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Indications, contraindications, outcomes, and complications of vertebral augmentation procedures are discussed.

Controversial Issues in Kyphoplasty and Vertebroplasty in Malignant Vertebral Fractures

Ioannis D. Papanastassiou, MD, Andreas K. Filis, MD,
Maria A. Gerochristou, MD, and Frank D. Vrionis, MD, PhD

Background: *Kyphoplasty (KP) and vertebroplasty (VP) have been successfully employed in the treatment of pathological vertebral fractures.*

Methods: *A critical review of the medical literature was performed and controversial issues were analyzed.*

Results: *Evidence supports KP as the treatment of choice to control fracture pain and the possible restoration of sagittal balance, provided that no overt instability or myelopathy is present, the fracture is painful and other pain generators have been excluded, and positive radiological findings are present. Unilateral procedures yield similar results to bilateral ones and should be pursued whenever feasible. Biopsy should be routinely performed and 3 to 4 levels may be augmented in a single operation. Higher cement filling appears to yield better results. Radiotherapy is complementary with KP and VP but must be individualized.*

Conclusions: *In cases of painful cancer fractures, if overt instability or myelopathy is not present, unilateral KP should be pursued, whenever feasible, followed by radiotherapy. The technological advances in hardware and biomaterials, as well as combining KP with other modalities, will help ensure a safe and more effective procedure.*

From the Neuro-Oncology Program at the H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida (IDP, AKF, FDV), and the Departments of Neurosurgery and Orthopedics at the University of South Florida Morsani College of Medicine, Tampa, Florida (IDP, AKF, FDV), the Department of Orthopedics at the General Oncological Hospital Kifisias Agioi Anargyroi, Athens, Greece (IDP), and the University of Athens Andreas Syngros Hospital, Athens, Greece (MAG).

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Address correspondence to Ioannis D. Papanastassiou, MD, Neuro-Oncology Program, Moffitt Cancer Center, 12902 Magnolia Drive, WCB-NEURO PROG, Tampa, FL 33612. E-mail: ioannis.papanastassiou@gmail.com

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Introduction

The skeletal system is the third most common site of metastases following the lung and liver, while breast, prostate, lung, bladder, and thyroid cancers show a predilection for bone involvement.^{1,2} Spine involvement leads to painful vertebral compression fractures (VCFs), epidural cord compression, or both.³⁻⁵ Vertebral augmentation procedures (VAPs) include kyphoplasty (KP) or vertebroplasty (VP), and have been employed in the treatment of those fractures in the setting of osteoporotic⁶ or neoplastic disease.⁷ Apart from nonrandomized trials, high-level evidence exists from the multicenter, randomized Cancer Patient Fracture Evaluation (CAFE) study of patients with malignant fractures being treated with KP (Table 1).⁸⁻²⁴

In this review, we aim to investigate the indications, contraindications, outcomes, and complications of VAPs, the relative superiority of KP compared with VP, technical issues, and the relation of VAPs with radiotherapy (RT) and other treatment modalities.

Indications

In cases of epidural spinal cord compression or vertebral fractures that require stabilization and open surgery, the estimated survival rate plays a critical role in the decision-making process; patients expected to live fewer than 6 months are not generally considered open surgical candidates.²⁵⁻²⁷ Various scores have been developed for estimating rates of patient survivorship, with those proposed by Tomita et al²⁶ and Tokuhashi et al²⁷ being the most commonly used, although the judgment of the health care professional is often the most accurate predictor.²⁸ However, in the case of VAPs, the expected survivorship rate does not dictate

Table 1. — Selected Studies Comparing KP and VP for the Management of Malignant Vertebral Fractures

