Health Quality Ontario

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ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Vertebral Augmentation Involving Vertebroplasty or Kyphoplasty for Cancer-Related Vertebral Compression Fractures: A Systematic Review

KEY MESSAGES

Cancer can start in one part of the body and spread to other regions, often involving the spine, causing significant pain and reducing a patient's ability to walk or carry out everyday activities such as bathing, dressing, and eating. When cancer spreads to or occurs in a bone of the spine (a vertebral bone), the cancer can weaken and break this bone. These fractures, if left untreated, can negatively affect the quality of life of terminally ill patients and their families.

Vertebroplasty and kyphoplasty are two types of procedures called vertebral augmentation. During vertebral augmentation, the physician injects bone cement into the broken vertebral bone to stabilize the spine and control pain. Kyphoplasty is a modified form of vertebroplasty in which a small balloon is first inserted into the vertebral bone to create a space to inject the cement; it also attempts to lift the fracture to restore it to a more normal position.

Medical therapy and bed rest are not very effective in cancer patients with painful vertebral fractures, and surgery is not usually an option for patients with advanced disease and who are in poor health. Vertebral augmentation is a minimally invasive treatment option, performed on an outpatient basis without general anesthesia, for managing painful vertebral fractures that limit mobility and self-care.

We reviewed the evidence to evaluate the safety and effectiveness of vertebroplasty and kyphoplasty in cancer patients. Both procedures rapidly reduce pain, decrease the need for pain medicine, and improve patients' ability to walk and carry out basic everyday activities. Serious complications after these procedures are rare.

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ABSTRACT

Background

Cancers that metastasize to the spine and primary cancers such as multiple myeloma can result in vertebral compression fractures or instability. Conservative strategies, including bed rest, bracing, and analgesic use, can be ineffective, resulting in continued pain and progressive functional disability limiting mobility and self-care. Surgery is not usually an option for cancer patients in advanced disease states because of their poor medical health or functional status and limited life expectancy. The objectives of this review were to evaluate the effectiveness and safety of percutaneous image-guided vertebral augmentation techniques, vertebroplasty and kyphoplasty, for palliation of cancer-related vertebral compression fractures.

Methods

We performed a systematic literature search for studies on vertebral augmentation of cancer-related vertebral compression fractures published from January 1, 2000, to October 2014; abstracts were screened by a single reviewer. For those studies meeting the eligibility criteria, full-text articles were obtained. Owing to the heterogeneity of the clinical reports, we performed a narrative synthesis based on an analytical framework constructed for the type of cancer-related vertebral fractures and the diversity of the vertebral augmentation interventions.

Results

The evidence review identified 3,391 citations, of which 111 clinical reports (4,235 patients) evaluated the effectiveness of vertebroplasty (78 reports, 2,545 patients) or kyphoplasty (33 reports, 1,690 patients) for patients with mixed primary spinal metastatic cancers, multiple myeloma, or hemangiomas.

Overall the mean pain intensity scores often reported within 48 hours of vertebral augmentation (kyphoplasty or vertebroplasty), were significantly reduced. Analgesic use, although variably reported, usually involved parallel decreases, particularly in opioids, and mean pain-related disability scores were also significantly improved. In a randomized controlled trial comparing kyphoplasty with usual care, improvements in pain scores, pain-related disability, and health-related quality of life were significantly better in the kyphoplasty group than in the usual care group.

Bone cement leakage, mostly asymptomatic, was commonly reported after vertebroplasty and kyphoplasty. Major adverse events, however, were uncommon.

Conclusions

Both vertebroplasty and kyphoplasty significantly and rapidly reduced pain intensity in cancer patients with vertebral compression fractures. The procedures also significantly decreased the need for opioid pain medication, and functional disabilities related to back and neck pain. Pain palliative improvements and low complication rates were consistent across the various cancer populations and vertebral fractures that were investigated.

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BACKGROUND

The increasing survival in patients with cancer is often accompanied by increasing morbidity, particularly adverse skeletal events such as spinal lesions and fractures that can occur more frequently during the disease process.[1-3] Cancers that spread or metastasize to the spine can result in severe pain, nerve root compression, vertebral fracture, spinal instability, or spinal cord compression.[4] Thirty percent of patients with advanced cancer have been reported to develop spinal metastases, and the rate is higher (70%) in those with cancers of the breast, lung, or prostate.[5] Multiple myeloma, a cancer that typically starts in the bone marrow, also has a substantial rate of spinal involvement causing vertebral fractures.[6,7]

Patients with spinal metastases are often in advanced stages of their disease and have a greatly reduced life expectancy. The median overall survival of patients with spinal metastases presenting to a multidisciplinary cancer treatment centre was less than 1 year, ranging from 8 days to 128 months.[5] The strongest predictor of survival with metastases is the type of primary (first) cancer, with lung cancer having the shortest life expectancy (3.9 months) and breast and renal cancers having the longest (24.2 and 24.5 months, respectively).

Treatment of cancer patients with metastatic disease is complex, requiring a multidisciplinary or integrated care approach.[8-10] Patients with cancer who present with vertebral fractures often have a long and detailed treatment history, including prior medical, surgical, and radiotherapy interventions for their primary cancer.[2,11] Also, many patients receive their first cancer diagnosis when they present with a spinal fracture.[12,13] Treatment decisions for patients with advanced cancer are often based on their general health condition or physical performance status. Care for those with an expected survival of less than 3 months is often considered to be conservative or supportive care.[9]

Untreated vertebral compression fractures can result in a range of morbidities, including acute and chronic pain and spinal deformity (kyphosis, an exaggerated backwards curvature). Spinal cord compression resulting in irreversible neurological symptoms and paraplegia is a serious potential complication of vertebral fractures.[12,14,15] Patients with spinal cord compression also experience a doubling of the time spent in hospital in their last year of life.[14] Pain intensity or the medications used to control pain can cause considerable functional impairment, severely restricting patients' mobility and ability to carry out activities of daily living.[16] This can negatively impact patients' remaining quality of life and impose a significant burden on caregivers.

Objectives of Analysis

The objectives of this analysis were to evaluate the effectiveness and safety of two percutaneous image-guided vertebral augmentation interventions—vertebroplasty or kyphoplasty—for cancer-related vertebral compression fractures and to evaluate their comparative effectiveness with conservative management.

Clinical Need and Target Population

In spinal metastatic disease, vertebral compression fractures commonly occur in the lumbar and thoracic regions of the spine and have been classically defined as a loss of vertebral body height of at least 20%.[17] Fractures can also occur in high-risk cervical areas and sacral regions of the spine, and patients can have complex multilevel fracture patterns involving all of these regions. The diagnosis and management of clinically relevant vertebral compression fractures are based on a clinical examination indicating pain localizing to the level of the fracture or imminent fracture defined on imaging.[18,19]

Health care professionals often initially recommend a range of conservative therapies (e.g., analgesics, physiotherapy, back or neck braces, bed rest) to manage pain in cancer patients with spinal metastatic disease and vertebral fractures. These therapies, however, have limited effectiveness for metastatic bone pain, and the therapies, particularly bed rest and immobilization, carry their own limitations and harms.[20]

Open instrumented surgery (i.e., the use of medical implants such as rods, plates, screws, etc.) can relieve pain and provide stabilization of the spine in cancer patients with metastatic disease; it is considered to be optimal management.[3] However, many of these patients are not surgical candidates because of their medical conditions or poor bone quality. Additionally, because of their short life expectancy, they are not anticipated to benefit from surgery because it involves a lengthy hospitalization and recovery period and interferes with other treatments.

Radiation, in addition to being the initial treatment of many cancers and commonly used adjunctively with spine surgery to decrease the potential for tumour growth, is often used as pain palliative treatment for patients with advanced metastatic cancers.[10] In Ontario in 2013, about 3,700 cancer patients underwent palliative spinal radiotherapy in the 14 regional cancer treatment centres in the province (personal communication, Eric Gutierrez, Program Manager, Radiation Treatment Program, Cancer Care Ontario, February 23, 2014).

Palliative radiotherapy, involving limited or single fractionation (one session) schedules and low doses, is usually intended to relieve pain rather than be ablative (i.e., kill the cancer cells). The treatment has some limitations for patients presenting with painful disabling vertebral fractures as palliative radiotherapy does not fix the spinal instability or vertebral fractures from spinal metastases. Additionally, if patients have already received the maximum tolerable dose, they may not be eligible for further radiation. Patients with these fractures may also be unresponsive to radiotherapy or have a delayed pain response, occurring weeks or months later.

Vertebral augmentation techniques—vertebroplasty or kyphoplasty—are percutaneous (through the skin) image-guided interventions often provided on an outpatient basis and are intended to reduce pain in patients with vertebral compression fractures.[20] Vertebral augmentation may be valuable for patients whose pain is unmanaged by current conservative treatment, with no other treatment options, who have poor functional status and limited life expectancy. Guidelines for the referral and use of vertebral augmentation have been established by the International Society of Interventional Radiology, Standards of Practice Committee[21]:

- *For a patient rendered nonambulatory as a result of pain from a weakened or fractured vertebral body, pain persisting at a level that prevents ambulation despite 24 hours of analgesic therapy;*

- *For a patient with sufficient pain from a weakened or fractured vertebral body that physical therapy is intolerable, pain persisting at that level despite 24 hours of analgesic therapy; or*

- *For any patient with a weakened or fractured vertebral body, unacceptable side effects such excessive sedation, confusion or constipation as a result of the analgesic therapy necessary to reduce pain to a tolerable level.*

The treatment objectives for patients with cancer are closely related to quality of life. Patients experiencing painful conditions have reported preferences for meaningful improvements with their treatments.[22-24] Ideally, they would like to have no pain, but a pain reduction of at least 50% has been reported to be acceptable. For patients with limited life expectancy, decreasing the time spent in emergency rooms or in hospitals is also a priority. Finally, when medical management involving high doses of opioids to control pain is the only option, the side effects of excessive drowsiness or sedation can severely limit interactions with family and friends.[25-27] Therefore, a decreased reliance on these types of medicines is also important.

Vertebral Augmentation Techniques

There are two types of vertebral augmentation procedures, vertebroplasty and kyphoplasty, which are typically provided by interventional radiologists or surgeons. Both of these procedures aim to primarily manage pain and involve the injection of bone cement (polymethylmethacrylate [PMMA]) into the vertebral body.[28] Kyphoplasty also aims to restore the height of the collapsed vertebrae and to correct spinal kyphosis, if present.[29] Kyphoplasty involves the use of an inflatable balloon catheter to create a cavity in which bone cement can be injected, and to attempt to restore the height of the collapsed vertebral body.

Vertebral augmentation procedures are generally performed by interventional radiologists in the angiography suite using conscious sedation and analgesia, or by surgeons in the operating theatre using general anaesthesia. Although vertebroplasty and kyphoplasty can be performed by both specialties, generally interventional radiologists perform vertebroplasty and surgeons perform kyphoplasty. The image guidance for the procedure involves computed tomography (CT) or fluoroscopic guidance to place the needle, and fluoroscopic guidance when injecting the cement.[19]

The access to the vertebral body can be transpedicular or extrapedicular (parapedicular), with a unilateral or bilateral approach depending on how adequately the cement fills the vertebral body. (In the transpedicular approach, the needle enters the vertebral body via the pedicle; in the extrapedicular approach, the needle enters the vertebral body directly.) Various grades of cement viscosity (low or high) are employed, and these vary depending on the operator, fracture pattern, and risk of cement leakage. To avoid procedural complications related to the volume of cement injected, various treatment limits have been suggested; these involve the maximum levels (often three or four) of vertebrae treated per session. In addition, complex patterns of multiple fractures can be treated over several sessions.

Regulatory Status

Health Canada has approved several medical devices for use in vertebral augmentation interventions. The devices and accessory needles, syringes, etc. are classified as Class II devices, and the bone cement products are classified as Class III devices.

DePuy Synthes, owned by Johnson and Johnson Medical Inc. Canada, has Health Canada regulatory approval for the SYNFLATE System (licence no. 91718, issued on July 22, 2013), a Class II device employed in vertebral augmentation interventions. In Ontario, there are about two centres that currently use SYNFLATE devices for kyphoplasty interventions (personal communication, Alex Paton, product manager at DePuy Synthes, May 20, 2015).

Medtronic Canada, which formally acquired Kyphon in 2007, has Health Canada regulatory approval for a range of Class II devices employed in vertebral augmentation: the 1st Generation

KYPHX Osteointroducers and 2nd Generation “One-Step” Osteointroducer Bone Access Devices (licence nos. 24649, issued on January 10, 2003, and 61350, issued on July 8, 2011) and the KYPHON Xpander II Inflatable Bone Tamp (licence no. 86203, issued on May 26, 2011). The Kyphon digital inflation syringe (licence no. 61350, issued on July 8, 2011) enables controlled balloon inflation lift pressure. Cement is implanted via a cement-delivery system (licence no. 85127, issued on February 10, 2011) or a manual bone-filler device (licence no. 24739, issued on May 25, 2009). In Ontario, there are about 14 centres currently employing the Medtronic Kyphon devices for vertebroplasty and kyphoplasty interventions (personal communication, Bruce McTavish, product manager, Balloon Kyphoplasty, Spine and Biologics, Medtronic Canada, May 25, 2015).

Stryker Canada has Health Canada regulatory approval for a Class II inflatable vertebral augmentation system, iVAS (licence no. 83722, issued on August 24, 2010).

Research Questions

What are the safety and effectiveness of vertebral augmentation techniques involving image-guided percutaneous interventions, either vertebroplasty or kyphoplasty, for treatment of cancer-related vertebral fractures?

- In particular what are the treatment safety and effectiveness of vertebral augmentation, either vertebroplasty or kyphoplasty, for cancer-related vertebral compression fractures in controlling pain, decreasing opioid use, improving function and mobility (impaired by pain or by medications used to control pain), decreasing spinal instability, restoring vertebral height, and/or preventing or decreasing kyphosis?
- What are the acceptability, patient satisfaction, and impact of vertebral augmentation interventions on patients’ health-related quality of life?
- What are the comparative safety and effectiveness of vertebral augmentation with conservative care for painful vertebral compression fractures?

METHODS

Literature Search

A literature search was performed on October 14, 2014, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, and EBM Reviews, for studies published from January 1, 2000, to October 2014. (Appendix 1 provides details of the search strategies.) Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. We also examined reference lists for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language full-text publications
- Studies published between January 1, 2000, and October 2014
- Reports including randomized controlled trials (RCTs), systematic reviews, meta-analyses, and observational studies including case reports
- Reports involving vertebral augmentation techniques such as vertebroplasty or kyphoplasty for cancer-related vertebral compression fractures

Exclusion Criteria

- Experimental or animal studies involving evaluations of technology performance
- Clinical reports not involving technical or clinical outcomes
- Studies involving vertebral augmentation techniques not performed percutaneously under imaging guidance
- Clinical studies mainly involving patients with osteoporotic or traumatic vertebral compression fracture etiologies
- Studies involving vertebral augmentation techniques performed simultaneously with spinal surgical interventions
- Narrative reviews and opinions or commentaries

Outcomes of Interest

- Patient satisfaction
- Pain intensity reduction, time course, and durability
- Fatigue, sleep disturbances, depression, anxiety
- Neurological symptoms or neurological status
- Safety, including procedural and post-procedural complications
- Degree of vertebral height restoration or kyphosis correction
- Mobility, activities of daily living, and self-care
- Analgesic drug use
- Disability related to back pain
- Health-related quality of life

Quality of Evidence

The quality of the body of evidence for each outcome was examined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria.[30] The overall quality was determined to be high, moderate, low, or very low using a step-wise, structural methodology.

Study design was the first consideration; the starting assumption was that RCTs are high quality, whereas observational studies are low quality. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. Finally, three main factors that may raise the quality of evidence were considered: the large magnitude of effect, the dose response gradient, and any residual confounding factors. For more detailed information, please refer to the latest series of GRADE articles.[31]

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	High confidence in the effect estimate—the true effect lies close to the estimate of the effect
Moderate	Moderate confidence in the effect estimate—the true effect is likely to be close to the estimate of the effect, but may be substantially different
Low	Low confidence in the effect estimate—the true effect may be substantially different from the estimate of the effect
Very Low	Very low confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of the effect

RESULTS

The database search was performed on October 14, 2014, and yielded 3,391 citations published between January 1, 2000, and October 2014. Figure 1 shows the breakdown of the exclusions of citations from the review.

The evidence search on vertebral augmentation interventions for cancer-related vertebral compression fractures identified relevant information on safety and effectiveness from systematic reviews, case reports, observational studies, and RCTs. The evidence base comprising all the clinical reports and studies evaluated in this review is outlined in Appendix 3.

The organization and analysis of this information are detailed in the following four sections:

- Section A. Systematic Reviews of Vertebral Augmentations
- Section B. Effectiveness of Vertebral Augmentation for Cancer-Related Vertebral Compression Fractures
- Section C. Effectiveness of Vertebral Augmentation for Special or High-Risk Cancer-Related Vertebral Compression Fractures
- Section D. Safety of Vertebral Augmentation in Cancer-Related Vertebral Compression Fractures

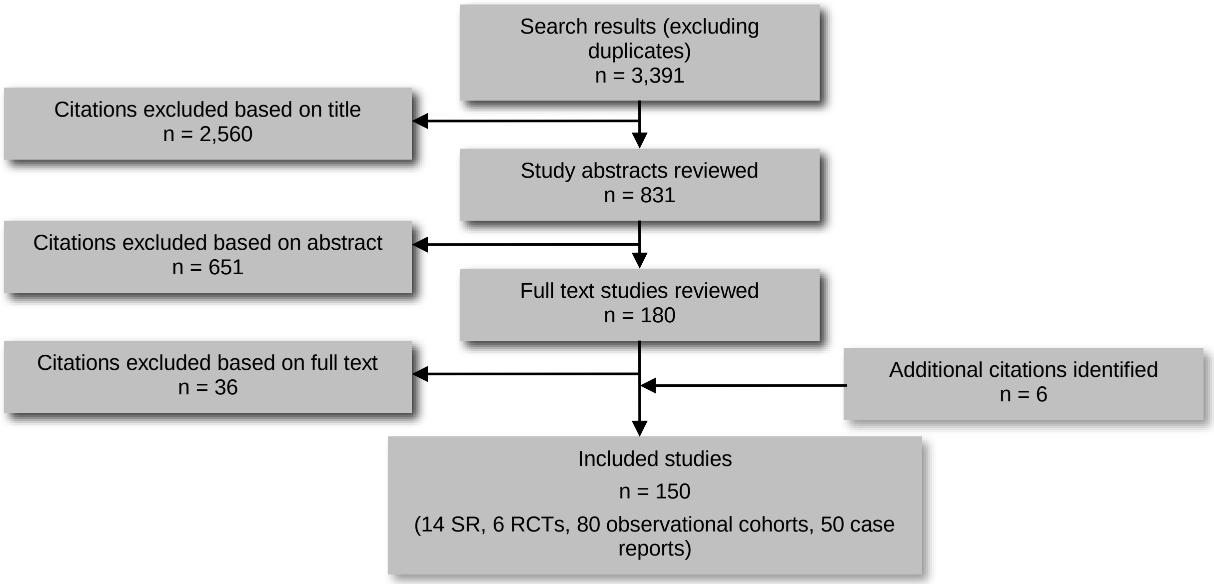

Figure 1: Citation Flow Chart

Section A. Systematic Reviews of Vertebral Augmentations

We identified 14 systematic reviews on vertebral augmentation for vertebral compression fractures. Table 1 presents a summary of the characteristics of these reviews.

We found that, for the purposes of this review, these systematic reviews were limited in several ways. First, the review objective of some systematic reviews involved only one vertebral augmentation technique for vertebral compression fractures—either vertebroplasty (one systematic review) or kyphoplasty (two systematic reviews). Second, the inclusion criteria for eight systematic reviews involved study populations having any pathology or etiology for the vertebral compression fractures. The inclusion of osteoporotic fractures, which occur more commonly than cancer-related vertebral compression fractures and involve a completely different disease process, would complicate our review process for cancer-related vertebral compression fractures.

Several systematic reviews did include cancer-related vertebral compression fractures as their review objective. However, one of these reviews[32] included only studies that compared vertebroplasty with kyphoplasty for cancer-related vertebral compression fractures. Two other systematic reviews were relevant for our review, including both vertebroplasty and kyphoplasty for cancer-related vertebral compression fractures, but were also limited. The review by Mendel et al[33] included both vertebroplasty or kyphoplasty for cancer-related vertebral compression fractures, but the search period for relevant studies was up to 2008 and only 50 reports were reviewed. The report by Khan et al[34] involved vertebroplasty or kyphoplasty interventions but only in cancer patients with multiple myeloma. That review involved a search strategy up to 2012, and 23 reports were reviewed. We used these systematic reviews to identify any additional original studies not identified in our search.

Table 1: Summary of Systematic Reviews of Vertebral Augmentation for Cancer-Related Vertebral Compression Fractures

Author, Year	Review Type	Vertebral Augmentation Intervention	Vertebral Fracture Etiology	Review Period	Reports Reviewed/ Citations Identified	Review Objective
Bouza et al, 2006[35]	SR and MA	KP	Any pathology	Inception to October 2004	26/79	To evaluate the safety and effectiveness of KP for VCFs
Bouza et al, 2009[36]	SR and MA	KP	Malignant: metastases and multiple myeloma	2003 to September 2008	11/208	To evaluate the safety and effectiveness of KP for spinal fractures in cancer patients
Chew et al, 2011[37]	SR	VP	Malignant: metastases and multiple myeloma	Inception to April 2010	30/760	To evaluate the efficacy and complications of VP in spinal metastases and multiple myeloma
Eck et al, 2008[38]	SR and MA	VP or KP	Any pathology	Inception to May 15, 2006	168/1,036	To compare pain relief and complication rates between VP and KP
Khan et al, 2014[34]	SR and MA	VP or KP	Multiple myeloma	Inception to June 12, 2012	23/154	To evaluate changes in pain, disability, and analgesic use with vertebral augmentation in multiple myeloma patients
Krueger et al, 2009[39]	SR	VP or KP	Any pathology	Inception to October 2008	387/1,222	To evaluate the incidence and management of pulmonary cement embolism following percutaneous VP or KP
Lee et al, 2009[40]	SR and MA	VP or KP	Any pathology	Inception to December 2006	121/NR	To compare complication rates between VP and KP
McGirt et al, 2009[41]	SR	VP or KP	Any pathology	1980 to 2008	127/NR	To evaluate outcomes following VP and KP and rate the evidence
Mendel et al, 2009[33]	SR	VP or KP or embolization	Malignant	To December 15, 2008	50/1,665	To review the safety and effectiveness of VP, KP, or embolization in the treatment of spinal tumours and make recommendations based on the literature and consensus expert opinion
Doidge et al, 2011[42]	SR	VP or KP	Any pathology	1987 to August 2010	183/9,893	To review the safety, effectiveness, and cost-effectiveness of VP and KP for VCFs
Nussbaum et al, 2004[43]	SR	VP or KP	Any pathology	1999 to June 27, 2003	58 reports	To review the complications reported for VP or KP in the FDA Manufacturer and User Facility Device Experience database (MAUDE)
Ehteshami Rad et al, 2012[44]	SR and MA	VP or KP	Any pathology	Up to March 2010	17/1,646	To review the association between the duration of pre-operative pain and pain improvement in vertebral augmentation
Schroeder et al, 2011[32]	SR	VP or KP	Tumour-related	Up to June 2011	2/36	To compare cement augmentation via VP or KP for spinal fractures caused by tumours, with each other or with other treatment methods

Author, Year	Review Type	Vertebral Augmentation Intervention	Vertebral Fracture Etiology	Review Period	Reports Reviewed/ Citations Identified	Review Objective
Taylor et al, 2006[45], 2007[46]	SR and MA	VP or KP	Any pathology	1983 to March 2004	76/487	To evaluate the safety and effectiveness of KP in patients with VCFs, update the previous review on safety and effectiveness of VP, and examine prognostic factors predicting outcome following the procedures

Abbreviations: FDA, United States Food and Drug Administration; KP, kyphoplasty; MA, meta-analysis; NR, not reported; SR, systematic review; VCF, vertebral compression fracture; VP, vertebroplasty.

Section B. Effectiveness of Vertebral Augmentation for Cancer-Related Vertebral Compression Fractures

The primary studies evaluating the effectiveness of vertebral augmentation interventions in cancer-related vertebral compression fractures were categorized by the type of vertebral augmentation intervention and by the cancer study population employed (Table 2). The vertebral augmentation interventions included vertebroplasty, kyphoplasty, or a combination of the procedures. The use of adjunctive interventions to effect local tumour control was also noted in the grouping of the studies. The primary tumour grouping of the included study populations involved mixed primary metastatic cancers, multiple myeloma, and vertebral hemangiomas. Four studies included vertebral fractures from a single primary metastatic cancer—two involved breast cancer,[47,48] one involved lung cancer,[49] and one involved thyroid cancer.[50] All studies involved vertebroplasty, and they are included in the totals in Table 2 for vertebroplasty of the mixed primary metastatic cancer group, owing to their small numbers.

We also categorized the studies by the use of vertebroplasty or kyphoplasty for a range of special or high-risk fractures. The risk conditions involved vertebral augmentation interventions for fractures such as those with spinal cord involvement or posterior vertebral wall compromise. Also detailed as risk fractures were cervical fractures; because of their location in the upper vertebrae, near major vascular and neurological structures, they required modifications to the vertebral augmentation techniques and specialized expertise. Sacral fractures that occurred in conjunction with higher-level vertebral fractures often presented with diffuse lesions and complex fracture patterns that were technically challenging. Symptomatic vertebral hemangiomas, because of their highly vascular nature, often required multiple staged interventions to not only manage the fracture but also limit the risk of bleeding or hemorrhage.

The primary clinical studies evaluating the treatment effectiveness of vertebroplasty or kyphoplasty, with or without adjunctive local tumour control interventions, are summarized and discussed below for average-risk vertebral compression fractures, usually in the lumbar or thoracic region. Section C discusses these interventions in high-risk or special vertebral compression fractures.

Table 2: Clinical Reports Evaluating Vertebral Augmentation Effectiveness by Technique and Primary Cancer Etiology

Intervention(s)	Primary Cancer Populations		Special or High-Risk Vertebral Fractures				Total
	Multiple Myeloma	Mixed Spinal Metastatic Cancers	Fractures With Spinal Cord Involvement or Vertebral Wall Compromise	Cervical Fractures	Sacral Fractures	Vertebral Hemangiomas	
Vertebroplasty	12 reports (447 patients)	14 reports (639 patients)	10 reports (418 patients)	9 reports (112 patients)	6 reports (156 patients)	6 reports (72 patients)	57 reports (1,844 patients)
Vertebroplasty and adjunctive local tumour control intervention	3 reports (115 patients)	11 reports (411 patients)	4 reports (116 patients)	1 report (1 patient)	2 reports (58 patients)	—	21 reports (701 patients)
Kyphoplasty	5 reports (110 patients)	6 reports (308 patients)	3 reports (46 patients)	1 report (2 patients)	—	4 reports (10 patients)	19 reports (476 patients)
Kyphoplasty and adjunctive local tumour control intervention	1 report (35 patients)	3 reports (85 patients)	—	—	—	—	4 reports (120 patients)
Kyphoplasty, vertebroplasty, and adjunctive local tumour control intervention	4 reports (488 patients)	4 reports (586 patients)	2 reports (20 patients)	—	—	—	10 reports (1,094 patients)
Total	25 reports (1,195 patients)	38 reports (2,029 patients)	19 reports (600 patients)	11 reports (115 patients)	8 reports (214 patients)	10 reports (82 patients)	111 reports (4,235 patients)

The clinical outcomes for vertebral augmentation interventions evaluated in the following sections of the review included pain intensity, analgesic use, physical performance (measured on scales of mobility and self-care), pain-related disability, and patient satisfaction and health-related quality of life. The radiological morphometric outcome measurements involved factors such as loss of vertebral body height and kyphosis. A brief description on the measurement and interpretation of these outcomes is provided in Appendix 2.

The subsections for the effectiveness outcome review of vertebral augmentation for cancer-related vertebral compression fractures are these: B1. Vertebroplasty; B2. Vertebroplasty and Adjunctive Local Tumour Control Interventions; B3. Kyphoplasty; B4. Kyphoplasty and Adjunctive Local Tumour Control Interventions; and B5. Kyphoplasty, Vertebroplasty, and/or Adjunctive Local Tumour Control Interventions.

B1. Effectiveness of Vertebroplasty

A summary of the characteristics of clinical studies evaluating the effectiveness of vertebroplasty for cancer-related vertebral compression fractures is outlined in Table 3. All but two studies involved experiences from single centres located in diverse health care jurisdictions. There were 12 reports (447 patients) on vertebroplasty for multiple myeloma–related vertebral compression fractures involving operators from interventional radiology (n = 8) and surgery (n = 4). There were 14 reports (639 patients) on vertebroplasty for metastatic cancer–related vertebral compression fractures involving operators from interventional radiology (n = 10), surgery (n = 3), and anaesthesiology (n = 1). The metastatic cancers resulting in vertebral compression fractures were a diverse group except for three studies, with two focusing on only breast cancer[47,48] and one on only thyroid cancer.[50]

Table 4 details the various outcome measures of treatment effectiveness of vertebroplasty for cancer-related vertebral compression fractures grouped by etiology of the primary cancer multiple myeloma and by mixed metastatic cancers. The clinical outcomes investigated in the studies included cancer pain intensity (visual analogue scale [VAS] scores, global subjective improvement ratings), analgesic use, mobility status and use of orthopedic walking aids, general physical performance status measures (Barthel Index, Karnofsky Performance Scale [KPS], Eastern Cooperative Oncology Group [ECOG] scale), pain-related disability (Oswestry Disability Index, Roland Morris Disability Questionnaire), and health-related quality of life measures (Short-Form Health Survey). Three studies reported on patient satisfaction with their treatment.[48,51,52]

Pain intensity. Almost all of the clinical studies reported mean VAS values for back pain intensity at baseline and post-procedurally, often within 24 or 48 hours, due to the expected rapidity of analgesia response. In all of the clinical studies, baseline mean VAS values for cancer pain, in both the multiple myeloma and mixed metastatic cancer groups, were in the high pain intensity levels (VAS ≥ 7.0). Post-procedurally the mean VAS values were reduced in all cases to mild pain intensity levels (VAS < 4.0), representing both statistically and clinically significant reductions.

Several studies reported pain intensity improvements in statements, allowing for an estimation of responder status (i.e., individual response to treatment). In the multiple myeloma group, “non-responder” was estimated variably in the studies, ranging from 7% to 33%. The estimates on non-response were based on different thresholds and included 7% with no change in pain score,[53] 8% with no change or increased pain,[54] 8% not having at least a 70% pain reduction,[51] 21% having no change or increased pain,[52] 23% not having at least a 50% pain reduction,[55] and

33% not having at least a 50% pain reduction.[56] In the mixed metastatic cancer group, non-responder status was estimated from three studies and ranged from 16% to 21%. The estimates included 16% with a VAS change of less than 3 points,[57] 20% with a less than excellent or good analgesic effect,[58] and 21% with no change or increased pain.[48]

Analgesic use. The reduction in pain intensity following vertebroplasty was also accompanied by a change in analgesics, particularly a reduction in opioids, either their discontinuation or a dose reduction.

In the multiple myeloma groups, three studies reported on patients discontinuing pain medications after vertebral augmentation: 51% (54/106),[59] 36% (10/29),[53] and 64% (7/11).[60] Two studies reported both discontinuation and reduction in analgesic use, respectively: 25% (6/24) and 75% (18/24) by Chen et al,[56] and 43% (3/7) and 43% (3/7) by Diamond et al.[61] Four studies reported on opioid use in myeloma patients before and after vertebroplasty.[53,54,59,62] In these studies, at baseline pain intensity was commonly (although variably) managed by opioids: 24% (7/29),[53] 56% (59/106),[59] 85% (56/66),[54] and 89% (25/28).[62]

After vertebroplasty, a discontinuation of opioid use, a decreased dose, or a change from intravenous or transdermal delivery from baseline use was reported for 89% (53/59),[59] 43% (3/7),[53] 64% (36/56),[54] and 88% (22/25).[62]

In the metastatic cancer groups, the change in analgesic use was reported less often and, when reported, involved a change in analgesic class score or in the number of analgesics taken. Trumm et al[48,52] provided the best comparison in overall analgesic use after vertebroplasty in patients with multiple myeloma[52] or metastatic cancer.[48] For the myeloma group and the metastatic cancer group (evaluating only patients with breast cancer), the analgesic changes were as follows: 64% (18/28) and 76% (32/42), respectively, for reduced analgesic use (stopping, reducing opioids, or replacing opioid with non-opioids); 21% (6/28) and 14% (6/42), respectively, for no change in analgesics; and 14% (4/28) and 10% (4/42), respectively, for increased analgesic use or a change up to opioids.

Pain-related disability and physical performance. Physical functioning (mobility), physical performance measures (KPS, ECOG scale, Barthel Index), or pain-related disability measures (Oswestry Disability Index or Roland Morris Disability Questionnaire) were evaluated in seven vertebroplasty studies involving patients with myeloma and three studies involving patients with metastatic cancer.

For patients with multiple myeloma, validated outcome measures of pain-related disability were reported in two studies[54,59]; both showed significant improvement, from high to low levels of disability. In the Anselmetti et al study,[59] the median Oswestry Disability Index score for 106 patients was significantly reduced from baseline to post-vertebroplasty (82% to 7%, $P < .001$). In the McDonald et al study,[54] the median Roland Morris Disability Questionnaire (RMDQ) score improvement for 66 patients was 11 points (95% confidence interval [CI] 7.7–14.3), with improvement persisting at the 1-year follow-up. Physical performance, ECOG scale scores,[51,62] and KPS scores[60] were also significantly improved after vertebroplasty. In addition, the impact of vertebroplasty on mobility was evidenced by the number of patients reported as no longer needing orthopedic braces or wheelchairs, no longer bedridden, and regaining mobility.[53,54,59,62]

For the metastatic cancer groups, significant improvements in RMDQ pain-related disability scores were reported in two studies.[63,64] In the Chew et al study[63] involving 128 cancer patients, mean RMDQ scores were significantly improved ($P < .001$) at 6 weeks following vertebroplasty, although only a minority of patients completed the questionnaire. The report by McDonald et al[64] involved an extensive analysis of RMDQ outcomes across multiple operators at the same site—most operators were experienced interventional neuroradiologists prior to their vertebroplasty training. The study also involved patients with diverse vertebral fracture etiologies, but a multivariate analysis showed that outcomes were independent of etiology. There was little variation in RMDQ baseline scores across operators (18.1 ± 3.3 to 20.2 ± 3.9) or in the significantly reduced RMDQ scores at 1 week post-vertebroplasty, ranging from 9.9 ± 5.9 to 11.1 ± 6.0.

Health-related quality of life and patient satisfaction. Health-related quality of life, evaluated using the Short-Form Health Survey, was reported in one study for patients with multiple myeloma.[56] The mean physical component summary score of the survey improved from 22.1 (range 20–25) at baseline to 41.8 (range 38–45), with scores remaining improved at the 1-year follow-up.

Patient satisfaction with the vertebroplasty procedure was reported in three studies.[48,51,52] In the Ramos et al study,[51] 63% (7/11) of patients reported being very satisfied. Trumm et al[48,52] reported satisfaction levels (satisfied, unsatisfied) for patients with multiple myeloma (64% [18/39] satisfied) and those with a mixed cancer etiology (62% [26/42] satisfied).[48,52] The dissatisfaction expressed regarding the procedure that was performed under conscious sedation involved the prolonged time in the prone position and discomfort during the needle insertion.

Table 3: Summary of Clinical Studies Evaluating the Effectiveness of Vertebroplasty for Cancer-Related Vertebral Compression Fractures

Author, Year Country	Report Type	Study Recruitment Period	Patients, N (F, M) Age, Mean ± SD (Range)[a]	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Multiple Myeloma as Primary Malignancy of Spinal Metastases					
Anselmetti et al, 2012[59] Italy	Single-site prospective study, consecutive cases	2002 to 2009	123 patients (58 F, 65 M) 70 years (35–92)	Interventional radiology VP in 124 sessions at 528 VB levels (C, T, L)	Treatment safety and efficacy, long-term Mean 28.2 ± 12.1 months
Bosnjakovic et al, 2009[53] Serbia	Single-site retrospective study	June 2002 to December 2006	29 patients (18 F, 11 M) 63 years (58–79)	Interventional radiology VP at 55 VB levels (17 T, 38 L)	Treatment effectiveness 12 months
Chen et al, 2012[56] China	Single-site retrospective study	August 2003 to July 2008	24 patients (20 F, 4 M) 67 years (54–81)	Orthopaedic surgery VP at 36 VB levels	Treatment safety and effectiveness 12 months
Diamond et al, 2004[61] Australia	Case series	2002 to 2003	7 patients (4 F, 3 M) Range 58–78 years	Interventional radiology VP at 14 VB levels (T, L); 1 had 7 VB levels	Treatment effectiveness for fracture and deformity 6 weeks
Garland et al, 2011[55] United Kingdom	Single-site retrospective study	2004 to 2009	26 patients (10 F, 16 M) 59.3 years (42–76)	Interventional radiology VP	Treatment safety and effectiveness of VP Mean 19 months (range 20 days to 42 months)
Masala et al, 2008[65] Italy	Multicentre retrospective study	February 2003 to December 2005	64 patients (30 F, 34 M) 71.4 ± 9.6 years	Interventional radiology VP at 198 VB levels (93 T, 105 L)	Treatment safety and effectiveness of VP for multiple-level myelomatous spinal fractures 6 months
McDonald et al, 2008[54] United States	Single-site retrospective registry review	October 2000 to March 2007	67 patients (30 F, 37 M) 66.2 years	Interventional radiology VP at 114 VB levels	Treatment effectiveness of VP in the myelomatous population 12 months
Ramos et al, 2006[51] Spain	Single-site prospective study, consecutive cases	June 2001 to March 2004	12 patients (3 F, 9 M) Multiple myeloma or plasmacytomas 66 years (54–80)	Orthopaedic surgery and radiology VP at 19 VB levels (T9 to L4)	Treatment safety and effectiveness of VP To 3 years
Simony et al, 2014[66] Denmark	Single-site retrospective study, consecutive cases	2004 to 2010	17 patients (7 F, 10 M) 62.5 years (46–76)	Surgery VP at 64 VB levels (T6 to S2)	Treatment safety and pain-reducing effectiveness 3 months

Author, Year Country	Report Type	Study Recruitment Period	Patients, N (F, M) Age, Mean ± SD (Range)[a]	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Tancioni et al, 2010[60] Italy	Single-site retrospective study	November 2003 to December 2005	11 patients (5 F, 6 M) Multiple myeloma stages IIA (n = 2), IIIA (n = 8), IIIB (n = 1) Median 56 years (45–76)	Neurosurgery VP in 14 sessions at 28 VB levels (C, T, L)	Treatment safety and effectiveness of VP for multiple myeloma with painful vertebral body in any disease stage
Tran Thang et al, 2008[62] Switzerland	Single-site retrospective study	1996 to 2002	28 patients (11 F, 17 M) Multiple myeloma stages I (n = 3), II (n = 4), III (n = 21) Median 65 years (40–89)	Interventional radiology VP in 33 sessions for 75 fractures and at 117 VB levels (57 T, 59 L, 1 S) VP performed at one level (n = 7), more than two levels (n = 21)	Treatment effectiveness of VP for painful spinal fractures related to multiple myeloma Median 41 months (range 3–81 months)
Trumm et al, 2012[52] Germany	Single-site retrospective study	December 2001 to August 2008	39 patients (17 F, 22 M) 65 ± 7 years	Interventional radiology VP in 44 sessions at 67 VB levels (3 C, 32 T, 27 L, 5 S)	Technical success and safety and treatment effectiveness of VP with primary CT-fluoroscopic guidance for multiple myeloma with spinal compression fractures 9 months
Mixed Cancers as Primary Malignancies for Spinal Metastases					
Burton et al, 2005[67] United States	Case series	NR	3 patients (2 F, 1 M) *Primary malignancies* Breast (n = 1), lung (n = 1), parotid gland (n = 1) 64 years (60–67)	Anaesthesiology VP at 6 VB levels (5 L, 1 T)	Treatment effectiveness of VP Until death
Calmels et al, 2007[58] France	Single-site retrospective study	1996 to 2002	52 patients (46 F, 6 M) *Primary malignancies* Breast (n = 40), prostate (n = 3), lung (n = 3), other (n = 6) Age NR	Interventional neuroradiology VP in 59 sessions at 103 VB levels	Treatment effectiveness: analgesic efficacy of blastic or mixed spinal metastases Mean 17 months, up to 5 years
Chen et al, 2011[68] China	Case reports	NR	4 patients (1 F, 3 M) *Primary malignancies* Lung (n = 2), prostate (n = 1), pancreas (n = 1) Range 47–67 years	Interventional radiology VP at 4 VB levels (T or L)	Treatment safety and effectiveness of osteoblastic spinal lesions 3 months

Author, Year Country	Report Type	Study Recruitment Period	Patients, N (F, M) Age, Mean ± SD (Range)[a]	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Chew et al, 2011[63] Scotland	Single-site prospective study, consecutive cases	June 2001 to June 2010	128 patients (60 F, 68 M) *Primary malignancies* Multiple myeloma (n = 41), breast (n = 22), lung (n = 16), lymphoma (n = 11), renal (n = 8), prostate (n = 5), other (n = 25) 60 years (31–88)	Interventional radiology VP in 158 sessions at 264 VB levels	Treatment safety and effectiveness of VP for multiple myeloma and spinal metastases Median 3 years (range 1–9 years)
Farrokhi et al, 2012[69] Iran	Single-site prospective study	NR	25 patients (14 F, 11 M) *Primary malignancies* Breast (n = 14), lung (n = 9), prostate (n = 2) 53.5 years (37–70)	Surgery VP at T3 to L4	Treatment palliative effectiveness
Kim et al, 2002[70] United States	Single site comparative retrospective cohort study, consecutive cases	January 1999 to September 2000	*Unipediculate* 41 patients (26 F, 15 M) 75.9 ± 7.9 years *Bipediculate* 24 patients (15 F, 9 M) 75.0 ± 7.1 years	Interventional radiology *Unipediculate* VP at 57 VB levels (8 T6 to T8; 16 T9 to T12; 22 L1 to L2; 11 L3 to L5) *Bipediculate* VP at 18 VB levels (1 T8, 9 T9 to T12; 4 L1 to L2; 4 L3 to L5)	Treatment safety and effectiveness of unilateral vs. bilateral transpedicular VP 6 weeks
Kobayashi et al, 2009[71] Japan	Multicentre prospective study	February 2003 to May 2006	33 patients (17 F, 16 M) *Primary malignancies* Lung (n = 7), breast (n = 7), colorectal (n = 7), liver (n = 4), myeloma (n = 3), other (n = 5) 62 years (37–87)	Interventional radiology VP at 42 VB levels (18 T, 24 L)	Treatment safety and effectiveness of VP for cancer-related vertebral fractures 1 month
Kushchayev et al, 2010[50] United States	Case reports	NR	2 patients (2 M) *Primary malignancy* Thyroid cancer (n = 2) 63-year-old and 60-year-old	Neurosurgery Case 1: VP at L5 Case 2: VP at L2 and L4, followed by transpedicular fixation at L1 to L3	Treatment effectiveness of VP for spinal metastatic thyroid cancer Until death
Lee et al, 2009[72] United Kingdom	Single-site retrospective study	2004 to 2008	19 patients (11 F, 8 M) *Primary malignancies* Breast (n = 8), prostate (n = 4), lung (n = 2), renal (n = 2), other (n = 3) 70 years (44–89)	Interventional radiology VP at 34 VB levels	Treatment effectiveness of VP and predictive factors Median 12 months (range 3–38 months)

Author, Year Country	Report Type	Study Recruitment Period	Patients, N (F, M) Age, Mean ± SD (Range)[a]	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
McDonald et al, 2009[64] United States	Single-site prospective study	January 1999 to May 2007	128 of 841 patients *Primary malignancies* Multiple myeloma (n = 67), metastatic cancers (n = 61) Age NR	Interventional neuroradiology VP	Treatment safety and effectiveness of VP by operator experience 12 months
Mikami et al, 2011[73] Japan	Single-site retrospective study	February 2002 to March 2008	69 patients (34 F, 35 M) *Primary malignancies* Breast (n = 12), lung (n = 8), prostate (n = 7), colon (n = 7) uterus (n = 5), liver (n = 5), kidney (n = 3), pancreas (n = 3), other (n = 19) 65.1 years (48–89)	Interventional radiology VP at 141 VB levels (47 T, 77 L, 17 S)	Treatment effectiveness of VP for vertebral metastases 6 months; 18 patients died within 6 months
Murphy et al, 2007[47] United States	Case report	NR	1 patient (F) *Primary malignancy* Breast 41-year-old	Interventional radiology VP at 1 VB level (T10)	Effectiveness of VP for vertebral osteoblastic metastases 3 years
Trumm et al, 2008[48] Germany	Single-site retrospective study	January 2003 to January 2007	53 patients (52 F, 1 M) *Primary malignancies* Breast (n = 53) 62 ± 13 years	Interventional radiology VP in 62 sessions at 86 VB levels (9 C, 55 T, 21 L, 1 S) VP performed at one level (n = 34), two levels (n = 27), three levels (n = 1)	Treatment safety and effectiveness of CT-fluoroscopic guided VP in osteolytic breast cancer metastases Mean 9.2 months; 4 patients died within 6 months
Tseng et al, 2008[57] China	Single-site retrospective study	January 2002 to December 2006	57 patients (32 F, 25 M) *Primary malignancies* Lung (n = 19), colon (n = 9), urinary tract (n = 8), gastrointestinal tract (n = 4), prostate (n = 4), thyroid (n = 3), breast (n = 3), other (n = 7) 65.2 years (40–86)	Neurosurgery VP at 78 VB levels (1 C, 33 T, 44 L) Vertebral fracture level (Genant) Grade 0 (n = 5), Grade 1 (n = 22), Grade 2 (n = 39), Grade 3 (n = 12)	Treatment effectiveness in reducing opioid drug use after VP for painful metastatic spine tumours Mean 24.3 months

Abbreviations: C, cervical; CT, computed tomography; F, female; L, lumbar; M, male; NR, not reported; S, sacral; SD, standard deviation; T, thoracic; VB, vertebral body; VP, vertebroplasty.
[a]Unless otherwise indicated.
[b]If reported in study.

Table 4: Clinical Outcomes in Studies Evaluating the Effectiveness of Vertebroplasty for Cancer-Related Vertebral Compression Fractures

Author, Year Country	Primary Malignancy Patients, N	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Multiple Myeloma as Primary Malignancy of Spinal Metastases					
Anselmetti et al, 2012[59] Italy	Multiple myeloma 106 patients	*Baseline* Median 9.0 (4–10) *Post-intervention (48 hours)* Median 0.01 (0–9), *P* < .001	*1 (no analgesic)* Pre-VP 0, post-VP 54 *2 (NSAIDs)* Pre-VP 47, post-VP 46 *3 (oral opioids)* Pre-VP 16, post-VP 3 *4 (transdermal/IV opioids)* Pre-VP 43, post-VP 3 *P* < .001	Orthopaedic brace *Baseline* No 25, Yes 81 *Post-intervention* No 95, Yes 11 *P* < .001	ODI, median (range) *Baseline* 82% (36%–89%) *Post-intervention* 7% (0%–82%), *P* < .001
Bosnjakovic et al, 2009[53] Serbia	Multiple myeloma 29 patients	*Baseline* 7.8 *Post-intervention* 2.3; remained low until 12 months *Pain status at 1 week* No pain: 10 Significant reduction: 17 No change: 2	*1 (no analgesic)* Pre-VP 1, post-VP 10 *2 (NSAIDs)* Pre-VP 21, post-VP 17 *3 (oral opioids)* Pre-VP 3, post-VP 1 *4 (transdermal/IV opioids)* Pre-VP 4, post-VP 3	*Normal, no pain* Pre-VP 1, post-VP 10 *Normal, with pain* Pre-VP 2, post-VP 12 *Limited, with pain* Pre-VP 4, post-VP 5 *Wheelchair* Pre-VP 19, post-VP 1 *Bedridden* Pre-VP 3, post-VP 1	NR
Chen et al, 2012[56] China	Multiple myeloma 24 patients	*Baseline* 9.0 (7–10) *Post-intervention* 24 hours: 3.8 (1–6); 16 reported pain decreased by 50% or more 3 months: 3.5 1 year: 4.7	*Baseline* NR *Post-intervention* Within 24 hours, 6 discontinued analgesics and the remaining 18 reduced analgesics by more than half	NR	SF-36 PCS, mean (range) *Baseline* 22.1 (20–25) *Post-intervention* 24 hours: 41.8 (38–45) 3 months: 40.7 (35–45) 1 year: 41.4 (38–45)
Diamond et al, 2004[61] Australia	Multiple myeloma 7 patients	NR	*Baseline* NR *Post-intervention* 3 patients ceased all analgesics; 3 reduced analgesics by > 50% within 24 hours; 1 patient with ongoing pain had resolution with a facet joint steroid injection	PDI score (0–25),[b] mean (95% CI) *Baseline* 19.0 (13.5–24.5) *Post-intervention (6 weeks)* 4.0 (0.4–7.6), *P* < .002	BI, mean (95% CI) *Baseline* 11.9 (7.6–16.1) *Post-intervention (6 weeks)* 18.7 (16.7–20.7), *P* < .002

Author, Year Country	Primary Malignancy Patients, N	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Garland et al, 2011[55] United Kingdom	Multiple myeloma 26 patients	*Baseline* Pain rating mild n = 0, moderate n = 9, severe n = 17 *Post-intervention* 77% (20/26) reported pain reduction; 7/9 moderate and 13/17 severe reported pain reduction	*Baseline* NR *Post-intervention* 58% (15/26) were able to reduce systemic analgesics; 9 stopped all forms of opioids, and others reduced doses by 30%–75%	NR	NR
Masala et al, 2008[65] Italy	Multiple myeloma 64 patients	*Baseline* 8.04 ± 1.4 *Post-intervention* 1 month: 1.82 ± 1.84 6 months: 1.92 ± 1.68 *P* < .01	NR	NR	NR
McDonald et al, 2008[54] United States	Multiple myeloma 67 patients	*Baseline* VAS (at rest): 3.9 ± 0.65 VAS (activity): 8.5 ± 0.35 *Post-intervention* VAS (at rest) decreased at 48 hours (*P* < .01). At 1 week, VAS had a median improvement of 2.7 points (25%, 95% CI 1.7 to –3.7) and remained improved at 6 months (*P* < .01) and at 1 year (*P* = .03) VAS (activity) at 1 week had a median improvement of 5.3 points (48%, 95% CI –4.2 to –6.4) Subjective global pain improvement rating at 24 hours (at rest/ activity): Complete resolution 22 (45%) /11 (22%) Significant resolution 18 (37%) / 33 (67%) No change 8 (16%) / 4 (8%) Increased pain 1 (2%) / 1 (2%)	*Baseline* 56 (84%) relied on narcotics for pain management *Post-intervention (1 week)* Discontinued opioid use: 9 (16%) Decreased opioid use: 27 (49%) No change in opioid use: 16 (29%) Increased opioid use: 3 (5%)	*Baseline* Walk > 1 block without need to rest or lie down: 23 (34%) Walk < 1 block: 21 (31%) Restricted movement, often confined to bed: 13 (19%) Complete restriction to bed: 6 (9%) *Post-intervention* 1 week post-VP, 47 (70%) reported some improvement in mobility and 13 (19%) no improvement in mobility	RMDQ, mean ± SD *Baseline* 19.5 ± 3.44 *Post-intervention (1 week)* Median improvement of 11 points (95% CI –7.7 to –14.3), *P* < .0001 Improvement persisted at 6 months (*P* < .0001) and 1 year (*P* < .01)

Author, Year Country	Primary Malignancy Patients, N	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Ramos et al, 2006[51] Spain	Multiple myeloma 12 patients	*Baseline* 7.5 (5–10) *Post-intervention* 24 hours: 3.7 (0–6), *P* < .001 At 3 months, 92% (11/12) showed ≥ 75% pain reduction; improvements remained stable until 3 years	NR	ECOG scale, mean (range) 0 = asymptomatic 1 = symptomatic but fully ambulatory 2 = symptomatic and in bed < 50% of the day 3 = symptomatic and in bed > 50% of day 4 = bedridden) *Baseline* 3.1 (1–4) *Post-intervention (48 hours)* 2.5 (1–4), *P* = .002 *Change in scale value (pre to post)* 0: n = 0 to 0 1: n = 1 to 12 2: n = 2 to 5 3: n = 4 to 5 4: n = 5 to 1	*Post-intervention* Patient satisfaction with procedure at study end: 63% were very satisfied and 37% were just satisfied
Simony et al, 2014[66] Denmark	Multiple myeloma 17 patients	*Baseline* 7.7 (6.9–8.3) *Post-intervention (3 months)* 3.4 (2.2–4.4), *P* < .005	NR	NR	NR
Tancioni et al, 2010[60] Italy	Multiple myeloma 11 patients	*Baseline* Median 7.0 *Post-intervention (24 hours)* Median 2.0	*Baseline* NR *Post-intervention (2 weeks)* –7 patients without analgesics	KPS, median (range) *Baseline* 50 (30–80); 8 needed orthopaedic walking devices *Post-intervention* KPS NR; 3 needed orthopaedic walking devices	NR

Author, Year Country	Primary Malignancy Patients, N	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Tran Thang et al, 2008[62] Switzerland	Multiple myeloma 28 patients	*Baseline* 7.5 (4–10) *Post-intervention (1 month)* 2.1 (0–10), *P* < .001	*Baseline* 25 patients were taking opioids preoperatively *Post-intervention* Opioids were stopped in 16 patients, partially reduced in 6 patients and remained at preoperative levels in 5 patients; overall, there was a 70% decrease in opioid doses	ECOG scale, mean 0 = asymptomatic 1 = symptomatic but fully ambulatory 2 = symptomatic and in bed < 50% of the day 3 = symptomatic and in bed > 50% of day 4 = bedridden *Baseline* 1.9 *Post-intervention* 0.86, *P* = .001	NR
Trumm et al, 2012[52] Germany	Multiple myeloma 39 patients	*Baseline* 6.4 *Post-intervention (24 hours)* 3.9, *P* = .030 *Post-intervention (9 months)* 3.2, *P* = .009 *Subjective global assessment (9 months)* 20 (71%) reported a reduction in pain; 4 (14%) reported no change, 4 (14%) reported an increase in pain	*Baseline* NR *Post-intervention (6 months)* Stopped analgesics: 10 (36%) Reduced analgesic dose by at least 50% or replaced opioids with non-narcotics: 8 (29%) No change to analgesics: 6 (21%) Increased analgesic use or changed to opioids: 4 (14%)	NR	*Post-intervention* Patient satisfaction with procedure at study end: 18 (64%) were satisfied with the procedure; 10 (36%) were unsatisfied with the procedure (with complaints about discomfort during the procedure under local anaesthesia, being placed in the prone position, the duration of the procedure, and the discomfort during needle insertion)
Mixed Cancers as Primary Malignancies for Spinal Metastases					
Burton et al, 2005[67] United States	Mixed metastatic advanced cancers 3 patients	*Baseline* 10, 10, 10 *Post-intervention (24 hours)* 1, 2, 2	*Baseline* All were on morphine, including IV PCA pump for resistant pain *Post-intervention (24 hours)* Reduction in opioids reported in all patients	KPS *Baseline* 50%, 40%, 40% *Post-intervention (24 hours)* 80%, 60%, 70%	NR

Author, Year Country	Primary Malignancy Patients, N	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Calmels et al, 2007[58] France	Mixed metastatic osteoblastic cancers 52 patients	*Baseline* NR *Post-intervention (24 hours)* Excellent analgesic result (residual pain VAS 0–2): 31 (67%) Good analgesic result (residual pain VAS 2.5–4.5): 9 (19%) Analgesic efficacy was similar for blastic or mixed lesion types	NR	NR	NR
Chen et al, 2011[68] China	Mixed metastatic osteoblastic cancers 4 patients	*Baseline* 8.5 ± 0.6 (8–9) *Post-intervention* 24 hours: 1.5 ± 0.6 (1–2) 1 month: 1.8 ± 0.5 (1–2)	*Baseline* All patients had pain that was unresponsive to opioid analgesics *Post-intervention* No patient required pain medications during follow-up	NR	NR
Chew et al, 2011[63] Scotland	Mixed metastatic osteoblastic cancers 128 patients	*Baseline* 7.6 ± 1.88 *Post-intervention (6 weeks)* 4.8 ± 2.67 by 50 patients, $P = .001$	NR	NR	RMDQ, mean ± SD *Baseline* 18.6 ± 4.79 *Post-intervention (6 weeks)* 13.5 ± 6.95, $P < .001$ for 38 patients
Farrokhi et al, 2012[69] Iran	Mixed metastatic cancers 25 patients	*Baseline* 8.2 *Post-intervention* 24 hours: 2.1 2 months: 1.0	NR	NR	NR
Kim et al, 2002[70] United States	*Unipediculate access* 32 patients	*Baseline* NR *Post-intervention* Mean decrease 6.6 ± 2.9	Medication score 0 = no medications 1 = over-the-counter medications 2 = non-narcotic prescription 3 = narcotics as needed 4 = routine scheduled narcotics *Baseline* NR *Post-intervention* 50% (16/32) had a decrease of at least 1 point Mean decrease of 1 point (range 0–4 points)	NR	NR

Author, Year Country	Primary Malignancy Patients, N	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
	Bipediculate access 17 patients	*Baseline* NR *Post-intervention* Mean decrease 7.3 ± 3.1	*Baseline* NR *Post-intervention* 59% (10/17) had a decrease of at least 1 point Mean decrease of 1.5 points (range 0–4 points)	NR	NR
Kobayashi et al, 2009[71] Japan	Mixed metastatic cancers 33 patients	*Baseline* 6.2 ± 2.1 *Post-intervention* 24 hours: 3.6 ± 2.6 3 days: 2.5 ± 2.6 4 weeks: 1.8 ± 2.3	*Baseline* NSAIDS: 9 Opioids: 10 Both: 11 *Post-intervention* NR	ECOG scale 0 = asymptomatic 1 = symptomatic but fully ambulatory 2 = symptomatic and in bed < 50% of the day 3 = symptomatic and in bed > 50% of day 4 = bedridden *Baseline* 0: n = 1 1: n = 7 2: n = 12 3: n = 13 *Post-intervention* NR	Treatment efficacy score Significantly effective (SE): VAS ≤ 2 or VAS decrease ≥5 Moderately effective (ME): VAS > 2 but decreased to <5 and - ≥2 Ineffective (NE): VAS deceased < 2 or VAS increased or also NE if there was any increased analgesics despite VAS score *Baseline* NR *Post-intervention* Significantly effective: 70% (95% CI 54%–83%) Moderately effective: 9% (n = 3)
Kushchayev et al, 2010[50] United States	Thyroid cancer metastases 2 patients	*Baseline* Case 1: 7 Case 2: 8 *Post-intervention* Case 1: 2 Case 2: 2	*Baseline* Case 1: oral opioids Case 2: NR *Post-intervention* Case 1: occasional non-narcotic analgesics Case 2: non-narcotic analgesics	NR	NR
Lee et al, 2009[72] United Kingdom	Mixed metastatic cancers 19 patients	*Baseline* All reported severe back pain, poorly controlled by analgesics and impeding mobility and ADLs *Post-intervention* Patient subjective report: 16 reported immediate pain relief (of these, 1 did not report analgesic reduction)	*Baseline* NR *Post-intervention* Patient subjective report: 15 reported reduced analgesic use	NR	NR

Author, Year Country	Primary Malignancy Patients, N	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
McDonald et al, 2009[64] United States	Mixed metastatic cancers 128 of 841 patients	Pain with activity *Baseline* Range across 7 operators from 8.15 ± 2.11 to 8.47 ± 1.78 *Post-intervention (24 hours)* Range across 7 operators from 3.12 ± 3.36 to 4.35 ± 3.29	*Baseline, range across 7 operators* 1, no narcotics: 14%–20% 2, occasional narcotics: 10%–19% 3, parenteral narcotics: 3%–9% 4, regular narcotics: 56%–69% *Post-intervention* NR	*Baseline, range across 7 operators* 1, walking > 1 block: 21%–32% 2, walking < 1 block: 30%–37% 3, bedridden: 15%–20% 4, restricted: 20%–28% *Post-intervention* NR	RMDQ, Mean ± SD *Baseline, range across 7 operators* 18.1 ± 3.31 to 20.2 ± 3.89 *Post-intervention, range across 7 operators* 1 week: 9.92 ± 5.86 to 11.1 ± 5.95 1 month: 9.13 ± 4.55 to 10.4 ± 5.43
Mikami et al, 2011[73] Japan	Mixed metastatic cancers 69 patients	*Baseline* 7.3; VAS 0–2.5 in 4% of patients *Post-intervention (at discharge)* 1.9 ± NR; VAS 0–2.5 in 65% of patients, *P* < .001	NR	NR	NR
Murphy et al, 2007[47] United States	Metastatic osteoblastic breast cancer 1 patient	*Baseline* NR *Post-intervention* Immediate pain relief, not quantified	NR	NR	NR
Trumm et al, 2008[48] Germany	Metastatic breast cancer 53 patients	*Baseline* 6.4 *Post-intervention* 24 hours: 5.1, *P* > .05 9 months: 3.4, *P* < .05 *Patient reported subjective assessment of change* Reduction in pain: 33 (79%) No change in pain: 6 (14%) Increased pain due to disease progression: 3 (7%)	*Baseline* NR *Post-intervention (9 months)* Stopped analgesics: 21 (50%) Reduced analgesic dose by at least 50% or replaced opioids with non-narcotics: 11 (26%) No change in analgesics: 6 (14%) Increased use of analgesics or changed to opioids: 4 (10%)	NR	Patient satisfaction with procedure *Baseline* NR *Post-intervention (study end)* Satisfied: 26 (62%) Unsatisfied: 16 (38%), due to the duration and discomfort during needle insertion

Author, Year Country	Primary Malignancy Patients, N	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Tseng et al, 2008[57] China	Mixed metastatic cancers 57 patients	*Baseline* 8.1 ± 0.67 (6–10) *Post-intervention (24 hours)* 3.8 ± 1.9 (1–8), *P* < .015 VAS decreased by > 3 points in 48 (84%) and by > 5 points in 37 (65%) *Post-intervention (6 months)* 2.8 ± 2.0 (0–9)	Mean ± SD number of *non-narcotic* analgesic agents Mean ± SD number of *narcotic* analgesic agents *Baseline* 1.98 ± 1.4 1.19 ± 0.73 *Post-intervention (48 hours)* 1.35 ± 0.70, *P* = .049 0.65 ± 0.53, *P* > .05 7 patients were free from pain and did not require any analgesics	NR	NR

Abbreviations: ADL, activity of daily living; BI, Barthel Index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; KPS, Karnofsky Performance Scale; NSAID, nonsteroidal anti-inflammatory drug; NR, not reported; ODI, Oswestry Disability Index; PCA, patient-controlled analgesia; PCS, physical component summary; PDI, Pain Disability Index; RMDQ, Roland Morris Disability Questionnaire; SD, standard deviation; SF-36, Short-Form Health Survey; VAS, visual analogue scale; VP, vertebroplasty.

