



Palliation of bone metastases—exploring options beyond radiotherapy

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Abstract: Multiple new options are available in the palliation of bone metastases. Most of these techniques can be used in conjunction with radiation therapy either before or after and are now giving patients who have reached dose limitations new options. These techniques can also be used with vertebroplasty (VP) to increase structural stability post tumor ablation. Localized percutaneous treatment in the bone such as thermal [radiofrequency ablation (RFA)] and light [photodynamic therapy (PDT)] have been used to destroy tumor prior to injection with cement. This educational review will discuss the safety profile, technique and indications for emerging technology in the area of locoregional treatment of bone metastases in conjunction with vertebral augmentation. It will not delve comprehensively into conventional lines of treatment where indications and outcomes have already been well established.

Keywords: Interventional radiology; vertebroplasty (VP); radiofrequency ablation (RFA); palliative therapy; bone metastases

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Introduction

While bone metastases can be asymptomatic, they can commonly cause significant morbidity due to pain, pathological fracture and spinal cord compression. The goals of palliative treatment are pain relief, preservation of function, and maintenance of skeletal structural integrity.

Radiation therapy is the mainstay of treatment for symptomatic bone metastases. The primary goal of radiation therapy is to palliate painful bone metastasis, achieve local tumor control and improve quality of life. Typically a palliative dose of conventionally delivered radiation is applied in a convenient scheme such as 8 Gy in a single fraction or 20 to 30 Gy in 5 to 10 fractions. The intent is predominantly pain relief which is thought to be achieved via decreasing the tumor size and surrounding inflammation (1).

For bone confined noncomplex metastases, the literature suggests high rates of control; however, for bulky “mass” type tumors tumor control is sub-optimal. This has resulted in the development of high total dose and short course radiation using advanced techniques that allows for dose escalation while respecting the spinal cord known as spine stereotactic body radiotherapy (SBRT). The biologically effective dose can range from 4 to 8 times that of conventional palliative radiation with the intent to improve complete response rates for pain and local control. At our centre, the approach has been to deliver 24 Gy in 2 fractions with mature outcomes reported and this fractionation is currently being evaluated to conventional radiation in a randomized trial [SC-24 phase III randomized trial (NCT02512965)].

Percutaneous vertebroplasty (VP) is a procedure aimed at

stabilizing the treated level and alleviating pain in patients with pathological vertebral body fractures (2-4). While VP can mechanically stabilize the vertebral body, it does not treat the local tumor (5). Tumor debulking can be achieved through various locoregional techniques such as thermal ablation, cryotherapy, photodynamic therapy (PDT), embolization (bland or chemoembolization), chemical ablation (alcohol) or external beam radiation. Combining these techniques with VP can treat the tumor and stabilize the fracture in a minimally invasive manner in one setting.

The following is a review of emerging interventional technologies in the palliation of bone metastases. These new techniques are meant to address those patients who have failed conventional lines of therapy and continue to be symptomatic.

Methods

A review of the literature was carried out using the PubMed database and the search terms 'external beam radiation' 'VP' 'radiofrequency ablation' 'RFA' 'bipolar radiofrequency ablation' 'bone metastases' and 'ablation'. The literature search was carried out August 2017.

Radiation therapy

There are various forms of radiation therapy with the mainstay being short course palliative radiation. There have been multiple randomized trials that have shown high partial response rates at approximately 60% and complete response rates ranging from 10% to 20% (6). The most common regimens include 8 Gy in 1 fraction, 20 Gy in 5 fractions and 30 Gy in 10 fractions. Fracture rates are typically 5% following these regimens but can vary depending on baseline factors as defined by the increasingly applied spinal instability in neoplasia score (7). SBRT has been developed to improve upon the low complete response rates associated with conventional radiation and to improve local control for complex metastases. Data suggest high rates of local control at 1 year ranging from 80% to 90%. At present a phase II randomized trial has been reported comparing 24 Gy in 1 SBRT fraction to 30 Gy in 10 SBRT fractions (8). Importantly this trial was not powered a priori and the result was a trend to higher complete response rates at 3 months at 44% *vs.* 17%, respectively. Randomized trials are in progress with the appropriate power to answer the question in the palliative patient with painful spinal metastases if spine SBRT is superior.