Study	Baseline Characteristics	Pain Relief	Disability/QOL	Kyphotic Angle/VH	Cement Leakage	New No.	Conclusions
Vrionis 2005 ¹⁹	41 patients 62 KP	95% partial or substantial pain relief	NR	6-degree correction with minimal loss of height at 1 year	13%	NR	KP safe, beneficial in painful compression fractures
Köse 2006 ¹⁵	34 patients 18 VP vs 16 KP 1-year FU MM cohort	VP and KP showed pain reduction at 6 months in favor of KP	Improved No further data	NR	None	No adjacent fracture	VP and BKP effective in improving QOL and pain
Pflugmacher 2008 ^{8,a}	65 patients 99 KP 2-year FU	VAS Significant improvement ≤ 2 years	ODI, SF36 scores significantly improved ≤ 2 years	Significant improvement ≤ 1 year	12.1%	8%	KP safe, provides immediate, long-term pain and disability improvement
Dudney 2002 ^{8,a}	18 patients 55 KP 7-month FU (mean)	Pain substantially reduced in all patients	SF36 score significantly improved	34% VH restoration	4%	NR	KP efficacious in MM, leads to early pain and disability improvement and height restoration
Berenson 2011 ^{24,b}	134 patients 65 KP vs 52 NSM 1-year FU Crossover after 1 month (38 patients)	VAS Significant difference in favor of KP (1 month) sustained until 1 year	RMDQ/SF-36 Significant difference in favor of KP (1 month) sustained until 1 year	Significant difference in favor of KP for midthoracic and transition zone fractures	NR	No difference (12 of 62 in KP vs 8 of 47 in NSM)	For painful VCFs KP is an effective and safe treatment, rapidly reduces pain, improves function
Kasperk 2012 ¹³	73 patients 35 KP vs 18 RT vs 20 medical treatment 2-year FU MM cohort	VAS KP superior to RT or medical treatment	ODI Significant improvement only in KP	Only KP group improved Height loss in RT and medical treatment groups	30.6%	KP (2%) and RT (4.8%) superior to medical treatment (9.7%)	KP more effective than RT or medical treatment in pain relief, disability improvement and incidence of new fractures

Eleraky 2011 ⁹	14 patients 30 KP (upper T-spine) 16-month FU (≥ 1 year)	VAS Significant improvement	ODI Significant improvement	NS	10%	No adjacent fracture	KP safe and efficient in upper T-spine
Mendoza 2012 ²⁰	79 patients 22 KP 37 VP 20 KP/VP hybrid MM cohort	BPI Significant improvement	ESAS Other symptoms reduced (anxiety, fatigue, depression), except insomnia	NR	NR	NR	Pain reduction after KP/VP was positively associated with reduction in other cancer-related symptoms
Burton 2011 ²¹	407 patients 156 KP 262 VP 111 KP/VP hybrids	BPI Significant improvement	ESAS Significant improvement in anxiety, fatigue, depression No significant improvement in insomnia, nausea	NR	VP: 24% KP: 19% (NS)	24% (new fracture) 18% (adjacent fracture)	KP/VP have good efficacy and low complication rate in painful cancer-related fractures
Lane 2004 ^{16,a}	19 patients 46 KP MM cohort	NR	ODI Significant improvement in majority of patients	Significant improvement in VH	26.3%	NR	KP is safe in patients with MM Efficacy comparable with osteoporotic-related fractures
Fourney 2003 ²²	56 patients 32 KP 65 VP	VAS Significant improvement ≤ 1 year Marked or complete pain relief in 84%	NR	KP: VH restoration = 42% (± 21%)	KP: None VP: 9.2%	NR	KP and VP are safe, effective for pain control (lasting effect) in cancer-related fractures
Erdem 2013 ¹⁰	41 patients 48 KP 6-month FU MM cohort	VAS Significant improvement ≤ 6 months	Activity assessment Significant improvement ≤ 6 months	NR	2%	NR	Radiofrequency KP has optimum safety and efficacy in the treatment of malignant VCFs
König 2012 ^{4,a}	11 patients 23 KP 1.4-year FU (mean) or death	VAS Improvement (4.5 points; statistics NR)	ECOG activity score Improvement (statistics NR)	NR	8.7%	4.3% (adjacent fracture)	Quick pain relief favors KP as effective and safe palliative tool
Hirsch 2011 ²³	201 patients 316 levels (KP/VP) 6-month FU (median)	VAS Significant improvement No difference regarding sequencing RT or VAPs	RMDQ Significant improvement	NR	NR	NR	KP/VP provide excellent palliation in malignant VCFs Sequence of KP/VP vs RT does not influence results
Papanastasiou in press ¹⁷	69 patients 105 KP (51 bilateral vs 54 unilateral) ≥ 3-month FU MM cohort	VAS Significant improvement No difference between bilateral/unilateral	NR	Significant improvement No difference between bilaterala/unilateral	18%	NR	KP provides significant pain relief, VH restoration No difference between bilateral/unilateral procedure

