A Classification System for the Spread of Polymethyl Methacrylate in Vertebral Bodies Treated with Vertebral Augmentation

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Abstract

In this study, we develop a classification system to describe polymethyl methacrylate spread in vertebral bodies after kyphoplasty or vertebroplasty for vertebral compression fractures, and assess whether polymethyl methacrylate spread varies between operators, vertebral compression fracture etiology, or vertebral level. Intraoperative fluoroscopic images were reviewed from 198 vertebral levels in 137 patients (84 women and 53 men, mean age 75.8±12.5, 63% with a diagnosis of osteoporosis) treated with kyphoplasty between 01/01/2010 and 05/31/2015 at a single center to create a 5-class descriptive system. Polymethyl methacrylate spread patterns in the same images were then classified by 2 board-certified radiologists, and a 3rd board-certified radiologist resolved conflicts. A total of 2 primary polymethyl methacrylate spread patterns were identified: Acinar and Globular, with subtypes Localized Acinar and Diffuse Globular, and lastly Mixed to describe an equal combination of patterns. Interrater reliability using the system was moderate (κ=0.47). After resolving conflicts, the most common spread class was globular (n=63), followed by mixed (n=58), diffuse globular (n=30), acinar (n=27), and localized acinar (n=20). Spread class after treatment by the 2 most frequent operators differed significantly (n₁=63, n₂=70; p<0.0001). There was no difference in spread class between vertebral compression fracture etiologies or vertebral levels. Polymethyl methacrylate spread may therefore be a modifiable parameter that affects kyphoplasty and vertebroplasty efficacy and adverse events.
**Introduction**

Vertebral compression fractures (VCFs) can be asymptomatic, or present with signs and symptoms such as height loss, kyphosis, and functional disability (1,2). Kyphoplasty (BKP) and vertebroplasty (PVP) are commonly used procedures performed under fluoroscopic guidance to treat painful VCFs refractory to medical management or bracing that are still the subject of investigation (3). Large open label trials have shown earlier decreased pain, decreased pain at 1 year, more pain-free days over 1 year, and decreased analgesic use among patients treated with vertebral augmentation compared to conservative therapy for painful acute VCFs (4,5). Serious adverse events are rarely caused by BKP or PVP, and a considerable proportion of those that due occur are due to cement embolism (6,7). We also reported a case of vertebral refracture after asymmetric PMMA spread (8). Biomechanical studies have shown that distribution of PMMA in vertebral bodies is correlated with strength and stiffness parameters that may impact treatment efficacy (9,10). Variability in how the procedures are performed presents an obstacle to effective analysis of adverse event frequency and pain-reducing efficacy (11). Absolute volume of injected polymethyl methacrylate (PMMA) has been shown to have large variability (12). Cement viscosity has been shown to significantly impact PMMA spread, yet, there is not routine quantitative measurement of viscosity prior to injection (13). Finally, properties of vertebrae itself are associated with PMMA spread (14).

Multiple known and unknown factors result in an ultimate PMMA spread pattern visible on radiographs. Currently, there is no standardized language to describe the imaging appearance of PMMA spread within a vertebral body. This prevents retrospective and prospective analysis of a possible association between PMMA spread
and BKP or PVP outcomes. The purpose of this study was to develop a classification system to describe PMMA spread in vertebral bodies, and assess whether PMMA spread varied between operators or due to properties of injected vertebrae.

**Methodology**

Approval for retrieval and analysis of electronic medical records (EpicCare EMR; Epic) was obtained from the local institutional review board, and informed consent was waived. Accessed records included demographic and clinical data, and intraoperative fluoroscopic images.

**Patient Population**

BKP was recommended for patients with acute VCFs refractory to conservative therapy whom exhibited edema on spinal magnetic resonance images (MAGNETOM Aera; Siemens) or active technetium-99m radiotracer (GE Healthcare) uptake on single-photon emission computed tomography/computed tomography (Optima NM/CT 640; GE Healthcare) bone scans, and had localized tenderness over the fractured level. Conservative therapy included thoracolumbarsacral orthosis bracing and/or pain medications.

A total of 198 VCFs in 84 women and 53 men (mean age 75.8±12.5, 63% with a diagnosis of osteoporosis) were treated with BKP between 01/01/2010 and 05/31/2015 at a single center. Patient characteristics are described in table 2. Radiofrequency ablation (SpineSTAR; DFine) was performed in addition to BKP in 6 patients with primary or metastatic osteolytic cancers at 9 total vertebral levels. A bone biopsy was collected in addition to BKP from 1 patient at 1 vertebral level.

