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REVIEW ARTICLE

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Image-guided ablation of painful metastatic bone tumors: a new and effective approach to a difficult problem

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Abstract Painful skeletal metastases are a common problem in cancer patients. Although external beam radiation therapy is the current standard of care for cancer patients who present with localized bone pain, 20–30% of patients treated with this modality do not experience pain relief, and few further options exist for these patients. For many patients with painful metastatic skeletal disease, analgesics remain the only alternative treatment option. Recently, image-guided percutaneous methods of tumor destruction have proven effective for treatment of this difficult problem. This review describes the application, limitations, and effectiveness of percutaneous ablative methods including ethanol, methyl methacrylate, laser-induced interstitial thermotherapy (LITT), cryoablation, and percutaneous radiofrequency ablation (RFA) for palliation of painful skeletal metastases.

Keywords Metastases · Bone · Palliation · Ablation · Percutaneous

Introduction

Image-guided percutaneous methods of tumor destruction have rapidly evolved and proven effective for treatment of benign skeletal lesions and, more recently, for palliation of painful metastatic skeletal disease. Treatment of primary bone tumors is largely restricted to benign lesions, such as osteoid osteomas, as a single modality treatment or as an adjunct to surgical resection [1–4]. The use of ablation techniques for treatment of painful metastatic disease has evolved because of the often disabling pain cancer patients experience, despite the use of conventional therapies including external beam radiation and narcotic analgesics.

Skeletal metastases are a common problem in cancer patients. Autopsy studies have shown that up to 85% of patients that die from breast, prostate and lung cancer have bone metastases at the time of death [5]. Complications due to skeletal metastases, including pain, fractures, and decreased mobility, can often affect a patient's quality of life, ultimately reducing performance status [5, 6]. In addition, these complications can affect a patient's mood, leading to associated depression and anxiety [5]. Current treatment for patients with bone metastases are primarily palliative and include localized therapies (radiation and surgery), systemic therapies (chemotherapy, hormonal therapy, radiopharmaceuticals, and bisphosphonates) and analgesics (opioids and non-steroidal anti-inflammatory drugs).

Skeletal metastases that cause pain but that are also at risk for impending fracture may be treated surgically with an intramedullary rod or other internal fixation in an extremity. However, lesions located in the spine and periacetabular regions require greater surgical intervention to effect stabilization. Recently, percutaneous methods have been developed to stabilize these types of lesions through the administration of methyl methacrylate into the tumor, with or without prior treatment with ablative methods.

The causes of pain in patients with bone metastases are not fully understood, and the presence of pain is not correlated with the type of tumor, location, number or size of metastases [6–8]. Possible mechanisms of pain include (1) stretching of the periosteum secondary to tumor growth, (2) fractures (both micro-fractures and macro-fractures), (3) cytokine-mediated osteoclastic bony destruction, resulting in stimulation of nerve endings in the endosteum

[9–15], and (4) tumor growth into surrounding nerves and tissues.

External beam radiation therapy (RT) is the current standard of care for cancer patients who present with localized bone pain. This treatment results in a reduction in pain for the majority of these patients; however, 20–30% of patients treated with this modality do not experience pain relief, and few options exist for these patients [16–21]. Unfortunately, patients who have recurrent pain at a metastatic site previously irradiated are often not eligible for further RT secondary to limitations in normal tissue tolerance. Additionally, metastatic disease in this patient population is often refractory to standard chemotherapy or hormonal therapy. Surgery, which is usually reserved for impending fracture, is not always an option when patients present with advanced disease and poor functional status. Radiopharmaceuticals, which have known benefit in patients with diffuse painful bony metastases, are not considered a standard of care for patients with isolated, painful lesions. For many patients with painful metastatic disease, analgesics remain the only alternative treatment option. Unfortunately, in order to obtain sufficient pain control for many of these patients, side effects such as constipation, nausea, and sedation, can be significant.

Percutaneous therapies for palliation of painful metastases

Because of the shortcomings of the currently available therapies for many patients with painful metastatic disease, investigators have explored alternative treatment strategies. Transcatheter embolization of skeletal neoplasms has been found as a helpful adjunct to surgery to minimize blood loss. These treatments may also relieve neurological compromise and pain [22–24] and have been reviewed elsewhere [25]. Several new treatment strategies have recently been reported for the treatment of painful metastatic disease. All these new methods are based on the use of percutaneous image-guided methods to deliver tissue ablative materials or devices into focal metastatic lesions. These methods include the use of ethanol, methyl methacrylate, laser-induced interstitial thermotherapy (LITT), cryoablation, and percutaneous radiofrequency ablation (RFA). The device-based ablation methods may also be combined with the use of methyl methacrylate for stabilization of bones at significant risk of fracture.

Percutaneous ethanol therapy

Gangi and colleagues described the use of CT-guided percutaneous administration of 95% ethanol for the palliation of pain from 27 metastatic bone lesions in 25 patients previously treated with radiotherapy and/or chemotherapy [26]. Sixteen lesions received a single dose of ethanol, while ten lesions received two doses and one lesion received three doses. The response of these patients to this treatment was assessed by the reduction in use of analgesic medicines 48 h and 2 weeks following therapy. Complete relief of pain was achieved in four patients, and very good but incomplete relief (75% analgesic medicine reduction) in 11 patients. Seven patients received little or no relief with the treatment.

Percutaneous methyl methacrylate treatment: acetabular and vertebral body lesions

Percutaneous delivery of methyl methacrylate has been used to palliate pain in patients with vertebral body neoplasms and to prevent pathological fractures [27–32]. The injection of bone cement into the vertebral body lesion results in reduction in pain and also provides stabilization of the involved bone. The approach used for treatment of malignant lesions in a vertebral body is identical to that used for treatment of painful insufficiency fractures of the spine.

