolved
Jandaghi et al., 2013	46	PVP at L3	Pathologic compression fracture in L3	Arterial cement embolism in the popliteal, anterior tibial, posterior tibial, peroneal arteries and left L3 lumbar artery extending into the abdominal aorta	Within the 1st hour of PVP, severe pain and numbness in the left leg due to acute left leg ischemia	Anticoagulation with aspirin, clopidogrel, IV heparin. Lower limb angiography and then transluminal angioplasty of the infrapopliteal arteries. Monitoring
Chen et al., 2014	39	PVP at T10, T11, L1, L2	Compression fracture of the T12 vertebral body and kyphotic deformity of the thoracic–lumbar junction with compression of the underlying spinal conus.	PCE	Asymptomatic, discovered incidentally	
Chai et al., 2016	51	PVP at T12, L2 and L3 PKP at L1	Extensive thoracolumbar vertebral metastatic disease and L1 pathologic fracture with 50% compression	Cement extension into the inferior vena cava, right atrium, right ventricle, main pulmonary artery, and right pulmonary artery and its branches	No symptoms	Treated with anticoagulation (enoxaparin 1 mg/kg subcutaneously twice daily).
O'Connor-Byrne et al., 2019	43	PVP at L4	L4 painful compression fracture	Cement in segmental and subsegmental pulmonary arteries.	No symptoms	Treated with antibiotics and anticoagulated with therapeutic dose of low-molecular-weight heparin.

Abbreviations: COPD, chronic obstructive pulmonary disease; n, number; ODI, Oswestry Disability Index; PCE, pulmonary cement embolism; PKP, percutaneous kyphoplasty; PVP, percutaneous vertebroplasty.

vertebral body compression fractures [46]. The primary endpoint was back-specific functional status measured by the RDQ score at 1 month. Patients in the kyphoplasty group had significant improvement in quality of life compared with the control group, with a mean RDQ score in the kyphoplasty group of 17.6 at baseline to 9.1 at 1 month (mean change -8.5 points; $p < 0.0001$). The mean score in the control group was 18.2 at baseline and 18.0 at one month (mean change 0.2 points; $p = 0.83$). Adverse events included back pain and symptomatic vertebral fracture, which were similar between the PKP arm and control arms [46].

There have also been meta-analyses and systematic reviews that have evaluated the safety and efficacy of vertebral augmentation in larger cohorts of patients. For example, one meta-analysis evaluated outcomes in 864 patients with metastatic spinal disease who underwent PVP or PKP [48]. After PVP, 62% of patients had an improvement in mobility and 91% had improvement in pain. After PKP, 69% of patients had an improvement in mobility and 93% of patients had an improvement in pain. Another systematic review included 111 clinical reports and 4235 patients evaluating the effectiveness of vertebroplasty (78 reports, 2545 patients) or kyphoplasty (33 reports, 1690 patients) for patients with mixed primary spinal metastatic cancers, multiple myeloma or hemangiomas. In this study, pain scores reduced significantly within 48 hours of PVP and PKP. Baseline VAS scores were high (VAS ≥ 7.0). After PVP and PKP, the mean VAS scores decreased in all patients to mild pain intensity levels (VAS < 4.0) which was statistically and clinically meaningful [4].

In addition, there are case reports that describe cement leakage after PVP or PKP, including some case reports of patients with metastatic breast cancer that are shown in Table 4 [10–17]. Most patients had no symptoms of cement leakage and were diagnosed incidentally based on imaging [11,12,15–17]. In three cases, the patients had symptoms including neurologic deficits and respiratory symptoms; two were treated with surgical decompression and angioplasty for neurologic complications, and two received anticoagulation with aspirin, clopidogrel, IV heparin [10,13,14].

3. Complications

Complications of vertebral augmentation include pain, infection, neurologic complications, and leakage of PMMA bone cement, which may cause spinal cord compression and/or cement embolism. The studies we included in this review include patients with all solid tumor types, so we cannot specifically quantify rates of complications in patients with breast cancer alone, but there is no reason to believe that rates of complication would be notably different across tumor types. A transient increase in pain during vertebroplasty is reported in most studies, with an incidence varying between 1–23% [48–50]. The pain may be due to an increase in pressure at the site of the painful vertebra, an inflammatory reaction to the PMMA, and/or osseous ischemia [51]. Infection is another possible complication of vertebral augmentation, although rates of infection are low. In a retrospective study of 826 cases of vertebral augmentation, the incidence of infection following PVP and PKP was 0.36% [52].

