Comprehensive Review

Vertebral Augmentation: Update on Safety, Efficacy, Cost Effectiveness and Increased Survival?

Ronil V. Chandra, MBBS, MMed, FRANZCR[1], Albert J. Yoo, MD[2], and Joshua A. Hirsch, MD[2]

From: [1]Interventional Neuroradiology Unit, Department of Diagnostic Imaging, Monash Medical Center, Melbourne, Australia; [2]Department of Radiology, Division of Diagnostic and Interventional Neuroradiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Address correspondence:
Dr. Ronil V. Chandra
Interventional Neuroradiology Unit
Department of Diagnostic Imaging
Monash Medical Center
Melbourne, Australia
E-mail:
ronilvchandra@gmail.com

Although over 300 articles have been published annually on vertebral augmentation in the last 5 years, there remains much debate about a fundamental question — is vertebral augmentation a safe and effective treatment to achieve analgesia, reduce disability, and improve quality of life in patients with a vertebral fracture? In this modern era of evidence-based clinical practice and public health care policy and funding, an evidentiary basis is needed to continue to perform vertebral augmentation.

The aim of this narrative review is to summarize the latest and highest quality evidence for efficacy, safety, cost effectiveness, and potential survival benefit after vertebroplasty and kyphoplasty. The design, major inclusion criteria, primary outcome measures, relevant primary baseline characteristics, primary outcomes, relevant secondary outcomes, and limitations of prospective multicenter randomized sham-controlled and conservative management-controlled trials are summarized. Recently published meta-analyses or systematic reviews of efficacy that include these recent prospective studies of vertebral augmentation are examined. The highest quality procedural safety data relating to medical complications, cement leaks, and subsequent vertebral fracture are reviewed. Publications from national databases analyzing potential reduction in length of hospital stay and reduction in mortality after vertebral augmentation are presented. Finally, emerging literature assessing the potential cost-effectiveness of vertebral augmentation is considered.

This narrative review will provide interventional pain physicians a summary of the latest and highest quality data published on vertebral augmentation. This will allow integration of the best available evidence with clinical expertise and patient wishes to make the most appropriate evidence-based clinical decisions for patients with symptomatic vertebral fracture.

Key words: Vertebroplasty, kyphoplasty, spinal fracture, osteoporosis, cancer

Pain Physician 2013; 16:309-320

Over 300 articles have been published annually on vertebral augmentation in the last 5 years. Nonetheless, there remains much debate about a fundamental question — is vertebral augmentation a safe and effective treatment to achieve analgesia, reduce disability, and improve quality of life in patients with a vertebral fracture? The publication of 2 highly publicized randomized controlled clinical trials designed to test the efficacy of vertebroplasty in the New England Journal of Medicine in 2009 resulted in a decrease in utilization of both vertebroplasty and kyphoplasty in the United States. Nonetheless, over 70 000 vertebral augmentation procedures were still performed in the Medicare and Medicaid population in 2010 (1). In this modern era of evidence-based public health care policy and funding, there needs

to be an evidentiary basis for performing vertebral augmentation.

The aim of this narrative review is to summarize the latest evidence for efficacy, safety, cost effectiveness, and potential mortality benefit after vertebroplasty and kyphoplasty. This was assessed by evaluation of the highest levels of evidence that existed in the current English language literature between January 2000 and April 2013. A portion of this comprehensive literature review was used by the authors to help establish practice guidelines for vertebral augmentation as part of the Standards of Practice Committee of the Society of NeuroInterventional Surgery (currently unpublished).

BACKGROUND

Vertebral Augmentation

Vertebral augmentation refers to vertebroplasty and/or kyphoplasty. Vertebroplasty is a minimally invasive, image-guided procedure that involves the injection of cement (typically Polymethylmethacrylate, PMMA) into a fractured vertebral body. Kyphoplasty involves the initial inflation of a balloon tamp that creates a low resistance cavity within the vertebral body, into which cement is subsequently injected. Kyphoplasty, as examined, did not include vertebral body stenting.

The majority of vertebral augmentation procedures are performed for symptomatic osteoporotic or cancer-related vertebral compression fractures. The primary clinical goal of augmentation for this patient cohort is pain reduction, reduced disability, and enhanced quality of life. Vertebral augmentation for traumatic fractures or symptomatic neoplasm without fracture was not examined, nor radiographic primary outcomes measures such as kyphosis correction.

Burden of Disease — Osteoporosis

The true clinical burden of osteoporotic vertebral fractures is not known. Overall, it has been estimated that 30 – 50% of women and 20 – 30% of men will develop vertebral fractures during their lives; half of these patients will develop multiple fractures (2). When large (> 5,000 patients) radiographic studies are examined for new vertebral fracture, the incidence of new vertebral fracture at age 50 – 79 years, is 1.1% per year in women and 0.6% per year in men (3). However, the risk across this age spectrum is not uniform — prior to age 50, the risk is close to zero with an exponential increase with age, to approximately 30 cases per 1,000 women per year by age 80 (2).

Most osteoporotic vertebral compression fractures are asymptomatic or result in minimal pain. It is estimated that only one third of vertebral fractures result in medical attention, and 10 – 20% result in hospitalization (2,4). In the vast majority of patients, acute back pain symptoms are mild and subside over 6 – 8 weeks as the fracture heals. Conservative medical therapy is thus appropriate for the vast majority of vertebral compression fractures. Vertebral augmentation is typically considered for patients presenting with a symptomatic vertebral fracture that results in severe disabling back pain, marked reduction in mobility, and quality of life. These patients typically represent a small fraction of patients who are hospitalized for a symptomatic vertebral fracture. Open surgical decompression and fusion is generally reserved for patients with associated neurological deficit; only 5% of those seeking medical attention receive open surgical intervention (5). Hybrid techniques such as short-segment spinal fusion combined with vertebroplasty are also typically limited to patients with associated neurological deficit (6).

Burden of Disease — Neoplasia

Vertebral fractures in cancer patients may be secondary to osteoporosis, primary neoplasm, metastasis, osteopenic effects of drug therapy, or effects of radiation therapy. Reduced bone mineral density is found in nearly half of all patients diagnosed with cancer and osteoporosis is more common when compared to the general population (7). Spinal metastases occur in up to 70% of patients with breast and prostate cancer (8). These weaken bony integrity which can be further compromised by the effects of therapy — aromatase inhibitors in breast carcinoma and androgen deprivation in prostate cancer markedly increase the rate of bone loss (9) and consequent fracture risk. Radiation treatment for spinal metastases also increases the risk of vertebral fracture from radiation necrosis of both tumor and bone (10-12).

