

## KEYNOTE ADDRESS

# The role of vertebral augmentation in multiple myeloma: International Myeloma Working Group Consensus Statement

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## Introduction

There are approximately 20 000 new patients diagnosed with myeloma in the United States each year.<sup>1</sup> With the availability of better treatments and resultant improved survival, there are currently close to 100 000 patients living with myeloma in the United States. Similar incidence and prevalence rates exist throughout Europe.<sup>2</sup> Of these patients, the spine is affected by osteolytic and/or osteopenic bone disease in 70%.<sup>3</sup> Myeloma is the commonest primary cancer affecting the spine. Painful vertebral compression fractures (VCFs) affect approximately 30% of myeloma patients. As myeloma patients live longer, it is especially relevant to provide the best available treatment for pain and reduce disabilities that can result from VCFs.<sup>4</sup>

The focus of this summary is to assess the role of minimally invasive percutaneous injection of polymethyl methacrylate (PMMA), first developed as 'vertebroplasty' in France in the late 1980s. Considerable experience accrued, especially in Europe, with the use of vertebroplasty as treatment for painful VCFs. The fractured bone fragments are stabilized and strengthened by PMMA and pain is substantially improved. A more recent modification of vertebroplasty is percutaneous balloon kyphoplasty whereby inflation of a balloon prior to PMMA injection

can restore vertebral height and reduce kyphotic deformity in addition to stabilizing the fractured vertebral body.

The first prospective trial evaluating the role of balloon kyphoplasty in multiple myeloma showed that over 80% of the treated patients experienced significant pain control.<sup>5</sup> In addition, there was an overall 30% height restoration with improvement of 60–70% of height restoration when the procedure was performed for fractures less than 6 months old.<sup>5</sup> The procedure was also noted to be effective and safe in other malignancies.<sup>6</sup> In another study of 20 multiple myeloma patients (48 levels) treated with balloon kyphoplasty, significant pain improvement as judged by visual analogue scale occurred within the first year of follow-up.<sup>7</sup> About 80% of patients with initial kyphotic deformity had post-operative kyphosis correction of approximately 6°, with only minimal loss of height after 1 year (~1.8°). The overall data related to both vertebroplasty and balloon kyphoplasty are addressed in a number of publications.<sup>5,8–20</sup>

In considering the potential benefit of PMMA injection, it is necessary to be aware of the biomechanics of pathologic spine fractures (Figure 1). With the occurrence of a VCF, the center of gravity moves forward. Because of the large bending moment created, the anterior spine, especially in the regions adjacent to the VCF, must resist larger compressive stresses. The posterior muscles and ligaments are additionally stressed, which can be an obvious source of pain. Early intervention is a way to reduce the risk of a 'domino effect' with increased forward movement of the center of gravity, additional compressive stresses and possible further VCFs. The consequences of progressively altered vertebral mechanics and the kyphosis-related VCFs in myeloma patients can be substantial as summarized in Table 1.

Obviously, the safety of vertebral augmentation is an important consideration. The potential complications of vertebral augmentation are summarized in Table 2. A literature review meta-analysis of procedure-related complications for balloon kyphoplasty and vertebroplasty indicates that complications such as extravasation of PMMA are less with balloon kyphoplasty.<sup>21</sup> It should be noted that asymptomatic extravasation of

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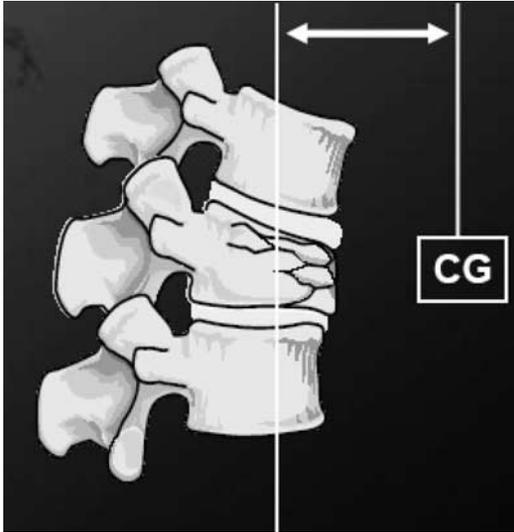
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**Figure 1** Movement of center of gravity (CG) forward with vertebral compression fracture.