[a]Unless otherwise indicated.

B2. Effectiveness of Vertebroplasty and Adjunctive Local Tumour Control Interventions

A summary of the characteristics of clinical studies evaluating the effectiveness of vertebroplasty and adjunctive local tumour control interventions for cancer-related vertebral compression fractures is outlined in Table 5. There were 14 clinical reports involving vertebroplasty and local tumour control interventions; three clinical reports (115 patients) involved multiple myeloma–related vertebral compression fractures involving operators from interventional radiology (n = 2) and surgery (n = 1). For vertebral compression fractures related to metastatic cancer, there were 11 clinical reports (411 patients) involving operators from interventional radiology (n = 7), surgery (n = 3), and both interventional radiology and surgery (n = 1).

The local tumour control interventions employed in eight studies involved adjunctive radiofrequency ablation with various devices (STAR, DFINE, Inc., San Jose, California; Cool-tip, Covidien, Minneapolis, Minnesota; Rita Medical Systems, Inc., Mountain View, California; MRAS-RC, Coagulator, Cosman Medical, Inc., Burlington, Massachusetts). The other adjunctive local tumour control interventions with vertebroplasty included chemotherapy in the multiple myeloma group; and external beam palliative radiotherapy,[74,75] radionuclide bone therapy,[76] and brachytherapy with iodine 125 (^{125}I) seed implantation in the group with mixed metastatic cancers.[77,78]

There were four RCTs in this section, each with different study comparators. Two RCTs included patients with multiple myeloma and involved vertebroplasty and radiofrequency ablation versus vertebroplasty only,[79] and vertebroplasty and chemotherapy versus chemotherapy only (6 weeks of maintenance therapy and interferon-α chemotherapy).[80] The two other RCTs involved the metastatic cancer group and included different comparisons of vertebroplasty with radiotherapy: an RCT of vertebroplasty and ^{125}I seed implantation for osteolytic spinal metastases,[78] and an RCT of vertebroplasty and ^{125}I seed implantation versus palliative radiotherapy for osteoblastic spinal metastases.[77]

Table 5: Summary of Clinical Studies Evaluating the Effectiveness of Vertebroplasty and Adjunctive Local Tumour Control Interventions for Cancer-Related Vertebral Compression Fractures

Author, Year Country	Report Type	Study Recruitment Period	Patients, N (F/M) Age, Mean ± SD (Range)[a]	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Multiple Myeloma as Primary Malignancy of Spinal Metastases					
Erdem et al, 2013[81] United States	Single-site retrospective study, consecutive cases	December 2008 to May 2009	41 patients (20 F, 21 M) 56.9 ± 14.2 years (24–86)	Interventional neuroradiology VP and RFA in 48 sessions at 139 VB levels (T, L, or S)	Treatment safety and effectiveness of VP and RFA (DFINE, Inc.) 6 months
Orgera et al, 2014[79] Italy	Single-site RCT	January 2008 to August 2012	36 patients (26 F, 10 M) 63.1 ± 7.2 years	Interventional radiology VP and RFA vs. VP only	Comparative effectiveness of RFA (Cool-tip) and VP vs. VP to control pain 6 weeks
Yang et al, 2012[80] China	Single-site RCT	February 2003 to July 2005	76 patients (37 F, 39 M) VP, chemotherapy, and bisphosphonate therapy: 38 patients 58.9 ± 4.3 years Chemotherapy and bisphosphonate therapy: 38 patients 59.6 ± 6.2 years	Orthopaedic surgery VP performed at one level (n = 3), two levels (n = 15), three levels or more (n = 20)	Comparative study of VP and chemotherapy vs. chemotherapy for multiple myeloma–associated spinal fractures 5 years; 19 died within 3-year follow-up (6 in VP and chemotherapy group and 13 in chemotherapy-only group)
Mixed Cancers as Primary Malignancies of Spinal Metastases					
Anchala et al, 2014[82] United States	Multicentre 5-site retrospective study, consecutive cases	March 2012 to March 2013	92 patients (NR) *Primary malignancy* Lung (n = 25), breast (n = 15), sarcoma (n = 8), other (n = 44) 60 years (35–84)	Interventional radiology VP and RFA	Treatment safety and effectiveness of VP and adjunctive RFA (STAR) 6 months
Gronemeyer et al, 2002[83] Germany	Single-site retrospective study, consecutive cases	November 1999 to January 2001	10 patients (NR) *Primary malignancy* Breast (n = 2), multiple myeloma (n = 1), melanoma (n = 2), renal (n = 2), prostate (n = 1), other (n = 2) Range 58–76 years	Interventional radiology VP and RFA (n = 4)	Treatment safety and effectiveness of RFA (RITA) prior to VP 6 months
Halpin et al, 2005[84] United States	Case report	NR	1 patient (F) *Primary malignancy* Lung 45-year-old	Interventional radiology VP and RFA at T9 and VP at T12	Treatment feasibility of combined RFA and VP for vertebral compression fractures

Author, Year Country	Report Type	Study Recruitment Period	Patients, N (F/M) Age, Mean ± SD (Range)[a]	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Jang et al, 2005[74] South Korea	Single-site prospective study	NR	28 patients (17 F, 11 M) *Primary malignancy* Metastases (n = 22), multiple myeloma (n = 6) Range 40–72 years	Surgery VP at 72 VB levels (9 C, 30 T, 33 L)	Treatment effectiveness of VP and EBRT Median 7.7 months; range 1 to 16 months; 21 died during follow-up
Lim et al, 2009[75] Korea	Single-site retrospective study	2001 to 2007	102 patients (42 F, 60 M) *Primary malignancy* Breast (n = 24), multiple myeloma (n = 19), lung (n = 16), liver (n = 10), colorectal (n = 10), stomach (n = 4), other (n = 19) Median 55 years (22–82)	Interventional radiology VP at 185 VB levels and spinal EBRT for 59 patients	Treatment effectiveness and long term-outcomes of VP and palliative EBRT To 12 months
Masala et al, 2004[85] Italy	Case series	January 2004 to May 2004	3 patients (2 F, 1 M) *Primary malignancy* Breast (n = 2), lung (n = 1) 63-year-old, 72-year-old, 82-year-old	Interventional radiology VP and RFA	Treatment effectiveness and safety of combined VP and RFA (MIRAS-RC)
Nakatsuka et al, 2004[86] Japan	Single-site prospective study	February 2002 to April 2003	17 patients (8 F, 9 M) *Primary malignancy* Metastatic cancers (n = 14), primary (multiple myeloma [n = 2], plasmacytoma [n = 1]) 61 ± 13 years	Interventional radiology VP and RFA	Feasibility, safety and effectiveness of RFA (Cosman coagulator) and cementoplasty Mean 6.3 ± 5 months; 6 patients died during follow-up
Rasulova et al, 2011[76] Uzbekistan	Single-site prospective study	December 2007 to December 2010	11 patients (5 F, 6 M) *Primary malignancy* Lung (n = 5), breast (n = 3), prostate (n = 3) 53.8 years (32–62)	Interventional radiology and orthopaedic surgery	Treatment effectiveness of consecutive VP treatments preceding radionuclide bone therapy 6–8 months
Toyota et al, 2005[87] Japan	Single-site retrospective study	October 2001 to January 2004	17 patients (1 F, 16 M) *Primary malignancy* Liver (n = 6), renal (n = 5), bladder (n = 2), other (n = 4) 64.2 years (54–81)	Interventional radiology VP and RFA in 53 sessions for 23 lesions	Treatment feasibility, safety and effectiveness of RFA (Cool-tip) with cementoplasty for painful bone metastases 12 months; 8 patients died during follow-up
Yang et al, 2009[78] China	Single-site RCT	July 2004 to July 2006	80 patients (39 F, 41 M) *Primary malignancy* Breast (n = 36), lung (n = 28), liver (n = 9), colon (n = 5), gastric (n = 2) VP: 58.8 ± 7.4 years VP and ISI: 61 ± 4.5 years	Orthopaedic surgery VP at 126 VB levels (T, L)	Comparative study of VP vs. a combined radiation therapy ^{125}I seed ISI followed by VP intervention for osteolytic spinal metastases 1 year; all survived to at least 1 year

Author, Year Country	Report Type	Study Recruitment Period	Patients, N (F/M) Age, Mean ± SD (Range)[a]	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Yang et al, 2013[77] China	Single-site RCT	May 2003 to June 2010	100 patients (61 F, 39 M) *Primary malignancy* Lung (n = 39), breast (n = 37), prostate (n = 21), colon (n = 3) VP and ISI: 50 patients, 61.1 ± 5.2 years Radiotherapy: 50 patients, 59.8 ± 6.6 years	Orthopaedic surgery VP at 89 VB levels	Comparative study of VP and radiation therapy ^{125}I seed ISI vs. palliative EBRT for osteoblastic spinal metastases 1 year

Abbreviations: C, cervical; EBRT, external beam radiotherapy; F, female; Ig, immunoglobulin; ISI, interstitial implantation; L, lumbar; M, male; NR, not reported; RCT, randomized, controlled trial; RFA, radiofrequency ablation; S, sacral; SD, standard deviation; T, thoracic; VB, vertebral body; VP, vertebroplasty.

[a]Unless otherwise indicated.

[b]If reported in study.

Table 6 details the outcome measures of treatment effectiveness of vertebroplasty and adjunctive local tumour control interventions for cancer-related vertebral compression fractures, grouped by etiology of the primary cancer multiple myeloma or mixed metastatic cancers. The clinical outcomes investigated in the studies included cancer pain intensity (VAS, Wong-Baker Faces, global subjective improvement ratings), analgesic use, mobility status and the use of orthopedic walking aids, physical performance status measures (KPS), pain-related disability (Oswestry Disability Index, Roland Morris Disability Questionnaire), and a health-related quality-of-life measure, the European Organization for Research and Treatment of Cancer Quality Life Questionnaire, Version 3.0 (EORTC-QLQC30). No studies reported on patient satisfaction.

Vertebroplasty and adjunctive systemic therapy. Yang et al[80] evaluated the effect of treating multiple myeloma patients diagnosed with fractures within an RCT that studied either vertebroplasty and chemotherapy or chemotherapy alone involving a maintenance plan and an interferon-α chemotherapy program for 6 weeks. In the trial, mean *pain intensity* (3.0 ± 0.62 vs. 6.0 ± 0.40, P = .032) and *physical performance* (KPS scores 89.4 ± 6.3 vs. 80.3 ± 7.2, P = .002) worsened in the chemotherapy-only group. Of interest, the height of the vertebral body was reported to be increased after vertebroplasty in the anterior position (15.71 ± 0.70 to 16.61 ± 0.67 mm, P = .002) and the midline (13.65 ± 0.59 to 14.52 ± 0.85 mm, P = .001), but not in the posterior position (15.71 ± 0.70 to 16.61 ± 0.67 mm, P = .002).

In the combined treatment group, the overall treatment efficacy rate (65.8% vs. 50%, P = .001) at 1 year was significantly higher than in the chemotherapy-only group. The advantages of the combined treatment group were maintained at the 3-year and 5-year follow-ups. In addition, the Kaplan-Meir 3-year survival rate was significantly better in the combined treatment group—74% (28/38) versus 53% (22/38, P < .05)—and during this time there were two cases of paraplegia in the chemotherapy-only group (none occurred in the combined treatment group). Survival estimates at the 5-year follow-up continued to be significantly higher for the combined treatment group—68.4% (26/38) versus 42.1% (16/38).

Vertebroplasty and adjunctive radiofrequency ablation. Eight studies,[79,81-84,86,87] one being an RCT,[79] investigated the outcomes of vertebroplasty and radiofrequency ablation as an adjunctive procedure for cancer-related vertebral compression fractures (Table 6). In all of the clinical studies, the reductions of mean VAS values for back *pain intensity* were similar to those seen with vertebroplasty alone—baseline high pain intensity levels decreasing to mild or moderate pain intensity levels, representing statistically and clinically significant improvements. In the four studies[79,81,84,87] reporting on *analgesic use*, all reported reductions in analgesics, although decreases were variably defined: prescribed narcotic reduction,[81] analgesic consumption score,[79] reductions in all pain medications,[84] and reduction in analgesic use.[87]

Validated outcome measures of *pain-related disability* (Roland Morris Disability Questionnaire) reported by Orgera et al[79] showed significant improvement (P < .00) after vertebroplasty and radiofrequency ablation. An overall *physical performance* assessment score (KPS) also showed significant improvement (P < .000) after vertebroplasty and radiofrequency ablation.[79] The Orgera et al study with multiple myeloma patients was the only RCT comparing vertebroplasty and radiofrequency ablation to vertebroplasty.[79] *Pain intensity*, *analgesic use*, and *pain-related disability* were improved in both groups, but differences between the groups were not significant at 24 hours or at 6 weeks.

Two studies[82,86] evaluated the effect of radiofrequency ablation–assisted vertebroplasty on tumour necrosis in mixed metastatic cancer groups. In the Anchala et al study,[82] 13 of the 34 patients at the largest centre had follow-up imaging, with 10 showing stable or improved metastatic disease and three showing progression at the level of treatment after 3 months. One of the three patients showing diffusely increased metastatic progression after 16 days underwent systemic treatment. In the Nakatsuka et al study,[86] of 23 treated bone lesions, 17 lesions were in the thoracic or lumbar regions, two were in the centre of the vertebral body, two had invaded the posterior cortex and faced the spinal canal, and 13 had invaded both the pedicle and the centre of the vertebral body. The therapeutic response to radiofrequency ablation in the study was estimated as the degree of tumour necrosis evaluated post-operatively by contrast-enhanced magnetic resonance imaging (MRI). Tumour necrosis is represented by the lack of tumour enhancement (visualized as black regions on images) on contrast-enhanced MRI. Investigators found the degree of tumour necrosis varied significantly ($P < .04$) by tumour size, with the mean tumour necrosis rates being 76% ± 23% for small tumours (≤ 5 cm) and 59% ± 22 for large tumours (5–15 cm).

Vertebroplasty and palliative radiotherapy. The utility of vertebroplasty and palliative radiotherapy was evaluated with two different study designs, each involving metastatic cancers with vertebral fractures. In the study by Jang and Lee,[74] the effectiveness of vertebroplasty and of palliative radiotherapy immediately following vertebroplasty were evaluated in a prospective cohort of patients. The combined procedures resulted in significant *pain intensity* reductions immediately post-operatively, and all patients on opioids pre-operatively (27/31) had their opioid *analgesic use* tapered off and then discontinued.

Lim et al[75] performed a comparative review of cancer patients with vertebral fractures undergoing either vertebroplasty alone or vertebroplasty with prior spinal palliative radiotherapy. However, they did not report dose and sequencing of radiotherapy with vertebroplasty. Differences in mean pain intensity between the study groups were not significantly different at 1 day, 3 months, 6 months, or 1 year (Table 6). *Pain intensity* levels in the combined study group were significantly reduced from baseline from 8.2 ± 0.81 to 3.59 ± 1.46 ($P = .0001$).

Radiological morphological outcomes in the Lim et al study,[75] reported as vertebral body compression ratios (anterior vertebral body height subtracted from posterior body height) and kyphotic angles (measured using the modified Cobb method; see Appendix 2), were available for 62% of the study patients. These measures were significantly improved in both groups over baseline at follow-up ($P < .05$); however, differences between the groups were not significantly different at any follow-up point. For the entire group, mean compression ratios significantly decreased from 21.3% ± 16.4% at baseline to 13.8% ± 12.2% (at 24 hours) to 14.4% ± 11.6% (at 3 months), 16.0% ± 10.7% (at 6 months), and 16.4% ± 10.8% (at 1 year). The mean kyphotic angle also significantly decreased from 15.4° ± 10.0° (range 5–25°) at baseline to 12.0° ± 9.9° (range 2–22°) at 24 hours, 13.6° ± 10.9° (range 3–24°) at 3 months, and 14.2° ± 11.1° (range 3–25°) at 6 months.[75]

Vertebroplasty and radiotherapy or nuclear medicine. Yang et al[77,78] evaluated the utility of vertebroplasty and brachytherapy with implanted ^{125}I radioisotope seeds for mixed cancer spinal metastases in two different RCTs.

In the first RCT by Yang et al,[78] vertebroplasty was compared with vertebroplasty followed by brachytherapy with an interstitial implantation of ^{125}I seeds (5–10 seeds/body, mean 6.5 seeds/body). The brachytherapy was performed during the vertebroplasty procedure, after the cement injection.

Pain intensity and *physical performance* levels were not reported for the early or immediate post-operative period. However, at the 6-month follow-up, mean VAS pain intensity (2.3 ± 1.05

vs. 5.4 ± 0.94, *P* = .028) and KPS scores (92.5 ± 7.1 vs. 87.7 ± 7.3, *P* = .009) showed improvement in both groups over baseline, but there was significantly more improvement in the combined treatment group. Although there were no cases of recurrent spinal pain in the combined treatment group at the 1-year follow-up, in the vertebroplasty-only treated group there were six cases of recurrent vertebral body pain but no compression of the vertebral body or new compression of adjacent vertebrae. However, the time to tumour progression (9.0 vs. 8.9 months) and the 1-year survival rates (82.5% vs. 80%) were not significantly different between the two groups.

In the second RCT by Yang et al,[77] vertebroplasty and brachytherapy with ^{125}I radioisotope treatment was compared with palliative external beam radiotherapy for osteoblastic spinal metastases. The number of implanted ^{125}I seeds ranged from 7 to 20 per body (mean 10.5 seeds/body). The external beam radiotherapy program included two different applied doses—a total dose of 3,500 to 4,600 centigray (cGy) with fractionated doses of 200 to 300 cGy, 5 times a week for severe cases; and a total dose of 2,500 to 3,500 cGy with fractionated doses of 200 to 300 cGy, 2 times a week for less severe cases.

The mean *pain intensity* scores in the combined treatment group were significantly improved at the 1-week follow-up over baseline (8.7 ± 0.54 to 3.7 ± 0.66, *P* < .001). In the radiotherapy group, mean pain intensity scores did not decrease from baseline (8.3 ± 0.31) until 1 month following treatment (5.5 ± 0.72), and mean VAS scores were still significantly higher than in the combined treatment group at 6 months (3.5 ± 0.35 vs. 1.3 ± 0.43) and at 1 year (4.7 ± 0.28 vs. 1.3 ± 0.37).

The assessment of the *health-related quality of life* of the study patients, using the EORTC-QLQC30, found results paralleling the pain improvement responses in the two groups. At the 1-week follow-up, the mean EORTC-QLQC30 scores were significantly improved over baseline in the vertebroplasty-radioisotope group (61.2 ± 3.21 to 47.4 ± 3.69, *P* < .01) and remained unchanged in the radiotherapy group (60.7 ± 4.03 to 60.2 ± 3.17). Health-related quality of life did improve in the radiotherapy-treated group at 1 month, but mean scores were still significantly poorer (higher score) than in the vertebroplasty-radioisotope group at 1 month (32.6 ± 4.3 vs. 24.2 ± 2.5), 6 months (36.6 ± 5.7 vs. 21.8 ± 4.1), and 1 year (40.2 ± 3.3 vs. 19.0 ± 4.8). In the first-year follow-up, no cases of vertebral compression fractures occurred in the combined treatment group, but 10 cases (two in the first month, seven in the sixth month, and one after a year) occurred in the radiotherapy-treated group, with three people experiencing paraplegia.

The use of radioisotope in conjunction with vertebroplasty was also evaluated by Rasulova et al[76] in a small series of patients who had widespread bone metastases and vertebral fractures or impending cord compression. Three to 7 days following vertebroplasty, a radiopharmaceutical called samarium 153 (^{153}Sm) ethylene diamine tetra methylene phosphonic acid (EDTMP) was administered at the standard bone palliation dose of 37 MBq/kg body weight. A significant reduction in back *pain intensity* was noted within hours of the vertebroplasty procedure (8.6 ± 0.2 to 4.4 ± 0.39), although patients still had residual bone pain. Following the ^{153}Sm EDTMP treatment, the mean pain intensity score decreased further to 0.55 ± 0.21 (range 0–2). None of the patients required analgesics after the procedure, and adverse skeletal events had not occurred by the 8-month follow-ups.

Table 6: Clinical Outcomes in Studies Evaluating the Effectiveness of Vertebroplasty and Adjunctive Local Tumour Control Interventions for Cancer-Related Vertebral Compression Fractures

Author, Year Country	Primary Malignancy Local Tumour Control Intervention Patients, N	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Multiple Myeloma as Primary Malignancy of Spinal Metastases					
Erdem et al, 2013[81] United States	Multiple myeloma RFA (DFINE Inc.) and VP 41 patients	*Baseline* 8.1 ± 1.7 (4.0–10) *Post-intervention (6 months)* 2.5 ± 2.4 (0–8.0) *Average VAS change* 5.6 ± 2.8 (0–10), *P* < .001	*Baseline* 36 (88%) of patients reported prescribed narcotics for pain relief *Post-intervention (6 months)* 22 (54%) reported prescribed narcotics for pain relief, *P* < .001	Maximum patient activity scores, baseline to 6 months 0, no limitation: n = 7 to 10 1, walking without assistance: n = 2 to 9 2, walking with needed frequent intervals of rest: n = 8 to 11 3, use of cane or walker: n = 13 to 12 4, use of wheelchair: n = 11 to 3 5, upright in chair or bed: n = 4 to 2 6, flat in bed: n = 7 to 1 Those with fully unassisted ambulation increased from 31% (n = 9) to 63% (n = 19) Those unable to ambulate decreased from 42% (n = 11) to 12% (n = 3)	NR
Orgera et al, 2014[79] Italy	Multiple myeloma RFA (Cool-tip) and VP 18 patients	*Baseline* 9.1 ± 0.9 *Post-intervention* 24 hours: 3.4 ± 1.2 6 weeks: 2.0 ± 0.9	Analgesic consumption change score, mean ± SD 1 = increased 2 = same 3 = decreased 2.7 ± 0.4	NR	RMDQ, mean ± SD *Baseline* 19.8 ± 1.5 *Post-intervention* 24 hours: 9.6 ± 1.2 6 weeks: 8.2 ± 1.0
	Multiple myeloma VP only 18 patients	*Baseline* 9.3 ± 0.6 *Post-intervention* 24 hours: 3.0 ± 0.9 6 weeks: 2.3 ± 0.9	Analgesic consumption change score, mean ± SD 1 = increased 2 = same 3 = decreased 2.7 ± 0.4	NR	RMDQ, mean ± SD *Baseline* 19.9 ±1.6 *Post-intervention* 24 hours: 9.5 ± 1.0 6 weeks: 8.7 ± 0.8

Author, Year Country	Primary Malignancy Local Tumour Control Intervention Patients, N	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Yang et al, 2012[80] China	Multiple myeloma VP and chemotherapy 38 patients	*Baseline* 9.0 ± 1.03 *Post-intervention* 3.0 ± 0.62	NR	KPS, mean ± SD *Baseline* 64.3 ± 6.7 *Post-intervention* 89.4 ± 6.3	Treatment efficacy score—overall response (complete response + near complete response and partial remission): 65.8%
	Chemotherapy 38 patients	*Baseline* 8.8 ± 0.96 *Post-intervention* 6.0 ± 0.40	NR	*Baseline* 67.4 ± 7.2 *Post-intervention* 80.3 ± 7.2	Treatment efficacy score—overall response (complete response + near complete response and partial remission): 50%
Mixed Cancers as Primary Malignancies of Spinal Metastases					
Anchala et al, 2014[82] United States	Mixed metastatic cancers RFA (STAR) and VP 92 patients	*Baseline* 7.5 ± 2.46 *Post-intervention* 1 week: 1.7 ± 2.28 1 month: 2.3 ± 2.44 6 months: 1.75 ± 2.62	NR	NR	NR
Gronemeyer et al, 2002[83] Germany	Mixed metastatic cancers RFA (RITA Medical system Inc.) and VP 4 of 10 patients	VAS 0, no pain to 100, worst pain *Baseline* 72 *Post-intervention* 17.5	NR	NR	KPS, mean *Baseline* 53% *Post-intervention* 73%
Halpin et al, 2005[84] United States	Metastatic lung cancer RFA (Rita Medical systems) and VP 1 patient	*Baseline* 10 *Post-intervention* 0 immediately following the procedure	*Baseline* Pain medications not specified *Post-intervention* Discontinued all pain medications	*Baseline* NR *Post-intervention* Resumed normal daily activities	NR

Author, Year Country	Primary Malignancy Local Tumour Control Intervention Patients, N	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Jang et al, 2005[74] South Korea	Mixed metastatic cancers VP and PRT immediately post-VP (300 cGy bolus to total dose 3000 cGy) 28 patients	*Baseline* 8.2 *Post-intervention* 24 hours: 3.0 3 days: marked to complete pain relief (VAS decrease by > 5 points) in 13 patients (48%) and moderate pain relief (VAS decrease by 3–5 points) in 11 patients (41%); 3 patients did not experience significant pain relief	*Baseline* Oral morphine (n = 24), epidural morphine injections (n = 3) *Post-intervention* All those on opioid analgesics and epidurals had opioids tapered off and then discontinued	*Baseline* NR *Post-intervention* 5 patients who had been non-ambulatory because of pain severity were able to walk after VP	NR
Lim et al, 2009[75] Korea	Mixed metastatic cancers VP followed by PRT 52 patients	*Baseline* 8.1 ± 0.84 *Post-intervention* 24 hours: median 3.0	NR	NR	NR
	Mixed metastatic cancers VP only 43 patients	*Baseline* 8.4 ± 0.75 *Post-intervention* 24 hours: median 3.0 Differences between groups at 24 hours, 3, 6 and 12 month follow-up were not statistically significant	NR	NR	NR
Masala et al, 2004[85] Italy	Mixed metastatic cancers RFA (MIRAS-RC) and VP 3 patients	*Baseline* 8.6 *Post-intervention* 2.6	NR	NR	NR
Nakatsuka et al, 2004[86] Japan	Mixed metastatic cancers RFA (Cosman Coagulator-1) and VP 17 patients	*Baseline* 8.4 ± 2.4 *Post-intervention* 1 week: 1.1 ± 1.8, $P < .0001$	NR	NR	NR

Author, Year Country	Primary Malignancy Local Tumour Control Intervention Patients, N	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Rasulova et al, 2011[76] Uzbekistan	Mixed metastatic cancers VP followed 3–7 days later with radionuclide therapy (Sm-153 EDTMP) 11 patients	*Baseline* 8.6 ± 0.2 (8.0–9.0) *Post-intervention* 12 hours: 4.36 ± 0.39, *P* < .0001 Time to pain relief occurred in a mean of 4.8 ± 1.2 hours (range 0.5 to 12 hours)	*Baseline* NR *Post-intervention* No patients needed analgesics after the procedures	NR	*Baseline* NR *Post-intervention* No new lesions of bone metastases occurred during follow-up
Toyota et al, 2005[87] Japan	Mixed metastatic cancers RFA (Cool-tip, Radionics) and VP (13 patients received PRT of mean 41 Gy prior to the combined therapy) 17 patients	Wong-Baker Faces pain rating (5 cartoon faces ranging from happy smiling [0, no pain] to tearful sad face [5, worst pain]) *Baseline* NR *Post-intervention* Pain improvement in all patients: down 4 scales (n = 2), 3 scales (n = 4), 2 scales (n = 9), and 1 scale (n = 2) Initial pain relief occurred 1 day (n = 8), 2 days (n = 7) and 3 days (n = 2) post-treatment	*Baseline* All patients were taking daily analgesics (not specified) *Post-intervention* Analgesic reduction occurred in 41% (7/17)	*Baseline* NR *Post-intervention* In ADLs, 3 bedridden patients were able to sit upright in a wheelchair, 2 patients using wheelchairs, 1 was able to stand and 1 could walk	NR
Yang et al, 2009[78] China	Mixed metastatic cancers VP and brachytherapy with ^{125}I seed ISI 40 patients	*Baseline* 8.9 ± 0.70 *Post-intervention* 6 months: 2.3 ± 1.05 12 months: 3.01 ± 0.62	NR	NR	KPS, mean ± SD *Baseline* 68.9 ± 7.9 *Post-intervention* 6 months: 92.5 ± 7.1 12 months: 89.4 ± 6.3
	Mixed metastatic cancers VP only 40 patients	*Baseline* 8.8 ± 0.54 *Post-intervention* 6 months: 5.4 ± 0.94 12 months: 5.97 ± 0.40	NR	NR	KPS, mean ± SD *Baseline* 69.4 ± 8.3 *Post-intervention* 6 months: 87.7 ± 7.3 12 months: 80.3 ± 7.2

Author, Year Country	Primary Malignancy Local Tumour Control Intervention Patients, N	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Yang Z et al, 2013[77] China	Mixed metastatic osteoblastic cancers Brachytherapy with ^{125}I seed ISI and VP 50 patients	*Baseline* 8.7 ± 0.54 *Post-intervention* 1 week: 3.7 ± 0.66 1 month: 2.5 ± 0.50 6 months: 1.3 ± 0.43 12 months: 1.3 ± 0.37	NR	NR	EORTC-QLQ-30, mean ± SD *Baseline* 61.23 ± 3.21 *Post-intervention* 1 week: 47.41 ± 3.69 1 month: 24.23 ± 2.45 6 months: 21.78 ± 4.11 12 months: 18.96 ± 4.79
	Mixed metastatic osteoblastic cancers PRT; total dose 3500-4600 cGy 50 patients	*Baseline* 8.34 ± 0.31 *Post-intervention* 1 week: 8.43 ± 0.34 1 month: 5.46 ± 0.72 6 months: 3.54 ± 0.35 12 months: 4.73 ± 0.28	NR	NR	EORTC-QLQ-30, mean ± SD *Baseline* 60.73 ± 4.03 *Post-intervention* 1 week: 60.20 ± 3.17 1 month: 32.57 ± 4.32 6 months: 36.64 ± 5.73 12 months: 40.19 ± 3.32

Abbreviations: ADL, activity of daily living; EDTMP, ethylene diamine tetra methylene phosphonic acid; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality Life Questionnaire version 30; ISI, interstitial implantation; KPS, Karnofsky Performance Scale; NR, not reported; PRT, palliative radiotherapy; RFA, radiofrequency ablation; RMDQ, Roland Morris Disability Questionnaire; SD, standard deviation; VAS, visual analogue scale; VP, vertebroplasty.

[a]Unless otherwise indicated.

B3. Effectiveness of Kyphoplasty

A summary of the characteristics of clinical studies evaluating the effectiveness of kyphoplasty for cancer-related vertebral compression fractures is outlined in Table 7. There were 11 reports (418 patients) involving kyphoplasty, of which five (110 patients) involved multiple myeloma–related fractures and six (308 patients) involved metastatic cancer–related fractures. The reports included practices from at least eight countries, and all operators were either orthopedic surgeons or neurosurgeons.

All reports involved retrospective or prospective clinical studies, except for two RCTs,[88,89] both involving metastatic vertebral compression fractures. One RCT was a multicentre trial comparing kyphoplasty and a control group having usual care or non-surgical care and allowing for crossovers.[88] The crossover feature was part of the study design and allowed for patients in the control group to have kyphoplasty if their symptoms had not improved or had worsened within a month. The other RCT involved a comparison between kyphoplasty and the Kiva device (Benvenue Medical, Santa Clara, California), an alternative method of mechanically reducing fractures and creating a space in which to more safely inject cement.[89] Unlike the kyphoplasty inflatable balloon, the Kiva device remains in the vertebral body and cement is injected into the device itself.

Table 7: Summary of Clinical Studies Evaluating the Effectiveness of Kyphoplasty for Cancer-Related Vertebral Compression Fractures

Author, Year Country	Report Type	Study Recruitment Period	Patients, N (F, M) Age, Mean ± SD (Range)[a]	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Multiple Myeloma as Primary Malignancy of Spinal Metastases					
Dudeney et al, 2002[90] United States	Single-site retrospective study, consecutive cases	NR	18 patients (NR) 63.5 years (48–79)	Orthopedic surgery KP in 27 sessions at 55 VB levels (T6 to L5)	Treatment safety and effectiveness Mean 7.4 months
Julka et al, 2014[91] United States	Single-site retrospective study, consecutive cases	NR	32 patients (14 F, 18 M) 64.3 years	Orthopedic surgery KP at 76 VB levels (34 T, 42 L)	Treatment safety and effectiveness of KP for multiple myeloma 24 months
Lane et al, 2004[92] United States	Single-site retrospective comparative study, consecutive cases	NR	19 patients (7 F, 12 M) *Diagnosis* Multiple myeloma (n = 19), osteoporosis (n = 26) 60.4 years (45–74)	Surgery KP (multiple myeloma) at 46 VB levels; KP (osteoporosis) at 37 VB levels	Treatment effectiveness of multilevel KP to relieve pain, improve function, and restore vertebral body height 3 months
Pflugmacher et al, 2006[93] Germany	Single-site prospective study	May 2002 to December 2003	20 patients (20 M) Age NR	Orthopedic surgery KP at 48 VB levels (T6 to L5)	Treatment effectiveness of KP for multiple myeloma 12 months
Zou et al, 2010[94] China	Single-site retrospective study	January 2003 to January 2008	21 patients (12 F, 9 M) 65.9 years (47–81)	Orthopedic surgery KP at 14 T and 15 L KP performed at one level (n = 2), two levels (n = 16), three levels (n = 3)	Treatment effectiveness of KP for multiple myeloma vertebral compression fractures 12 months
Mixed Cancers as Primary Malignancies of Spinal Metastases					
Berenson et al, 2011[88] Australia, Canada, Europe, United States	Multicentre multinational RCT at 22 sites	May 2005 to March 2008	129 patients (75 F, 54 M) *Primary malignancies* Multiple myeloma (n = 49), breast (n = 28), lung (n = 11), prostate (n = 8), others (n = 33) KP (n = 68): 64.8 years (38–88) Controls (n = 61): 63 years (40–83)	Surgery KP at 247 VB levels	Treatment safety and effectiveness of KP vs. nonsurgical management 12 months
Chen et al, 2013[95] China	Case series	May 2005 to January 2012	6 patients (3 F, 3 M) *Primary malignancies* Breast (n = 2), lung (n = 2), liver (n = 1), prostate (n = 1) 59.3 years (50–73)	Orthopedic surgery KP (T or L)	Technical feasibility, safety, and effectiveness of KP for osteoblastic spinal lesions 3 months (16–96 weeks)

Author, Year Country	Report Type	Study Recruitment Period	Patients, N (F, M) Age, Mean ± SD (Range)[a]	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Konig et al, 2012[96] United Kingdom	Single-site prospective study, consecutive cases	February 2001 to September 2002	11 patients (7 F, 4 M) *Primary malignancies* Breast (n = 3), myeloma (n = 1), non-Hodgkin lymphoma (n = 2), gastric (n = 1), cervical (n = 1), prostate (n = 1), lung (n = 1), bladder (n = 1) Range 52–77 years	Surgery KP at 23 VB levels (T2 to L3)	Treatment safety and effectiveness of KP for cancer-related vertebral fractures Until death
Korovessis et al, 2014[89] Greece	Prospective parallel comparative RCT	March 2010 to March 2012	47 patients (26 F, 21 M) *Primary malignancies* Breast, colon and lung cancers (numbers NR) 24 KP and 23 Kiva	Orthopedic surgery KP at T7 to L5 Kiva at T11 to S2	Comparison of 2 different vertebral augmentation techniques: KP or the Kiva implant 1 month
Pflugmacher et al, 2008[97] Germany	Single-site prospective study, consecutive cases	May 2001 to November 2004	65 patients (28 F, 37 M) *Primary malignancies* Metastatic cancers (breast, ovary, cervix, rectum, lung, pancreas, prostate, skin, gastrointestinal; numbers NR) 66 ± 9 years	Orthopedic surgery KP at 99 VB levels KP performed at one level (n = 37), two levels (n = 23), three levels (n = 4), four levels (n = 1)	Treatment safety and effectiveness of KP for osteolytic thoracic and lumbar fractures To 24 months; 13 patients died before 1-year follow-up, and 13 patients died between 12 and 24 months
Vrionis et al, 2005[98] United States	Single-site retrospective study	2002 to 2004	50 patients (33 F, 17 M) *Primary malignancies* Multiple myeloma (n = 23), lung (n = 11), breast (n = 8), prostate (n = 4), other (n = 4) 63 years (36–81)	Neurosurgery KP at 128 VB levels (83 T, 45 L)	Treatment effectiveness of KP for painful spinal compression fractures Mean 9 months; 14 patients died during follow-up

Abbreviations: CAFE, Cancer Patient Fracture Evaluation; F, female; KP; kyphoplasty; L, lumbar; M, male; NR, not reported; RCT, randomized controlled trial; S, sacral; T, thoracic; VB, vertebral body.
[a]Unless otherwise indicated.
[b]If reported in study.

Table 8 details the outcome measures of treatment effectiveness of kyphoplasty for cancer-related vertebral compression fractures grouped by etiology of the primary cancer multiple myeloma and by mixed metastatic cancers. The clinical outcomes investigated in the studies included cancer pain intensity (VAS scores, global subjective improvement ratings) and analgesic use with general categories. Physical performance was evaluated using general mobility rankings with or without orthopedic aids, and standardized physical performance measures including the KPS and ECOG scale. The studies usually evaluated pain-related disability using the Oswestry Disability Index or the Roland Morris Disability Questionnaire score,[88] and health-related quality of life measures using the Short-Form Health Survey. Radiological morphometric outcomes such as corrections for vertebral body height and kyphosis are outlined separately in Table 9.

Pain intensity. Two[93,94] of the five studies involving kyphoplasty for multiple myeloma patients and all seven studies involving kyphoplasty for metastatic cancer patients reported VAS pain scores, and these involved significant reductions in pain intensity over baseline at follow-up (Table 8). In all of the clinical studies, the baseline mean VAS values for cancer pain, in both groups, were in the high pain intensity levels (VAS ≥ 7.0) and were reduced post-procedurally to low pain intensity levels (VAS < 4.0), representing both statistically and clinically significant pain intensity reductions. In the RCT by Berenson et al,[88] the pain intensity at 1 week in the control group receiving usual care was unchanged, at VAS 7.0. At 1 week, the difference in pain intensity scores between the groups over baseline was significantly better ($P < .0001$) in the kyphoplasty group, at 3.5 points (95% CI 3.2–3.8). In one study,[98] a global statement by patients on their pain response change after kyphoplasty allowed for an estimate of individuals experiencing pain relief with kyphoplasty.[98] After kyphoplasty, 20% (10/50) reported having no pain, 76% (38/50) reported a significant pain reduction, and 4% (2/50) reported no difference in their pain intensity.

Analgesic use. Analgesic use after kyphoplasty was infrequently reported. Two studies,[88,93] each involving metastatic cancer patient groups, did report on analgesics. In the study by Pflugmacher et al,[93] no opioids were required after kyphoplasty; however, the investigators did not report baseline use. In the study by Berenson et al,[88] an RCT comparing kyphoplasty with usual or conservative care, use of any analgesic medication decreased from 91% (64/70) at baseline to 49% (34/70) at the 1-month follow-up. In the control group, the use of analgesic medication changed from 80% (51/64) at baseline to 64% (41/64) at 1 month.

Physical performance. Outcome measures involving mobility or physical functioning after kyphoplasty were not reported in any of the studies involving multiple myeloma. Physical performance was evaluated in two studies involving metastatic cancer–related vertebral compression fractures. Measurements included general ambulation mobility rankings with or without orthopedic aids, and standardized measures including the KPS[88] and the ECOG scale.[96]

In the RCT by Berenson et al,[88] there was a decrease in the number of patients needing assisted ambulation, either walking aids or wheelchairs, from 39% (27/70) at baseline to 24% (17/70) at the 1-month follow-up; in contrast, the number requiring assisted ambulation in the control group with usual care did not change from 39% (25/64) at baseline. In the same study, the KPS score was used to evaluate physical functioning and showed a mean improvement of 15.3 points (95% CI 13.5–17.1), which was significantly better than in the control group. A KPS score of 70 or higher is usually considered a threshold for self-care; in the kyphoplasty-treated group, the proportion of patients above this threshold was 75% (47/63), compared with 39% (19/49) in the usual care group.

Pain-related disability. Validated outcome measures of back pain–related physical disability were reported using the Oswestry Disability Index in six studies[89,91-93,95,97] (three with multiple myeloma patients[91-93]) and the Roland Morris Disability Questionnaire scales in one study, the RCT by Berenson et al.[88] For the patients with multiple myeloma, the mean Oswestry Disability Index scores at baseline were all in the severe (49%[92]) or very severe (63%,[94] 72%[93]) levels of disability. Mean values were significantly reduced ($P < .01$) to moderate levels at 24 hours (37%[94]) and at 3 months (33%[92], 28%[93]) and 24 months (30%[91]).

In the group with metastatic cancer–related vertebral compression fractures, the Oswestry Disability Index scores at baseline were also all in the very severe levels of disability, ranging from 74%[95] to 79%[89] to 81%.[97] In all studies, these values were significantly decreased to moderate levels at 24 hours (39%[97]), 3 days (32%[95]), and 3 months (33%[97]) after kyphoplasty. In the study by Pflugmacher et al,[97] follow-up continued at 1 and 2 years, with disability scores remaining low in surviving patients: 32% at 1 year and 35% at 2 years.

In the RCT by Berenson et al,[88] pain-related physical disability, measured using the Roland Morris Disability Questionnaire, significantly improved ($P < .0001$) at 1 month (9.1 points) compared with baseline (17.6 points) in the kyphoplasty arm, for a mean improvement of 8.3 (95% CI 6.4–10.2). The score in the control group with usual care did not change from baseline to follow-up: 18.2 to18.0.

Health-related quality of life and patient satisfaction. Health-related quality-of-life measures evaluated using the Short-Form Health Survey were reported in two studies, by Dudeney et al[90] and Berenson et al.[88] The former[90] involved patients with multiple myeloma; mean survey scores for bodily pain, physical functioning, vitality, and social functioning were significantly improved at the 7-month follow-up. Berenson et al[88] found that at the 1-month follow-up, the physical component summary score (8.4 points, 95% CI 7.7–9.1, $P < .0001$) and the mental health component summary score (11.1 points, 95% CI 10.7–11.5, $P < .0001$) of the Short-Form Health Survey had both significantly improved. In the control group, the physical and mental health components had not significantly improved over baseline at follow-up.

One study, involving multiple myeloma patients, reported on patient satisfaction with kyphoplasty treatment.[93] In that study, at 1 year patients rated their overall satisfaction with their treatment as being excellent (65%, 13/20), good (25%, 5/20), and fair (10%, 2/20).

Table 8: Clinical Outcomes in Studies Evaluating the Effectiveness of Kyphoplasty for Cancer-Related Vertebral Compression Fractures

Author, Year Country	Primary Malignancy Patients, N	Pain Intensity, VAS Mean ± SD (Range)[a]	Mobility	Pain-Related Disability Health-Related Quality of Life
Multiple Myeloma as Primary Cancer of Spinal Metastases				
Dudeney et al, 2002[90] United States	Multiple myeloma 18 patients	NR	NR	SF-36, mean *Baseline* Bodily pain: 23.2 Physical functioning: 21.3 Vitality: 31.3 Social functioning: 40.6 *Post-intervention (7 months)* Bodily pain: 55.4, *P* = .0008 Physical functioning: 50.6, *P* = .0010 Vitality: 47.5, *P* = .012 Social functioning: 64.8, *P* = .014 General health, mental health, role physical and role emotional did not improve significantly
Julka et al, 2014[91] United States	Multiple myeloma 32 patients	NR	NR	*Baseline* NR *Post-intervention (24 months)* Mean ODI score 29.6% (range 2%–46%)
Lane et al, 2004[92] United States	Multiple myeloma 19 patients	NR	NR	ODI, mean ± SD (range) *Baseline* 48.9% ± 16.6 (20%–80%) *Post-intervention (3 months)* 32.6% ± 13.6 (8%–56%), *P* < .001
Pflugmacher et al, 2006[93] Germany	Multiple myeloma 20 patients	*Baseline* 8.2 *Post-intervention* 24 hours: 2.2, *P* < .05 12 months: 3.1	NR	ODI, mean (range) *Baseline* 71.5% (range, 39%–89%) *Post-intervention* 3 months: 27.5% (range, 11%–41%) 1 year: 31.2% (range, 13%–52%) At 1 year, patient satisfaction with overall outcome: excellent (n = 13), good (n = 5), fair (n = 2)

Author, Year Country	Primary Malignancy Patients, N	Pain Intensity, VAS Mean ± SD (Range)[a]	Mobility	Pain-Related Disability Health-Related Quality of Life
Zou et al, 2010[94] China	Multiple myeloma 21 patients	*Baseline* 8.1 ± 1.5 *Post-intervention* 24 hours: 3.6 ± 1.8, *P* < .001 3 months: 3.2 ± 1.1, *P* < .001 6 months: 3.3 ± 1.2, *P* < .001 12 months: 3.4 ± 1.1, *P* < .001	ODI, mean ± SD *Baseline* 63.2% ± 15.9 *Post-intervention* 24 hours: 37.1% ± 10.2, *P* < .001 3 months: 36.8% ± 9.3, *P* < .001 6 months: 37.8% ± 9.2, *P* < .001 12 months: 39.9% ± 10.5, *P* < .001	SF36, mean ± SD *Baseline* General health: 48.8 ± 19.2 Social functioning: 31.6 ± 11.3 Bodily pain: 21.3 ± 10.5 Mental health: 50.2 ± 17.1 Vitality: 34.2 ± 10.1 Physical functioning: 31.8 ± 12.6 Role physical: 13.1 ± 9.3 Role emotional: 42.1± 10.3 *Post-intervention (24 hours, 12 months)* General health: 51.3 ± 10.4, 53.2 ± 11.9 Social functioning: 39.9 ± 12.5, 38.2 ± 10.3 Bodily pain: 44.7 ± 12.6, 48.3 ± 12.5, *P* < .05 Mental health: 74.1 ± 16.1, 72.8 ± 13.4, *P* < .05 Vitality: 41.2 ± 12.3, 43.5 ± 13.5, *P* < .05 Physical functioning: 46.7 ± 15.9, 47.9 ± 12.1, *P* < .05 Role physical: 13.2 ± 10.1, 32.1 ± 10.1, *P* < .05 Role emotional: 60.5 ± 13.2, 61.1 ± 14.3, *P* < .05
Mixed Metastatic Cancers as Primary Malignancy of Spinal Metastases				
Berenson et al, 2011[88] Australia, Canada, Europe, United States	Mixed metastatic cancers KP 68 patients	*Baseline* 7.3 *Post-intervention (7 days)* 3.5, *P* < .0001 *Difference in change between groups over baseline* 7 days: –3.5 (95% CI, –3.8 to –3.2) *P* < .0001 1 month: –3.3 (–3.6 to –3.0), *P* < .0001	Ambulation score *Change pre-KP to 1 month post-KP* 1 (assisted ambulation, walking aids): n = 22 to 16 2 (wheelchairs): n = 5 to 1 3 (bed rest): n = 29 to 15 KPS, mean (95% CI) *Improvement at 1 month* 15.3 points (13.5–17.1), *P* < .0001 compared control group (see row below) At 1 month, the proportion of patients with a KPS ≥ 70 (threshold score for self-care) was 75% (47/63) in the KP group vs. 39% (19/49) in the control group	RMDQ, mean ± SD *Baseline* 17.6 *Post-intervention (1 month)* 9.1 Mean change –8.3 (95% CI, –6.4 to –10.2) *P* < .0001 SF-36, mean (95% CI) Improvement compared to the usual care group at 1 month PCS: 8.4 (95% CI, 7.7–9.1), *P* < .0001 MHS: 11.1 (95% CI, 10.7–11.5), *P* < .0001

Author, Year Country	Primary Malignancy Patients, N	Pain Intensity, VAS Mean ± SD (Range)[a]	Mobility	Pain-Related Disability Health-Related Quality of Life
	Conservative, usual care 61 patients	*Baseline* 7.3 *Post-intervention (7 days)* 7.0	Ambulation score *Change pre-KP to 1 month post-KP* 1 (assisted ambulation, walking aids): n = 22 to 23 2 (wheelchairs): n = 3 to 2 3 (bed rest): n = 32 to 23	RMDQ, mean ± SD *Baseline* 18.2 *Post-intervention (1 month)* 18.0 Mean change –0.1 (95% CI, –0.8 to 1.0), *P* = .83
Chen et al, 2013[95] China	Mixed metastatic osteoblastic cancers 6 patients	*Baseline* 8.3 ± 0.5 (8.0–9.0) *Post-intervention* 3 days: 1.8 ± 0.8 (1–3) 1 month: 1.5 ± 0.5 3 months: 1.3 ± 0.5	NR	ODI, mean ± SD *Baseline* 74.4 % ± 10.6 *Post-intervention* 3 days: 31.8 % ± 10.2 1 month: 30.5% ± 8.5 3 months: 29.7% ± 7.4
Konig et al, 2012[96] United Kingdom	Mixed metastatic cancers 11 patients	*Baseline* 7.5 ± 92 (6.0–10) *Post-intervention* VAS scores graphical; all except 1 patient had reduced pain scores at discharge	ECOG scale *Change pre-KP to discharge* 0 (asymptomatic): n = 0 to 0 1 (symptomatic but fully ambulatory): n = 1 to 1 2 (symptomatic and in bed < 50% of the day): n = 3 to 4 3 (symptomatic and in bed > 50% of day): n = 3 to 5 4 (bedridden): n = 4 to 1	NR
Korovessis et al, 2014[89] Greece	Mixed metastatic cancers Kiva stent 23 patients	*Baseline* 8.3 ± 3.2 *Post-intervention (1 month)* 3.2 ± 2, *P* < .001	NR	ODI, mean ± SD *Baseline* 81% ± 7 *Post-intervention (1 month)* 38% ± 8, *P* < .001
	Mixed metastatic cancers KP 24 patients	*Baseline* 8.1 ± 4 *Post-intervention* 3.0 ± 2.5, *P* < .001	NR	ODI, mean ± SD *Baseline* 79% ± 8 *Post-intervention* 37% ± 9, *P* < .001

Author, Year Country	Primary Malignancy Patients, N	Pain Intensity, VAS Mean ± SD (Range)[a]	Mobility	Pain-Related Disability Health-Related Quality of Life
Pflugmacher et al, 2008[97] Germany	Mixed metastatic cancers 65 patients	*Baseline* 8.3 ± 1.5 *Post-intervention* 24 hours: 3.3 ± 0.9, $P < .0001$ 3 months: 2.9 ± 0.9, $P < .0001$ 12 months: 3.1 ± 1.0, $P < .0001$ 24 months: 3.2 ±1.0, $P < .0001$	NR	ODI, mean ± SD *Baseline* 81% ± 8 *Post-intervention* 24 hours: 39% ± 7, $P < .0001$ 3 months: 33% ± 6, $P < .0001$ 12 months 32% ± 7, $P < .0001$ 24 months 35% ± 6, $P < .0001$
Vrionis et al, 2005[98] United States	Mixed metastatic cancers 50 patients	*Baseline* NR *Post-intervention* VAS NR, but post-operatively, 20% had no pain, 76% had significant pain improvement, and 4% had no difference in pain	NR	NR

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; KP, kyphoplasty; KPS, Karnofsky Performance Scale; MHS, mental health component summary score, SF-36; NR, not reported; ODI, Oswestry Disability Index; PCS, physical component summary score, SF-36; RMDQ, Roland Morris Disability Questionnaire; SD, standard deviation; SF-36, Short-Form Health Survey; VAS, visual analogue scale.

[a]Unless otherwise indicated.

Radiological morphometric outcomes. Five studies involving patients with multiple myeloma and vertebral compression fractures estimated radiological morphometric vertebral outcomes after kyphoplasty, including changes in vertebral body height and kyphosis (Table 9).[90-94] Three studies[90-92] evaluated changes in vertebral body height only, and two studies[93,94] evaluated vertebral body height and spinal kyphosis. Of the three studies involving metastatic cancer–related vertebral compression fractures, one evaluated only vertebral height changes[88] and the other two[89,97] evaluated both vertebral height and kyphosis.

Vertebral body height. The radiological morphometric measurements were usually based on standing lateral plain radiographs, although several different methods were used to estimate the degree of height restoration of the collapsed vertebral body. Also, it was not always possible for investigators to report on height measurements because of the poor quality of radiographs owing to the nature of tumour osteolysis, particularly of the vertebral endplates that are used as reference points for morphometric measurements. Dudeney et al[90] were unable to report height measurements for 29% (16/55) of those treated with kyphoplasty because of the quality of the radiographs.

In addition, kyphoplasty was not always performed for vertebral height restoration as the degree of vertebral collapse varied widely from mild deformity levels of 20% vertebral height loss to severe deformity with ≥ 40% loss. Absolute values for significant vertebral height loss have not been generally defined, but Dudeney et al[90] reported that 18% of the kyphoplasty-treated vertebral levels had minimal height loss, defined as ≤ 2 mm.

Three of the studies reporting vertebral height improvements (partial or full) for patients with multiple myeloma reported variable effects for fracture levels. Restoration of vertebral height at the anterior location was reported for 42% (32/76),[91] 56% (27/48),[93] 69% (27/39),[90] and 76% (35/46)[92] of the vertebral levels treated, in most cases with bilateral kyphoplasty. It is unclear whether these results were due to a failure of kyphoplasty to restore heights or the fact that the degree of height loss was too small for kyphoplasty to effect a change.

Measurement of vertebral height restoration varied in the studies, with restoration reported in terms of absolute height measurements, a percentage of height restoration, or both. Height restoration was defined as the height gained divided by the height lost, where heights were taken as the distance between the inferior and superior endplates in the anterior, midline, or posterior position of the vertebral body. The normal height (height before the fracture) for a fractured vertebra was estimated by taking the average heights (distance in millimetres from superior to inferior endplate) of the vertebrae above and below the fractured vertebra. The mean percentage height restoration was reported by Dudeney et al[90] for all levels as 34% (range 0%–100%) for the midbody positions, and by Lane et al[92] for the restored levels as 38% ± 26.9% for the anterior and 53% ± 29.1% for the midbody vertebral positions. Julka et al[91] reported height restoration as a change in Genant grade or categories of vertebral collapse as an average improvement in grade of 0.37 per treated level or 0.88 per treated level.

Pflugmacher et al[97] were the only investigators to evaluate vertebral height changes over a longer-term follow-up—1 year for vertebral fractures related to multiple myeloma[93] and 2 years for those related to metastatic cancer. In the multiple myeloma report, mean increases in absolute height were reported post-operatively for the anterior (3.8 mm, range 0–16 mm) and mid-vertebral (4.3 mm, range 0–17.5 mm) body positions. At 1 year's follow-up, in the anterior position there was a mean decrease in 52% of the treated vertebrae of 1.3 mm (range 0–1.5 mm), and in the midbody position there was a decrease in 44% of the treated vertebrae of 1.1 mm (range 0–1.1 mm), essentially representing a stabilization of the fracture heights.

In the metastatic cancer vertebral fracture 2-year follow-up study, Pflugmacher et al[97] reported a change in vertebral height at baseline and at 3 days post-operatively from 23.7 ± 2.4 mm to 24.2 ± 2.4 mm in the anterior position and from 24.5 ± 1.8 mm to 24.8 ± 1.9 mm in the midbody vertebral position. However, the height measurements in both positions declined to baseline levels at 6 months and remained at 12 and 24 months.

In the only RCT comparing the impact of kyphoplasty with usual care, Berenson et al[88] reported height restoration in the anterior, midpoint, and posterior points at three spine levels—the mid-thoracic level (T5–T10), transition zone (T11–L2), and lower lumbar region (L3–L5). At the 1-month follow-up, there were no significant differences between the study groups in height restoration in the lumbar region at any point of the vertebrae. There were significant improvements in the kyphoplasty group, compared with the usual care group, at the mid-thoracic level in the anterior (P = .15), mid- (P = .15), and posterior (P = .034) points. However, the mean gains in height with kyphoplasty at these points were 1.0 mm, 1.5 mm, and 1.5 mm, respectively.

The improvements in the transition zone were more significant (P < .0001) in all three vertebral body points. The mean height gains in these regions were similar to those in the mid-thoracic region, but the deterioration or loss of height in the usual care group was much higher in the transition zone, creating a bigger difference. Therefore, the mean gain or loss of vertebral height in these regions (kyphoplasty vs. usual care) were a 2.0 mm gain versus a 0.5 mm loss in the anterior location, a 2.5 mm gain versus a 0.5 mm loss in the midpoint, and a 1.5 mm gain versus a 0.5 mm loss in the posterior position. The absolute height change at the midpoint level of the mid-thoracic region, the best region in terms of vertebral height gained in the kyphoplasty group and deterioration or loss in the usual care group, was cited as a 2.4 mm gain from the 15.5 mm original height with kyphoplasty, and a 0.7 mm loss from the 17.2 mm original height in the usual care group, resulting in a treatment difference of 3.1 mm (95% CI 2.1–4.1, P < .0001).

Kyphosis. The impact of kyphoplasty on local fracture kyphosis was evaluated in four studies, one using the Cobb angle,[94] one using the Gardner angle (see Appendix 2),[89] and two in which the method of evaluation was not reported.[93,97] In the study by Pflugmacher et al[93] involving patients with multiple myeloma, a “kyphotic deformity” (not defined) was present in 70% (14/20) of the patients. Kyphosis was not found for any lower lumbar biconcave fractures. Of the patients with kyphosis, the mean kyphotic angle at baseline was 12.3° (range 3–19°), and there was a mean correction of 6.3° (range 0–18°). In an evaluation by the same authors of kyphosis with metastatic cancer–related vertebral compression fractures, also without reporting the kyphotic angle measurement, investigators noted that the kyphotic angle after kyphoplasty remained unchanged from baseline, 12.0° ± 2.3° to 11.1° ± 2.4°.[97]

A report by Korovessis et al[89] using the Gardner angle for kyphosis also showed no significant change from baseline (12.1° ± 9.0°) after kyphoplasty (10.0° ± 6.8°). Zou et al,[94] using the Cobb kyphotic angle, reported a significant (P < .001) decrease in the kyphotic angle from 17.1° ± 7.2° at baseline to 8.9° ± 6.4° after kyphoplasty.