Most spinal metastases are asymptomatic at time of radiographic discovery (13). As the spinal tumor progresses, stretching or invasion of the periosteum causes local somatic pain. Foraminal or epidural extension resulting in nerve root or cord compression causes neuropathic pain. Between 10 – 20% of patients experience symptomatic cord compression (14); 90% of these patients experience pain (15). The prevalence of malignant vertebral fractures is unknown. Even in patients with known history of malignancy and vertebral fracture, malignancy is only identified in about half of

patients undergoing biopsy of the fractured vertebra (16). Regardless of the etiology, fractures in patients with cancer cause significant exacerbation of local pain, and can be disabling.

In cancer patients, palliative treatments that provide rapid pain relief with improved functional status and quality of life are important. Conservative medical therapy with appropriate narcotic and non-narcotic pharmacologic pain management is the mainstay. Palliative radiotherapy for pain relief from painful spinal metastasis results in complete and partial pain relief in 20% and 50% of patients by 3 months (17). However median time to response is approximately 3 weeks (18). Moreover new or worsening vertebral fractures occur in 10 – 40% of patients after spinal radiotherapy (10-12). This typically occurs at a median of 3 months, and in larger lytic metastases of the lower spine (11,12).

Vertebral augmentation is another option for cancer patients presenting with a symptomatic fracture that results in severe disabling back pain and marked reduction in quality of life; patients with significant epidural tumoral extension or neural compression are typically excluded. Open surgical decompression and fixation is typically reserved for patients with symptomatic focal cord compression, good baseline performance status, and reasonable life expectancy (19).

EFFICACY

Evidence based medicine involves the integration of the best available evidence with clinical expertise and patient values. The best evidence arises from prospective randomized trials and meta-analysis of these trials, as their design overcomes many biases in observational studies. Multicenter studies increase the generalizability of the trial result. The design, major inclusion criteria, primary outcome measures, relevant primary baseline characteristics, primary outcomes, relevant secondary outcomes, and limitations of prospective multicenter randomized sham-controlled and conservative management-controlled trials are summarized.

Prospective Randomized Sham-controlled Studies

The *Investigational Vertebroplasty Safety and Efficacy Trial* (INVEST) was an international prospective multicenter blinded randomized sham-controlled trial of vertebroplasty for osteoporotic fracture published in 2009 (20). A total of 131 patients were randomized to vertebroplasty (n = 68) and sham procedure arms (n = 63).

Major Inclusion Criteria

This included back pain intensity of 3 or more (scale 0 – 10) of less than 12-month duration with inadequate pain relief with standard medical therapy; one to 3 painful osteoporotic vertebral compression fractures between vertebral levels T4 and L5. For fractures of uncertain age, an additional requirement was increased uptake on bone scan or marrow edema on MRI.

Primary Outcome Measures

The primary outcome measure was back-pain intensity scores during the preceding 24 hours (on a scale of 0 to 10, with higher scores indicating more severe pain) and scores on the modified Roland–Morris Disability Questionnaire (RDQ), both at one month.

Relevant Primary Baseline Characteristics

Average back pain intensity in last 24 hours was 7 in both arms. Mean back pain duration was 16 weeks in the vertebroplasty arm and 18 weeks in the control arm. Pain for greater than 6-months duration was present in one-third of patients in both arms. Mean RDQ score was 17 in the vertebroplasty arm and 18 in the control arm.

Primary Outcome

There was no significant difference in back pain intensity or modified RDQ score at one month (*P* = 0.19 and *P* = 0.49 at one month, respectively).

Relevant Secondary Outcomes

There were no differences in further measures of pain, disability, and quality of life between the 2 groups at one month. In a post hoc analysis, there was a trend toward a higher rate of clinically meaningful improvement in pain (a 30% decrease from baseline) in the vertebroplasty group compared to the control group (64% vs. 48%, *P* = 0.06).

Relevant Limitations

A major limitation of the INVEST trial was the inclusion of fractures up to 12 months old and the lack of a physical examination component. Marrow edema on magnetic resonance imaging (MRI) or uptake on bone scan was only required for those fractures of indeterminate clinical age; however, the rate of usage of MRI or bone scan was not initially published. Importantly, the lack of MRI or bone scan correlation could mean that a radiographically occult adjacent level vertebral fracture responsible for the back pain was not treated

in the vertebroplasty arm. Furthermore, in the sham procedure arm, infiltration of local anesthetic to the periosteum may have resolved pain that primarily arose from facet joints, pedicle, or paravertebral soft tissues that were unrelated to the vertebral fracture. Moreover, there was no standardization or report of the additional medical treatments that the patient received during the follow-up period. In addition, by 3 months, 27 patients (43%) in the control arm had crossed over to the intervention arm and no longer-term comparisons were possible.

Similarly, an Australian prospective multicenter blinded randomized sham-controlled trial of vertebroplasty for osteoporotic fracture was published in 2009 (21,22). A total of 78 patients were randomized to vertebroplasty (n = 38) and sham procedure (n = 40) arms.

Major Inclusion Criteria

This included back pain of less than 12-month duration and the presence of one or 2 recent vertebral fractures, defined as vertebral collapse and MRI bone marrow edema, a fracture line or both.

Primary Outcome Measure

The primary outcome measure was the score for overall back pain (over the course of the previous week) as measured on a scale of 0 to 10 (with 0 indicating no pain, 10 indicating the maximum imaginable pain) at 3 months.

Relevant Primary Baseline Characteristics

Average back pain intensity in last 24 hours was 7 and median back pain duration was 9 weeks in both arms. Pain for greater than 6-weeks duration was present for 70% of patients in both arms.

Primary Outcomes

There was no significant difference in overall back pain intensity at 3 months. In the vertebroplasty arm there was a reduction in overall back pain intensity by 2.6+/-2.9 compared to 1.9+/-3.3; the absolute adjusted between-group mean difference was 0.6 in favor of vertebroplasty (95% confidence interval [CI]; -0.8 to 1.8).

Relevant Secondary Outcomes

There was no significant difference in back pain scores at one week, one month, or at 6 months. Additional measures of pain, disability, and quality of life also did not differ between the 2 groups.