A downside of SBRT in the spine is an increased risk of vertebral compression fractures. Rates range from 10% to 40% and there is a dose-complication relationship with the highest rates of vertebral compression fracture (VCF) following 24 Gy in 1 fraction (9,10). Other factors that influence risk include lytic disease, baseline VCF, and spinal malalignment (10). A review of the pathophysiology suggest early fractures occurring within the first 3 months associated with the intense edema and inflammation and late fractures associated with a smoldering radiation necrosis. As a result of SBRT, there is increasing use of salvage stabilization interventions upon fracturing, and prophylactic stabilization interventions in high risk patients eligible for SBRT. Evidence is still needed to determine which patients are at the highest risk of developing post-SBRT VCF to justify prophylactic interventions which are most commonly cement augmentation procedures. Another limitation of SBRT lies in the treatment of high-grade epidural disease. SBRT is contraindicated at this time for the treatment of malignant spinal cord compression and there has been an association with epidural disease grade and local control. At present, patients with symptomatic spinal cord compression and single level are potential surgical candidates and if not then conventional palliative radiation is still the standard of care. In those operated upon, post-operative radiation is a standard of care. In keeping with intact metastases, SBRT is also increasingly applied in the post-operative patient. The evidence is limited for this indication and high-quality data is in need as it can be a much more technically difficult application. Ultimately a randomized trial will be needed to clarify the role of post-op SBRT. If symptomatic lesions are widespread such as the prostate patient with a super scan, radiopharmaceuticals or hemibody radiation may be used as palliative alternatives. There is increasing use of radiopharmaceuticals especially for prostate cancer with a recent randomized trial evaluating radium 226 in castrate resistant prostate cancer showed a survival advantage (11).

VP

Polymethylmethacrylate (PMMA) is injected into the bone via percutaneously inserted needles under radiological guidance. PMMA is a commonly used biological cement and has a well-documented safety profile as it is used extensively in hip and knee replacements. The cement flows into spaces as a liquid filling the cavities and then solidifying through an exothermic reaction. Once hardened, PMMA cement is extremely stable and acts as a glue between

fragments of bone. In some patients the analgesic effects of VP can be seen rapidly within 24–48 hours (12) while in others it is usually obtained within 2–10 days; often once bruising from the needle access subsides. VP does not reduce tumor burden at the site so it is often paired with other percutaneous locoregional techniques or done in conjunction with radiotherapy.

Kyphoplasty is an analogous technique to VP except that it creates a cavity within the bone using a high-pressure balloon. Liquid cement is then injected into the preformed mechanically created cavity in a very controlled manner. Kyphoplasty enhances control when injecting cement. Radiofrequency ablation (RFA) assisted VP can provide similar enhancement of control (13). Kyphoplasty has a mechanically created cavity whereas RFA has a cavity created by heat and dessication of the target tissue. Cement can be injected into both cavities safely with decreased incidence of potentially dangerous posterior leaks. There is no high quality, objective evidence that kyphoplasty can permanently restore height or correct spinal curvature. This is important information in managing our patient's expectations.

Both VP and kyphoplasty are tools in alleviating pain and enhancing structural stability of load bearing bone.

Methods of tumor destruction

Ablative techniques allow for both tumor destruction as well as palliation of pain from metastatic disease (14,15). Tumor destruction can be achieved through a variety of methods.

Thermal ablation

With thermoablative procedures, the goal is to induce coagulative necrosis with heat, ideally around 70 °C for bone lesions (16).

RFA

Currently RFA is the most frequently utilized thermoablative procedure for bone tumors. RFA is dependent on the conductive properties of the target tissue. It works by conducting an alternating current through a probe placed within a lesion (17). This results in the deposition of energy within tissue which induces coagulative necrosis (18,19). Ablation is controlled based on a feedback system dependent on tissue impedance which is often high in bone. RFA devices are usually monopolar or bipolar. Many have features that allow for shaft cooling.