A potential serious complication of vertebral augmentation is the leakage of PMMA bone cement into the spinal canal or paravertebral venous plexus, which may lead to spinal compression [53,54]. Leakage of cement into spinal canal is well tolerated in most cases, but can rarely cause serious neurological complications and even paraplegia. Intraforaminal leakage is more serious which can be associated with radiculopathy. In most patients, neurological complications are transient and respond to nerve root blocks, oral medications, or surgical decompression if needed [51]. The overall risk of neurologic complications due to embolization was 4.0%. Transient neurologic deficits were reported in 2.5% of patients in a systematic review [55]. These patients experienced paraparesis, a conus medullaris syndrome with urinary retention, numbness of the lower extremity, myoclonus, dizziness, and progressive

lower extremity weakness. Four patients experienced permanent neurologic complications including asymptomatic cerebellar infarcts seen on magnetic resonance imaging and two major brain stem infarcts after the embolization of two cervical tumors [55]. Previous studies demonstrated that secondary fractures adjacent to augmented vertebrae can occur. The risk of secondary fracture increases with a greater degree of augmentation. The location of the adjacent vertebrae at the thoracolumbar junction is considered a risk factor for spinal cord complications [56]. Other complication related to local trauma include rib fractures which occur in $< 1\%$ of cases [57].

Another complication of PMMA leakage is the development of cement emboli. The PMMA cement used in both PVP and PKP usually rapidly polymerizes in the spine, but occasionally it can inadvertently travel from the paravertebral veins to the inferior vena cava (IVC), renal veins, right heart, brain (as a result of a patent foramen ovale), or the pulmonary arterial system [58]. The resulting symptom(s) of these cement emboli depends on the location and extent of the emboli. For example, cement emboli that lodge in the renal veins can cause hypertension and cement emboli in the brain can cause neurologic complications. When the cement lodges in the pulmonary arterial system, it is called a PCE. The incidence of PCE after PVP ranges from 2.1% to 26% depending on the study and imaging modality [59,60]. Most patients with PCE are asymptomatic, but it can cause arrhythmias, chest pain, hypotension, dyspnea, or hypoxia [60,61]. Symptoms may develop during the procedure, but more commonly patients present with symptoms days to weeks, or sometimes up to months, after the procedure. If PCE is suspected, cross sectional chest imaging is recommended [62]. Routine use of imaging tests to evaluate for PCE following vertebral augmentation is generally not recommended in the absence of symptoms, and the use of chest radiograph after cement placement is controversial [61]. Unlike a classic pulmonary thromboembolism (PE), PMMA cement has a high density and is seen as hyperattenuation in the pulmonary vasculature, differentiating PCE from PE [63].

4. Procedural approaches to reduce or minimize complications of vertebral augmentation techniques

Prevention of PCE and post-procedural monitoring are active areas of research. In general, it is recommended that these procedures are performed by providers/medical centers with sufficient volume and experience. In terms of patient positioning, there is some data that prone positioning during the procedure is useful to maintain elevated intrathoracic pressures to reduce the risk of cement embolization [64]. There are also technical considerations that are important to improve outcomes. First, it is important to use a beveled puncture needed to accurately place the needle tip into the tumor under CT-guidance [65]. Second, it is important to use high-viscosity cement and inject it under fluoroscopy control with smooth, consistent pressure [66]. Cement leakage occurs more frequently when the cement is too fluid or if it is administered with too much pressure via a small needle (11–13 gauge) [61]. Third, it is important to reduce the amount of cement injected; generally 2–4 ml per pedicle is required depending on the location of the vertebra and the grading of vertebral collapse. Avoid filling the entire cavity with cement due to the risk of dislodging the tumor fragments into the spinal canal and causing/worsening neurological deficits. In addition, the proceduralist should minimize the dispersion of bone cement to avoid distribution to the posterior vertebral body [67]. Finally, after the procedure, the patient should be monitored for respiratory distress or hemodynamic changes which may be early signs of PCE.