^aProspective study.

^bRandomized control trial.

BKP = balloon kyphoplasty, BPI = Brief Pain Inventory, ECOG = Eastern Cooperative Oncology Group, ESAS = Edmonton Symptom Assessment Scale, FU = follow-up, KP = kyphoplasty, MM = multiple myeloma, NR = not reported, NS = not significant, NSM = nonsurgical management, ODI = Oswestry Disability Index, QOL = quality of life, RMDQ = Roland Morris Disability Questionnaire, RT = radiotherapy, SF36 = Short Form-36, VAP = vertebral augmentation procedure, VAS = visual analog scale, VCF = vertebral compression fracture, VH = vertebral height, VP = vertebroplasty.

treatment options. If overt instability does not exist (the Spinal Instability Neoplastic Score is used to determine spinal stability²⁹), KP/VP may be performed for pain control. The most important criteria are^{7,12}:

- The intensity of pain must be at least a 4 out of 10 (on a 0 to 10 pain scale).
- Clinical examination should correspond with imaging studies (ie, exclude other pain generators unrelated to the fracture).¹¹
- Edema must be seen on the involved vertebrae on magnetic resonance imaging (MRI; short T1 inversion recovery images). If MRI cannot be performed, then the bone scan must be positive, indicating a recent neoplastic process.^{9,10,12,16} However, as discussed further below, good results have been obtained in subacute or chronic fractures; therefore, in carefully selected cases, VAPs are still valuable regardless of status on MRI.³⁰

Although kyphotic deformity may be partially restored with KP,^{8,9,12,13,17,18,24} this is not considered a primary indication per se, either in osteoporotic- or cancer-related fractures. Particularly in patients with cancer, kyphosis reduction is frequently without significant clinical implications, because a long-term survival rate is not anticipated, and pain reduction, early mobilization, and an improvement in quality of life are the goals of treatment.

Contraindications

Table 2 summarizes absolute and relative contraindications.¹² Overt instability and cord compression with neurological symptoms are the most established contraindications. In such cases, vertebral augmentation can be combined with laminectomy, with or without instrumentation.³¹ Radiographic cord compression is considered by many to be a relative contraindication (without myelopathy),^{9,32,33} and our approach is to perform VAPs under neuromonitoring or local anesthesia with an anterior delivery of cement.⁹ The same is true for upper thoracic or cervical spine locations.^{9,34,35}

Table 2. — Summary of Absolute and Relative Contraindications for Kyphoplasty/Vertebroplasty in Malignant Vertebral Fractures¹²

Overt instability
Cord compression with clinical myelopathy
Infection at the fracture site
Bleeding disorder
Low platelet count
Contraindications to local/general anesthesia
Allergy to contrast medium
Data from reference 12