Relevant Limitations

Major limitations of this trial are the inclusion of fractures up to 12 months old, the lack of a minimum back pain intensity score, the lack of a physical examination component, and small patient numbers. In addition, the outcomes may have been weighted to the treatment effect at a single center — 70% of patients were recruited at one of the 4 recruiting centers; 2 of the recruiting sites enrolled only 5 patients.

Prospective Multicenter Randomized Conservative Management-controlled Studies

The VERTOS trial was a multicenter open label randomized conservative management controlled trial of vertebroplasty for osteoporotic fracture published in 2007 (23). A total of 34 patients were randomized to vertebroplasty (n = 18) and medical management (n = 16).

Major Inclusion Criteria

This included invalidating back pain that was refractory to medical therapy for at least 6 weeks but not longer than 6 months, focal tenderness on physical examination at the fractured level, and bone marrow edema on MRI scan (defined as a decreased signal intensity on T1-weighted images and increased signal intensity on short tau inversion recovery [STIR] images).

Primary Outcome Measure

The primary outcome measure was the score for overall back pain (using the Visual Analogue Scale [VAS] [24]) as measured on a scale of 0 to 10 (with 0 indicating no pain, 10 indicating the maximum imaginable pain) at 2 weeks.

Relevant Primary Baseline Characteristics

Baseline mean VAS scores were 7.1 and 7.6 in the vertebroplasty and conservative arms, respectively. Mean duration of back pain was almost 3 months.

Primary Outcomes

By day one post vertebroplasty, the mean VAS scores were 4.7 and 7.1 in the vertebroplasty and medical arms, respectively, with a significant difference between the 2 arms of -2.4 (95% CI; -3.7 to -1.0) in favor of vertebroplasty. By 2 weeks, the difference in the VAS scores was no longer significant (difference between the 2 arms of -1.5 (95% CI; -3.2 to 0.2).

Relevant Secondary Outcomes

Analgesic use was also reduced in the vertebroplasty arm (-1.4; 95% CI; -2.1 to -0.8). There were significant improvements in disability and quality of life in the vertebroplasty arm over conservative management at 2 weeks. The mean difference in the RDQ scores between the 2 groups at 2 weeks was -5 points (95% CI; -8.4 to -1.2); the mean difference in the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) scores between the 2 groups at 2 weeks was -14 points (95% CI; -24.7 to -3.4).

Relevant Limitations

The major limitation of the VERTOS trial was the small size and lack of blinding. Moreover, as crossover was allowed after 2 weeks, no long-term follow-up was possible. Notably, 14 of the 16 patients in the conservative arm requested vertebroplasty after 2 weeks.

The Fracture Reduction Evaluation trial (FREE) trial was an international multicenter open label randomized conservative management controlled trial of kyphoplasty for osteoporotic fractures published in 2009 (25,26). A total of 300 patients were randomized and divided into kyphoplasty (n = 149) and conservative medical management arms (n = 151).

Major Inclusion Criteria

This included severe back pain with intensity score of 4 or more (on 10 point scale) that was present for less than 3 months, bone marrow edema or pseudoarthrosis on MRI scans, and fracture level of T5 or lower. Fractures from primary or secondary osteoporosis, multiple myeloma, or osteolytic metastatic tumors were included. Patients with osteoblastic tumors and radicular or spinal cord compression pain syndromes were excluded.

Primary Outcome Measure

The primary outcome measure was the difference in a global quality of life measure weighted on physical abilities, using the short-form-36 physical component summary (SF36-PCS) scale between the kyphoplasty and control groups.

Relevant Primary Baseline Characteristics

Mean duration of back pain was approximately 6 weeks. Mean time between randomization and kyphoplasty was 7 days. SF-36 PCS scores were approximately 25 in both groups.

Primary Outcomes

Kyphoplasty resulted in significantly improved quality of life over conservative treatment at one month. The improvement in mean SF-36 PCS score from baseline to one month was 5.2 points (95% CI; 2.9 – 7.4) more in the kyphoplasty group than in the conservatively managed arm ($P < 0.0001$). The minimum clinically important difference (MCID) is a quantitative assessment of clinical relevance for a given magnitude of health related quality of life or disability score change. Scores above the MCID are indicative of a potentially important change. The MCID threshold proposed for SF-36 PCS scores after lumbar spine surgery is 4.9 (27).

Relevant Secondary Outcomes

Secondary outcome measures were SF-36 PCS and other quality of life scores, back pain and disability scores at one, 3, 6, and 12 months. There remained significant improvements in the SF-36 PCS scores in favor of kyphoplasty at 3 and 6 months ($P = 0.0008$ and $P = 0.0064$) but not at 12 months ($P = 0.208$). Back pain scores were significantly reduced at one week ($P < 0.0001$) and 12 months $P = 0.0034$). Reductions in the RDQ disability scores in favor of kyphoplasty were significant at one month ($P < 0.0001$) and 12 months ($P = 0.0012$). Kyphoplasty patients were less likely to be using narcotic analgesia between one and 6 months; patients in the kyphoplasty arm reported 3 fewer days of restricted activity per fortnight (1.3 – 4.6; $P = 0.0004$) because of back pain at one month. This was no longer significant at 12 months (1.6 days, –0.1 to 3.3; $P = 0.0678$). There remained a significant reduction in back pain scores for patients in the kyphoplasty arm compared to conservative therapy at 24 months ($P = 0.009$), there were no significant differences in the SF-36 PCS or RDQ scores at 24 months (25).

Relevant Limitations

A major limitation to the FREE trial was the lack of blinding, which can overestimate treatment benefit (28). Furthermore, cancer related fractures were also included; however, only 4 of the 300 patients randomized had pathological fractures.

The VERTOS II trial was an international multicenter open label randomized conservative management controlled trial of vertebroplasty for osteoporotic fracture published in 2010 (29). A total of 202 patients were equally randomized into vertebroplasty (n = 101) and conservative medical management (n = 101) arms.

Major Inclusion Criteria

This included severe back pain with VAS intensity score of 5 or more that was present for 6 weeks or less, focal tenderness on physical examination at the fractured level, bone marrow edema on MRI scan, and fracture level of T5 or lower.

Primary Outcome Measure

The primary outcome measure was pain relief at one month and one year, measured with a VAS score.

Relevant Primary Baseline Characteristics

Baseline mean VAS scores were 7.8 and 7.5 in the vertebroplasty and conservative arms, respectively. Mean duration of back pain was approximately 30 days. Vertebroplasty was performed at a mean of 5.6 weeks post symptom onset.