**Table 1** Consequences of VCF-related kyphosis

*Compression of abdominal contents*

- Anorexia, weight loss

*Decreased lung capacity*

- Limited exercise tolerance/physical activity

*Anterior loading of spine (Figure 1)*

- Subsequent fractures
- Increasing kyphosis and deformity

Abbreviation: VCF, vertebral compression fracture.

**Table 2** Potential complications of vertebral augmentation

- Extravasation of PMMA cement<sup>a</sup>
  - Local effects
  - Systemic effects including pulmonary
- Cord compression (spinal cord)
- Radiculopathy (foramina)
- Pneumothorax
- Retroperitoneal hematoma
- Infection: local/systemic

Abbreviation: PMMA, polymethyl methacrylate.

<sup>a</sup>See text for discussion.

**Table 3** Outcomes with balloon kyphoplasty at H Lee Moffitt Cancer Center<sup>a</sup>

- 41 patients; 62 kyphoplasties
- 13% PMMA extravasation
- 1 case of pneumothorax; resolved
- 95% partial or substantial pain relief
- All patients discharged within 23 h (i.e. < 1 day)

Abbreviation: PMMA, polymethyl methacrylate.

<sup>a</sup>Data published under Vrionis et al.<sup>21</sup>

PMMA occurs in about 7% balloon kyphoplasty versus 19.7% vertebroplasty but rarely leads to clinical complications.<sup>22</sup> As an example, the single center experience at Moffitt Cancer Center

gives a realistic expectation as to outcomes in a center specializing in myeloma care (Table 3). The presence of any plasmacytoma tissue between the PMMA and the fractured cortical bone can lead to suboptimal improvement in stabilization and any subsequent pain relief from any form of vertebral augmentation.<sup>9</sup> Active awareness of potential complications and careful patient selection are obviously crucial.

The role of vertebral augmentation in the treatment of myeloma of the spine is still evolving. The impact of VCFs upon quality of life and survival is illustrated by results of a large study in women aged  $\geq 65$  years. In this study of a total of 9575 women aged 65 years or older, 1915 of the women (20.0%) were diagnosed as having VCF secondary to osteoporosis. The fractures were not only associated with increased morbidity, but also with increased mortality.<sup>23</sup> The increased mortality was particularly from pulmonary complications.<sup>23</sup> Moreover, patient mortality increased with greater numbers of vertebral fractures, from 19 per 1000 woman-years in women with no fractures to 44 per 1000 woman-years in those with five or more fractures ( $P < 0.001$ ).

These data accentuate the need for management guidelines for VCFs. Formal guidelines on the use of vertebral augmentation for myeloma in the spine are missing. The purpose of this paper is to review the evidence regarding the role of vertebral augmentation in the spine and to provide a consensus statement on the role of vertebral augmentation for the management of myeloma affecting the spine. Those aspects of therapy were reviewed, discussed and considered by the International Myeloma Working Group and a special advisory board convened at the time of the XI International Myeloma Workshop KOS Greece on 29 June 2007.

**The following is the consensus statement from the International Myeloma Working Group:**

1. **Indications for vertebral augmentation:** The indications are summarized in Table 4. These indications apply, provided contraindications are not present as summarized in Table 5. If severe pain is present, the advisory board reached a consensus that it is very reasonable to proceed with immediate vertebral augmentation. A major advantage is the rapid pain relief especially compared with alternative analgesic strategies summarized in Table 6. Early augmentation also proactively reduces the risk of the vicious cycle of further VCFs as described above as well as providing the maximum chance of restoring height and correcting angular deformity. Early augmentation also does not preclude additional or subsequent use of any of the alternative strategies such as those summarized in Table 6. In the absence of severe pain, augmentation is a proactive measure to preserve structural integrity. When there is severe bone destruction and in anticipation of potential long patient survival, this secondary indication is very much a viable option to maximize quality of life by preventing potential VCFs.
2. **Identification of patients suitable for vertebral augmentation:** The four major components of the recommended baseline evaluation are summarized in Table 7. Obviously, one must be certain that the pain is emanating from the collapsed or damaged vertebra(e). In addition to X-ray, which most patients will have undergone to diagnose the problem, more detailed evaluation with magnetic resonance imaging (including STIR (Short T<sub>1</sub> Inversion Recovery) images) is essential particularly to determine the presence or absence of spinal cord compression and/or edema. Also, the potential for retropulsion and/or direct leakage of PMMA can be