Overall in the studies, the baseline degree of fracture kyphosis in both the patients with multiple myeloma and those with metastatic cancer was in the mild range, given that (1) thoracolumbar spine regions have a natural kyphotic angle of about 5%[99] and (2) the reliability for kyphotic angle measures on plain radiography evaluated as the absolute mean difference (and 95% CI) for repeated measures was 2.1° ± 6.1° with the Cobb angle and 2.4° ± 6.7° with the Gardner angle.[100] In addition, the threshold for consideration of surgical intervention for spinal sagittal deformity is a 30° or greater kyphotic angle.[101,102]

Table 9: Radiological Morphometric Vertebral Outcomes After Kyphoplasty for Cancer-Related Vertebral Compression Fractures

Author, Year Country	Patients, N Treated VB Levels	Measurement	Vertebral Body, Anterior Height	Vertebral Body, Midline Height	Kyphosis
Multiple Myeloma as Primary Malignancy of Spinal Metastases					
Dudeney et al, 2002[90] United States	18 patients 55 VB levels	On lateral radiographs, percentage of height restored (height regained / height lost) Height regained = post-treatment height – pre-fracture height Height lost = estimated normal height – pretreatment fracture height Normal height estimated by the average heights of the vertebrae above and below the fracture vertebrae	NR	*Pre-operative* Height measurements were possible in only 39/55 levels Mean central VH loss: 7 mm (2–17 mm) In 7 levels, there was minimal height loss (≤ 2 mm) *Post-operative* Data reported only as summary Mean % height restoration in all levels was 34% (0%–100%) In 12 VB levels (31%), there was no height restoration In 23 VB levels, there was some height restoration In 4 VB levels, there was complete restoration	NE
Julka et al, 2014[91] United States	32 patients 76 VB levels (bilateral KP on 71)	Degree of VB collapse estimated semi-quantitatively by Genant vertebral fracture score: Grade 0, normal Grade 1, mildly deformed (20–25% reduction in the anterior, middle, and/or posterior height and a reduction of area 10–20%) Grade 2, mildly deformed (25–40% reduction in any height and a reduction in area 20–40%) Grade 3, severely deformed (about 40% reduction in any height and area)	*Pre-operative* Genant fracture grade for 75 levels, mean 1.9 *Post-operative* Height location not specified; 32/75 levels showed radiographic improvement Of those at 2 weeks, mean grade of 1.53, average improvement of 0.37 grade per level $P < .0001$	Unknown	NE

Author, Year Country	Patients, N Treated VB Levels	Measurement	Vertebral Body, Anterior Height	Vertebral Body, Midline Height	Kyphosis
Lane et al, 2004[92] United States	19 patients 46 VB levels	Lateral radiographs, assessments in the anterior and midline heights, reported as % restoration of lost height from normalized adjacent vertebral bodies	*Pre-operative* NR *Post-operative* Data reported only as summary VH restoration (partial or full) was obtained in 91% (35/46) of fractured VB levels. Of these, the mean VH restoration (for the 35 levels) was 37.8% ± 26.9 of the available defect	*Pre-operative* NR *Post-operative* Midbody height restoration was achieved to some extent in 42/46 levels Of the 42 restored levels, restoration was 53.4% ± 29.1 of the available defect	NE
Pflugmacher et al, 2006[93] Germany	20 patients 48 VB levels	Lateral radiographs, assessments in the anterior and midline heights defined as distance between upper and lower end plates Normal heights were the sum of corresponding heights of the adjacent superior and inferior non-fractured vertebrae divided by 2 Kyphosis angle measurement not noted	*Pre-operative* Mean normal: 32.1 mm Mean post-fracture: 23.4 mm *Post-operative* Post-operative increase of 56% (27/48) of fractured VB levels, with mean increase of 3.8 mm (range 0–16 mm); $P < .05$ At 1 year, a mean decrease in 25/48 fractured bodies, with a mean decrease of 1.3 mm (range, 0–1.5 mm)	*Pre-operative* Mean normal: 31.2 mm Mean post-fracture: 22.1 mm *Post-operative* Post-operative increase of 65% (31/48) of fractured VB levels with mean increase of 4.3 mm (range, 0–17.5 mm), $P < .05$ At 1 year, a mean decrease in 21/48 fractured bodies, with a mean decrease of 1.1 mm (range, 0–1.1 mm)	*Pre-operative* Kyphosis deformity observed in 14/20 patients, with mean kyphotic angle of 12.3° (range 3–19°) Lower lumbar biconcave fractures did not result in kyphotic deformity *Post-operative* Kyphosis deformity was corrected in 11/14 patients, with a mean correction of 6.3° (range 0–18°) $P < .05$ At 1 year, slight loss in kyphosis correction in 6/14 patients with a mean loss of correction of 1.8° (0–1.6°) In 5 patients, the kyphotic correction was maintained

Author, Year Country	Patients, N Treated VB Levels	Measurement	Vertebral Body, Anterior Height	Vertebral Body, Midline Height	Kyphosis
Zou et al, 2010[94] China	21 patients 43 VB levels	Lateral radiographs (as Pflugmacher, above) by 3 spine surgeons, blinded to case details % height variation = fractured vertebrae height/normal estimated vertebral height x 100% Kyphosis evaluated by the Cobb kyphotic angle was measured from the superior end plate of 1 VB 1 level above the injured VB to the inferior end plate of the VB 1 level below	% VH variation (fracture VH/normal VH), mean ± SD *Pre-operative* 56.9 ± 14.2 *Post-operative* Post-operative (same day): 82.9 ± 11.2, *P* < .001 3 months: 84.9 ± 10.2 6 months: 84.1 ± 10.2 12 months: 85.2 ± 9.3, *P* < .001	% VH variation (fracture VH/normal VH), mean ± SD *Pre-operative* 71.0 ± 13.4 *Post-operative* Post-operative (same day): 81.1 ± 6.4, *P* < .001 3 months: 79.2 ± 9.2 6 months: 80.5 ± 9.7 12 months: 84.6 ± 8.5, *P* < .001	Cobb angle, mean ± SD *Pre-operative* 17.1° ± 7.2 *Post-operative* Post op: 8.9° ± 6.4, *P* < .001 3 months: 8.6° ±7.8 6 months: 8.5° ± 8.4 12 months: 8.9° ± 7.9, *P* < .001
Mixed Cancers as Primary Malignancies of Spinal Metastases					
Berenson et al, 2011[88] Australia, Canada, Europe, United States	KP group 70 patients NR	Standing lateral spine radiographs; height by x-ray at posterior margin, anterior margin and midpoint by midthoracic, transition and lumbar regions	NR	*Pre-operative* Mean mid-VH in index T11–L2 fractures: 15.5 mm *Post-operative* At 1 month, height improved 2.4 mm (compared to control group; difference = 3.1 mm) (95% CI, 2.1–4.1; *P* < .0001) Overall, there was significant height restoration in the KP group compared to the control group for mid-thoracic and transition zone (T11–L2) There was no improvement between groups in the lumbar vertebrae or in the anterior measurements for mid-thoracic vertebrae	NE
	Usual care group 64 patients NR	*See above*	*Pre-operative* NR *Post-operative* NR	*Pre-operative* Mean mid-VH in index T11–L2 fractures: 17.2 mm *Post-operative* At 1-month, height worsened by 0.7 mm	NE

Author, Year Country	Patients, N Treated VB Levels	Measurement	Vertebral Body, Anterior Height	Vertebral Body, Midline Height	Kyphosis
Korovessis et al, 2014[89] Greece	Kiva stent 23 patients 41 VB levels	Standing AP and lateral plain radiographs; changes in anterior, posterior and midline vertebral body and degree of segmental kyphosis (Gardner angle) Normal height estimated by the sum of corresponding heights of adjacent superior and inferior non-fractured vertebrae divided by 2	VB height ratio, mean ± SD *Pre-operative* 0.95 ± 0.09 *Post-operative* 0.98 ± 0.05	VB height ratio, mean ± SD *Pre-operative* Middle: 0.94 ± 0.13 Posterior middle: 16 ± 9.15 *Post-operative* Middle: 0.99 ± 0.13 Posterior middle VB: 3.3 ± 7.6	Kyphosis Gardner angle, mean ± SD *Pre-operative* 13.7° ± 11.2 *Post-operative* 14.7° ± 10.6
	KP 24 patients 43 VB levels	*See above*	VB height ratio, mean ± SD *Pre-operative* 0.89 ± 0.19 *Post-operative* 0.96 ± 0.07	VB height ratio, mean ± SD *Pre-operative* Middle: 0.87 ± 0.22 Posterior middle 0.94 ± 0.10 *Post-operative* Middle: 0.93 ± 0.11 Posterior middle: 0.94 ± 0.12	Kyphosis Gardner angle, mean ± SD *Pre-operative* 12.1° ± 9.0 *Post-operative* 10.0° ± 6.8
Pflugmacher et al, 2008[97] Germany	65 patients 99 VB levels	Plain radiographs with anterior and midpoint defined as distance between upper and lower end plates, and normal heights were the sum of corresponding heights of adjacent superior and inferior nearest non-fractured vertebrae divided by 2	VB height, mm, mean ± SD *Pre-operative* 23.7± 2.4 *Post-operative* 3 days: 24.2 ± 2.4 3 months: 24.2 ± 2.5 6 months: 23.9 ± 2.5 12 months: 23.6 ± 2.4 24 months: 23.7± 2.3	VB height, mm, mean ± SD *Pre-operative* 24.5 ± 1.8 *Post-operative* 3 days: 24.8 ± 1.9 3 months: 24.8 ± 1.9 6 months: 24.6 ± 1.9 12 months: 24.5 ± 1.9 24 months: 24.5 ± 1.9	Kyphotic angle, mean ± SD *Pre-operative* 12.0° ± 2.3 *Post-operative* Post-operative: 11.1° ± 2.4 3 months: 11.5° ± 2.4 6 months: 11.8° ± 2.4 12 months: 11.8° ± 2.4 24 months: 12.0° ± 3.3

Abbreviations: CI, confidence interval; KP, kyphoplasty; L, lumbar; NE, not evaluated; NR, not reported; SD, standard deviation; T, thoracic; VB, vertebral body; VH, vertebral height.

B4. Effectiveness of Kyphoplasty and Adjunctive Local Tumour Control Interventions

A summary of the characteristics of clinical studies evaluating the effectiveness of kyphoplasty and local tumour control interventions for cancer-related vertebral compression fractures is outlined in Table 10. Four studies (120 patients) involved these interventions.[103-106] All operators in these studies were surgeons.

One comparative study involved 35 patients with multiple myeloma, treated with kyphoplasty and systemic therapy, palliative external beam radiotherapy and systemic therapy, or systemic therapy alone.[104] The other three studies involved 85 patients with metastatic cancers.[103,105,106] These three studies employed a different local tumour control intervention strategy along with kyphoplasty, including spinal stereotactic radiosurgery,[103] external beam radiotherapy,[105] and radiofrequency ablation using generators and electrodes from Rita Medical Systems, Inc.[106]

The clinical outcomes after these interventions are detailed in Table 11, and the radiological morphometric outcomes, either vertebral height or kyphosis, are outlined in Table 12.

Kyphoplasty and radiotherapy. In the study by Kasperk et al,[104] *pain intensity* levels reported at 1 month following treatment for multiple myeloma were reduced to similar levels in the groups treated with either kyphoplasty or palliative external beam radiotherapy. Pain levels in both groups were significantly lower than those in the group treated with only systemic therapy. *Pain-related disability* evaluated using the Oswestry Disability Index was significantly improved from baseline at the 1-year follow-up in both the kyphoplasty group (53% ± 3.8% to 30% ± 4.5%) and the external beam radiotherapy group (43% ± 7.3% to 35% ± 5.6%), but not the systemic therapy–only group (36% ± 4.8% to 30% ± 5.2%). The baseline mean pain-related disability scores varied for patients undergoing different treatments, but generally disability values were much lower (generally moderate disability) than those in previous reports on vertebral augmentation.

Two other studies, one by Gerszten et al[103] evaluating kyphoplasty with radiosurgery using CyberKnife (Accuray, Sunnyvale, California) and one by Qian et al[105] evaluating kyphoplasty followed by palliative external beam radiotherapy, showed significant reductions in *pain intensity* in follow-up. *Pain-related disability* evaluated using the Oswestry Disability Index and *health-related quality of life* assessed using the Short-Form Health Survey both showed significant improvement in the Qian et al study.[105]

In the Kasperk et al study,[104] the loss in *vertebral heights* at fracture in patients with multiple myeloma was similar at baseline for the three treatment groups (Table 12). Vertebral heights were not greatly increased after kyphoplasty; but in the 2-year follow-up, the height had stabilized and had not reduced further. In comparison, in both the external beam radiotherapy and systemic therapy–only groups, vertebral heights continued to decrease over follow-up. At 1 year, the mean vertebral height in the systemic therapy group was significantly ($P < .001$) below that in the kyphoplasty group; and at 2 years, values for both the external beam radiotherapy ($P = .007$) and systemic therapy ($P = .025$) groups were significantly below those for the kyphoplasty group.

Qian et al[105] also evaluated the impact of kyphoplasty (and external beam radiotherapy) on *vertebral height and kyphosis* for metastatic cancer fractures. Vertebral heights were restored (percentage of original height estimated by averaging the heights of unfractured vertebrae above and below the fractured vertebra) both in the anterior (52.7% ± 16.8% to 85.3% ± 13.2%) and the midline (69.4% ± 12.5% to 82.4% ± 9.6%) positions, and restored heights were maintained over the 2-year follow-up. Kyphosis, measured by the Cobb angle, was also significantly improved over baseline at 24 hours (16.4° ± 4.7° to 8.4° ± 2.5°, $P < .001$), and improvements were maintained over the 2-year follow-up.

Table 10: Summary of Clinical Studies Evaluating the Effectiveness of Kyphoplasty and Adjunctive Local Tumour Control Interventions for Cancer-Related Vertebral Compression Fractures

Author, Year Country	Report Type	Study Recruitment Period	Patients, N (F, M) Age, Mean ± SD (Range)[a]	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Multiple Myeloma as Primary Malignancy of Spinal Metastases					
Kasperk et al, 2012[104] Germany	Comparative retrospective cohort study	2003 to 2006	35 of 73 patients (14 F, 21 M) *Treatment arms* KP + systemic therapy (n = 35), EBRT + systemic therapy (n = 18), systemic therapy only (n = 20) 58.9 ± 10.3 years	Surgery KP at 111 VB levels	Treatment safety and effectiveness of clinical pathway for multiple myeloma, including KP, EBRT, and systemic therapy (VAD-like chemotherapy, stem cell transplantation, bisphosphonates, and pain medications as tolerated) 2 years
Mixed Cancers as Primary Malignancy of Spinal Metastases					
Gerszten et al, 2005[103] United States	Single-site retrospective study, consecutive cases	NR	26 patients (20 F, 6 M) *Primary malignancies* Lung (n = 11), breast (n = 9), renal (n = 4), other (n = 2) 72 years (47–83)	Neurosurgery KP and CKRS at 26 VB levels (16 T, 10 L)	Treatment safety and effectiveness of KP and spinal stereotactic radiosurgery (CKRS) Range 11–24 months
Qian et al, 2011[105] China	Single-site prospective study	January 2003 to January 2008	48 patients (29 F, 19 M) *Primary malignancies* Breast (n = 16), lung (n = 10), prostate (n = 6), stomach (n = 6), cervical (n = 4), other (n = 6) 68.5 years (52–85)	Orthopaedic surgery KP at 124 VB levels (T5 to L5)	Treatment feasibility, safety, and effectiveness of KP followed by EBRT for metastatic vertebral compression fractures 24 months; 7 patients died during follow-up
Sandri et al, 2010[106] Italy	Single-site prospective study	2007 to 2009	11 patients (9 F, 2 M) *Primary malignancies* Multiple myeloma (n = 7), thyroid (n = 2), breast (n = 1), kidney (n = 1) 68 years (58–82)	Orthopaedic surgery RFA and KP at 11 VB levels (1 C, 9 T, 1 L)	Treatment safety and efficacy of combined RFA and KP for spinal lesions 12 months (range 4–18 months); 5 patients died during follow-up

Abbreviations: C, cervical; EBRT, external beam radiotherapy; F, female; KP, kyphoplasty; L, lumbar; M, male; RFA, radiofrequency ablation; SD, standard deviation; T, thoracic; VAD, vincristine, Adriamycin (doxorubicin), and dexamethasone; VB, vertebral body.
[a]Unless otherwise indicated.
[b]If reported in the study.

Table 11: Clinical Outcomes in Studies Evaluating the Effectiveness of Kyphoplasty and Adjunctive Local Tumour Control Interventions for Cancer-Related Vertebral Compression Fractures

Author, Year Country	Interventions Patients, N	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Multiple Myeloma as Primary Malignancy of Spinal Metastases					
Kasperk et al, 2012[104] Germany	KP and systemic therapy (VAD-like chemotherapy, stem cell transplantation, bisphosphonate therapy) and pain medications 35 patients	VAS 0 (no pain) to 100 (worst pain) *Baseline* 81 ± 4.9 *Post-intervention* 1 month: 37 ± 6.1, *P* < .001 1 year: 23 ± 4.9, *P* < .001 2 years: 23 ± 7.1	NR	NR	ODI, mean ± SD *Baseline* 53% ± 3.8 *Post-intervention* 1 year, 30% ± 4.5, *P* < .001
	EBRT and systemic therapy 18 patients	VAS 0 (no pain) to 100 (worst pain) *Baseline* 63 ± 9.7 *Post-intervention* 1 month: 38 ± 8.5, *P* = .002 1 year: 34 ± 8.7, *P* < .001 2 years: 31 ± 9.9	NR	NR	ODI, mean ± SD *Baseline* 43% ± 7.3 *Post-intervention* 1 year: 35% ± 5.6, *P* = .085
	Systemic therapy only 20 patients	VAS 0 (no pain) to 100 (worst pain) *Baseline* 65 ± 7.4 *Post-intervention* 1 month: 48 ± 7.6, *P* = .057 1 year: 35 ± 7.0, *P* < .001 2 years: 38 ± 20.1	NR	NR	ODI, mean ± SD *Baseline* 36% ± 4.8 *Post-intervention* 1 year: 30% ± 5.2, *P* = .236
Mixed Cancers as Primary Malignancy of Spinal Metastases					
Gerszten et al, 2005[103] United States	KP and CyberKnife radiosurgery 26 patients	*Baseline* Graphical results only; mean VAS > 7.0 *Post-intervention (1 month)* Graphical results only; mean VAS reduced to below 3.0	NR	NR	NR

Author, Year Country	Interventions Patients, N	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Qian et al, 2011[105] China	KP and EBRT 1 to 2 weeks post-KP Total: 48 patients 2-year follow-up: 39 patients	*Baseline* 7.4 ± 2.1 *Post-intervention* 24 hours: 3.8 ± 1.6, *P* < .001 1 month: 3.6 ± 1.4, *P* < .001 6 months: 3.2 ± 1.0, *P* < .001 1 year: 3.3 ± 1.5, *P* < .001 2 years: 3.5 ± 1.2, *P* < .001	NR	ODI, mean ± SD *Baseline* 71.5% ± 16.7, *P* < .001 *Post-intervention* 24 hours: 32.4% ± 9.6, *P* < .001 1 month: 31.7% ± 8.8, *P* < .001 6 months: 29.5% ± 10.2, *P* < .001 1 year: 30.4% ± 12.8, *P* < .001 2 years: 31.7% ± 9.5, *P* < .001	SF-36, mean ± SD *Baseline* Bodily pain: 22.5 ± 7.8 Physical functioning: 34.3 ± 10.8 Vitality: 38.5 ± 12.6 Social functioning: 27.1 ± 7.5 *Post-intervention (24 hours)* Bodily pain: 48.5 ± 11.8 Physical functioning: 51.0 ± 9.5 Vitality: 48.3 ± 11.4 Social functioning: 35.4 ±13.5 *Post-intervention (1 month)* Bodily pain: 51.7 ± 8.0 Physical functioning: 52.8 ± 11.2 Vitality: 50.8 ± 9.7 Social functioning: 36.8 ± 9.4 All values remained significantly (*P* < .05) improved over baseline at 24 hours, 6 month, 1 year and 2 year follow-up
Sandri et al, 2010[106] Italy	RFA (Rita Medical Systems, Inc.) and KP 11 patients	*Baseline* 8.0 (7.0–10) *Post-intervention* 72 hours: 1.8 (0–3.0) 6 weeks: 1.9 (1.0–3.0)	A reduction in analgesic use was reported for all cases; details not reported	NR	NR

Abbreviations: EBRT, external beam radiotherapy; KP, kyphoplasty; NR, not reported; ODI, Oswestry Disability Index; RFA, radiofrequency ablation; SD, standard deviation; SF-36, Short-Form Health Survey; VAD, vincristine, Adriamycin (doxorubicin), and dexamethasone; VAS, visual analogue scale.

[a]Unless otherwise indicated.

Table 12: Radiological Morphometric Vertebral Outcomes After Kyphoplasty and Adjunctive Local Tumour-Control Interventions for Cancer-Related Vertebral Compression Fractures

Author, Year Country	Interventions Patients, N Treated VB Levels	Vertebral Body, Anterior Height	Vertebral Body, Midline Height	Kyphosis
Multiple Myeloma as Primary Malignancy of Spinal Metastases				
Kasperk et al, 2012[104] Germany	KP and systemic therapy 35 patients	NR	Percentage of original height (estimated by height of nearest non-deformed vertebral body), mean ± SD *Pre-operative* 64.4% ± 1.8 *Post-op* 1 month: 68.6% ± 1.6, *P* = .044 1 year: 67.6 ± 1.8 2 year: 66.4 ± 2.0	NE
	EBRT and systemic therapy 18 patients	NR	Percentage of original height (estimated by height of nearest non-deformed vertebral body), mean ± SD *Pre-operative* 66.5% ± 4.1 *Post-operative* 1 year: 59.5 ± 4.5, *P* = .071 2-year: 51.3 ± 5.5	NE
	Systemic therapy 20 patients	NR	Percentage of original height (estimated by height of nearest non-deformed vertebral body), mean ± SD *Pre-op* 62.6% ± 4.1 *Post-op* 1 year, 49.3 ± 4.1 *P* = .006 2 year, 46.8 ± 8.5	NE
Mixed Cancers as Primary Malignancies of Spinal Metastases				
Qian et al, 2011[105] China	KP and EBRT 48 patients 124 VB levels	Percentage of original height (estimated as the average of the heights of the nearest unfractured vertebrae above and below the fractured vertebrae), mean ± SD *Pre-operative* 52.7% ± 16.8 *Post-operative* 24 hours: 85.3% ± 13.2, *P* < .001 1 month: 86.2% ± 9.8, *P* < .001 6 months: 86.8% ± 10.5, *P* < .001 1 year: 86.5% ± 11.0, *P* < .001 2 years: 86.9% ± 8.5, *P* < .001	Percentage of original height (estimated as the average of the heights of the nearest unfractured vertebrae above and below the fractured vertebrae), mean ± SD *Pre-operative* 69.4% ± 12.5 *Post-operative* 24 hours: 82.4% ± 9.6, *P* < .001 1 month: 82.9% ± 11.0, *P* < .001 6 months: 83.1% ± 8.7, *P* < .001 1 year: 83.0% ± 10.4, *P* < .001 2 years: 83.3% ± 9.7, *P* < .001	Cobb angle, mean ± SD *Pre-operative* 16.4° ± 4.7 *Post-operative* 24 hours: 8.4° ± 2.5, *P* < .001 1 month: 8.6° ± 2.2, *P* < .001 6 months: 8.7° ± 1.9, *P* < .001 1 year: 8.7° ± 1.5, *P* < .001 2 years: 8.8° ± 2.1, *P* < .001

Abbreviations: EBRT, external beam radiotherapy; KP, kyphoplasty; NE, not evaluated; NR, not reported; SD, standard deviation; VB, vertebral body.

B5. Effectiveness of Kyphoplasty, Vertebroplasty, and Adjunctive Local Tumour Control Interventions

A summary of the characteristics of clinical studies evaluating the effectiveness of vertebroplasty, kyphoplasty, or both with or without local tumour control interventions for cancer-related vertebral compression fractures is outlined in Table 14. The clinical outcomes are listed in Table 15.

Eight studies (1,074 patients) reported on these interventions, of which four (488 patients) involved the multiple myeloma group and four (586 patients) involved the metastatic cancer group. The operators for these interventions were interventional radiologists (n = 5), a surgeon (n = 1), and an anaesthesiologist (n = 1), and there was also a joint effort in which an interventional radiologist performed the vertebroplasty and an orthopedic surgeon performed the kyphoplasty.

Two of these studies[107,108] investigated the effects of palliative external beam radiotherapy along with vertebral augmentation interventions. In the study by Hirsch et al,[107] a course of palliative external beam radiotherapy was given to a subset of patients undergoing either vertebroplasty or kyphoplasty. In the Li et al study,[108] all patients received a course of palliative external beam radiotherapy following vertebroplasty or kyphoplasty.

Eight studies involved vertebroplasty or kyphoplasty procedures chosen in different ways. Four of the studies[109-112] involved treatment choices of vertebroplasty, kyphoplasty, or both procedures for different fractures within patients (Table 13). In four studies,[107,108,113,114] patients were treated with either vertebroplasty or kyphoplasty. The decisions behind the choice of vertebroplasty or kyphoplasty were reported in three studies. Fourney et al[110] reported decisions based on a treatment algorithm that involved providing kyphoplasty for significant kyphosis, defined as greater than 20°, or significant loss (> 50%) in vertebral height. Bartolozzi et al[113] reported that vertebroplasty was preferred in the case of a collapsed vertebral body, wide destruction of posterior lamina, and increased bone density (blastic rather than lytic tumour involvement); kyphoplasty was preferred when the risk of cement leakage was high. Kose et al[114] reported that kyphoplasty was used to treat a more than 50% collapse in vertebral height, whereas vertebroplasty was used for vertebral collapse less than 50%.

Table 13: Choice of Vertebroplasty, Kyphoplasty, or Both for Cancer-Related Vertebral Compression Fractures

Author, Year	Patients, N	VCF Etiology	Vertebroplasty	Kyphoplasty	Kyphoplasty and Vertebroplasty
Reported as Percentage of Cases Receiving Single or Joint Interventions					
Erdem et al, 2013[109]	361	Multiple myeloma	74%	13%	13%
Fourney et al, 2003[110]	56	Metastases	61%	27%	13%
Jha et al, 2010[111]	249	Metastases	19%	39%	42%
Mendoza et al, 2012[112]	79	Multiple myeloma	47%	28%	25%
Reported as Percentage of Cases Receiving a Single Intervention					
Bartolozzi et al, 2006[113]	14	Multiple myeloma	64%	71%	—
Hirsch et al, 2011[107]	201	Metastases	NR	NR	—
Kose et al, 2006[114]	34	Multiple myeloma	47%	52%	—
Li et al, 2014[108]	80	Metastases	48%	53%	—

Abbreviations: NR, not reported; VCF, vertebral compression fracture.

Clinical outcomes. The reports by Erdem et al[109] and Mendoza et al[112] involved large numbers of patients, but they were selected from much larger patient populations undergoing vertebral augmentation at their respective centres. All studies, except for one not evaluating pain intensity,[114] reported a significant reduction in pain intensity following the various vertebral augmentation interventions. Several studies reported on categories of pain reduction efficacy by defining a responder as one experiencing complete, improved, or partial relief of pain; responder rates by these definitions were high, at 84%,[110] 88%,[107] and 93%.[111] Several studies compared differences between vertebroplasty and kyphoplasty in outcomes of pain intensity reduction, and they reported no differences in pain control.[108-110,114]

Three of the studies[109,110,114] also reported reductions in analgesics, all with different measures after vertebral augmentation interventions—narcotic use,[109] analgesic use per week,[114] and analgesic class.[110] Mendoza et al[112] were the only investigators to evaluate the impact of vertebral augmentation on other pain-related symptoms such as fatigue, depression, anxiety, etc. The Edmonton Symptom Assessment Scale, a scale used in palliative care settings, showed significant improvement for fatigue ($P = .01$), depression ($P = .03$), anxiety ($P < .001$), insomnia ($P = .04$), and well-being ($P < .001$). Results for drowsiness ($P = .004$) and difficulty thinking clearly ($P = .04$)—likely more related to pain medications, particularly narcotics—were also significantly improved.

Three studies reported improvements in physical functioning; these used different measures, an increased KPS score,[113] decreased pain disability index,[114] and improved ambulatory capacity.[110] They did not evaluate other pain-related disability measures such as the Oswestry Disability Index or Roland Morris Disability Questionnaire.

Radiological morphometric outcomes. Only one study report radiological morphometric outcomes after kyphoplasty.[110] Investigators evaluated the impacts of kyphoplasty on both the restoration of vertebral body height and correction of kyphosis; the protocol involved kyphoplasty for vertebral compression fractures that were significant, that is, involved more than 50% compression and kyphosis of 20° or higher. The vertical heights from endplate to endplate at the midpoint of the vertebroplasty were measured, and estimates of pre-fracture height were based on the heights of the unfractured vertebrae above the fractured vertebra. The mean height lost prior to kyphoplasty was 9.7 ± 5.1 mm, and the mean height regained was 4.5 ± 3.6 mm. The mean percentage of vertebral height restoration (height regained/height lost × 100) was 42% ± 21%. Kyphosis was measured using the Gardner angle; findings showed a significant reduction ($P = .001$) in the mean kyphotic angle from 25.7° ± 9.7° at pre-treatment to 20.5° ± 8.7° after kyphoplasty.

Table 14: Summary of Clinical Studies Evaluating the Effectiveness of Kyphoplasty, Vertebroplasty, and/or Adjunctive Local Tumour Control Interventions for Cancer-Related Vertebral Compression Fractures

Author, Year Country	Report Type	Study Recruitment Period	Patients, N (F, M) Age, Mean ± SD (Range)[a]	Operator Interventions and Treated Spinal Levels	Study Objectives Follow-Up[b]
Multiple Myeloma as Primary Malignancy of Spinal Metastases					
Bartolozzi et al, 2006[113] Italy	Single-site prospective study	September 2003 to January 2005	14 patients (4 F, 10 M) 54 years (49–72)	Interventional neuroradiology VP at 9 VB levels or KP at 10 VB levels in 19 sessions (T6 to S1)	Treatment safety and effectiveness of VP or KP 10 months (range 1–16 months)
Erdem et al, 2013[109] United States	Single-site retrospective study	January 2001 to May 2007	361 of 792 patients (134 F, 227 M)	Interventional neuroradiology VP and/or KP in 447 sessions VP for 83% of VB levels 68% involved VA at ≥ 2 VB levels VA performed in: one session (75%), two sessions (18%), three to six sessions (7%)	Treatment safety and effectiveness of VP or KP
Kose et al, 2006[114] Turkey	Single-site retrospective study	June 2003 to June 2005	34 patients (18 F, 16 M) KP 63.7 years (48–82) VP 62.2 years (45–80)	Orthopaedic surgery KP at 22 VB levels in 18 patients VP at 28 VB levels in 16 patients	Treatment safety and effectiveness of VP or KP for multiple myeloma
Mendoza et al, 2012[112] United States	Single-site retrospective study	January 2001 to May 2008	79 of 175 patients (32 F, 47 M) 60.1 ± 9.8 years	Anaesthesiology VP (n = 37); KP (n = 22) VP + KP (n = 20) VP performed at: one level (n= 49), two levels (n = 26), three levels or more (n = 4)	Treatment effectiveness of VP or KP to reduce pain and decrease related symptoms such as fatigue, sleep disturbances, depression, and anxiety Mean 1 month (range 11–56 days)
Mixed Cancers as Primary Malignancies of Spinal Metastases					
Fourney et al, 2003[110] United States	Single-site retrospective study	October 2000 to February 2002	56 patients (25 F, 31 M) *Primary malignancy* Multiple myeloma (n = 21), breast (n = 9), lung (n = 6), lymphoma (n = 6), prostate (n = 5), other (n = 9) Median 64 years (30–82)	Neurosurgery or interventional radiology VP and/or KP	Treatment safety and effectiveness of VP or KP Median 4.5 months (range 1 day to 20 months)
Hirsch et al, 2011[107] United States	Single-site retrospective study, consecutive cases	2003 to 2009	201 patients (NR) *Primary malignancies* Multiple myeloma, breast or lung cancer (n = 137); other NR	Interventional radiology VP or KP at 316 VB levels (T11 to L3) and palliative EBRT for 57 patients (pre-VA in 49 patients and post-VA in 8 patients)	Treatment effectiveness of VP or KP and palliative EBRT

Author, Year Country	Report Type	Study Recruitment Period	Patients, N (F, M) Age, Mean ± SD (Range)[a]	Operator Interventions and Treated Spinal Levels	Study Objectives Follow-Up[b]
Jha et al, 2010[111] United States	Retrospective database comparative review	May 2003 to March 2008	*VCF of known metastatic etiology* 147 patients with 238 VCFs (83 F, 64 M) Primary malignancies Multiple myeloma (n = 54), breast (n = 25), lung (n = 26), other (n = 42) 71 ± 12 years *VCF of unknown metastatic etiology* 102 patients with 174 VCF (55 F, 47 M) 69 ± 13 years	Interventional neuroradiology VP (n = 48) or KP (n = 96) or both (n = 105) at 236 VB levels (T, L)	Treatment effectiveness of VP or KP in cancer patients with a known metastatic VCF, compared with cancer patients with a VCF of unknown etiology
Li et al, 2014[108] China	Single-site comparative retrospective database review	January 2003 to January 2008	80 patients (43 F, 37 M) *Primary malignancies* Breast (n = 30), lung (n = 18), prostate (n = 14), stomach (n = 11), other (n = 7) *Kyphoplasty* 42 patients (24 F, 18 M) 68.4 years (52–85) *Vertebroplasty* 38 patients (19 F, 19 M) 65.2 years (49–83)	Orthopaedic surgery (KP) and interventional radiology (VP) KP at 83 VB levels (T, L) VP at 76 VB levels (T, L)	Comparative treatment safety and effectiveness of KP and VP followed by palliative EBRT and/or other antitumour therapy 12 months

Abbreviations: EBRT, external beam radiation therapy; F, female; KP, kyphoplasty; M, male; NR, not reported; SD, standard deviation; VA, vertebral augmentation; VB, vertebral body; VCF, vertebral compression fracture; VP, vertebroplasty.
[a]Unless otherwise indicated.
[b]If reported in study.

Table 15: Clinical Outcomes in Studies Evaluating the Effectiveness of Kyphoplasty, Vertebroplasty, and/or Adjunctive Local Tumour Control Interventions for Cancer-Related Vertebral Compression Fractures

Author, Year Country	Patients, N VB Levels Treated, n	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Multiple Myeloma as Primary Malignancy of Spinal Metastases					
Bartolozzi et al, 2006[113] Italy	14 patients 19 VB levels: 10 KP, 9 VP	*Baseline* Median 9.0 (8.0–10) *Post-intervention (24 hours)* Median 3.0 (2.0–5.0)	NR	NR	KPS, median (range) *Baseline* 50 (30–70) *Post-intervention (24 hours)* 70 (60–90)
Erdem et al, 2013[109] United States	361 patients 447 sessions: 74% VP, 13% KP, 13% VP and KP Selected outcome study group from 792 patients with 1,072 sessions	*Baseline* 6.9 *Post-intervention* 2.7 Mean decrease 4.4 (95% CI, 4.0–4.5)	Pain medications reported in 437 pre/post sessions by 355 patients *Baseline* 70% of patients were using narcotic pain medications, 12% no pain medications *Post-intervention (1 month)* 48% were using narcotic pain medications, 34% using no pain medications	*Baseline* No ambulation difficulties (i.e., walking without assistance) in 28% of patients *Post-intervention* No ambulation difficulties (i.e., walking without assistance) in 59% of patients	NR
Kose et al, 2006[114] Turkey	18 patients (KP) 22 VB levels	NR	Analgesic use, times per week (combined KP and VP groups), median (range) *Baseline* 9 (5–14) *Post-intervention* 6 weeks: 5 (2–9) 6 months: 2 (0–5) 1 year: 3 (0–7)	NR	PDI, mean ± SD (score of 0 to 50 on a 5-item scale*:* pain at rest [VAS 0–10], walking [VAS 0–10], sitting-standing [VAS 0–10], taking a shower [VAS 0–10], wearing clothes [VAS 0–10]) *Baseline* 36 ± 4.5 *Post-intervention* 6 weeks: 12.1 ± 3.6 6 months: 8.6 ± 2.3 12 months: 9.7 ± 2.4, *P* < .001
	16 patients (VP) 28 VB levels	NR	See above	NR	PDI, mean ± SD *Baseline* 37.8 ± 3.3 *Post-intervention* 6 weeks: 15.3 ± 4.1 6 months: 12.2 ± 3.0 12 months: 13.5 ± 2.9 *P* < .001

Author, Year Country	Patients, N VB Levels Treated, n	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Mendoza et al, 2012[112] United States	79 patients (VP in 37 [47%], KP in 22 [28%], VP + KP in 20 [25%])	BPI, median, mean ± SD *Baseline* Least pain: 3.0, 3.8 ± 2.3 Worst pain: 8.0, 8.1 ± 2.0 Pain now: 6.0, 5.6 ± 2.4 Pain on average: 5.0, 5.2 ± 2.2 *Post-intervention (within 2 months)* Least pain: 2.0, 2.3 ± 2.0, *P* < .001 Worst pain: 7.0, 6.3 ± 2.9, *P* < .001 Pain now: 4.0, 3.9 ± 2.5, *P* < .001 Pain, on average: 4.0, 3.9 ± 2.4, *P* < .001	NR	ESAS other symptoms (11-point scale, 0 [none/best] to 10 [worst]), median, mean ± SD *Baseline* Fatigue: 5, 5 ± 3.0 Nausea: 0, 1.6 ± 2.4 Depression: 2, 2.8 ± 2.6 Anxiety: 3, 3.3 ± 2.8, Drowsiness: 2, 3.2 ± 3.2 Difficulty thinking clearly: 1, 2.7 ± 3.1 Shortness of breath: 0, 2.3 ± 2.9 Poor appetite: 2, 2.8 ± 2.8 Insomnia: 1, 2.4 ± 2.9 Well-being: 4, 4 ± 3.1 *Post-intervention (within 2 months)* Fatigue: 4, 3.9 ± 2.8, *P* = .01 Nausea: 0, 1.3 ± 2.4, *P* = .44 Depression: 1, 2.1 ± 2.6, *P* = .03 Anxiety: 1, 2.0 ± 2.5, *P* < .001 Drowsiness: 0, 2.0 ± 2.7, *P* = .004 Difficulty thinking clearly, 1, 2.0 ± 2.4, *P* = .04 Shortness of breath: 0, 1.8 ± 2.4, *P* = .12 Poor appetite: 2, 2.6 ± 3.1, *P* = .12 Insomnia: 1, 2.3 ± 2.8, *P* = .04 Well-being: 2, 2.6 ± 2.8, *P* < .001	NR

Author, Year Country	Patients, N VB Levels Treated, n	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Mixed Cancers as Primary Malignancies of Spinal Metastases					
Fourney et al, 2003[110] United States	56 patients (34 VP [61%], 15 KP [27%], 7 VP + KP [13%]) 97 VB levels (65 VP and 32 KP)	*Baseline* Median 7.0 *Post-intervention (24 hours)* Median 2.0, $P < .001$ Improvement or complete pain relief was achieved following 49 procedures (84%); there was no change in pain following 5 procedures (9%); There was no difference in pain reduction between the 3 groups	Analgesic class, median Class 1: none Class 2: NSAIDS, acetaminophen Class 3: codeine, hydrocodone, oxycodone, propoxyphene hydrochloride Class 4: morphine (slow-intermediate release), fentanyl (transdermal), oxycodone (slow-intermediate release) Class 5: intravenous narcotic agent *Baseline* 3.0 *Post-intervention* 3.0 *Change from pre-op to 1 month post-op, n* Class 1: n = 3 to 5 Class 2: n = 1 to 3 Class 3: n = 18 to 18 Class 4: n = 16 to 14 Class 5 n = 3 to 1	Subjective ambulatory capacity assessment *Post-intervention* 2 of the 13 patients walking with assistive devices were able to walk unaided by 1 month 2 patients who were wheelchair-bound due to severe back pain were walking with assistive devices by 1 month Ambulatory status was not worsened in any patient	NR
Hirsch et al, 2011[107] United States	201 patients 316 VB levels VP or KP not reported; 57 patients also received palliative EBRT either pre- (n = 49) or post- (n = 8) VA procedure	Responder status[b] *Post-intervention* 88% responders; of those, 39% had complete pain relief Non-responders: 4% reported worse pain	Pain medication 5-point score 0 = no medication 1 = NSAIDS and over-the counter 2 = short-acting opioids 3 = long-acting opioids 4 = pump, patch or IV medication Distribution NR	NR	RMDQ only for 18 patients

Author, Year Country	Patients, N VB Levels Treated, n	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Jha et al, 2010[111] United States	249 patients (48 VP, 96 KP, 105 VP + KP) 236 VB levels 102 with VCF and documented metastases by imaging or pathology	Responder status[b] *Post-intervention* 93% responders in the VCF documented metastases group (30% complete pain relief, 59% improved pain) 89% responders in the undocumented metastases group 89% (31% complete pain relief, 60% improved pain) No difference in responder status across the 3 groups	NR	NR	NR
Li et al, 2014[108] China	42 patients (KP) 83 VB levels	Baseline 7.4 ± 2.0 *Post-intervention* 24 hours: 3.8 ± 1.6, *P* < .001 12 months: 3.2 ± 1.4, *P* < .001 Differences between groups were not significant at any time point	NR	NR	NR
	38 patients (VP) 76 VB levels	*Baseline* 6.7 ± 2.4 *Post-intervention* 24 hours: 3.7 ± 1.4, *P* < .001 12 months: 3.1 ± 1.3, *P* < .001	NR	NR	NR

Abbreviations: BPI, Brief Pain Inventory; CI, confidence interval; EBRT, external beam radiation therapy; ESAS, Edmonton Symptom Assessment Scale; KP, kyphoplasty; KPS, Karnofsy Performance Scale; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; PDI, pain disability index; PRT, palliative radiotherapy; RMDQ, Roland Morris Disability Questionnaire; SD, standard deviation; VA, vertebral augmentation; VAS, visual analogue scale; VB, vertebral body; VCF, vertebral compression fracture; VP, vertebroplasty.
[a]Unless otherwise indicated.
[b]Responder status: those with improved or resolved pain. Non-responder: no change, or worsening of pain. Pain categorized using a 4-level scale: 1, complete resolution of pain; 2, improvement in fracture-related pain; 3, no change in pain; 4, worsening of pain.

Section C. Effectiveness of Vertebral Augmentation for Special or High-Risk Vertebral Compression Fractures

The subsections for the effectiveness outcome review of vertebral augmentation for special or high-risk cases are these: C1. Vertebral Fractures With Neurological Symptoms, Posterior Vertebral Wall Defects, or Spinal Canal Compromise; C2. Cervical Vertebral Fractures; C3. Sacral Vertebral Compression Fractures; and C4. Vertebral Hemangiomas.

C1. Effectiveness of Vertebral Augmentation for Vertebral Fractures With Neurological Symptoms, Posterior Vertebral Wall Defects, or Spinal Canal Compromise

Table 16 outlines a summary of the characteristics of clinical studies evaluating the effectiveness of vertebral augmentation interventions with or without adjunctive local tumour control interventions for high-risk cancer-related vertebral compression fractures. The studies each included cases having one or more contraindications to vertebral augmentation—such as presenting with neurological symptoms, having a vertebral compression fracture involving defects in the posterior wall vertebral body, or having tumour encroachment on or within the spinal cord, with varying cord involvement or narrowing. All of the studies, except for one involving multiple myeloma,[115] dealt with vertebral compression fractures due to metastatic cancers.

Overall there were 19 reports (649 patients) involving vertebral augmentation interventions: 14 reports (534 patients) about vertebroplasty and five (46 patients) on kyphoplasty (two of these involved kyphoplasty and vertebroplasty interventions[116,117]). Of the 19 studies, four discussed adjunctive local tumour control interventions (all with vertebroplasty)—three involving radiofrequency ablation[118-120] and one[121] involving an interventional tumour removal device.

The operators for the vertebral augmentation intervention studies (vertebroplasty or vertebroplasty and kyphoplasty) were interventional radiologists (n = 11), a surgeon (n = 1), an anaesthesiologist (n = 1), and in one study both an interventional radiologist and an orthopedic surgeon. All of the procedures were performed with conscious sedation. In the kyphoplasty intervention studies, the operators were interventional radiologists (n = 2), surgeons (n = 2), and an anaesthesiologist (n = 1). The kyphoplasty procedures were also performed using conscious sedation, except for one study that involved general anaesthesia.[122]

Clinical outcomes after vertebroplasty. For the vertebroplasty clinical studies, baseline measures of back pain intensity were reported in eight of 14 reports—all were in the high pain intensity levels (Table 17).[115,120,123-128] Pain intensity was reported as resolved or significantly improved post-procedurally in the majority of cases. Although radicular (leg) pain was reported in several articles, back and leg pain levels were often not reported distinctly. Analgesic use was discussed in five studies, all reporting reduced analgesics, mainly the reduction or elimination of narcotics.[119,120,123,124,129] Three reports documented the impact of vertebroplasty on mobility; generally, they found improved ambulation after the procedure.[123,128,130]

Four studies evaluated neurological symptoms or degree of cord tumour involvement or compression after vertebroplasty.[121,130-132] Two reports[130,132] stratified patients undergoing vertebroplasty in groups with MRI-documented increasing epidural involvement (none, mild, and moderate); the impact of vertebroplasty was evaluated in one of these studies as a change in mobility[130] and in the other by a change in the American Spinal Injury Association neurological impairment score (ASIA score) or neurological symptoms.[126] Shimony et al[130] found that improvement in mobility status was more likely in patients with no (57%, 8/14) or mild (61%, 11/18) epidural involvement than in those with moderate (39%, 7/18) epidural involvement. However, mobility status was not more likely to deteriorate in patients with moderate epidural involvement—mobility status decreased in only five patients (10%) out of the entire study group. In the Sun et al study,[126] none of the patients were reported to have a worsening of spinal cord or cauda equina compression, and six of the 13 patients with neurological deficits rated as incomplete impairment (ASIA scale classification C or D) had their symptoms of neurological compression improve.

The study by Saliou et al[131] included patients with posterior vertebral wall destruction and more severe neurological deficits: 11 patients were evaluated as having complete paraplegia or no motor function (ASIA scale A or B), and four patients had incomplete paraplegia (ASIA scale C or D). Although there was no deterioration in patients presenting with clinical symptoms of cord or cauda equina compression after vertebroplasty, there was also no modification of paraplegia in any of these patients.

In the Li et al study,[121] a non-randomized comparison was made between vertebroplasty and the use of an interventional device along with vertebroplasty to simultaneously remove tumour mass from the vertebral body. The majority of the patients in both groups were assessed with neurological deficits at the ASIA scale C or D for incomplete paraplegia—92% (22/24) in the combined treatment group and 96% (27/28) in the vertebroplasty-only group. The recovery or improvement of neurological symptoms of cord compression was higher in the combined treatment group (83%, 95% CI 66%–99%) than in the vertebroplasty-only group (43%, 95% CI 23%–62%).

Of the three studies using radiofrequency ablation in conjunction with vertebroplasty for these high-risk fractures,[119,120,125] only one reported neurological assessments.[125] In that study of case reports by Mazumdar et al,[125] pain and lower extremity weakness improved and both patients were able to walk freely.

Clinical outcomes after kyphoplasty. There were fewer studies (five reports[116,117,122,133,134]) employing kyphoplasty for high-risk vertebral fractures, and only one[133] reported changes in neurological deficits. In this study by Dalbayrak et al,[133] 10 patients had epidural tumour extension and the ASIA impairment scale scores at baseline were D (incomplete impairment) in 11 patients and E (normal) in 20 patients. Post-procedurally, 30 patients achieved the normal ASIA E score and one still had an ASIA D score. The Hentschel et al study[116] was the only one to choose vertebroplasty or kyphoplasty for two different patient subgroups—those with or without a contraindication to vertebral augmentation. Kyphoplasty was chosen if there was significant kyphosis with a relatively acute fracture. Vertebroplasty was more commonly performed than kyphoplasty for both fractures without (78% and 89 levels vs. 22% and 25 levels) and with contraindications (72% and 13 levels vs. 28% and 5 levels). None of the patients in either group had evidence of cord compression; although, in the group with contraindications, two patients had tumour cord involvement and two had radiculopathy. After vertebroplasty, the radiculopathy resolved in both patients.

Radiological morphometric outcomes were reported in two of the studies involving kyphoplasty.[122,133] Dalbayrak et al[133] evaluated the impact of kyphoplasty on both vertebral height restoration and the correction of Cobb kyphotic angles in 31 patients. The mean percentage of vertebral body height loss significantly decreased ($P < .05$) from baseline to post-kyphoplasty, from 27.8% ± 1.3% to 22.4% ± 10.0% in the thoracic fracture region and from 27.7% ± 12.5% to 18.4% ± 1.4% in the lumbar fracture region. The absolute heights of the vertebral body were not reported; therefore, the magnitude of change could not be interpreted.

Although the mean kyphotic angles in both the thoracic and lumbar fracture regions were significantly improved ($P < .05$), the mean angles in both regions were not considered to be clinically significant. Pre-operative to post-operative values in the thoracic region changed from 21.2° ± 11.4° to 17.0° ± 9.8° and in the lumbar region changed from 15.3° ± 8.8° to 10.4° ± 7.2°. In the Eleraky et al study,[122] involving 14 patients, five with cord compression, investigators evaluated the mean kyphotic angle (defined by the inferior and superior plate heights of the affected vertebrae, an alternative to using the Cobb angle). The 25.0° kyphosis angle pre-procedurally and the post-procedural angles of 22.7° and 26.3° at follow-up were not significantly different.

Table 16: Summary of Clinical Studies Evaluating the Effectiveness of Vertebral Augmentation for High-Risk Vertebral Compression Fractures

Author, Year Country	Report Type	Study Recruitment Period	Patients, N (F, M) Age, Mean ± SD (Range)[a]	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Vertebroplasty for Spinal Fractures With Neurological Symptoms or Spinal Canal and/or Posterior Wall Compromise					
Alvarez et al, 2003[123] Spain	Single-site retrospective study, consecutive cases	April 1996 to February 2002	21 patients (14 F, 7 M) *Primary malignancies* Lung (n = 4), gastrointestinal stromal (n = 3), renal (n = 3), breast (n = 3), prostate (n = 2), uterine (n = 1), other (n = 5) 58 years (27–78)	Interventional neuroradiology VP at 27 VB levels (T, L)	Treatment effectiveness, procedural outcomes, and quality of life
Appel et al, 2004[124] United States	Single-site retrospective study	June 9 to July 1, 2002	23 patients (NR) Cancers (primary malignancy NR) (n = 7); osteoporosis (n = 16)	Interventional radiology 23 patients (7 with cancer) from 288 patients in 350 VP sessions at 686 VB levels	Treatment safety and effectiveness of VP with spinal cord compromise
Basile et al, 2011[115] Italy	Single-site prospective study	January 2007 to January 2010	24 patients (13 F, 11 M) *Primary malignancy* Multiple myeloma (n = 24) 54.7 years (42–67)	Interventional radiology VP at 34 VB levels (16 T, 18 L)	Treatment safety with VP and delayed cement infusion with osteolysis or fracture of posterior wall
Georgy et al, 2009[118] United States	Single-site retrospective study, consecutive cases	NR	37 patients (21 F, 16 M) *Primary malignancies* Breast (n = 9), lung (n = 6), multiple myeloma (n = 6), other (n = 16) Range 34–89 years	Interventional radiology RFA (Cavity Spine Wand) and VP at 44 VB levels and KP at 14 VB levels	Technical outcomes and safety of RFA and VA, VP or KP
Hentschel et al, 2004[129] United States	Case report	August 2001	1 patient (F) *Primary malignancy* Renal cell carcinoma and thymic cancer 60-year-old	Neurosurgery VP at T7	Treatment safety and effectiveness of VP for vertebra plana VCF with cord compression
Li et al, 2013[121] Gu et al, 2014[135] China	Single-site comparative cohort study	October 2009 to June 2012	52 of 63 patients (18 F, 34 M) *Primary malignancies* Lung (n = 27), liver (n = 5), thymic (n = 5), colon (n = 3), prostate (n = 3), breast (n = 2), multiple myeloma (n = 2), other (n = 5) 59.6 years (37–90)	Interventional radiology VP at 94 VB levels	Treatment safety and effectiveness of VP compared to VP and ITR in patients with VCFs and neurological symptoms of cord compression Mean 11 ± 6.3 months (VP + ITR) Mean 14.3 ± 6.7 months (VP)

Author, Year Country	Report Type	Study Recruitment Period	Patients, N (F, M) Age, Mean ± SD (Range)[a]	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Mazumdar et al, 2010[125] United States	Case reports	NR	2 patients (1 F, 1 M) *Primary malignancies* Breast cancer (n = 1), multiple myeloma (n = 1) 71-year-old (F), 60-year-old (M)	Interventional radiology VP at L4 and L3 VB levels	Treatment effectiveness for VCF and radicular symptoms of pain and lower-extremity weakness
Prologo et al, 2013[119] United States	Single-site retrospective study	September 2007 to September 2012	15 patients (8 F, 7 M) *Primary malignancies* Lung (n = 4), breast (n = 3), prostate (n = 2), other (n = 6) 67.8 ± 15.3 years	Interventional radiology RFA and VP at 15 VB levels (3 T, 12 L)	Treatment feasibility, safety, and effectiveness of RFA (Cavity Spine Wand) and VP for VCFs with and without epidural involvement
Saliou et al, 2010[131] France	Single-site retrospective study	1990 to 2006	51 of 508 consecutive patients (22 F, 29 M) *Primary malignancies* Breast (n = 8), lung (n = 8), kidney (n = 7), multiple myeloma (n = 5), plasmacytoma (n = 3), bladder (n = 4), other (n = 16) 62.5 years (28–85)	Interventional neuroradiology VP at 74 VB levels	Treatment feasibility, safety, and effectiveness of VP for malignant spine fractures with epidural involvement To 5 years
Shimony et al, 2004[130] United States	Single-site prospective comparative study	June 1998 to April 2002	50 of 277 patients (25 F, 25 M) *Primary malignancies* Multiple myeloma (n = 14), lung (n = 13), breast (n = 8), prostate (n = 3), lymphoma (n = 3), other (n = 9) *Epidural involvement* Group 1, none (n = 14), Group 2, mild (n = 18), Group 3, moderate (n = 18) 62.7 ± 14 years	Interventional radiology VP in 60 sessions at 129 VB levels (T1 to L5) VP performed at one level (n = 14), two levels (n = 16), three levels (n = 10), four levels (n = 3), five levels (n = 2), six levels (n = 4), seven levels (n = 1)	Treatment safety and effectiveness of VP with malignant compression fractures and epidural involvement To 2 years; median 3 months; 45 patients died during follow-up
Sun et al, 2011[132], 2014[126] China	Single-site retrospective study, consecutive cases	March 2000 to May 2012	43 patients (24 F, 19 M) *Primary malignancies* Lung (n = 13), breast (n = 12), kidney (n = 5), stomach (n = 4), bladder (n = 3), uterine (n = 3), colon (n = 2), ovary (n = 1) *Epidural involvement* Group 1 none (n = 25 levels); Group 2, mild (n = 23 levels); Group 3 moderate (n = 21 levels) 64.1 years (34–84)	Interventional radiology VP at 69 VB levels (T3 to L5)	Treatment safety and effectiveness of VP for painful spinal metastases with epidural encroachment 12 months

Author, Year Country	Report Type	Study Recruitment Period	Patients, N (F, M) Age, Mean ± SD (Range)[a]	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Trumm et al, 2012[127] Germany	Single-site retrospective study	December 2001 to June 2009	202 patients (116 F, 86 M) *Primary malignancies* Breast (n = 68), multiple myeloma (n = 40), lung (n = 22), renal (n = 10), prostate (n = 8), leukemia/lymphoma (n = 7), sarcoma (n = 6), pancreas (n = 5), thyroid (n = 4), other (n = 32) 63.2 ± 8.6 years	Interventional radiology VP in 231 sessions at 331 VB levels VP performed at one level (n = 140), two levels (n = 82), three levels (n = 9)	Technical procedure and treatment safety and effectiveness of VP with primary CT-fluoroscopic guidance for painful malignant vertebral osteolytes with and without fractures, and with and without epidural involvement
Van der Linden et al, 2007[120] Netherlands	Single-site retrospective study	July 2003 to December 2005	12 patients (4 F, 8 M) *Primary malignancies* Renal (n = 4), breast (n = 2), lung (n = 2), multiple myeloma (n = 2), B-cell lymphoma (n = 1), chondrosarcoma (n = 1) 57 years (31–79)	Interventional radiology and orthopedic surgery RFA and VP at 12 VB levels (6 L, 4 T, 2 C)	Treatment safety and effectiveness of RFA (RITA and Cool-tip) and VP in patients with posterior vertebral wall defects, with and without spinal canal involvement 3 months; 4 patients died during follow-up
Woo et al, 2013[128] Korea	Case report	NR	1 patient (M) Cholangiocarcinoma 52-year-old	Anaesthesiology VP at L4	Treatment effectiveness and safety of VP for spinal metastases and radicular pain due to metastatic compression of dorsal root ganglion resistant to multiple spinal injection blocks
Kyphoplasty or Kyphoplasty and Vertebroplasty for Spinal Fractures With Neurological Symptoms or Spinal Cord and/or or Posterior Wall Compromise					
Dalbayrak et al, 2010[133] Turkey	Single-site retrospective review	NR	31 patients (17 F, 14 M) *Primary malignancies* Gastric (n = 7), breast (n = 6), lung (n = 4), multiple myeloma (n = 6), other (n = 8) 62 years (35–78)	Neurosurgery KP at 39 VB levels (T or L)	Procedural and treatment safety and effectiveness Follow-up NR; half with epidural involvement
Eleraky et al, 2011[122] United States	Single-site retrospective study	NR	14 of 23 patients (6 F, 8 M) *Primary malignancies* Multiple myeloma (n = 6), lung (n = 3), breast (n = 2), other (n = 3) 62 years (41–71)	Neurosurgery KP at 30 VB levels (T1 to T5)	Treatment effectiveness of KP for upper thoracic VCFs Mean 16 months; minimum 1 year

Author, Year Country	Report Type	Study Recruitment Period	Patients, N (F, M) Age, Mean ± SD (Range)[a]	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Hentschel et al, 2005[116] United States	Single-site consecutive comparative registry review	January 2001 to July 2003	66 patients (32 F, 34 M) *Group 1 (no contraindication)* 49 patients (24 F, 25 M) Primary malignancies Multiple myeloma (n = 24), metastases (n = 8), hemangioma (n = 2) osteoporosis (n = 15) Median 64 years (29–88) *Group 2 (contraindication)* 17 patients (8 F, 9 M) Primary malignancies Multiple myeloma (n = 11), metastases (n = 5), hemangioma (n = 0); osteoporosis (n = 1) Median 61 years (42–75)	Interventional radiology *Group 1 (no contraindication)* VP at 89 VB levels KP at 22 VB levels *Group 2 (contraindication)* VP at 13 VB levels KP at 5 VB levels	Comparative treatment safety and effectiveness of VP or KP in groups with contraindicated conditions and those with conventional criteria
Knight et al, 2008[117] Canada	Case series	NR	3 patients (3 F) *Primary malignancies* Breast (n = 1), lung (n = 1), multiple myeloma (n = 1) 32-year-old, 59-year-old, 67-year-old	Interventional radiology KP at T9 VP at T6 VP at T9	Effectiveness of spinal cement augmentation under C-arm CT guidance with spinal column narrowing
Lim et al, 2011[134] Korea	Case report	NR	1 patient (F) *Primary malignancy* Gastric cancer and cholangiocarcinoma 76-year-old	Anaesthesiology KP at T12 and L1	Treatment safety and effectiveness of KP with VCF with large vertebral bony defect and neurological symptoms

Abbreviations: CT, computed tomography; F, female; ITR, interventional tumour removal; KP, kyphoplasty; L, lumbar; M, male; NR, not reported; RFA, radiofrequency ablation; SD, standard deviation; T, thoracic; VB, vertebral body; VCF, vertebral compression fracture; VP, vertebroplasty.
[a]Unless otherwise indicated.
[b]If reported in study.