For example, a patient was treated in our center for pain due to a thoracic vertebral body compression fracture resulting from metastatic myeloma. Under biplane fluoroscopy, a 13 G bone biopsy needle is advanced through the center of a pedicle into the vertebral body and the malignant lesion (Fig. 1). Intraosseous venography may be performed to exclude direct venous continuity to central or epidural veins, although the benefit of this imaging is debated due to potential poor visualization of bone cement from pooled residual contrast [27, 31, 33–38]. Barium sulfate and possibly an antibiotic are mixed with methyl methacrylate powder. Liquid monomer is added to the powder to form a tooth-paste consistency. The material is then injected under fluoroscopic control until it fills the lesion without leakage into the disk space or perivertebral tissues, with constant vigilance for undesired leakage into veins, neural foramina, epidural space or joints.

Weill and colleagues used percutaneous injection of methyl methacrylate cement to treat 37 patients with 52 procedures for spinal metastases causing pain (33/37) or in order to stabilize a vertebral body (4/37). Vertebroplasty was performed alone in 25 sessions and combined with surgery and/or radiation therapy in the remainder of treatments. By Kaplan–Meier analysis, they estimated that 73% and 65% of the patients had durable pain relief at 6 months and 1 year, respectively, as defined by a 50% reduction in narcotic analgesic use or the use of non-narcotic analgesia for pain relief [27]. Gangi and colleagues described the treatment of 36 vertebral body and 12 acetabular malignancies, with 85% of patients deriving moderate relief (decreased pain score ≥2/10) within 12–48 h of the treatment [29]. Deramond and colleagues reported the treatment of 101 patients at risk for vertebral body collapse due to malignancy. They found an improve-

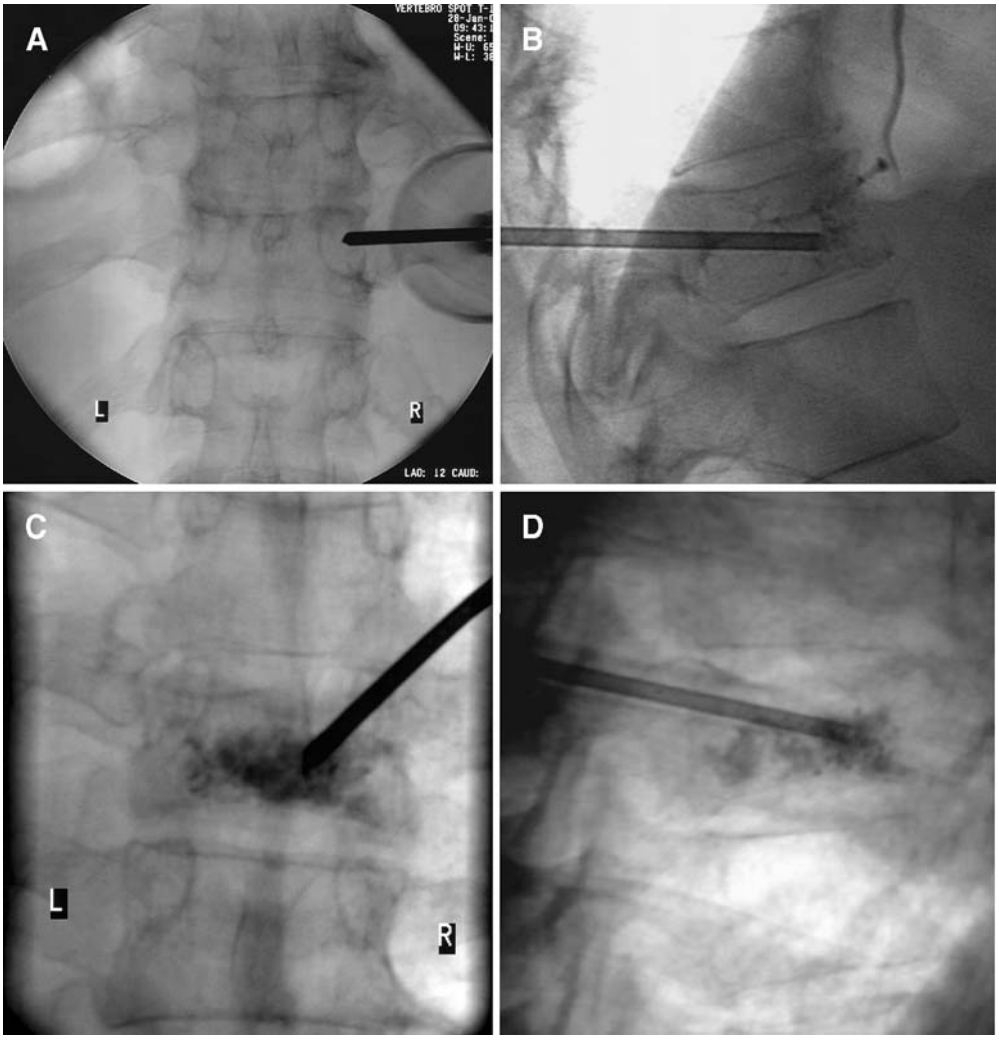

Fig. 1 Fluoroscopic spot films of the lower thoracic spine. **A** Bone biopsy device aligned along the right pedicle of a slightly compressed vertebral body. **B** Bone biopsy device placed in the mid-vertebral body, with contrast injection demonstrating venous communication. The device is advanced slightly, with no subsequent venous enhancement. **C,D** Injection of methyl methacrylate with excellent spread of material

ment in patient quality of life in more than 80%. These authors recommend radiation therapy following administration of methyl methacrylate, as radiation complements the analgesic effect of methyl methacrylate. Local recurrence is rare following the procedure, even without additional radiation therapy [31].

Methyl methacrylate has also been used for the treatment of periacetabular metastases. In our center we treat periacetabular metastases for pain or for lesions, that, with progression, would likely lead to fracture. Our approach for these periacetabular metastases has been first to ablate the lesion, with either cryoablation or radiofrequency ablation, followed the next day by the cementoplasty procedure. For example, this approach was used to treat a 65-year-old man with a painful metastatic lesion involving the left periacetabular region (Fig. 2). This patient experienced complete pain relief, which has been sustained for 11 months. He has also been able to avoid both a fracture and the morbidity associated with operative acetabular stabilization.