Monopolar RFA has a circuit which is between the electrode tip which acts as the cathode and a grounding pad placed externally on the patient which acts as the anode. The ionic current induces frictional heat production which generates an ablation zone. Downsides of a monopolar system include long ablation times and the 'heat-sink effect'. The 'heat-sink' effect relates to tumors adjacent to large vessels (20,21). When tumor is located adjacent to a large vessel the energy flows from the electrode through the highly conductive liquid to the grounding pad thereby bypassing the tumor (22).

Bipolar RFA creates a circuit between two electrodes in close proximity at the tip of the needle. Energy is then dissipated between the two electrodes ablating the intervening tissue (23). Bipolar systems have faster ablation times, require less power, are less susceptible to the heat sink effect and do not need external grounding pads on the patient. Bipolar RFA has also been shown to produce larger ablation zones when compared to monopolar devices (24).

Internally cooled electrodes use an interior lumen along the shaft of the needle that is filled with a circulating liquid.

This helps to remove heat from the tip of the electrode, prevents charring which can create an insulative sleeve around the needle tip and allows for better heat dispersion which often results in a larger ablation zone. This technique can be used in conjunction with monopolar and bipolar devices.

An example of a monopolar internally cooled radiofrequency probe is the cool-tip electrode (Medtronic). Traditional monopolar devices struggle with bone ablation due to the inherently poor conductive properties of bone. Monopolar systems use an electrical circuit between the placed electrode and a grounding pad in order to create a current which results in heat production and thermal ablation. This common setup used by a monopolar system has a major drawback for use in bone. Osseous tissue has semi-insulative electrical and thermal properties which generates high impedance when completing the circuit from the probe to the grounding pad. This will limit the size of the ablation. Another downside with a monopolar system is that bone marrow within trabeculae may act as a heat sink resulting in a smaller ablation zone. These factors limit the efficacy of monopolar devices in bone applications. Monopolar systems are much better suited to soft tissue ablation where impedance is usually much lower.

OsteoCool RF Ablation system (Medtronic) is an example of a bipolar system engineered to overcome the limitations of a monopolar device in bone. It is a coaxial

bipolar probe with internal cooling. While traditional bipolar systems have required the use of two probes, the OsteoCool probe incorporates the active and grounding electrodes on the tip of a single probe (25). This eliminates the need for placement of a second probe. The benefit of a bipolar system in bone is primarily the ability to bypass the insulative properties of cortical bone. This allows for lower power requirements as the system has less impedance to overcome. The internal cooling component of the device minimizes tissue charring at the probe tip which allows for formation of a larger ablation zone. The 17 gauge probe can be placed through a variety of cannulas with the minimum requirement in size being 13 gauge. Probes come with different active tips; specifically 1, 10 and 20 mm. An independent thermocouple (20 G) can be inserted



Figure 1 Dual probe OsteoCool RF Ablation system.

into sensitive areas to avoid ablation of critical surrounding structures. The generator monitors temperature and moderates power to maintain 70°C at the probe tip.

The first study to evaluate the safety of the OsteoCool RF Ablation system was published in 2017. This study determined that RFA assisted VP using a bipolar device was safe (13). RFA allowed for controlled injection of cement into a cavity created by the ablation. There was a significant decrease in venous and posterior cement leaks; presumably due to thrombosis of these vessels during the ablation. Aside from this single center experience trial no other clinical trials with the OsteoCool system have been done at this time. Further clinical evaluation needs to be done in order to understand the long-term impact of bipolar RFA on tumor and bone and whether there are any additional benefits in pairing VP with RFA; such studies are currently ongoing (*Figures 1-4*).

Cryotherapy

The development of cryoprobes to treat bone lesions is relatively new. Argon gas is delivered through a partially insulated probe which is positioned at the center of a tumor. The gas lowers the probe temperature to -100°C (26). Cell death is due to loss of cell membrane integrity. An important advantage is that since ice can penetrate bone this can treat osteoblastic metastases. Other advantages include the created ice ball is easily seen by ultrasound (US) or computed tomography (CT). Disadvantages include cryochock which