Primary Outcomes

Vertebroplasty resulted in significantly greater pain relief at one month than did conservative treatment. The mean reduction of VAS score from baseline was 2.6 (95% CI; 1.74 – 3.37, $P < 0.0001$) greater in the vertebroplasty arm at one month. This was a durable effect, with the reduction in the mean VAS score at one year of 2.0 (1.13 – 2.80, $P < 0.0001$). The MCID threshold proposed for 0 – 10 pain rating scales after lumbar spine surgery is 1.2 (27).

Relevant Secondary Outcomes

Secondary outcomes were cost-effectiveness at one month and one year; medical costs, time without burdensome pain, and quality-adjusted survival time were also reported. The cost difference between vertebroplasty and conservative treatment at one year was approximately the cost of vertebroplasty for the trial (€2463 or approximately $3,500 US dollars). An average of 120 (95% CI; 163 – 177) pain-free days (VAS 0 – 3) were gained in the 12 months after vertebroplasty. Significant pain relief (reduction of VAS from baseline by 3 points or more) was achieved earlier and in more patients after vertebroplasty (30 days until significant pain relief, 95% CI; 11 – 48) than with conservative treatment (116 days, 95% CI; 86 – 145) ($\chi 2 = 55.6$, $P < 0.0001$).

Relevant Limitations

A major limitation to the VERTOS II trial was the lack of blinding, which can overestimate treatment benefit (28). Notably, later analysis of the patients in the conservatively treated arm by the VERTOS II investigators revealed that 60% of patients in the conservatively treated arm had sufficient pain relief (VAS ≤ 3) at 12 months, with the vast majority achieving this within 3 months (30).

The Cancer Patient Fracture Evaluation (CAFE) trial was an international multicenter open label randomized conservative management controlled trial of kyphoplasty for fractures in cancer patients published in 2011 (31). A total of 134 patients were randomized into balloon kyphoplasty (n = 70) and conservative therapy arms (n = 64).

Major Inclusion Criteria

This included severe disabling back pain with an intensity score of 4 or more (on 10 point scale) and RDQ score of 10 or more from a clinically diagnosed vertebral fracture in a patient with cancer. Fractures were confirmed with plain radiographs or MRI; patients were aged 21 years or older. Patients with primary or osteoblastic bone tumors were excluded.

Primary Outcome Measure

The primary outcome measure was change in RDQ score at one month.

Relevant Primary Baseline Characteristics

Median estimated symptomatic fracture age was 3.5 months; 70% of patients had edema on MRI. Mean baseline RDQ scores were 17.6 points in the kyphoplasty group and 18.2 in the control group.

Primary Outcomes

Kyphoplasty resulted in significantly reduced back pain related disability than did conservative treatment. Mean baseline RDQ scores were 17.6 points in the kyphoplasty group and 18.2 in the control group. By one month, the mean RDQ score in the kyphoplasty group was 9.1, while the mean RDQ score in the control group was 18.0. The treatment effect for kyphoplasty on RDQ at one month was 8.4 points (95% CI; -7.6 to -9.2; $P < 0.0001$). The MCID in RDQ ranges between 2 and 3 points (32). By one month, 51 of 63 patients in the kyphoplasty group improved by at least 2 RDQ points compared with 14 of 50 patients randomly assigned to non-surgical management ($P < 0.0001$).

Relevant Secondary Outcomes

Secondary outcomes included back pain scores, Karnofsky performance status scores, and quality of life (measured by SF-36 PCS) at one, 3, 6, and 12 months.

Patients in the kyphoplasty group had significant reductions in back pain. Both groups had baseline mean back pain score of 7.3; the mean score at 7 days was 3.5 in the kyphoplasty arm compared with 7.0 in the conservative arm ($P < 0.0001$). This difference remained of similar magnitude and significance at one month ($P < 0.0001$). Mean baseline Karnofsky performance score was approximately 56 in both the kyphoplasty and control groups. The MCID estimate for KPS in cancer patients is about 5 points (33); 70 points is a clinically meaningful threshold for self-care (34). By one month, the mean Karnofsky score in the kyphoplasty group had increased by 15.3 points (95% CI; 13.5 – 17.1; $P < 0.0001$) compared to no significant change in the control group. By one month 75% of the patients in the kyphoplasty group had improved to a KPS score of at least 70 compared to 39% of the conservative arm. Patients in the kyphoplasty arm also had significant increases in the SF-36 PCS scores at one month (8.4 points) (95% CI; 7.7 – 9.1; $P < 0.0001$) compared to the conservative arm.

Relevant Limitations

A limitation of the CAFE trial is the lack of histological confirmation of vertebral fracture etiology. Thus individual fractures may have been caused by metastasis, osteoporosis, radionecrosis, or a combination of all of these etiologies. Nonetheless, 78% of patients in the kyphoplasty arm had stable or progressive cancer (mainly multiple myeloma or breast cancer), and 34% had received previous radiation for spinal or bony metastasis. Thus a high rate of metastatic fractures can be expected. Further limitations include the lack of blinding that can overestimate treatment benefit and the significant crossover from the control group — 34 of 64 patients randomized to the conservative arm crossed over to kyphoplasty; 21 patients crossed over within one week of the one-month assessment. Nonetheless, these cross-over patient outcomes were separately reported and no patients were allowed to cross over before the one-month assessment, thus the one-month outcome measures remain robust.

Meta-analyses or Systematic Reviews of Efficacy Including Recent Prospective Studies of Vertebral Augmentation

A pooled analysis using data from the prospective multicenter sham-controlled studies was published in 2011 (35). The primary aim was to assess whether vertebroplasty was more effective than a sham procedure for a subgroup of patients with recent onset (6 weeks or less) or severe (score of 8 or more) pain. Outcome data for the total 209 patients at one month was analyzed, as the INVEST trial allowed patient cross over after one month. For participants with pain of recent onset or severe pain, there was no significant difference in pain (VAS) and disability (RDQ) at one month. The authors also report extension of their analysis to match the inclusion criteria of the VERTOS II trial and were unable to show treatment benefit for vertebroplasty (data not published). Although some of the statistical power limitations in the original 2 studies may have been overcome, the remainder of the limitations to interpretation of the original data in the 2 studies as previously detailed remains.