**Procedure**
BKP, which has been previously described (15), was performed at all treated vertebral levels. Briefly, a bone tamp was inserted into the vertebral body under fluoroscopic guidance, the inner stylet removed leaving the trocar, and a kyphoplasty balloon inserted through the trocar (Kyphon; Medtronic). The balloon was inflated with radiocontrast medium, which allows for visualization, compacts cancellous bone, and re-expands the vertebral body. Lastly, the balloon was deflated and removed, and PMMA from the Kyphon kit injected through the trocar under fluoroscopic guidance. The method of vertebral body access was recorded for BKP at 160 levels. A unipedicular approach was used at 111 (69.4%) vertebral levels, and a bipedicular approach at 49 (39.6%) vertebral levels. Fluoroscopy time was recorded during 96 procedures for treatment of 137 vertebral levels, and mean time was 10.2±5.9 minutes per procedure or 8.3±4.1 minutes per vertebral level.

**Polymethyl Methacrylate Spread Classification**

We developed a 5-class system to describe PMMA spread after review of anterior-posterior and lateral intraoperative fluoroscopic images from all procedures. A preliminary classification system was developed while viewing the complete image set the first time. The system was refined in subsequent review of the images by the same viewers. The same intraoperative fluoroscopic images were then reviewed by 2 additional board-certified radiologists who classified PMMA spread at each level according to the system. A 3rd board-certified radiologist resolved conflicts.

**Statistics**

Continuous variables were expressed as mean ± standard deviation. Interrater reliability was assessed using Cohen’s kappa coefficient. Associations between PMMA
spread characteristics and categorical variables were assessed using Pearson’s chi-
squared tests. The 5th-8th and 9th-11th thoracic vertebrae, 12th thoracic vertebra through 2nd
lumbar vertebra, and 3rd-5th lumbar vertebrae were binned together to meet expected cell-
count assumptions of chi-squared tests. All analyses were performed using SAS 9.3 and
SAS Enterprise Guide 5.1.

**Results**

**Description of the 5-Class System**

We identified 2 primary patterns of PMMA spread visible on intraoperative
fluoroscopic images. Sub-classification of these patterns considering the amount of the
vertebral body infiltrated with PMMA and pattern admixture yielded a total of 5 PMMA
spread classes: Acinar and Globular, with subtypes Localized Acinar and Diffuse
Globular, and lastly Mixed to describe an equal combination of patterns within the
vertebral body. Prototypes are shown in Fig. 1.

The acinar pattern of spread was defined as that as expected when filling complex
cortical bone with a low viscosity fluid. Characteristics commonly associated with acinar
pattern spread included numerous small dot-like collections of PMMA interrupted by a
web of trabecular bone. The globular pattern was defined by much larger, potentially
solitary accumulations of PMMA demonstrating lobular smooth margins and
homogeneous texture. The prototypical globular pattern was a circular cannonball
without extension across the vertebral body midline. However, globular pattern variants
also included more lobulated amorphous shapes. Vertebral bodies showing a mixture of
at least 40% both acinar and globular spread pattern components on at least one imaging
angle were classified as having mixed spread.
A substantial proportion of treated vertebral bodies demonstrated near complete PMMA filling in at least one viewing angle. Diffuse spread was defined by >90% of the anterior-posterior or medial-lateral axis of the vertebral body making up the border of PMMA spread on at least one viewing angle with spread height and pattern homogeneity throughout. Globular pattern spread was most often localized and not diffuse. Therefore, diffuse globular spread was considered a subtype. Acinar pattern spread was most often diffuse. Similarly, localized acinar spread was considered another subtype. Theoretically, diffuse mixed spread would appear as layers of globular and acinar spread extending across the vertebral body, although this was not observed in our sample.

Interrater reliability using the entire system was moderate (κ=0.47). Similarly, interrater reliability was moderate for assessing PMMA infiltration (κ=0.49) and pattern (κ=0.48). A total of 51.2% of the levels were classified as having the same spread class by the first 2 raters. Of the vertebral levels not assigned the same spread class by the first 2 raters, 68.8% were assigned spread classes considered to be most similar (Fig. 2). Raters assigned 78.3% of the levels as having the same degree of PMMA infiltration (localized vs. diffuse) and 60.1% of the levels as having the same spread pattern (acinar vs. globular vs. mixed). Examples of difficult to classify images are in Fig. 3.