Others have used cementoplasty alone to treat periacetabular metastases, lower extremity lesions, and pelvic bone metastases [29, 39–43]. Cotten and colleagues treated 12 periacetabular metastases in 11 patients that could not be treated surgically because of the location, extent, or number of the metastases or because of the patients' associated comorbidities [39, 40]. Each patient also underwent radiation therapy an average of 21 days following the procedure. The authors found an improvement in pain in most patients soon after the procedure that was sustained in nine patients and improved walking in each patient an average of 3 days following the procedure. One patient subsequently suffered an acetabular fracture with increased pain. Bone cement leaked into the joint space in one patient, with transitory increased pain but with no impact on subsequent pain relief or walking improvement. Hokotate and colleagues reported percutaneous administration of methyl methacrylate for a painful periacetabular hepatocellular carcinoma metastasis that was unresponsive

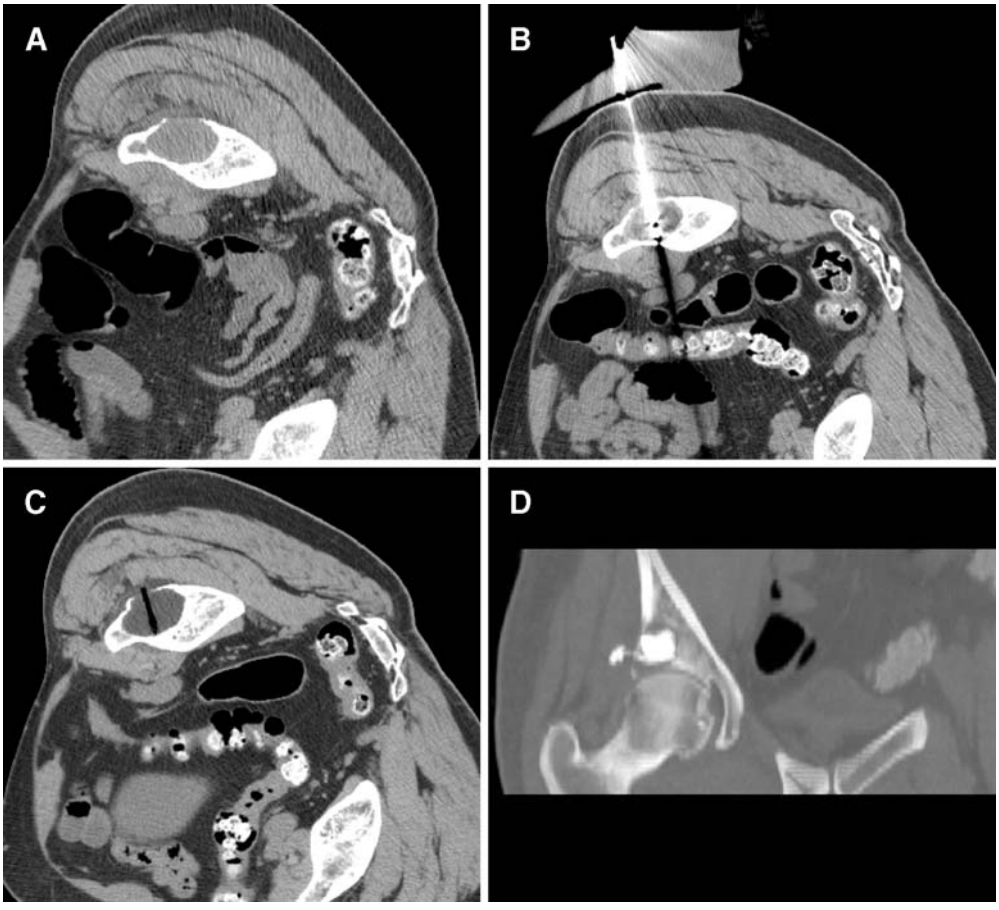

Fig. 2 Pain palliation and stabilization of a non-small cell lung cancer metastatic lesion, involving the periacetabular region, using cryoablation followed by cementoplasty. **A** Non-contrast-enhanced CT of the pelvis demonstrates an osteolytic lesion in the left supra-acetabular region. The patient had difficulty walking without the use of a cane prior to the procedure. **B** Non-contrast CT of the pelvis showing two cryoprobes placed into the lesion. **C** Non-contrast CT of the pelvis immediately following removal of the cryoprobes shows the low attenuation ice ball encompassing the malignant lesion. **D** 3D volumetric image showing methyl methacrylate cement filling the supra-acetabular defect. The patient also received 3,000 cGy in ten fractions. The patient continues to be pain-free and is walking normally 11 months after the treatment

to chemoembolization and radiation therapy. This patient obtained pain relief, within 1 day of the treatment, which persisted for 3 months until the patient's death [41]. Marcy and colleagues described the use of bone cement for the treatment of 18 patients with painful metastatic lesions in the acetabulum, iliac bone, and sacrum [42]. They found mild–moderate pain relief at 1 month follow-up and improved walking in all but two patients. One patient suffered an acetabular fracture 15 days following the procedure. Hierholzer and colleagues reported substantial immediate pain relief, in five patients with painful metastases to the pelvis and femur, following injection of bone cement with elimination of the need for pain medication in the follow-up period [43].

Percutaneous laser-induced interstitial thermotherapy

Gröenemeyer and colleagues reported the treatment of three patients, with spinal metastases, using a Nd:YAG laser with a wavelength of 1,064 and a 400 μm fiber [44]. With local anesthesia and CT guidance, a coaxial system was used via a transpedicular approach. Laser energy was applied at a power of 4–10 W with a pulse length of 0.1–1.0 s at 1 s intervals. In order to achieve coverage greater than 7 mm, the fiber was repositioned and the thermal treatment repeated, completing the procedure in 60–90 min. Three months after treatment, the patients had 45%, 30%, and 35% pain reduction.