A systematic review and meta-analysis limited to prospective randomized and non-randomized controlled studies comparing kyphoplasty, vertebroplasty, and non-surgical management for osteoporotic vertebral fractures was published in 2012 (36). Twenty-seven trials were included. Both vertebroplasty and kyphoplasty resulted in greater pain relief (10 point scale) and reduced disability (RMD and Oswestry Disablity Index) compared to conservative management.

Another meta-analysis limited to prospective randomized controlled trials comparing vertebroplasty or kyphoplasty to conservative or sham treatment for osteoporotic fractures was published in 2012 (37). Six trials compared vertebroplasty or kyphoplasty to conservative management or a sham procedure— the INVEST, Australian, VERTOS, VERTOS II, and FREE trials were included. Outcomes were analyzed as early (≤ 12 weeks) and late (≥ 26 weeks) effects on pain relief (VAS score), disability (RDQ or Oswestry), and quality of life measures (QUALEFFO and the EuroQol-5 dimensions [EQ5-D]). Overall, the meta-analysis showed greater pain relief, reduced disability, and improved quality of life in favor of vertebral augmentation for treatment of symptomatic osteoporotic compression fractures.

A further meta-analysis that included prospective randomized and non-randomized controlled trials comparing vertebroplasty to conservative or sham treatment for osteoporotic fractures was also published in 2012 (38). Nine trials (total n = 886) were analyzed, including the INVEST, Australian, and VERTOS II trials. There was no difference in pain scores (VAS) between the vertebroplasty group and the sham treatment group at 1 – 29 days and 90 days ($P = 0.68$ and 0.29, respectively). Vertebroplasty resulted in significantly greater pain relief than did conservative medical treatment at all time points, including in patients with frac-

tures less than 6 weeks old. There were also significant reductions in disability and improvement in quality of life as measured by RDQ and QUALEFFO at 30 days in favor of vertebroplasty.

There is only a single randomized controlled trial of vertebral augmentation in cancer patients; thus no meta-analysis in this cohort is possible.

Procedural Safety

Randomized trials offer the best approach for providing safety data but are limited in the detection of rare harms. Overall, major complications occur in less than one percent of patients treated for osteoporotic compression fractures and in less than 5% of treated patients with neoplastic involvement (39).

In the meta-analyses limited to prospective randomized controlled trials comparing vertebroplasty or kyphoplasty to conservative or sham treatment for osteoporotic fractures there were no statistically significant differences in medical adverse events between the conservative and vertebral augmentation arms (37). Minor procedural complications in the vertebral augmentation arm included asymptomatic cement leaks, soft tissue hematoma, exacerbation of asthma, and vasovagal reactions. Major procedural complications included one postoperative osteomyelitis following vertebroplasty in a patient who did not receive prophylactic antibiotics, and severe radiculopathy secondary to cement leakage that required laminectomy. No death was directly related to either conservative or vertebral augmentation therapy. In the only prospective randomized conservative management-controlled clinical trial for patients with painful vertebral compression fractures in cancer patients, the only procedural complications were one superficial wound infection and one patient with a cement leakage to the adjacent disc who had an adjacent fracture the day after the procedure (31).

Although uncommon, the potential complications that have been reported in the literature include symptomatic cement leakage, nerve or spinal cord injury resulting in paralysis or bowel/bladder dysfunction or need for emergent decompression; cement or fat pulmonary emboli; osteomyelitis; vascular injury; rib, pedicle, or vertebral fracture; hypotension or depressed myocardial function; pneumothorax (for thoracic levels); and death from cardiovascular collapse or anaphylaxis to the cement.

Cement leakage is common after vertebral augmentation. In VERTOS II, 72% of treated vertebral bodies had leaks on post procedural computed tomogra-

phy (CT) (29). No leaks were into the spinal canal; all patients were asymptomatic. For kyphoplasty, there is theoretically a lower rate of cement leakage, as balloon tamp inflation creates a large low resistance cavity with cancellous bone compacted around the periphery prior to infusing PMMA. In FREE, cement extravasation occurred in 27% of treated vertebrae; however, this was assessed with intra-operative fluoroscopy and postoperative radiographs (26). No leaks were into the spinal canal; all patients were asymptomatic. In the CAFE trial, cement leaks were reported in 2 of 70 patients, one of which was discal and associated with adjacent level vertebral body fracture the following day (31). No patients experienced procedure related neurological deterioration or pulmonary embolism.

There are conflicting results when individual trials are examined with regard to the incidence of secondary fractures after vertebral augmentation compared to conservative management. However in the 3 recent meta-analyses presented, the risk of secondary fractures after vertebral augmentation is not higher than in patients managed conservatively (36-38).

Cost Effectiveness And... Increased Survival?

In order to justify resource allocation for vertebral augmentation, it is important to consider cost-effectiveness data. Studies that model cost effectiveness must take into account the potential health related quality of life benefits, length of hospital stay, and potential mortality benefits. Health related quality of life data is available from the randomized controlled trials published to date and those powered to detect improvements in health related quality of life measures as primary outcomes have been summarized above.

Large cohort length of stay data has recently become available. Patients hospitalized for vertebral fractures and treated with vertebral augmentation are discharged from hospital earlier and less likely to be re-admitted in the short term. Examination of North American national databases reveals a mean length of stay of 10 days for patients hospitalized for a vertebral fracture that receive conservative management (40,41); those treated with vertebral augmentation have an average length of stay of between 3–6 days (42). (42). An analysis of the French Hospital National Database for admissions for osteoporotic vertebral fractures during 2009 (n= 13,624), revealed that patients undergoing vertebroplasty were significantly more likely to be discharged within 1 week compared to conservatively

managed patients (68% vs 47%; $P < 0.0001$) (43). However these patients were also younger and had less co-morbidities. A nationwide cohort study from Taiwan (n = 9,238) revealed a 2 day reduction in length of stay in patients treated with augmentation compared to conservative management, in spite of those treated with augmentation being older and less healthy (44). Furthermore, re-admission for fracture or musculoskeletal concerns within 7 and 30 days were significantly lower in patients treated with vertebral augmentation. By 6 months there were no longer significant differences in re-admission rates.

