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Percutaneous Minimally Invasive Techniques in the Treatment of Spinal Metastases

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Opinion Statement

Spinal metastases are a common and morbid condition in America. Of the 1.6 million new cases of cancer estimated to be diagnosed in the USA in 2015, approximately 5–10 % will develop spinal metastases. This number is expected to increase as the life expectancy of cancer patients increases. Patients with osteolytic spinal metastases experience severe and often debilitating pain, which significantly reduces quality of life. Due to the morbidity of open surgery, particularly in oncologic patients, the treatment paradigm has shifted towards minimally invasive therapy. The advent and evolution of percutaneous treatments of spinal metastases has shown progressive success in reducing pain, improving function, and providing mechanical stability. There are various currently available interventions including vertebroplasty, vertebral augmentation, and coblation and radiofrequency ablation systems. For more complex spinal metastases, combined treatments including vertebral augmentation in conjunction with radiofrequency ablation, external beam radiation, and the novel treatment of intraoperative radiotherapy are also available. Ultimately, the goal of treatment in this patient population is palliative with the intention of improving the remaining quality of life. There is no established algorithm or specific technique that has proved best for the many variations of vertebral compression fractures (VCFs), so treatment tends to be dependent on the operator and/or based on institution preference or bias. Each technique provides its own unique value in the various types of metastatic VCFs encountered, and understanding the uses, advantages, and safety profile of each specific treatment is imperative in providing the best patient care. Percutaneous treatment of metastatic spinal disease is an excellent alternative to medical and surgical management in carefully selected patients. We believe that a multidisciplinary approach and combination therapy allows for optimal pain reduction and improvement of function.

Introduction

Spinal metastasis is a common and morbid condition in America. Spinal metastases are found in more than two thirds of patients who die of cancer [1]. The cancers which most commonly metastasize to the spine are breast, prostate, lung, kidney, thyroid, and multiple myeloma [2]. The skeletal system is the third most common site of metastasis after the liver and lungs, and the spine is the most common site of painful skeletal metastases [1]. Metastases to the spine are predominantly found in the vertebral body due to its rich blood supply. Severe back pain is the most common manifestation in patients with metastatic spinal tumors, in addition to decreased mobility, marked kyphosis with resulting height loss, neurologic complications, functional impairment, and respiratory compromise [1]. Collectively, these symptoms lead to progressive morbidity with mortality rates approximately double that of age-matched controls [3].

Nonsurgical conservative methods are commonly used as first-line treatment for the symptoms related to acute vertebral compression fractures (VCFs). The goals of nonsurgical management are to reduce pain, improve functional status, and prevent future fractures [4]. However, nonsurgical management of VCFs has limited long-term effectiveness and may ultimately exacerbate bone loss, increase the risk for subsequent fractures, and promote decreased mobility [3]. Open surgical techniques with instrumentation can stabilize VCFs, but because patients typically have poor bone quality, these techniques are often reserved for patients with neurological deficits [4]. In addition, open surgery necessitates extended recovery time and poses significant risks to the patient. Therefore, the paradigm has shifted towards minimally invasive therapy including percutaneous vertebroplasty, vertebral augmentation, and coblation and radiofrequency ablation systems, which are currently widely used to treat painful VCFs caused by metastatic tumors. Many combined treatments are also used for more complex disease, and the novel treatment of intraoperative radiotherapy is routinely being performed in Europe. These treatments offer the potential for vertebral height restoration and more immediate and sustained pain relief and with shorter recovery times and lower complication rates [3]. This review discusses the historical significance, indications, techniques, and advantages of the various currently available interventions, as well as the potential complications for each modality. Understanding the indications, technique, safety profile, and potential adverse events is crucial for the appropriate clinical utilization of percutaneous minimally invasive spine techniques.

Percutaneous Vertebroplasty

Percutaneous vertebroplasty (PV) was introduced in France in 1984 by the interventional neuroradiologist Dr. Herve Deramond for the treatment of a painful cervical hemangioma [5]. The procedure begins with placing unipedicular or bipedicular bone needle cannulas into the fractured vertebral body. Subsequently, a quick-setting bone cement, polymethylmethacrylate (PMMA), is mixed and then delivered through the needle directly into the vertebral body under continuous fluoroscopy. The highly compression resistant cement sets via an exothermic reaction, which immediately stabilizes the vertebral body, preventing further vertebral body height loss and reducing back pain. The pain reduction is thought to occur through two mechanisms: the exothermic reaction searing the adjacent nerves and mechanical stabilization of the fracture (Fig. 1). The procedures are identical when treating both osteoporotic and malignant VCFs. Not all vertebral compression fractures in patients