Percutaneous cryoablation

Cryoablation has a long history of successful treatment of neoplasms in several organs, including prostate, kidney, liver, and the uterus. First-generation devices were limited to intraoperative use because of their large diameter, the use of liquid nitrogen for tissue cooling, and the lack of well-insulated probes. Newly developed percutaneous cryoprobes are based on delivery of argon gas through a segmentally insulated probe, with rapid expansion of the gas that results in rapid cooling, reaching −100°C within a few seconds. The use of sealed cryoprobes with small diameters (1.7 mm and 2.4 mm) and with insulation along the shaft allows the use of these devices either percutaneously or intraoperatively. Active thawing of the ice ball is achieved by the active instillation of helium gas, instead of argon gas, into the cryoprobes. The Endocare Incorporated (Irvine, Calif, USA) system allows the independent operation of up to eight cryoprobes at a time. A single cryoprobe

provides an ice ball of approximately 3.5 cm diameter. A great advantage of the cryoablation systems is that the use of multiple cryoprobes allows the generation of large ice balls (>8 cm diameter), possible shaping of the ablation zone through varied geometry of probe placement, and decreased procedure time for large lesions by avoiding the need to perform the time-consuming overlapping ablations needed with other ablation techniques. Importantly, synchronous ablation with several cryoprobes eliminates possible residual disease that can result from the use of overlapping ablation at the single ablation interfaces [45].

Cell death from cryoablation is due to two causes. First, rapid freezing immediately adjacent to the probe results in intracellular ice formation and subsequent cell destruction. At a further distance from the probe, relative gradual cooling causes osmotic differences across the cell membrane, with secondary cellular dehydration and death. Given relative cellular tolerance to freezing temperatures, cell death occurs within about 3 mm internal to the ice ball margin [46, 47].

Preliminary data suggest that cryoablation is effective in treating painful primary and secondary bone neoplasms [48]. In this preliminary work, 16 tumors in 14 patients were treated with percutaneous cryoablation using MR guidance. These investigators reported a significant reduction in patients' pain in the immediate postoperative period. This pain relief continued over the long term, with associated significant improvement in patients' quality of life.

As part of an on-going prospective clinical trial, we have treated ten patients with painful metastatic disease involving bone. This effort involves treating patients who have one or two painful lesions that cause ≥4/10 pain in a 24 h period. We are assessing patients pain regularly over a 2 year period, using the Cleeland Brief Pain Inventory [49, 50], a validated visual analogue scale for assessment of patient pain. Although statistical evaluation is premature, preliminary data are encouraging.

As an example of the successful use of percutaneous cryoablation, we treated a patient with a single painful metastatic focus of paraganglioma involving the left clavicular head. Unfortunately, this patient also suffered from

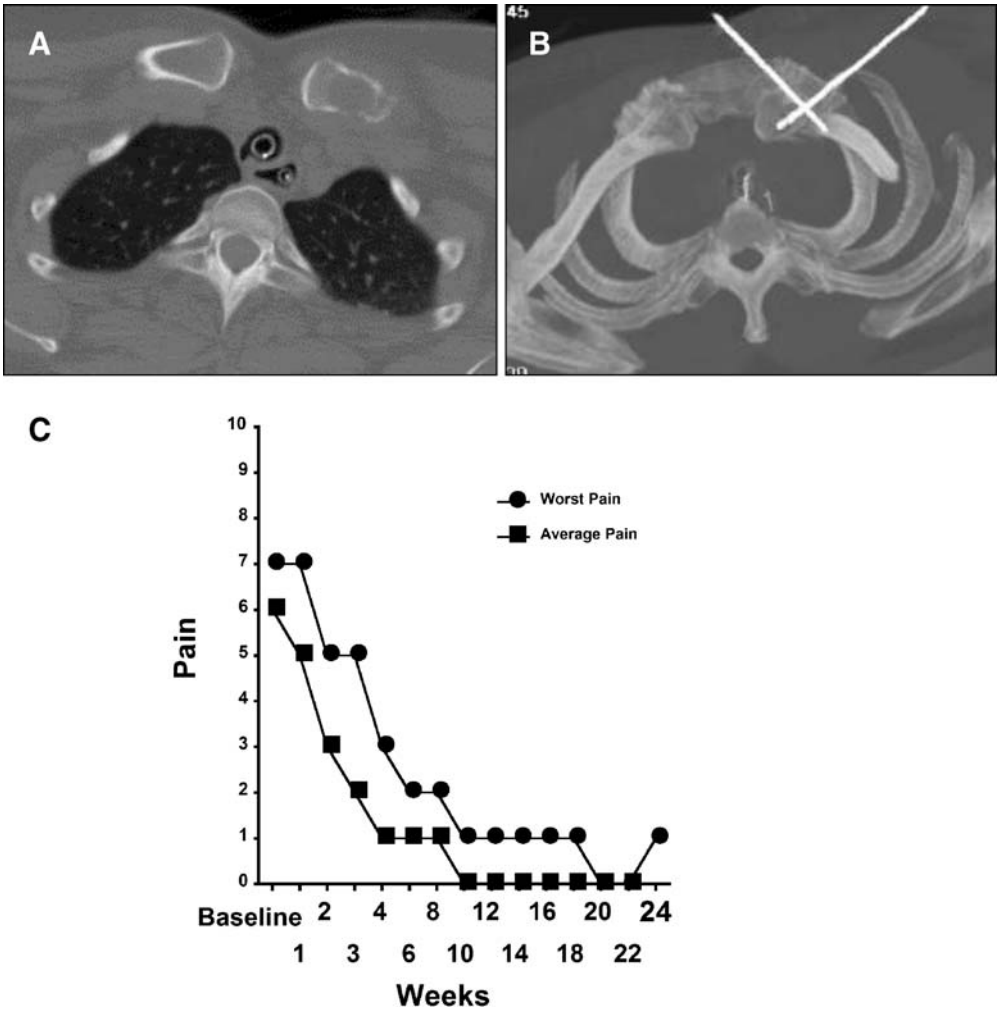

Fig. 3 Metastatic paraganglioma involving the clavicular head treated with cryoablation. **A** Non-contrast CT demonstrates an osteolytic lesion involving the left clavicle. The lesion caused 7/10 worst pain in a 24 h period prior to treatment. **B** 3D volumetric CT scan showing two cryoprobes placed into the lesion. **C** Worst and average pain scores over a 24 h period at baseline and over a 2 year follow-up period

the systemic effect of the catecholamine-releasing tumor, with palpitations and elevated blood pressure. Following appropriate premedication with metoprolol, phenoxybenzamine and metyrosine, two crossing probes were placed into the lesion, with both ultrasound and CT guidance. An ice ball was generated that completely encompassed the lesion (Fig. 3). The patient experienced excellent durable reduction in her pain and also, importantly, her catecholamine levels returned to normal and her blood pressure stabilized.