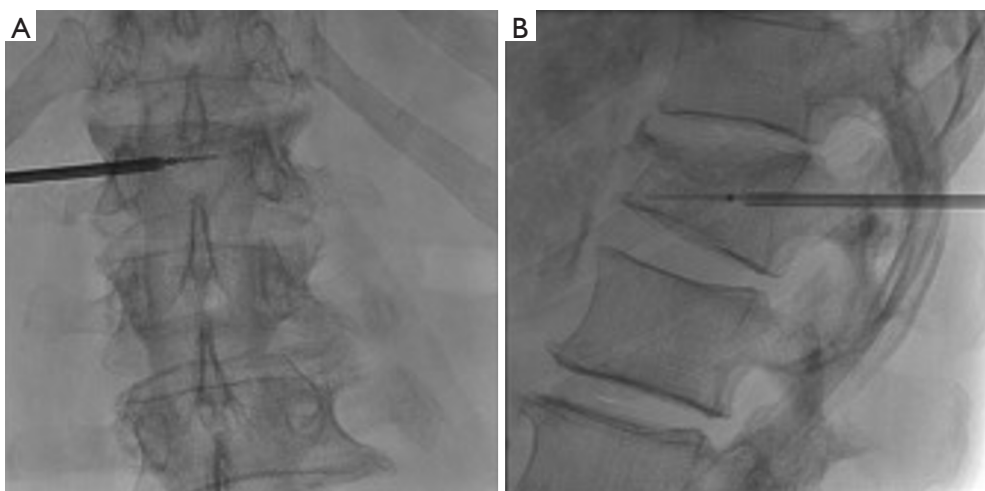


Figure 2 Fluoroscopic images after placement of an 11 gauge Cook M1M Osteosite needle into the L1 vertebral body. (A) Anteroposterior and; (B) lateral images with the outer needle pulled back and a 2 cm OsteoCool needle has been placed through the shaft into the tumor. Ablation can be performed for up to 15 minutes.

occurs due to the sudden release of tumor cellular contents with the thawing of tissue (2). Other disadvantages include high equipment cost and long operative times.

At this time early evidence does show that cryotherapy is effective at treating primary and metastatic bone tumors. Seventeen tumors in 15 patients were treated with cryoablation using image guidance. This study showed immediate pain relief post procedure with long-term benefits and improvement in quality of life (27).



Figure 3 In the same patient after RFA PMMA cement can be injected. The cement fills the thermal cavity created by the ablation. RFA, radiofrequency ablation; PMMA, Polymethylmethacrylate.

PDT

PDT is a relatively new approach to ablation which is not widely available commercially at this point and is mostly utilized in research applications. PDT combines a systemically injected photosensitizing agent with locally applied light at a specific wavelength (typically infrared). The photosensitizing agent accumulates in neoplastic cells over 25 minutes. The agent is then locally activated by light at a low power. Once the agent is activated this generates a cytotoxic singlet oxygen that results in tumor destruction. On a cellular level this occurs due to microvascular injury resulting in tissue hypoxia, infiltration of activated neutrophils and cell apoptosis (28). This efficacy of PDT depends on the light energy which is applied, tissue oxygenation and the optical properties of the tissue. There are many different photosensitizing agents available on the market. At this time, there are no known contraindications to the use of PDT when paired with radiotherapy, RFA or surgery. The use of PDT to treat spinal metastases is currently being investigated; however, early evidence shows that it can safely be used in conjunction with both RFA and VP (29).

PDT can easily be performed in conjunction with VP with the light fiber inserted through the existing bone trocar. At our institution we have safely used RFA in conjunction with PDT. For large lytic lesions which are close to the posterior cortical margin RFA was used in conjunction with PDT to control cement deposition. So far in treatments done using PDT no neurotoxicity was encountered.