Large cohort long and short-term baseline mortality data has been recently published. Population studies reveal excess mortality in vertebral fracture patients compared to age-matched controls that persists for at least 5 years (45). A retrospective review of the US Medicare dataset between 1997 and 2004 identified a total of 97,142 patients vertebral fracture patients that were compared with 428,956 controls. The mortality rate after a vertebral fracture was twice that of controls. Mortality rates at 3, 5 and 7 years for vertebral fracture patients were 46%, 69% and 90% compared to 22%, 36% and 48% for matching controls (46). The cause of this excess mortality is not known; a cause and effect should not be assumed. Notably most deaths after osteoporotic fractures occur within the first 3—6 months (47). The 6-month mortality rate after a vertebral fracture from the Korean National Claim Registry sample was approximately 5 and 10% for women and men aged 50 and older (48).

Given the baseline elevated mortality risk in vertebral fracture patients, it has been postulated that vertebral augmentation could reduce excess mortality. A retrospective review of the US Medicare dataset between 2005 and 2008 identified a total of 858,978 vertebral fracture patients, of which 182,946 underwent vertebroplasty or kyphoplasty (49,50). Patient in the vertebral augmentation cohort had a higher adjusted survival rate of 61% compared with 50% for conservatively managed patients ($P < .001$) at 4 years of follow up (49). Furthermore, life expectancy gains of between 1 – 9.5 years were estimated, which were higher after kyphoplasty compared to vertebroplasty (50). Notably, the conservatively managed patient group had higher rates of stroke and pneumonia. A much smaller analysis of 524 vertebroplasty patients at a single institution did not confirm this benefit (51). None of the currently published prospective multicenter randomized controlled trials were powered to demonstrate a reduction

in mortality, and they have not shown mortality benefit. Further large cohort data to clarify these findings has yet to be published.

If there is increased quality of life combined with reduced length of stay and potential reduction in mortality, vertebral augmentation may be cost effective. The same authors that analyzed the US Medicare dataset subsequently modeled cost effectiveness of performing vertebral augmentation compared to conservative management. The cost per life-year gained in the vertebral augmentation cohort was reasonably cost efficient, ranging from $US1,863 to $US13,543 (52,53). Analysis of a hospitalized vertebral fracture cohort in the United Kingdom concluded that kyphoplasty may be more cost effective than both conservative management and vertebroplasty (54). However these analyses are particularly sensitive to potential increased quality of life and reduced mortality benefit from vertebral augmentation; if these benefits do not exist, conservative management is the most cost effective treatment strategy. Importantly, the mortality data used in the base analysis was not from a randomized controlled trial, but from the retrospective review of the US Medicare dataset that was funded by a manufacturer grant (49). Moreover, a small Swedish prospective multicenter cost-effectiveness trial of 63 patients randomized between kyphoplasty (n=32) and conservative management (n=31) failed to demonstrate cost effectiveness of kyphoplasty with a cost per qualityadjusted life year gained of approximately $US134,000 (55).

Conclusion

For treatment of individual patients, we must integrate the best available evidence with clinical expertise and patient values. For cancer patients with disabling pain from vertebral fractures, there is a good quality randomized controlled trial that demonstrates that kyphoplasty is a safe and effective treatment that rapidly reduces disability and pain and increases quality of life. However a prospective randomized controlled trial of kyphoplasty compared to a sham procedure has not been performed and there are no data to assess the cost effectiveness of kyphoplasty in patients with cancer.

For patients with osteoporotic fractures, the data is conflicting. Two small double blind randomized controlled trials published in 2009 did not show efficacy for vertebroplasty over a sham procedure. Two larger open label randomized controlled trials, the VERTOS II and FREE trials show efficacy for vertebroplasty and kyphoplasty respectively over conservative medical manage-

ment. All published randomized controlled trials in vertebral augmentation have limitations. Meta-analyses of prospective randomized controlled studies provide evidence in favor for the use of vertebral augmentation for osteoporotic fractures with a good safety profile. There are health related quality of life benefits and possible reductions in long term mortality; it remains unknown whether vertebral augmentation for patients with osteoporotic fractures is cost effective.

Ultimately, further randomized controlled trials of vertebral augmentation in both osteoporotic and cancer patients are required to improve the strength of evidence available to assess these procedures. Until then, the balance of evidence favors the use of verte-

bral augmentation in a small select cohort of patients with severe and disabling back pain refractory to conservative medical therapy. Experienced clinicians should select these patients for treatment by localizing pain to specific fractured vertebral levels using both clinical examination and modern imaging techniques such as MRI with STIR imaging. Experienced practitioners should perform vertebral augmentation to maximize the safety profile; these procedures should be performed in the setting of clinical trials or quality improvement programs where the clinical effectiveness, safety and cost effectiveness of vertebral augmentation can be best examined.

REFERENCES

1. Long SS, Morrison WB, Parker L. Vertebroplasty and kyphoplasty in the United States: provider distribution and guidance method, 2001-2010. *AJR Am J Roentgenol* 2012:199: 1358-1364.

2. Ross PD. Clinical consequences of vertebral fractures. *Am J Med* 1997:103: 30S-42S; discussion 42S-43S.

3. European Prospective Osteoporosis Study G. Felsenberg D, Silman AJ, Lunt M, Armbrecht G, Ismail AA, Finn JD, Cockerill WC, Banzer D, Benevolenskaya, LI, Bhalla A, Bruges AJ, Cannata JB, Cooper C, Dequeker J, Eastell R, Felsch B, Gowin W, Havelka S, Hoszowski K, Jajic I, Janott J, Johnell O, Kanis JA, Kragl G, Lopes Vaz A, Lorenc R, Lyritis G, Masaryk P, Matthis C, Miazgowski T, Parisi G, Pols HA, Poor G, Raspe HH, Reid DM, Reisinger W, Schedit-Nave C, Stepan JJ, Todd CJ, Weber K, Woolf AD, Yershova OB, Reeve, J, O'Neill TW. Incidence of vertebral fracture in europe: results from the European Prospective Osteoporosis Study (EPOS). *J Bone Miner Res* 2002:17: 716-724.

4. Cooper C, O'Neill T, Silman A. The epidemiology of vertebral fractures. European Vertebral Osteoporosis Study Group. *Bone* 1993:14 Suppl 1: S89-97.

5. Shen M, Kim Y. Osteoporotic vertebral compression fractures: a review of current surgical management techniques. *Am J Orthop* 2007:36: 241-248.