The most common spread class after resolving conflicts was globular (n=63), followed by mixed (n=58), diffuse globular (n=30), acinar (n=27), and localized acinar (n=20). Therefore, 80.1% of levels were considered localized and 19.9% diffuse. The distribution of levels assigned various spread patterns was 23.7% acinar, 47.0% globular, and 29.3% mixed.

Spread Pattern Varies by Operator
There was a significant difference in spread class of vertebral bodies treated by
the 2 most frequent operators (n1=63, n2=70; \( p<0.0001 \)). PMMA infiltration also differed
by operator (\( p<0.0001 \)), and there was a marginal difference in spread pattern between
operators (\( p=0.07 \)). The 2 most common spread patterns for operator 1 were mixed and
globular, whereas the 2 most common spread patterns for operator 2 were diffuse
globular and acinar.

**No Association Between Spread Pattern and Vertebral Parameters**

There was no difference in spread class (\( p=0.55 \)), PMMA infiltration (\( p=0.72 \)), or
spread pattern (\( p=0.28 \)) in treated osteoporotic VCFs compared to VCFs of other
etiologies. Additionally, there was no difference in spread class (\( p=0.80 \)), PMMA
infiltration (\( p=0.28 \)), or spread pattern (\( p=0.52 \)) between different vertebral levels.

**Discussion**

We reviewed 198 vertebral levels treated with BKP in 137 patients at a single
institution to develop a classification system for PMMA spread after BKP or PVP. We
then applied the classification system to all treated vertebral levels in order to assess
interrater reliability and whether PMMA spread differs significantly by operator or due to
properties of the VCF. A 5-class system was developed that had moderate interrater
reliability. PMMA spread was found to differ significantly between operators, but not
between VCF etiologies or by vertebral level.

Descriptions of the various appearances of PMMA spread have varied between
reports. To remedy this, we created a classification system that can be used with minimal
training. Examples of previous descriptions of PMMA spread include Anselmetti and
colleagues’ contrasting “spherical” to “diffuse and irregular” spread patterns, which
correspond to our globular and acinar types (13). In another clinical trial, no description of PMMA spread was provided despite analysis of radiographic outcomes such as height and kyphotic angle restoration (16). Baroud and colleagues stated that an appearance similar to a “single, uniformly expanding cloud” was preferable to that like the “fingers of a glove”, which again correspond to our globular and acinar types without distinguishing localized from diffuse spread or describing mixed spread (17). A case report attributed lateral wedging after BKP to “abnormal spatial distribution of PMMA cement… [with] insufficient filling of PMMA cement… on the right side” (18). Radiopacity was highlighted as a major imaging difference between two cements used in an \textit{ex vivo} biomechanical study (19). In another \textit{ex vivo} study, Loeffel and colleagues made the sole quantification of PMMA spread by calculating circularity (a ratio of the actual distribution perimeter to the perimeter of a circle with equal area) and mean cement spreading distance (14). However, these measurements did not assess the pattern within the filled area, which may reflect the concentration of PMMA. Our classification system did require assessment of spread pattern within the filled area, as well as assessment of the degree of PMMA infiltration into the vertebral body. Interrater agreement was considered moderate based on a frequently cited scale (20,21), which is similar to agreement found using current prostate cancer (22), pancreatic cancer (23), and pulmonary nodule (24) protocols. Our system’s categories are related and image interpretation disagreement was most often between closely related categories (Fig. 2). This gives the classification system utility in outcomes trials beyond what its moderate interrater reliability suggests because the affect of related classes on outcomes is likely similar and the affect of less related classes divergent. Raters agreed more frequently on
spread pattern (acinar vs. globular vs. mixed) and PMMA infiltration (localized vs. diffuse) than on spread class. However, interrater reliability was similar between all 3 measures, indicating reducing the number of spread classes would not make the system more robust.

We used the newly created classification system to first assess differences in PMMA spread between operators. It is paramount to understand interoperator variability in BKP and PVP as the largest clinical trials to date have been conducted at multiple sites and have not adjusted for potential heterogeneity between operators (4,5,25,26). McDonald and colleagues showed, in a sample of 2 operators experienced in PVP and 5 novice operators, that several procedural measures and short-term clinical outcomes significantly change as novice operators gain experience (27). Other studies have found that the volume of PMMA injected is an important operator-dependent variable in BKP and PVP (28,29). Additionally, the time between PMMA mixing and delivery modifies viscosity, which may impact the risk of adverse events (13,17). We showed that 2 experienced operators achieved significantly different PMMA spreads. The first most often created localized PMMA infiltration with a trend towards a globular pattern, whereas the other most often created diffuse spread without a trend towards an acinar or globular pattern. This indicates that there is significant heterogeneity even between experienced operators. Clinical outcomes could differ between approaches.