5. Management of complications

Management of PCE depends on the amount of cement embolized and the severity of symptoms. If the patient is asymptomatic, typically no treatment is required. If the patient is symptomatic from PCE,

respiratory monitoring, anticoagulation, corticosteroids, and rarely surgery are considered. Kruger et al. reported a treatment algorithm for PCE [61]. In a central and/or symptomatic embolism, they recommend initiating anticoagulation with heparin followed by 6 months of oral or subcutaneous anticoagulation therapy. Surgical embolectomy is the treatment of choice for large central cement pulmonary emboli. The decision to anticoagulate patients and the optimal duration of anticoagulation are not clearly defined in evidence-based guidelines. Moreover, the benefit of anticoagulation in patients with peripheral PCE and asymptomatic embolism is not clear [61]. Future studies are needed to better understand the most safe and effective management options for patients with PCE.

6. Two case reports describing complications of vertebral augmentation in patients with metastatic breast cancer

Here, we present two cases of patients with metastatic breast cancer who developed vascular complications after injection of PMMA, including their presenting symptoms, imaging findings, management, and long-term outcomes. First, we describe a case of PCE and renal vein cement embolism after PKP, and then a case of PCE after PVP.

6.1. Case Report-1

The first patient is a 40-year-old woman who first developed back pain which she treated with anti-inflammatory medications. She subsequently noticed a mass in her left breast. A core needle biopsy revealed grade II invasive ductal carcinoma that was estrogen receptor (ER)+ (>90%), progesterone receptor (PR)+ (60%), and human epidermal growth factor receptor 2 (HER2) negative. MRI of the lumbar spine showed an L2 vertebral body pathologic fracture with approximately 60% height loss, with associated osseous retropulsion, causing moderate spinal canal stenosis and effacement of the left lateral recess. A positron emission tomography (PET)–CT scan revealed extensive bone metastasis, including involvement of the femurs, ribs, and spine, with pending cord compression in the thoracic spine. A biopsy of the left sacrum confirmed metastatic adenocarcinoma of breast origin that was ER+ (>95%), PR+ (20%), and HER2 negative. Due to pending cord compression, the patient underwent T8–T10 transpedicular corpectomies for tumor removal, T7–T10 laminectomies and stabilization, and bilateral L1, L2 and L5 PKP to improve structural stability. She was started on ovarian suppression with monthly goserelin, followed by oral letrozole and palbociclib. Immediately after surgery, the patient was noted to have new hypertension (systolic blood pressure [SBP] 150s), for which she was started on lisinopril. Four weeks later, the patient presented with shortness of breath, and she was found to be hypoxic (88–89%). She was also tachycardic (heart rate [HR] 104 bpm) with normal blood pressure on lisinopril (SBP 100s). CT of her spine demonstrated a spinal fluid collection and a CT of her chest revealed linear high-density filling defects within multiple segmental and subsegmental pulmonary arteries, compatible with PCE. CT of her abdomen/pelvis showed lumbar and left renal vein cement thrombi extending to the IVC (Fig. 1). Her shortness of breath and hypoxia were attributed to the PCE. Imaging was also notable for cement deposition in the left renal vein, which was thought to explain her new-onset hypertension. Two years after her kyphoplasty, the bilateral lobar and segmental emboli are still visible and unchanged on chest CT but she has no pulmonary symptoms. She still requires lisinopril to maintain normotension. Her breast cancer responded to ovarian suppression, letrozole, and palbociclib for 29 months until she had progression of disease in the breast and bone, prompting a change in therapy.