6. Kashii M, Yamazaki R, Yamashita T, Okuda S, Fujimori T, Nagamoto Y, Tamura Y, Oda T, Ohwada T, Yoshikawa H, Iwasaki, M. Surgical treatment for osteoporotic vertebral collapse with neurological deficits: Retrospective comparative study of three procedures-anterior surgery versus posterior spinal shorting osteotomy versus posterior spinal fusion using vertebroplasty. *Eur Spine J* 2013. Apr 3. [Epub ahead of print]

7. Reuss-Borst M, Hartmann U, Scheede C, Weiss J. Prevalence of osteoporosis among cancer patients in Germany: prospective data from an oncological rehabilitation clinic. *Osteoporos Int* 2012:23: 1437-1444.

8. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. *Clin Cancer Res* 2006:12: 6243s-6249s.

9. Tipples K, Robinson A. Optimal Management of Cancer Treatment-Induced Bone Loss: Considerations for Elderly Patients. *Drugs Aging* 2011:28:867-883

10. Rose PS, Laufer I, Boland PJ, Hanover A, Bilsky MH, Yamada J, Lis E. Risk of fracture after single fraction image-guided intensity-modulated radiation therapy to spinal metastases. *J Clin Oncol* 2009:27: 5075-5079.

11. Cunha MV, Al-Omair A, Atenafu EG, Masucci GL, Letourneau D, Korol R, Yu E, Howard P, Lochray F, da Costa LB, Fehlings MG, Sahgal A. Vertebral compression fracture (VCF) after spine stereotactic body radiation therapy (SBRT): analysis of predictive factors. *Int J Radiat Oncol Biol Phys* 2012:84: e343-349.

12. Boehling NS, Grosshans DR, Allen PK, McAleer MF, Burton AW, Azeem S, Rhines LD, Chang EL. Vertebral compression fracture risk after stereotactic body radiotherapy for spinal metastases. *J Neurosurg Spine* 2012:16: 379-386.

13. Front D, Schneck SO, Frankel A, Robinson E. Bone metastases and bone pain in breast cancer. Are they closely associated? *JAMA* 1979:242: 1747-1748.

14. Klimo P, Jr., Schmidt MH. Surgical management of spinal metastases. *Oncologist* 2004:9: 188-196.

15. Dunning EC, Butler JS, Morris S. Complications in the management of metastatic spinal disease. *World J Orthop* 2012:3: 114-121.

16. Zhang L, Li J, Yang H, Luo Z, Zou J. Histological evaluation of bone biopsy results during PVP or PKP of vertebral compression fractures. *Oncol Lett* 2013:5: 135-138.

17. Howell DD, James JL, Hartsell WF, Suntharalingam M, Machtay M, Suh JH, Demas WF, Sandler HM, Kachnic LA, Berk LB. Single-fraction radiotherapy versus multifraction radiotherapy for palliation of painful vertebral bone metastases-equivalent efficacy, less toxicity, more convenient: a subset analysis of Radiation Therapy Oncology Group trial 97-14. *Cancer* 2013:119: 888-896.

18. Steenland E, Leer JW, van Houwelingen H, Post WJ, van den Hout WB, Kievit J, de Haes H, Martijn H, Oei B, Vonk E, van der Steen-Banasik E, Wiggenraad RG, Hoogenhout J, Warlam-Rodenhuis C, van Tienhoven G, Wanders R, Pomp J,

van Reijn M, van Mierlo I, Rutten E. The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. *Radiother Oncol* 1999;52: 101-109.

19. Loblaw DA, Mitera G, Ford M, Laperriere, NJ. A 2011 updated systematic review and clinical practice guideline for the management of malignant extradural spinal cord compression. *Int J Radiat Oncol Biol Phys* 2012:84: 312-317.

20. Kallmes DF, Comstock BA, Heagerty PJ, Turner JA, Wilson DJ, Diamond TH, Edwards R, Gray LA, Stout L, Owen S, Hollingworth W, Ghdoke B, Annesley-Williams DJ, Ralston SH, Jarvik J G. A randomized trial of vertebroplasty for osteoporotic spinal fractures. *N Engl J Med* 2009;361: 569-579.

21. Buchbinder R, Osborne RH, Ebeling PR, Wark JD, Mitchell P, Wriedt CJ, Wengier L, Connell D, Graves SE, Staples MP, Murphy, B. Efficacy and safety of vertebroplasty for treatment of painful osteoporotic vertebral fractures: a randomised controlled trial [AC-TRN012605000079640]. *BMC Musculoskelet Disord* 2008:9: 156.

22. Buchbinder R, Osborne RH, Ebeling PR, Wark JD, Mitchell P, Wriedt C, Graves S, Staples MP, Murphy B. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *N Engl J Med* 2009;361: 557-568.

23. Voormolen MH, Mali WP, Lohle PN, Fransen H, Lampmann LE, van der Graaf Y, Juttmann JR, Jansssens X, Verhaar HJ. Percutaneous vertebroplasty compared with optimal pain medication treatment: short-term clinical outcome of patients with subacute or chronic painful osteoporotic vertebral compression fractures. The VERTOS study. *AJNR Am J Neuroradiol* 2007;28: 555-560.

24. Bouvard B, Hoppe E, Soulie P, Georgin-Mege M, Jadaud E, Abadie-Lacourtoisie S, Petit Le Manac'h A, Laffitte A, Levasseur R, Audran M, Chappard D, Legrand E. High prevalence of vertebral fractures in women with breast cancer starting aromatase inhibitor therapy. *Ann Oncol* 2012:23: 1151-1156.

25. Boonen S, Van Meirhaeghe J, Bastian L, Cummings SR, Ranstam J, Tillman JB, Eastell R, Talmadge K, Wardlaw D. Balloon kyphoplasty for the treatment of acute vertebral compression fractures: 2-year results from a randomized trial. *J Bone Miner Res* 2011:26: 1627-1637.

26. Wardlaw D, Cummings SR, Van Meirhaeghe J, Bastian L, Tillman JB, Ranstam J, Eastell R, Shabe P, Talmadge K, Boonen S. Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomised controlled trial. *Lancet* 2009:373: 1016-1024.

27. Copay AG, Glassman SD, Subach BR, Berven S, Schuler TC, Carreon LY. Minimum clinically important difference in lumbar spine surgery patients: a choice of methods using the Oswestry Disability Index, Medical Outcomes Study questionnaire Short Form 36, and pain scales. *Spine J* 2008:8: 968-974.