**Table 4** Indications for vertebral augmentation<sup>a</sup>

- Primary: severe pain present (pain > 7/10 on VAS)*
- Collapse of one or more vertebra (VCF)
  - Bone destruction (osteolytic/osteopenic) with high risk of collapse of one or more vertebra
- Secondary: severe pain absent (pain ≤ 7/10 on VAS)*
- Significant loss of height and/or structural integrity or stability

Abbreviations: VAS, visual analogue scale; VCF, vertebral compression fractures.

<sup>a</sup>Provided no contraindications (Table 5).

**Table 5** Contraindications to vertebral augmentation

Absolute	Relative
<ul style="list-style-type: none"> <li>● Contraindications to general or local anesthesia</li> <li>● Pregnancy</li> <li>● Bleeding disorder</li> <li>● Infection at the site</li> </ul>	<ul style="list-style-type: none"> <li>● Lesions above T3</li> </ul>
<ul style="list-style-type: none"> <li>● Pain unrelated to vertebral collapse</li> <li>● Cord compression</li> <li>● Presence of overt instability</li> <li>● Severe cardiopulmonary insufficiency</li> <li>● Allergy to procedure-related drugs/contrast</li> </ul>	<ul style="list-style-type: none"> <li>● Osteoblastic metastases</li> <li>● Patient &lt; 40 years of age</li> <li>● Technically not feasible (vertebra plana)</li> <li>● Fractures with obstructing plasmacytoma(ta)</li> <li>● Retropulsed bone</li> </ul>

**Table 6** Alternatives for pain therapy

Options	Discussion
PMMA vertebral augmentation	<ul style="list-style-type: none"> <li>● Rapid pain relief</li> </ul>
Radiation therapy	<ul style="list-style-type: none"> <li>● Simple procedure</li> <li>● Pain relief has slower onset and less complete</li> <li>● Reduces tumor mass swelling and may eliminate plasmacytoma(ta) locally</li> </ul>
Systemic anti-myeloma therapy	<ul style="list-style-type: none"> <li>● Destroys bone marrow stem cells locally</li> <li>● Can be fast acting</li> </ul>
Bisphosphonates	<ul style="list-style-type: none"> <li>● May or may not relieve severe local pain related to bone fragment movement</li> <li>● Does not correct structural integrity</li> <li>● Can give rapid pain relief</li> <li>● May or may not relieve pain from bone fragments</li> <li>● Gives systemic benefit</li> <li>● Generally very safe</li> </ul>
Analgesics	<ul style="list-style-type: none"> <li>● Can be rapid acting and effective</li> <li>● Efficacy relative to augmentation awaits the results of CAFE trial (Table 8).</li> </ul>

Abbreviation: PMMA, polymethyl methacrylate.

assessed. Computed tomography scanning in addition may be helpful especially if some combined surgical procedure plus PMMA injection procedure is being considered. It is helpful to know to what extent systemic antimyeloma therapy will be required and assess absolute or relative contraindications as summarized in Table 5.

**Table 7** Identification of patients suitable for vertebral augmentation

- 1 Careful pain assessment to determine source/severity of pain.
- 2 MRI is essential to document the anatomy and assess spinal cord edema/compression
- 3 Assessment of myeloma disease status and potential anti-myeloma treatment needs
- 4 Assessment of other pain therapy options (Table 6)

Abbreviation: MRI, magnetic resonance imaging.