Table 17: Clinical Outcomes in Studies Evaluating the Effectiveness of Vertebral Augmentation for High-Risk Vertebral Compression Fractures

Author, Year Country	Patients, N Risks VB Levels Treated, n	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Vertebroplasty for Spinal Fractures with Neurological Deficits or Spinal Canal and/or Posterior Wall Compromise					
Alvarez et al, 2003[123] Spain	21 patients Neurological deficits (n = 10), radiculopathy pyramidal irritation (n = 8), no risk (n = 3) 27 VB levels 15 received PRT; 3 received neural decompression surgery	*Baseline* Range 8.0–10 *Post-intervention* VAS reduced in all cases 24 hours: 16 patients with a VAS ≤ 4.0 3 months: 17 patients with a VAS ≤ 4.0	*Baseline* 14 patients were on high morphine doses *Post-intervention* 7 of the 14 patients did not require pain medication	Gait *Group change in gait from pre-op to post-op* Group 1 (non-ambulatory): n = 11 to 3 Group 2 (gait with a cane): n = 2 to 2 Group 3 (gait without support): n = 8 to 16	Tokuhashi score, mean (range) *Baseline* 5.5 (2.0–9.0) *Post-intervention* Tokuhashi scores were maintained in all but 2, whose scores improved by 1 point Patient satisfaction: very satisfied (n = 7), satisfied (n = 10), acceptable (n = 2), dissatisfied (n = 2)
Appel et al, 2004[124] United States	23 patients (7 were cancer cases) VCF with MRI-defined effacement of the epidural space or spinal cord deformity due to VCF 26 VB levels	*Baseline* 7.6 (2.0–10) *Post-intervention* 24 hours: 1.7 (0–5.0) 1 hour: 12 patients reported complete resolution of pain	*Baseline* NR *Post-intervention* 11 patients were no longer taking any pain medication	NR	NR
Basile et al, 2011[115] Italy	24 patients VCF with posterior wall osteolysis or fracture 34 VP-treated VB levels	*Baseline* NR *Post-intervention (24 hours)* 5.0 (2.0–7.0)	NR	*Baseline* 19 were on complete bed rest due to pain *Post-intervention* NR	*Baseline* NR *Post-intervention* 2 of the 3 patients with tumour extended into the epidural space had cement dorsal leakage without increased neurological symptoms
Georgy et al, 2009[118] United States	37 patients VCF with VB cortical disruption, epidural extension, paraspinal extension or a combination 44 RFA- and VP-treated VB levels	*Baseline* NR *Post-intervention* 89% reported pain relief	NR	NR	NR

Author, Year Country	Patients, N Risks VB Levels Treated, n	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Hentschel et al, 2004[129] United States	1 patient VCF with MRI-defined vertebra plana; 85% collapse of anterior ¾ of T7 and associated epidural hematoma secondary to metastases	*Baseline* NR *Post-intervention* Near complete relief of axial and radicular pain at rest and with movement	*Baseline* NR *Post-intervention* Required significantly less opioid medication	NR	NR
Li et al, 2013[121] Gu et al, 2014[135] China	24 patients had VCF with neurological symptoms of cord compression 38 VP- and ITR-treated VB levels	*Baseline* NR *Post-intervention* Pain resolved or improved in 96% (23/24)	NR	*Baseline* ASIA impairment scale: Complete paraplegia (A or B): n = 2 Incomplete paraplegia (C or D): n = 22 *Post-intervention* Neurological symptoms of cord compression recovered (n = 9) or improved (n = 10): 83% (95% CI, 66%–99%)	NR
	38 patients VCF with neurological symptoms of cord compression 56 VP-treated VB levels	*Baseline* NR *Post-intervention* Pain resolved or improved in 100% (28/28)	NR	*Baseline* ASIA impairment scale: Complete paraplegia (A or B): n = 1 Incomplete paraplegia (C or D): n = 27 *Post-intervention* Neurological symptoms of cord compression recovered (n = 2) or improved (n = 10): 43% (95% CI, 23%–62%)	NR
Mazumdar et al, 2010[125] United States	2 patients VCF with posterior wall degradation and cord compression radicular pain 2 VP- and coblation RFA–treated VB levels	*Baseline* 8.0, 10.0 *Post-intervention* Complete relief of pain and lower-extremity weakness in both patients	NR	NR	NR

Author, Year Country	Patients, N Risks VB Levels Treated, n	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Prologo et al, 2013[119] United States	15 patients VCF with posterior wall defects and/or epidural involvement 15 VP- and coblation RFA–treated VB levels	*Baseline* NR *Post-intervention (24 hours)* All patients reported marked improvement in pain	Narcotic use, morphine equivalent mg/24 hours, mean ± SD *Baseline* 266 ± 120.13 *Post-intervention* 180 ± 134.4 10 patients reported reduced opioid use; 3 patients discontinued opioid use	NR	NR
Saliou et al, 2010[131] France	51 patients VCF with posterior wall destruction and/or epidural involvement 74 VP-treated VB levels	*Baseline* NR *Post-intervention (24 hours)* 94% (48/51) significant pain relief; 6% (3/51) no significant pain relief	NR	*Baseline* ASIA impairment scale Complete paraplegia (A or B): n = 11 (5 central cord, 3 conus medullaris, 3 cauda equina) Incomplete paraplegia (C or D): n = 4 (all central cord) Normal (E): n = 37 *Post-intervention* No deterioration of neurological symptoms occurred among those with neurological symptoms of the spinal cord or cauda equina compression and no modification of paraplegia was observed in any patient	NR
Shimony et al, 2004[130] United States	50 patients VCF with epidural space involvement 129 VP-treated VB levels Group 1, no epidural involvement (n = 14)	*Baseline* NR *Post-intervention* Pain response: resolved (n = 5), decreased (n = 8), no change (n = 1), increased (n = 0)	NR	*Baseline* NR *Post-intervention* Change in mobility status: increased (n = 8); no change (n = 5); decreased (n = 1)	NR

Author, Year Country	Patients, N Risks VB Levels Treated, n	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
	Group 2, mild epidural involvement (n = 18)	*Baseline* NR *Post-intervention* Pain response: resolved (n = 9), decreased (n = 6), no change (n = 1), increased (n = 2)	NR	*Baseline* NR *Post-intervention* Change in mobility status: increased (n = 11); no change (n = 5); decreased (n = 2)	NR
	Group 3, moderate epidural involvement (n = 18)	*Baseline* NR *Post-intervention* Pain response: resolved (n = 4), decreased (n = 9), no change (n = 4), increased, (n = 1)	NR	*Baseline* NR *Post-intervention* Change in mobility status: increased (n = 7); no change (n = 9); decreased (n = 2)	NR
Sun et al, 2011,[132] 2014[126] China	43 patients VCF with epidural encroachment, with or without neurological deficits by ASIA scales 69 VP-treated VB levels; 14 patients had neurological signs of spinal cord or cauda equina compression, ASIA scale A (n = 1) and ASIA scale C or D (n = 13)	*Baseline* 7.6 (6.0–10) *Post-intervention* Effective pain relief (≥ 50% improved VAS scores) 24 hours: 93% (40/43) 1 week: 95% (41/43) No effective pain relief 1 week: 5% (2/43)	NR	*Baseline* Group A: no epidural encroachment (23 VB levels) Group B: mild epidermal encroachment without cord deformity (23 VB levels) Group C: epidermal encroachment with spinal cord deformity (21 VB levels) *Post-intervention* No patient reported worsening of spinal cord or cauda equina compression symptoms 6 of 13 patients with incomplete impairment had improved neurological compression symptoms 3 patients reported no change in radiculopathy and were treated with selective nerve blocks; transient improved pain in 2 patients	NR

Author, Year Country	Patients, N Risks VB Levels Treated, n	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Trumm et al, 2012[127] Germany	202 patients Posterior wall osteolytic destruction and epidural involvement 331 VP-treated VB levels	*Baseline* 6.2 ± 3.1 *Post-intervention* 24 hours: 4.0 ± 3.5 6 months: 2.9 ± 2.8	NR	NR	NR
Van der Linden et al, 2007[120] Netherlands	12 patients Posterior wall defects and/or spinal canal narrowing) VP- and RFA (RITA Medical Systems or Radionics Cool-tip)–12 treated VB levels	VAS (0, no pain to 20, worst pain) *Baseline* 17.3 ± 2.5 (13–20) *Post-intervention* 1 week: 9.3 ± 4.8 (2.0–18.0), $P < .001$ 4 patients also had additional radicular pain, which decreased somewhat in 3 of 4	*Baseline* Opioid use: n = 10 NSAIDs: n = 2 *Post-intervention (4 weeks)* Opioid use: n = 5 NSAID: n = 3 No analgesics: n = 1	NR	*Baseline* NR *Post-intervention* Treatment satisfaction: well satisfied (n = 11)
Woo et al, 2013[128] Korea	1 patients Posterior wall defect and symptomatic compression MRI-defined of dorsal root ganglion VP-treated L4	*Baseline* 8.0 *Post-intervention* 24 hours: 1.0	NR	*Baseline* Unable to stand due to weakness or able to lie supine due to radiating pain *Post-intervention* Able to walk without radicular pain	NR
Kyphoplasty or Kyphoplasty and Vertebroplasty for Fractures with Neurological Symptoms or Spinal Cord and/or Posterior Wall Compromise					
Dalbayrak et al, 2010[133] Turkey	31 patients Posterior wall defects and/or epidural involvement 39 KP-treated VB levels No epidural tumour extension (n = 29 VB levels)	*Baseline* 7.4 ± 2.2 *Post-intervention* 24 hours: 1.3 ± 1.4	NR	ASIA impairment scale *Baseline* Incomplete paraplegia (D): n = 11 Normal (E): n = 20 *Post-intervention (24 hours)* Incomplete paraplegia (D): n = 1 Normal (E): n = 30	NR
	Epidural tumour extension (n = 10 VB levels)	*Baseline* 7.0 ± 1.8 *Post-intervention (24 hours)* 2.0 ± 1.1	NR	Reported above for whole group	NR

Author, Year Country	Patients, N Risks VB Levels Treated, n	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Eleraky et al, 2011[122] United States	14 patients Cord compression (n = 5) 30 KP-treated VB levels	VAS (0, no pain to 100, worst pain) *Baseline* 79 ± 12.9 *Post-intervention* 24 hours: 37 ± 9.9, *P* < .001 3 months: 22 ± 8.9, *P* < .001 6 months: 22 ± 6.9, *P* < .001 12 months: 30 ± 8.2, *P* < .001	NR	NR	ODI, mean ± SD *Baseline* 83% ± 12.4 *Post-intervention* 24 hours: 40% ± 15.1, *P* < .001 3 months: 30% ± 6.7, *P* < .001 6 months: 30% ± 10.3, *P* < .001 12 months: 33% ± 7.4, *P* < .001
Hentschel et al, 2005[116] United States	66 patients 102 VP-treated VB levels 30 KP-treated VB levels Group 1 (without risk): 49 patients with 89 VP- and 25 KP-treated VB levels	*Baseline* Median 7.0 (3.0–10) *Post-intervention (24 hours)* Median 2.0 (1.0–5.0), *P* = .0002	NR	NR	NR
	Group 2 (a contraindicated procedure, severe VB collapse [>75%], posterior wall defect, epidural involvement (2 patients) and/or radicular pain (2 patients)]: 17 patients with 13 VP- and 5 KP-treated VB levels	*Baseline* Median 8.0 (3.0–10) *Post-intervention (24 hours)* Median 3.0 (1.0 – 5.0), *P* < .0001	NR	NR	NR
Knight et al, 2008[117] Canada	3 patients Posterior wall defects Patient 1: KP at T9 Patient 2: VP at T6 Patient 3: VP at T9	*Baseline* Patient 1: 8.0 Patient 2: 7.0 Patient 3: NR *Post-intervention* Patient 1: 3.0 at 14 days Patient 2: Marked pain improvement at 48 hours Patient 3: Immediate pain relief	*Baseline* Patient 1: heavy narcotic use Patient 2: NR Patient 3: NR	NR	NR

Author, Year Country	Patients, N Risks VB Levels Treated, n	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Lim et al, 2011[134] Korea	1 patient Neurological deficits and anterior wall destruction resulting in segment displacement into the spinal cord causing cord compression KP-treated T12 and L1	*Baseline* 8.0–9.0 *Post-intervention* 3.0–4.0	*Baseline* Strong opioids *Post-intervention* No pain medication needed	*Baseline* Unable to move from bed, neurological symptoms including lower extremity weakness and loss of voiding sensation *Post-intervention* Improved motor function, ambulating freely and voiding sensation returned	NR

Abbreviations: ASIA, American Spinal Injury Association; CI, confidence interval; ITR, interventional tumour removal; MRI, magnetic resonance imaging; NR, not reported; NSAID, non-steroidal anti-inflammatory drug; ODI, Oswestry Disability Index; PRT, palliative radiotherapy; RFA, radiofrequency ablation; SD, standard deviation; VAS, visual analogue scale; VB, vertebral body, VCF, vertebral compression fracture; VP, vertebroplasty.

[a]Unless otherwise indicated.

C2. Effectiveness of Vertebral Augmentation for Cervical Vertebral Fractures

Malignant fractures in the cervical region occur much less commonly than those in the thoracic and lumbar regions—ranging from 8% to 20% of spinal fractures depending on whether estimates are based on symptomatic or asymptomatic fractures.[136] Malignant fractures occurring at the upper cervical region or the cervical junction (C1 or C2 levels) are even more uncommon, representing less than 1% of all fractures caused by spinal metastases.[136,137] Rodriguez-Catarino et al[138] discussed the case of a patient with multiple myeloma who received vertebroplasty for a C2 level fracture. This patient was the only person with a C2 fracture treated at the authors' centre during a 5-year period in which 14 of the 350 (4%) treated vertebrae involved metastases to the cervical region.

Management of cervical fractures can vary depending on the level of cervical involvement. Malignant involvement of the subaxial (C3–C7) level is more likely to result in cord compression because of the smaller canal size at this region and the greater volume of cancellous bone in the vertebral bodies where tumour can deposit.[136] The management of malignant fractures in the atlantoaxial (C1 or C2) region is more challenging than in other spinal regions for minimally invasive or surgical intervention because of its complex anatomy and closeness to vital neurovascular structures such as the vertebral artery, internal jugular vein, internal carotid artery, and cranial nerves. The occiput-C1-C2 region is also complex, with anatomy affording a range of movements including flexion-extension, lateral bending, and axial rotations.[139,140]. Minimally invasive non-surgical interventions such as vertebral augmentation are of particular value in these regions because they do not restrict the mobility of the upper cervical joints.

A summary of the characteristics of clinical studies evaluating the effectiveness of vertebral augmentation interventions for cervical-level cancer-related vertebral compression fractures is outlined in Table 18. The studies involved mixed primary metastatic spinal cancers, except for two,[138,141] which were case reports of multiple myeloma.

Overall there were 11 reports (115 patients) involving vertebral augmentation interventions, one of which also involved an adjunctive radiofrequency ablation intervention of coblation (nonthermal ablation) using Spine Wand (ArthroCare, Austin, Texas).[142] The majority of the reports (10 reports, 113 patients) involved vertebroplasty for the cervical fractures. Except for three studies,[143-145] all were case reports. The report by Masala et al,[144] with the largest patient group, involved a multicentre collaboration. Kyphoplasty was reported for malignant cervical fractures in one study[146] involving two case reports.

The operators for the vertebral augmentation interventions in these studies were interventional radiologists (n = 8) and anaesthesiologists (n = 2). An orthopedic surgeon performed the only kyphoplasty interventions. The vertebral augmentation procedures in the cervical region were more commonly performed using general anaesthesia. The percutaneous approaches employed in this region were more varied, involving an anterolateral, translateral, or posterolateral approach, each having different risks and advantages, particularly in the upper cervical region.[145] The anterolateral approach, which is commonly used, was cited as presenting a high risk, particularly at the C2 level, since it places several neurovascular structures in jeopardy—the spinal accessory, lingual, hypoglossal, vagus, marginal, and laryngeal nerves as well as the carotid and vertebral arteries.[143] For these reasons, Anselmetti et al[143] employed a direct transoral approach, requiring general anaesthesia, in their series of malignant C2 cases. The other large series, by Masala et al,[144] employed both a transoral approach for C1-C2 level fractures and a monolateral percutaneous approach, either anterolateral or posterolateral, for the C3 to C7 level fractures.

Clinical outcomes. The clinical outcomes following vertebroplasty and kyphoplasty for cervical-level cancer-related fractures are outlined in Table 19. In all studies, pain intensity levels were significantly reduced after vertebroplasty, performed at various cervical levels. Patients with cervical-level cancer-related fractures usually experience neck pain; and unlike pain associated with thoracic or lumbar-level fractures, it was not relieved at rest and often resulted in significant sleep disruption. Two studies reported on the impact of vertebroplasty on sleep disruption.[145,147] Yoon et al[147] presented the case of a patient who required a cervical collar and had difficulty sleeping; after vertebroplasty, the patient no longer required the cervical collar or experienced sleep disruption. The study by Sun et al[145] was the only one in this review to incorporate the outcome of sleep disruption into treatment efficacy. A complete response was defined as an absence of pain (seven patients), and a partial response was defined as pain that had decreased to only a moderate level, with undisturbed general sleep (four patients). Two patients had their pain improved, but still experienced sleep disturbance.

The impact of vertebroplasty on analgesic use was reported in the two studies.[143,144] One reported a significant reduction in opioid use (prior to vertebroplasty all were on opioids, and post-vertebroplasty only one remained on opioids),[143] and the other reported a reduction in the median number of daily analgesic pills (from 2 to 0).[144] Functional improvement, particularly range of motion, was not formally evaluated in any of the studies. The discontinuation of cervical collars, however, was cited as a measure of treatment efficacy in several reports.[138,147] In the study by Anselmetti et al,[143] prior to vertebroplasty, all patients with painful C2 level malignant involvement were using external cervical bracing, either a halo vest (n = 4) or minerva neck-body brace (n = 21). Following vertebroplasty, the majority of patients (n = 23) no longer required a brace.

Table 18: Summary of Clinical Studies Evaluating the Effectiveness of Vertebral Augmentation for Cervical Vertebral Compression Fractures

Author, Year Country	Report Type	Study Recruitment Period	Patients, N (F, M) Age, Mean ± SD (Range)[a]	Operator Interventions and Treated Spinal Levels	Study Objectives Follow-Up[b]
Vertebroplasty for Cervical Spinal Compression Fracture					
Anselmetti et al, 2012[143] Italy	Single-site retrospective study, consecutive cases	July 2003 to January 2010	25 patients (16 F, 9 M) *Primary malignancies* Breast (n = 9), gastric (n = 1), renal (n = 2), uterine (n = 1), sarcoma (n = 1), nasopharyngeal (n = 2), colon (n = 1), histiocytosis (n=1), myeloma (n = 5), thyroid (n = 1), hepatic (n = 1) 59 ± 11.5 years (39–77)	Interventional radiology VP by trans-oral route for impending C2 VB level fracture	Treatment safety and efficacy, long-term Mean 21.8 ± 16.3 months (range 6–60)
Chen et al, 2014[148] China	Case series	NR	4 patients (2 F, 2 M) *Primary malignancies* Breast (n = 2), lung (n = 1), esophagus (n = 1) 57.5 years (46–72)	Interventional radiology VP at C levels (1 C5, 2 C6, 2 C7)	Treatment feasibility of VP for fractures at the C level
Cianfoni et al, 2012[142] Italy	Case report	NR	1 patient (F) *Primary malignancy* Intestinal carcinoid 36-year old	Interventional neuroradiology VP and RFA (coblation with Spine Wand) at C1 VB level	Treatment safety and effectiveness of VP and RFA for high cervical fracture 2 months
Huegli et al, 2005[149] Switzerland	Case report	NR	1 patient (F) *Primary malignancy* Adenocarcinoma of unknown origin with hypervascularization of C4 lesion 76-year-old	Interventional radiology VP at 2 VB levels (C1, C4)	Treatment effectiveness of hybrid CT and fluoroscopic guidance for C-level lesions
Masala et al, 2011[144] Italy	Multi-site retrospective review	May 2005 to May 2009	62 patients (38 F, 24 M) *Primary malignancies* Breast (n = 16), multiple myeloma (n = 11), lung (n = 10), gastric (n = 7), other (n = 18) Median 61.5 years (31–85)	Interventional radiology VP (38 trans-orally, anterolateral/ posterolateral [n = 32]) at 70 VB levels (3 C1, 32 C2, 3 C3, 11 C4, 15 C5, 4 C6, 2 C7)	Treatment safety, feasibility, and effectiveness of VP for cervical metastatic fractures 3 months
Mont'Alverne et al, 2009[141] France	Case series	January 1994 to October 2007	4 patients (1 F, 3 M) *Primary malignancy* Multiple myeloma (n = 4) 45 years (39–50)	Interventional neuroradiology VP at 5 VB levels (1 C2, 2 C3, 2 C4)	Treatment effectiveness of VP in the cervical spine Mean 28 months (range 1–96)

Author, Year Country	Report Type	Study Recruitment Period	Patients, N (F, M) Age, Mean ± SD (Range)[a]	Operator Interventions and Treated Spinal Levels	Study Objectives Follow-Up[b]
Rodriguez-Catarino et al, 2007[138] Sweden	Case report	NR	1 patient (F) *Primary malignancy* Multiple myeloma 47-year-old	Interventional neuroradiology VP at C2 VB level	Treatment effectiveness of VP for painful unstable cervical spine fracture 18 months
Seo et al, 2013[150] Korea	Case report	NR	1 patient (F) *Primary malignancy* Breast 51-year-old	Anaesthesiology VP at C7 VB level	Treatment effectiveness of a VP anterolateral approach for C7-level fracture
Sun et al, 2013[145] China	Single-site retrospective study	March 2003 to May 2012	13 patients (5 F, 8 M) *Primary malignancies* Lung (n = 6), breast (n = 3), bladder (n = 2), kidney (n = 1), colon (n = 1) 59.8 years (41–73)	Interventional radiology VP at C2 VB level	Treatment safety and effectiveness of VP with anterolateral for C2 osteolytic cervical metastases 12 months; 8 patients died within follow-up
Yoon et al, 2008[147] Korea	Case report	NR	1 patient (M) *Primary malignancy* Lung cancer 67-year-old	Anaesthesiology VP at C2 VB level	Treatment effectiveness of VP by anterolateral VP approach and upper cervical facet joint block for C2-level metastatic VCF Patient died 4 months post-procedure
Kyphoplasty for Cervical Vertebral Compression Fractures					
Lykomitros et al, 2010[146] Greece	Case reports	December 2007 to February 2008	2 patients (2 M) *Primary malignancies* Lung (n = 1), gastric (n = 1) 48-year old, 70-year-old	Orthopaedic surgery KP at 2 VB levels per patient (C2/C6 and C3/C5)	Treatment effectiveness of KP anterolateral approach for cervical spine metastatic lytic lesions

Abbreviations: C, cervical; CT, computed tomography; F, female; KP, kyphoplasty; M male; RFA, radiofrequency ablation; SD, standard deviation; VB, vertebral body; VP, vertebroplasty.
[a]Unless otherwise indicated.
[b]If reported in study.

Table 19: Clinical Outcomes in Studies Evaluating the Effectiveness of Vertebral Augmentation for Cervical Vertebral Compression Fractures

Author, Year Country	Patients, N VB Levels Treated, n	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility Range of Motion	Pain-Related Disability Health-Related Quality of Life
Vertebroplasty for Cervical Vertebral Compression Fractures					
Anselmetti et al, 2012[143] Italy	25 patients (VP, trans-oral approach) 25 C2 levels	*Baseline* Median 8.0 (5.0–10) *Post-intervention (48 hours)* Median 0 (0–10), *P* < .0001 20 patients achieved complete pain relief at day 15	Analgesic class, change from pre-op to post-op 1 (No analgesics): n = 0 to 17 2 (NSAIDS): n = 0 to 7 3 (Oral opioids): n = 21 to 1 (previously on transdermal opioids) 4 (Transdermal/IV opioids): n = 4 to 0	*Baseline* 25 patients used external orthopaedic cervical bracing (Halo vest in 4, Minerva in 21) *Post-intervention* 23 patients no longer used a cast, *P* < .001	NR
Chen et al, 2014[148] China	4 patients 5 VB levels (1 C5, 2 C6, 2 C7)	*Baseline* NR *Post-intervention* Pain relief was immediate	NR	NR	NR
Cianfoni et al, 2012[142] Italy	1 patient (RFA [coblation with Spine Wand] and VP) C1	*Baseline* 8.0 *Post-intervention (12 hours)* 3.0	NR	*Baseline* NR *Post-intervention* Improved range of motion reported	NR
Huegli et al, 2005[149] Switzerland	1 patient C1 and C4	*Baseline* NR *Post-intervention* Substantial pain relief reported, stable pain relief at 6 months	*Baseline* Pain medication NR *Post-intervention* No longer required pain medication	NR	NR
Masala et al, 2011[144] Italy	62 patients (VP, trans-oral [n = 38] or anterolateral/ posterolateral [n = 32]) 70 cervical levels (3 C1, 32 C2, 3 C3, 11 C4, 15 C5, 4 C6, 2 C7)	*Baseline* 7.9 ± 1.7 *Post-intervention (24 hours)* 1.5 ± 2.0, *P* < .001 25 patients achieved complete pain relief at 24 hours	*Baseline* All taking analgesics Median analgesic use, 2 pills daily (range 0–3) *Post-intervention* Analgesic use eliminated (n = 34), decreased (n = 26), or continued (n = 2) Median analgesic use 0 pills daily (range, 0–3)	NR	NR

Author, Year Country	Patients, N VB Levels Treated, n	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility Range of Motion	Pain-Related Disability Health-Related Quality of Life
Mont'Alverne et al, 2009[141] France	4 patients (VP in multiple myeloma) 5 VB levels, 4 with cortical rupture: 1 C2, 2 C3, 2 C4	*Baseline* NR *Post-intervention (1 month)* Excellent pain relief in all cases (pain completely resolved or diminished by 75% or more)	NR	NR	NR
Rodriguez-Catarino et al, 2007[138] Sweden	1 patient (VP in multiple myeloma) C2	*Baseline* Wearing cervical collar, experiencing high levels of pain, and requiring higher doses of analgesics and sedatives *Post-intervention* Pain completely relieved and cervical collar removed after 3 weeks	NR	NR	*Baseline* NR *Post-intervention* Patient back to work and experienced a remarkable improvement in quality of life
Seo et al, 2013[150] Korea	1 patient C7	*Baseline* NR *Post-intervention* Immediately following the procedure, the patient could stand and sit without pain	NR	NR	NR
Sun et al, 2013[145] China	13 patients (VP, anterolateral approach) C2	*Baseline* 7.6 ± 0.9 *Post-intervention* 3 days: 2.1 ± 1.9, *P* < .001 1 month: 1.8 ± 1.7, *P* < .001 3 months: 1.7 ± 1.8, *P* < .001 6 months: 0.9 ± 0.8, *P* < .001 12 months: 0.6 ± 0.5, *P* < .001 *Responder status* Complete response, no pain after treatment: n = 7 Partial response, pain improved and now only moderate with undisturbed general sleep: n = 4 Moderate response, pain improved but still apparent and sleep still disturbed: n = 2	*Baseline* NR *Post-intervention* Patients maintained their narcotic doses post-procedure for 48 hours, after which analgesics were discontinued according to pain levels	*Baseline* Rigid cervical collars were employed for all patients *Post-intervention* NR	NR

Author, Year Country	Patients, N VB Levels Treated, n	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility Range of Motion	Pain-Related Disability Health-Related Quality of Life
Yoon et al, 2008[147] Korea	1 patient (VP, anterolateral approach, followed by facet-joint blocks post-VP) C2	*Baseline* Progressively increasing severe pain, limiting position and disrupting sleep while wearing a cervical collar *Post-intervention* Pain was relieved immediately, and both head and neck pain were absent at 4- and 6-week follow-up	*Baseline* Transdermal fentanyl patches (75 µg/hour) *Post-intervention* NR	*Baseline* Patient used a cervical collar for support *Post-intervention* Although the cervical collar was not needed, there was a residual suboccipital headache aggravated by lateral rotation and flexion/extension of the cervical spine; pain from upper cervical facet joints was relieved by an additional facet joint block at the atlantooccipital and atlantoaxial joints 3 days post-VP	NR
Kyphoplasty for Cervical Vertebral Compression Fractures					
Lykomitros et al, 2010[146] Greece	2 patients (KP, anterolateral) Patient 1: C2, C6 Patient 2: C3, C5	VAS (0, no pain to 100, worst pain) *Baseline* Patient 1: 85 Patient 2: 95 *Post-intervention* Patient 1: 30 Patient 2: 30	NR	*Baseline* Limited range of motion in cervical spine due to pain, without neurological deficits (normal strength in all muscle groups and normal sensation) *Post-intervention* NR	KPS *Baseline* Patient 1: 40 Patient 2: 30 *Post-intervention (7 months)* Patient 1: 80 Patient 2: 70

Abbreviations: C, cervical; KP, kyphoplasty; KPS, Karnofsky Performance Scale; NR, not reported; RFA, radiofrequency ablation; VAS, visual analogue scale; VB, vertebral body; VP, vertebroplasty.
[a]Unless otherwise indicated.

C3. Effectiveness of Vertebral Augmentation for Sacral Vertebral Compression Fractures

A summary of the characteristics of clinical studies evaluating the effectiveness of vertebral augmentation interventions for sacral-level cancer-related vertebral compression fractures is outlined in Table 20. Overall there were eight reports (214 patients) involving vertebroplasty interventions. Two of these reports[151,152] involved adjunctive local tumour control interventions with radiofrequency ablation (58 patients). The studies involved mixed metastatic spinal cancers, except for two reports,[49,153] one involving patients with multiple myeloma[153] and the other a large cohort of patients with metastatic lung cancer.[49] There were no published reports involving kyphoplasty for cancer-related fractures in the sacral region.

The operators for the vertebroplasty interventions in these studies were interventional radiologists. The procedures were as likely to be performed using general anaesthesia as conscious sedation.

This section also involves procedures for a diverse range of bone metastases in the vertebrae, sacrum, pelvis, and other long bones. Vertebral augmentation performed in the sacrum or in other bony regions such as the pelvis is also referred to as sarcoplasty or osteoplasty. However, the procedure for all was basically the same—injecting bone cement under fluoroscopic guidance. Because of the different anatomy, the access approach in these regions differed from that in other regions, and a trans-sacroiliac joint approach first recommended by Dehdashti et al[154,155] was often employed.[155]

Tumour lesions still more commonly occurred in the thoracic or lumbar regions. In the Wang et al study,[49] involving a large cohort of patients with metastatic lung cancer, the majority of vertebroplasty-treated lesions were in the thoracic (134 lesions) or lumbar (119 lesions) regions. There were, however, 26 osteoplasty-treated lesions in the sacrum (four lesions), pelvis (12 lesions), ilium (eight lesions), and femur (two lesions), and 16% (14/90) of the patients had both a vertebroplasty and an osteoplasty performed.

Because of the larger bone volumes, tumour involvement in these areas tended to result in more widespread bone destruction. Consequently, larger volumes of bone cement were often used in these regions than in the lumbar and thoracic vertebrae. In a case report by Wee et al[156] involving vertebral augmentation in the sacrum in a patient hospitalized for pain control, 6 mL of bone cement was injected into the right sacral ala and 8 mL into the left sacral ala. In the Hoffman et al study[151] employing vertebroplasty and radiofrequency ablation, mean bone cement volumes injected were 2.9 mL (range 1.8–4.8 mL) for the vertebrae; 8.7 mL (range 4.5–10 mL) for the sacrum, acetabulum, and pelvis; and 6.7 mL (range 3.2–8.0 mL) for the ilium, tibia, and femur.

Clinical outcomes. The clinical outcomes following vertebroplasty for cancer-related fractures in the sacrum and for surrounding tumour-involved areas in the pelvis and femur are outlined in Table 21. The impact of vertebroplasty on pain intensity was reported in all studies, and VAS scores were again significantly reduced within 24 hours of the procedure. Three studies reported pain intensity levels within responder status groups, all with different response categories.[49,155,157] Botton et al[157] defined treatment efficacy as good (57%, 24/42) if there was a reduction in opioid dose of > 10%; a patient formerly unable to walk could walk again; there was a pain decrease > 1 point on VAS at rest or during effort; or there were concordant opinions of patient and physician. In the Sun et al study,[155] good pain relief following vertebroplasty (71%, 5/7) was defined as a VAS score of 0 to 3; at baseline, the VAS scores ranged from 8.0 to 10. In the Wang et al study,[49] those having a pain intensity reduction of at least 50% were considered treatment responders (82%, 75/92).

Four studies reported on changes in analgesic use after vertebroplasty.[151,153,157,158] Three reported different improvement outcomes: 100% (8/8) discontinued or reduced opioids,[153] 100% (5/5) discontinued all analgesics,[158] and 68% (15/22) reduced analgesic use or switched from opioids to non-opioids.[151] In the Botton et al study,[157] analgesic use, measured by the mean morphine equivalent dose, was not significantly reduced after vertebroplasty.

Mobility, or the ability to ambulate freely, was a key outcome measure after vertebroplasty in the sacral and pelvic regions. Three studies reported on ambulation.[49,156,157] In the Botton et al study,[157] 16 of 22 patients formerly unable to walk were able to walk again. Wee et al[156] reported that two patients who had been hospitalized and confined to a wheelchair improved and became independently mobile. Wang et al[49] used a mobility score to evaluate recovery at follow-up in a large group of patients with spinal metastatic lung cancer. By 1 month post-procedure, of the 12 who had been bedridden prior to vertebroplasty, only two remained bedridden, and of the 23 patients who had had limited mobility requiring orthopedic aids, 16 no longer required them. Measures of pain-related disability, such as the Oswestry Disability Index or the Roland Morris Disability Questionnaire, were not reported in any of the studies. The KPS, a measure of physical performance reported in one study,[49] showed clinically and statistically significant improvements. Another orthopedic measure of functional ability, the Harris hip score, was reported in the Wang et al study[49] and also showed significant improvements.

Table 20: Summary of Clinical Studies Evaluating the Effectiveness of Vertebral Augmentation for Sacral Vertebral Compression Fractures

Author, Year Country	Report Type	Study Recruitment Period	Patients, N (F, M) Age, Mean ± SD (Range)[a]	Operator Interventions and Treated Spinal Levels	Study Objectives Follow-Up[b]
Vertebroplasty for Sacral Vertebral Compression Fractures					
Basile et al, 2010[153] Italy	Case series	April 2007 to May 2009	8 patients (4 F, 4 M) *Primary malignancy* Multiple myeloma (n = 8) 57.8 years (47–68)	Interventional radiology VP (S)	Treatment effectiveness of VP in the sacral region Mean 12.5 months (range 3–27)
Botton et al, 2012[157] France	Single-site retrospective study	January 2007 to July 2009	42 patients (24 F, 18 M) *Primary malignancies* Multiple myeloma (n = 15), colon (n = 5), kidney (n = 5), liver (n = 3), lung (n = 2), uterus (n = 2), other (n = 10) Median 59 years (21–81)	Interventional radiology VP (10 long bone, 13 spinal [T or L], 20 pelvis)	Treatment effectiveness of VP Maximum 27 months
Hierholzer et al, 2003[158] Germany	Case series	NR	5 patients (2 F, 3 M) *Primary malignancies* Lung (n = 3), breast (n = 1), colon (n = 1) 63 years (52–76)	Interventional radiology VP at 5 bone lesion sites (acetabulum, ilium, pubis, femur, sacrum)	Treatment effectiveness of VP for various painful bony lesions in the sacrum, ileum, and femur Maximum 24 weeks
Hoffman et al, 2008[151] Germany	Single-site retrospective study	2002 to 2005	22 patients (7 F, 15 M) *Primary malignancies* Multiple myeloma (n = 5), breast (n = 3), lung (n = 4), thyroid (n = 2), renal cell (n = 5), unknown (n = 3) Median 64 years (41–86)	Interventional radiology VP and RFA at 28 lesions (6 pelvis and acetabulum, 2 femur, 1 tibia, 6 thoracic, 10 lumbar, 3 sacrum)	Treatment effectiveness of VP and RFA (RITA) for various painful bony lesions in the vertebrae and other skeletal metastases
Lane et al, 2011[152] Canada [earlier Munk et al, 2009[159]]	Single-site retrospective study	June 2006 to January 2009	36 patients (NR) *Primary malignancies* Breast (n = 12), lung (n = 5), multiple myeloma (n = 6), prostate (n = 2), renal (n = 2), other (n = 9) 57.6 ± 12.6 years (34–81)	Interventional radiology KP (in only 3 patients, no longer used) or VP and RFA in 34 vertebrae (20 L, 14 T), 14 acetabulae, 3 sacra, 1 pubic symphysis, 1 humerus	Treatment safety and effectiveness of RFA (Cool-tip or Radiotherapeutics) and cementoplasty (VP or KP) for bony metastases
Sun et al, 2012[155] China	Case series	2001 to 2010	7 patients (2 F, 5 M) *Primary malignancies* Lung (n = 3), breast (n = 2), liver (n = 1), kidney (n = 1) 55.7 years (47–64)	Interventional radiology VP at 14 levels (2 T, 5 L, 7 S)	Treatment safety and effectiveness of VP (sarcoplasty) trans-sacroiliac joint approach with 3-D C-arm CT guidance 6 months

Author, Year Country	Report Type	Study Recruitment Period	Patients, N (F, M) Age, Mean ± SD (Range)[a]	Operator Interventions and Treated Spinal Levels	Study Objectives Follow-Up[b]
Wang et al, 2012[49] China	Single-site retrospective study	June 2007 to December 2010	92 patients (NR) *Primary malignancy* Lung cancer (n = 92) 57 years (33–79)	Interventional radiology 283 osteoplasties, in first session (4 C, 134 T, 119 L, 4 S, 12 pelvic, 8 iliac, 2 femoral); 14 patients had both VP and osteoplasty	Treatment effectiveness of osteoplasty for bone metastases to the spine (vertebroplasty) and pelvis (acetabuloplasty) To 3 months; 2 patients died during follow-up
Wee et al, 2008[156] United Kingdom	Case reports	2005, 2006	2 patients (2 M) *Primary malignancies* Renal cell carcinoma (n = 1), multiple myeloma (n = 1) 55-year-old, 66- year-old	Interventional radiology VP at sacral ala	Treatment effectiveness of VP for cases with extensive sacral destruction and no surgical alternatives
Kyphoplasty for Sacral Vertebral Compression Fractures					
No studies found					

Abbreviations: CT, computed tomography; F, female; KP, kyphoplasty; L, lumbar; M, male; NR, not reported; RFA, radiofrequency ablation; S, sacral; SD, standard deviation; T, thoracic; VP, vertebroplasty.
[a]Unless otherwise indicated.
[b]If reported in study.

Table 21: Clinical Outcomes of Studies Evaluating the Effectiveness of Vertebral Augmentation for Sacral Vertebral Compression Fractures

Author, Year Country	Patients, N Risks VB Levels Treated, n	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Vertebroplasty for Sacral Vertebral Compression Fractures					
Basile et al, 2010[153] Italy	8 patients VP in multiple myeloma; RFA and VP in 2 patients 6 patients had persistent pain despite prior cementoplasty	*Baseline* 7.5 (6.0–10) *Post-intervention (24 hours)* 2.1 (0–5.0)	*Baseline* Fentanyl: n = 7 Morphine and fentanyl: n = 1 *Post-intervention* Analgesia use decreased in all patients No analgesics: n = 3 Decreased fentanyl dose, 75 or 100 µg/h to 25 µg/h: n = 4 Decreased fentanyl 75 µg/h and morphine 60 µg/h via epidural catheter to fentanyl 50 µg/h: n = 1	*Baseline* All had difficulty walking due to pain *Post-intervention* NR	NR
Botton et al, 2012[157] France	42 patients VP in 10 long bone, 13 spinal [T or L], 20 pelvis; 36 patients had PRT before or after VP	Treatment efficacy score; Good result—reduction of > 10% of opioid dose OR resumption of walking in those formerly unable to OR decreased pain at rest or during effort of > 1 point on VAS OR concordant opinion of patient or physician Partial result—pain relieved only moderately or temporarily Failure—unrelieved pain *Post-intervention* Good result: n = 24 Partial result: n = 13	*Baseline* Mean morphine oral equivalent dose: 256 mg *Post-intervention (post-op)* Post-op: mean morphine oral equivalent dose: 254 mg, *P* = .11 1 month: 217 mg	*Baseline* Ambulation was prohibited due to fracture risk or impossible due to pain (n = 22) *Post-intervention* Of the 22 unable to ambulate, 16 were able to resume walking	NR
Hierholzer et al, 2003[158] Germany	5 patients VP for 5 lesions in pelvic and sacral metastases	Score 0 (no pain) to 6 (maximum pain) *Baseline* 6.0 (all patients) *Post-intervention (24 hours)* 0.5 (0–1.0)	*Baseline* NR *Post-intervention* No longer required any pain medication	NR	NR

Author, Year Country	Patients, N Risks VB Levels Treated, n	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Hoffman et al, 2008[151] Germany	22 patients VP and RFA for 28 lesions in the thoracic and lumbar spine, sacrum, pelvis, acetabulum, femur and tibia	*Baseline* 8.5 *Post-intervention* 24 hours: 5.5, *P* < .01 3 months: 3.5, *P* < .01	*Baseline* NR *Post-intervention* Reduction in analgesic use or switch to weaker analgesics (non-opioids from opioids): n = 15 Analgesics remained the same: n = 5 Increase in medication or stronger medication (due to tumour progression elsewhere): n = 2	NR	NR
Lane et al, 2011[152] Canada (earlier Munk et al, 2009[159])	36 patients 53 lesions; RFA (Cool-tip or Radiotherapeutics) and VP for 34 vertebrae, 14 acetabulae, 3 sacra, 1 pubic symphysis, 1 humerus	*Baseline* 7.2 ± 1.7 (3.0–9.0) *Post-intervention (24 hours)* 3.4 ± 1.7 (0–7.0), *P* < .01	NR	NR	NR
Sun et al, 2012[155] China	7 patients VP for 14 VB levels: 2 T, 5 L, 7 S	*Baseline* 8.6 (8.0–10) *Post-intervention (1 month)* 3.3 (2.0–5.0) *Pain relief (1 month)*[c] Good (VAS 0–3): n = 5 Partial (VAS 4–6): n = 2 Insufficient or none (VAS 7–10): n = 0	NR	NR	NR

Author, Year Country	Patients, N Risks VB Levels Treated, n	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Wang et al, 2012[49] China	92 patients VP for 283 VB levels; lesions in pelvis, ilium, and femur	*Baseline* 6.1 ± 1.4 *Post-intervention* 24 hours: 3.5 ± 1.2 1 month: 3.3 ± 1.2 3 months: 2.9 ± 1.5 At 3 months, 82% reported pain reduction of at least 50%; 8% reported less than 25% pain reduction	NR	Mobility score change, pre-op to 24 hours to 1 month to 3 months, n of patients 0 (no limitation): n = 33 to 36 to 47 to 48 1 (limitation but without the need for orthopedic aids): n = 24 to 29 to 36 to 34 2 (limitation requiring orthopedic aids): n = 23 to 20 to 7 to 7 3 (bedridden) n = 12 to 7 to 2 to 1 Change from pre-op to 24 hours (*P* > .05), to 1 month (*P* < .05) and to 3 months (*P* < .05)	KPS, mean ± SD *Baseline* 69 ± 5.5 *Post-intervention* 24 hours: 75 ± 5.4 1 month: 77 ± 5.8 3 months: 80 ± 5.8, *P* < .05 HHS, mean ± SD *Baseline* 35.8 ± 5.5 *Post-intervention* 24 hours: 41.3 ± 5.7 1 month: 70.5 ± 5.2 3 months: 80.9 ± 6.1, *P* < .05
Wee et al, 2008[156] United Kingdom	2 patients VP at sacral ala	*Baseline* Patient 1: 10.0 Patient 2: 7.0 *Post-intervention (24 hours)* Patient 1: 3.0 Patient 2: 2.0	*Baseline* Patient 1: hospitalized for pain control Patient 2: high opioid doses *Post-intervention* NR	*Baseline* Patient 1: hospitalized, confined to bed Patent 2: confined to a wheelchair *Post-intervention* Patient 1: immediately able to sit up post-operatively and gradually mobilizing Patient 2: independently mobile	NR
Kyphoplasty for Sacral Vertebral Compression Fractures					
No studies found					

Abbreviations: HHS, Harris hip score; KPS, Karnofsky Performance Score; L, lumbar; NR, not reported; PRT, palliative radiotherapy; RFA, radiofrequency ablation; S, sacral; SD, standard deviation; T, thoracic; VAS, visual analogue scale; VB, vertebral body; VP, vertebroplasty.
[a]Unless otherwise indicated.

C4. Effectiveness of Vertebral Augmentation Interventions for Vertebral Hemangiomas

Vertebral hemangiomas are common benign vascular tumours with an estimated 10% to 12% occurrence in the population, based on autopsy series; they account for 2% to 3% of spinal tumours.[160] They are generally asymptomatic and rarely enlarge or expand into the vertebral body causing pain or vertebral fractures, or into the spinal column causing cord compression and neurological deficits. Several studies evaluating the natural history of vertebral hemangiomas have shown that incidentally detected hemangiomas associated with pain rarely progress to spinal cord compression.[160,161] A cohort study of vertebral hemangiomas seen at one institute over a 10-year period reported that 3.4% (2/59) of cases initially presenting with painful lesions later developed cord compression.[160]

Based on symptoms and lesions, vertebral hemangiomas have been classified into four disease stages: stage 1, asymptomatic or latent with mild bone destruction; stage 2, symptomatic with bone destruction; stage 3, aggressive with epidural or soft tissue extension but asymptomatic; and stage 4, aggressive with epidural or soft tissue extension and with neurological deficits.[162,163] The radiological features of aggressive hemangiomas are defined by their involvement of the entire vertebra, poorly defined cortical bone, and paravertebral soft tissue mass.[164]

Treatment is usually based on the presence of symptoms and the degree of aggressiveness. For symptomatic hemangiomas, there is a range of interventions including conservative medical therapy, radiotherapy, and various embolization techniques involving either transarterial particulate embolization of the feeding arteries or direct ethanol or liquid injection into the lesion through the standard transpedicular vertebral augmentation approach.[165,166]

Vertebroplasty has increasingly been used as an alternative or an adjunctive intervention for these cases. For advanced and aggressive hemangiomas, spinal surgery is usually the optimal treatment choice. However, because of their high degree of vascularity and their location in the vertebrae, surgical management can have high risks, particularly for transfusion-dependent hemorrhage and increased mortality. In these cases, pre-operative embolization techniques are often employed to reduce the intraoperative blood loss, commonly in the range of 5 L.[167] All of these treatments have been employed, particularly for stage 3 hemangiomas, and it is difficult to analyze the effectiveness of these different approaches.[168]

A summary of the characteristics of clinical studies evaluating the effectiveness of vertebral augmentation interventions for vertebral hemangioma fractures or lesions is outlined in Table 22. Overall there were 10 reports (82 patients) involving vertebral augmentation, either vertebroplasty (six reports, 72 patients) or kyphoplasty (four reports, 10 patients). The operators for vertebroplasty in these studies were interventional radiologists (n = 4) or surgeons (n = 2), and for kyphoplasty were surgeons (n = 3) or anaesthesiologists (n = 1).

Vertebroplasty interventions were performed under conscious sedation or general anaesthesia, but all of the kyphoplasty interventions were performed using general anaesthesia. Although symptomatic hemangiomas were treated with vertebroplasty at all vertebral levels, including cervical and sacral, the thoracic and lumbar regions remained the most commonly treated locations. The patients in these studies were young, in their forties and some in their twenties. There was also a tendency for more females to be affected than males, as opposed to the more even gender split seen with other tumours affecting the spine.

Management of symptomatic and aggressive hemangiomas. Two studies primarily evaluated the multidisciplinary management that was performed for symptomatic patients having pain and neurological deficits.[165,168] This included radiotherapy, surgery, and embolization, in addition to vertebroplasty. In both of the studies, surgery was performed for the majority of the patients because of the benign nature of hemangiomas, the younger age of the patients, and the generally good patient health status compared with patients with metastatic spinal tumours.

In the Acosta et al study,[165] 16 patients with hemangiomas presented either with pain (n = 9) or with neurological symptoms with or without pain (n = 7). They were treated with vertebroplasty (n = 4, all with pain), spinal decompression surgery (n = 8, seven with cord compression), or transarterial embolization (n = 4, three with pain, one with pain and neurological deficits). Radiotherapy was used post-operatively in one patient to prevent tumour progression.

Treatment patterns were complex in the study by Jiang et al,[168] which included 29 symptomatic hemangioma cases, all with neurological deficits including radiculopathy (n = 10), myelopathy (n = 18), and cauda equina syndrome (n = 1). First-line treatment included radiotherapy (n = 23, seven as primary and 16 as adjunctive to surgery). Most patients underwent spinal surgery (n = 21), which involved decompression in 18 cases and spondylectomy in three cases. Pre-operative embolization was performed in 19 of the surgical cases. Vertebroplasty was also performed adjunctively in eight of the decompression surgeries; 12 surgeries did not include vertebroplasty. The average estimated blood loss in those undergoing vertebroplasty and surgery (mean 1,093 mL, range 400–3,000 mL) was much less than in those undergoing just surgery (mean 1,900 mL, range 500–4,100 mL). Vertebroplasty was also performed adjunctively with one radiotherapy case.

Two other studies reported vertebroplasty to treat symptomatic hemangiomas; no other interventions were reported.[169,170] The Guarnieri et al study[169] included mainly symptomatic hemangiomas, although seven of the 24 cases were aggressive. In the study by Hao and Hu,[170] all were symptomatic without neurological deficits. Unlike in spinal surgery, the intraoperative blood loss in the vertebroplasty procedures ranged from 1 to 3 mL.[170]

Clinical outcomes. All studies reported a reduction in pain intensity, although VAS values were not always reported in the vertebroplasty[165,168,169] or the kyphoplasty studies[171,172] (Table 23). None of the studies reported analgesic use. Also, pain-related disability or mobility scores by any measure were generally not reported. In the two studies[169,173] that reported Oswestry Disability Index measurements, only the Hadjipavlou et al study[173] reported both pre- and post-procedural disability values. In that study, involving kyphoplasty, disability scores were significantly improved. Health-related quality of life was measured in one study[170] involving vertebroplasty for 26 patients, and a significant improvement ($P < .05$) was reported for both physical and mental health summary scores.

Table 22: Summary of Clinical Studies Evaluating the Effectiveness of Vertebral Augmentation for Vertebral Hemangiomas

Author, Year Country	Report Type	Study Recruitment Period	Patients, N (F, M) Age, Mean ± SD (Range)[a]	Operator Interventions and Spinal Levels	Study Objective Follow-Up[b]
Vertebroplasty for Vertebral Hemangioma					
Acosta et al, 2006[165] United States	Case series	1984 to 2004	4 of 16 patients (1 F, 3 M) Vertebral hemangioma 42.5 years (29–56)	Interventional radiology VP at 4 VB levels (T7, T8, T9, L3)	Treatment outcomes for multidisciplinary management strategies of symptomatic vertebral hemangiomas
Fuwa et al, 2006[164] Japan	Case report	NR	1 patient (F) Vertebral hemangioma 42-year-old	Interventional radiology VP at T10	Treatment effectiveness of VP for a vertebral hemangioma invading the neural arch 6 months
Guarnieri et al, 2009[169] Italy	Single-site retrospective study, consecutive cases	January 2003 to December 2007	24 patients (14 F, 10 M) Vertebral hemangioma 63 years	Interventional neuroradiology VP at 36 VB levels (2 C, 10 T, 24 L)	Treatment safety and effectiveness of VP with long-term follow-up 4 years
Hao et al, 2012[170] China	Single-site retrospective study, consecutive cases	January 2007 to March 2011	26 patients (18 F, 8 M) Vertebral hemangioma 49 years (23–70)	Orthopaedic surgery VP at 28 VB levels (17 T, 11 L)	Treatment safety and effectiveness of VP for vertebral hemangioma Mean 8.6 months (range 3–24 months)
Jian, 2013[174] China	Case series	December 2008 to February 2012	8 patients (5 F, 3 M) Cervical hemangioma 43 years (31–52)	Surgery VP at 8 VB levels (C3 to C6)	Treatment effectiveness of VP for cervical vertebral hemangioma
Jiang et al, 2014[168] China	Single-site retrospective consecutive study	2001 to 2013	9 of 29 patients (6 F, 3 M) Vertebral hemangioma 44 years (21–72)	Orthopaedic surgery VP for 9 patients at 11 VB levels (2 C, 8 T, 1 L)	Treatment safety and effectiveness of multidisciplinary treatment including VP for vertebral hemangiomas with neurological deficit
Kyphoplasty for Vertebral Hemangioma					
Atalay et al, 2006[175] Turkey	Case report	NR	1 patient (F) Sacral hemangioma 74-year-old	Neurosurgery KP	Treatment advantages of KP in relieving sacral hemangioma–related pain
Hadjipavlou et al, 2007[173] Greece	Case series	NR	6 patients (5 F, 1 M) Vertebral hemangioma 45.6 years (14–75)	Orthopaedic surgery KP in 8 sessions at 11 levels (5 T, 6 L); 3 patients also had spinal surgery, 2 had ethanol injections	Treatment safety and effectiveness of KP for vertebral hemangioma Mean 22 months (range 12–36 months)
Jones et al, 2009[171] United States	Case reports	NR	2 patients (1 F, 1 M) Vertebral hemangioma 75 year-old female, 38-year-old male	Anaesthesiology KP at 2 VB levels (L5, T12)	Treatment safety and effectiveness KP for vertebral hemangioma that was unresponsive to other treatments

Author, Year Country	Report Type	Study Recruitment Period	Patients, N (F, M) Age, Mean ± SD (Range)[a]	Operator Interventions and Spinal Levels	Study Objective Follow-Up[b]
Zapalowicz et al, 2008[172] Poland	Case report	NR	1 patient (F) Cervical hemangioma 49-year old	Neurosurgery KP at C7	Treatment effectiveness of KP for C7 vertebral hemangioma with posterior wall defects 13 months

Abbreviations: C, cervical; F, female; KP, kyphoplasty; L, lumbar; M, male; NR, not reported; T, thoracic; VB, vertebral body; VP, vertebroplasty.
[a]Unless otherwise indicated.
[b]If reported in study.

Table 23: Clinical Outcomes in Studies Evaluating the Effectiveness of Vertebral Augmentation for Vertebral Hemangiomas

Author, Year Country	Patients, N VB Levels Treated, n	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Vertebroplasty for Vertebral Hemangiomas					
Acosta et al, 2006[165] United States	4 of 16 patients with pain and without neurological symptoms	*Baseline* NR *Post-intervention* Decreased pain in 3 patients; 1 with initial improvement had recurrence of mild back pain at follow-up	NR	NR	NR
Fuwa et al, 2006[164] Japan	1 patient T10, neural arch	*Baseline* 9.0 *Post-intervention (24 hours)* 1.0	NR	*Baseline* Increasing back instability and unable to walk without a corset *Post-intervention* Walking comfortably without corset support	NR
Guarnieri et al, 2009[169] Italy	24 patients 36 VB levels that were symptomatic but not aggressive (n = 18), symptomatic and MRI-detected signs of aggressiveness (n = 4), symptomatic with epidural compression (n = 2)	*Baseline* NR *Post-intervention* Complete resolution of pain within 24 or 72 hours (VAS NR)	NR	NR	*Baseline* NR *Post-intervention* Within 24–72 hours, ODI < 40% in all patients
Hao et al, 2012[170] China	26 patients 28 VB levels (17 T, 11 L)	*Baseline* 7.4 ± 1.6 *Post-intervention* 24 hours: 1.7 ± 0.6, $P < .05$ 3 months: 0.7 ± 0.4	NR	NR	SF-36, mean ± SD *Baseline* PFS score f: 18.4 ± 4.6 MHS score: 20.6 ± 4.4 *Post-intervention (24 hours)* PFS score: 27.4 ± 3.5, $P < .05$ MHS score: 23.5 ± 2.2, $P < .05$
Jian, 2013[174] China	8 patients 8 VB levels (2 C3, 3 C4, 2 C5, 1 C6) with neck and/or shoulder pain without radiculopathy or myelopathy	*Baseline* 6.9 ± 0.6 *Post-intervention* 24 hours: 1.3 ± 0.5, $P < .01$ Last follow-up: 1.2 ± 0.5	NR	NR	NR

Author, Year Country	Patients, N VB Levels Treated, n	Pain Intensity, VAS Mean ± SD (Range)[a]	Analgesic Use	Mobility	Pain-Related Disability Health-Related Quality of Life
Jiang et al, 2014[168] China	9 of 29 patients Vertebral hemangioma and neurological deficits; 9 treated with VP (VP and RT [n = 1], VP and decompression surgery [n = 2], VP and RT and decompression surgery [n = 6])	NR	NR	NR	NR
Kyphoplasty for Vertebral Hemangiomas					
Atalay et al, 2006[175] Turkey	1 patient KP for sacrum and subsequently L3	*Baseline* 9.0 *Post-intervention (24 hours)* 0	NR	*Baseline* Unable to walk due to pain *Post-intervention* Able to walk without pain	NR
Hadjipavlou et al, 2007[173] Greece	6 patients KP (n = 4), KP and surgery (n = 2, 11 VB levels); symptomatic and aggressive (n = 4)	*Baseline* 8.0 *Post-intervention (24 hours)* 1.7 Pain was immediately relieved in all patients post-operatively	NR	*Baseline* 1 patient was paraplegic Frankel B partial sensory deficit *Post-intervention* NR	ODI, mean (range) *Baseline* 40% (30%–60%) *Post-intervention* 10% (0%–20%)
Jones et al, 2009[171] United States	2 patients KP at 2 VB levels, L5, T12	*Baseline* Patient 1: NR Patient 2: 10.0 *Post-intervention* Patient 1: 0 Patient 2: middle and lower back pain totally resolved	*Baseline* Patient 1: epidural steroid injections and dorsal column nerve stimulator for pain Patient 2: lumbosacral median branch nerve blocks, RFA and trigger point injections *Post-intervention* NR	NR	*Baseline* NR *Post-intervention* Patient 1: resumed all previous activities due to significant pain relief Patient 2: NR
Zapalowicz et al, 2008[172] Poland	1 patient KP at C7 without neurological deficit or cord involvement, but with disrupted posterior VB wall	*Baseline* 8.0; persistent neck pain increasing with motion, upper extremity numbness and frequent headaches *Post-intervention* VAS NR; at 24 hours, pain completely disappeared	NR	NR	*Baseline* NR *Post-intervention* Patient resumed former social and professional life

Abbreviations: C, cervical; KP, kyphoplasty; L, lumbar; MHS, mental health component summary score; MRI, magnetic resonance imaging; NR, not reported; ODI, Oswestry Disability Index; PFS, physical functioning score; RFA, radiofrequency ablation; RT, radiation therapy; SD, standard deviation; SF-36, Short-Form Health Survey; T, thoracic; VAS, visual analogue scale; VB, vertebroplasty.
[a]Unless otherwise indicated.

Section D. Safety of Vertebral Augmentation for Cancer-Related Vertebral Compression Fractures

The review on safety of vertebroplasty and kyphoplasty interventions for cancer-related vertebral compression fractures includes information from multiple sources. Data on complications or adverse events were extracted from all of the previously cited clinical studies in this report that evaluated effectiveness of vertebral augmentation. We also included studies evaluating only safety with vertebral augmentation interventions, as well as case reports of adverse events.

In addition, we reviewed complications reported in any clinical cohort or comparative cohort studies and classified these as minor or major based on the Society of Interventional Radiology Standards of Practice Committee's classification of outcomes.(91) Major complications were defined as those requiring therapy or minor hospitalization (< 48 hours); requiring major therapy, an unplanned increase in the level of care, or prolonged hospitalization (> 48 hours); having permanent adverse sequelae; or resulting in death.

For both vertebroplasty and kyphoplasty there are several potential procedure-related complications such as hematoma or pain at the needle-entry site, pedicle fracture, infection, and spinal nerve or cord injury. For both procedures, bone cement leakage and migration are considered the main potential complications—cement can leak into the spinal cord and cause cord compression or can enter the venous system resulting in a pulmonary or cardiac embolism or other damage to the vascular system. Asymptomatic bone cement leakage was noted in this review as a minor complication. However, we recorded asymptomatic pulmonary embolism as a major adverse event because of the uncertain clinical management, subsequent health impact, and potential need for ongoing clinical monitoring. Kyphoplasty has potential additional risks associated with the use of general anaesthesia and with balloon inflation of the vertebral body prior to cement injection.