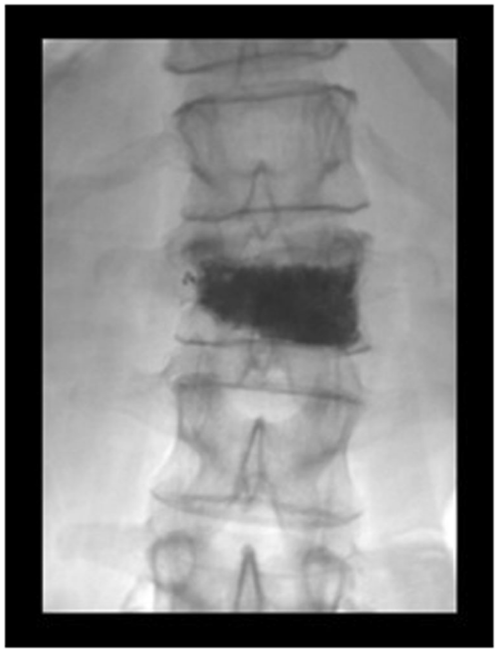

Fig. 1. AP view of the spine post-vertebroplasty.

with cancer are malignant. Due to advanced age, cachexia, and effects of chemotherapeutic drugs, osteoporotic compression fractures also occur. The similar clinical symptoms of malignant and osteoporotic compression fractures as well as the overlapping patient population may explain why the treatments demonstrate similar efficacy [6].

The first PV case was first performed in the USA in 1993 and quickly gained popularity demonstrating excellent clinical results. However, there were numerous reports of cement extravasation beyond the vertebral body. Most of these reports were benign, but a few reported devastating complications including pulmonary embolism and spinal canal leakage. Despite these reports, most studies have found PV to be safe, effective, and cost-effective [3]. Several nonrandomized and randomized trials comparing PV with conservative care or a simulated procedure report no statistically significant differences in sustained pain relief. A randomized, controlled trial published in the New England Journal of Medicine in 2009 called the Investigational Vertebroplasty Safety and Efficacy Trial (INVEST) controversially demonstrated no significant difference in pain improvement and pain-related disability in patients with painful osteoporotic compression fractures treated with PV compared to a simulated procedure without PMMA [7, 8]. Over the intervening 6 years, criticism of the enrollment process has emerged and high-quality randomized controlled trials have been undertaken which support the use of vertebroplasty in osteoporotic compression fractures [9, 10]. The unmasked, randomized, controlled trial called Vertebroplasty versus Conservative Treatment in Acute Osteoporotic Vertebral Compression Fractures (VERTOS II) published in 2010 demonstrated greater pain relief in PV compared to conservative treatment in patients with osteoporotic vertebral compression fractures [9].

Vertebroplasty studies specific to spinal metastases have demonstrated pain improvement among 73 to 100 % of patients [11, 12]. The goal of vertebroplasty in metastatic disease is to reduce back pain and to improve the remaining quality of life. Yang et al. conducted the largest vertebroplasty study in patients with malignant spinal tumors with 196 patients [13]. Pain improvement was seen in 98.5 % as well as statistically significant improvements in vertebral body height. Although few studies exist that have documented changes in mobility, McDonald et al. observed an improvement in mobility among 70 % of the 67 multiple myeloma participants [14]. A well-respected study including 65 patients found Roland-Morris disability scores decreased, analgesic use decreased, Karnofsky performance scores increased, and SF-36 physical and mental components increased significantly at 1 month post-PV versus no significant change in control [4]. An uncontrolled study which included 32 biopsy-proven cancer-associated VCFs found a significant reduction in pain on post-procedure day 1, continuing for 1 year [15].

There are several concerns regarding vertebroplasty. The first and most salient concern is cement leakage. Anterior or lateral leakage is not ideal but does not necessitate further intervention or drastically increase morbidity. Leakage into the vascular channel has been reported to cause pulmonary embolism, ranging from 4.6 to 23 % [16]. The majority of these cases are asymptomatic. One study found a 23 % incidence of cement emboli in their series of 61 positive cases, the largest of which measured 4 mm. Posterior cement that leaks into the spinal column may cause devastating neurological deficits necessitating emergent open neurosurgery. A past concern was that vertebroplasty increased the rate of adjacent segment fractures; however, recent studies have refuted this and found no increased incidence of vertebral fractures compared to control [4].