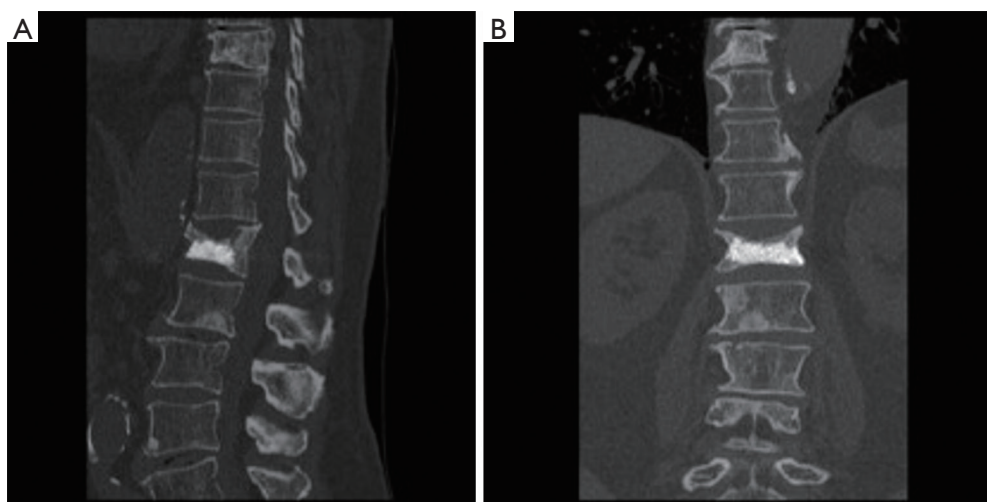


Figure 4 Post procedure CT in the same patient confirming cement distribution. (A) Sagittal and; (B) coronal images showing cement dispersion within the vertebral body. CT, computed tomography.

Benefits of PDT include not only ablating vertebral tumors but also the enhancement of vertebral structure (30). Studies have shown periosteal new bone formation within the majority of PDT treated vertebral bodies (31). Other studies have shown that PDT is successful not only destroying vertebral osteolytic tumors but also enhancing vertebral structure particularly when combined with bisphosphonates (32) (*Figures 5-9*).

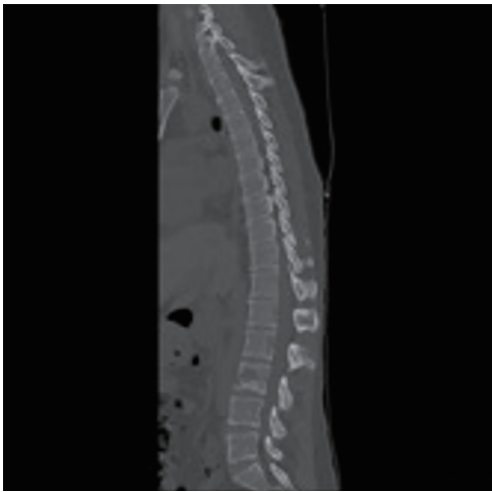


Figure 5 Patient with a painful metastasis to L3. Previously had radiation therapy however pain persisted.

Endovascular embolization

Embolization is the selective occlusion of blood vessels, in this case the blood vessels feeding the tumor. Embolization induces tumor necrosis by occluding these feeding vessels thereby having an analgesic effect. Embolization is typically using calibrated microparticles polyvinyl alcohol (PVA) or trisacryl gelatin microspheres. Chemoembolization combines highly selective arterial embolization with the delivery of

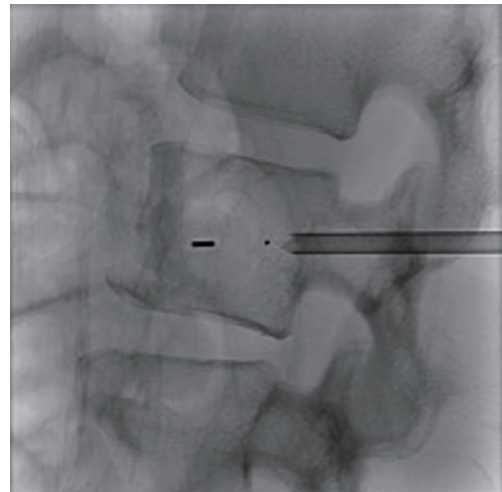


Figure 6 Vertebroplasty trocar has been placed into the L3 vertebral body. Through this trocar an optical fiber is placed prior to PDT. The drug used was Visudyne and it was given intravenously 25 minutes prior to light activation. PDT, photodynamic therapy.