For several reasons, it was difficult to evaluate the occurrence of subsequent fractures following vertebroplasty or kyphoplasty. First, the investigation of subsequent fractures was not systematically evaluated at follow-up and was reported only sporadically. It was also difficult to determine when subsequent fractures were attributable as a complication owing to altered structural forces and spinal alignment or to disease progression at other levels. The occurrences of these events, when reported, are recorded in the complication tables, but they were not counted as complication events.

The subsections for the safety outcome review of vertebral augmentation for cancer-related vertebral compression fractures are these: D1. Vertebroplasty; D2. Kyphoplasty; and D3. Vertebroplasty or Kyphoplasty for High-Risk or Special Vertebral Compression Fractures.

D1. Safety of Vertebroplasty

Vertebroplasty for multiple myeloma and metastatic cancers. Complications reported in clinical studies evaluating the effectiveness of vertebroplasty are outlined in Table 25. The vertebral fractures in this section mainly involved the thoracic or lumbar regions, and vertebroplasty was generally not performed for contraindicated conditions. Three studies evaluated only safety in vertebroplasty interventions: reports by Kruger and Faciszewski[176] on radiation exposure, Barragan-Campos et al[177] on overall complications, and Corcos et al[178] on cement leakage. Kruger and Faciszewski[176] found that the annual occupational dose limits would be exceeded by performing 34 vertebroplasty procedures per year. However, various shielding interventions used during the procedure were found to reduce radiation exposure by 43% to 86%.

In the 12 studies of vertebroplasty involving 447 patients with multiple myeloma, there were seven major complications (1.6%), all from the same study.[59] The events included five asymptomatic pulmonary embolisms, one spinal infection, and one disseminated intravascular coagulopathy immediately following vertebroplasty. There were no urgent repair or rescue spinal surgeries or deaths in this study group.

In the 14 studies of vertebroplasty evaluating 639 patients with primary metastatic cancers, there were 18 major complications (2.8%), five involving asymptomatic pulmonary embolisms (Table 25). One of the complications involved a hematoma requiring surgery. The other major adverse events included cement leaks into the spinal cord resulting in nerve compression (n = 2), neurological deficits (n = 3), and cauda equina syndrome (n = 1); and leaks into the vascular system affecting the respiratory system (pulmonary embolisms [n = 2] and dyspnea without apparent pulmonary embolisms [n = 2]) and the cardiovascular system (an inferior vena cava filter was placed to prevent leaks). The complications resulted in seven spinal surgeries after vertebroplasty. Overall in the studies, there were four deaths (0.6%). Two occurred immediately following vertebroplasty: one caused by pulmonary cement embolism, and the other resulting from interstitial pneumonia without apparent pulmonary embolism. The other two deaths occurred from post-operative sepsis following surgical decompression and fixation performed after the vertebroplasty procedure.

Asymptomatic bone cement leakage was reported in 14 studies involving vertebroplasty for cancer-related vertebral fractures. Leaks were reported both per treated case and per treated vertebra (Table 24) and were more commonly reported per treated case for patients with multiple myeloma and per treated vertebra for those with metastatic cancers. Estimates of cement leakage ranged widely for both study groups, for both treated cases and treated vertebrae. Leakages in patients with multiple myeloma ranged from 12% to 29% of treated cases and from 13% to 84% of treated vertebrae. Leakages in those with metastatic cancers ranged from 22% to 70% of treated vertebrae; only one study[73] reported leaks per treated case (49%).

Table 24: Asymptomatic Bone Cement Leakage After Vertebroplasty for Cancer-Related Vertebral Fractures

Author, Year	Leaks Per Treated Case	Leaks Per Treated Vertebra
Multiple Myeloma		
Chen et al, 2012[56]	17% (4/24)	NR
Garland et al, 2011[55]	12% (3/26)	NR
McDonald et al, 2008[54]	19% (13/67)	NR
Tancioni et al, 2010[60]	27% (3/11)	NR
Tran Thang et al, 2008[62]	29% (8/28)	NR
Ramos et al, 2006[51]	NR	84% (16/19)
Simony et al, 2014[66]	NR	13% (8/64)
Trumm et al, 2012[52]	NR	51% (34/67)
Metastatic Cancers		
Mikami et al, 2011[73]	49% (34/69)	NR
Calmels et al, 2007[58]	NR	50% (52/103)
Corcos et al, 2014[178]	NR	53% (43/81)
Farrokhi et al, 2012[69]	NR	43% (6/14)
Trumm et al, 2008[48]	NR	70% (60/86)
Tseng et al, 2008[179]	NR	22% (17/78)

Vertebroplasty and adjunctive local tumour control interventions. Complications occurring in studies evaluating vertebroplasty and adjunctive local tumour control interventions are outlined in Table 26. There were three studies involving 115 patients with multiple myeloma, and 11 studies involving 411 patients with primary metastatic cancers.

The adjunctive procedures involved radiofrequency ablation in eight studies, one being an RCT.[79] Two of the studies involved non-thermal radiofrequency ablation.[79,87] Interventional radiologists were the operators for all radiofrequency ablation procedures. The other adjunctive procedures included palliative radiotherapy, either traditional external beam radiotherapy pre- or post-vertebroplasty in two studies,[74,75] or brachytherapy with implanted ^{125}I seeds in two studies (both RCTs).[77,78] The operators in these studies were surgeons.

Overall, there were seven major complications, all involving primary metastatic cancer fracture populations, from two studies. One study involved radiofrequency ablation–assisted vertebroplasty,[86] and one involved vertebroplasty followed by palliative radiotherapy.[74] The major complications were related to bone cement leakage: pulmonary embolism (n = 3) and tumour invasion resulting in neurological deficits (n = 4). None of the complications required additional spinal surgeries, and no deaths were reported.

Eight studies discussed asymptomatic bone cement leakage, reported per treated case or per treated vertebra (Table 26). One of the objectives of radiofrequency ablation–assisted vertebroplasty was to create a cavity within the vertebral body thermally, instead of mechanically as with kyphoplasty, to more safely inject cement. The asymptomatic bone cement leakages reported in three studies involving radiofrequency ablation–assisted vertebroplasty occurred in 2% (1/41),[81] 9% (2/22),[79] and 2% (2/92)[82] of treated cases.

Case reports of complication events with vertebroplasty. Thirteen case reports for complications following vertebroplasty for vertebral compression fractures were reported from seven countries; 12 of these were published over an 8-year period (2007–2014), and one was reported in 2001 (Table 27). The case reports involved 10 females and three males. The primary cancers for the females were breast cancer (n = 3), multiple myeloma (n = 1), lymphoma (n = 1), lung cancer (n = 1), hemangioma (n = 1), and unreported etiologies (n = 3). For the males, primary cancers were lung cancer (n = 2) and non-Hodgkin lymphoma (n = 1).

The major complications involved bone cement leakage in eight cases, resulting in pulmonary embolism (n = 3), aortic embolism (n = 1), cardiac and pulmonary embolisms (n = 3), and cord compression (n = 1). In five cases, these complications required major surgical rescue or repair—two spinal surgeries[180,181] and three cardiac surgeries.[182-184] The bone cement leakage resulted in death in two cases.[182,185] The other major complications involved spinal infection (n = 1)[186] and needle-tract metastases (n = 2).[187,188] Spinal surgeries were performed for the cases involving tumour seeding along the vertebroplasty needle tracts, both involving lung cancer. Death occurred within months in both cases because of the rapid progression of the disease.

One case report involved a minor but unusual complication of contact dermatitis, a delayed hypersensitivity response that cleared easily with corticosteroids.[189] Another case report involved more of a technical failure of the vertebroplasty procedure owing to prior treatment with denosumab, which had been used to prevent skeletal events in a patient with metastatic lung cancer.[190] The drug had induced a rapid and marked sclerotic change in the vertebral bone, which prevented needle insertion for the cement injection.

Table 25: Complications Reported in Clinical Studies of Vertebroplasty for Cancer-Related Vertebral Compression Fractures

Author, Year Country	Patients, N (F, M) Age, Mean ±SD (Range)[a] Follow-Up	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Multiple Myeloma as Primary Malignancy of Spinal Metastases				
Anselmetti et al, 2012[59] Italy	123 patients (58 F, 65 M) 70 years (35–92) 28.2 ± 12.1 months	Interventional radiology VP in 124 sessions at 528 VB levels (C, T, L); post-op CT	None reported 16 patients reported new-onset back pain due to new vertebral collapse associated with disease progression; all were treated with second VP	n = 7 Bone cement PE, all asymptomatic (n = 5) Disseminated intravascular coagulopathy 10 days post-VP (n = 1) Bacterial infection *(Staphylococcus aureus)* of treated vertebrae 30 days post-VP requiring long-term IV antibiotic chemotherapy (n = 1)
Bosnjakovic et al, 2005[53] Serbia	29 patients (18 F, 11 M) 63 years (58–79) 12 months	Interventional radiology VP at 55 VB levels (17 T, 38 L)	None reported Recurrence of back pain in 9 patients at non-treated levels due to new lesions	None reported
Chen et al, 2012[56] China	24 patients (20 F, 4 M) 67 years (54–81) NR	Orthopedic surgery VP at 36 VB levels	Asymptomatic bone cement leakage occurred in 17% (4/24) of the cases; leaks were through the vertebral inferior end plate into the disc (n = 2) and into the paravertebral vessels (n = 2)	None reported
Diamond et al, 2004[61] Australia	7 patients (4 F, 3M) Range 58–78 years 6 weeks	Interventional radiology VP at 14 VB levels (T, L); 1 had 7 levels	No bone cement leakages (paravertebral or foraminal) were reported	None reported
Garland et al, 2011[55] United Kingdom	26 patients (10 F, 16 M) 59.3 years (42–76) Mean 19 months	Interventional radiology VP at 57 VB levels (T6 to L5) VP performed at one level (n = 8), two levels (n = 5), and three levels (n = 13)	Asymptomatic bone cement leakages occurred in 12% (3/26) of the cases: small (< 1 mL) leaks during the procedure (n = 3), 2 of which were associated with increased pain on waking from anaesthetic and resolving within 24 hours 6 patients without cement leaks experienced pain following the procedure, but it resolved within 24 hours; anaesthetic respiratory compromise in 1 patient with a pre-existing lung condition resolved within 72 hours	None reported
Masala et al, 2008[65] Italy	64 patients (30 F, 34 M) 71.4 ± 9.6 years 6 months	Interventional radiology VP at 198 VB levels (93 T, 105 L)	None reported	None reported
McDonald et al, 2008[54] United States	67 patients (30 F, 37 M) 66.2 years 12 months	Interventional radiology VP at 114 VB levels	Asymptomatic bone cement leakage occurred in 19% (13/67) of cases: leaks were in the epidural veins (n = 3), adjacent discs (n = 6) and paravertebral space (n = 4)	None reported

Author, Year Country	Patients, N (F, M) Age, Mean ±SD (Range)[a] Follow-Up	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Ramos et al, 2006[51] Spain	12 patients (3 F, 9 M) 66 years (54–80) 3 years	Orthopedic surgery and radiology VP at 19 VB levels (T9 to L4)	Asymptomatic bone cement leakage occurred in 84% (16/19) of treated vertebrae: leaks were in the venous plexus (n = 13), spinal canal (n = 2), and adjacent discs (n = 3)	None reported
Simony et al, 2014[66] Denmark	17 patients (7 F, 10 M) 62.5 years (46–76) 3 months	Surgery VP at 64 VB levels (T6 to S2)	n = 1 1 patient developed peroneal paresis 12 weeks post-VP, with full function gained spontaneously; x-rays did not show cement leakage and MRI did not show compression of nerve structures Asymptomatic bone cement leakages occurred in 13% (8/64) of the treated vertebrae: leaks were to the spinal cord (n = 3) with none developing neurological complications	None reported
Tancioni et al, 2010[60] Italy	11 patients (5 F, 6 M) Median 56 years (45–76) 12 months	Neurosurgery VP in 14 sessions at 28 VB levels (1 C, 17 T, 10 L)	Asymptomatic bone cement leakages occurred in 27% (3/11) of cases: leaks were through a fractured end plate into adjacent disc space (n = 10) and into the anterior spinal space (n = 2)	None reported
Tran Thang et al, 2008[62] Switzerland	28 patients (11 F, 17 M) Median 65 years (40–89) Median 41 months	Interventional radiology VP in 33 sessions for 75 fractures and at 117 VB levels (57 T, 59 L, 1 S) VP performed at one level (n = 7), two or more levels (n = 21)	n = 3 Bone cement leakage along the L5 nerve root associated with a transient sensitive defect resolving within 3 weeks (n = 1) Transient thoracic pain or dyspnea following VP with PE ruled out by lung CT and pulmonary scintigraphy (n = 2) Bone cement leakages of small size (< 1 cm) occurred in 29% (8/28) of cases	None reported

Author, Year Country	Patients, N (F, M) Age, Mean ±SD (Range)[a] Follow-Up	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Trumm et al, 2012[52] Germany	39 patients (17 F, 22 M) 65 ± 7 years 6 months	Interventional radiology VP in 44 sessions at 67 VB levels (3 C, 32 T, 27 L, 5 S)	n = 4 Generalized seizure after local anaesthetic, successfully managed (n = 1) Decreased oxygen saturation following midazolam requiring oxygen and administration of flumazenil (n = 1) Prolonged bleeding at skin incision and needle entry site managed by compression and additional sutures (n = 2) Asymptomatic bone cement leakages occurred in 50.7% (34/67) of the treated vertebrae: leaks were in the paravertebral soft tissues (n = 16, 15 with segmental vein), intraspinal/epidural space (n = 13, 6 with basivertebral vein) and neighbouring intervertebral discs (n = 8)	None reported
Mixed Metastatic Cancers as Primary of Spinal Metastases				
Barragan-Campos et al, 2006[177] France	117 patients (79 F, 38 M) 58.2 ± 12.5 years (27–88)	Interventional neuroradiology VP in 159 sessions at 304 VB levels	n = 6 The 423 technical incidents of bone cement leaks from 304 treated vertebrae led to 8 (6.8%) complications: 6 (5.1%) local and 2 (1.7%) systemic Local events included puncture site soft-tissue hematoma (n = 2), both resolving spontaneously over 2 weeks; and radicular pain (n = 4) attributed to ipsilateral foraminal venous cement leakage in 2 cases with neither vascular nor nonvascular leakages responsible for the other 2 cases—radicular pain resolved in all cases without the need for surgical debulking of cement	n = 2 PE after VP for breast and lung cancer VCF within 30 days (n = 2) In one of the cases, cement migration from the paravertebral venous plexus through the vena cava was significantly associated with PE. The PE in the lung cancer case was symptomatic, developing ventilator and hemodynamic symptoms; despite oral anticoagulants, the patient died 8 days post-VP No neurological deficits related to spinal cord or radicular compression occurred
Burton et al, 2005[67] United States	3 patients (2 F, 1 M) 64 years (60–67) Until death	Anaesthesiology VP at 6 VB levels (5 L, 1 T)	None reported	None reported

Author, Year Country	Patients, N (F, M) Age, Mean ±SD (Range)[a] Follow-Up	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Calmels et al, 2007[58] France	52 patients (46 F, 6 M) Mean 17 months	Interventional neuroradiology VP in 59 sessions at 103 treated VB levels	n = 2 Transient radiculalgia caused by a foraminal leak resolved with analgesia and corticosteroid treatment (n = 1) A moderate-sized hemothorax (n = 1) caused by a leak along the puncture path during a posterolateral approach for a pure blastic lesion at the thoracic level resolved spontaneously Bone cement leaks occurred in 50% (52/103) of the treated vertebrae: leaks were in the venous system [perivertebral (n = 8), epidural (n = 10) towards azygous vein (n = 2)], intradiscal region (n = 3), and soft tissue regions [spinal canal (4), posterior-mediastinal space (n = 24) and puncture path (n = 1)]	n = 5 Asymptomatic PE (n = 2) without overt clinical signs that it resolved with anticoagulant treatment after cement leakage toward the azygous vein Transient radiculalgia due to foraminal leak (n = 2); in one case, the foraminal leak was associated with posterior wall disruption with tumoral epidural extension and was successfully treated with surgery; in the other, the posterior wall was not disrupted and the patient was also treated with surgery Cauda equina syndrome occurred after an intracanalar leak although the vertebrae (n = 1); originally the patient was treated for a pure blastic lesion with epidural tumoral extension and a constitutional canal stenosis worsened by an exophytic left pedicular metastatic extension; the case resulted in surgical treatment with removal of epidural component, L4 vertebrectomy and osteosynthesis
Chen et al, 2011[68] China	4 patients (1 F, 3 M) Range 47–67 years 3 months	Interventional radiology VP at 4 VB levels (T or L)	n =1 Asymptomatic bone cement leakage into anterior vertebral vein	None reported
Chew et al, 2011[63] Scotland	128 patients (60 F, 68 M) 60 years (31–88) Median 3 years	Interventional radiology VP in 158 sessions at 264 VB levels	n = 2 Local hematoma (n = 1) Loss of sensation at the T1 dermatome (n = 1)	n = 4 Cement leakage into the inferior vena cava followed by an IVC filter placed prophylactically (n = 1) Asymptomatic pulmonary emboli (n = 3) in which one underwent a groin cut down and extraction of cement due to the embolic size
Corcos et al, 2014[178] France	56 patients (30 F, 26 M) 56 ± 12 years (21–79)	Interventional radiology VP in 58 sessions at 81 VB levels (34 T, 46 L, 1 S)	Asymptomatic bone cement leakage occurred in 53% (43/81) of the treated vertebrae: leaks were vascular (n = 20) and through the cortical bone (n = 26)	n = 1 Asymptomatic pulmonary embolism
Farrokhi et al, 2012[69] Iran	25 patients (14 F, 11 M) 53.5 (37–70) 2 months	Neurosurgery VP at 14 VB levels (T3 to L4)	Asymptomatic bone cement leakages occurred in 43% (6/14) of the treated vertebrae: leaks were in the paravertebral (n = 5), discal (n = 4) and epidural (n = 2) regions	None reported
Kobayashi et al, 2009[71] Japan	33 patients (17 F, 16 M) 62 years (37–87) 1 month	Interventional radiology VP at 42 VB levels (18 T, 24 L)	n = 2 Bleeding at puncture site (n = 1) Grade 2 serum hypoalbuminemia (n = 1)	None reported

Author, Year Country	Patients, N (F, M) Age, Mean ±SD (Range)[a] Follow-Up	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Kushchayev et al, 2010[50] United States	2 patients (2 M) 63-year-old, 60-year-old Until death	Surgery VP at L5; VP at L2, followed by transpedicular fixation at L1 to L3	None reported	None reported
Lee et al, 2009[72] United Kingdom	19 patients (11 F, 8 M) 70 years (44–89) Median 12 months	Interventional radiology VP at 34 levels (T, L)	n = 1 Pain due to bone cement leakage at injection site	None reported
McDonald et al, 2009[64] United States	128 of 841 patients NR 12 months	Interventional neuroradiology VP (levels NR)	Procedural complications (not stated) ranged among 7 operators from 22% (37/168) to 39% (28/71) of cases	NR
Mikami et al, 2011[73] Japan	69 patients (34 F, 35 M) 65.1 years (48–89) 6 months	Interventional radiology VP at 141 VB levels (47 T, 77 L, 17 S)	Bone cement leakage occurred in 49% (34/69) of cases	n = 2 Dyspnea occurred in 2 cases, with an uncertain link to VP One case involved an 82-year-old male with lung cancer who required oxygen on discharge, thought to be due to adult respiratory distress syndrome The second case involved a 54-year-old woman with recurrent breast cancer and painful metastatic L4 vertebrae, admitted prior to VP for distress related to carcinomatosis, lymphangiosis, and disseminated intravascular coagulopathy; dyspnea followed VP requiring oxygen and interstitial pneumonia, verified by CT with no apparent PE, and despite steroid pulse therapy progressed rapidly to death 7 days post-VP
Murphy et al, 2007[47] United States	1 patient (F) 41-year-old	Interventional radiology VP at T10	None reported	None reported

Author, Year Country	Patients, N (F, M) Age, Mean ±SD (Range)[a] Follow-Up	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Trumm et al, 2008[48] Germany	53 patients (52 F, 1 M) 62 ± 13 years Mean 9.2 months	Interventional radiology VP in 62 sessions at 86 VB levels (9 C, 55 T, 21 L, 1 S) VP performed at one level (n = 34), two levels (n = 27), and three levels (n = 1)	n = 4 Sudden sickness with needle insertion, successfully treated with 10 mg IV metoclopramide (n = 1) Exacerbation of pain during needle insertion (n = 1) or during cement injection (n = 2), managed by conscious sedation of 5 mg IV midazolam and 15 mg piritramide Asymptomatic bone cement leakage occurred in 70% (60/86) of treated vertebrae: leaks were in the intervertebral disc (n = 21) or intraspinal (n = 67)	None reported
Tseng et al, 2008[57], 2008[179] China	57 patients (32 F, 25 M) 65.2 years (40–86) Mean 24.3 months	Neurosurgery VP at 78 levels (1 C, 33 T, 44 L) Vertebral fracture level (Genant) Grade 0 (n = 5) Grade 1 (n = 22) Grade 2 (n = 39) Grade 3 (n = 12)	n = 1 Post-operative hematoma resolving without surgery (n = 1) Bone cement leakage occurred in 22% (17/78) of the treated vertebrae: 14 patients had no neurological deficits and 3 patients had neurological symptoms requiring decompression surgery (2 undergoing laminectomy and internal fixation and 1 undergoing laminectomy only)	n = 4 Post-operative hematoma requiring surgery (n = 1) Cement leakage with neurological deficits (n = 3); all 3 underwent spinal decompression surgery; 2 underwent laminectomy and internal fixation, and 1 underwent laminectomy only; 2 died from post-operative sepsis

Abbreviations: CT, computed tomography; F, female; L, lumbar; M, male; NR, not reported; PE, pulmonary embolism; S, sacrum; T, thoracic; VP, vertebroplasty.
[a]Unless otherwise indicated.

Table 26: Complications Reported in Clinical Studies of Vertebroplasty and Adjunctive Local Tumour Control Interventions for Cancer-Related Vertebral Compression Fractures

Author, Year Country	Patients, N (F, M) Age, Mean ± SD (Range)[a] Follow-Up	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Multiple Myeloma as Primary of Spinal Metastases				
Erdem et al, 2013[81] United States	41 patients (20 F, 21 M) 56.9 ± 14.2 years (24–86) 6 months	Interventional neuroradiology VP and RFA in 48 sessions for 139 VB levels (T, L, or S)	Asymptomatic bone cement leakage occurred in 2% (1/41) of cases; leaks were in the intervertebral disc space	None reported
Orgera et al, 2014[79] Italy	36 patients (26 F, 10 M) 63.1 ± 7.2 years 6 weeks	Interventional radiology VP and RFA (18 patients, 22 procedures; 8 T, 14 L) vs. VP only (18 patients, 28 procedures, 11 T, 17 L)	Asymptomatic bone cement leakage occurred in 11% (4/36) of the entire group, 2 patients in each group, and of the treated vertebrae 9% (2/22) in the combined treatment group and in 7% (2/28) in the VP-only treated group	None reported
Yang et al, 2012[80] China	76 patients (37 F, 39 M) VP, chemotherapy, and bisphosphonate group: 58.9 years ± 4.3 years Chemotherapy and bisphosphonate group: 59.6 years ± 6.2 years	Orthopaedic surgery VP and chemotherapy (38 patients and 93 VB levels) VP performed at one level (n = 3), two levels (n = 15), or three or more levels (n = 20)	n = 3 Decreased blood pressure, oxygen saturation and pressure and increased thromboxane level managed with supplemental oxygen and IV injection of dexamethasone (n = 3) Asymptomatic cement leakage occurred in 53% (20/38) of cases; leaks were to the anterior or lateral side vertebral body without signs of cord or nerve root compression	None reported
Mixed Metastatic Cancers as Primary of Spinal Metastases				
Anchala et al, 2014[82] United States	92 patients 60 years (35–84) 6 months	Interventional radiology VP at 96 VB levels and RFA at 128 levels	Asymptomatic bone cement leakage occurred in 2% (2/92) of the cases: 1 into a draining vein and 1 into a sacral neural foramen	None reported
Gronemeyer et al, 2002[83] Germany	10 patients Range 58–76 years 6 months	Interventional radiology RFA and VP (n = 4)	n = 1 Passage-related transient contralateral paresthesia following RFA	None reported
Halpin et al, 2005[84] United States	1 patient (F) 45-year-old NR	Interventional radiology VP and RFA at T9 and VP at T12	None reported	None reported

Author, Year Country	Patients, N (F, M) Age, Mean ± SD (Range)[a] Follow-Up	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Jang et al, 2005[74] South Korea	28 patients (17 F, 11 M) Range 40–72 years 7 months	Surgery VP at 72 VB levels (9 C, 30 T, 33 L), followed by PRT	Asymptomatic bone cement leakage occurred in 72% (52/72) of the treated vertebrae; leaks were in the spinal canal (n =12), neural foramen (n = 2), adjacent disc (n = 17), paravertebral tissues (n = 18), and veins (n = 15)	n = 3 Bone cement pulmonary embolism (n = 3); 2 patients experienced mild dyspnea and chest discomfort, resolving with supplemental oxygen and anticoagulation therapy; 1 patient was asymptomatic; no perfusion defects were detected with ventilation perfusion scanning in any of the patients
Lim et al, 2009[75] Korea	102 patients (42 F, 60 M) Median 55 years (22–82) 12 months	Neurosurgery 185 VP-treated vertebrae; of those, 126 were treated by VP and 59 were treated by VP and PRT	Overall, asymptomatic bone cement leakages occurred in 17% (32/185) of treated vertebrae; leaks were in the epidural space (n = 13), adjacent discs (n = 13) and in venous plexus (n = 6)	None reported
Masala et al, 2004[85] Italy	3 patients (2 F, 1 M) 72.3 years (63, 72, 82)	Interventional radiology 3 VP- and RFA-treated vertebrae	No bone cement leakages to the epidural or foraminal sites with marrow or radicular compression occurred	None reported
Nakatsuka et al, 2004[86] Japan	17 patients (8 F, 9 M) 61 ± 13 years 6 months	Interventional radiology VP and RFA for 23 bone lesions	All patients experienced radiating pain of lower extremities during RFA	n = 4 Neural complications (n = 4); in 3 patients, tumours invading the posterior cortex of the vertebral body resulted in incomplete hemiplegia; in 1 patient, a tumour invading the pedicle resulted in radiculopathy; symptoms in 3 were improved by rehabilitation and unchanged in 1
Rasulova et al, 2011[76] Uzbekistan	11 patients (5 F, 6 M) 53.8 years (32–62) 6–8 months	Interventional radiology and orthopaedic surgery	No symptomatic bone cement leakage occurred	None reported
Toyota et al, 2005[87] Japan	17 patients (1 F, 16 M) 64.2 years (54–81) 12 months	Interventional radiology RFA and VP in 53 sessions for 23 lesions	n = 2 Hematomas at psoas muscle (n = 1) and at the puncture site (n = 1); transient localized pain occurred at the puncture site in most patients	None reported

Author, Year Country	Patients, N (F, M) Age, Mean ± SD (Range)[a] Follow-Up	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Yang et al, 2009[78] China	80 patients (39 F, 41 M) VP: 58.8 ± 7.4 years VP and radiotherapy ^{125}I seed ISI: 61 ± 4.5 years 12 months	Orthopaedic surgery ^{125}I seed ISI and VP (40 patients with 62 vertebral lesions) vs. VP (40 patients with 64 vertebral lesions); overall, 126 VB levels (T, L)	Overall asymptomatic bone cement leakage occurred in 16% (13/80) of cases: 6 in the combined treatment group and 7 in the VP-only group; leaks were minor in the paravertebral region No cases of PE, nerve or cord compression occurred; no radiation myelitis, leukopenia, decreased immunologic function or seed abscission	None reported
Yang et al, 2013[77] China	100 patients (61 F, 39 M) VP and radiotherapy ^{125}I seed ISI: 61.1 ± 5.2 years Radiotherapy group: 59.8 ± 6.6 years 1 year	Orthopaedic surgery ^{125}I seed ISI and VP (50 patients, 71 vertebral levels) vs. PRT (50 patients, 74 vertebral lesions) for osteoblastic lesions	n = 2 Decreased blood pressure, oxygen saturation and pressure and thromboxane level increased, managed with supplemental oxygen and IV injection of dexamethasone (n = 2) Asymptomatic cement leakage occurred in 42% (21/50) of the cases; leaks were to the anterior or lateral side of the vertebral body	None reported

Abbreviations: C, cervical; F, female; ISI, interstitial seed implantation; IV, intravenous; L, lumbar; M, male; PE, pulmonary embolism; PRT, palliative radiotherapy; RFA, radiofrequency ablation; S, sacral; SD, standard deviation; T, thoracic; VB, vertebral body; VP, vertebroplasty.

Table 27: Complication Case Reports Involving Vertebroplasty for Cancer-Related Vertebral Compression Fractures

Author, Year Country	Patient and Primary Malignancy	Clinical History	Operator Interventions and Treated Spinal Levels	Adverse Event	Outcome
Abdelrahman et al, 2013[186] Germany	69-year-old male with non-Hodgkin's lymphoma	After receiving chemotherapy for non-Hodgkin's lymphoma, presented with L4 VCF without neurological deficits	Surgery VP at L4	*Spinal infection:* 2 weeks after VP, the patient presented with increasing low back pain and radiculopathy; laboratory and imaging showed spondylitis; *Streptococcus agalactiae* was the isolated organism, and clindamycin was prescribed for 6 weeks	Anterior corpectomy and reconstruction with corpectomy cage and bone graft using a mini-laparotomy approach combined with posterior transpedicular fusion
Alcibar et al, 2011[185] Spain	74-year-old male with lung cancer metastases	High blood pressure, dyslipidemia and lung adenocarcinoma (T4N3M0); received chemotherapy and radiation therapy and about a year later, was admitted with intense lumbar pain and hospitalized for 10 days	Neuroradiology Bilateral transpedicular VP at L2 under general anaesthesia	*Bone cement PE:* bone cement fragments in both lungs and 1 larger round fragment in the segmental branch of the inferior left lobule were detected; some material was successfully removed percutaneously, but fragments remained in the inferior and suprahepatic venae cavae and segmental branches of both lungs	Despite treatment with antibiotics for pneumonia *(Staphylococcus aureus)*, the patient's condition worsened, with severe respiratory insufficiency, hypoxemia, and respiratory acidosis; the patient died 12 days post-procedure
Amoretti et al, 2007[191] France	72-year-old female with breast cancer metastases	NR	Interventional radiology VP at L3 under local anaesthesia using a unilateral approach under CT and C-arm fluoroscopy guidance	*Arterial bone cement leakage and embolism:* during the procedure, CT confirmed cement migration into the aorta via the lumbar artery; a CT 4 months post-procedure showed cement remaining in the aorta and lumbar artery	The patient remained asymptomatic without vascular symptoms 4 months following the procedure, without anticoagulant therapy
Chen et al, 2014[192] China	39-year-old female with breast cancer metastases	Presented with 2-week history of backache, bilateral leg weakness and urinary incontinence; radiography and MRI demonstrated a VCF at T12 and a kyphotic deformity at the thoracic-lumbar junction, with compression of underlying spinal conus	Surgery VP at T10, T11, L1, L2; laminectomies with screw fixation at 4 VB levels	*Bone cement PE:* CT revealed diffuse branching hyperdense intraluminal opacities throughout the left main pulmonary artery, peripheral segmental pulmonary arteries, azygos and hemiazygos veins, and vertebral venous plexus	Echocardiography revealed normal systolic pulmonary artery pressure (28 mm Hg) and normal right ventricular size and function

Author, Year Country	Patient and Primary Malignancy	Clinical History	Operator Interventions and Treated Spinal Levels	Adverse Event	Outcome
Chen et al, 2007[187] China	76-year-old male with lung cancer metastases	Diagnosed with adenocarcinoma of the lung (T2N3M1); did not receive chemotherapy or radiation; 1 month later, underwent VP for severe back pain	Orthopaedic surgery VP at 2 VB levels (L1, L3)	*Local metastases along VP needle tract:* 3 months post-procedure, condition worsened with recurrent pain and bilateral leg weakness; MRI revealed contrast-enhanced lesions at the posterior aspect of L1 with extension to the adjacent anterior epidural space of L1 and posterior epidural space along T12 to L3 with compression to adjacent dura sac; further ill-defined lesions were seen with contrast enhancements	Surgeries were performed, including laminectomy, excision of the epidural tumour (which encompassed the dura from T12 to L3) and posterior spinal fusion with instrumentation; neurological deficits did not improve post-operatively, and after a progressively deteriorating condition, the patient died 2 months later
Chou et al, 2013[182] China	62-year-old female with multiple myeloma, IgG-kappa stage III	NR	Orthopaedic surgery VP at 4 VB levels: T12, L1, L2, and L3	*Fatal bone cement–induced PE:* patient experienced sudden-onset dyspnea following the procedure, and an echocardiogram revealed dilation of right ventricular chamber with tricuspid regurgitation and increased peak systolic pressure gradient, suggesting pulmonary hypertension; chest radiographs showed opacified lesions over the right pulmonary artery, suggesting bone cement–induced PE; CT angiography showed high-density lesions in the inferior vena cava and both pulmonary arteries, confirming PE	Pulmonary thrombectomy by cardiac catheterization was conducted because of worsening pulmonary distress despite oxygen supplementation and use of anticoagulants; only 1 piece of bone cement (15 mm) could be retrieved, and the patient died of cardiopulmonary failure

Author, Year Country	Patient and Primary Malignancy	Clinical History	Operator Interventions and Treated Spinal Levels	Adverse Event	Outcome
Lee et al, 2014[193] Korea	61-year-old female with lung cancer metastases	Diagnosed with adenocarcinoma of the lung (T2aN3M1b) 31 months earlier and underwent PRT; 5 months later was diagnosed with T4–T6 vertebral fracture	Neurosurgery 5 days following the fracture diagnosis, VP was performed at 3 VB levels (T4 to T6); difficulty injecting due to high pressure was reported 4 days following VP, the patient underwent chemotherapy and PRT at T3–T6 VB levels, at a dose of 30 Gy (3 Gy per fraction); a brace was recommended, but not worn due to inconvenience	*Needle tract seeding after VP:* about 5 months following VP, the patient presented with a painful 4 cm back mass near the VP needle site; CT imaging revealed a subcutaneous mass extending to the right T5 pedicle, with an extension to the adjacent epidural space T4 to T7	Surgeries were performed, including excision of the back and epidural tumour and posterior spinal fusion; after surgery, the back pain resolved and weakness improved, but the patient died 2 months after surgery due to lung cancer progression
Lim et al, 2007[183] Korea	55-year-old female with unreported etiology of VCF	Presented with mild dyspnea and edema lasting 4 weeks	Anaesthesiology Underwent VP for L2 after a VP for L5 VCF 5 years earlier	*Bone cement leakage causing multiple cardiac perforations and PE:* initial work-ups of a chest radiograph and an abdominal ultrasound revealed a foreign body in the inferior vena cava reaching the right atrium; a transesophageal echocardiograph revealed a right atrial thrombus (2.5 cm diameter) and 2 fixed tubular structures, 1 extending from the hepatic vein into the right atrium and the other connected to the thrombus; CT angiography showed a linear foreign body extending from the right hepatic vein to the right atrium, where it appeared divided in 2 parts; a PE obstructing the orifice of the left lower lobar branch was also observed; lung scanning perfusion demonstrated ventilation-perfusion mismatch with decreased blood flow to the left lower lobe	Anticoagulation was initiated, and open-heart surgery for foreign body removal and atrial thrombectomy were performed under cardiopulmonary bypass; chemical analysis revealed bone cement as a key component of the thrombus; the patient made an uneventful recovery and was discharged 7 days post-surgery

Author, Year Country	Patient and Primary Malignancy	Clinical History	Operator Interventions and Treated Spinal Levels	Adverse Event	Outcome
Lim et al, 2008[184] Korea	59-year-old female with unreported etiology of VCF	Presented with chest pain radiating to both shoulders and dyspnea	Surgery Repeated VP at T12 (2 months) and L1 (9 days) to relieve back pain	*Multiple cardiac perforations and PE caused by cement leakage:* routine chest x-ray revealed 3 linear radio-opaque opacities with cardiac shadow and a linear opacity at the right upper lung, suggesting the presence of a foreign body and PE caused by bone cement: a CT revealed fish bone–like material piercing 3 sites of the right ventricle, with moderate pericardial effusion; in addition, 1 piece was stuck in the free wall of the right ventricle and 1 piece had perforated the ventricle	Cardiopulmonary bypass was carried out to repair multiple perforations of the right ventricle and remove bone cement material from the right ventricle and the pulmonary artery of the right upper lobe; the patient was discharged 15 days after surgery and experienced no sequelae except continuous low back pain
Mahadevia et al, 2007[189] United States	52-year-old female with unreported etiology of VCF	Patient was allergic to penicillin, sulfa drugs, and intravenous contrast media	Interventional neuroradiology VP at T12	*Contact dermatitis, delayed-type hypersensitivity after VP:* 1 day following VP, the patient developed a 4- x 2-inch region of blistering at the injection site, was intermittently itchy with some weeping, but no purulent drainage	A 1-week course of topical corticosteroids applied twice daily eliminated the itching and weeping and decreased the size of the injection-site lesion
Mattei et al, 2014[190] United States	41-year-old female with stage IV metastatic non-small-cell lung cancer	Presented 3 months earlier with acute onset mid-thoracic pain, CT showing VCF at T5 and T6; initiated chemotherapy, erlotinib, and denosumab because of widespread metastatic bone lesions; mid-thoracic pain persisted after 6 weeks despite use of narcotics, and VP was offered	Interventional radiology Unsuccessful VP at 1 VB level (T6)	*VP failure for VCF in patients undergoing medical therapy with denosumab:* during the VP procedure it was extremely difficult to penetrate the pedicle with an 11-gauge needle, and because of needle deviations, it was not possible to penetrate the VB and perform cement injection	A post-procedure CT demonstrated remodelling of medullary bone of the vertebral bodies, with marked sclerotic appearance of previously lytic bony lesions compared with a CT from 6 weeks earlier

Author, Year Country	Patient and Primary Malignancy	Clinical History	Operator Interventions and Treated Spinal Levels	Adverse Event	Outcome
Omidi-Kashani et al, 2009[180] Iran	14-year-old female with vertebral hemangioma	Presented with a year of chronic low back pain, having undergone prolonged homemade treatments and numerous bone setters; plain radiograph confirmed a vertebral hemangioma, and the patient was offered a 2-month course of conservative treatment and physiotherapy; pain did not resolve, and because of concern for an impending fracture, VP was conducted	Orthopaedic surgery VP at L3	*Bone cement leakage with neuroforamen involvement, resulting in neurological symptoms requiring surgical intervention:* the pain completely resolved after the VP, and after 2 months a radicular right leg pain occurred and progressed unremittingly; after 12 months, the pain was so severe the child was unable to attend school, and the pain regularly interfered with sleep; a plain radiograph and CT revealed right-sided cement leakage and L3 to L4 neuroforamen involvement; an electrodiagnostic study was compatible with chronic L4 and L5 demyelinating radiculopathy	Decompressive spinal surgery was conducted with limited laminotomy and foraminotomy; cement pieces extruding posterolaterally were excised, and the L4 root was decompressed completely; pain was completely reduced immediately, and muscular power returned after a month
Ratliff et al, 2001[181] United States	50-year-old female with infiltrating ductal breast cancer	Presented with disabling thoracic back pain radiating into the shoulders 4 years after diagnosis of breast cancer that was treated with modified radical mastectomy, axillary node dissection, adjuvant chemotherapy, and local radiation; subsequent metastases to the clavicle and ilium were treated with radiotherapy; no motor or sensory deficits were present, and bowel or bladder dysfunctions were absent	Surgery VP for T1 VCF without cord compression	*Cement leakage causing symptomatic nerve root and spinal cord compression:* during the procedure and after injection, the patient reported hypoalgesia of the left fifth finger with cement injection; a portable CT confirmed that bone cement had leaked into the C8 and T1 foramina and the spinal cord; the procedure was terminated after the left-sided injection; over the next 48 hours, the patient developed weakness of left-hand intrinsics (3 to 4/5), abductor digiti minimi (3/5) and opponens pollicis (2/5); sensory deficits spread to the left ulnar forearm and third and fourth digits, and the lower extremity became hyperreflexic	Surgical intervention included an anterior cervicothoracic approach via median sternotomy to remove bone cement from the vertebral body, foramina and epidural space; the bony defect was instrumented with a Harms cage and overlying anterior locking plate; following surgery, the weakness and hyperreflexia resolved and the patient returned to work 6 weeks later; at 6 months, the patient continued to have good pain relief

Abbreviations: C, cervical; CT, computed tomography; Ig, immunoglobulin; L, lumbar; MRI, magnetic resonance imaging; NR, not reported; PE, pulmonary embolism; PRT, palliative radiotherapy; T, thoracic; TNM, tumour-node-metastasis; VB, vertebral body; VCF, vertebral compression fracture; VP, vertebroplasty.

D2. Safety of Kyphoplasty

Complications reported in studies evaluating effectiveness of kyphoplasty are outlined in three tables: Table 29 for kyphoplasty only, Table 30 for kyphoplasty and adjunctive local tumour control interventions, and Table 31 for kyphoplasty, vertebroplasty, and local tumour control interventions. Three studies evaluated only safety in kyphoplasty interventions, and these were reports by Mroz et al[194] on radiation exposure, by Huber et al[195] on 30-day post-operative complications, and by Li and Yao[196] on single-session multilevel kyphoplasty.

Mroz et al[194] reported on radiation exposure to both patients and operators during kyphoplasty procedures. The hands and eyes of the operators are unprotected during fluoroscopic procedures and are at particular risk. In this study, kyphoplasty was performed at 52 vertebral body levels for 27 patients and involved 16 different staff surgeons. The kyphoplasty procedures were at the T4 to L5 regions and were performed in one session at a single level (n = 10), at two levels (n = 9), and at three levels (n = 8). Eye and hand exposures per treated vertebra were 0.271 millisievert (mSv) and 1.744 mSv, respectively. The occupational exposure limit is an annual dose of 150 mSv for the lens of the eye and 500 mSv for the extremities. The authors concluded that without protection, the total exposure dose to the hands could exceed the limit after 300 kyphoplasty levels, and the total exposure dose to the eyes would reach approximately 50% of the limit with this number of procedures.

Kyphoplasty for multiple myeloma and metastatic primary cancers. The spinal fractures for these cases were again mainly at the thoracic and lumbar levels, and the operators for the kyphoplasty interventions were surgeons, predominantly orthopedic surgeons. The procedures were performed under general anaesthesia, and more than one vertebral level was commonly treated with kyphoplasty. However, investigators did not always report whether the multilevel treatments were performed in one or more sessions.

In the six studies involving kyphoplasty for 186 patients with multiple myeloma, there were three major complications (1.6%) (Table 29). These included bone cement leakage resulting in pulmonary embolism and spinal cord compromise,[195] and an incident adjacent-level fracture occurring 2 weeks following kyphoplasty.[93] Surgery was required in one case to remove cement that was compromising the spinal cord.[195] There were no deaths in this study group.

In the seven studies evaluating kyphoplasty for 261 patients with metastatic cancer, there were 18 major complications (6.9%). These involved cardiac complications occurring during or at the end of the procedure (n = 11),[88,98,196] deep vein thrombosis (n = 1),[96] and incident adjacent-level fractures following kyphoplasty (n = 6).[96,97] A re-intervention with a second kyphoplasty was performed for a symptomatic adjacent-level fracture.[96]

Li and Yao[196] compared (1) complications occurring in procedures performed in one session or in a single stage where one or two vertebral body levels were treated with (2) complications with multiple-level treatments involving three or more vertebral body levels performed in a single session. The cardiac complications, seven cases of arrhythmias during the procedure that required medication, all occurred in the multi-level treated group. Three deaths were reported in two studies,[88,98] both occurring shortly after kyphoplasty; however, all were judged to be unrelated to the procedure.

Thirteen studies reported asymptomatic bone cement leakage, per treated vertebra or per treated case (Table 28). In the multiple myeloma cases, cement leaks ranged from 4% to 26% per treated vertebra, and one study reported leaks in 38% of treated cases. In the metastatic group, cement leaks per treated vertebra ranged from 9% to 14% and per treated case ranged from 3% to 18%.

Table 28: Asymptomatic Bone Cement Leakage After Kyphoplasty for Cancer-Related Vertebral Compression Fractures

Author, Year	Leaks Per Treated Case	Leaks Per Treated Vertebra
Multiple Myeloma		
Dudeney et al, 2002[90]	NR	4% (2/55)
Huber et al, 2009[195]	NR	18% (35/190)
Julka et al, 2014[91]	38% (12/32)	15% (11/71)
Lane et al, 2004[92]	NR	26% (10/38)
Pflugmacher et al, 2006[93]	NR	10% (5/48)
Zou et al, 2010[94]	NR	5% (2/43)
Metastatic Cancers		
Berenson et al, 2011[88]	3% (2/68)	NR
Chen et al, 2013[95]	17% (1/6)	NR
Konig et al, 2012[96]	18% (2/11)	NR
Vrionis et al, 2005[98]	6% (3/50)	NR
Korovessis et al, 2014[89]	NR	9% (4/43)
Li et al, 2014[196]	NR	14% (7/50)
Pflugmacher et al, 2008[97]	NR	12% (12/99)

Kyphoplasty and adjunctive local tumour control interventions. Four studies evaluated kyphoplasty and adjunctive interventions (Table 30). One study, involving 35 cases with primary multiple myeloma, involved kyphoplasty with palliative external beam radiotherapy.[104]

Three studies in patients with primary metastatic cancer patients involved different adjunctive approaches (Table 30)—palliative external beam radiotherapy,[105] radiosurgery with CyberKnife,[103] and radiofrequency ablation.[106] The operators for the kyphoplasty procedures were surgeons in collaboration with interventional radiologists for the radiofrequency ablation, and surgeons with radiation oncologists for the radiotherapy interventions. The procedures were all performed using general anaesthesia.

There were two major complications involving the 39 patients with multiple myeloma (5%), both occurring in the Kasperk et al study.[104] Each involved symptomatic bone cement leakage at the thoracic level, resulting in neurological symptoms in one case and asymptomatic spinal stenosis in the other. Both were corrected by spinal surgeries. In the three studies involving 85 patients with metastatic cancers, there were no major complications. No surgeries or deaths were reported in this group.

Kyphoplasty, vertebroplasty, and adjunctive local tumour control interventions. Eight studies evaluated the performance of kyphoplasty and vertebroplasty; four studies[109,112-114] in patients with multiple myeloma and four[107,108,110,111] in those with primary metastatic cancers (Table 31). Only two studies[107,108] involved adjunctive procedures—palliative external beam radiotherapy pre- or post-vertebral augmentation. The operators in these studies included surgeons, both orthopedic surgeons and neurosurgeons, interventional radiologists, and pain physicians or anaesthesiologists.

The decisions of which procedure to use were based on different criteria. At some centres, the individual operators made the choice and their decision was based on the level and degree of fracture in each patient. At other centres, vertebral augmentation was performed collaboratively, with vertebroplasty only performed by interventional radiologists and kyphoplasty only performed by surgeons.

What constituted "minor complications" was also considered differently by operators. One operator reported that balloon ruptures during the procedure and instances of asymptomatic bone cement leakage were not considered complications, and no minor complications were reported in that study for the 249 patients who underwent vertebroplasty or kyphoplasty.[111] Another study of 201 patients also reported that there were no minor complications.[107]

In the four studies[109,112-114] evaluating 488 patients with multiple myeloma, there were two major complications (0.4%), both involving local spinal infections that were successfully treated with antibiotics.[109] In the four studies[107,108,110,111] involving 586 patients with metastatic cancer, there were three major complications (0.5%). These were the exacerbation of pre-existing congestive heart failure post-kyphoplasty, with hospitalization (n = 1)[110]; paraplegia secondary to progressive epidural metastases post-vertebroplasty (n = 1)[110]; and the laceration of a lumbar artery during vertebroplasty (n = 1).[111] No deaths were reported in any of the studies.

Case reports of complication events with kyphoplasty. Six case reports (involving two females and four males) involving major complications after kyphoplasty are outlined in Table 32. These were reported from four countries over a 10-year period (2005–2014). They involved kyphoplasty for different primary metastatic cancers—lung cancer (n = 1), melanoma (n = 1), multiple myeloma (n = 1), oral carcinoma (n = 1), renal cancer (n = 1), and an unreported etiology.

The reported major complications involved bone cement leakage resulting in pulmonary embolism (n = 1),[197] cord compression (n = 1),[198] venous system migration with perforation of the right ventricle causing cardiac tamponade (n = 1),[199] tumour extravasation (n = 2),[188] and an incident fracture (n = 1) occurring after kyphoplasty performed for prophylactic vertebral body stabilization.[200] The two patients with tumour extravasation died shortly after the procedure because of their disease progression.[188] The case involving cord compression occurred because of retropulsion of the tumour mass into the ventral spinal canal, and this required emergent spinal decompression.[198] Migration of a cement embolism to the ventricle was an unusual and life-threatening complication, and in this case the cement was removed both percutaneously and surgically.[199]

Table 29: Complications Reported in Clinical Studies of Kyphoplasty for Cancer-Related Vertebral Compression Fractures

Author, Year Country	Patients, N (F, M) Age, Mean ± SD (Range)[a] Follow-Up	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Multiple Myeloma as Primary for Spinal Metastases				
Dudeney et al, 2002[90] United States	18 patients (NR) 63.5 years (48–79) 7.4 months	Orthopedic surgery KP under general anaesthesia in 27 sessions at 55 VB levels (T6 to L5)	Asymptomatic bone cement leakage occurred in 4% (2/55) of the treated vertebrae; leaks occurred in the epidural space (n = 1) and sidewall cortical crack (n = 1)	None reported
Huber et al, 2009[195] Germany	76 patients (31 F, 45 M) Median 62 years (28–76) 1 month	Orthopedic surgery KP under general anaesthesia at 190 VB levels (T6 to L5)	Bone cement leakage occurred in 18% (35/190) of treated vertebrae	n = 2 Thoracic-level bone cement leakage, firmly attached to the posterior wall of the vertebrae, compromising the spinal cord and leading to bilateral leg motor deficits that resolved after surgical removal of the cement and laminectomy (n = 1) PE detected in an anteroposterior radiograph (n = 1)
Julka et al, 2014[91] United States	32 patients (14 F, 18 M) 64.3 years 24 months	Orthopedic surgery KP under general anaesthesia at 76 VB levels (34 T, 42 L)	Asymptomatic bone cement leakage occurred in 38% (12/32) of cases or 15% (11/71) of treated vertebrae; leakage site(s) could not be identified in 1 patient undergoing KP at 5 levels (excluded from the level total)	None reported
Lane et al, 2004[92] United States	19 patients (7 F, 12 M) 60.4 years (45–74) 3 months	Surgery KP under general anaesthesia at 46 VB levels (18 T, 14 thoracolumbar [T12 or L1], 14 L)	Images were available for 38 of the 46 treated levels; asymptomatic bone cement leakage occurred in 26% (10/38) of treated vertebrae	None reported
Pflugmacher et al, 2006[93] Germany	20 patients (20 M) NR 12 months	Orthopedic surgery KP under general anaesthesia at 48 VB levels (T6 to L5)	Asymptomatic bone cement leakage occurred in 10% (5/48) treated vertebrae; leaks occurred intradiscally (n = 3) and paravertebrally (n = 2) through the lateral wall	n = 1 Incident adjacent-level fracture occurred 2 weeks post-operatively
Zou et al, 2010[94] China	21 patients (12 F, 9 M) 65.9 years (47–81) 12 months	Orthopedic surgery KP under general anaesthesia at 43 VB levels (14 T, 14 TL, 15 L) KP performed at one level (n = 2), two levels (n = 16), or three levels (n = 3)	Asymptomatic bone cement leakage occurred in 5% (2/43) of treated vertebrae; leaks were in the paravertebral region	None reported

Author, Year Country	Patients, N (F, M) Age, Mean ± SD (Range)[a] Follow-Up	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Mixed Metastatic Cancers as Primary for Spinal Metastases				
Berenson et al, 2011[88] Australia, Canada, Europe, United States	KP group 68 patients (40 F, 28 M) 64.8 years (38–88) 1 year	Orthopedic surgery KP under general anaesthesia at 247 VB levels	n = 11 Infections (n = 6): urinary tract (n = 2), wound (n = 1), other unspecified (n = 3) Balloon rupture (n = 1) Symptomatic fracture (n = 2) Paresis (n = 1) Dyspnea (n = 1) Bone cement leakage in 3% (2/68) of treated cases	n = 3 Myocardial infarct (n = 1) Arrhythmia (n = 2) Two deaths occurred, but were related to events occurring prior to the procedure
Chen et al, 2013[95] China	6 patients (3 F, 3 M) 59.3 years (50–73) 3 months	Orthopedic surgery KP under general anaesthesia for osteoblastic lesions in T or L VBs	Asymptomatic bone cement leakage occurred in 17% (1/6) of cases; leak was into the anterior vertebral vein (n = 1)	None reported
Konig et al, 2012[96] United Kingdom	11 patients (7 F, 4 M) Range 52–77 years Until death	Surgery KP under general anaesthesia (local anaesthesia for 1 patient) at 23 VB levels (T2 to L3)	Asymptomatic epidural bone cement leakage occurred in 18% (2/11) of cases	n = 2 Subsequent adjacent-level fracture 3 weeks post-surgery, treated with KP (n = 1) Deep vein thrombus (n = 1)
Korovessis et al, 2014[89] Greece	KP group 24 patients (13 F, 11 M) 70 ± 11 years 1 month	Orthopedic surgery KP under general anaesthesia at VB T7 to L5 KP performed at one level (n = 20) or two to five levels (n = 4)	Asymptomatic bone cement leakage occurred in 9% (4/43) of treated vertebrae; leaks were anterior (n = 1), to the adjacent disc (n = 1), and posterior to the spinal canal without impairment (n = 2)	None reported
Li et al, 2014[196] China	37 of 100 patients (excluded 63 cases of severe osteoporosis) NR Operative and postoperative period	Orthopedic surgery KP under general anaesthesia in a single session for 1 or 2 VB levels (n = 50) or a single session for multiple VB levels (3 to 6) (n = 50)	n = 10 During the procedure, increased respiration with decreased (below 90%) oxyhemoglobin saturation occurred in multiple-level KP (n = 10 cases); none occurred in the single-level group. Bone cement leakage occurred in 14% (7/50) of multiple-level KP cases (perivertebrae [n = 4], intrapulmonary [n = 1], intercostal nerve stimulation [n = 2]) and in 10% (5/50) of single-level KP cases (perivertebrae [n = 3], intrapulmonary [n = 1], intercostal nerve stimulation [n = 1])	n = 7 Cardiac arrhythmia during the procedure, requiring medication occurred in the multiple-level KP group (7 cases); none occurred in the single-level group

Author, Year Country	Patients, N (F, M) Age, Mean ± SD (Range)[a] Follow-Up	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Pflugmacher et al, 2008[97] Germany	65 patients (28 F, 37 M) 66 ± 9 years 24 months	Orthopedic surgery KP under general anaesthesia at 99 VB levels KP performed at one level (n = 37), two levels (n = 23), three levels (n = 4), or four levels (n = 1)	Asymptomatic bone cement leakage (detected by radiographs) occurred in 12% (12/99) of treated vertebrae	n = 5 Incident adjacent-level fractures (n = 5), 3 occurring within 6 months post-operatively
Vrionis et al, 2005[98] United States	50 patients (33 F, 17 M) 63 years (36–81) 9 months	Neurosurgery KP under general anaesthesia at 128 VB levels (83 T, 45 L); 12 patients were treated for 1 level only, and the maximum number of levels treated in a single session was 6 (2 patients)	Asymptomatic bone cement leakage of posterior cortex in 6% (3/50) of cases	n = 1 Cardiac asystole at the end of surgery; patient was successfully resuscitated, recovering to pre-operative level, but died from unrelated causes 1 month post-operatively (n = 1); patient had lung cancer and multiple brain metastases and had been on oral steroids for 2 years

Abbreviations: F, female; KP, kyphoplasty; L, lumbar; M, male; NR, not reported; PE, pulmonary embolism; SD, standard deviation; T, thoracic; VB, vertebral body; VP, vertebroplasty.
[a]Unless otherwise indicated.

Table 30: Complications Reported in Clinical Studies of Kyphoplasty and Adjunctive Local Tumour Control Interventions for Cancer-Related Vertebral Compression Fractures

Author, Year Country	Patients, N (F, M) Age, Mean ± SD (Range)[a] Follow-Up	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Multiple Myeloma as Primary for Spinal Metastases				
Kasperk et al, 2012[104] Germany	35 (KP) of 73 patients (33 F, 40 M) 58.9 ± 10.3 years 2 years	Surgery KP (n = 35) under general anaesthesia at 111 VB levels and palliative EBRT	Bone cement leakage occurred at 31% (34/111) of treated vertebrae; leaks were mostly minor (< 5 mm protruding out of vertebral body), and all but 1 were asymptomatic	n = 2 Bone cement leakage at the thoracic level required revision surgery, with pain and neurological symptoms resolving after hemilaminectomy and removal of intraspinal cement (n = 1) Revision surgery was performed for asymptomatic spinal stenosis detected on post-operative MRI (n = 1)
Mixed Metastatic Cancers as Primary for Spinal Metastases				
Gerszten et al, 2005[103] United States	26 patients (20 F, 6 M) 72 years (47–83) 11 to 24 months	Neurosurgery KP under general anaesthesia for T and L VB levels followed by CyberKnife radiosurgery using a single-fraction technique (20–25 Gy)	None reported	None reported
Qian et al, 2011[105] China	48 patients (29 F, 19 M) 68.5 years (52–85) 24 months	Orthopaedic surgery KP under general anaesthesia for a mean of 2.6 levels per patient; total of 124 VB levels (T or L); radiation therapy for 1 to 2 weeks post-operatively	Asymptomatic bone cement leaks (detected intraoperatively by fluoroscopy and post-operatively by CT) occurred in 19% (18/97) of treated vertebrae; leaks were in the venous plexus (n = 11), paravertebral tissues (n = 4), and adjacent disks (n = 3)	None reported
Sandri et al, 2010[106] Italy	11 patients (9 F, 2 M) 68 years (58–82) 12 months	Orthopaedic surgery KP and simultaneous RFA under general anaesthesia at 11 VB levels (1 C, 9 T, 1 L)	Asymptomatic bone cement leaks (detected by post-operative CT) occurred in 9% (1/11) of cases	None reported

Abbreviations: C, cervical; CT, computed tomography; EBRT; external beam radiotherapy; F, female; KP, kyphoplasty; L, lumbar; M, male; MRI, magnetic resonance imagery; RFA, radiofrequency ablation; SD, standard deviation; T, thoracic; VB, vertebral body.
[a]Unless otherwise indicated.