28. Schulz KF, Grimes DA. Blinding in randomised trials: hiding who got what. *Lancet* 2002:359: 696-700.

29. Klazen CA, Lohle PN, de Vries J, Jansen FH, Tielbeek AV, Blonk MC, Venmans A, van Rooij WJ, Schoemaker MC, Juttmann JR, Lo TH, Verhaar HJ, van der Graaf Y, van Everdingen KJ, Muller AF, Elgersma OE, Halkema DR, Fransen H, Janssens X, Buskens E, Mali WP. Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): an open-label randomised trial. *Lancet* 2010:376: 1085-1092.

30. Venmans A, Klazen CA, Lohle PN, Mali W P, van Rooij WJ. Natural history of pain in patients with conservatively treated osteoporotic vertebral compression fractures: results from VERTOS II. *AJNR Am J Neuroradiol* 2012:33: 519-521.

31. Berenson J, Pflugmacher R, Jarzem P, Zonder J, Schechtman K, Tillman JB, Bastian L, Ashraf T, Vrionis F. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. *Lancet Oncol* 2011:12: 225-235.

32. Roland M, Fairbank J. The Roland-Morris Disability Questionnaire and the Oswestry Disability Questionnaire. *Spine* 2000:25: 3115-3124.

33. Ringash J, O'Sullivan B, Bezjak A, Redelmeier DA. Interpreting clinically significant changes in patient-reported outcomes. *Cancer* 2007:110: 196-202.

34. Yates JW, Chalmer B, McKegney FP. Evaluation of patients with advanced cancer using the Karnofsky performance status. *Cancer* 1980:45: 2220-2224.

35. Staples MP, Kallmes DF, Comstock BA,

Jarvik JG, Osborne RH, Heagerty PJ, Buchbinder R. Effectiveness of vertebroplasty using individual patient data from two randomised placebo controlled trials: meta-analysis. *BMJ* 2011:343: d3952.

36. Papanastassiou ID, Phillips FM, Van Meirhaeghe J, Berenson JR, Andersson GB, Chung G, Small BJ, Aghayev K, Vrionis FD. Comparing effects of kyphoplasty, vertebroplasty, and non-surgical management in a systematic review of randomized and non-randomized controlled studies. *Eur Spine J* 2012:21: 1826-1843.

37. Anderson PA, Froyshteter AB, Tontz WL, Jr. Meta-analysis of vertebral augmentation compared to conservative treatment for osteoporotic spinal fractures. *J Bone Miner Res* 2013: 28: 372-382.

38. Shi MM, Cai XZ, Lin T, Wang W, Yan SG. Is there really no benefit of vertebroplasty for osteoporotic vertebral fractures? A meta-analysis. *Clin Orthop Relat Res* 2012:470: 2785-2799.

39. McGraw JK, Cardella J, Barr JD, Mathis JM, Sanchez O, Schwartzberg MS, Swan TL, Sacks D, Society of Interventional Radiology Standards of Practice, Committee. Society of Interventional Radiology quality improvement guidelines for percutaneous vertebroplasty. *J Vasc Interv Radiol* 2003:14: S311-315.

40. Phillips S, Fox N, Jacobs J, Wright WE. The direct medical costs of osteoporosis for American women aged 45 and older, 1986. *Bone* 1988:9: 271-279.

41. Papaioannou A, Adachi JD, Parkinson W, Stephenson G, Bedard M. Lengthy hospitalization associated with vertebral fractures despite control for comorbid conditions. *Osteoporos Int* 2001:12: 870-874.

42. Ong KL, Lau E, Kemner JE, Kurtz SM. Two-year cost comparison of vertebroplasty and kyphoplasty for the treatment of vertebral compression fractures: Are initial surgical costs misleading? *Osteoporos Int* 2013:24: 1437-1445

43. Maravic M, Taupin P, Roux C. Hospital burden of vertebral fractures in France: influence of vertebroplasty. *Osteoporos Int* 2013. Jan 23. [Epub ahead of print]

44. Tsai YW, Hsiao FY, Wen YW, Kao YH, Chang LC, Huang WF, Peng LN, Liu CL, Chen LK. Clinical outcomes of vertebroplasty or kyphoplasty for patients with vertebral compression fractures: a nationwide cohort study. *J Am Med Dir Assoc* 2013:14: 41-47.

45. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. *JAMA* 2009:301: 513-521.

46. Lau E, Ong K, Kurtz S, Schmier J, Edidin A. Mortality following the diagnosis of a vertebral compression fracture in the Medicare population. *J Bone Joint Surg Am* 2008:90: 1479-1486.

47. Abrahamsen B, van Staa T, Ariely R, Olson M, Cooper C. Excess mortality following hip fracture: a systematic epidemiological review. *Osteoporos Int* 2009:20: 1633-1650.

48. Lee YK, Jang S, Jang S, Lee HJ, Park C, Ha YC, Kim DY. Mortality after vertebral fracture in Korea: analysis of the National Claim Registry. *Osteoporos Int* 2012:23:

1859-1865.

49. Edidin AA, Ong KL, Lau E, Kurtz SM. Mortality risk for operated and nonoperated vertebral fracture patients in the medicare population. *J Bone Miner Res* 2011:26: 1617-1626.

50. Edidin AA, Ong KL, Lau E, Kurtz SM. Life expectancy following diagnosis of a vertebral compression fracture. *Osteoporos Int* 2013:24: 451-458.

51. McDonald RJ, Achenbach SJ, Atkinson EJ, Gray LA, Cloft HJ, Melton LJ 3rd, Kallmes DF. Mortality in the vertebroplasty population. *AJNR Am J Neuroradiol* 2011:32: 1818-1823.

52. Edidin AA, Ong KL, Lau E, Schmier JK, Kemner JE, Kurtz SM. Cost-effectiveness analysis of treatments for vertebral compression fractures. *Appl Health Econ*

Health Policy 2012:10: 273-284.

53. Owens DK. Interpretation of cost-effectiveness analyses. *J Gen Intern Med* 1998:13: 716-717.

54. Svedbom A, Alvares L, Cooper C, Marsh D, Strom O. Balloon kyphoplasty compared to vertebroplasty and nonsurgical management in patients hospitalised with acute osteoporotic vertebral compression fracture: a UK cost-effectiveness analysis. *Osteoporos Int* 2013:24: 355-367.

55. Fritzell P, Ohlin A, Borgstrom F. Cost-effectiveness of balloon kyphoplasty versus standard medical treatment in patients with osteoporotic vertebral compression fracture: A Swedish multicenter randomized controlled trial with 2-year follow-up. *Spine* 2011:36: 2243-2251.