Another example of the use of cryoablation involved a patient with metastatic ovarian cancer who presented with 7/10 pain in the right groin region. CT examination found a small metastatic lesion in the right pelvis (Fig. 4). Unfortunately, at the time of ablation of this pelvic metastasis, the right colon was in contact with the lesion. We attempted to displace the colon with sterile water; however, the displacement was insufficient to allow a safe ablation. An important advantage of cryoablation over high temperature ablation methods is the option to use tissue displacement devices such as balloons to avoid damaging adjacent normal tissue. This approach was successful, as deployment of a small balloon allowed safe ablation to be performed. This patient experienced mild transient perineal pain, which resolved over a 4 week period. She also reported marked improvement in her typical pain, with a great improvement in her quality of life over a 2 year period of follow-up.

Percutaneous radiofrequency ablation

Recently, several case reports have appeared that describe the treatment of painful metastatic lesions with percutaneous radiofrequency ablation. Included below are descriptions of several of these case reports. Following this, we include a summary of results of a completed prospective clinical trial designed to determine the clinical magnitude and durability of the use of radiofrequency ablation for the treatment of painful metastatic disease involving bone.

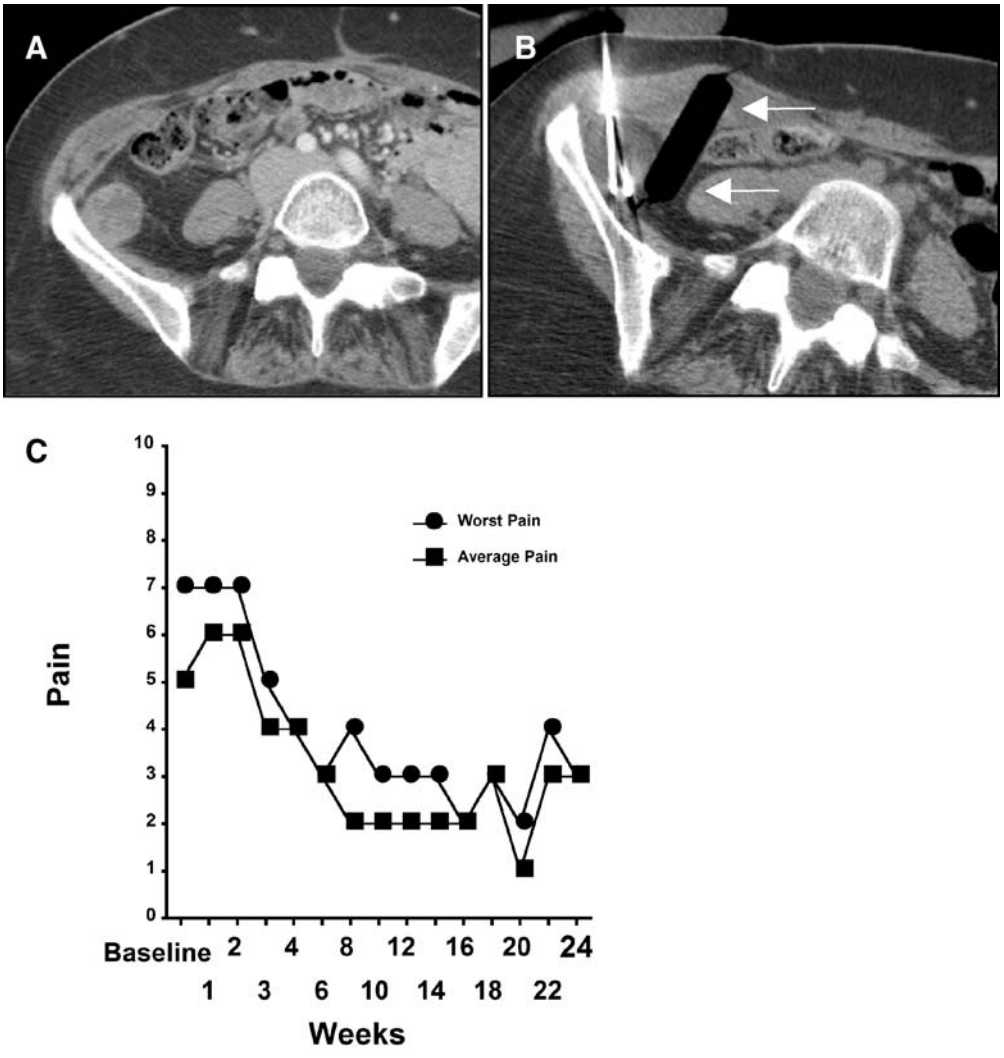

Fig. 4 Metastatic ovarian cancer abutting the right iliac bone, resulting in 7/10 worst pain in a 24 h period prior to treatment. **A** Contrast-enhanced CT of the pelvis demonstrates a metastatic mass in the right pelvis. **B** Non-contrast CT of the pelvis showing two cryoprobes placed into the lesion, with an ice ball encompassing the lesion. A balloon was deployed at the time of the procedure to displace the adjacent ascending colon (*arrows*). **C** Worst and average pain scores over a 24 h period at baseline and over a 2 year follow-up period

Percutaneous radiofrequency ablation: case reports and series

As a prelude to treatment of spinal metastatic disease, Dupuy and colleagues used a pig model to examine the temperature distribution within a vertebral body and the adjacent spinal canal, with the radiofrequency ablation electrode placed within the vertebral body [51]. They found decreased heat transmission in cancellous bone and an insulative effect of cortical bone. Importantly, temperature elevations in the epidural space were not high enough to cause injuries to the adjacent spinal cord. Subsequently, these workers reported the treatment of a woman with a painful osteolytic focal metastatic hemangiopericytoma lesion in the anterior aspect of a lumbar vertebral body. Using local anesthesia and conscious sedation, the authors accessed the lesion using a far lateral approach, passing through intact cortex with a 14-gauge Ackermann bone biopsy needle (Cook, Bloomington, Ind., USA). Subsequently, a 3 cm exposed-tip Radionics radiofrequency electrode (Tyco Healthcare Group LP, Burlington, Mass., USA) was used to treat the lesion. The patient had improved pain control at the latest follow-up evaluation of 13 months. It is important to note that careful patient selection is important in the treatment of vertebral body lesions. Intact bone provides at least partial insulation of the spinal canal from excessive heat. However, if cortical destruction is present this insulative barrier is also destroyed, and spinal cord or major nerve injury may result if ablation is performed in this region.