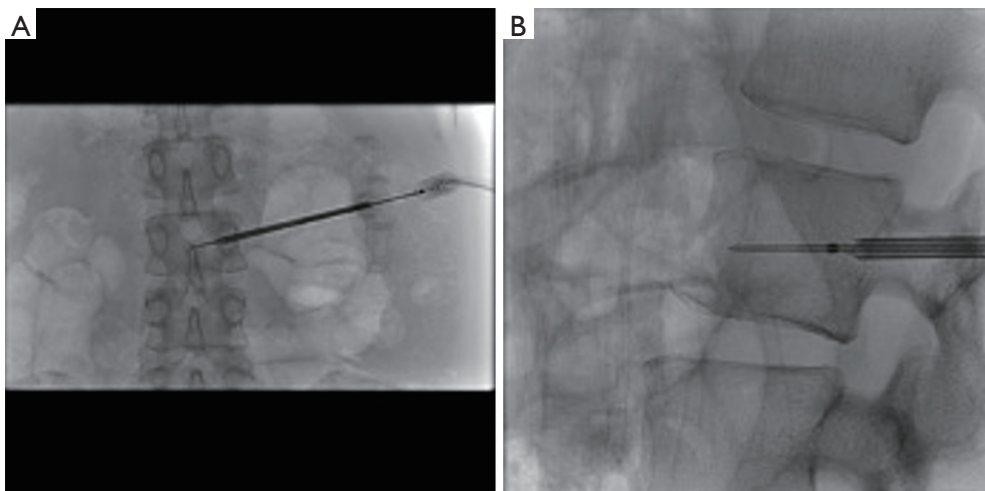


Figure 7 Post PDT RFA was performed at the L3 level to optimize the ablation zone and enhance control in cement injection. (A) Anteroposterior and; (B) lateral images demonstrating the in place RFA probe. RFA, radiofrequency ablation; PDT, photodynamic therapy.

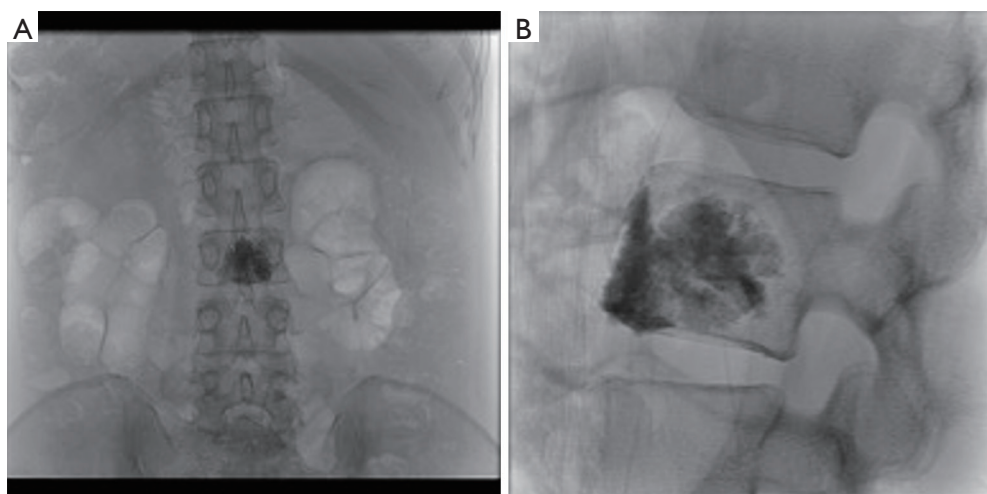


Figure 8 Fluoroscopic images in the same patient demonstrating post RFA vertebroplasty cement dispersion. (A) Anteroposterior and; (B) lateral fluoroscopic images showing cement injected into the created cavity. RFA, radiofrequency ablation.