Vertebral Augmentation

Balloon Kyphoplasty

In an effort to improve the limitations of PV, vertebral augmentation was developed with the goal of restoring vertebral body height, improving the kyphotic angle, and reducing the risk of cement extravasation. The most widely performed vertebral augmentation technique, balloon kyphoplasty (BK), was conceived by an orthopedic surgeon Dr. Mark Reiley in the early 1990s. Like PV, BK also utilizes bone needle cannulas to deliver bone cement (PMMA) into the fractured vertebral body. Unlike PV, it utilizes a drill to create bilateral channels in the fractured vertebral body, which allows for the placement of inflatable balloon tamps. The balloons are slowly inflated under fluoroscopy to maximally improve the kyphotic angle with a resulting cavity in the center of the vertebral body. Bone cement is then injected into this cavity under low pressure, resulting in vertebral body stabilization as well as vertebral body height restoration (Fig. 2). Balloon kyphoplasty is similar to PV in procedural duration and effectiveness yet has a lower total and posterior leak rate [17•, 18, 19•].

The Cancer Patient Fracture Evaluation (CAFE) multicenter randomized controlled trial (RCT) compared kyphoplasty (70 patients) to conservative treatment (64 patients) for metastatic vertebral compression

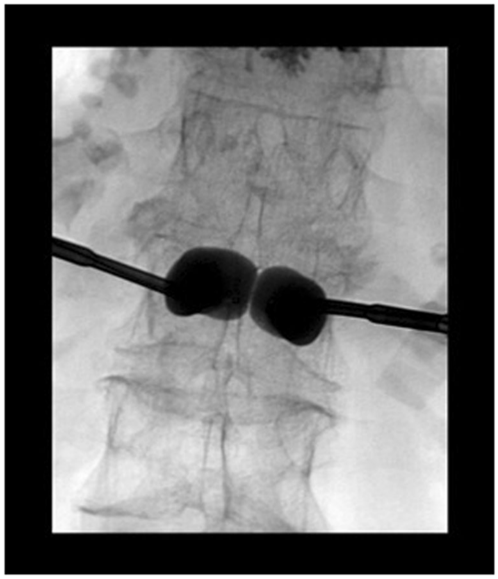

Fig. 2. AP view of “kissing” kyphoplasty balloons.

fractures. Kyphoplasty was found to nearly halve the RDQ disability score from 17.6 to 9.1 at 1 month, significantly increase quality of life, and significantly decrease analgesic use at 1 month, while conservative treatment had no significant change in the disability score, quality of life, or analgesic use [4].

The Fracture Reduction Evaluation (FREE) multicenter randomized controlled trial is the largest RCT to compare kyphoplasty to conservative treatment; however, it only included two patients with VCFs secondary to metastases. Its results are in accordance with the exclusively metastatic fractures of the CAFE trial, demonstrating improvement in objective and subjective scores of physical ability and pain, strongest in the 1- to 6-month period, gradually losing significance at 12 and 24 months when compared to conservative treatment [20–22].

As mentioned above, compared to PV, BK demonstrates similar effectiveness yet has fewer cement leaks. A randomized trial comparing the efficacy and safety of both procedures for osteoporotic compression fractures was published in the American Journal of Neuroradiology in 2014 which observed similar pain and function improvements. BK demonstrated lower cement extravasation (157 patients out of 214) versus PV (164 patients out of 201) which was statistically significant [17•]. Another RCT published in 2013 also demonstrated the number of levels with leaks and the total number of leaks per level to be significantly reduced in BK compared to PV. In addition, fewer lateral cortical and spinal canal (posterior) leaks occurred in the BK group [19•].

Adjunct Devices

A further innovation to vertebral augmentation called the Kiva Treatment System was first performed in the USA in early 2014 and was the first new approach to the treatment of VCFs in over a decade. The system includes a flexible cylindrical implant made from a medical polymer that is designed to provide a very predictable mechanical support structure for the vertebral body and to serve as a reservoir to contain and direct the flow of bone cement. The implant is delivered into the vertebral body percutaneously over a removable guidewire via a unipedicular approach with subsequent PMMA injection into the lumen of the implant, allowing the treating physician to ultimately deliver a much more consistent result than PV and BK (Fig. 3).