Adverse Events

Pain relief of approximately 4 to 5 points on a visual analog scale has been described in previous studies and should be anticipated in properly selected patients.^{6,10,14,17,24,36,37} The best results are seen with acute or hyperacute fractures^{6,24}; however, satisfactory results have also been reported in patients with older fractures.²⁴ The initial hypothesis for the possible mechanism of pain resolution was that polymethyl methacrylate (PMMA) polymerization causes an exothermic reaction, thus inducing ablation of intraosseous nerve endings and pain fibers or direct toxicity from the monomer.³⁸⁻⁴¹ However, other studies refuted this notion because minimal osteonecrosis has been seen,^{42,43} no evidence exists of intraosseous neural tissue necrosis,⁴³ and similar results have been replicated following an injection of calcium phosphate cement, which crystallizes at body temperature.⁴⁴ It is more likely that the cement acts as a means of internal fixation, either in the form of a solid, hard ball (KP) or interdigitation in the bony trabeculae (VP).⁴² Mechanical stability may prevent pain fiber irritation in the periosteum, bone marrow, and the haversian system.⁴⁴

Height restoration up to 34% to 38% of preoperative values and sagittal alignment improvement of 3 to 7.6 degrees have both been described.^{8,9,11-13,16-18,24} These changes have established beneficial effects, including reducing flexion moments of affected vertebrae, encouraging upright posture, and reducing subsequent fractures.^{45,46}

Adjacent/subsequent fractures may occur,^{18,24} but the incidence is similar²⁴ or reduced compared with conservative management.^{6,13,36,47} Leakage of cement into the disk space,⁴⁸⁻⁵⁰ osteoporosis, and the magnitude of corrected sagittal alignment predisposes the patient to adjacent fractures,^{47,49,50} which can be addressed by performing prophylactic VP/KP.^{51,52}

Numerous complications have been noted in the literature, with fatal penetration of vital structures (eg, lungs, pericardium, aorta), and PMMA has been found throughout the human body, including in segmental arteries, the foot (dorsalis pedis artery), heart, and lungs.⁵³⁻⁵⁷ However, the rate of serious complications is low, with the most common complication being asymptomatic PMMA extravasation, which, in general, occurs less frequently in KP than VP.^{6,9,12,18}

KP vs VP

Controversy exists regarding the value of VP after Buchbinder et al⁵⁸ and Kallmes et al⁵⁹ showed no benefit of VP over a sham procedure, leading the American Academy of Orthopaedic Surgeons to advise against the use of VP.⁶⁰ Within the setting of cancer, 1 small study by Köse et al¹⁵ revealed an advantage of KP over VP in pain control; overall, however, the authors considered both procedures successful. The

randomized CAFE trial strongly favored KP over non-surgical management.²⁴ Because no level 1 or 2 studies exist for VP, a safe profile has been proven with KP (ie, a low incidence of PMMA extravasation), and more potential exists for kyphosis restoration with KP, we favor KP over VP, particularly in cases of vertebra plana.^{7,15} However, VP may be performed in patients with nonindex fractures or nondeformed vertebrae; it may also be considered to reduce implant cost, particularly with ultra-high viscosity cements.^{61,62}

Technical Considerations

Bilateral vs Unilateral Procedures

Traditionally, KP and VP have been performed with bilateral pedicle cannulation⁶³; however, surgeons now use extrapedicular approaches,^{34,64,65} allowing the procedure to be unilaterally performed. Growing evidence suggests that the unilateral and bilateral approaches are equivalent whenever the former is technically feasible in terms of pain control or kyphotic reduction.^{17,66-68} For patients with cancer-related fractures in whom pain relief is the main goal and multiple levels have been augmented, we recommend unilateral VAPs as the gold standard because they reduce operative time and radiation exposure. MRI may determine which levels are amenable for unilateral cannulation.¹⁷ A role still exists for bilateral VAPs, including when the unilateral approach appears hazardous from preoperative planning, when central placement of the balloon cannot be accomplished, or in cases of severely crushed vertebrae in which the lateral pillars of the vertebrae are better preserved than the middle portion.¹⁷

Technical Advances

Ultra-high viscosity cements and special cement delivery instruments allow for slow and uniform PMMA filling, thus reducing the rate of cement extravasation.^{61,62} Curved curettes allow the procedures to be unilaterally performed.^{18,62} Novel devices utilized for cavity creation, rather than the traditional balloons, show promising results.^{18,61,62,69}