Gröenemeyer and colleagues reported the radiofrequency ablation treatment of ten patients with 21 unresectable painful spinal metastases, using an expandable-type electrode (RITA Medical Systems, Mountain View, Calif., USA) with a 50 W generator. The patients were treated with local anesthesia only. Target temperature for the ablations was chosen on the basis of distance from the spinal cord and patient tolerance for the procedure. Four of the patients were also treated with vertebroplasty, receiving 3–5.5 ml of polymethyl methacrylate 3–7 days following radiofrequency ablation [52]. At last follow-up, nine of the ten patients reported reduced pain, with an average pain reduction of 74%. Although it may be possible to treat selected patients with local anesthesia, in most cases a minimum of conscious sedation is necessary, and, for many patients, general anesthesia is indicated for adequate pain control.

Patti and colleagues reported the treatment of a patient with metastatic fallopian tube carcinoma with multiple painful subcutaneous masses [53]. Using conscious sedation and local anesthesia, they treated the lesions for 10 min at a target temperature of 110°C with a model 70 electrode and 50 W generator. Immediately following treatment, the patient had no pain at the treated sites and reported 1–3/10 pain 1 month later.

Ohhigashi and colleagues reported the RF ablation treatment of painful recurrent rectal cancer in the pelvis [54]. Notably, recurrent rectal cancer may produce local pain, rectal bleeding, or bowel obstruction, with resultant poor quality of life. Although a curative approach, such as total pelvic exenteration, is possible, few patients are eligible for this treatment [55]. Unfortunately, radiation therapy is palliative only and of limited clinical benefit [56]. These workers treated two patients with 4 cm diameter and 6 cm diameter recurrent rectal carcinomas located anterior to the sacrum, which had not responded to chemotherapy or radiation therapy. Using epidural catheter mediated analgesia, they placed a LeVeen RF electrode (Boston Scientific Corp., Tokyo, Japan) into the lesions using CT guidance. Both patients reported a decrease in pain following the treatment and a reduction in oral analgesic requirements.

Schaefer and colleagues described the combined use of percutaneous radiofrequency ablation, with subsequent administration of bone cement, for a painful pathological fracture of the tibial plateau. The patient was able to resume walking 1 day after the procedure, and follow-up imaging at 3 months showed no change in the position of the bone cement [57].

Percutaneous radiofrequency ablation: clinical trial

Because of the several reports suggesting the potential benefits of RFA for palliation of pain from metastatic disease, we conducted and published the results a feasibility clinical trial to determine the safety and benefits of RFA in patients with painful metastatic lesions involving bone [58]. Our preliminary data showed that this procedure was safe and resulted in significant relief of pain; therefore, the study was expanded to enroll patients from other centers in the United States of America and Europe. We reported an analysis of the multicenter trial data following the treatment of 43 patients, again finding highly significant reductions in patient pain following treatment with radiofrequency ablation [59, 60].

The completed multicenter trial involved the treatment of 62 patients at five centers in the USA and Europe over a 2 year period. Patients that were included had ≥4/10 worst pain over a 24 h period from ≤2 painful sites of metastases based on the Brief Pain Inventory (BPI) [49, 50]. In the BPI, patients are asked to rate their worst, least and average pain in the past 24 h, with allowed responses ranging from 0 to 10 (0 = no pain, 10 = pain as bad as you can imagine). Relief of pain secondary to the RFA procedure or to pain medication is scored on a scale of 0% (no relief) to 100% (complete relief). Pain interference with daily living is evaluated by questions concerning general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life, also on a 0–10 scale (0 = no interference, 10 = completely interferes).

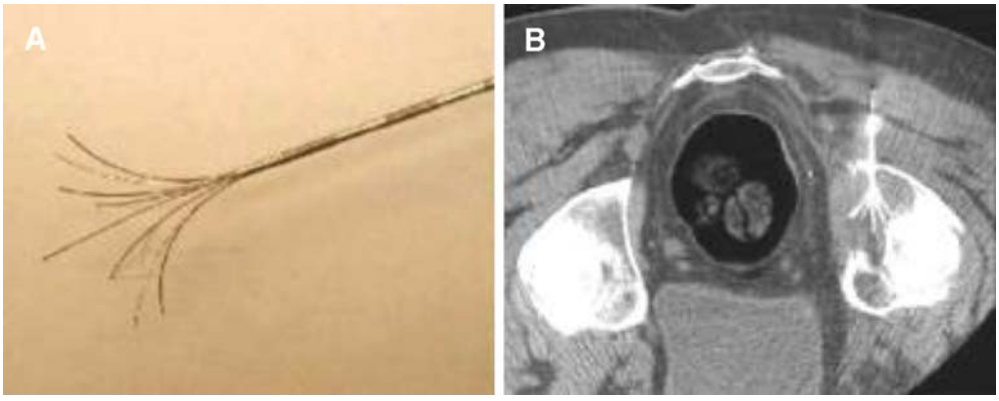

Fig. 5 **A** RF ablation electrode with full deployment (Starburst XL electrode, RITA Medical Systems). **B** CT scan with RF ablation electrode deployed in an osteolytic lesion in the acetabular region

Patients were treated under conscious sedation or general anesthesia at the discretion of the individual investigator. All patients included in the study were treated with a Starburst XL model needle (RITA Medical Systems), a 14 gauge/6.4 Fr device, with an active electrode trocar tip and nine electrodes spread in a ball-like fashion that generates up to a 5 cm diameter zone of necrosis (Fig. 5).