6.2. Case Report-2

The second patient is a 38-year-old woman who self-palpated a right breast mass, and then subsequently developed progressive back pain. A

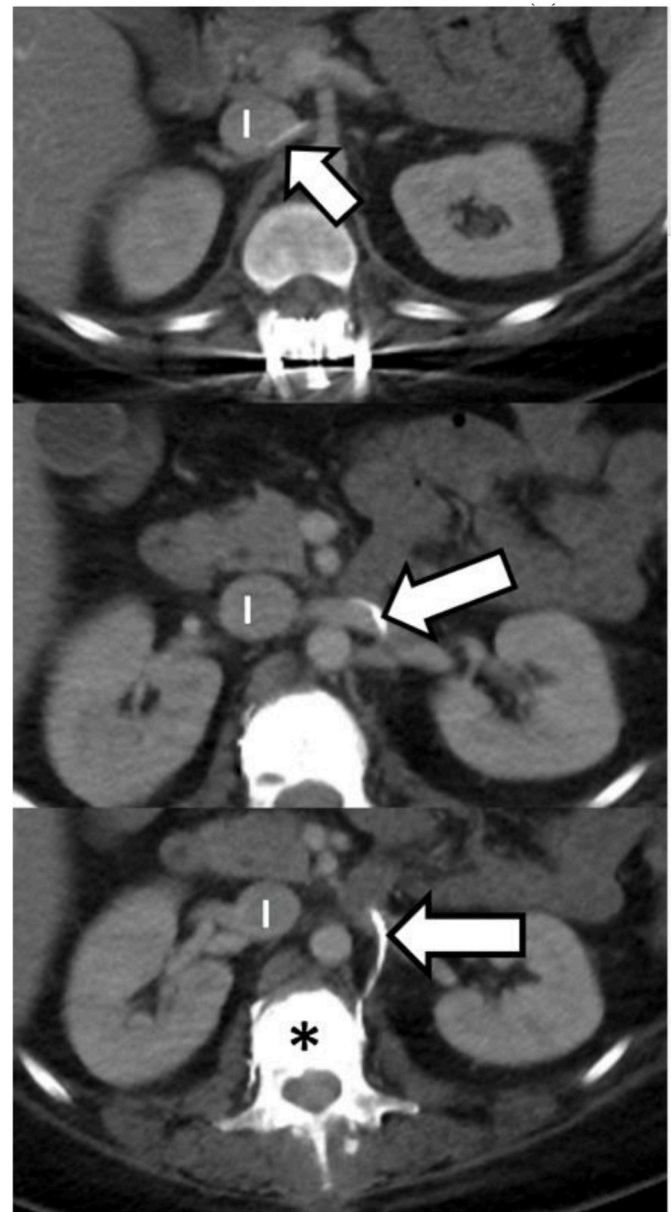


Fig. 1. Three select axial CT images through the upper abdomen showing dense kyphoplasty material in the upper lumbar spine (*) with venous extravasation of cement material into the lumbar veins (arrow) that extends directly into the left renal vein and IVC (I).

core biopsy of the right breast mass revealed grade II invasive ductal carcinoma of the breast, which was ER+ (90%), PR+ (60%), and HER2 negative. A breast MRI showed extensive involvement throughout the right breast. A PET-CT revealed hypermetabolic hepatic lesions and osseous lesions involving the spine, bilateral scapula, ribs, pelvis, and left femur, consistent with metastatic disease. An MRI of the spine demonstrated numerous lytic metastases throughout the cervical and lumbar spine, with associated multiple pathologic fractures, neuroforaminal stenosis, and spinal canal stenosis due to epidural and paraspinal disease extension. The patient underwent emergent C3 to T6 posterior spinal screw rod fixation, T2–4 laminectomy, and removal of the epidural tumor. PVP with cement was performed at T1, T4, and T6 to relieve pain and restore mobility. Histopathologic examination confirmed the presence of metastatic breast cancer. One week after surgery, the patient presented to the emergency department with chest pain, dyspnea (respiratory rate [RR] = 16), and mild hypoxia (oxygen

saturation 95% on room air). A chest CT revealed numerous pulmonary artery cement emboli involving the right upper lobar pulmonary artery and additional segmental pulmonary artery branches throughout all pulmonary lobes (Fig. 2). She was treated with pain medications and hydration with gradual resolution of her symptoms. After discharge she was started on goserelin, palbociclib, and letrozole, and received palliative radiation therapy. Her pulmonary symptoms resolved over the course of one month. Twenty-eight months after her surgery, bilateral segmental cement emboli are still noted on chest CT but she does not have any pulmonary symptoms.