Table 31: Complications Reported in Clinical Studies of Kyphoplasty, Vertebroplasty, and/or Adjunctive Local Tumour Control Interventions for Cancer-Related Vertebral Compression Fractures

Author, Year Country	Patients, N (F, M) Age, Mean ± SD (Range)[a] Follow-Up	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Multiple Myeloma as Primary for Spinal Metastases				
Bartolozzi et al, 2006[113] Italy	14 patients (4 F, 10 M) 54 years (49–72) 10 months	Interventional radiology Procedures under conscious sedation and analgesia; 19 treated vertebrae (10 KP, 9 VP)	None reported	None reported
Erdem et al, 2013[109] United States	361 patients (134 F, 227 M) Selected outcome study group from 792 patients with 1,072 sessions	Interventional neuroradiology Procedures under conscious sedation and analgesia; 447 VB levels (74% VP, 13% KP, 13% VP and KP)	None reported	n = 2 Local infection, antibiotics administered (n = 2)
Kose et al, 2006[114] Turkey	34 patients (18 F, 16 M) KP (n = 18): 63.7 years (47–82) VP (n = 16): 62.2 years (45–80)	Orthopaedic surgery VP and KP under conscious sedation and analgesia; KP at 22 treated vertebrae, VP at 28 treated vertebrae	n = 1 Balloon rupture (n = 1)	None reported
Mendoza et al, 2012[112] United States	79 of 175 patients (32 F, 47 M) 60.1 ± 9.8 years	Pain physicians, anaesthesiology VP only (n = 37), KP only (n = 22) and VP and KP (n = 20) KP performed at ; one level (n = 49), two levels (n = 26), ≥ three levels (n = 4)	None reported	None reported
Mixed Metastatic Cancers as Primary for Spinal Metastases				
Fourney et al, 2003[110] United States	56 patients (25 F, 31 M) Median 64 years (30–82)	Neurosurgery or interventional radiology General anaesthesia or conscious sedation and analgesia; VP (n = 34), KP (n = 15) and VP and KP (n = 7)	Asymptomatic bone cement leakage at 9.2% (6/65) treated vertebrae, all during VP; leakage occurred through a fractured end plate into adjacent disc space in 5 cases and into anterior perivertebral soft tissue (n = 1); no leakages occurred in the epidural space or neural foramen	n = 2 Patient readmitted to hospital 15 days post-KP for exacerbation of pre-existing congestive heart failure (n = 1); sudden paraplegia 13 days post–L1 VP secondary to progressive T8 epidural metastases (n = 1)
Hirsch et al, 2011[107] United States	201 (NR)	Interventional radiology VP or KP at 316 levels (T11 to L3)	None reported	None reported

Author, Year Country	Patients, N (F, M) Age, Mean ± SD (Range)[a] Follow-Up	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Jha et al, 2010[111] United States	249 patients (138 F, 111 M) 102 VCFs of known metastatic etiology (55 F, 47 M) 147 VCFs of unknown etiology (83 F, 64 M)	Interventional neuroradiology Conscious sedation and analgesia; VP (n = 48), KP (n = 96), and both (n = 105) at 236 VB levels	Intramedullary balloon rupture or asymptomatic cement leaks were not considered complications	n = 1 Laceration of a left-sided L2 lumbar artery during VP in a patient with spinal meningioma invasion of the VB; the segmental artery was sacrificed, and no additional therapy or transfusion was required (n = 1)
Li et al, 2014[108] China	80 patients (43 F, 37 M) 42 KP (24 F, 18 M) 68.4 years (52–85) 38 VP (19 F, 19 M) 65.2 years (49–83)	Interventional radiology with conscious sedation (VP); orthopaedic surgery with general anaesthesia for (KP) KP at 83 treated vertebrae (T and L) and performed at one level (n = 16), two levels (n = 14), three levels (n = 9), or four levels (n = 3) VP at 76 treated vertebrae (T, L) and performed at one level (n = 11), two levels (n = 17), three levels (n = 9), or four levels (n = 1)	Asymptomatic cement leakage with VP occurred in 30% (23/76) of treated vertebrae; leaks were in the venous plexus (n = 13), paravertebral tissues (n = 7), and adjacent discs (n = 3) Asymptomatic cement leakage with KP occurred in 17% (14/83) of treated vertebrae; leaks were in the venous plexus (n = 9), paravertebral tissues (n = 4), and adjacent discs (n = 1)	None reported

Abbreviations: F, female; KP, kyphoplasty; L, lumbar; M, male; NR, not reported; SD, standard deviation; T, thoracic; VB, vertebral body; VP, vertebroplasty.
[a]Unless otherwise indicated.

Table 32: Complication Case Reports Involving Kyphoplasty for Cancer-Related Vertebral Compression Fractures

Author, Year Country	Patient and Primary Malignancy	Clinical History	Operator Interventions and Treated Spinal Levels	Adverse Event	Outcome
Cruz et al, 2014[188] Canada	48-year-old female Melanoma	History of diffuse metastatic melanoma in the axial skeleton, liver, lungs and subsequently multifocal spinal metastases; unprovoked acute back pain, refractory to opioids and NSAIDs and unable to walk; cancer was judged to be inoperable	Interventional neuroradiology KP at T10; MRI revealed complete replacement of the marrow of the VB by tumour, focal cortical disruption of the posterior vertebral body wall, and soft-tissue extension of the tumour into the epidural space; the VCF was < 50% of original vertebral height, with bulging of the posterior wall into the spinal canal; there were 2 small metastases in the T6 and T9; KP was immediately followed by SRS (24 Gy in 2 fractions) to T10	*Tumour extravasation following KP*: during the procedure, minor posterior epidural venous cement leaks and some migration of cement along the path of the left cannula into the pedicle occurred; an MRI 2 months post-procedure suggested the tumour had spread cranially and caudally to T9 and T11; there was an opening of the basilar vein where the tumour also propagated to the posterior aspect of the T9 VB	There was no other disease progression in the spine, suggesting that tumour migration through the venous system accounted for the unusual spread to the adjacent level; the patient died 6 months later of extraspinal metastases
	73-year-old male Non-small-cell lung cancer	History of non-small cell lung cancer; sudden unprovoked mechanical back pain that was refractory to opioids and NSAIDs; cancer was judged to be inoperable	Interventional neuroradiology KP was performed for T9 VCF followed by conventional radiotherapy (20 Gy at 5 daily fractions); target was not amenable to SRS due to inadequate targeting precision; the VCF had > 50% height loss, bulging of anterior and posterior wall, complete replacement of the vertebral body marrow with tumour extending to both pedicles and paravertebral soft tissues, and focal disruption of the posterior wall	*Tumour extravasation following KP*: 2½ weeks following KP, the patient had recurrent back and bilateral flank pain; a 4-week follow-up MRI showed anterior subligamentous tumour spread to the immediate adjacent cranial and caudal vertebral levels, extension into the paravertebral soft tissues beyond the boundaries of the T9 VB, and involvement of the pedicles along the path of the KP cannulas; the disease spread was considered to be due to increased VB internal pressure, disruption of the tissue during balloon inflation and cement application, forcing the soft-tissue tumour beyond the vertebral bony boundaries through cortical defects and involving adjacent levels through subligamentous spread	Despite palliative conventional radiotherapy, the patient died a month later due to progression of systemic disease

Author, Year Country	Patient and Primary Malignancy	Clinical History	Operator Interventions and Treated Spinal Levels	Adverse Event	Outcome
Elshinawy et al, 2005[197] United States	62-year-old male Multiple myeloma	A long history of multiple myeloma and prostate cancer, coronary artery disease, and PE; warfarin was discontinued before surgery	Surgery KP under general anaesthesia for VCFs at 3 levels (L1, L2, L3) for severe pain resulting from osteoporotic fractures	*Bone cement PE:* towards the end of the cement injection, a small vein of the left side of L2 indicated cement had entered the paravertebral venous system; although injection was stopped, cement was visualized entering the systemic venous system; fever (38.4° C, 101.1° F) and tachycardia (heart rate 110 beats per minute) developed without blood pressure or respiration changes; a chest radiograph showed linear, tortuous radiopaque density over the right medial hemithorax, and a chest CT showed new metallic density anteriorly along the right main pulmonary artery representing a cement PE	The patient was treated with supportive care and intravenous antibiotics for presumed pneumonia; fever and tachycardia resolved within 24 hours without respiratory symptoms, and warfarin was resumed; follow-up radiographs continue to show pulmonary cement embolus
Esmende et al, 2013[198] United States	65-year-old male Oral carcinoma	History of metastatic squamous-cell carcinoma of the tongue	Orthopedic surgery KP for VCF at T9	*Spinal cord compression after KP for cancer-related VCF requiring surgical intervention:* immediately following the procedure, the patient developed progressive bilateral lower-extremity numbness and weakness; CT and MRI revealed cement in the T9 vertebral body and retropulsion of the tumour mass into the ventral spinal canal	Emergent posterolateral decompression with T9 vertebrectomy, anterior reconstruction T8–T10 and posterior instrumented spinal fusion were performed; full strength, sensation, and ambulation were recovered post-operatively
Langdon et al, 2009[200] United Kingdom	53-year-old male Renal cell carcinoma with pulmonary metastases	MRI-identified metastases on anterior half of T10; no fracture seen, but superior and inferior end plate indentations were present	Orthopedic surgery KP at T10	*New fracture occurrence behind the cement:* 2 days following prophylactic KP for imminent fracture, VAS increased to 8/10 and an MRI scan with T1-weighted images and edema on the STIR sequence detected a fracture behind the cement	The patient was managed conservatively; pain resolved within 7 days, and the patient remained free of pain at 14-month follow-up

Author, Year Country	Patient and Primary Malignancy	Clinical History	Operator Interventions and Treated Spinal Levels	Adverse Event	Outcome
Tran et al, 2013[199] Germany	68-year-old female Etiology NR	Presented with acute chest pain and dyspnea a day after KP	Neurosurgery KP at 2 VB levels (L4, L3)	*Cement embolism migration in the venous system and perforation of right ventricle causing cardiac tamponade:* 2 days after KP, a coronary angiogram showed no coronary artery disease, but a radio-opacified structure was detected on the right side of the heart; shortly after the angiogram, the patients' hemodynamic status deteriorated developing into cardiac shock; echocardiography showed diffuse moderate pericardial effusion and urgent pericardial drainage (400 mL) was performed; CT showed a cement embolus that had perforated the right ventricle, causing pericardial tamponade	Using a snare catheter and a percutaneous approach, the cement material was removed from the right ventricle to the vena femoralis communis via the inferior vena cava; because of its fragile nature, the cement was removed surgically from the venous circulation; the patient's course was uneventful at 3-month follow-up

Abbreviations: CT, computed tomography; KP, kyphoplasty; L, lumbar; MRI, magnetic resonance imaging; NR, not reported; NSAID, non-steroidal anti-inflammatory drug; PE, pulmonary embolism; SRS, stereotactic radiosurgery; STIR, short tau inversion recovery; T; thoracic; VAS, visual analogue scale; VB, vertebral body; VCF, vertebral compression fracture.

D3. Safety of Vertebroplasty or Kyphoplasty for High-Risk or Special Vertebral Compression Fractures

Vertebral fractures with posterior wall defects or spinal cord compromise. The complications reported in studies evaluating vertebral augmentation for high-risk vertebral compression fractures, usually involving the lumbar and thoracic levels, are outlined in Table 34. The risk condition for the vertebral compression fractures in these studies involved either spinal cord tumour involvement, with or without neurological symptoms, or various degrees of posterior vertebral wall disruption. The largest operator experience for vertebroplasty for these risk fractures was reported by interventional radiologists (n = 10), and the procedures were performed using conscious sedation and analgesia. There were five studies in which kyphoplasty or kyphoplasty and/or vertebroplasty were performed. In these studies, surgeons were the operators for kyphoplasty for these risk fractures.

Overall in the 14 studies evaluating vertebroplasty for high-risk vertebral compression fractures, there were 22 major complications in 533 patients (4.1%). The major complications in the vertebroplasty studies involved bone cement leaks resulting in pulmonary embolism (n = 12) and spinal canal compromise (n = 3). The other complications, all from one study, [130] involved new or increased pain following vertebroplasty; this occurred only in patients with epidural tumour involvement. Immediate pain was treated with epidural or intravenous steroids, and delayed increased pain with neuroforaminal epidural nerve root blocks. There were no major complications occurring in the two studies[122,133] (45 patients) that evaluated only kyphoplasty for high-risk vertebral compression fractures.

Only one surgery was reported for the entire group, and that was for symptoms of cord compression after vertebroplasty.[131] There were also no reported deaths in any of the studies after vertebral augmentation for contraindicated fractures.

As with fractures in the thoracic or lumbar region without contraindication, asymptomatic bone cement leakage occurred commonly. Eight studies evaluating vertebroplasty and two studies evaluating kyphoplasty for these fractures reported asymptomatic bone cement leaks, all reported per treated vertebra (Table 33). Rates of asymptomatic cement leaks for these risk fractures were variable, ranging from 44% to 70% (except for the outlier of 6%); but the incidence of cement leaks was consistently higher than 50% for vertebroplasty for fractures without contraindications. Kyphoplasty procedures were not as commonly performed for these risk fractures. In the study by Hentschel et al,[116] bone cement leakage was reported to be higher in the group undergoing vertebral augmentation (either vertebroplasty or kyphoplasty) for contraindicated fractures than in those without contraindications—39% (7/18) versus 11% (13/114) per treated vertebra.

The report by Trumm et al[127] involved the largest study group and the most detailed evaluation of cement leakage after vertebroplasty. Overall there was a 59% (194/331) rate of cement leakage of treated vertebrae, with bone cement–related pulmonary embolism occurring in 5% (11/202) of the cases. The authors also noted that cement leaks were not associated with the degree of osteolytic or epidural soft tissue involvement or the presence of fractured endplates.

Table 33: Asymptomatic Bone Cement Leakage After Vertebroplasty or Kyphoplasty for Contraindicated Cancer-Related Vertebral Fractures

Author, Year	Leaks per Vertebroplasty-Treated Contraindicated Vertebra Fracture	Leaks per Kyphoplasty-Treated Contraindicated Vertebra Fracture
Alvarez et al, 2003[123]	44% (12/27)	Not performed
Basile et al, 2011[115]	6% (2/34)	Not performed
Georgy et al, 2009[118a]	70% (31/44)	Not performed
Li et al, 2013[121b]	52% (29/56)	Not performed
Li et al, 2013[121c]	32% (12/38)	Not performed
Saliou et al, 2010[131]	61% (45/74)	Not performed
Shimony et al, 2004[130]	70% (48/69)	Not performed
Trumm et al, 2012[127]	59% (194/331)	Not performed
Van der Linden et al, 2007[120a]	58% (7/12)	Not performed
Dalbayrak et al, 2010[133]	Not performed	35% (13/39)
Eleraky et al, 2011[122]	Not performed	10% (3/30)

[a]These studies involved radiofrequency ablation–assisted vertebroplasty.
[b]Study patient subgroup treated with VP only.
[c]Study patient subgroup treated with VP and interventional tumour removal.

Cervical-level fractures. The complications reported in studies evaluating vertebral augmentation at the cervical level are outlined in Table 35. Most of these reports involve vertebroplasty; kyphoplasty was reported in only one study involving two case reports of cervical-level fractures.[146] As discussed earlier these types of fractures present risks owing to their closeness to numerous critical vascular and neurological structures. The spinal column is narrower at this level, and the pedicles, the usual site of access for injection into the vertebral body, are also smaller and more difficult to access than in the thoracic and lumbar vertebrae.

The vertebroplasty studies were performed by interventional radiologists, although anaesthesiologists or pain physicians reported on their experiences in two case reports. The largest experience with this fracture level was reported by interventional radiologists, who used a varied access approach. Anselmetti et al[143] employed the transoral approach with 25 patients, and Masala et al,[144] in a multicentre study, employed both the transoral and the anterolateral or posterolateral percutaneous approaches in 62 patients.

There were no major complications reported in any of the studies, and no surgeries or deaths were reported for vertebroplasty interventions for fractures at the cervical junction level (C1 or C2) or the lower axial level (C3–C7). Asymptomatic bone cement leaks were reported per treated case as 24% (6/25)[143] and 39% (5/13)[201] for C2 treated vertebral fractures and 3% (2/62) for C1 to C7 level treated fractures.[144]

Sacral-level fractures. The complications reported in studies evaluating vertebroplasty for fractures at the sacral level are outlined in Table 36. These studies often included patients with complex bony lesions and fracture patterns that involved the pelvis and other long bones in addition to the vertebrae. We did not find any studies evaluating kyphoplasty for these fractures.

The operators for vertebroplasty interventions in these regions were also interventional radiologists, and the procedures were performed using conscious sedation or general anaesthesia, depending on location and degree of bone involvement. Three of the studies[151-153] involved the use of adjunctive radiofrequency ablation, and one[157] involved palliative external beam radiotherapy pre- or post-vertebroplasty.

There were three major complications in 214 patients (1.4%) reported in eight studies evaluating vertebroplasty for sacral and other bone metastases. All were reported in the study by Lane et al.[152] The major complications were symptomatic bone cement leaks involving the sciatic nerve, resulting in sensory disturbances and epidural leaks with pain and pulmonary embolism. The complications were all transient, and none required surgical intervention.

Vertebral hemangiomas. Table 37 outlines the complications reported in studies evaluating vertebral augmentation for symptomatic hemangiomas causing pain or neurological deficits. The risk with these benign tumours involves their high degree of vascularity; this makes a surgical or even minimally invasive procedure such as vertebral augmentation difficult because of the potential for significant blood loss or hemorrhage. Because of this, vertebral augmentation or surgery for this condition often involves transarterial embolization in an attempt to minimize this risk. Vertebral augmentation for this condition was performed by interventional radiologists, neurosurgeons, orthopedic surgeons, pain physicians, and anaesthesiologists.

Two studies[165,168] reported on multidisciplinary management of symptomatic vertebral hemangioma that included complex treatment pathways of transarterial embolization, spinal surgery, radiotherapy, and vertebroplasty, usually as an adjunctive procedure. In the Jiang et al study,[168] vertebroplasty was performed as an adjunct to radiotherapy (n = 1), decompression surgery (n = 2), and decompression surgery and radiotherapy (n = 6). In that study, as discussed earlier in clinical outcomes, intraoperative bleeding in cases involving surgery and vertebroplasty was greatly reduced compared with surgery alone (mean estimated blood loss 1,093 mL vs. 1,900 mL). Two surgeries had to be aborted due to excessive bleeding. Nineteen of the 29 patients had undergone pre-operative embolization.

In the six studies (72 patients) evaluating vertebroplasty for vertebral hemangiomas, there was one major complication[170]; and in the four studies (10 patients)[171-173,175] evaluating kyphoplasty for hemangioma, there were no major complications. The major complication in the vertebroplasty study involved bone cement leakage into the spinal canal and intervertebral foramen, compressing the left nerve root and causing leg numbness.[170] Surgery was performed to decompress and remove the bone cement. There were no deaths reported in any of the studies. Asymptomatic bone cement leaks were reported per treated cases, and occurrences were as follows: 12% (3/26),[170] 17% (4/24),[169] and 25% (2/8).[174]

Table 34: Complications Reported in Clinical Studies of Vertebral Augmentation for High-Risk Vertebral Compression Fractures

Author, Year Country	Patients, N (F, M) Age, Mean ± SD (Range)[a] Primary Cancer, Risk Features	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Vertebroplasty for Vertebral Fractures with Spinal Canal and/or Posterior Wall Defects				
Alvarez et al, 2003[123] Spain	21 patients (14 F, 7 M) 58 years (27–78) All had nonskeletal metastases, 76% had concomitant bone metastases elsewhere, and 10 had neurological deficits Mixed metastatic cancers	Interventional neuroradiology VP under conscious sedation and analgesia at 27 VB levels and subsequent PRT (n = 15) and neural decompression (n = 3)	n = 1 Bone cement leakage caused a transient radicular neuritis (n = 1) Bone cement leakage detected by CT occurred in 44% (12/27) of treated vertebrae; leaks were in the disc (n = 1), entry site (n = 1), and epidural veins (n = 10)	None reported
Appel et al, 2004[124] United States	23 patients (17 F, 6 M) Age NR All had MRI-defined varying degrees of spinal canal compromise; cancer-related (n = 7) and osteoporotic (n = 16)	Interventional radiology VP under conscious sedation and analgesia at 26 VB levels (19 T, 7 L)	n = 3 Post-procedural dyspnea with decreased oxygen saturation requiring up to 4 L of oxygen by nasal cannula after a 4-level VP (n = 1) A chest radiograph showed segmental atelectasis, and PE was excluded by clinical examination and ventilation-perfusion scintigraphy (n = 1) After initial decreased pain, pain occurred bilaterally in lower extremities; no radiographic complications were noted, neurological exam findings were nonfocal, and symptoms improved without further intervention (n = 1) Bone cement leakage occurred, but the events were only reported as asymptomatic	None reported
Basile et al, 2011[115] Italy	24 patients (13 F, 11 M) 54.7 years (42–67) Multiple myeloma	Interventional radiology VP at 34 VB levels (16 T, 18 L)	Asymptomatic bone cement leakage occurred in 6% (2/34) of treated vertebrae; all had large epidural space extension without increased neurological symptoms	None reported

Author, Year Country	Patients, N (F, M) Age, Mean ± SD (Range)[a] Primary Cancer, Risk Features	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Georgy et al, 2009[118] United States	37 patients (21 F, 16 M) Range 34–89 years	Interventional radiology RFA and VP at 44 VB levels	n = 3 3 patients underwent selective nerve blocks after VP, 2 being symptomatic due to tumour extension into the neural foramina Asymptomatic bone cement leakage occurred in 70% (31/44) of treated vertebrae; leaks were venous (n = 18, 40%), cortical (n = 10, 22%) and discal (n = 5, 11%)	n = 1 2 small epidural leaks were noted; 1 occurred adjacent to the neural foramen, associated with radicular symptoms; the patient was treated with selective nerve root blocks, resulting in pain relief
Hentschel et al, 2004[202] United States	1 patient (1 F) 60-year-old Vertebra plana (85% collapse of anterior T7) with an associated epidural hematoma and retropulsion into the ventral aspect of the spinal cord, compressing the anterior thoracic spinal cord; thymic cancer and history of renal cell carcinoma	Neurosurgery VP at T7 VB; during the procedure, the thoracic VB was compressing and expanding about 30% of its height during breathing	Post-operative imaging revealed anterior placement of cement without leakage into the spinal canal or neural foramina	None reported
Li et al, 2013[121] Gu et al, 2014[135] China	28 of 52 patients 59.6 years (37–90) Neurological symptoms of cord compression	Interventional radiology VP under conscious sedation and analgesia at 56 VB levels	Bone cement leakage occurred in 52% (29/56) of treated vertebrae; leaks were in the intervertebral disc (n = 6), access site (n = 3), paravertebral space (n = 7), veins (n = 12) or spinal canal (n = 1)	n = 1 Bone cement leakage into the spinal canal resulted in complete paraplegia
	24 of 52 patients 59.6 years (37–90) Neurological symptoms of cord compression	VP and ITR under conscious sedation and analgesia at 38 VB levels	n = 2 Increased acute pain following the procedure, resolved with IV corticosteroids (n = 2) Asymptomatic cement leakage occurred in 32% (12/38) of treated vertebrae; leaks were in the intervertebral disc (n = 3), access site (n = 2), paravertebral space (n = 4), or veins (n = 3); none were in the spinal canal	None reported

Author, Year Country	Patients, N (F, M) Age, Mean ± SD (Range)[a] Primary Cancer, Risk Features	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Mazumdar et al, 2010[125] United States	*Case 1* 1 patient (F) 71-year old Metastatic breast cancer *Case 2* 1 patient (M) 60-year-old Multiple myeloma Both had radiculopathy when upright and relieved when recumbent	Interventional radiology *Case 1* VP at L4 for pain and lower-extremity weakness *Case 2* RFA (coblation) and VP at L3 with tumour filling the vertebrae and compressing the spinal canal and having radicular pain and mild right-leg weakness	None reported	None reported
Prologo et al, 2013[119] United States	15 patients (8 F, 7 M) 67.8 ± 15.3 years Mixed metastatic cancers and multiple myeloma; risk features involved cortical disruption, retropulsion of bony fragments, tumour invasion epidural space, and/or spinal canal stenosis at the disease level	Interventional radiology RFA (coblation) and VP at 15 VB levels (3 T, 12 L) under biplane fluoroscopy (n = 8), CT (n = 2), or combined CT fluoroscopy (n = 5)	n = 1 Transient hypotension due to IV sedatives resolving without medical intervention (n = 1) No cement leakage occurred (on CT, MRI, PET-CT)	None reported
Saliou et al, 2010[131] France	51 patients (22 F, 29 M) 62.5 years (28–85) Mixed metastatic cancers and multiple myeloma; VCFs with epidural involvement of at least 1 level and with or without neurological symptoms; 15 patients had signs of spinal cord or cauda equina compression—11 with complete paraplegia and 4 with incomplete paraplegia; 3 patients underwent surgical laminectomy at the level of epidural involvement 48 hours prior to VP	Interventional neuroradiology VP under conscious sedation and analgesia or general anaesthesia (depending on the patients' condition and number of treated vertebrae) at 74 VB levels—50 with vertebral wall destruction and associated epidural involvement; PRT was administered in 40 cases (10 cases before VP and 30 cases after)	Bone cement leakage occurred in 61% (45/74) of treated vertebrae; all but 1 were asymptomatic	n = 1 A 74-year-old woman with metastatic pancreatic adenocarcinoma who had radiculopathy and no prior neurological symptoms underwent PRT prior to VP for a L3 VCF with posterior wall destruction and epidural involvement; 2 days post-VP, she experienced symptoms of cauda equina that were managed by emergency decompression surgery with good results

Author, Year Country	Patients, N (F, M) Age, Mean ± SD (Range)[a] Primary Cancer, Risk Features	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Shimony et al, 2004[130] United States	50 patients (25 F, 25 M) 62.7 years ± 14 years Mixed metastatic cancers and multiple myeloma; epidural tumour involvement: none (n = 14), mild (n = 18), or moderate (n = 18)	Interventional radiology VP under conscious sedation and analgesia at 129 VB levels in 60 sessions	None reported Asymptomatic cement leakages were not counted	n = 7 14% (7/50) of cases experienced new or increased pain (3 at the level of the treated vertebrae), none requiring surgery Those with immediate pain were treated with central epidural or intravenous steroid injections; those with delayed increased pain were treated with neuroforaminal epidural nerve root blocks Of the 7 cases, none occurred in those without epidural involvement; 3 were in those with minimal epidural involvement and 4 were in those with moderate epidural involvement
Sun et al, 2011[132] , 2014[126] China	43 patients (24 F, 19 M) 64.1 years (34–84) Mixed metastatic cancers; VCF with involvement of the epidural space around the cord and/or cord compression; study group from 412 consecutive spinal metastases	Interventional radiology VP under conscious sedation and analgesia at 69 VB (T3 to L5) levels; radiation therapy was not indicated in 27 patients who had already had the maximum radiation dose for local lesions; radiation therapy had been delayed or incomplete in 16 patients	Asymptomatic bone cement leakage occurred in 70% (48/69) of treated vertebrae; leaks were in the intervertebral disc (n = 15), paravertebral (n = 12), epidural space (n = 14), foramina (n = 3), and access track (n = 4) Overall extraosseous bone cement leakage was not related to epidural involvement, but leakage in the spinal canal was associated (*P* = .017) with the degree of fracture tumour epidural involvement with or without spinal cord deformity	None reported

Author, Year Country	Patients, N (F, M) Age, Mean ± SD (Range)[a] Primary Cancer, Risk Features	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Trumm et al, 2012[127] Germany	202 patients (116 F, 86 M) 63.2 ± 8.6 years Mixed metastases and multiple myeloma; vertebral fractures had varying degrees of associated spinal column tumour involvement: none (n = 260), mild (n = 43), or moderate (n = 28)	Interventional radiology VP only under CT-guidance in 231 sessions at 331 VB levels VP performed at one level (n = 140), two levels (n = 82), or three levels (n = 9)	n = 6 Transient chest pain during cement injection resolving after VP (n = 2) Transient radiating gluteal pain resolving after VP (n = 1) Inadequate per-interventional analgesia (n = 1) Inadvertent radicular irritation during unsuccessful positioning of VP cannula at C7; VP was abandoned and anterior instrumentation from C6 to T1 was performed (n = 1) Decreased oxygen saturation after administration of 1.5 mg midazolam during RFA requiring antidote flumazenil (n = 1) Bone cement leakage occurred in 59% (194/331) of treated vertebrae; leaks were in the intervertebral discs (n = 85) or paravertebral (n = 79 with 65 leaks to segmental vein), intraspinal (n = 69 with 55 leaks to the basivertebral vein) or foraminal (n = 2) regions; leaks were not associated with epidural soft tissue involvement, degree of osteolytic involvement or fractured end plate	n = 11 Pulmonary bone cement embolism occurred in 5% (11/202) of cases; 10 patients had segmental PE (6 with single embolus in 1 lobe, 3 with emboli in 2 different lobes, 1 with emboli in all 5 lobes) and 1 patient showed a combination of 1 major central and 2 segmental embolisms
Van der Linden et al, 2007[120]	12 patients (4 F, 8 M) 57 years (31–79) Mixed metastatic cancers and multiple myeloma; VCFs with posterior wall defect and a maximum ⅓ spinal canal area obstruction (3 cases) unresponsive to medical therapy, radiation therapy and/or medical therapy	Interventional radiology and orthopaedic surgery VP and RFA under conscious sedation and analgesia (general anaesthesia for C level) for 12 vertebrae (2 C, 4 T, 6 L)	Asymptomatic bone cement leakage occurred in 58% (7/12) treated vertebrae Leaks were in the venous plexus (n = 5), through the posterior cortical wall defect (n = 2)	n = 1 Pneumonia occurred 30 days post-procedure for a patient treated for a T4 VCF (n = 1)

Author, Year Country	Patients, N (F, M) Age, Mean ± SD (Range)[a] Primary Cancer, Risk Features	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Woo et al, 2013[128] Korea	1 patient (M) 52-year-old Cholangiocarcinoma; extensive VCFs with L4 dorsal root nerve compression and neurological symptoms	Anaesthesiology VP for 2 masses extending to the posterior-inferior portion of the L4 vertebral body and the lowest level of the left pedicle, with compression of the left L4 nerve root in the left foraminal region without motor deficits; bilateral L4/5 transforaminal epidural blocks unsuccessfully managed bilateral radiating leg pain; patient was unable to stand due to weakness	None reported	None reported
Kyphoplasty or Kyphoplasty and Vertebroplasty for Vertebral Fractures with Spinal Cord and/or Posterior Wall Defects				
Dalbayrak et al, 2010[133] Turkey	31 patients (17 F, 14 M) 62 years (35–78) Mixed metastatic cancers and multiple myeloma	Neurosurgery KP under conscious sedation and analgesia at 39 VB levels (T or L) KP performed at one level (n = 22), two levels (n = 8), or three levels (n = 1)	Asymptomatic bone cement leakage occurred in 33% (13/39) of treated vertebrae; leaks occurred at the epidural (n = 4), upper intervertebral disc (n = 2), lower intervertebral disc (n = 4), and paravertebral muscles (n = 3)	None reported
Eleraky et al, 2011[122] United States	14 of 23 patients (6 F, 8 M) 62 years (41–71) Mixed metastatic cancers and multiple myeloma	Neurosurgery KP under general anaesthesia at 30 VB levels (T1 to T5) KP performed at one level (n= 5), two levels (n = 2), or three levels (n = 7)	Asymptomatic bone cement leakage occurred in 10% (3/30) of treated vertebrae	None reported
Hentschel et al, 2005[116] United States	66 patients *Group 1 (no contraindications)* 49 patients (24 F, 25 M) Median 64 years (29–88) *Group 2 (contraindications)* 17 patients (8 F, 9 M) Median 61 years (42–75)	Neurosurgery *Group 1* VP at 89 VB levels KP at 22 VB levels *Group 2* VP at 13 VB levels KP at 5 VB levels	Bone cement leakage in Group 1 occurred in 11% (13/114) of treated vertebrae and in Group 2 occurred in 39% (7/18) of treated vertebrae The most common site of leaks in both groups was anterior to the VB in the retroperitoneal space surrounding the vertebrae or prevertebrally (11/20) and intradiscally or anterior to the VB (8/20)	n = 1 In 1 patient, cement extrusion into the intervertebral foramen resulted in transient radicular pain, which resolved with a short course of corticosteroids (n = 1)

Author, Year Country	Patients, N (F, M) Age, Mean ± SD (Range)[a] Primary Cancer, Risk Features	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Knight et al, 2008[117] Canada	3 patients (3 F) 32-year-old, 59-year-old, 67-year-old Spinal canal narrowing due to retropulsed fragments	Interventional radiology 2 VP and 1 KP under C-arm cone-beam CT guidance	Asymptomatic cement leakage in all cases	None reported
Lim et al, 2011[134] Korea	1 patient (F) 76-year-old Gastric cancer and hilar cholangiocarcinoma; cauda equina syndrome due to VCF and with epidural involvement	Interventional radiology KP under conscious sedation and analgesia; compression fractures with fluid-filled clefts in T12 and L1, and retropulsion of mass into epidural space with compression of the conus medullaris at the T12–L1 level	No cement leakage was observed with a controlled 2-stage injection method	None reported

Abbreviations: C, cervical; CT, computed tomography; F, female; ITR, interventional tumour removal; IV, intravenous; KP, kyphoplasty; L, lumbar; M, male; MRI, magnetic resonance imaging; NR, not reported; PE, pulmonary embolism; PET, positron-emission tomography; PRT, palliative radiotherapy; RFA, radiofrequency ablation; SD, standard deviation; T, thoracic; VB, vertebral body; VCF, vertebral compression fracture; VP, vertebroplasty.
[a]Unless otherwise indicated.

Table 35: Complications Reported in Clinical Studies of Vertebral Augmentation for Cervical Vertebral Compression Fractures

Author, Year Country	Patients, N (F, M) Age, Mean ± SD (Range)[a] Follow-Up	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Vertebroplasty for Cervical Vertebral Compression Fractures				
Anselmetti et al, 2012[143] Italy	25 patients (16 F, 9 M) 59 ± 11.5 years (39–77)	Interventional radiology VP via trans-oral route under general anaesthesia for 25 C2 VB levels	Asymptomatic bone cement leakage occurred in 24% (6/25) of cases; leaks occurred in the submucosal tissue along the needle tract (n = 5) and left pedicular joint (n = 1)	None reported
Chen et al, 2014[148] China	4 patients (2 F, 2 M) 57.5 years (46–72)	Interventional radiology VP at 5 VB levels (1 C5, 2 C6, 2 C7)	Asymptomatic bone cement leakage occurred in 25% (1/4) of cases; leak was in the intervertebral disc	None reported
Cianfoni et al, 2012[142] Italy	1 patient (F) 36-year-old	Interventional neuroradiology VP and RFA coblation under general anaesthesia at C1 VB level	Asymptomatic cement leakage occurred posteriorly and superiorly along the horizontal V3 segment of the vertebral artery casting but not compressing the artery, which remained patent	None reported
Huegli et al, 2005[149] Switzerland	1 patient (F) 76-year-old	Interventional radiology VP under general anaesthesia at C1 and C4 VB levels	Asymptomatic cement leakage occurred at the C1 level, with leaks into the intervertebral space	None reported
Masala et al, 2011[144] Italy	62 patients (38 F, 24 M) Median 61.5 years (31–85)	Interventional radiology VP under general anaesthesia (transoral at C1 and C2 [n = 33] or monolateral [anterolateral or posterolateral access] for the other C VB levels); VP at 70 levels (3 C1, 32 C2, 3 C3, 11 C4, 15 C5, 4 C6, 2 C7)	Asymptomatic cement leakage occurred in 3% (2/62) of cases, with leaks into the soft tissues	None reported
Mont'Alverne et al, 2009[141] France	4 patients (1 F, 3 M) 45 years (39–50)	Interventional neuroradiology VP by anterolateral access under general anaesthesia at 5 VB levels (2 C3, 2 C4, 1 C2)	Asymptomatic leaks occurred in 60% (3/5) of treated vertebrae, 3 of 4 treated patients; leaks were mainly in the venous network (6 of 8 leaks)—epidural veins (n = 3), radicular foraminal veins (n = 2), paraspinal soft tissue (n = 2), transverse foraminal veins (n = 1)	None reported
Rodriguez-Catarion et al, 2007[138] Sweden	1 patient (F) 47-year-old	Interventional neuroradiology VP under general anaesthesia at C2 VB level	None reported	None reported
Seo et al, 2013[150] Korea	1 patient (F) 51-year-old	Anaesthesiology VP under conscious sedation and analgesia at C7 VB level	None reported	None reported

Author, Year Country	Patients, N (F, M) Age, Mean ± SD (Range)[a] Follow-Up	Operator Interventions and Treated Spinal Levels	Minor Complications, n	Major Complications, n
Sun et al, 2010[201], 2013[145] China	13 patients (5 F, 8 M) 59.8 years (41–73)	Interventional radiology VP (anterolateral approach) under conscious sedation and analgesia at C2 VB levels; 4 patients with multilevel metastases underwent multiple-level VPs	Asymptomatic bone cement leakages occurred in 39% (5/13) of treated cases; leaks occurred in the anterior epidural space (n = 1), pre- or paravertebral space (n = 3), or epidural plexus (n = 1) Mild odynophagia occurring post-procedure and resolving within 3 days (n = 4)	None reported
Yoon et al, 2008[147] Korea	1 patient (M) 67-year-old	Anaesthesiology VP with an anterolateral approach under conscious sedation for C2 followed 3 days after with therapeutic facet joint block at the atlantooccipital and atlantoaxial joints at C2 for residual suboccipital headache	None reported	None reported
Kyphoplasty for Cervical Vertebral Compression Fractures				
Lykomitros et al, 2010[146] Greece	2 patients (2 M) 48-year-old, 70-year-old	Orthopaedic surgery KP (anterolateral approach) under general anaesthesia for C2/C6 and C3/C5 VB levels	Asymptomatic bone cement leakage occurred in 1 treated vertebrae laterally to the C2 VB	None reported

Abbreviations: C, cervical; F, female; KP, kyphoplasty; M, male; RFA, radiofrequency ablation; SD, standard deviation; VB, vertebral body; VP, vertebroplasty.
[a]Unless otherwise indicated.

Table 36: Complications Reported in Clinical Studies of Vertebral Augmentation for Sacral Vertebral Compression Fractures

Author, Year Country	Patients, N (F, M) Age, Mean ± SD (Range)[a]	Operator Interventions and Spinal Levels	Minor Complications, n	Major Complications, n
Vertebroplasty for Sacral Vertebral Compression Fractures				
Basile et al, 2010[153] Italy	8 patients (4 F, 4 M) 57.8 years (47–68)	Interventional radiology VP under conscious sedation (RFA and VP in 2 patients); 3 patients had massive involvement of the sacrum	Asymptomatic bone cement leakage occurred in 13% (1/8) of cases; leak at the foramina	None reported
Botton et al, 2012[157] France	42 patients (24 F, 18 M) Median 59 years (21–81)	Interventional radiology VP under general anaesthesia for 10 long bone, 13 spinal [T or L], 20 pelvis); the majority (n = 36) received PRT pre- or post-VP	n = 7 Temporary increased pain (n = 6); iatrogenic radiculalgia by direct contusion of the nerve root during transpedicular puncture (n = 1) Asymptomatic bone cement leakage occurred in 26% (11/42) of treated vertebrae; leaks were in the soft tissues (n = 8), intervertebral discs (n = 2) and epidural region (n = 1)	None reported
Hierholzer et al, 2003[158] Germany	5 patients (2 F, 3 M) 63 years (52–76)	Interventional radiology VP (osteoplasty) under conscious sedation and analgesia for 5 lesions (1 sacrum, 1 acetabulum, 1 femur, 1 ilium, 1 pubis)	Asymptomatic bone cement leakage occurred in 40% (2/5) of cases VP abandoned because of extensive destruction of os pubis and extensive leakage of contrast agent on CT	None reported
Hoffman et al, 2008[151] Germany	22 patients (7 F, 15 M) Median 64 years (41–86)	Interventional radiology RFA (Rita Starburst) for 15 patients (28 lesions in 36 sessions) and VP under conscious sedation and analgesia for 28 lesions (6 pelvis and acetabulum, 2 femur, 1 tibia, 6 T, 10 L, 3 S)	n = 2 Hematoma at needle insertion (n = 2) Asymptomatic bone cement leakage occurred in 57% (8/14) of cases with vertebrae metastases; leaks were in the paravertebral soft tissue (n = 6), in paravertebral tissue and toward the spinal canal (n = 2)	None reported

Author, Year Country	Patients, N (F, M) Age, Mean ± SD (Range)[a]	Operator Interventions and Spinal Levels	Minor Complications, n	Major Complications, n
Lane et al, 2011[152] Canada (earlier Munk et al, 2009[159])	36 patients (NR) 57.6 ± 12.6 years (34–81)	Interventional radiology VP and RFA (Valleylab); under general anaesthesia or conscious sedation with analgesia for 53 bony lesions, including 34 VB levels (20 L, 14 T) and 14 acetabulae, 3 sacra, 1 pubic symphysis, 1 humerus (KP in 3 patients)	Bone cement leakage occurred in 47% (17/36) of cases; 16 of 19 leaks were asymptomatic; leaks occurred in the adjacent muscle (n = 5), needle track (n = 4), basivertebral veins (n = 3), anterior central canal (n = 3), adjacent disc space (n = 2), femoral-acetabular joint space (n = 1), and to base of right lung (n = 1)	n = 3 Symptomatic bone cement leakage in 3 cases Cement leakage and contact with the sciatic nerve; resulted in mixed sensory disturbance with below-the-knee weakness (n = 1); occurred during RFA and acetabuloplasty for metastatic non-small cell lung carcinoma; by 48 hours, the patient had an almost complete neurological recovery Anterior epidural leaks after VP for breast metastases (n = 2); 1 leak resulted in transient generalized pain in treated area quickly resolving within 24 hours; 1 leak involved a cement embolus to the right lung base with no change in respiratory status, heart rate or oxygen saturation noted
Sun et al, 2012[155] China	7 patients (2 F, 5 M) 55.7 years (47–64)	Interventional radiology VP under conscious sedation and analgesia at 14 VB levels (2 T, 5 L, 7 S)	Asymptomatic cement leakage at S1 foramina of a treated sacrum	None reported
Wang et al, 2012[49] China	92 patients (NR) 57 years (33–79)	Interventional radiology 283 VP and osteoplasties in first session (134 T, 119 L, 4 S, 12 pelvic, 8 iliac, 2 femoral); 14 patients had both VP and osteoplasty	Asymptomatic bone cement leakage occurred in 37% (105/283) of treated lesions	None reported
Wee et al, 2008[156] United Kingdom	2 patients (2 M) 55-year-old, 66 year-old	Interventional radiology VP under conscious sedation for 2 VB levels: right sacral ala in patient 1 and left/right sacral ala in patient 2	Asymptomatic bone cement leakage breached the anterior cortex and was distant from the lumbar plexus	None reported
Kyphoplasty for Sacral Vertebral Compression Fractures				
No studies found				

Abbreviations: CT, computed tomography; F, female; KP, kyphoplasty; L, lumbar; M, male; NR, not reported; PRT, palliative radiotherapy; RFA, radiofrequency ablation; S, sacral; SD, standard deviation; T, thoracic; VB, vertebral body; VP, vertebroplasty.
[a]Unless otherwise indicated.

Table 37: Complications Reported in Clinical Studies of Vertebral Augmentation for Vertebral Hemangiomas

Author, Year Country	Patients, N (F, M) Age, Mean ± SD (Range)[a]	Operator Interventions and Spinal Levels	Minor Complications, n	Major Complications, n
Vertebroplasty				
Acosta et al, 2006[165] United States	4 of 16 patients (1 F, 3 M) 42.5 years (29–56)	Interventional radiology VP at 4 VB levels (T9, T7, T8, L3)	None reported	None reported
Fuwa et al, 2006[164] Japan	1 patient (F) 42-year-old	Interventional radiology VP under conscious sedation and analgesia for the T10 neural arch (VB and right pedicle)	None reported	None reported
Guarnieri et al, 2009[169] Italy	24 patients (14 F, 10 M) 63 years	Interventional neuroradiology VP under conscious sedation and analgesia (general anaesthesia for C level) at 36 levels (2 C, 10 T, 24 L)	Asymptomatic bone cement leakage occurred in 17% (4/24) of treated cases	None reported
Hao et al, 2012[170] China	26 patients (17 F, 9 M) 49 years (23–70)	Orthopaedic surgery VP under conscious sedation and analgesia at 28 levels (17 T, 11 L)	Bone cement leakage occurred in 12% (3/26) of treated cases; leaks were in the paravertebrae (n = 2) and the spinal canal and intervertebral foramen (n = 1)	n = 1 Bone cement leakage in the spinal canal and intervertebral foramen compressed the left nerve root with slight leg numbness; surgery was undertaken to decompress and remove the cement (n = 1)
Jian, 2013[174] China	8 patients (5 F, 3 M) 43 years (31–52)	Orthopaedic surgery VP under conscious sedation and analgesia at 8 VB levels (2 C3, 3 C4, 2 C5, 1 C6)	Asymptomatic bone cement leakage occurred in 25% (2/8) of treated cases; leaks were in the paravertebrae	None reported
Jiang et al, 2014[168] China	9 of 29 patients (6 F, 3 M) 39 years (21–57)	Orthopaedic surgery Surgery, radiotherapy and/or VP at 29 VB levels with neurological deficits (3 C, 21 T, 5 L) VP was adjunctive with radiotherapy (n = 1), decompression surgery (n = 2), and decompression surgery and radiotherapy (n = 6)	None reported	None reported
Kyphoplasty				
Atalay et al, 2006[175] Turkey	1 patient (F) 74-year-old	Neurosurgery KP under general anaesthesia for sacral hemangioma and subsequent KP for L3 VB level	None reported	None reported
Hadjipavlou et al, 2007[173] Greece	6 patients (5 F, 1 M) 45.6 years (14–75)	Orthopaedic surgery KP under general anaesthesia (n = 5) and conscious sedation and analgesia (n = 1) in 8 sessions at 11 VB levels (5 T, 6 L); 3 patients also had spinal surgery, 2 had ethanol injections	None reported	None reported

Author, Year Country	Patients, N (F, M) Age, Mean ± SD (Range)[a]	Operator Interventions and Spinal Levels	Minor Complications, n	Major Complications, n
Jones et al, 2009[171] United States	2 patients (1 F, 1 M) 75 year-old female, 38-year-old male	Anaesthesiology KP under conscious sedation and analgesia at 2 VB levels (L5, T12)	None reported	None reported
Zapalowicz et al, 2008[172] Poland	1 patient (F) 49-year old	Neurosurgery KP at C7 with posterior wall defect	Asymptomatic bone cement leakage occurred in the left epidural vein	None reported

Abbreviations: C, cervical; F, female; KP, kyphoplasty; L, lumbar; M, male; SD, standard deviation; T, thoracic; VB, vertebral body; VP, vertebroplasty.
[a]Unless otherwise indicated.

CONCLUSIONS

Studies on vertebroplasty and kyphoplasty included palliative treatment for painful spinal metastases from diverse cancer populations of primary metastatic cancers, multiple myeloma, and hemangiomas. Both interventions are also applied to a range of high-risk fracture situations caused by the extent of vertebral tumour lesions, invasion or involvement of the spinal cord, or their upper spinal column location, closer to critical vascular and neurological structures.

Procedurally, vertebroplasty and kyphoplasty differ by anaesthesia, operators, image guidance, and degree of invasiveness, and although several reports included both procedures in their study population, the studies were not designed or intended to compare the procedures. The choice of procedure was usually a clinical one based on the features of the spinal fracture, perceived risks, treatment intent, or operator experience.

Both vertebroplasty and kyphoplasty rapidly reduced pain intensity levels in cancer patients with spinal fractures that were refractory to conservative care, usually bed rest and opioids. The procedures also decreased the need for analgesics, particularly opioids, and significantly decreased functional disabilities related to back or neck pain. These palliative improvements were consistent across the various cancer populations and vertebral fractures that were investigated. Improvements of vertebral height and kyphotic angles occurring after kyphoplasty, however, were variable, limited by fracture level and location, and were potentially only short term. The clinical significance of these improvements, even when achieved, for cancer patients with advanced stages of disease is uncertain.

Overall, although there was a large body of evidence from observational studies for both vertebroplasty and kyphoplasty for cancer-related spinal fractures, there were only a small number of RCTs comparing vertebral augmentation to conservative management or to different methods of adjunctive local tumour control.

The comprehensive management of cancer-related fractures often required adjunctive interventions for local control of vertebral tumour mass involvement. When spinal fractures were associated with significant tumour mass, adjunctive procedures (usually radiofrequency ablation) were performed, and these occurred more often with vertebroplasty than kyphoplasty. Palliative radiation therapy was also often employed in this patient population, but its use, either before or after vertebral augmentation, was generally not systematically reported in clinical studies evaluating vertebral augmentation interventions. At this time, there is insufficient evidence to determine appropriate methods of adjunctive procedures or their sequencing with vertebral augmentation interventions for optimal fracture management and local tumour control.

Both vertebroplasty and kyphoplasty were associated with a low-risk safety profile. Major complications rarely occurred for any of the cancer populations studied. The most common adverse event was bone cement leakage, which frequently occurred with both procedures and in most cases was asymptomatic.

ABBREVIATIONS

^{125}I	Iodine 125
ASIA	American Spinal Injury Association
CI	Confidence interval
ECOG	Eastern Cooperative Oncology Group
EORTC-QLQC30	European Organization for Research and Treatment of Cancer Quality Life Questionnaire, Version 3.0
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
KPS	Karnofsky Performance Scale
MRI	Magnetic resonance imaging
RCT	Randomized controlled trial
RMDQ	Roland Morris Disability Questionnaire
VAS	Visual analogue scale

APPENDICES

Appendix 1: Literature Search Strategies

Search date: October 14, 2014
Librarians: Corrine Holubowich, Kellee Kaulback
Databases searched: Ovid MEDLINE, Ovid MEDLINE In-Process, Embase, all EBM databases (see below)
Limits: 2000–current; English
Filters: none

Database: EBM Reviews—Cochrane Database of Systematic Reviews <2005 to September 2014>, EBM Reviews—ACP Journal Club <1991 to September 2014>, EBM Reviews—Database of Abstracts of Reviews of Effects <3rd Quarter 2014>, EBM Reviews—Cochrane Central Register of Controlled Trials <September 2014>, EBM Reviews—Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews—Health Technology Assessment <3rd Quarter 2014>, EBM Reviews—NHS Economic Evaluation Database <3rd Quarter 2014>, Embase <1980 to 2014 Week 41>, Ovid MEDLINE(R) <1946 to October Week 1 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <October 13, 2014>

Search Strategy:

1	Spinal Fractures/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or spine fracture/ use emez	21096	Advanced
2	Fractures, Compression/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or compression fracture/ use emez	4407	Advanced
3	(((spinal or spine or vertebr* or compression) adj2 fracture*) or VCF).ti,ab.	30822	Advanced
4	or/1-3	42124	Advanced
5	exp Multiple Myeloma/	81736	Advanced
6	Spinal Neoplasms/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp spine tumor/ use emez	17288	Advanced
7	((myeloma* adj (plasma-cell* or multiple*)) or myelomatos#s or ((spinal or spine*) adj (neoplasm* or tumo?r* or cancer* or metastas#s))).ti,ab.	8957	Advanced
8	or/5-7	103018	Advanced
9	or/4,8	143274	Advanced
10	Kyphoplasty/	2296	Advanced
11	Vertebroplasty/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or percutaneous vertebroplasty/ use emez	4827	Advanced
12	(kyphoplast* or vertebroplast* or ((vertebr* or cement spinal) adj augment*) or percutaneous osteoplast* or (balloon adj2 (spine or spinal or vertebr*))).ti,ab.	7353	Advanced
13	or/10-12	8411	Advanced
14	9 and 13	6246	Advanced
15	limit 14 to (english language and yr="2000 -Current") [Limit not valid in CDSR,ACP Journal Club,DARE,CLCMR; records were retained]	5183	Advanced
16	remove duplicates from 15	3391	

Appendix 2: Clinical Outcomes in Clinical Studies Involving Vertebral Augmentation for Cancer-Related Vertebral Compression Fractures

Pain Intensity

Cancer pain intensity, usually referencing currently experienced back pain, was mostly rated on a visual analogue scale (VAS) or numerical rating scale (NRS) of 0 to 10, with 10 being the worst pain and 0 being no pain. Pain intensity levels were rated as mild (NRS 1 to 4), moderate (NRS 5 to 6), and severe (NRS 7 to 10) based on the impact of pain severity on function.[24] In some cases, pain at rest or with activity or movement was also rated by the patient. The time course of pain palliation was usually evaluated post-procedurally at 24 hours, 48 hours, or 7 days, reflecting the expected rapid analgesic effect of the intervention. Follow-up for the durability of the analgesic effect was usually limited to months because of the limited survival of patients with spinal metastatic disease. In many cases it can be difficult to determine if new pain is primarily caused by disease progression or other overall systemic pain or by a relapse of treated site-specific pain.

Effective pain relief for a group has been reported as different from effective pain relief for individuals. The former has been estimated to be a mean change of 2 points on a VAS or NRS scale.[23,203] Effective pain relief from an individual patient's perspective can be influenced by pain intensity, among other factors, but decreases of at least 4 points or a 50% reduction in pain represents a substantial improvement, which patients consider treatment success.[203] Ratings of patients' individual global or overall improvement have been reported to more accurately reflect changes in pain status. Global change rating scales, such as *very much worse*, *no change*, or *very much better*, were also employed to represent the overall impact of pain reduction for patients.

Analgesic Use

Most patients with cancer-related vertebral compression fractures are on various pain management regimens; if their pain is poorly managed, even with high levels of opioids, they are referred for more effective pain control. One of the measures of analgesic treatment effectiveness is the change in pain medication following the treatment, either a reduction in the total dose or the elimination of the need for opioids. A pain management index was developed by one group to represent adequate pain management, also referred to as the quality of analgesic care.[204] The index is based on the relationship between pain intensity and the level of analgesic care. Pain intensity is rated along a scale of none (0), mild (1), moderate (2), or severe (3); analgesic care is rated along a level of increasingly strong analgesics: no analgesics (0), non-opioids (1), weak opioids (2), and strong opioids (3). The presence of moderate or severe pain even with strong opioids would represent inadequate pain management. An intervention that successfully manages site-specific pain, such as vertebroplasty or kyphoplasty, is unlikely to be associated with an increase in analgesic use.

For clinical trials involving palliative radiotherapy for bony metastases, the American Society for Radiation Oncology, based on an international consensus, has defined pain treatment efficacy as a joint outcome of pain intensity reduction and a corresponding change in pain medication status, either stable or reduced.[205,206] However, the degree of pain intensity reduction that is considered effective should be declared a priori. The society defined a complete response as no pain (VAS = 0) at the treated site with no increase in analgesic use (stable or reduced analgesics in daily morphine equivalents). It defined a partial response as either a pain reduction ≥ 2 VAS points with no analgesic increase (stable), or a reduction in analgesic use of 25% or more from baseline without any increase in pain score.

Physical Performance

Several physical performance status measurements, which rate mobility and self-care, were employed in the vertebral augmentation intervention studies. These included the Barthel Index (BI),[207] the Karnofsky Performance Scale (KPS),[208,209] and the Eastern Cooperative Oncology Group (ECOG) Performance Status scale.[210] To interpret health measurement scores, it is important to understand the *minimum clinically important difference* for outcome measures[211,212]; this has been defined as the "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troubling side effects and excessive cost, a change in patient management."[213]

The KPS has 10 performance levels ranging from 100% ("normal" health) to 50% (the person requires considerable assistance and frequent medical care) to 10% (the person is moribund or near death). The minimum clinically important difference in cancer patients for KPS on a 100-point scale has been cited as 4 points for the smallest favourable change and 10 points for smallest unfavourable change.[212]

The ECOG scale has five performance grades ranging from grade 0 (no disability) to grade 3 (limited self-care and confined to bed for more than half of the waking day) to grade 4 (completely disabled and confined to a bed or chair). A linkage between KPS and ECOG scale values has been estimated, with an ECOG scale score of 0 or 1 being considered equal to a KPS score of 80% to 100%; an ECOG scale score of 2 equalling KPS 60% to 70%; an ECOG scale score of 3 or 4 equalling KPS 10% to 50%; and an ECOG scale score of 5 equalling KPS 0%.[214]

The Barthel Index consists of 10 questions relating to activities of daily living, such as mobility, bathing, dressing, grooming, feeding, toilet activities, climbing stairs, and transferring (e.g., from a bed to a chair). The Barthel Index score ranges from 0 (maximum disability) to 100 (no functional disability).

The Edmonton Symptom Assessment Scale (ESAS) is a validated instrument that was used in these studies to evaluate physical and psychological distress in palliative care. In this setting, symptom control and health-related quality of life are the main objectives of health care.[215-219]

Pain-Related Disability

Two validated measures of back pain–related disability, the Oswestry Disability Index (ODI)[220,221] and the Roland Morris Disability Questionnaire (RMDQ),[222] were employed as outcomes measures for treatment efficacy in both vertebroplasty and kyphoplasty studies. Both indices evaluate the current impact of pain on physical abilities, but neither measures the psychological distress of pain.

The Roland Morris Disability Questionnaire consists of 24 items rated 0 or 1; the overall score ranges from 0 (no disability) to 25 (maximum disability). The questions evaluate the impact of pain on physical functions such as walking, bending, sitting, lying down, dressing, sleeping, self-care, and daily activities. Disability categories for the questionnaire have been designated and include low (10.8 points), mild (15.7 points), moderate (17.5 points), and severe disability (19.0 points).[223] The smallest change shown to be clinically significant is between 2.5 and 5 points.[222] Others have suggested that the minimum clinically important difference depends on the level of disability; for example, for those with little disability a change of 1 or 2 points is important, whereas for those with high levels of disability a change of 7 or 8 points is important.[224]

The Oswestry Disability Index consists of 10 items, each rated on a scale of 0 to 5, for a maximum total score of 50. The sum of the scores is expressed as a percentage of the total. Its questions evaluate the impact of pain on physical functions such as personal care, lifting, walking, sitting, standing, sleeping, and social life. Disability categories include minimal (0%–20%), moderate (20%–40%), severe (40%–60%), and severely disabled in several areas (≥ 60%). The minimum clinically important difference for mean index scores between groups has been defined as a 4-point difference.[225] For major spinal surgery, the US Food and Drug Administration has defined a 15-point minimum change in Oswestry Disability Index scores to be a minimum clinically important difference.[226]

Health-Related Quality of Life and Patient Satisfaction
The impact of vertebral augmentation on overall health-related quality of life in cancer patients with vertebral compression fractures was evaluated using the Short-Form Health Survey (SF-36),[227] a generic measure of health-related quality of life.

Patient satisfaction with treatment was evaluated using simple satisfaction scales.

Radiological Morphometric Outcomes
Compression fractures can occur at any level of the spinal column. There are 33 vertebrae in the spinal column named after different anatomic regions, and they include seven cervical vertebrae (C1–C7); 12 thoracic vertebrae (T1–T12); five lumbar vertebrae (L1–L5); and, at the bottom of the spine, the sacrum, which has five vertebrae (S1–S5) that are fused into one large bone.[228] The functions of the vertebrae are varied and include support, protection, and movement.

Mechanical instability of the spine is one of the main indications for interventions in patients with spinal metastases. Instability has been defined by the Spine Oncology Study Group as the "loss of spinal integrity as a result of a neoplastic process that is associated with movement-related pain, symptomatic or progressive deformity and/or neural compromise under physiological loads."[229] The Study Group also defined a spinal instability neoplastic score (SINS), based on six criteria ranging from 0 to 3 depending on severity. The criteria include the location of the tumour, presence of pain, bone lesion histology (lytic or blastic), radiographic spinal alignment, extent of vertebral body collapse (> 50% collapse or > 50% body involvement), and posterolateral involvement of spinal elements (facet, pedicle, costovertebral joint fracture, or tumour replacement). Scores range from 0 to 18, where 0 to 6 represent stability, 7 to 12 indicate indeterminate, and 13 to 18 represent instability. A surgical consultation is recommended for cancer patients with SINS scores greater than 7.[229]

The location of tumour involvement in the spine is a particular risk factor for instability because of the natural variation in the mobility along the spine, depending on the functions of the region. Mobility of the spine decreases from the top to the bottom, and the different regions have been classified as follows[228]: very mobile (junctional regions of occiput or C0 to C2, C7 to T2, T11 to L1, and L5 to S1); mobile (C3 to C6 and L2 to L4 regions); semi-rigid (T3 to T10 region); and rigid (sacral or S2 to S5 region).Tumour involvement in more mobile areas of the spine presents a greater risk of instability.

Other authors have developed instability measures for individual vertebrae.[228] The three-column model by Denis[230] proposes that damaging two of three columns produces instability. The three columns, based on radiological criteria, are the anterior column (the anterior longitudinal ligament and anterior half of the vertebral body), the middle column (the posterior half of the vertebral body and posterior longitudinal ligament), and the posterior column (the posterior elements including pedicles, facet joints, and interspinous ligaments).

A vertebral body collapse of more than 50% is given high scores in instability indices.[229] Depending on the thresholds used, the amount of vertebral body collapse that would constitute a vertebral fracture has been classically defined as being either a 15% or 20% or greater reduction in vertebral body height compared with the same or adjacent vertebrae.[17] Reductions in vertebral height can occur in the anterior, middle, or posterior regions of the vertebral body, leading to morphological classifications of fractures as wedge, biconcave, or crush deformities.