The safety and effectiveness of the Kiva System has been described in several peer-reviewed reports. Korovessis et al. treated 42 VCFs in 26 patients with osteoporotic or pathologic vertebral fractures and reported no cement leakage. Back pain improved 71 % and function improved 56 % from baseline to 6 months post-treatment [23]. The most robust evidence of the safety and effectiveness of the Kiva System to date is the Kiva System as a Vertebral Augmentation Treatment (KAST) trial, which enrolled 300 patients and demonstrated that Kiva met or exceeded the performance of BK on every endpoint measured. Both Kiva and BK restored vertebral body height and improved back pain and function; however, Kiva resulted in a 34 % reduction in cement extravasation over BK [24••]. Kiva also demonstrated a reduced rate of adjacent level fractures as compared to BK. Combined with KAST, Kiva has been shown in at least three comparative studies with a total of more than 500 patients to meet or exceed BK's performance on safety and efficacy and kyphotic angle restoration with a lower amount of cement leakage [23]. The only study comparing Kiva to BK in the treatment of specifically osteolytic metastases demonstrated equally significant back pain relief in patients with cancer. Similar to other studies, it demonstrated a lack of cement leakage in the Kiva cases and concluded that the implant safety in augmenting severely destructed spinal metastases was increased compared to BK [23].

Radiofrequency Ablation

Radiofrequency ablation (RFA) is a thermal ablative technique which uses alternating current to generate frictional heat (60–100 °C) causing protein denaturation and cell death. This offers nonsurgical, localized treatment in patients with unresectable painful spinal metastases by killing the targeted tissue/tumor while sparing the surrounding healthy

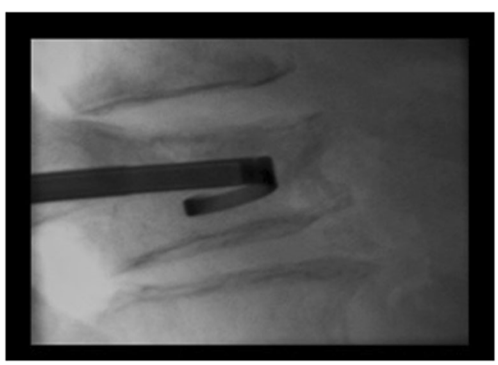

Fig. 3. Lateral view of Ninitol curved wire over which the implant is placed.

tissue. The percutaneous technique uses imaging guidance to place a needle through the skin directly into the tumor. From the tip of the needle, radiofrequency energy is transmitted into the target tissue, where it produces heat and kills the tumor. The proposed mechanisms by which RFA decreases pain may involve pain transmission inhibition by destroying sensory nerve fibers in the bone, reduction of lesion volume, destruction of tumor cells that are producing nerve-stimulating cytokines, and inhibition of osteoclast activity [25]. RFA is widely used in treating lung, kidney, and liver tumors.

A multicenter study involving 43 patients with painful osseous metastases was carried out in 2004 by Goetz et al. and showed significant reduction of pain and decrease in the use of opioids, with only minor complications [26]. In 2008, another study involving 30 patients demonstrated a significant decrease in the mean score for worst pain, average pain, and pain interference during daily life 4 and 8 weeks after treatment. There was also a marked decrease in the use of analgesics [27].

Although RFA shrinks tumor tissue and decreases pain, vertebral body height is not restored and pathologic fracture is not prevented. Consequently, RFA was carried out in conjunction with vertebroplasty and first performed in 2002 [28]. This technique attempts to shrink the tumor and create a cavity using RFA and subsequently fill the cavity with PMMA cement.

In 2014, a preliminary study of the safety and efficacy of RFA with BK demonstrated that image-guided RFA with kyphoplasty was safe and effective for thoracolumbar vertebral metastasis treatment when used with careful consideration of bone cement volume/viscosity, injection location, and temperature [29]. Another study published in JVIR combined RFA and the injection of PMMA cement and concluded the procedure to be safe and effective in the treatment of painful neoplastic lesions of bone [30].

Thus far, the entirety of the data gathered compared to other procedures consists of small case series. One such study included 18 patients with multiple myeloma metastases to their vertebral bodies undergoing RFA and vertebroplasty versus 18 patients undergoing vertebroplasty alone found no change in technical success rate or additional benefit in VAS or RMQ out to 6 weeks post-procedure [28]. This raises the question of the value of this combined treatment and the need for further studies to establish its utility.