6.3. Case discussions

Here, we report the cases of two patients with metastatic breast cancer who developed symptomatic PCE following PKP and PVP including long-term follow-up data. In both cases, at over two years of follow-up, there is still radiographic evidence of PCE on surveillance imaging. Fortunately, neither patient has long-term pulmonary symptoms. In patients with malignancy, the long-term imaging changes are important to note, as we typically follow these patients with serial CT scans over time to evaluate for disease progression. Imaging findings related to PCE may complicate scan interpretation, potentially making it more difficult to detect classic PEs or to identify new subtle metastatic disease. Since the cement appears to remain in the pulmonary vasculature over time, it is unknown whether these patients may have sub-clinical decreases in pulmonary function and/or increased risk of future pulmonary compromise or toxicity. This is particularly important in patients with cancer with higher risk of pulmonary complications such as PEs, pulmonary metastases, infection, and pulmonary toxicity from systemic therapies. Future studies are needed to better understand the long-term imaging and clinical implications of PCE in patients with metastatic malignancy.

Our first patient also had deposition of cement in the renal vasculature, causing new onset hypertension and prompting the initiation of lisinopril. At over two years of follow-up, she still requires lisinopril to maintain normal blood pressure. There is little data about the diagnosis and management of cement emboli in the renal veins. Further studies are needed to understand the renovascular complications of PCE and determine best-practices [68].

Neither patient here received anticoagulation after the cement emboli were identified. As discussed above, the use and duration of anticoagulation for cement emboli is controversial and poorly studied, and additional data is needed to better understand the risks and benefits of anticoagulation for these patients.

7. Conclusion

In conclusion, the deposition of cement emboli in the vasculature is a complication that can occur with PKP and PVP. While most patients are asymptomatic, long-term radiographic and clinical consequences are possible. It is important for clinicians to be aware of cement emboli to facilitate timely diagnosis and treatment if needed. Future studies are needed to better understand the long-term radiographic and clinical consequences of cement emboli, particularly in patients with advanced malignancy with other risk factors for pulmonary involvement and toxicity.

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Declaration of competing interest

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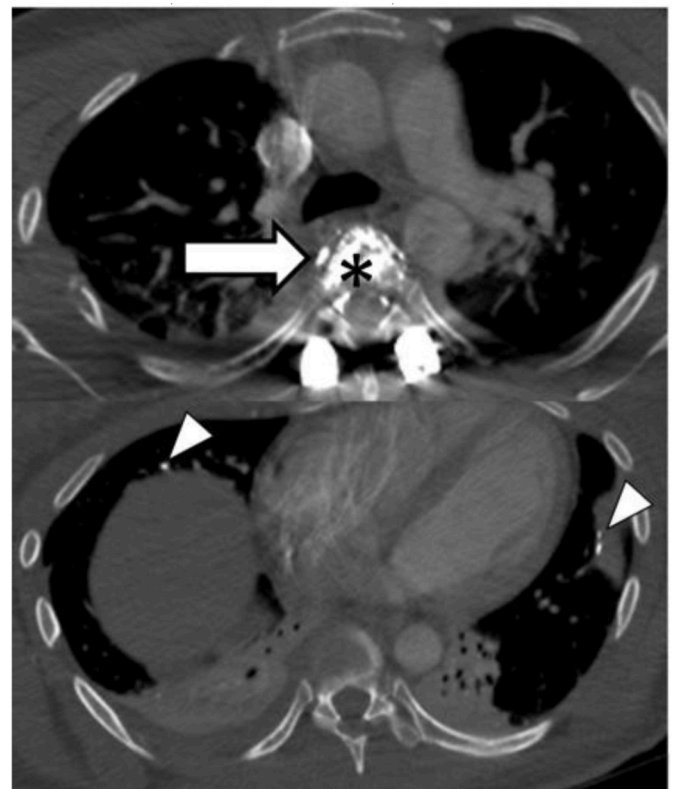


Fig. 2. Two axial CT images through the chest demonstrating dense kyphoplasty material in the vertebral body (*) with venous extravasation into the veins (arrow) as well as small bilateral subsegmental cement pulmonary artery emboli (arrowheads).

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