3. **Timing for the vertebral augmentation:** Early intervention is currently being investigated in the CAFE (Cancer Fracture Evaluation) trial in which immediate and delayed vertebral augmentation are being contrasted and compared. The group reviewed available data and clinical experience available now and agreed to the following:

- **Immediate vertebral augmentation** is a treatment option for acute VCF with severe pain or VCF at high risk for progressive deformity. Excellent short- and long-term results have been achieved in this setting;
- **For patients with lesser pain and/or vertebral damage**, a trial of analgesic therapy with supportive measures including bisphosphonates and/or systemic therapy is generally recommended. The appropriate duration of this type of therapeutic trial relates to the severity of the pain and potential reversibility with systemic measures. In general, augmentation can be considered as soon as feasible especially if pain worsens and/or persists and/or to prevent further vertebral collapse. Early intervention is especially important if stabilizing the spinal structure and/or restoring the height are critical. Excellent results have been achieved in these settings. Results of the ongoing randomized CAFÉ trial evaluating pain relief and quality of life with immediate versus delayed balloon kyphoplasty are eagerly awaited;
- **If pain persists at the site of VCF**, there is no upper time limit beyond which augmentation cannot be considered. However, earlier intervention is preferred to achieve maximal stabilization and/or correction of deformities.

4. **Number of levels to be considered for treatment:**

- Multiple augmentation procedures may be necessary and appropriate. In general, three to four vertebrae per intervention is considered reasonable and feasible during a single procedure (if required). As many as 16 augmentations have been performed on an individual myeloma patient in separate sessions or stages.
- Vertebral augmentation for adjacent or suspect vertebrae without fracture may be necessary. Such augmentations can be considered when there is a fracture with kyphosis in the thoracolumbar region because the stress due to the deformity in this region is very high. It is particularly common to consider the performance of an additional augmentation procedure in a vertebra when it is located between two fractured vertebrae such as T11 and L1 requiring treatment for T12 to avoid post-procedure T12 collapse.

5. **The highest level of augmentation** to be performed was briefly discussed. It was decided that experienced operators can perform vertebral augmentation to levels as high as the cervical area and that this can be effective and safe. For practical purposes, T<sub>3</sub>–L<sub>5</sub> is the range that can be performed safely by the percutaneous route.

6. **The method of vertebral augmentation:** The risk of complications, especially the risk of PMMA leakage, is greater with vertebroplasty. However, it was agreed that both the utility and the likelihood of clinically significant complications are very much dependent upon the experience of the operator. It is therefore recommended that the choice of balloon kyphoplasty versus vertebroplasty be left to the discretion of the operator and be based upon the goals of the procedure.
7. **Use of vertebral augmentation versus radiation therapy:** Vertebral augmentation is considered the procedure of choice to improve quality of life for painful VCFs. However, external beam radiotherapy (EBR) is a valid option that requires careful consideration. EBR is simple and can be performed in one session without risks of anesthesia, bleeding, infections or compromise of vital structures. Local marrow stem cell damage is most likely minimally different with 30 Gy of EBR versus the impact of heated PMMA injected into one to three vertebral bodies. Thus, if discreet plasmacytomata exist within a vertebra and/or there is a symptomatic extramedullary mass or impending/overt spinal cord compression occurs, the use of EBR can be the option of choice. Systemic antimyeloma therapy is an alternative for rapid reduction in myeloma tumor burden. In addition, medical pain therapy can provide helpful relief as necessary.
8. **Physical rehabilitation:** To maximize the recovery from augmentation, a physical rehabilitation program is recommended. Ideally, this should be in the form of water aerobics and thoracolumbar stabilization with an extension directional focus, under the supervision of a physical therapist.
9. **Further trials** are still required to clarify the role of vertebral augmentation in a variety of situations including the following:
  - prevention of further fractures in asymptomatic patients;
  - treating asymptomatic fractures; and
  - treating asymptomatic fractures compromising the spinal structure or pulmonary capacity

## Discussion

This International Myeloma Working Group Consensus Statement is the latest in a series of publications from the working group as summarized in Table 8. Additional consensus statements scheduled for 2008 include the role of free light-chain analysis; guidelines for use of Epoetin; the role of imaging; and a new genetic classification for myeloma.