Immediate post-procedural pain has been treated with epidural or intravenously administered opioid analgesics. Depending on the size of the treated lesion and the degree of post-operative pain, patients were typically observed overnight in the hospital. Patients with persistent post-procedural pain were switched to oral opioid analgesics at the time of discharge.

Representative cases and lessons learned

Importance of treatment of the bone–tumor interface

Figure 5 shows the needle fully deployed, and deployment of the tines into an osteolytic lesion in the periacetabular region. This figure illustrates that the electrode is advanced into the soft-tissue portion of the lesion to be treated and the tips of the tines of the electrode are placed against the soft-tissue/bone interface. Figure 6 shows another example of an osteolytic lesion that involves the L5 vertebral body, with associated partial destruction. The RF electrode is placed with the tines driven against the bone–soft tissue interface. Subsequent electrode deployments (not shown) are performed to completely treat the portion of bone involved in the destructive metastatic lesion. Electrode deployment diameters are chosen to cover the metastatic lesion adequately without damaging nearby normal, uninvolved tissues.

In other centers some lesions have been treated with placement of the electrode into the center of the lesion with resultant debulking of the lesion but with incomplete ablation of the soft-tissue bone interface. Figure 7 shows a large osteolytic metastatic lesion involving the sacrum 6 weeks following RF ablation. This image shows central low attenuation within the metastatic lesion consistent with necrosis from the RF ablation procedure. Residual tumor is clearly present along the medial aspect of the sacrum and against the adjacent iliac bone. Following this treatment, the patient failed to derive reduction of pain and received no clear benefit from the procedure.

Importance of localizing source of pain

It is critically important to examine each patient prior to the RF ablation treatment to determine whether the patient's pain corresponds to an identifiable lesion on CT, MRI, or US imaging. Figure 8 shows a prone CT scan of a metastatic osteolytic lesion involving the mid-sacrum. The patient was examined, and a metallic marker was placed on the skin overlying the site of greatest pain. As shown in Fig. 8, the site of pain corresponded to a sacral fracture on

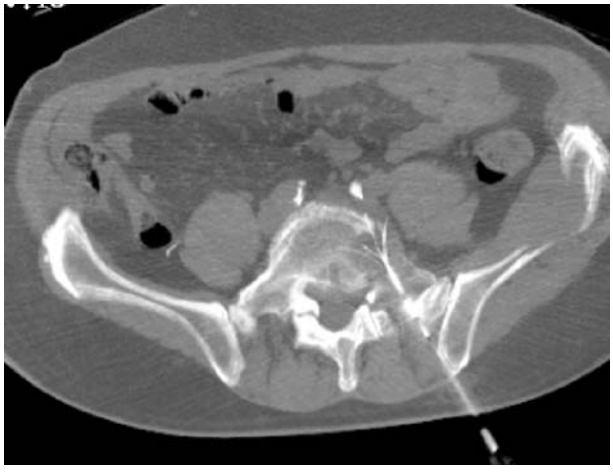

Fig. 6 RF ablation treatment of the bone–tumor interface. CT demonstrates osteolytic destruction involving the left aspect of the L5 vertebral body. The electrode is deployed with the tines engaging the destroyed margin of the involved bone. Incidentally noted is an old pars interarticularis fracture on the right. The bone–tumor interface is a key site for electrode deployment in order to destroy nerve endings that are a likely cause of pain

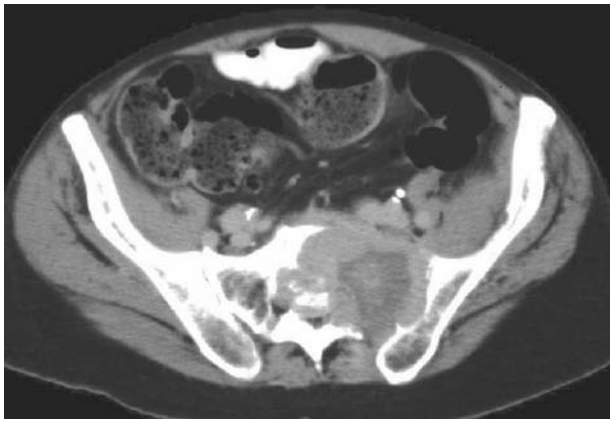

Fig. 7 Failed palliation of pain due to RF ablation treatment of the central portion of a metastatic lesion without treatment of the tumor–bone interface. CT performed 6 weeks after RF ablation demonstrates necrosis in the treated central portion of the tumor, with moderate residual tumor involving the sacrum and iliac bone. To be effective, the RF ablation treatment should be at the tumor–bone interface. Debulking of the central portion of metastatic lesions is not effective in reducing pain

the side opposite the destructive sacral lesion. Because the patient's pain likely resulted from the underlying sacral fracture, we did not treat the adjacent destructive sacral lesion.

Painful metastases involving the sacrum

Patients who have locally recurrent metastatic rectal carcinomas involving the sacrum or the presacral space often have pain associated with their disease. Several patients were treated for recurrent or residual metastatic rectal carcinoma centered anterior to the sacrum in the presacral space, often with associated osteolytic destruction of the underlying sacrum. Figure 9 shows a typical lesion in a 38-year-old man, measuring approximately 3 cm in diameter and located at the level of the coccyx, with 8/10 pain. The patient's pain had decreased to 2/10 at week 4, and he reported 1/10 pain at the treated site at the latest follow-up interview, 24 months following treatment.