Plasma-Mediated Radiofrequency Ablation (Coblation)

Coblation is an ablative technique performed in conjunction with cementoplasty in patients with advanced metastatic lesions who are considered high-risk for conventional PV and BK. It has been shown that the risk of previously described complications such as cement extravasation or even tumor extravasation is higher in advanced metastatic lesions, especially if the lesions have posterior cortical disruption, paraspinal extension, or epidural tumor extension [31]. These findings are considered relative contraindications for conventional PV or BK. Coblation prior to cementoplasty was introduced to address these limitations in this high-risk population. Coblation creates a cavity at a lower temperature (40–70 °C) than RFA via electrical excitation of plasma into a high-energy state causing dissolution of molecular bonds in soft tissue. This results in the volumetric removal of target tissue, providing a cavity, while preserving the integrity of the surrounding tissue. The cavity is then filled with PMMA cement which is directed away from the disrupted posterior vertebral wall and along a path of lesser resistance into the vertebral body. In contrast to other thermal techniques, coblation diminishes the hyperthermic effects, reducing the risk of damage to the spinal cord and surrounding tissues. Thus, coblation provides an alternative treatment option for previously considered high-risk patients; however, despite its initial efficacy, there have been few reports about this technique. The majority of the data gathered consists of small case series without comparative trials to PV or BK alone or versus RFA in conjunction with cementoplasty [31–34].

Emerging Technologies for Treatment of Complex and Advanced Metastatic Disease

Kyphoplasty-Intraoperative Radiotherapy

Metastatic spinal tumor treatment requires a multidisciplinary approach which integrates interventional radiology, surgery, and radiation and medical oncology. Over the past two decades, treatment has evolved from simple decisions regarding the need for either surgery or conventional external beam radiation therapy (EBRT) to complex multimodality assessments that require the integration of new technologies and services [35]. Conventional EBRT is a widely used treatment option that provides both symptomatic relief and satisfactory local control rates for patients with radiosensitive tumors [35]. However, the onset of pain relief can be delayed for up to 2 weeks post-therapy [36]. In addition, radiation alone does not provide vertebral stabilization and in some cases, only delayed pain relief is observed. Single fraction radiation therapy for metastatic spine lesions has also been shown to increase the risk of vertebral fracture by 39 % [37]. Furthermore, despite the success in pain control after vertebral augmentation, most cancer patients are also treated with irradiation to control the underlying malignant process.

For these reasons, ERBT is now commonly used in conjunction with the percutaneous treatments described above [38]. Various methods of pre- or post-procedure EBRT are possible; however, they require different dates of treatment which can delay results of pain relief. Because of the limited survival time of patients with metastatic cancer, more convenient treatments are desired [39].

A novel treatment for painful spinal metastases involving intraoperative radiotherapy during BK has been performed in Europe since 2010 and is currently under investigation in the USA. This combines stabilizing surgery and radiotherapy in one visit. The procedure begins similarly to the percutaneous treatments discussed above with placement of unipedicular or bipedicular trocar needles into the fractured vertebral body. Next, specifically designed metallic sleeves are inserted to guide the Intrabeam radiation applicator device. The positioning of the guiding sleeves is confirmed using biplanar fluoroscopy. The Intrabeam tube applicator is then inserted, and a radiation dose is delivered to the center of the metastasis. Once the radiation dose is completed, the Intrabeam device is removed from the vertebrae. The kyphoplasty balloon is inserted and inflated, and PMMA cement is injected in the same manner that BK alone is performed (Fig. 4).

An investigation performed in Germany demonstrated that Kyphoplasty-Intraoperative Radiotherapy (Kypho-IORT) can decrease the overall treatment time for up to 34 % of patients who usually receive radiotherapy for spinal metastases [39]. Further studies are necessary to evaluate the long-term effectiveness of this treatment.

Conclusions

The treatment of metastatic spinal disease has significantly evolved over the last few decades. Each new generation of treatments has attempted to address the concerns of its predecessors. Ultimately, the goal of treatment in this patient population is palliative with the intention of improving the remaining quality of life. There is no established algorithm or specific technique that has proved best for the many variations of VCFs, so treatment tends to be dependent on the operator and/or based on institution preference or bias. Each technique provides its own unique value in the various types of osteolytic VCFs encountered, and understanding the uses, advantages, and safety profile of each specific treatment is imperative in providing the best patient care. For example, we now understand that cement leakage is very common and it is typically used by the treating physician as an endpoint for the cessation of cement injection. Percutaneous treatment of metastatic spinal disease

Fig. 4. Lateral view of spine with intraoperative radiation probe at T10 and bilateral bone trocar/drill.

is an excellent alternative to medical and surgical management in carefully selected patients. We believe that a multidisciplinary approach and combination therapy allows for optimal pain reduction and improvement of function.

Compliance with Ethical Standards

Conflict of Interest
Mara Bozza Stephenson, Bryan Glaenzer, and Angelo Malamis declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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