Vertebral augmentation techniques discussed as part of this consensus statement can be used for both acute and chronic fractures. Myeloma patients with mechanical pain, that is pain that is most significant in the upright position, standing or walking and significantly decreased in a reclining position, which anatomically correlates with the area of the fracture, are most likely to benefit from vertebral augmentation. Other types or causes of pain (radicular, dysesthetic, discogenic or degenerative) should be carefully assessed as they can coexist with pain related to compression fractures and are unlikely to respond to vertebral augmentation interventions.

Absolute contraindications to augmentation including myelopathy or cauda equine syndrome are listed in Table 5. Relative contraindications include coagulopathy, neutropenia, allergy to substances used for the procedure and high anesthetic risks (Table 5).

**Table 8** International Myeloma Working Group Consensus Statements

Article	Reference
Criteria for classification of monoclonal gammopathies Myeloma Management Guidelines	<i>Br J Haematol</i> 2003; <b>121</b> :749–57 <i>Hematology Journal</i> 2003;4:379–98
International Staging System (ISS) for myeloma	<i>JCO</i> 2005; <b>23</b> (15):1–9
International Uniform Response Criteria for Multiple Myeloma	<i>Leukemia</i> 2006 (1–7)
Use of Bisphosphonates in Myeloma	<i>Mayo Clinic Proceedings</i> 2007; <b>85</b> :516–22
Prevention of Thalidomide and Lenalidomide associated Thrombosis in Myeloma	<i>Leukemia</i> 2008; <b>22</b> :414–23
Myeloma in Patients Under Age 50	<i>Blood</i> , April 2008; <b>111</b> (8): 4039–47

Currently, there are no specific guidelines or contraindications regarding factors such as kyphosis, retropulsion and caudal compromise or degree of vertebral body collapse. The issue of spinal instability and its effect on overall decision making need to be determined on an individual basis by the treating spine expert. The unstable spine is at risk of progressive deformity or impairment of the neural elements. Generally, operative care with open surgery rather than percutaneous augmentation techniques is most valuable in the setting of spinal instability. In addition, the number of fractures that can be treated at each intervention or stage; the amount of methylmethacrylate to be injected; the need to treat adjacent or intervening nonfractured segments; the issue of unilateral or bilateral, transpedicular or extra-pedicular; open or percutaneous approaches under local or general anesthesia all need to be determined by the treating surgeon or radiologist. However, it is recommended that not more than three or four fractures are treated per stage as the risk of pulmonary complications increases with the number of treated fractures. The advisory board delegated the details of this decision making, related to numbers and methodology, to the selected operators of the augmentation procedures.

In general, vertebral augmentation is not recommended for asymptomatic fractures unless there is documented increased collapse and deformity progression or in the context of an adjacent or intervening segment. This could be documented by follow-up radiologic studies performed every 3 months or sooner if the clinical picture dictates. The role of skeletal augmentation for sacral or iliac fractures in patients with myeloma is currently unknown.

As noted above, vertebral augmentation should be considered as the procedure of choice to improve quality of life for painful compression spinal fractures in myeloma patients instead of EBR or placement of intrathecal morphine pumps. In patients with plasmacytomata in bone or extramedullary plasmacytomata extending into the epidural space, open surgical decompression or radiation therapy with or without augmentation may be appropriate. In patients with a stable spine without fracture or progressive deformity, radiotherapy should be considered first. Receiving radiation therapy does not preclude future augmentation. Vertebral augmentation and radiation can be viewed as complementary, with augmentation restoring anatomy and radiation ablating symptomatic disease. Augmentation has the advantage of rapid relief in a single sitting, which should allow patients requiring radiation to be treated in a more comfortable state. This is particularly important for individuals undergoing

radiosurgery where treatment time approaches an hour and immobility is crucial for accuracy.

In summary, patients with plasmacytomata, extramedullary masses and cord compromise should be considered for use of up-front radiotherapy. Vertebral augmentation is a developing field with current and future trials being necessary to further define what constitutes an 'impending fracture' and establish the role of pre-emptive augmentation procedures. Having all options available for multiple myelomas, patients insure optimal therapeutic intervention to improve both quality of life and overall survival.

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