Spinal deformity has also been semi-quantitatively assigned severity grades (Genant grade) based on loss of vertebral height and area: grade 0, normal; grade 0.5, borderline; grade 1, mild deformity with a 20% to 25% reduction in height and a 10% to 20% reduction in area; grade 2, moderate deformity with a 25% to 40% reduction in height and a 20% to 40% reduction in area; and grade 3, severe deformity with a 40% or greater reduction in any height or area.[17] Although percentage height loss has mostly been cited as a key outcome measure for vertebral fractures, some have suggested that a minimum change in vertebral height (e.g., 4 mm) should be the standard, although this has been employed less often.[231]

Estimation of vertebral height loss or restoration in vertebral compression fractures has been shown to vary considerably with the method of measurement.[231,232] One study that used four different methods to measure vertebral height on standing lateral and anteroposterior radiographs found considerable variation, nearly fourfold across different measurements used and for varying initial fracture severities.[232] The different measurement methods included (1) absolute restoration in millimetres, (2) percent restoration relative to initial fracture height, (3) percent restoration relative to lost vertebral height, and (4) percent restoration relative to referent vertebral height. The authors of this report recommended that an adequate interpretation of radiological morphometric measures of vertebral height should include all index vertebral height measurements (anterior, middle, and posterior); include absolute measurements of all referent vertebral heights; be reported relative to a referent normal height; include a correction for inter-radiographic measurement error; take into account the potential dynamic mobility of some fractures; and include the precision error for all measurements. They also recommended that these measurements be systematically reported.

An additional difficulty in interpreting radiographic measurements of change relates to the dynamic mobility of a fracture; this refers to the potential for significant height recovery and sagittal alignment (kyphotic angle) with careful positioning alone.[233] Dynamic mobility can be assessed by comparing pre-operative standing lateral radiographs with pre-operative supine cross-lateral extension radiographs, and it has been suggested that claims of vertebral height restoration should adjust for this phenomenon.[233]

Kyphotic spinal deformity at the thoracic, thoracolumbar, or lumbar region is an important criterion that guides treatment decision-making in the setting of traumatic fractures in order to prevent further painful deformity or worsening neurological function.[102] Various criteria along with the degree of the kyphotic angle have been cited as thresholds for surgical intervention for fracture with kyphosis: kyphosis greater than 30°,[234] kyphosis progressing 20° or more in the presence of a neural defect,[235] and kyphosis greater than 30° and a greater than 50% canal compromise.[236] The natural curvature of the spine involves different curvatures along the various spinal segments, from a kyphosis at the upper thoracic level (5° kyphosis), to a smaller curvature (0° kyphosis) in the middle lumbar regions, to an opposite curvature or lordosis (−10°

kyphosis) in the lower lumbar region.[100] The degree of kyphosis or lordosis also changes with age; older adults can have greater kyphotic angles.[237]

The ability to differentiate between real change and measurement error is particularly important for radiographic measurements. Although the Cobb angle is the most widely used measure of fracture kyphosis, several other measurements have also been employed, such as the Gardner angle (the angle obtained by a line parallel to the inferior plate of the fractured vertebra and that to the superior endplate of the vertebra above) and the sagittal index (the segmental deformity at the level of a given segment corrected for the normal sagittal contour at the level of the deformed segment).[100]

The reliability of these measures has been shown to vary considerably.[101,238] In a study evaluating reliability of thoracic and lumbar fracture kyphosis, five different kyphotic measures were evaluated by three different raters.[101] These measurements primarily varied by the choice of endplates used to draw reference lines for the determination of angles, and they included (1) measuring from the superior endplate of the vertebral body one level above the injured vertebral body to the inferior endplate of the vertebral body below (Cobb angle); (2) measuring from the superior endplate of the vertebral body just above the fracture to the inferior endplate of the fractured vertebral body; (3) measuring the angle between the posterior vertebral body above and below the fractured vertebrae; (4) measuring from the inferior endplate of the vertebrae above the injury and the superior endplate of the vertebrae below the injury and (5) measuring from the superior endplate to the inferior endplate of the injured vertebrae. The most consistent measures in this study (intra- and inter-rater variability) were for the first method, or the Cobb angle (intraclass correlation coefficient = 0.81; 95% confidence interval [CI] 0.71–0.88). The intraclass correlation coefficients for the other methods ranged from 0.58 (95% CI 0.42–0.72) to 0.71 (95% CI 0.59–0.81). The Spine Trauma Study Group have recommended that the Cobb angle be used to assess sagittal alignment.[99]

It should be noted, however, that the high degree of reliability of these measurements, all based on trauma fractures, may not be directly applicable to disease-based vertebral fractures. In many cancer-related vertebral compression fractures, measurements based on vertebral endplates may be problematic due to the distortions and loss of vertebral integrity that can occur with disease invasion.

Appendix 3: Evidence Base

Table A1: Evidence Base of Reports of Vertebral Augmentation Techniques Involving Vertebroplasty or Kyphoplasty for Palliation of Cancer-Related Vertebral Compression Fractures

Author, Year Country	Report Type	Study Recruitment Period	Patients, n (F, M) Age, Mean ± SD (Range)[a]	Primary Malignancy of Spinal Metastases	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Abdelrahman et al, 2013[186] Germany	Case report	January 1997 to June 2012	1 patient (M) 69-year-old	Non-Hodgkin's lymphoma (n = 1)	Surgery VP at L4	To review cases of local spinal infection following VP or KP
Acosta et al, 2006[165] United States	Case series	1984 to 2004	4 patients (1 F, 3 M) 42.5 years (29–56)	Vertebral hemangioma (n = 4)	Interventional radiology VP at 4 VB levels (T7, T8, T9, L3)	Multidisciplinary management strategies including VP of symptomatic vertebral hemangiomas
Alcibar et al, 2012[185] Spain	Case report	February 2011	1 patient (M) 74-year-old	Lung (n = 1)	Neuroradiology VP at L2	Complication report; fatal PE following VP
Alvarez et al, 2003[123] Spain	Single-site retrospective study, consecutive cases	April 1996 to February 2002	21 patients (14 F, 7 M) 58 years (27–78)	Lung (n = 4), gastrointestinal stromal (n = 3), renal (n = 3), breast (n = 3), prostate (n = 2), uterine (n = 1), other (n = 5)	Interventional neuroradiology VP at 27 VB levels (T, L)	Treatment effectiveness, procedural outcomes, and quality of life
Amoretti et al, 2007[191] France	Case report	NR	1 patient (F) 72-year-old	Breast (n = 1)	Interventional radiology VP at L3	Complication report; aortic embolism of cement after lumbar VP
Anchala et al, 2014[82] United States	Multicentre retrospective study, consecutive cases	March 2012 to March 2013	92 patients 60 years (35–84)	Lung (n = 25), breast (n = 15), sarcoma (n = 8), other (n = 44)	Interventional radiology VP and RFA	Treatment safety and effectiveness of VP and adjunctive RFA
Anselmetti et al, 2012[59] Italy	Single-site prospective study, consecutive cases	2002 to 2009	123 patients (58 F, 65 M) 70 years (35–92)	Multiple myeloma (n = 123)	Interventional radiology VP in 124 sessions at 528 levels (C, T, L)	Treatment safety and efficacy, long-term Mean 28.2 ± 12.1 months

Author, Year Country	Report Type	Study Recruitment Period	Patients, n (F, M) Age, Mean ± SD (Range)[a]	Primary Malignancy of Spinal Metastases	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Anselmetti et al, 2012[143] Italy	Single-site retrospective study, consecutive cases	July 2003 to January 2010	25 patients (16 F, 9 M) 59 ± 11.5 years (39–77)	Breast (n = 9), gastric (n = 1), renal (n = 2), uterine (n = 1), sarcoma (n = 1), nasopharyngeal (n = 2), colon (n = 1), histiocytosis (n = 1), myeloma (n = 5), thyroid (n = 1), hepatic (n = 1)	Interventional radiology VP by trans-oral route for C2 VB level fracture	Treatment safety and efficacy of VP for cervical VB fractures, long-term Mean 21.8 ± 16.3 months (range 6–60)
Anselmetti et al, 2013[239] Italy	Single-site prospective study	February 2010 to January 2012	40 patients (22 F, 18 M) 66.8 ± 12.4 years	Metastatic (n = 31), multiple myeloma (n = 9)	Interventional radiology VP at 43 VB levels	Treatment safety and effectiveness of VP
Appel et al, 2004[124] United States	Single site case series	June 9 to July 1, 2002	7 patients (NR)	Cancer-related (n = 7)	Interventional radiology 23 patients (7 with cancer) from 288 patients in 350 VP sessions at 686 VB levels	Treatment safety and effectiveness of VP with spinal cord compromise
Atalay et al, 2006[175] Turkey	Case report	NR	1 patient (F) 74-year-old	Sacral hemangioma	Neurosurgery KP	Treatment advantages of KP in relieving sacral hemangioma–related pain
Barragan-Campos et al, 2006[177] France	Single-site retrospective study	2001 to 2002	117 patients (69 F, 38 M) 58.2 ± 12.5 years (27–88)	[143]Breast (n = 53), lung (n = 17), myeloma (n = 9), other cancers (n = 38)	Interventional neuroradiology VP in 159 sessions at 304 VB levels	Procedural technical and safety review of VP
Bartolozzi et al, 2006[113] Italy	Single-site prospective study	September 2003 to January 2005	14 patients (4 F, 10 M) 54 years (49–72)	Multiple myeloma (n = 14)	Interventional neuroradiology VP (n = 9) or KP (n = 10) in 19 sessions (T6 to S1)	Treatment safety and effectiveness of VP and KP 10 months (range 1–16)
Basile et al, 2010[153] Italy	Case series	April 2007 to May 2009	8 patients (4 F, 4 M) 57.8 years (47–68)	Multiple myeloma (n = 8)	Interventional radiology VP (S)	Treatment effectiveness of VP in the sacral region Mean 12.5 months (range 3–27)
Basile et al, 2011[115] Italy	Single-site prospective study	January 2007 to January 2010	24 patients (13 F, 11 M) 54.7 years (42–67)	Multiple myeloma (n = 24)	Interventional radiology VP at 34 VB levels (16 T, 18 L)	Treatment safety with VP and delayed cement infusion with osteolysis or fracture of posterior wall

Author, Year Country	Report Type	Study Recruitment Period	Patients, n (F, M) Age, Mean ± SD (Range)[a]	Primary Malignancy of Spinal Metastases	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Berenson et al, 2011[88] Australia, Canada, Europe, United States	Multicentre multinational RCT at 22 sites	May 2005 to March 2008	134 patients (129 randomized) (75 F, 54 M) KP: 64.8 years (38–88) Controls: 63 years (40–83)	Multiple myeloma (n = 49), breast (n = 28), lung (n = 11), prostate (n = 8), other (n = 33)	Orthopaedic surgery KP at 247 VB levels	Comparative treatment safety and effectiveness vs. non-surgical management 1 month
Bosnjakovic et al, 2009[53] Serbia	Single-site retrospective study	June 2002 to December 2006	29 patients (18 F, 11 M) 63 years (58–79)	Multiple myeloma (n = 29)	Interventional radiology VP at 55 VB levels (17 T, 38 L)	Treatment effectiveness of VP 12 months
Botton et al, 2012[157] France	Single-site retrospective study	January 2007 to July 2009	42 patients (24 F, 18 M) Median 59 years (21–81)	Multiple myeloma (n = 15), colon (n = 5), kidney (n = 5), liver (n = 3), lung (n = 2), uterus (n = 2), other (n = 10)	Interventional radiology VP (10 long bone, 13 spinal [T or L], 20 pelvis)	Treatment effectiveness of VP in the spine and pelvis Maximum 27 months
Burton et al, 2005[67] United States	Case series	NR	3 patients (2 F, 1 M) 64 years (60–67)	Breast (n = 1), lung (n = 1), parotid gland (n = 1)	Anaesthesiology VP at 6 VB levels (5 L, 1 T)	Treatment effectiveness of VP Until death
Calmels et al, 2007[58] France	Single-site retrospective study	1996 to 2002	52 patients (46 F, 6 M)	Breast (n = 40), prostate (n = 3), lung (n = 3), other cancers (n = 6)	Interventional neuroradiology VP in 59 sessions at 103 VB levels	Treatment effectiveness – analgesic efficacy of VP for blastic or mixed spinal metastases Mean 17 months, up to 5 years
Chen et al, 2014[192] China	Case report	NR	1 patient (F) 39-year-old	Breast (n = 1)	Surgery VP at 4 VB levels (T10, T11, L1, L2)	Complication report; cement PE
Chen et al, 2007[187] China	Case report	November 2004	1 patient (M) 76-year-old	Lung (n = 1)	Orthopaedic surgery VP at 2 VB levels (L1, L3)	Complication report with VP; local metastases along VP needle tract
Chen et al, 2013[95] China	Case series	May 2005 to January 2012	6 patients (3 F, 3 M) 59.3 years (50–73)	Breast (n = 2), lung (n = 2), liver (n = 1), prostate (n = 1)	Orthopaedic surgery KP (T or L)	Technical feasibility, safety and effectiveness of KP for osteoblastic spinal lesions 3 months (range 16–96 weeks)
Chen et al, 2012[56]	Single-site retrospective study	August 2003 to July 2008	24 patients (20 F, 4 M) 67 years (54–81)	Multiple myeloma (n = 24)	Orthopaedic surgery VP at 36 VB levels	Treatment safety and effectiveness of VP 12 months

Author, Year Country	Report Type	Study Recruitment Period	Patients, n (F, M) Age, Mean ± SD (Range)[a]	Primary Malignancy of Spinal Metastases	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Chen et al, 2011[68] China	Case series	NR	4 patients (1 F, 3 M) Range 47–67 years	Lung (n = 2), prostate (n = 1), pancreas (n = 1)	Interventional radiology VP at 4 VB levels (T or L)	Treatment safety effectiveness of VP for osteoblastic spinal lesions 3 months
Chen et al, 2014[148] China	Case series	NR	4 patients (2 F, 2 M) 57.5 years (46–72)	Metastatic cancers	Interventional radiology VP at C levels (1 C5, 2 C6, 2 C7)	Treatment feasibility of VP for fractures at the C level
Chew et al, 2011[63] Scotland	Single-site prospective study, consecutive cases	June 2001 to June 2010	128 patients (60 F, 68 M) 60 years (31–88)	Multiple myeloma (n = 41), breast (n = 22), lung (n = 16), lymphoma (n = 11), renal (n = 8), prostate (n = 5), other (n = 25)	Interventional radiology VP in 158 sessions at 264 VB levels	Treatment safety and effectiveness of VP for multiple myeloma and spinal metastases Median 3 years (range 1–9 years)
Chou et al, 2013[182] China	Case report	NR	1 patient (F) 62-year-old	Multiple myeloma (n = 1) IgG-kappa stage III	Orthopaedic surgery VP (T12 to L3)	Complication report with VP; fatal bone-cement induced PE
Cianfoni et al, 2012[142] Italy	Case report	NR	1 patient (F) 36-year old	Intestinal carcinoid (n = 1)	Interventional neuroradiology VP and RFA with coblation at C1 VB level	Treatment safety and effectiveness of VP and RFA for high cervical fracture 2 months
Corcos et al, 2014[178] France	Single-site retrospective study, consecutive cases	April 2010 to July 2011	56 patients (30 F, 26 M) 56 ± 12 years (21–79)	Lung (n = 16), breast (n = 10), neuroendocrine (n = 10), other cancers (n = 20)	Interventional radiology VP at 81 VB levels (34 T, 46 L, 1 S) in 58 sessions	Safety report with VP; to evaluate incidence of cement leakage and risk factors
Cruz et al, 2014[188] Canada	Case reports	NR	2 patients (1 F, 1 M) 48-year-old, 73-year-old	Lung (n = 1), melanoma (n = 1)	Interventional neuroradiology KP at T9, T10	Safety report with KP; tumour extravasation following KP for cancer-related VCF
Dalbayrak et al, 2010[133] Turkey	Single-site retrospective review	NR	31 patients (17 F, 14 M) 62 years (35–78)	Gastric (n = 7), breast (n = 6), lung (n = 4), multiple myeloma (n = 6), other (n = 8)	Neurosurgery KP at 39 VB levels (T or L)	Procedural and treatment safety and effectiveness of KP with high-risk fractures Follow-up NR
Diamond et al, 2004[61] Australia	Case series	2002 to 2003	7 patients (4 F, 3M) Range 58–78 years	Multiple myeloma (n = 7)	Interventional radiology VP at 14 VB levels (T, L); 1 had 7 levels	Treatment effectiveness of VP for fracture and deformity 6 weeks

Author, Year Country	Report Type	Study Recruitment Period	Patients, n (F, M) Age, Mean ± SD (Range)[a]	Primary Malignancy of Spinal Metastases	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Dudeney et al, 2002[90] United States	Single-site retrospective study, consecutive cases	NR	18 patients (NR) 63.5 years (48–79)	Multiple myeloma (n = 18)	Orthopaedic surgery KP in 27 sessions at 55 VB levels (T6 to L5)	Treatment safety and effectiveness of KP Mean 7.4 months
Eleraky et al, 2011[122] United States	Single-site retrospective study	NR	14 of 23 patients (6 F, 8 M) 62 years (41–71)	Multiple myeloma (n = 6), lung (n = 3), breast (n = 2), other (n = 3)	Neurosurgery KP for 30 VB levels (T1 to T5)	Treatment effectiveness of KP for upper thoracic VCFs Mean 16 months; minimum 1 year
Elshinawy et al, 2005[197] United States	Case report	NR	1 patient (M) 62-year-old	Multiple myeloma (n = 1)	Surgery KP at 3 levels (L1, L2, L3)	Complication report; bone cement PE following KP
Erdem et al, 2013[81] United States	Single-site retrospective study, consecutive cases	December 2008 to May 2009	41 patients (20 F, 21 M) 56.9 ± 14.2 years (24–86)	Multiple myeloma (n = 41)	Interventional neuroradiology VP and RFA in 48 sessions at 139 VB levels (T, L, or S)	Treatment safety and effectiveness of VP and RFA 6 months
Erdem et al, 2013[109] United States	Single-site retrospective study	January 2001 to May 2007	361 of 792 patients (134 F, 227 M)	Multiple myeloma (n = 361)	Interventional neuroradiology VP or KP in 447 sessions	Treatment safety and effectiveness of VP or KP
Esmende et al, 2013[198] United States	Case report	NR	1 patient (M) 65-year-old	Oral carcinoma (n = 1)	Orthopaedic surgery KP 1 level (T9)	Complication report; spinal cord compression after KP for cancer-related VCF requiring surgical intervention
Farrokhi et al, 2012[69] Iran	Single-site prospective study	NR	25 patients (14 F, 11 M) 53.5 years (37–70)	Breast (n = 14), lung (n = 9), prostate (n = 2)	Neurosurgery VP at T3 to L4	Treatment palliative effectiveness of VP
Fourney et al, 2003[110] United States	Single-site retrospective study	October 2000 to February 2002	56 patients (25 F, 31 M) Median 64 years (30–82)	Multiple myeloma (n = 21), breast (n = 9), lung (n = 6), lymphoma (n = 6), prostate (n = 5), other (n = 9)	Neurosurgery or interventional radiology VP and/ or KP	Treatment safety and effectiveness of VP or KP Median 4.5 months; range 1 day to 20 months
Fuwa et al, 2006[164] Japan	Case report	NR	1 patient (F) 42-year-old	Vertebral hemangioma	Interventional radiology VP at T10	Treatment effectiveness of VP for a vertebral hemangioma involving the neural arch 6 months

Author, Year Country	Report Type	Study Recruitment Period	Patients, n (F, M) Age, Mean ± SD (Range)[a]	Primary Malignancy of Spinal Metastases	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Garland et al, 2011[55] United Kingdom	Single-site retrospective study	2004 to 2009	26 patients (10 F, 16 M) 59.3 years (42–76)	Multiple myeloma (n = 26)	Interventional radiology VP	Treatment safety and effectiveness of VP for multiple myeloma Mean 19 months (range 20 days to 42 months)
Georgy et al, 2009[118] United States	Single-site retrospective study, consecutive cases	NR	37 patients (21 F, 16 M) Range 34–89 years	Breast (n = 9), lung (n = 6), multiple myeloma (n = 6), other (n = 16)	Interventional radiology VP and/or KP followed by RFA at 44 VB levels	Technical outcomes and safety of VP or KP followed by RFA
Gerszten et al, 2005[103] United States	Single-site retrospective study, consecutive cases	NR	26 patients (20 F, 6 M) 72 years (47–83)	Lung (n = 11), breast (n = 9), renal (n = 4), other (n = 2)	Neurosurgery KP and CKRS at 26 VB levels (16 T, 10 L)	Treatment safety and effectiveness of KP and spinal radiosurgery (CKRS) Range 11 to 24 months
Gronemeyer et al, 2002[83] Germany	Single-site retrospective study, consecutive cases	November 1999 to January 2001	10 patients (NR) Range 58–76 years	Breast (n = 2), multiple myeloma (n = 1), melanoma (n = 2), renal (n = 2), prostate (n = 1), other (n = 2)	Interventional radiology RFA and VP (n = 4)	Safety and effectiveness of RFA prior to VP 6 months
Gu et al, 2014[135] Li et al, 2013[121] China	Single-site retrospective study, consecutive cases	October 2009 to July 2012	31 patients (NR) 58 ± 8.8 years (37–73)	Lung (n = 19), thyroid (n = 3), breast (n = 2), prostate (n = 2), colon (n = 2), other cancers (n = 3)	Interventional radiology VP and ITR	Treatment safety and effectiveness of ITR with VP Mean 12 ± 6 months range 3 to 25 months (every 6 months until death)
Guarnieri et al, 2009[169] Italy	Single-site retrospective study, consecutive cases	January 2003 to December 2007	24 patients (14 F, 10 M) 63 years	Vertebral hemangioma (n = 24)	Interventional neuroradiology VP at 36 VB levels (2 C, 10 T, 24 L)	Treatment safety and effectiveness of VP with long-term follow-up 4 years
Hadjipavlou et al, 2007[173] Greece	Case series	NR	6 patients (5 F, 1 M) 45.6 years (14–75)	Vertebral hemangioma (n = 6)	Orthopaedic surgery KP in 8 sessions at 11 VB levels (5 T, 6 L); 3 patients also had spinal surgery, 2 had ethanol injections	Treatment safety and effectiveness of KP for vertebral hemangioma Mean 22 months (range 12–36)
Halpin et al, 2005[84] United States	Case report	NR	1 patient (F) 45-year-old	Lung (n = 1)	Interventional radiology VP and RFA at T9 and VP at T12	Treatment feasibility of combined RFA and VP for VCF

Author, Year Country	Report Type	Study Recruitment Period	Patients, n (F, M) Age, Mean ± SD (Range)[a]	Primary Malignancy of Spinal Metastases	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Hao et al, 2012[170] China	Single-site retrospective study, consecutive cases	January 2007 to March 2011	26 patients (17 F, 9 M) 49 years (23–70)	Vertebral hemangioma (n = 26)	Orthopaedic surgery VP at 28 VB levels (17 T, 11 L)	Treatment safety and effectiveness of VP for vertebral hemangioma Mean 8.6 months (range 3–24)
Hentschel et al, 2005[116] United States	Single-site comparative registry review	January 2001 to July 2003	66 patients *Group 1 (no contraindications)* 49 patients (24 F, 25 M) Median 64 years (29–88) *Group 2 (contraindications)* 17 patients (8 F, 9 M) Median 61 years (42–75)	*Group 1* Multiple myeloma (n = 24), metastases (n = 8), hemangioma (n = 2), osteoporosis (n = 15) *Group 2* Multiple myeloma (n = 11), metastases (n = 5), hemangioma (n = 0), osteoporosis (n = 1)	Neurosurgery *Group 1* VP at 89 VB levels KP at 22 VB levels *Group 2* VP at 13 VB levels KP at 5 VB levels	Comparative treatment safety and effectiveness of VP or KP for contraindicated VB fractures vs. those with conventional criteria
Hentschel et al, 2004[202] United States	Case report	August 2001	1 patient (F) 60-year-old	Renal cell carcinoma and thymic cancer (n = 1)	Neurosurgery VP at T7	Treatment safety and effectiveness of VP for vertebra plana (severely collapsed vertebrae)
Hierholzer et al, 2003[158] Germany	Case series	NR	5 patients (2 F, 3 M) 63 years (52–76)	Lung (n = 3), breast (n = 1), colon (n = 1)	Interventional radiology VP at 5 lesion sites (acetabulum, ilium, pubis, femur, sacrum)	Treatment effectiveness of VP for various painful bony lesions in the sacrum, ileum and femur Maximum 24 weeks
Hirsch et al, 2011[107] United States	Single-site retrospective study, consecutive cases	2003 to 2009	201 patients (NR)	Multiple myeloma, breast or lung cancer (n = 137); other NR	Interventional radiology VP or KP for 316 VB levels (T11 to L3)	Treatment effectiveness of VP or KP and palliative EBRT
Hoffman et al, 2008[151] Germany	Single-site retrospective study	2002 to 2005	22 patients (7 F, 15 M) Median 64 years (41–86)	Multiple myeloma (n = 5), breast (n = 3), lung (n = 4), thyroid (n = 2), renal cell (n = 5), unknown primary (n = 3)	Interventional radiology VP and RFA at 28 lesions (6 pelvis and acetabulum, 2 femur, 1 tibia, 6 T, 10 L, 3 S)	Treatment effectiveness of VP and RFA for various painful bony lesions in the vertebrae and other skeletal metastases
Huber et al, 2009[195] Germany	Single-site prospective study, consecutive cases	December 2001 to December 2008	76 patients (31 F, 45 M) Median 62 years (28–76)	Multiple myeloma (n = 76)	Orthopaedic surgery KP at 190 VB levels	Treatment safety of KP 30-day review

Author, Year Country	Report Type	Study Recruitment Period	Patients, n (F, M) Age, Mean ± SD (Range)[a]	Primary Malignancy of Spinal Metastases	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Huegli et al, 2005[149] Switzerland	Case report	NR	1 patient (F) 76-year-old	Adenocarcinoma of unknown origin with hypervascularization of C4 lesion	Interventional radiology VP at 2 VB levels (C1, C4)	Treatment effectiveness of hybrid CT and fluoroscopic guidance for C-level lesions
Jang et al, 2005[74] South Korea	Single-site prospective study	NR	28 patients (17 F, 11 M) Range 40–72 years	Metastases (n = 22), multiple myeloma (n = 6)	Surgery VP at 72 VB levels (9 C, 30 T, 33 L)	Treatment effectiveness of VP and EBRT Median 7.7 months (range 1–16); 21 died during follow-up
Jha et al, 2010[111] United States	Retrospective database comparative review	May 2003 to March 2008	249 patients *VCF of known metastatic etiology* 147 patients with 238 VCFs (83 F, 64 M) 71 ± 12 years *VCF of unknown metastatic etiology* 102 patients with 174 VCF (55 F, 47 M) 69 ± 13 years	Primary malignancies (VCF of known metastatic etiology) Multiple myeloma (n = 54), breast (n = 25), lung (n = 26), other (n = 42)	Interventional neuroradiology VP (n = 48) or KP (n = 96) or both (n = 105) at 236 VB levels (T, L)	Treatment effectiveness of VP or KP in cancer patients with a known metastatic VCF, compared with cancer patients with a VCF of unknown etiology
Jian, 2013[174] China	Case series	December 2008 to February 2012	8 patients (5 F, 3 M) 43 years (31–52)	Cervical hemangioma (n = 8)	Surgery VP at 8 VB levels (C3 to C6)	Treatment effectiveness VP for cervical vertebral hemangioma
Jiang et al, 2014[168] China	Single-site retrospective study, consecutive cases	2001 to 2013	9 of 29 patients (17 F, 12 M) 44 years (21–72)	Vertebral hemangioma (n = 29)	Orthopaedic surgery VP at 9 patients at 11 VB levels (2 C, 8 T, 1 L)	Treatment safety and effectiveness of multidisciplinary treatment including VP for vertebral hemangiomas with neurological deficit
Jones et al, 2009[171] United States	Case reports	NR	2 patients (1 F, 1 M) 75 year-old female, 38-year-old male	Vertebral hemangioma (n = 2)	Anaesthesiology KP (L5, T12)	Treatment safety and effectiveness VP for vertebral hemangioma unresponsive to other treatments
Julka et al, 2014[91] United States	Single-site retrospective study, consecutive cases	NR	32 patients (14 F, 18 M) 64.3 years	Multiple myeloma (n = 32)	Orthopaedic surgery KP at 76 VB levels (34 T, 42 L)	Treatment safety and effectiveness of KP for multiple myeloma 24 months

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Kasperk et al, 2012[104] Germany	Comparative retrospective cohort study	2003 to 2006	73 patients (33 F, 40 M) 60.2 ± 9.5 years	Multiple myeloma (n = 73)	Surgery 35 KP at 111 VB levels	Treatment safety and effectiveness of clinical pathway for multiple myeloma, including KP, EBRT, and systemic therapy (VAD-like chemotherapy, stem cell transplantation, bisphosphonates, and pain medications as tolerated) 2 years
Kim et al, 2002[70] United States	Single site comparative retrospective cohort study, consecutive cases	January 1999 to September 2000	*Unipediculate* 41 patients (26 F, 15 M) 75.9 ± 7.9 years *Bipediculate* 24 patients (15 F, 9 M) 75.0 ± 7.1 years	NR	Interventional radiology *Unipediculate* VP at 68 levels (8 T6 to T8, 16 T9 to T12, 22 L1 to L2, 11 L3 to L5) *Bipediculate* VP at 29 levels (1 T8, 9 T9 to T12, 4 L1 to L2, 4 L3 to L5)	Treatment safety and effectiveness of unilateral vs. bilateral transpedicular VP 6 weeks
Knight et al, 2008[117] Canada	Case series	NR	3 patients (3 F) 32-year-old, 59-year-old, 67-year-old	Breast (n = 1), lung (n = 1), multiple myeloma (n = 1)	Interventional radiology KP at T9 VP at T6 VP at T9	Effectiveness of spinal cement augmentation under c-arm CT guidance with spinal column narrowing
Kobayashi et al, 2009[71] Japan	Multicentre prospective study	February 2003 to May 2006	33 patients (17 F, 16 M) 62 years (37–87)	Lung (n = 7), breast (n = 7), colorectal (n = 7), liver (n = 4), myeloma (n = 3), other (n = 5)	Interventional radiology VP at 42 VB levels (18 T, 24 L)	Treatment safety and effectiveness of VP for cancer-related vertebral fractures
Konig et al, 2012[96] United Kingdom	Single-site prospective study, consecutive cases	February 2001 to September 2002	11 patients (7 F, 4 M) Range 52–77 years	Breast (n = 3), myeloma (n = 1), non-Hodgkin lymphoma (n = 2), gastric (n = 1), cervical (n = 1), prostate (n = 1), lung (n = 1), bladder (n = 1)	Surgery KP at 23 VB levels (T2 to L3)	Treatment safety and effectiveness of KP for cancer-related vertebral fractures Until death
Kose et al, 2006[114] Turkey	Single-site retrospective study	June 2003 to June 2005	34 patients (18 F, 16 M) KP: 63.7 years (48–82) VP: 62.2 years (45–80)	Multiple myeloma (n = 34)	Orthopaedic surgery KP at 22 VB levels in 18 patients VP at 28 VB levels in 16 patients	Treatment safety and effectiveness of VP or KP for multiple myeloma

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Kruger et al, 2003[176] United States	Single-site prospective study	NR	36 patients	NR	Orthopaedic surgery VP	Treatment safety and radiation dose levels during VP
Kushchayev et al, 2010[50] United States	Case reports	NR	2 patients (2 M) 63-year-old, 60-year-old	Thyroid cancer (n = 2)	Neurosurgery Case 1: VP at L5 Case 2: VP at L2 and L4, followed by transpedicular fixation at L1 to L3	Treatment effectiveness of VP for spinal metastatic thyroid cancer Until death
Lane et al, 2004[92] United States	Single-site retrospective study, consecutive cases	NR	19 patients (7 F, 12 M) 60.4 years (45–74)	Multiple myeloma (n = 19), osteoporosis (n = 26)	Surgery KP (multiple myeloma) at 46 VB levels; KP (osteoporosis) at 37 VB levels	Treatment effectiveness of multilevel KP to relieve pain, improve function, and restore vertebral body height 3 months
Lane et al, 2011[152] Canada (earlier Munk et al, 2009[159])	Single-site retrospective study	June 2006 to January 2009	36 patients (NR) 57.6 ± 12.6 years (34–81)	Breast (n = 12), lung (n = 5), multiple myeloma (n = 6), prostate (n = 2), renal (n = 2), other (n = 9)	Interventional radiology VP and RFA in 34 vertebrae (20 L, 14 T), 14 acetabulae, 3 sacra, 1 pubic symphysis, 1 humerus; KP in only 3 patients, no longer used	Treatment safety and effectiveness of combination RFA and cementoplasty (VP or KP) for bony metastases
Langdon et al, 2009[200] United Kingdom	Case report	NR	1 patients (M) 53 years	Renal carcinoma (n = 1)	Orthopaedic surgery KP at T10	Prophylactic KP stabilization of vertebral body invaded by renal metastases to prevent vertebral fracture 14 months
Lee et al, 2009[72] United Kingdom	Single-site retrospective study	2004 to 2008	19 patients (11 F, 8 M) 70 years (44–89)	Breast (n = 8), prostate (n = 4), lung (n = 2), renal (n = 2), other (n = 3)	Interventional radiology VP at 34 VB levels	Treatment effectiveness of VP and predictive factors Median 12 months (range 3–38)
Lee et al, 2014[193] Korea	Case report	NR	1 patient (F) 61-year-old	Lung (n = 1)	Neurosurgery VP at 3 VB levels (T4 to T6)	Complication report; needle tract seeding after VP
Li et al, 2014[196] China	Single-site retrospective comparative cohort study	January 2006 to January 2011	37 of 100 patients	Metastatic (n = 26), vertebral hemangioma (n = 11), severe osteoporosis (n = 63)	Orthopaedic surgery KP single (1 or 2) level (n = 50) or multiple (> 2) levels (n = 50) in a single session	Safety of KP in a single session at a single VB level or at multiple levels Operative and post-operative period

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Li et al, 2013[121] Gu et al, 2014[135] China	Single-site comparative cohort study	October 2009 to June 2012	52 of 63 patients (18 F, 34 M) 59.6 years (37–90)	Lung (n = 27), liver (n = 5), thymic (n = 5), colon (n = 3), prostate (n = 3), breast (n = 2), multiple myeloma (n = 2), other (n = 5)	Interventional radiology VP at 94 VB levels	Treatment safety and effectiveness of VP compared to VP and ITR in patients with VCFs and neurological symptoms of cord compression Mean 11 ± 6.3 months (VP + ITR) Mean 14.3 ± 6.7 months (VP)
Li et al, 2014[108] China	Single-site comparative retrospective database review	January 2003 to January 2008	*Kyphoplasty* 42 patients (24 F, 18 M) 68.4 years (52–85) *Vertebroplasty* 38 patients (19 F, 19 M) 65.2 years (49–83)	Breast (n = 30), lung (n = 18), prostate (n = 14), stomach (n = 11), other (n = 7)	Orthopaedic surgery (KP) and interventional radiology (VP) KP at 83 levels (T, L) VP at 76 levels (T, L)	Comparative treatment safety and effectiveness of VP and KP followed by palliative EBRT and/or other antitumour therapy 12 months
Lim et al, 2009[75] Korea	Single-site retrospective study	2001 to 2007	102 patients (42 F, 60 M) Median 55 years (22–82)	Breast (n = 24), multiple myeloma (n = 19), lung (n = 16), liver (n = 10), colorectal (n = 10), stomach (n = 4), other (n = 19)	Interventional radiology VP at 185 VB levels and spinal EBRT for 59 patients	Treatment effectiveness and long-term outcomes of VP and palliative EBRT To 12 months
Lim et al, 2011[134] Korea	Case report	NR	1 patient (F) 76-year-old	Gastric cancer and cholangiocarcinoma (n = 1)	Anaesthesiology KP at 2 VB levels (T12, L1)	Treatment safety and effectiveness of KP with VCF with large vertebral bony defect and neurological symptoms 6 months
Lim et al, 2007[134]	Case report	NR	1 patient (F) 55-year-old	Unknown etiology	Anaesthesiology VP at L2	Complication report: delayed intraatrial thrombus resulting in pulmonary thromboembolism following VP
Lim et al, 2008[184] Korea	Case report	NR	1 patient (F) 59-year-old	NR	Surgery VP at 2 levels (T12, L1)	Complication report; multiple cardiac perforations and PE caused by cement leakage after VP
Lykomitros et al, 2010[146] Greece	Case reports	December 2007 to February 2008	2 patients (2 M) 48-year-old, 70-year-old	Lung (n = 1), gastric (n = 1)	Orthopaedic surgery KP at 2 levels per patient (C2, C6 and C3, C5)	Treatment effectiveness of anterolateral KP approach for cervical spine metastatic lytic lesions

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Mahadevia et al, 2007[189] United States	Case report	NR	1 patient (F) 52-year-old	NR	Interventional neuroradiology VP at T12	Complication report; contact dermatitis, delayed-type hypersensitivity after VP
Masala et al, 2004[85] Italy	Case series	January 2004 to May 2004	3 patients (2 F, 1 M) 72.3 years (63, 72, 82)	Breast (n = 2), lung (n = 1)	Interventional radiology VP and RFA	Treatment effectiveness and safety of combined VP and RFA
Masala et al, 2008[65] Italy	Multicentre retrospective study	February 2003 to December 2005	64 patients (30 F, 34 M) 71.4 ± 9.6 years	Multiple myeloma (n = 64)	Interventional radiology VP at 198 VB levels (93 T, 105 L)	Treatment safety and effectiveness of VP for multiple level myelomatous spinal fractures 6 months
Masala et al, 2011[144] Italy	Multi-site retrospective review	May 2005 to May 2009	62 patients (38 F, 24 M) Median 61.5 years (31–85)	Breast (n = 16), multiple myeloma (n = 11), lung (n = 10), gastric (n = 7), other (n = 18)	Interventional radiology VP (33 trans-orally) at 70 VB levels (3 C1, 32 C2, 3 C3, 11 C4, 15 C5, 4 C6, 2 C7)	Treatment safety, feasibility, and effectiveness of VP for cervical metastatic fractures 3 months
Mattei et al, 2014[190] United States	Case report	November 2010 to June 2013	1 patient (F) 41-year-old	Lung (n = 1)	Interventional radiology VP at 1 level (T6)	Complication report; VP failure for VCF in patients undergoing medical therapy with denosumab
Mazumdar et al, 2010[125] United States	Case reports	NR	2 patients (1 F, 1 M) 71-year-old (F), 60-year-old (M)	Breast cancer (n = 1), multiple myeloma (n = 1)	Interventional radiology VP at L4 and L3 VB levels	Treatment effectiveness for VCF and radicular symptoms of pain and lower-extremity weakness
McDonald et al, 2008[54] United States	Single-site retrospective registry review	October 2000 to March 2007	67 patients (30 F, 37 M) 66.2 years	Multiple myeloma (n = 67)	Interventional radiology VP at 114 VB levels	Treatment effectiveness of VP in the myelomatous population 12 months
McDonald et al, 2009[64] United States	Single-site prospective study	January 1999 to May 2007	128 of 841 patients	Multiple myeloma (n = 67), metastatic cancers (n = 61)	Interventional neuroradiology VP	Treatment safety and effectiveness of VP by operator experience 12 months

Author, Year Country	Report Type	Study Recruitment Period	Patients, n (F, M) Age, Mean ± SD (Range)[a]	Primary Malignancy of Spinal Metastases	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Mendoza et al, 2012[112] United States	Single-site retrospective study	January 2001 to May 2008	79 of 175 patients (32 F, 47 M) 60.1 ± 9.8 years	Multiple myeloma (n = 79)	Anaesthesiology VP (n = 37), KP (n = 22) VP + KP (n = 20) Procedures at one VB level (n = 49), two VB levels (n = 26), 3 or more VB levels (n = 4)	Treatment effectiveness of VP or KP to reduce pain and decrease related symptoms such as fatigue, sleep disturbances, depression, and anxiety Mean 1 month (range 11–56 days)
Mikami et al, 2011[73] Japan	Single-site retrospective study	February 2002 to March 2008	69 patients (34 F, 35 M) 65.1 years (48–89)	Breast (n = 12), lung (n = 8), prostate (n = 7), colon (n = 7) uterus (n = 5), liver (n = 5), kidney (n = 3), pancreas (n = 3), other (n = 19)	Interventional radiology PV at 141 levels (47 T, 77 L, 17 S)	Treatment effectiveness of VP for vertebral metastases 6 months; 18 died within 6 months
Mont'Alverne et al, 2009[141] France	Case series	January 1994 to October 2007	4 patients (1 F, 3 M) 45 years (39–50)	Multiple myeloma (n = 4)	Interventional neuroradiology VP at 5 VB levels (1 C2, 2 C3, 2 C4)	Treatment effectiveness of VP in the cervical spine Mean 28 months (range 1–96)
Mroz et al, 2008[194] United States	Single-site retrospective study	NR	27 patients 69.7 years (49–86 years)	Multiple myeloma, metastatic cancers and osteoporosis (NR)	Surgery KP at 52 levels (T4 –L5); KP at one level (n = 10), two levels (n = 9), three levels (n = 8)	Safety report; radiation exposure to surgeon and patient during kyphoplasty
Munk et al, 2009[159] Canada (Later Lane et al, 2011[152])	Single-site prospective study	22-months	19 patients (5 F, 14 M) 58.9 years (42–82)	Lung (n = 7), breast (n = 3), other cancers (n = 9)	Interventional radiology 11 VP and 14 KP and 236 RFA applications	Safety and effectiveness of VA and RFA for painful neoplastic lesions
Murphy et al, 2007[47] United States	Case report	NR	1 patient (F) 41-year-old	Breast (n = 1)	Interventional radiology VP at 1 level (T10)	Effectiveness of VP for vertebral osteoblastic metastases 3 years
Nakatsuka et al, 2004[86] Japan	Single-site prospective study	February 2002 to April 2003	17 patients (8 F, 9 M) 61 ± 13 years	Metastatic cancers (n = 14), primary [multiple myeloma (n = 2), plasmacytoma (n = 1)]	Interventional radiology VP and RFA	Feasibility, safety and effectiveness of RFA and VP (cementoplasty) Mean 6.3 ± 5 months; 6 patients died during follow-up

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Omidi-Kashani et al, 2009[180] Iran	Case report	NR	1 patient (F) 14-year-old	Vertebral hemangioma (n = 1)	Orthopaedic surgery VP at L3	Complication report; cement leakage with neuroforamen involvement, resulting in neurological symptoms requiring surgical intervention
Orgera et al, 2014[79] Italy	Single-site prospective RCT	January 2008 to August 2012	36 patients (26 F, 10 M) 63.1 ± 7.2 years	Multiple myeloma (n = 36)	Interventional radiology VP and RFA vs. VP only	Comparative effectiveness of RFA and VP vs. VP to control pain To 6 weeks
Panagiotis et al, 2014[89] Greece	Prospective parallel comparative RCT	March 2010 to March 2012	47 patients	Breast, colon and lung cancers (n = NR)	Orthopaedic surgery KP (n = 24) for T7 to L5 Kiva (n = 23) T11 to S2	Comparison of 2 different vertebral augmentation techniques: KP or the Kiva implant 1 month
Pflugmacher et al, 2006[93] Germany	Single-site prospective study	May 2002 to December 2003	20 patients (20 M)	Multiple myeloma (n = 20)	Orthopaedic surgery KP at 48 VB levels (T6 to L5)	Treatment effectiveness of KP for multiple myeloma 12 months
Pflugmacher et al, 2008[97] Germany	Single-site prospective study, consecutive cases	May 2001 to November 2004	65 patients (28 F, 37 M) 66 ± 9 years	Metastatic cancers (breast, ovary, cervix, rectum, lung, pancreas, prostate, skin, gastrointestinal; numbers NR)	Orthopaedic surgery KP at 99 VB levels KP performed at one level (n = 37), two levels (n = 23), three levels (n = 4), and four levels (n = 1)	Treatment safety and effectiveness of KP for osteolytic thoracic and lumbar fractures To 24 months; 13 patients died before 1-year follow-up, and 13 patients died between 12 and 24 months
Prologo et al, 2013[119] United States	Single-site retrospective study	September 2007 to September 2012	15 patients (8 F, 7 M) 67.8 ± 15.3 years	Lung (n = 4), breast (n = 3), prostate (n = 2), other (n = 6)	Interventional radiology RFA and VP at 15 VB levels (3 T, 12 L)	Treatment feasibility, safety, and effectiveness of RFA and VP for VCFs with and without epidural involvement
Qian et al, 2011[105] China	Single-site prospective study	January 2003 to January 2008	48 patients (29 F, 19 M) 68.5 years (52–85)	Breast (n = 16), lung (n = 10), prostate (n = 6), stomach (n = 6), cervical (n = 4), other (n = 6)	Orthopaedic surgery KP at 124 VB levels (T5 to L5)	Treatment feasibility, safety and effectiveness of KP followed by EBRT for metastatic VCF 24 months; 7 patients died during follow-up

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Ramos et al, 2006[51] Spain	Single-site prospective study, consecutive cases	June 2001 to March 2004	12 patients (3 F, 9 M) 66 years (54–80)	Multiple myeloma or plasmacytomas (n = 12)	Orthopaedic surgery and interventional radiology VP at 19 VB levels (T9 to L4)	Treatment safety and effectiveness of VP To 3 years
Rasulova et al, 2011[76] Uzbekistan	Single-site prospective study	December 2007 to December 2010	11 patients (5 F, 6 M) 53.8 years (32–62)	Lung (n = 5), breast (n = 3), prostate (n = 3)	Interventional radiology and orthopaedic surgery	Treatment effectiveness of consecutive treatments of VP preceding radionuclide bone therapy 6 to 8 months
Ratliff et al, 2001[181] United States	Case report	NR	1 patient (F) 50-year-old	Breast (n = 1)	Surgery VP at T1	Complication report; cement leakage into C8 and T1 foramina and spinal canal resulting in neurological deficits requiring surgical intervention after VP
Rodriguez-Catarion et al, 2007[138] Sweden	Case report	NR	1 patient (F) 47-year-old	Multiple myeloma (n = 1)	Interventional neuroradiology VP at C2 VB level	Treatment effectiveness of VP for painful unstable cervical spine fracture 18 months
Saliou et al, 2010[131] France	Single-site retrospective study	1990 to 2006	51 of 508 consecutive patients (22 F, 29 M) 62.5 years (28–85)	Breast (n = 8), lung (n = 8), kidney (n = 7), multiple myeloma (n = 5), plasmacytoma (n = 3), bladder (n = 4), other (n = 16)	Interventional neuroradiology VP at 74 VB levels	Treatment feasibility, safety, and effectiveness of VP for malignant spine fractures with epidural involvement To 5 years
Sandri et al, 2010[106] Italy	Single-site prospective study	2007 to 2009	11 patients (9 F, 2 M) 68 years (58–82)	Multiple myeloma (n = 7), thyroid (n = 2), breast (n = 1), kidney (n = 1)	Orthopaedic surgery RFA and KP at 11 VB levels (1 C, 9 T, 1 L)	Treatment safety and efficacy of combined RFA and KP for spinal lesions 12 months; range 4–18 months; 5 patients died during follow-up
Seo et al, 2013[150] Korea	Case report	NR	1 patient (F) 51-year-old	Breast (n = 1)	Anaesthesiology VP at C7 VB level	Treatment effectiveness of a VP anterolateral approach for C7-level fracture

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Shimony et al, 2004[130] United States	Single-site prospective comparative study	June 1998 to April 2002	50 of 277 patients (25 F, 25 M) 62.7 years ± 14 years	Multiple myeloma (n = 14), lung (n = 13), breast (n = 8), prostate (n = 3), lymphoma (n = 3), other (n = 9) *Epidural involvement* Group 1 none (n = 14), Group 2 mild (n = 18), Group 3 moderate (n = 18)	Interventional radiology VP in 60 sessions at 129 levels (T1 to L5) VP performed at: one level (n = 14), two levels (n = 16), three levels (n = 10). four levels (n = 3), five levels (n = 2), six levels (n = 4), seven levels (n = 1)	Treatment safety and effectiveness of VP with malignant compression fractures and epidural involvement To 2 years; median 3 months; 45 patients died during follow-up
Simony et al, 2014[66] Denmark	Single-site retrospective study, consecutive cases	2004 to 2010	17 patients (7 F, 10 M) 62.5 years (46–76)	Multiple myeloma (n = 17)	Surgery VP at 64 VB levels (T6 to S2)	Treatment safety and pain-reducing effectiveness 3 months
Sun et al, 2012[155] China	Case series	2001 to 2010	7 patients (2 F, 5 M) 55.7 years (47–64)	Lung (n = 3), breast (n = 2), liver (n = 1), kidney (n = 1)	Interventional radiology VP at 14 VB levels (2 T, 5 L, 7 S)	Treatment safety and effectiveness of VP (sarcoplasty) trans-sacroiliac joint approach with 3-D C-arm guidance 6 months
Sun et al, 2010,[240] 2013[145] China	Single-site retrospective study	March 2003 to May 2012	13 patients (5 F, 8 M) 59.8 years (41–73)	Lung (n = 6), breast (n = 3), bladder (n = 2), kidney (n = 1), colon (n = 1)	Interventional radiology VP at C2 VB level	Treatment safety and effectiveness of VP with anterolateral for C2 osteolytic cervical metastases 12 months; 8 patients died within follow-up
Sun et al, 2011,[132] 2014[126] China	Single-site retrospective study, consecutive cases	March 2000 to May 2012	43 patients (24 F, 19 M) 64.1 years (34–84)	Lung (n = 13), breast (n = 12), kidney (n = 5), stomach (n = 4), bladder (n = 3), uterine (n = 3), colon (n = 2), ovary (n = 1)	Interventional radiology VP at 69 VB levels (T3 to L5) *Epidural involvement* Group 1, none (n = 25 levels); Group 2, mild (n = 23 levels); Group 3 moderate (n = 21 levels)	Treatment safety and effectiveness of VP for painful spinal metastases with epidural encroachment 12 months
Tancioni et al, 2010[60] Italy	Single-site retrospective study	November 2003 to December 2005	11 patients (5 F, 6 M) Median 56 years (45–76)	Multiple myeloma (n = 11) Stages IIA (n = 2), IIIA (n = 8), IIIB (n = 1)	Neurosurgery VP in 14 sessions at 28 VB levels (C, T, L)	Treatment safety and effectiveness of VP for multiple myeloma with painful vertebral body in any disease stage

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Toyota et al, 2005[87] Japan	Single-site retrospective study	October 2001 to January 2004	17 patients (1 F, 16 M) 64.2 years (54–81)	Liver (n = 6), renal (n = 5), bladder (n = 2), other (n = 4)	Interventional radiology VP and RFA in 53 sessions for 23 lesions	Treatment feasibility, safety and effectiveness of RF ablation with cementoplasty for painful bone metastases 12 months; 8 patients died during follow-up
Tran et al, 2013[199] Germany	Case report	NR	1 patient (F) 68-year-old	NR	Neurosurgery KP at 2 VB levels (L4, L3)	Complication report with KP; cement embolism migration in the venous system and perforation of right ventricle, causing cardiac tamponade
Tran Thang et al, 2008[62] Switzerland	Single-site retrospective study	1996 to 2002	28 patients (11 F, 17 M) Median 65 years (40–89)	Multiple myeloma (n = 28) Stages I (n = 3), II (n = 4), III (n = 21)	Interventional radiology VP in 33 sessions for 75 fractures and at 117 levels (57 T, 59 L, 1 S) VP at one level (n = 7), two or more levels (n = 21)	Treatment effectiveness of VP for painful spinal fractures related to multiple myeloma Median 41 months (range 3–81 months)
Trumm et al, 2012[52] Germany	Single-site retrospective study	December 2001 to August 2008	39 patients (17 F, 22 M) 65 ± 7 years	Multiple myeloma (n = 39)	Interventional radiology VP in 44 sessions at 67 VB levels (3 C, 32 T, 27 L, 5 S)	Technical success and safety and treatment effectiveness of VP with primary CT-fluoroscopic guidance for multiple myeloma with spinal compression fractures 6 months
Trumm et al, 2012[127] Germany	Single-site retrospective study	December 2001 to June 2009	202 patients (116 F, 86 M) 63.2 ± 8.6 years	Breast (n = 68), multiple myeloma (n = 40), lung (n = 22), renal (n = 10), prostate (n = 8), leukemia/ lymphoma (n = 7), sarcoma (n = 6), pancreas (n = 5), thyroid (n = 4), other (n = 32)	Interventional radiology VP in 231 sessions at 331 levels VP performed at: one level (n = 140), two levels (n = 82), or three levels (n = 9)	Technical procedure and treatment safety and effectiveness of VP with primary CT-fluoroscopic guidance for painful malignant vertebral osteolytes with and without fractures and with and without epidural involvement
Trumm et al, 2008[48] Germany	Single-site retrospective study	January 2003 to January 2007	53 patients (52 F, 1 M) 62 ± 13 years	Breast (n = 53)	Interventional radiology VP in 62 sessions at 86 VB levels (9 C, 55 T, 21 L,1 S) VP performed at: one level (n = 34), two levels (n = 27), or three levels (n = 1)	Treatment safety and effectiveness of CT-fluoroscopic guided VP in osteolytic breast cancer metastases Mean 9.2 months; 4 patients died within 6 months

Author, Year Country	Report Type	Study Recruitment Period	Patients, n (F, M) Age, Mean ± SD (Range)[a]	Primary Malignancy of Spinal Metastases	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Tseng et al, 2008[57] China	Single-site retrospective study	January 2002 to December 2006	57 patients (32 F, 25 M) 65.2 years (40–86)	Lung (n = 19), colon (n = 9), urinary tract (n = 8), gastrointestinal tract (n = 4), prostate (n = 4), thyroid (n = 3), breast (n = 3), other (n = 7)	Neurosurgery VP at 78 VB levels (1 C, 33 T, 44 L) Vertebral fracture grade level (Genant) Grade 0 (n = 5), Grade 1 (n = 22), Grade 2 (n = 39), Grade 3 (n = 12)	Treatment effectiveness in reducing opioid drug use after VP for painful metastatic spine tumours Mean 24.3 months
Van der Linden et al, 2007[120] Netherlands	Single-site retrospective study	July 2003 to December 2005	12 patients (4 F, 8 M) 57 years (31–79)	Renal (n = 4), breast (n = 2), lung (n = 2), multiple myeloma (n = 2), B-cell lymphoma (n = 1), chondrosarcoma (n = 1)	Interventional radiology and orthopaedic surgery RFA and VP at 12 VB levels (6 L, 4 T, 2 C)	Treatment safety and effectiveness of RFA and VP in patients with posterior vertebral wall defects, with and without spinal canal involvement 3 months; 4 patients died during follow-up
Vrionis et al, 2005[98] United States	Single-site retrospective study	2002 to 2004	50 patients (33 F, 17 M) 63 years (36–81)	Multiple myeloma (n = 23), lung (n = 11), breast (n = 8), prostate (n = 4), other (n = 4)	Neurosurgery KP at 128 VB levels (83 T, 45 L)	Treatment effectiveness of KP for painful spinal compression fractures Mean 9 months; 14 patients died during follow-up
Wang et al, 2012[49] China	Single-site retrospective study	June 2007 to December 2010	92 patients (NR) 57 years (33–79)	Lung cancer (n = 92)	Interventional radiology 283 osteoplasties in first session (134 T, 119 L, 4 S, 12 pelvic, 8 iliac, 2 femoral); 14 patients had both VP and osteoplasty	Treatment effectiveness of osteoplasty for bone metastases to the spine (vertebroplasty) and pelvis (acetabuloplasty) To 3 months; 2 patients died during follow-up
Wee et al, 2008[156] United Kingdom	Case reports	2005, 2006	2 patients (2 M) 55-year-old, 66- year-old	Renal cell carcinoma (n = 1), multiple myeloma (n = 1)	Interventional radiology VP at sacral ala	Treatment effectiveness of VP for cases with extensive sacral destruction and no surgical alternatives
Woo et al, 2013[128] Korea	Case report	NR	1 patient (M) 52-year-old	Cholangiocarcinoma (n = 1)	Anaesthesiology VP (L4)	Treatment effectiveness and safety of VP for spinal metastases and radicular pain due to metastatic compression of dorsal root ganglion resistant to multiple spinal injection blocks

Author, Year Country	Report Type	Study Recruitment Period	Patients, n (F, M) Age, Mean ± SD (Range)[a]	Primary Malignancy of Spinal Metastases	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Yang et al, 2009[78] China	Single-site RCT	July 2004 to July 2006	80 patients (39 F, 41 M) VP: 58.8 ± 7.4 years VP and ISI: 61 ± 4.5 years	Breast (n = 36), lung (n = 28), liver (n = 9), colon (n = 5), gastric (n = 2)	Orthopaedic surgery VP at 126 VB levels (T, L)	Comparative study of VP versus a combined radiation therapy ^{125}I seed interstitial implantation followed by VP for osteolytic spinal metastases 1 year; all survived to at least 1 year
Yang et al, 2013[77] China	Single-site RCT	May 2003 to June 2010	100 patients (61 F, 39 M) VP and ISI: 61.1 ± 5.2 years Radiotherapy: 59.8 ± 6.6 years	Lung (n = 39), breast (n = 37), prostate (n = 21), colon (n = 3)	Orthopaedic surgery VP at 89 VB levels	Comparative study of VP and radiation therapy ^{125}I seed interstitial implantation vs. radiotherapy for osteoblastic spinal metastases 1 year
Yang et al, 2012[80]	Single-site RCT	February 2003 to July 2005	76 patients (37 F, 39 M) VP, chemotherapy and bisphosphonate therapy: 58.9 years ± 4.3 years Chemotherapy and bisphosphonate therapy: 59.6 years ± 6.2 years	Multiple myeloma (n = 76)	Orthopaedic surgery VP performed at one level (n = 7), two levels (n = 27), or three or more levels (n = 41)	Comparative study of. combined VP and chemotherapy vs chemotherapy for multiple myeloma–associated spinal fractures 5 years; 19 died within 3-year follow-up (6 in VP and chemotherapy group and 13 in chemotherapy-only group)
Yoon et al, 2008[147] Korea	Case report	NR	1 patient (M) 67-year-old	Lung cancer (n = 1)	Anaesthesiology VP at C2 VB level	Treatment effectiveness of VP by anterolateral VP approach and upper cervical facet joint block for C2-level metastatic VCFs Patient died 4 months post-procedure
Zapalowicz et al, 2008[172] Poland	Case report	NR	1 patient (F) 49-year old	Cervical hemangioma (n = 1)	Neurosurgery KP at C7	Treatment effectiveness of KP for C7 vertebral hemangioma with posterior wall defects 13 months

Author, Year Country	Report Type	Study Recruitment Period	Patients, n (F, M) Age, Mean ± SD (Range)[a]	Primary Malignancy of Spinal Metastases	Operator Interventions and Treated Spinal Levels	Study Objective Follow-Up[b]
Zou et al, 2010[94] China	Single-site retrospective study	January 2003 to January 2008	21 patients (12 F, 9 M) 65.9 years (47–81)	Multiple myeloma (n = 21)	Orthopaedic surgery KP at 14 T, 14 TL and 15 L KP performed at one level (n = 2), two levels (n = 16), or three levels (n = 3)	Treatment effectiveness of KP for multiple myeloma VCFs 12 months

Abbreviations: C, cervical; CAFE Cancer Patient Fracture Evaluation; CKRS, CyberKnife radiosurgery; CT, computed tomography; EBRT, external beam radiotherapy; F, female; Ig, immunoglobulin; ISI, interstitial implantation; ITR, interventional tumour removal; KP, kyphoplasty; L, lumbar; M, male; NR, not reported; RCT, randomized controlled trial; RFA, radiofrequency ablation; S, sacral; SD, standard deviation; T, thoracic; VAD, vincristine, Adriamycin (doxorubicin), and dexamethasone; VB, vertebral body; VCF, vertebral compression fracture; VP, vertebroplasty.
[a]Unless otherwise indicated.
[b]If reported in study.

Table A2: GRADE Evidence Profile for Vertebroplasty Palliation of Vertebral Compression Fractures

Number of Studies (Design) Initial GRADE	Risk of Bias[a]	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Pain Intensity							
30 (observational pre-post cohort) Low	No serious limitations	No serious limitations	Serious limitations (–1)[b]	No serious limitations	Unevaluated	Large magnitude of effect, rapid response (+2)[c]	⊕⊕⊕ Moderate
Analgesic Use							
26 (observational pre-post cohort) Low	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Unevaluated	Large magnitude of effect (+1)[d]	⊕⊕⊕ Moderate
Physical Function Performance							
30 (observational pre-post cohort) Low	No serious limitations	No serious limitations	Serious limitations (–1)[e]	No serious limitations	Unevaluated	Large magnitude of effect, rapid response (+2)[f]	⊕⊕⊕ Moderate
Health-Related Quality of Life							
3 (observational pre-post cohort) Low	No serious limitations	No serious limitations	Serious limitations (–1)[g]	No serious limitations	Unevaluated	NA	⊕⊕ Low
Patient Satisfaction							
4 (observational pre-post cohort) Low	No serious limitations	No serious limitations	No serious limitations	Serious limitations (–1)[h]	Unevaluated	NA	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NA, not applicable.