There are several mechanisms through which PMMA spread could affect BKP or PVP outcomes. Liu and colleagues found that PMMA distribution in the inferior portion of the vertebral body or along the endplate increases the risk of adjacent level refracture (30). Biomechanical and finite-element analysis studies have shown that limited
distribution of PMMA after unipedicular BKP or PVP potentially result in biomechanical imbalance, which could lead to lateral wedge deformities or painful toggling (9,10). Intraosseous nerve damage has been hypothesized as a potential mechanism for pain relief after BKP or PVP (31). PMMA spread could therefore impact which nerves and how many nerves are damaged within the vertebral body. Operators may use the classification system presented in this study to quickly evaluate cement spread after procedures. Although clear recommendations do not currently exist, previous reports suggest globular diffuse spread provides maximal biomechanical support to treated vertebral bodies with minimal risk of cement extravasation (9,10,17).

The next step in our study was to assess whether VCF etiology or vertebral level were associated with PMMA spread class. Loeffel and colleagues found that artificial media with smaller pores aided in creating denser, more circular PMMA spread (14). They interpreted this to indicate that PMMA will spread widely and unevenly in osteoporotic bone. There are few in vivo comparisons of spread between VCFs of different etiologies. In one study without a systematic approach for assessing spread, PMMA spread appearance was interpreted as different in VCFs due to osteoporosis compared to metastatic lesions (13). However, other studies that included patients with VCFs secondary osteoporosis and osteolytic lesions did not compare appearance (4,32–34). There have been no in vivo comparisons of PMMA spread within vertebrae from different levels. In contrast to previous reports, we found no difference in PMMA spread class between fracture etiologies. We also did not observe a difference between vertebral levels.
Limitations of our study must be acknowledged. First, the sample was drawn from a single center and only 2 operators performed a sufficient number of procedures to be compared. However, 198 total vertebral levels were treated, and finding differences in a small sample of operators may indicate that heterogeneity is prevalent. Second, VCF etiology was not uniformly reported. Despite this, an adequate number were available for comparison. Our analysis was limited to fluoroscopic images during BKP, but the classification system encompasses PMMA distributions expected after PVP. Lastly, standardized follow-up was not obtained from patients, which prevents analysis of a potential association between PMMA spread class with adverse events and pain reduction in this sample. However, the classification scheme we developed will enable future assessment of this.

We created a standardized language with which to describe PMMA spread after BKP or PVP. PMMA spread is primarily operator dependent, and therefore may be a modifiable parameter that affects BKP and PVP outcomes. Future research is needed to determine if PMMA spread classes are associated with clinical outcomes after BKP or PVP.

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**Disclosure**

Nothing to disclose.
References


Figure Legends

Figure 1, a-e
Intraoperative medial-lateral fluoroscopic images of prototypical PMMA spread patterns. Acinar (a) and localized acinar (b) spread both appear pockmarked with areas of lucency. Mixed spread (c) has >40% acinar and globular components. Globular (d) and diffuse globular (e) spread both have a homogenous smooth texture.

Figure 2
Schematic of relationships between spread patterns. Each pattern is most similar to adjacent patterns and most distinct from nonadjacent patterns.

Figure 3
(a) Images with heterogeneous spread but few entirely lucent areas presented difficulties to raters. This image was ultimately classified as mixed. (b) Images with considerable obstruction and poorer quality were also more likely to received discordant ratings from raters. This image was ultimately classified as mixed.
**Tables**

Table 1: Patient Characteristics

<table>
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<th></th>
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<th>Female</th>
<th>Combined</th>
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<tr>
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<tr>
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<td>49/7/14/0</td>
<td>70/18/21/2</td>
</tr>
<tr>
<td>Etiology by Level&lt;sup&gt;a&lt;/sup&gt;</td>
<td>35/19/7/2</td>
<td>73/14/17/0</td>
<td>108/33/24/2</td>
</tr>
</tbody>
</table>

<sup>a</sup>Fracture etiology was recorded for 111 patients treated at 167 levels. Counts are listed as osteoporosis/cancer/trauma/other.