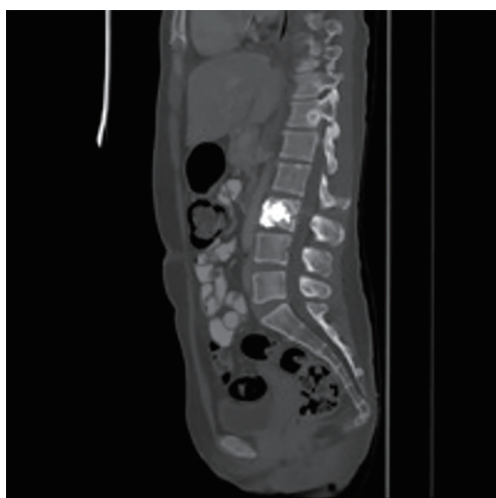


Figure 9 Final sagittal CT image post procedure showing cement injection into the L3 vertebral body. CT, computed tomography.

intraarterial chemotherapy. Advantages of chemoembolization include that the intraarterial infusion of anti-cancer agents during embolization concentrates the anti-tumor effect 20–40 times and in some cases after destroying osteolytic bone metastases, new healthy bone is deposited (26). The main disadvantage is if the anti-cancer drug comes in contact with nerve roots this can result in neurotoxicity. Arterial embolization of spinal metastases at our institution is used chiefly to devascularize tumors prior to surgical stabilization to minimize intraoperative blood loss.

Endovascular embolization is mainly used to devascularize

tumors before surgery and as a palliative pain relieving procedure. This is mainly performed for renal cell carcinoma metastases. Pain relief is almost consistently obtained but varies in duration from 3 weeks to 8 months, depending on the aggressiveness of the tumor (33) (*Figures 10–12*).

Chemical

Percutaneous injection of 95% ethanol in combination with a contrast agent into spinal tumors is a fairly old technique (34). The alcohol induces tumor necrosis (35).

Ethanol created an analgesic effect by destroying the nerve endings adjacent to the tumor thereby providing dramatic and nearly immediate analgesia. In a study of 27 metastatic bone tumors in 25 patients treated with CT guided percutaneous administration of 95% ethanol the outcomes were mixed. Four patients experienced complete relief, 11 had 75% reduction in symptoms while 7 had no relief if pain. This study also found that the analgesic effect does not usually last longer than 3–5 months (34).

Why combine RFA and vertebroplasty

While RFA and vertebroplasty can each be used alone to treat spinal metastases there is a potential synergistic effect in combining both (36–38). While RFA alone can reduce tumor burden and control local disease progression, studies have found that RFA treated bone can be less structurally stable. Once tumor is destroyed by any means, radiation,

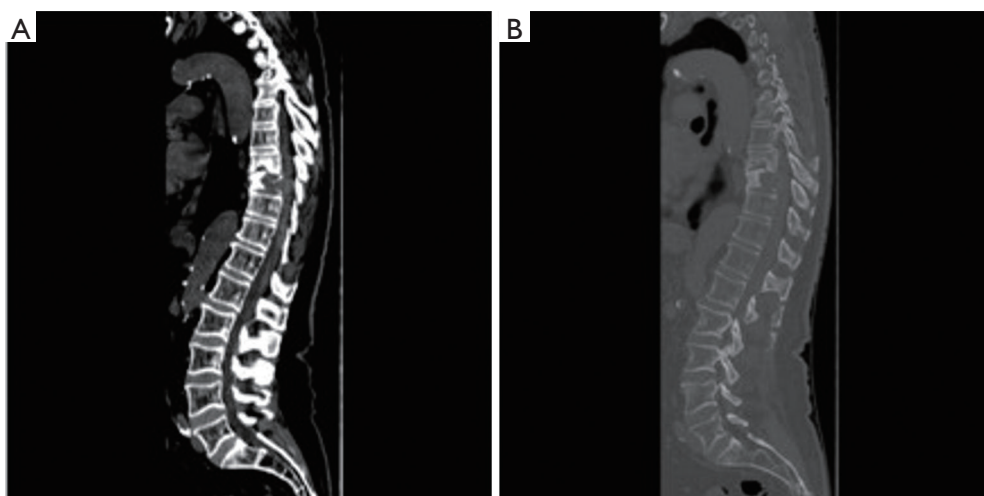


Figure 10 CT in (A) soft tissue and (B) bone windows showing the renal cell carcinoma metastasis to the posterior T9 vertebral body with involvement of the posterior cortex. Embolization is performed prior to surgery for stabilization.