[a]Bias was assessed in individual observational pre-post studies for several criteria at the pre-intervention, intervention, and post-intervention stages. Among the criteria considered: prospective study design, eligibility criteria, interventions and co-interventions, outcome measurement, and follow-up. Although the reporting of these factors was variably performed in individual studies, overall there was sufficiency in the reports (most information was from studies of low risk) to evaluate bias as not having serious limitations.

[b]Indirectness limitations with pain intensity reductions involved the lack of direct comparisons with groups receiving usual care.

[c]Upgrade considerations based on statistically and clinically significant improvements; very large magnitude of effect with validated outcome measures and temporal relationship of improvements to intervention involving rapid pain reduction, reported often within hours of the procedures and followed by subsequent improvements in mobility and decreasing analgesic use.

[d]Upgrade consideration for analgesic use, particularly high-level opioid use, was the dramatic reduction after vertebroplasty procedures.

[e]Indirectness limitations with physical function performance involved the lack of direct comparisons with groups receiving usual care.

[f]Upgrade considerations based on statistically and clinically significant improvements; very large magnitude of effect with validated outcome measure and improvements in mobility and self-care within days of the procedure.

[g]Indirectness limitations with health-related quality of life involved the lack of direct comparisons with groups receiving usual care. Additionally, as patients with metastatic disease are often in advanced stages of disease, treatment objectives are more realistically only about symptom palliation with improvements in self-care, rather than with the broader overall quality of life domains measured by the generic (not disease-specific) SF-36.

[h]Patient satisfaction was evaluated in only a few studies with small patient groups and limited outcome measures.

Table A3: GRADE Evidence Profile for Kyphoplasty Palliation of Vertebral Compression Fractures

Number of Studies (Design) Initial GRADE	Risk of Bias[a]	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Pain Intensity							
19 (observational pre-post cohort) Low	No serious limitations	No serious limitations	Serious limitations (–1)[b]	No serious limitations	Unevaluated	Large magnitude of effect (+2)[c]	⊕⊕⊕Moderate
1 (RCT) High	No serious limitations	No serious limitations	Serious limitations (–1)[d]	No serious limitations	Unevaluated	NA	⊕⊕⊕ Moderate
Analgesic Use							
4 (observational pre-post cohort) Low	No serious limitations	No serious limitations	No serious limitations	Serious limitations (–1)[e]	Unevaluated	Large magnitude of effect (+1)[f]	⊕⊕⊕ Moderate
1 (RCT) High	No serious limitations	No serious limitations	No serious limitations	Serious limitations (–1)[g]	Unevaluated	NA	⊕⊕⊕ Moderate
Physical Function Performance							
18 (observational pre-post cohort) Low	No serious limitations	No serious limitations	Serious limitations (–1)[h]	No serious limitations	Unevaluated	Large magnitude of effect (+2)[i]	⊕⊕⊕Moderate
1 (RCT) High	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Unevaluated	NA	⊕⊕⊕⊕ High
Health-Related Quality of Life							
3 (observational pre-post cohort) Low	No serious limitations	No serious limitations	Serious limitations (–1)[j]	No serious limitations	Unevaluated	NA	⊕⊕ Low
1 (RCT) High	No serious limitations	No serious limitations	Serious limitations (–1)[k]	No serious limitations	Unevaluated	NA	⊕⊕⊕ Moderate
Vertebral Height							
10 (observational pre-post cohort) Low	No serious limitations	Serious limitations (–1)[l]	Serious limitations (–1)[m]	No serious limitations	Unevaluated	NA	⊕⊕ Low
1 (RCT) High	No serious limitations	Serious limitations (–1)[n]	Serious limitations (–1)[o]	No serious limitations	Unevaluated	NA	⊕⊕ Low

Number of Studies (Design) Initial GRADE	Risk of Bias[a]	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Kyphosis							
6 (observational pre-post cohort) Low	No serious limitations	No serious limitations	Serious limitations (–1)[p]	No serious limitations	Unevaluated	NA	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NA, not applicable; RCT, randomized controlled trial.

[a]Bias was assessed in individual observational pre-post studies for several criteria at the pre-intervention, intervention, and post-intervention stages. Among the criteria considered: prospective study design, eligibility criteria, interventions and co-interventions, outcome measurement, and follow-up. Although the reporting of these factors was variably performed in individual studies, overall there was sufficiency in the reports (most information was from studies of low risk) to evaluate bias as not having serious limitations.

[b]Indirectness limitations with pain intensity involved the lack of direct comparisons with groups receiving usual care.

[c]Upgrade considerations for pain intensity were based on statistically and clinically significant improvements; very large magnitude of effect with validated outcome measures and parallel temporal response involving rapid pain reductions, reported often within hours of the procedures and followed by subsequent improvements in mobility and decreasing analgesic use.

[d]Indirectness limitations with the RCT for pain intensity involved a highly select small number of cases with restricted fracture locations and complexity from many centres.

[e]Imprecision limitations with analgesic use involved variable measurement.

[f]Upgrade considerations for analgesic use involved a dramatic reduction, particularly for high-level opioids, after kyphoplasty procedures.

[g]Imprecision limitations with analgesic in the RCT involved limited or generalized measurement of analgesic use.

[h]Indirectness limitations with physical function performance involved the lack of direct comparisons with groups receiving usual care.

[i]Upgrade considerations for physical function performance were based on statistically and clinically significant improvements; very large magnitude of effect with validated outcome measure and improvements in mobility and self-care following within days of the procedure.

[j]Indirectness limitations with health-related quality of life involved the lack of direct comparisons with groups receiving usual care.

[k]Indirectness limitations with health-related quality of life in the RCT involved the select group of cases with limited fracture profiles.

[l]Inconsistency limitations with vertebral height involved the variable estimates of vertebral height restoration within and between studies.

[m]Indirectness limitations with vertebral height involved the uncertain clinical significance of vertebral height restoration and the lack of direct comparison of groups receiving usual care.

[n]Inconsistency limitations with vertebral height in the RCT involved the within-study variation in height restoration.

[o]Indirectness limitations with vertebral height in the RCT involved the uncertain clinical significance of vertebral height restoration.

[p]Indirectness limitations with kyphosis involved the uncertain clinical significance of local angle correction.

REFERENCES

(1) Brenner H, Gondos A, Pulte D. Expected long-term survival of patients diagnosed with multiple myeloma in 2006-2010. Haematologica. 2009;94(2):270-5.

(2) Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res. 2006;12(20 Pt 2):6243s-9s.

(3) Sciubba DM, Petteys RJ, Dekutoski MB, Fisher CG, Fehlings MG, Ondra SL, et al. Diagnosis and management of metastatic spine disease. a review. J Neurosurg Spine. 2010;13(1):94-108.

(4) Sutcliffe P, Connock M, Shyangdan D, Court R, Kandala NB, Clarke A. A systematic review of evidence on malignant spinal metastases: natural history and technologies for identifying patients at high risk of vertebral fracture and spinal cord compression. Health Technol Assess. 2013;17(42):1-274.

(5) Wibmer C, Leithner A, Hofmann G, Clar H, Kapitan M, Berghold A, et al. Survival analysis of 254 patients after manifestation of spinal metastases: Evaluation of seven preoperative scoring systems. Spine (Phila Pa 1976). 2011;36(23):1977-86.

(6) Callander NS, Roodman GD. Myeloma bone disease. Semin Hematol. 2001;38(3):276-85.

(7) Lecouvet FE, Malghem J, Michaux L, Michaux JL, Lehmann F, Maldague BE, et al. Vertebral compression fractures in multiple myeloma. Part II. Assessment of fracture risk with MR imaging of spinal bone marrow. Radiology. 1997;204(1):201-5.

(8) Georgy BA. Metastatic spinal lesions: state-of-the-art treatment options and future trends. AJNR Am J Neuroradiol. 2008;29(9):1605-11.

(9) Kaloostian PE, Yurter A, Etame AB, Vrionis FD, Sciubba DM, Gokaslan ZL. Palliative strategies for the management of primary and metastatic spinal tumors. Cancer Control. 2014;21(2):140-3.

(10) Lutz S, Berk L, Chang E, Chow E, Hahn C, Hoskin P, et al. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. Int J Radiat Oncol Biol Phys. 2011;79(4):965-76.

(11) Mundy GR. Metastasis to bone: causes, consequences and therapeutic opportunities. Nat Rev Cancer. 2002;2(8):584-93.

(12) Schiff D, O'Neill BP, Suman VJ. Spinal epidural metastasis as the initial manifestation of malignancy: clinical features and diagnostic approach. Neurology. 1997;49(2):452-6.

(13) Zaikova O, Giercksky KE, Fossa SD, Kvaloy S, Johannesen TB, Skjeldal S. A population-based study of spinal metastatic disease in South-East Norway. Clin Oncol (R Coll Radiol). 2009;21(10):753-9.

(14) Loblaw DA, Laperriere NJ, Mackillop WJ. A population-based study of malignant spinal cord compression in Ontario. Clin Oncol (R Coll Radiol). 2003;15(4):211-7.

(15) Zaikova O, Giercksky KE, Fossa SD, Kvaloy S, Johannesen TB, Skjeldal S. A population-based study of spinal metastatic disease in South-East Norway. Clin Oncol (R Coll Radiol). 2009;21(10):753-9.

(16) Costa L, Badia X, Chow E, Lipton A, Wardley A. Impact of skeletal complications on patients' quality of life, mobility, and functional independence. Support Care Cancer. 2008;16(8):879-89.

(17) Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res. 1993;8(9):1137-48.

(18) Fourney DR, Gokaslan ZL. Spinal instability and deformity due to neoplastic conditions. Neurosurg Focus. 2003;14(1):e8.

(19) Jakobs TF, Trumm C, Reiser M, Hoffmann RT. Percutaneous vertebroplasty in tumoral osteolysis. Eur Radiol. 2007;17(8):2166-75.

(20) Barr JD, Jensen ME, Hirsch JA, McGraw JK, Barr RM, Brook AL, et al. Position statement on percutaneous vertebral augmentation: a consensus statement developed by the Society of Interventional Radiology (SIR), American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS), American College of Radiology (ACR). J Vasc Interv Radiol. 2014;25(2):171-81.

(21) Baerlocher MO, Saad WE, Dariushnia S, Barr JD, McGraw JK, Nikolic B. Quality improvement guidelines for percutaneous vertebroplasty. J Vasc Interv Radiol. 2014;25(2):165-70.

(22) Chow E, Doyle M, Li K, Bradley N, Harris K, Hruby G, et al. Mild, moderate, or severe pain categorized by patients with cancer with bone metastases. J Palliat Med. 2006;9(4):850-4.

(23) Dworkin RH, Turk DC, McDermott MP, Peirce-Sandner S, Burke LB, Cowan P, et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. Pain. 2009;146(3):238-44.
(24) Serlin RC, Mendoza TR, Nakamura Y, Edwards KR, Cleeland CS. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. Pain. 1995;61(2):277-84.
(25) Del Fabbro E, Reddy SG, Walker P, Bruera E. Palliative sedation: when the family and consulting service see no alternative. J Palliat Med. 2007;10(2):488-92.
(26) Reddy A, Yennurajalingam S, Desai H, Reddy S, de la Cruz M, Wu J, et al. The opioid rotation ratio of hydrocodone to strong opioids in cancer patients. Oncologist. 2014;19(11):1186-93.
(27) Vayne-Bossert P, Zulian GB. Palliative sedation: from the family perspective. Am J Hosp Palliat Care. 2013;30(8):786-90.
(28) Provenzano MJ, Murphy KPJ, Riley ILH. Bone cements: review of their physiochemical and biochemical properties in percutaneous vertebroplasty. AJNR Am J Neuroradiol. 2004;25(7):1286-90.
(29) Cloft HJ, Jensen ME. Kyphoplasty: an assessment of a new technology. AJNR Am J Neuroradiol. 2007;28(2):200-3.
(30) Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011;64(4):380-2.
(31) Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol. 2011;64(12):1311-6.
(32) Schroeder JE, Ecker E, Skelly AC, Kaplan L. Cement augmentation in spinal tumors: a systematic review comparing vertebroplasty and kyphoplasty. Evid Based Spine Care J. 2011;2(4):35-43.
(33) Mendel E, Bourekas E, Gerszten P, Golan JD. Percutaneous techniques in the treatment of spine tumors: what are the diagnostic and therapeutic indications and outcomes? Spine (Phila Pa 1976). 2009;34(22 Suppl):S93-100.
(34) Khan OA, Brinjikji W, Kallmes DF. Vertebral augmentation in patients with multiple myeloma: a pooled analysis of published case series. AJNR Am J Neuroradiol. 2014;35(1):207-10.
(35) Bouza C, Lopez T, Magro A, Navalpotro L, Amate JM. Efficacy and safety of balloon kyphoplasty in the treatment of vertebral compression fractures: a systematic review. Eur Spine J. 2006;15(7):1050-67.
(36) Bouza C, Lopez-Cuadrado T, Cediel P, Saz-Parkinson Z, Amate JM. Balloon kyphoplasty in malignant spinal fractures: a systematic review and meta-analysis. BMC Palliat Care. 2009;8:12.
(37) Chew C, Craig L, Edwards R, Moss J, O'Dwyer PJ. Safety and efficacy of percutaneous vertebroplasty in malignancy: a systematic review. Clin Radiol. 2011;66(1):63-72.
(38) Eck JC, Nachtigall D, Humphreys SC, Hodges SD. Comparison of vertebroplasty and balloon kyphoplasty for treatment of vertebral compression fractures: a meta-analysis of the literature. Spine J. 2008;8(3):488-97.
(39) Krueger A, Bliemel C, Zettl R, Ruchholtz S. Management of pulmonary cement embolism after percutaneous vertebroplasty and kyphoplasty: a systematic review of the literature. Eur Spine J. 2009;18(9):1257-65.
(40) Lee MJ, Dumonski M, Cahill P, Stanley T, Park D, Singh K. Percutaneous treatment of vertebral compression fractures: a meta-analysis of complications. Spine (Phila Pa 1976). 2009;34(11):1228-32.
(41) McGirt MJ, Parker SL, Wolinsky JP, Witham TF, Bydon A, Gokaslan ZL. Vertebroplasty and kyphoplasty for the treatment of vertebral compression fractures: an evidenced-based review of the literature. Spine J. 2009;9(6):501-8.
(42) Doidge J, Merlin T, Liufu Z, Tamblyn D, Jia L, Hiller J. Review of interim funded services: vertebroplasty and new review of kyphoplasty. MSAC Application 27.1. Canberra, Australia: Commonwealth of Australia; 2011.
(43) Nussbaum DA, Gailloud P, Murphy K. A review of complications associated with vertebroplasty and kyphoplasty as reported to the Food and Drug Administration medical device related web site. J Vasc Interv Radiol. 2004;15(11):1185-92.

(44) Ehteshami Rad A, Luetmer MT, Murad MH, Kallmes DF. The association between the duration of preoperative pain and pain improvement in vertebral augmentation: a meta-analysis. AJNR Am J Neuroradiol. 2012;33(2):376-81.
(45) Taylor RS, Taylor RJ, Fritzell P. Balloon kyphoplasty and vertebroplasty for vertebral compression fractures: a comparative systematic review of efficacy and safety. Spine (Phila Pa 1976). 2006;31(23):2747-55.
(46) Taylor RS, Fritzell P, Taylor RJ. Balloon kyphoplasty in the management of vertebral compression fractures: an updated systematic review and meta-analysis. Eur Spine J. 2007;16(8):1085-100.
(47) Murphy KJ, Nwankwo IJ, Gailloud P. Percutaneous vertebroplasty in the treatment of blastic vertebral column metastasis from breast cancer. J Vasc Interv Radiol. 2007;18(2):321-3.
(48) Trumm CG, Jakobs TF, Zech CJ, Helmberger TK, Reiser MF, Hoffmann RT. CT fluoroscopy-guided percutaneous vertebroplasty for the treatment of osteolytic breast cancer metastases: results in 62 sessions with 86 vertebrae treated. J Vasc Interv Radiol. 2008;19(11):1596-606.
(49) Wang Z, Zhen Y, Wu C, Li H, Yang Y, Shen Z, et al. CT fluoroscopy-guided percutaneous osteoplasty for the treatment of osteolytic lung cancer bone metastases to the spine and pelvis. J Vasc Interv Radiol. 2012;23(9):1135-42.
(50) Kushchayev S, Kushchayeva Y, Theodore N, Preul MC, Clark OH. Percutaneous vertebroplasty for thyroid cancer metastases to the spine. Thyroid. 2010;20(5):555-60.
(51) Ramos L, De Las Heras JA, Sanchez S, Gonzalez-Porras JR, Gonzalez R, Mateos MV, et al. Medium-term results of percutaneous vertebroplasty in multiple myeloma. Eur J Haematol. 2006;77(1):7-13.
(52) Trumm C, Jakobs T, Pahl A, Stahl R, Helmberger T, Paprottka P, et al. CT fluoroscopy-guided percutaneous vertebroplasty in patients with multiple myeloma: analysis of technical results from 44 sessions with 67 vertebrae treated. Diag Interv Radiol. 2012;18(1):111-20.
(53) Bosnjakovic P, Ristic S, Mrvic M, Miljkovic AE, Vukicevic T, Marjanovic G, et al. Management of painful spinal lesions caused by multiple myeloma using percutaneous acrylic cement injection. Acta Chir Iugosl. 2009;56(4):153-8.
(54) McDonald RJ, Trout AT, Gray LA, Dispenzieri A, Thielen KR, Kallmes DF. Vertebroplasty in multiple myeloma: outcomes in a large patient series. AJNR Am J Neuroradiol. 2008;29(4):642-8.
(55) Garland P, Gishen P, Rahemtulla A. Percutaneous vertebroplasty to treat painful myelomatous vertebral deposits-long-term efficacy outcomes. Ann Hematol. 2011;90(1):95-100.
(56) Chen LH, Hsieh MK, Niu CC, Fu TS, Lai PL, Chen WJ. Percutaneous vertebroplasty for pathological vertebral compression fractures secondary to multiple myeloma. Arch Orthop Trauma Surg. 2012;132(6):759-64.
(57) Tseng YY, Lo YL, Chen LH, Lai PL, Yang ST. Percutaneous polymethylmethacrylate vertebroplasty in the treatment of pain induced by metastatic spine tumor. Surg Neurol. 2008;70(Suppl 1):S78-S83.
(58) Calmels V, Vallee JN, Rose M, Chiras J. Osteoblastic and mixed spinal metastases: evaluation of the analgesic efficacy of percutaneous vertebroplasty. AJNR Am J Neuroradiol. 2007;28(3):570-4.
(59) Anselmetti GC, Manca A, Montemurro F, Hirsch J, Chiara G, Grignani G, et al. Percutaneous vertebroplasty in multiple myeloma: prospective long-term follow-up in 106 consecutive patients. Cardiovasc Intervent Radiol. 2012;35(1):139-45.
(60) Tancioni F, Lorenzetti M, Navarria P, Nozza A, Castagna L, Gaetani P, et al. Vertebroplasty for pain relief and spinal stabilization in multiple myeloma. Neurol Sci. 2010;31(2):151-7.
(61) Diamond TH, Hartwell T, Clarke W, Manoharan A. Percutaneous vertebroplasty for acute vertebral body fracture and deformity in multiple myeloma: a short report. Br J Haematol. 2004;124(4):485-7.
(62) Tran Thang NN, Abdo G, Martin JB, Seium-Neberay Y, Yilmaz H, Verbist MC, et al. Percutaneous cementoplasty in multiple myeloma: a valuable adjunct for pain control and ambulation maintenance. Support Care Cancer. 2008;16(8):891-6.
(63) Chew C, Ritchie M, O'Dwyer PJ, Edwards R. A prospective study of percutaneous vertebroplasty in patients with myeloma and spinal metastases. Clin Radiol. 2011;66(12):1193-6.
(64) McDonald RJ, Gray LA, Cloft HJ, Thielen KR, Kallmes DF. The effect of operator variability and experience in vertebroplasty outcomes. Radiology. 2009;253(2):478-85.

(65) Masala S, Anselmetti GC, Marcia S, Massari F, Manca A, Simonetti G. Percutaneous vertebroplasty in multiple myeloma vertebral involvement. J Spinal Disord Tech. 2008;21(5):344-8.
(66) Simony A, Hansen EJ, Gaurilcikas M, Abildgaard N, Andersen MO. Pain reduction after percutaneous vertebroplasty for myeloma-associated vertebral fractures. Dan Med J. 2014;61(12):A4945.
(67) Burton AW, Reddy SK, Shah HN, Tremont-Lukats I, Mendel E. Percutaneous vertebroplasty—a technique to treat refractory spinal pain in the setting of advanced metastatic cancer: a case series. J Pain Symptom Manage. 2005;30(1):87-95.
(68) Chen L, Ni RF, Liu SY, Liu YZ, Jin YH, Zhu XL, et al. Percutaneous vertebroplasty as a treatment for painful osteoblastic metastatic spinal lesions. J Vasc Interv Radiol. 2011;22(4):525-8.
(69) Farrokhi MR, Nouraei H, Kiani A. The efficacy of percutaneous vertebroplasty in pain relief in patients with pathological vertebral fractures due to metastatic spinal tumors. Iran Red Crescent Med J. 2012;14(9).
(70) Kim AK, Jensen ME, Dion JE, Schweickert PA, Kaufmann TJ, Kallmes DF. Unilateral transpedicular percutaneous vertebroplasty: initial experience. Radiology. 2002;222(3):737-41.
(71) Kobayashi T, Arai Y, Takeuchi Y, Nakajima Y, Shioyama Y, Sone M, et al. Phase I/II clinical study of percutaneous vertebroplasty (PVP) as palliation for painful malignant vertebral compression fractures (PMVCF): JIVROSG-0202. Ann Oncol. 2009;20(12):1943-7.
(72) Lee B, Franklin I, Lewis JS, Coombes RC, Leonard R, Gishen P, et al. The efficacy of percutaneous vertebroplasty for vertebral metastases associated with solid malignancies. Eur J Cancer. 2009;45(9):1597-602.
(73) Mikami Y, Numaguchi Y, Kobayashi N, Fuwa S, Hoshikawa Y, Saida Y. Therapeutic effects of percutaneous vertebroplasty for vertebral metastases. Jpn J Radiol. 2011;29(3):202-6.
(74) Jang JS, Lee SH. Efficacy of percutaneous vertebroplasty combined with radiotherapy in osteolytic metastatic spinal tumors. J Neurosurg Spine. 2005;2(3):243-8.
(75) Lim BS, Chang UK, Youn SM. Clinical outcomes after percutaneous vertebroplasty for pathologic compression fractures in osteolytic metastatic spinal disease. J Korean Neurosurg Soc. 2009;45(6):369-74.
(76) Rasulova N, Lyubshin V, Djalalov F, Kim KH, Nazirova L, Ormanov N, et al. Strategy for bone metastases treatment in patients with impending cord compression or vertebral fractures: a pilot study. World J Nucl Med. 2011;10(1):14-9.
(77) Yang Z, Tan J, Zhao R, Wang J, Sun H, Wang X, et al. Clinical investigations on the spinal osteoblastic metastasis treated by combination of percutaneous vertebroplasty and (125)I seeds implantation versus radiotherapy. Cancer Biother Radiopharm. 2013;28(1):58-64.
(78) Yang Z, Yang D, Xie L, Sun Y, Huang Y, Sun H, et al. Treatment of metastatic spinal tumors by percutaneous vertebroplasty versus percutaneous vertebroplasty combined with interstitial implantation of 125I seeds. Acta Radiol. 2009;50(10):1142-8.
(79) Orgera G, Krokidis M, Matteoli M, Varano GM, La Verde G, David V, et al. Percutaneous vertebroplasty for pain management in patients with multiple myeloma: is radiofrequency ablation necessary? Cardiovasc Intervent Radiol. 2014;37(1):203-10.
(80) Yang Z, Tan J, Xu Y, Sun H, Xie L, Zhao R, et al. Treatment of MM-associated spinal fracture with percutaneous vertebroplasty (PVP) and chemotherapy. Eur Spine J. 2012;21(5):912-9.
(81) Erdem E, Akdol S, Amole A, Fryar K, Eberle RW. Radiofrequency-targeted vertebral augmentation for the treatment of vertebral compression fractures as a result of multiple myeloma. Spine (Phila Pa 1976). 2013;38(15):1275-81.
(82) Anchala PR, Irving WD, Hillen TJ, Friedman MV, Georgy BA, Coldwell DM, et al. Treatment of metastatic spinal lesions with a navigational bipolar radiofrequency ablation device: a multicenter retrospective study. Pain Physician. 2014;17(4):317-27.
(83) Gronemeyer DH, Schirp S, Gevargez A. Image-guided radiofrequency ablation of spinal tumors: preliminary experience with an expandable array electrode. Cancer J. 2002;8(1):33-9.
(84) Halpin RJ, Bendok BR, Sato KT, Liu JC, Patel JD, Rosen ST. Combination treatment of vertebral metastases using image-guided percutaneous radiofrequency ablation and vertebroplasty: a case report. Surg Neurol. 2005;63(5):469-74.

(85) Masala S, Roselli M, Massari F, Fiori R, Ursone A, Fossile E, et al. Radiofrequency heat ablation and vertebroplasty in the treatment of neoplastic vertebral body fractures. Anticancer Res. 2004;24(5B):3129-33.
(86) Nakatsuka A, Yamakado K, Maeda M, Yasuda M, Akeboshi M, Takaki H, et al. Radiofrequency ablation combined with bone cement injection for the treatment of bone malignancies. J Vasc Interv Radiol. 2004;15(7):707-12.
(87) Toyota N, Naito A, Kakizawa H, Hieda M, Hirai N, Tachikake T, et al. Radiofrequency ablation therapy combined with cementoplasty for painful bone metastases: initial experience. Cardiovasc Intervent Radiol. 2005;28(5):578-83.
(88) Berenson J, Pflugmacher R, Jarzem P, Zonder J, Schechtman K, Tillman JB, et al. 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(3):225-35.
(89) Korovessis P, Vardakastanis K, Vitsas V, Syrimpeis V. Is Kiva implant advantageous to balloon kyphoplasty in treating osteolytic metastasis to the spine? Comparison of 2 percutaneous minimal invasive spine techniques: a prospective randomized controlled short-term study. Spine (Phila Pa 1976). 2014;39(4):E231-9.
(90) Dudeney S, Lieberman IH, Reinhardt MK, Hussein M. Kyphoplasty in the treatment of osteolytic vertebral compression fractures as a result of multiple myeloma. J Clin Oncol. 2002;20(9):2382-7.
(91) Julka A, Tolhurst SR, Srinivasan RC, Graziano GP. Functional outcomes and height restoration for patients with multiple myeloma-related osteolytic vertebral compression fractures treated with kyphoplasty. J Spinal Disord Tech. 2014;27(6):342-6.
(92) Lane JM, Hong R, Koob J, Kiechle T, Niesvizky R, Pearse R, et al. Kyphoplasty enhances function and structural alignment in multiple myeloma. Clin Orthop Relat Res. 2004(426):49-53.
(93) Pflugmacher R, Kandziora F, Schroeder RJ, Melcher I, Haas NP, Klostermann CK. Percutaneous balloon kyphoplasty in the treatment of pathological vertebral body fracture and deformity in multiple myeloma: a one-year follow-up. Acta Radiol. 2006;47(4):369-76.
(94) Zou J, Mei X, Gan M, Yang H. Kyphoplasty for spinal fractures from multiple myeloma. J Surg Oncol. 2010;102(1):43-7.
(95) Chen G, Luo ZP, Zhang H, Nalajala B, Yang H. Percutaneous kyphoplasty in the treatment of painful osteoblastic metastatic spinal lesions. J Clin Neurosci. 2013;20(7):948-50.
(96) Konig MA, Jehan S, Balamurali G, Bierschneider M, Grillhosl A, Boszczyk BM. Kyphoplasty for lytic tumour lesions of the spine: prospective follow-up of 11 cases from procedure to death. Eur Spine J. 2012;21(9):1873-9.
(97) Pflugmacher R, Taylor R, Agarwal A, Melcher I, Disch A, Haas NP, et al. Balloon kyphoplasty in the treatment of metastatic disease of the spine: a 2-year prospective evaluation. Eur Spine J. 2008;17(8):1042-8.
(98) Vrionis FD, Hamm A, Stanton N, Sullivan M, Obadia M, Miguel RV. Kyphoplasty for tumor-associated spinal fractures. Tech Reg Anesth Pain Manag. 2005;9(1):35-9.
(99) Keynan O, Fisher CG, Vaccaro A, Fehlings MG, Oner FC, Dietz J, et al. Radiographic measurement parameters in thoracolumbar fractures: a systematic review and consensus statement of the spine trauma study group. Spine (Phila Pa 1976). 2006;31(5):E156-65.
(100) Jiang SD, Wu QZ, Lan SH, Dai LY. Reliability of the measurement of thoracolumbar burst fracture kyphosis with Cobb angle, Gardner angle, and sagittal index. Arch Orthop Trauma Surg. 2012;132(2):221-5.
(101) Kuklo TR, Polly DW, Owens BD, Zeidman SM, Chang AS, Klemme WR. Measurement of thoracic and lumbar fracture kyphosis: evaluation of intraobserver, interobserver, and technique variability. Spine (Phila Pa 1976). 2001;26(1):61-5; discussion 6.
(102) Street J, Lenehan B, Albietz J, Bishop P, Dvorak M, Fisher C. Intraobserver and interobserver reliability of measures of kyphosis in thoracolumbar fractures. Spine J. 2009;9(6):464-9.
(103) Gerszten PC, Germanwala A, Burton SA, Welch WC, Ozhasoglu C, Vogel WJ. Combination kyphoplasty and spinal radiosurgery: a new treatment paradigm for pathological fractures. J Neurosurg Spine. 2005;3(4):296-301.
(104) Kasperk C, Haas A, Hillengass J, Weiss C, Neben K, Goldschmidt H, et al. Kyphoplasty in patients with multiple myeloma a retrospective comparative pilot study. J Surg Oncol. 2012;105(7):679-86.

(105) Qian Z, Sun Z, Yang H, Gu Y, Chen K, Wu G. Kyphoplasty for the treatment of malignant vertebral compression fractures caused by metastases. J Clin Neurosci. 2011;18(6):763-7.
(106) Sandri A, Carbognin G, Regis D, Gaspari D, Calciolari C, Girardi V, et al. Combined radiofrequency and kyphoplasty in painful osteolytic metastases to vertebral bodies. Radiologia Medica. 2010;115(2):261-71.
(107) Hirsch AE, Jha RM, Yoo AJ, Saxena A, Ozonoff A, Growney MJ, et al. The use of vertebral augmentation and external beam radiation therapy in the multimodal management of malignant vertebral compression fractures. Pain Physician. 2011;14(5):447-58.
(108) Li Z, Ni CF, Chen L, Sun ZY, Chao Y, Zhao X, et al. Kyphoplasty versus vertebroplasty for the treatment of malignant vertebral compression fractures caused by metastases: a retrospective study. Chin Med J. 2014;127(8):1493-6.
(109) Erdem E, Samant R, Malak SF, Culp WC, Brown A, Peterson L, et al. Vertebral augmentation in the treatment of pathologic compression fractures in 792 patients with multiple myeloma. Leukemia. 2013;27(12):2391-3.
(110) Fourney DR, Schomer DF, Nader R, Chlan-Fourney J, Suki D, Ahrar K, et al. Percutaneous vertebroplasty and kyphoplasty for painful vertebral body fractures in cancer patients. J Neurosurg. 2003;98(1):21-30.
(111) Jha RM, Hirsch AE, Yoo AJ, Ozonoff A, Growney M, Hirsch JA. Palliation of compression fractures in cancer patients by vertebral augmentation: a retrospective analysis. J Neurointerv Surg. 2010;2(3):221-8.
(112) Mendoza TR, Koyyalagunta D, Burton AW, Thomas SK, Phan MHV, Giralt SA, et al. Changes in pain and other symptoms in patients with painful multiple myeloma-related vertebral fracture treated with kyphoplasty or vertebroplasty. J Pain. 2012;13(6):564-70.
(113) Bartolozzi B, Nozzoli C, Pandolfo C, Antonioli E, Guizzardi G, Morichi R, et al. Percutaneous vertebroplasty and kyphoplasty in patients with multiple myeloma. Eur J Haematol. 2006;76(2):180-1.
(114) Kose KC, Cebesoy O, Akan B, Altinel L, Dincer D, Yazar T. Functional results of vertebral augmentation techniques in pathological vertebral fractures of myelomatous patients. J Natl Med Assoc. 2006;98(10):1654-8.
(115) Basile A, Cavalli M, Fiumara P, Di Raimondo F, Mundo E, Caltabiano G, et al. Vertebroplasty in multiple myeloma with osteolysis or fracture of the posterior vertebral wall. Usefulness of a delayed cement injection. Skeletal Radiol. 2011;40(7):913-9.
(116) Hentschel SJ, Burton AW, Fourney DR, Rhines LD, Mendel E. Percutaneous vertebroplasty and kyphoplasty performed at a cancer center: refuting proposed contraindications. J Neurosurg Spine. 2005;2(4):436-40.
(117) Knight JR, Heran M, Munk PL, Raabe R, Liu DM. C-arm cone-beam CT: applications for spinal cement augmentation demonstrated by three cases. J Vasc Interv Radiol. 2008;19(7):1118-22.
(118) Georgy BA. Bone cement deposition patterns with plasma-mediated radio-frequency ablation and cement augmentation for advanced metastatic spine lesions. AJNR Am J Neuroradiol. 2009;30(6):1197-202.
(119) Prologo JD, Buethe J, Mortell K, Lee E, Patel I. Coblation for metastatic vertebral disease. Diagn Interv Radiol. 2013;19(6):508-15.
(120) van der Linden E, Kroft LJM, Dijkstra PDS. Treatment of vertebral tumor with posterior wall defect using image-guided radiofrequency ablation combined with vertebroplasty: preliminary results in 12 patients. J Vasc Interv Radiol. 2007;18(6):741-7.
(121) Li Y, Gu YF, Sun ZK, Wu CG, Li YD, Wang W, et al. Comparison of percutaneous vertebroplasty with and without interventional tumour removal for malignant vertebral compression fractures with symptoms of neurological compression. Eur Radiol. 2013;23(10):2754-63.
(122) Eleraky M, Papanastassiou I, Setzer M, Baaj AA, Tran ND, Vrionis FD. Balloon kyphoplasty in the treatment of metastatic tumors of the upper thoracic spine. J Neurosurg Spine. 2011;14(3):372-6.
(123) Alvarez L, Perez-Higueras A, Quinones D, Calvo E, Rossi RE. Vertebroplasty in the treatment of vertebral tumors: postprocedural outcome and quality of life. Eur Spine J. 2003;12(4):356-60.
(124) Appel NB, Gilula LA. Percutaneous vertebroplasty in patients with spinal canal compromise. AJR Am J Roentgenol. 2004;182(4):947-51.
(125) Mazumdar A, Gilula LA. Relief of radicular pain in metastatic disease by vertebroplasty. Acta Radiol. 2010;51(2):179-82.

(126) Sun G, Li L, Jin P, Liu XW, Li M. Percutaneous vertebroplasty for painful spinal metastasis with epidural encroachment. J Surg Oncol. 2014;110(2):123-8.
(127) Trumm CG, Pahl A, Helmberger TK, Jakobs TF, Zech CJ, Stahl R, et al. CT fluoroscopy-guided percutaneous vertebroplasty in spinal malignancy: technical results, PMMA leakages, and complications in 202 patients. Skeletal Radiol. 2012;41(11):1391-400.
(128) Woo JH, Park HS, Han JI, Kim DY. Vertebroplasty for the compression of the dorsal root ganglion due to spinal metastasis. Pain Physician. 2013;16(4):E405-10.
(129) Hentschel SJ, Rhines LD, Shah HN, Burton AW, Mendel E. Percutaneous vertebroplasty in vertebra plana secondary to metastasis. J Spinal Disord Tech. 2004;17(6):554-7.
(130) Shimony JS, Gilula LA, Zeller AJ, Brown DB. Percutaneous vertebroplasty for malignant compression fractures with epidural involvement. Radiology. 2004;232(3):846-53.
(131) Saliou G, Kocheida EM, Lehmann P, Depriester C, Paradot G, Le Gars D, et al. Percutaneous vertebroplasty for pain management in malignant fractures of the spine with epidural involvement. Radiology. 2010;254(3):882-90.
(132) Sun G, Jin P, Li M, Lu Y, Liu X, Li F, et al. Percutaneous vertebroplasty for pain management in spinal metastasis with epidural involvement. Technol Cancer Res Treat. 2011;10(3):267-74.
(133) Dalbayrak S, Onen MR, Yilmaz M, Naderi S. Clinical and radiographic results of balloon kyphoplasty for treatment of vertebral body metastases and multiple myelomas. J Clin Neurosci. 2010;17(2):219-24.
(134) Lim BG, Lee JY, Lee MK, Lee DK, Kim JS, Choi SS. Kyphoplasty for the treatment of vertebral compression fractures in a cancer patient with neurological deficits and anterior vertebral wall destruction. Pain Physician. 2011;14(6):539-44.
(135) Gu YF, Li YD, Wu CG, Sun ZK, He CJ. Safety and efficacy of percutaneous vertebroplasty and interventional tumor removal for metastatic spinal tumors and malignant vertebral compression fractures. AJR Am J Roentgenol. 2014;202(3):W298-305.
(136) Jenis LG, Dunn EJ, An HS. Metastatic disease of the cervical spine. a review. Clin Orthop Relat Res. 1999(359):89-103.
(137) Sherk HH. Lesions of the atlas and axis. Clin Orthop Relat Res. 1975;109:33-41.
(138) Rodriguez-Catarino M, Blimark C, Willen J, Mellqvist UH, Rodjer S. Percutaneous vertebroplasty at C2: case report of a patient with multiple myeloma and a literature review. Eur Spine J. 2007;16(Suppl 3):S242-9.
(139) Ishii T, Mukai Y, Hosono N, Sakaura H, Nakajima Y, Sato Y, et al. Kinematics of the upper cervical spine in rotation: in vivo three-dimensional analysis. Spine (Phila Pa 1976). 2004;29(7):E139-44.
(140) Takasaki H, Hall T, Oshiro S, Kaneko S, Ikemoto Y, Jull G. Normal kinematics of the upper cervical spine during the Flexion-Rotation Test—in vivo measurements using magnetic resonance imaging. Man Ther. 2011;16(2):167-71.
(141) Mont'Alverne F, Vallee JN, Guillevin R, Cormier E, Jean B, Rose M, et al. Percutaneous vertebroplasty for multiple myeloma of the cervical spine. Neuroradiology. 2009;51(4):237-42.
(142) Cianfoni A, Distefano D, Chin SH, Varma AK, Rumboldt Z, Bonaldi G. Percutaneous cement augmentation of a lytic lesion of C1 via posterolateral approach under CT guidance. Spine J. 2012;12(6):500-6.
(143) Anselmetti GC, Manca A, Montemurro F, Tutton S, Chiara G, Battistella M, et al. Vertebroplasty using transoral approach in painful malignant involvement of the second cervical vertebra (C2): a single-institution series of 25 patients. Pain Physician. 2012;15(1):35-42.
(144) Masala S, Anselmetti GC, Muto M, Mammucari M, Volpi T, Simonetti G. Percutaneous vertebroplasty relieves pain in metastatic cervical fractures. Clin Orthop Relat Res. 2011;469(3):715-22.
(145) Sun G, Wang LJ, Jin P, Liu XW, Li M. Vertebroplasty for treatment of osteolytic metastases at C2 using an anterolateral approach. Pain Physician. 2013;16(4):E427-E34.
(146) Lykomitros V, Anagnostidis KS, Alzeer Z, Kapetanos GA. Percutaneous anterolateral balloon kyphoplasty for metastatic lytic lesions of the cervical spine. Eur Spine J. 2010;19(11):1948-52.
(147) Yoon JY, Kim TK, Kim KH. Anterolateral percutaneous vertebroplasty at C2 for lung cancer metastasis and upper cervical facet joint block. Clin J Pain. 2008;24(7):641-6.

(148) Chen L, Su IC, Ni CF, Wang ZT. Percutaneous vertebroplasty performed with an 18-gauge needle for treatment of metastatic severe compression fracture of the cervical vertebral body. J Vasc Interv Radiol. 2014;25(9):1413-7.
(149) Huegli RW, Schaeren S, Jacob AL, Martin JB, Wetzel SG. Percutaneous cervical vertebroplasty in a multifunctional image-guided therapy suite: hybrid lateral approach to C1 and C4 under CT and fluoroscopic guidance. Cardiovasc Intervent Radiol. 2005;28(5):649-52.
(150) Seo SS, Lee DH, Kim HJ, Yoon JW, Kwon OS, Kim KH. Percutaneous vertebroplasty at C7 for the treatment of painful metastases—a case report. Korean J Anesthesiol. 2013;64(3):276-9.
(151) Hoffmann RT, Jakobs TF, Trumm C, Weber C, Helmberger TK, Reiser MF. Radiofrequency ablation in combination with osteoplasty in the treatment of painful metastatic bone disease. J Vasc Interv Radiol. 2008;19(3):419-25.
(152) Lane MD, Le HB, Lee S, Young C, Heran MK, Badii M, et al. Combination radiofrequency ablation and cementoplasty for palliative treatment of painful neoplastic bone metastasis: experience with 53 treated lesions in 36 patients. Skeletal Radiol. 2011;40(1):25-32.
(153) Basile A, Tsetis D, Cavalli M, Fiumara P, Di Raimondo F, Coppolino F, et al. Sacroplasty for local or massive localization of multiple myeloma. Cardiovasc Intervent Radiol. 2010;33(6):1270-7.
(154) Dehdashti AR, Martin JB, Jean B, Rufenacht DA. PMMA cementoplasty in symptomatic metastatic lesions of the S1 vertebral body. Cardiovasc Intervent Radiol. 2000;23(3):235-7.
(155) Sun G, Jin P, Li M, Liu XW, Li FD. Three-dimensional C-arm computed tomography reformation combined with fluoroscopic-guided sacroplasty for sacral metastases. Support Care Cancer. 2012;20(9):2083-8.
(156) Wee B, Shimal A, Stirling AJ, James SL. CT-guided sacroplasty in advanced sacral destruction secondary to tumour infiltration. Clin Radiol. 2008;63(8):906-12.
(157) Botton E, Edeline J, Rolland Y, Vauleon E, Le Roux C, Mesbah H, et al. Cementoplasty for painful bone metastases: a series of 42 cases. Med Oncol. 2012;29(2):1378-83.
(158) Hierholzer J, Anselmetti G, Fuchs H, Depriester C, Koch K, Pappert D. Percutaneous osteoplasty as a treatment for painful malignant bone lesions of the pelvis and femur. J Vasc Interv Radiol. 2003;14(6):773-7.
(159) Munk PL, Rashid F, Heran MK, Papirny M, Liu DM, Malfair D, et al. Combined cementoplasty and radiofrequency ablation in the treatment of painful neoplastic lesions of bone. J Vasc Interv Radiol. 2009;20(7):903-11.
(160) Fox MW, Onofrio BM. The natural history and management of symptomatic and asymptomatic vertebral hemangiomas. J Neurosurg. 1993;78(1):36-45.
(161) Pastushyn AI, Slin'ko EI, Mirzoyeva GM. Vertebral hemangiomas: diagnosis, management, natural history and clinicopathological correlates in 86 patients. Surg Neurol. 1998;50(6):535-47.
(162) Boriani S, Weinstein JN, Biagini R. Primary bone tumors of the spine. Terminology and surgical staging. Spine (Phila Pa 1976). 1997;22(9):1036-44.
(163) Enneking WF. A system of staging musculoskeletal neoplasms. Clin Orthop Relat Res. 1986;204:9-24.
(164) Fuwa S, Numaguchi Y, Kobayashi N, Saida Y. Percutaneous pediculoplasty for vertebral hemangioma involving the neural arch: a case report. Cardiovasc Intervent Radiol. 2008;31(1):189-92.
(165) Acosta FL Jr, Dowd CF, Chin C, Tihan T, Ames CP, Weinstein PR. Current treatment strategies and outcomes in the management of symptomatic vertebral hemangiomas. Neurosurgery. 2006;58(2):287-95.
(166) Prince EA, Ahn SH. Interventional management of vertebral body metastases. Semin Intervent Radiol. 2013;30(3):278-81.
(167) Berkefeld J, Scale D, Kirchner J, Heinrich T, Kollath J. Hypervascular spinal tumors: influence of the embolization technique on perioperative hemorrhage. AJNR Am J Neuroradiol. 1999;20(5):757-63.
(168) Jiang L, Liu XG, Yuan HS, Yang SM, Li J, Wei F, et al. Diagnosis and treatment of vertebral hemangiomas with neurologic deficit: a report of 29 cases and literature review. Spine J. 2014;14(6):944-54.
(169) Guarnieri G, Ambrosanio G, Vassallo P, Pezzullo MG, Galasso R, Lavanga A, et al. Vertebroplasty as treatment of aggressive and symptomatic vertebral hemangiomas: up to 4 years of follow-up. Neuroradiology. 2009;51(7):471-6.

(170) Hao J, Hu Z. Percutaneous cement vertebroplasty in the treatment of symptomatic vertebral hemangiomas. Pain Physician. 2012;15(1):43-9.
(171) Jones JO, Bruel BM, Vattam SR. Management of painful vertebral hemangiomas with kyphoplasty: a report of two cases and a literature review. Pain Physician. 2009;12(4):E297-303.
(172) Zapalowicz K, Skora P, Myslinski R, Karnicki F, Radek A. Balloon kyphoplasty for painful C-7 vertebral hemangioma. J Neurosurg Spine. 2008;8(5):458-61.
(173) Hadjipavlou A, Tosounidis T, Gaitanis I, Kakavelakis K, Katonis P. Balloon kyphoplasty as a single or as an adjunct procedure for the management of symptomatic vertebral haemangiomas. J Bone Joint Surg Br. 2007;89(4):495-502.
(174) Jian W. Symptomatic cervical vertebral hemangioma treated by percutaneous vertebroplasty. Pain Physician. 2013;16(4):E419-E25.
(175) Atalay B, Caner H, Yilmaz C, Altinors N. Sacral kyphoplasty for relieving pain caused by sacral hemangioma. Spinal Cord. 2006;44(3):196-9.
(176) Kruger R, Faciszewski T. Radiation dose reduction to medical staff during vertebroplasty: a review of techniques and methods to mitigate occupational dose. Spine (Phila Pa 1976). 2003;28(14):1608-13.
(177) Barragan-Campos HM, Vallee JN, Lo D, Cormier E, Jean B, Rose M, et al. Percutaneous vertebroplasty for spinal metastases: complications. Radiology. 2006;238(1):354-62.
(178) Corcos G, Dbjay J, Mastier C, Leon S, Auperin A, De Baere T, et al. Cement leakage in percutaneous vertebroplasty for spinal metastases: a retrospective evaluation of incidence and risk factors. Spine (Phila Pa 1976). 2014;39(5):E332-8.
(179) Tseng YY, Yang ST, Tu PH, Yang TC, Lo YL. Minimally invasive vertebroplasty in the treatment of pain induced by spinal metastatic tumor. Minim Invasive Neurosurg. 2008;51(5):280-4.
(180) Omidi-Kashani F, Ebrahimzadeh M, Peivandy M. Late onset sciatalgia as a rare complication of percutaneous vertebroplasty; a case report. Cases J. 2009;2(8).
(181) Ratliff J, Nguyen T, Heiss J. Root and spinal cord compression from methylmethacrylate vertebroplasty. Spine (Phila Pa 1976). 2001;26(13):E300-2.
(182) Chou CW, Teng CLJ, Hwang WL. Bone cement-induced pulmonary embolism in a myeloma patient. Br J Haematol. 2013;161(4):459.
(183) Lim KJ, Yoon SZ, Jeon YS, Bahk JH, Kim CS, Lee JH, et al. An intraatrial thrombus and pulmonary thromboembolism as a late complication of percutaneous vertebroplasty. Anesth Analg. 2007;104(4):924-6.
(184) Lim SH, Kim H, Kim HK, Baek MJ. Multiple cardiac perforations and pulmonary embolism caused by cement leakage after percutaneous vertebroplasty. Eur J Cardiothorac Surg. 2008;33(3):510-2.
(185) Alcibar J, Blanco R, Garcia K, Pena N, Fernandez L, Arriola J. Multiple fatal pulmonary embolism during polymethyl-methacrylate vertebroplasty with successful percutaneous retrieval of a large cement fragment. Rev Esp Cardiol. 2012;65(6):571-2.
(186) Abdelrahman H, Siam AE, Shawky A, Ezzati A, Boehm H. Infection after vertebroplasty or kyphoplasty. a series of nine cases and review of literature. Spine J. 2013;13(12):1809-17.
(187) Chen YJ, Chang GC, Chen WH, Hsu HC, Lee TS. Local metastases along the tract of needle: a rare complication of vertebroplasty in treating spinal metastases. Spine (Phila Pa 1976). 2007;32(21):E615-E8.
(188) Cruz JP, Sahgal A, Whyne C, Fehlings MG, Smith R. Tumor extravasation following a cement augmentation procedure for vertebral compression fracture in metastatic spinal disease. J Neurosurg Spine. 2014;21(3):372-7.
(189) Mahadevia AA, Weiland D, Kvamme P, Murphy KPJ, Srinivas A, Wyse G. Polymethylmethacrylate contact dermatitis after vertebroplasty. J Vasc Interv Radiol. 2007;18(4):585.
(190) Mattei TA, Mendel E, Bourekas EC. Vertebral compression fractures in patients under treatment with denosumab: a contraindication for percutaneous vertebroplasty? Spine J. 2014;14(6):e29-35.
(191) Amoretti N, Hovorka I, Marcy PY, Grimaud A, Brunner P, Bruneton JN. Aortic embolism of cement: a rare complication of lumbar percutaneous vertebroplasty. Skeletal Radiol. 2007;36(7):685-7.

(192) Chen CY, Cheng WE, Lin CH, Chen SC, Shih CM. Tadpoles in the lungs. Cement pulmonary embolism complicating vertebroplasty of spinal metastasis. Am J Respir Crit Care Med. 2014;190(3):340-1.
(193) Lee CH, Lee JW, Hyun SJ, Kim KJ, Jahng TA, Kim HJ. Needle-tract seeding after percutaneous vertebroplasty: a case report. Spine (Phila Pa 1976). 2014;39(12):E752-6.
(194) Mroz TE, Yamashita T, Davros WJ, Lieberman IH. Radiation exposure to the surgeon and the patient during kyphoplasty. J Spinal Disord Tech. 2008;21(2):96-100.
(195) Huber FX, McArthur N, Tanner M, Gritzbach B, Schoierer O, Rothfischer W, et al. Kyphoplasty for patients with multiple myeloma is a safe surgical procedure: results from a large patient cohort. Clin Lymphoma Myeloma. 2009;9(5):375-80.
(196) Li K, Yao B Jr. Research on safety of single-stage multisegmental thoracolumbar percutaneous balloon vertebroplasty. J Spinal Disord Tech. 2014;27(6):E205-11.
(197) Elshinawy A, Boland P, White DA. A patient with cement pulmonary embolus following kyphoplasty. J Respir Dis. 2005;26(1):23-4.
(198) Esmende SM, Daniels AH, Palumbo MA. Spinal cord compression after percutaneous kyphoplasty for metastatic compression fracture. Spine J. 2013;13(7):831-2.
(199) Tran I, Gerckens U, Remig J, Zintl G, Textor J. First report of a life-threatening cardiac complication after percutaneous balloon kyphoplasty. Spine (Phila Pa 1976). 2013;38(5):E316-8.
(200) Langdon J, Bernard J, Molloy S. Prophylactic stabilization of vertebral body metastasis at risk of imminent fracture using balloon kyphoplasty. Spine (Phila Pa 1976). 2009;34(13):E469-72.
(201) Sun G, Jin P, Li M, Liu X, Li F, Yu AKF, et al. Percutaneous vertebroplasty for treatment of osteolytic metastases of the C2 vertebral body using anterolateral and posterolateral approach. Technol Cancer Res Treat. 2010;9(4):417-22.
(202) Hentschel SJ, Rhines LD, Shah HN, Burton AW, Mendel E. Percutaneous vertebroplasty in vertebra plana secondary to metastasis. J Spinal Disord Tech. 2004;17(6):554-7.
(203) Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain. 2008;9(2):105-21.
(204) Te Boveldt N, Vernooij-Dassen M, Burger N, Ijsseldijk M, Vissers K, Engels Y. Pain and its interference with daily activities in medical oncology outpatients. Pain Physician. 2013;16(4):379-89.
(205) Chow E, Hoskin P, Mitera G, Zeng L, Lutz S, Roos D, et al. Update of the international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. Int J Radiat Oncol Biol Phys. 2012;82(5):1730-7.
(206) Chow E, Wu JS, Hoskin P, Coia LR, Bentzen SM, Blitzer PH. International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. Radiother Oncol. 2002;64(3):275-80.
(207) Wade DT, Collin C. The Barthel ADL Index: a standard measure of physical disability? Int Disabil Stud. 1988;10(2):64-7.
(208) Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. J Clin Oncol. 1984;2(3):187-93.
(209) Yates JW, Chalmer B, McKegney FP. Evaluation of patients with advanced cancer using the Karnofsky performance status. Cancer. 1980;45(8):2220-4.
(210) Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.
(211) Barrett B, Brown D, Mundt M, Brown R. Sufficiently important difference: expanding the framework of clinical significance. Med Decis Making. 2005;25(3):250-61.
(212) Ringash J, O'Sullivan B, Bezjak A, Redelmeier DA. Interpreting clinically significant changes in patient-reported outcomes. Cancer. 2007;110(1):196-202.
(213) Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials. 1989;10(4):407-15.
(214) Buccheri G, Ferrigno D, Tamburini M. Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution. Eur J Cancer. 1996;32A(7):1135-41.

(215) Chang VT, Hwang SS, Feuerman M. Validation of the Edmonton Symptom Assessment Scale. Cancer. 2000;88(9):2164-71.
(216) Dudgeon DJ, Harlos M, Clinch JJ. The Edmonton Symptom Assessment Scale (ESAS) as an audit tool. J Palliat Care. 1999;15(3):14-9.
(217) Hui D, Shamieh O, Paiva CE, Perez-Cruz PE, Kwon JH, Muckaden MA, et al. Minimal clinically important differences in the Edmonton Symptom Assessment Scale in cancer patients: a prospective, multicenter study. Cancer. 2015;121(17):3027-35.
(218) Oldenmenger WH, de Raaf PJ, de Klerk C, van der Rijt CC. Cut points on 0-10 numeric rating scales for symptoms included in the Edmonton Symptom Assessment Scale in cancer patients: a systematic review. J Pain Symptom Manage. 2013;45(6):1083-93.
(219) Rees E, Hardy J, Ling J, Broadley K, A'Hern R. The use of the Edmonton Symptom Assessment Scale (ESAS) within a palliative care unit in the UK. Palliat Med. 1998;12(2):75-82.
(220) Fairbank JC. Oswestry Disability Index. J Neurosurg Spine. 2014;20(2):239-41.
(221) Fairbank JC, Pynsent PB. The Oswestry Disability Index. Spine (Phila Pa 1976). 2000;25(22):2940-52; discussion 52.
(222) Roland M, Morris R. A study of the natural history of back pain. Part I: development of a reliable and sensitive measure of disability in low-back pain. Spine (Phila Pa 1976). 1983;8(2):141-4.
(223) Trout AT, Kallmes DF, Gray LA, Goodnature BA, Everson SL, Comstock BA, et al. Evaluation of vertebroplasty with a validated outcome measure: the Roland-Morris Disability Questionnaire. AJNR Am J Neuroradiol. 2005;26(10):2652-7.
(224) Stratford PW, Binkley JM, Riddle DL, Guyatt GH. Sensitivity to change of the Roland-Morris Back Pain Questionnaire: part 1. Phys Ther. 1998;78(11):1186-96.
(225) Meade TW, Dyer S, Browne W, Frank AO. Randomised comparison of chiropractic and hospital outpatient management for low back pain: results from extended follow up. BMJ. 1995;311(7001):349-51.
(226) Roland M, Fairbank J. The Roland-Morris Disability Questionnaire and the Oswestry Disability Questionnaire. Spine (Phila Pa 1976). 2000;25(24):3115-24.
(227) Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.
(228) Filis AK, Aghayev KV, Doulgeris JJ, Gonzalez-Blohm SA, Vrionis FD. Spinal neoplastic instability: biomechanics and current management options. Cancer Control. 2014;21(2):144-50.
(229) Fisher CG, DiPaola CP, Ryken TC, Bilsky MH, Shaffrey CI, Berven SH, et al. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. Spine (Phila Pa 1976). 2010;35(22):E1221-9.
(230) Denis F. The three column spine and its significance in the classification of acute thoracolumbar spinal injuries. Spine (Phila Pa 1976). 1983;8(8):817-31.
(231) Black DM, Palermo L, Nevitt MC, Genant HK, Christensen L, Cummings SR. Defining incident vertebral deformity: a prospective comparison of several approaches. The Study of Osteoporotic Fractures Research Group. J Bone Miner Res. 1999;14(1):90-101.
(232) McKiernan F, Faciszewski T, Jensen R. Reporting height restoration in vertebral compression fractures. Spine (Phila Pa 1976). 2003;28(22):2517-21.
(233) McKiernan F, Jensen R, Faciszewski T. The dynamic mobility of vertebral compression fractures. J Bone Miner Res. 2003;18(1):24-9.
(234) Gertzbein SD. Scoliosis Research Society. Multicenter spine fracture study. Spine (Phila Pa 1976). 1992;17(5):528-40.
(235) McAfee PC, Yuan HA, Lasda NA. The unstable burst fracture. Spine (Phila Pa 1976). 1982;7(4):365-73.
(236) Krompinger WJ, Fredrickson BE, Mino DE, Yuan HA. Conservative treatment of fractures of the thoracic and lumbar spine. Orthop Clin North Am. 1986;17(1):161-70.
(237) Milne JS, Lauder IJ. Age effects in kyphosis and lordosis in adults. Ann Hum Biol. 1974;1(3):327-37.
(238) Goh S, Price RI, Leedman PJ, Singer KP. A comparison of three methods for measuring thoracic kyphosis: implications for clinical studies. Rheumatology (Oxford). 2000;39(3):310-5.

(239) Anselmetti GC, Manca A, Tutton S, Chiara G, Kelekis A, Facchini FR, et al. Percutaneous vertebral augmentation assisted by PEEK implant in painful osteolytic vertebral metastasis involving the vertebral wall: experience on 40 patients. Pain Physician. 2013;16(4):E397-404.
(240) Sun H, Nemecek AN. Optimal management of malignant epidural spinal cord compression. Hematol Oncol Clin North Am. 2010;24(3):537-51.

About Health Quality Ontario

Health Quality Ontario is the provincial advisor on the quality of health care. We are motivated by a single-minded purpose: **Better health for all Ontarians.**

Who We Are.

We are a scientifically rigorous group with diverse areas of expertise. We strive for complete objectivity, and look at things from a vantage point that allows us to see the forest and the trees. We work in partnership with health care providers and organizations across the system, and engage with patients themselves, to help initiate substantial and sustainable change to the province's complex health system.

What We Do.

We define the meaning of quality as it pertains to health care, and provide strategic advice so all the parts of the system can improve. We also analyze virtually all aspects of Ontario's health care. This includes looking at the overall health of Ontarians, how well different areas of the system are working together, and most importantly, patient experience. We then produce comprehensive, objective reports based on data, facts and the voice of patients, caregivers and those who work each day in the health system. As well, we make recommendations on how to improve care using the best evidence. Finally, we support large scale quality improvements by working with our partners to facilitate ways for health care providers to learn from each other and share innovative approaches.

Why It Matters.

We recognize that, as a system, we have much to be proud of, but also that it often falls short of being the best it can be. Plus certain vulnerable segments of the population are not receiving acceptable levels of attention. Our intent at Health Quality Ontario is to continuously improve the quality of health care in this province regardless of who you are or where you live. We are driven by the desire to make the system better, and by the inarguable fact that better has no limit.

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About OHTAS

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