Levels and Cement

Three to 4 levels may be augmented without a significant increase in the operative time or morbidity rate.^{12,17} In addition to the index fracture, prophylactic augmentation may be performed in “sandwich” vertebrae (ie, when both adjacent vertebrae have been augmented), if PMMA extravasation occurs in the disk space, or in tumor-infiltrated, nondeformed vertebrae to prevent future fracture.^{7,51,52}

The optimal amount of cement has not been established. Biomechanical and clinical studies suggest that smaller PMMA volumes may suffice to restore body stiffness and strength and achieve good clinical

results.^{70,71} However, other authors propose a larger amount of cement filling for better biomechanical behavior,^{72,73} and growing evidence suggests that larger cement volumes yield superior outcomes. For example, Roder et al⁷⁴ found that the most important predictor for pain alleviation was cement volume following a dose-dependent pattern. Recent studies report that cement volume is of the utmost importance for correcting deformities and maintaining vertebral height.^{75,76} We share the same experience and try to achieve maximum filling in a safe manner, particularly when the anterior column is substantially compromised, if concomitant percutaneous screw fixation is performed,⁷⁷ or VAPs are performed in combination with laminectomy (without instrumentation), leading to loss of the posterior tension band and further instability.

Biopsy

Biopsy should be routinely performed because it does not add to the morbidity or procedure length; moreover, biopsy can reveal information that can help dictate future treatment, such as confirming the presence of metastasis or revealing a new neoplasm.^{7,78}

VAP vs RT

VAP and RT modalities are complementary. RT destroys tumor cells but also has known detrimental effects on bone cell biology,^{79,80} leading to higher incidences of vertebral fractures ($\leq 40\%$ in radiosurgical cases).^{81,82} VAPs strengthen the vertebral body and ameliorate this effect of radiation while also exerting pain control.^{7,46} The therapeutic sequence has not been determined from previous studies and does not affect pain palliation²³; therefore, its use should be determined on an individualized basis.⁷ Kasperk et al¹³ conducted the only retrospective study to date comparing RT with KP in a cohort of patients with multiple myeloma. They found that KP was superior to RT in terms of pain and disability improvement, new fractures, and vertebral height restoration.

Combining VAPs and Other Modalities

VAPs can be combined with other treatment modalities. Conventional RT has been the cornerstone of therapy for alleviating pain and preventing local disease progression. With the advent of stereotactic radiosurgery, the spinal cord may be spared from unnecessary irradiation.

CyberKnife (Accuray, Sunnyvale, California) is a safe and effective salvage therapy in patients who have received RT, with some authors suggesting that it may be combined with KP as a treatment paradigm.^{83,84}

Radiofrequency ablation has been coupled with KP for the treatment of pathological spinal fractures. To reduce pain, radiofrequency destroys the tumor cells and the sensory nerve fibers in the periosteum.

By contrast, PMMA has a toxic effect on neoplastic cells due to the monomer toxicity and the exothermic reaction from the polymerization process. Studies have reported an improvement in visual analog scale and Oswestry Disability Index scores after combining KP with ablation over a single augmentation.⁸⁵

Cryotherapy is a tumoricidal method that may be used in conjunction with VAPs if a probe-based cryosurgical system is available.⁸⁶ In cases in which gross instability is present and KP or VP alone is deemed insufficient from a biomechanical standpoint, percutaneous screw fixation can offer further stability.⁷⁷

Conclusions

In cases of painful malignant fractures, unilateral kyphoplasty should be employed, whenever feasible, if overt instability or myelopathy does not exist. It is complementary with radiotherapy and may be combined with other modalities, such as ablation, cryosurgery, and percutaneous screws. The technological advances in hardware, delivery systems, and biomaterials, as well as combining kyphoplasty with other modalities, will help ensure a safe and more effective procedure.

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