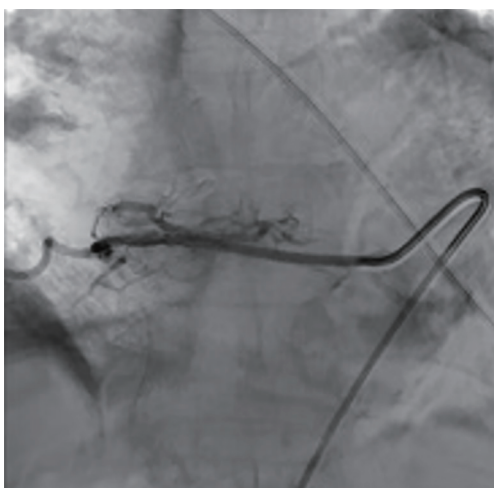


Figure 11 Pre embolization angiogram of a hypervascular renal cell carcinoma metastasis to the T9 vertebral body.

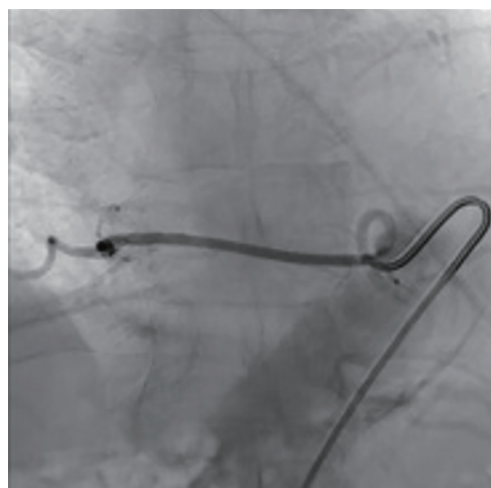


Figure 12 Post embolization image shows pruning of parent intercostal artery supplying the tumor. Embolization was performed with 300–500 micron PVA particles.

thermal ablation or chemical means; a cavity would have to exist and this would certainly decrease the stability of load bearing bone. The cement adds mechanical stability and potentially prevents future fractures in weakened bone (39,40). Cement injection also appears to be more controlled post RFA especially with posterior leaks and this may be due to tissue dissection and vascular thrombosis that allows cement to be well contained within the cavity created by the ablation (13). An advantage of kyphoplasty over vertebroplasty is the deposition of cement into a mechanically created cavity created by inflation of a high

pressure balloon. RFA assisted vertebroplasty allows for controlled cement deposition into a thermally created cavity. There may be additional benefits of combining RFA, radiation and vertebroplasty in increasing time to recurrence but this has to be investigated in future trials.

Surgery

Although the treatment for spinal metastases is largely palliative in certain circumstances spinal surgery can be a

part of the treatment algorithm. Rarely curative surgery can be the goal if the spine is the only known site of metastasis. Curative spinal surgery is mainly seen with renal cell carcinoma metastases (41). In other cases, obvious spinal instability, clinically significant neural compression or intractable pain unresponsive to nonoperative measures can require surgery. Generally, surgery is offered to those patients with a life expectancy greater than 3 months and those who would be able to tolerate the procedure (42).

In general, the goals of surgery are to correct and prevent any further deformity by stabilizing the spine and decompressing neural structures.

Conclusions

Locoregional techniques are yet another option in the management of symptomatic bone metastases. Devices for thermal ablation of bone are now widely available on the market. Chemical devices may soon be available. The addition of vertebroplasty to these techniques can improve the mechanical stability of treated bone especially if load bearing. RFA assisted vertebroplasty can also be safely used with more experimental treatments such as PDT. As systemic treatments improve, patients are living longer with bone metastases. In the subset of patients where radiotherapy treatments have been exhausted or are contraindicated, localized techniques paired with cement offer additional options to patients struggling with pain and impaired mobility. The goal in cancer care is not only to live longer but to live with functional status intact and palliating pain is essential to reaching this goal. Locoregional treatments targeting sites of pain and active disease will increasingly take on an important role in palliating patients and maintaining quality of life. All these treatments may also have a synergistic effect when paired with radiotherapy. Further studies are required to establish the optimal sequence of these different interventions in the palliation of bone metastases.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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