Remarkably, even large painful lesions may be treated effectively with RF ablation. Figure 10 shows a portion of a destructive infiltrative metastatic rectal carcinoma lesion involving the sacrum. This lesion measured approximately 11 cm in diameter and involved the majority of the sacrum. Figure 10A is a CT scan at the level of the lower sacrum that shows the large destructive lesion. The patient was unable to sit or lie on his back due to severe pain, which he rated as 8/10. Prior treatments included resection of the

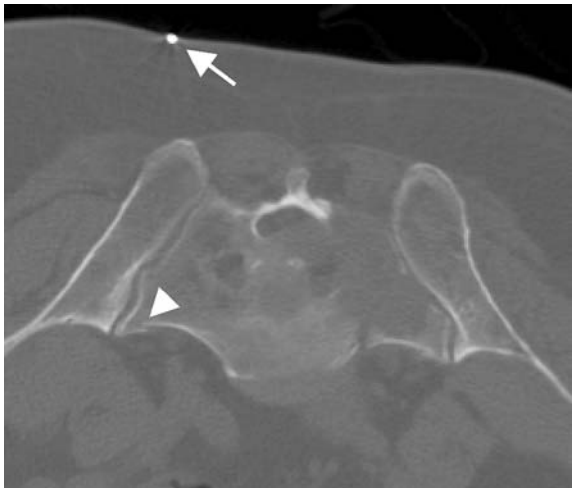

Fig. 8 Importance of determining exact site of pain. In this case pain is due to a sacral fracture rather than osteolytic tumor. Prior to CT examination, the patient was examined, and a metallic marker (*arrow*) was placed on the skin overlying the site of focal pain. CT scan shows an osteolytic destructive lesion, involving the sacrum, opposite a sacral fracture (*arrowhead*). This lesion was not treated, as the patient's pain was more likely due to the sacral fracture than to the adjacent osteolytic lesion

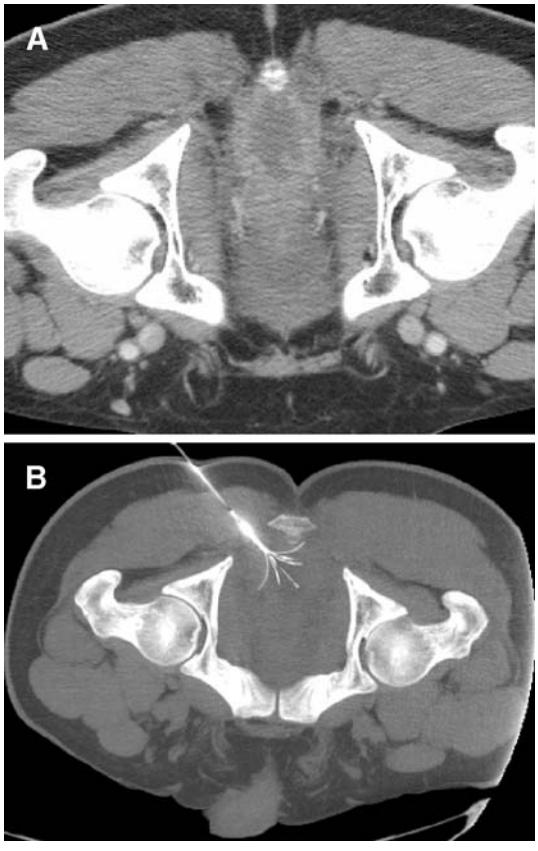

Fig. 9 Metastatic presacral rectal carcinoma. **A** Prone contrast-enhanced CT demonstrates a peripherally enhancing soft-tissue mass anterior to the coccyx. **B** Prone CT demonstrates the RF ablation electrode deployed within the mass. The patient's pain had decreased from 8/10 to 1/10 4 weeks after treatment. The patient continued to report 0–1/10 pain at this site 24 months after treatment

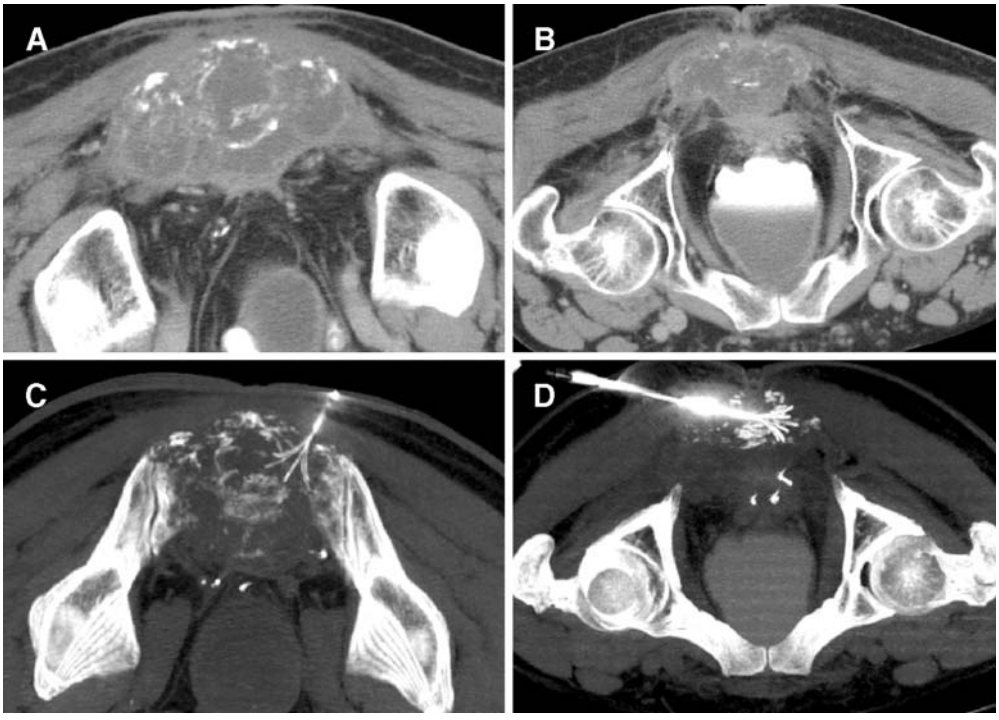

Fig. 10 RF ablation of a large sacral metastasis. **A,B** Prone CT demonstrates near-complete replacement of the sacrum by metastatic rectal carcinoma. **C,D** RF ablation electrodes deployed to 5 cm. These were two of seven electrode placements during the first of stage of treatment for the ablation of much of the caudal aspect of the osteolytic lesion. The second-stage treatment of the mid-sacrum was performed 6 weeks later. The patient was unable to sit prior to treatment and had resting pain of 8/10. One day following the ablation the patient was able to sit. His pain had decreased to 3/10 following the first stage and to 0/10 soon after the second stage of treatment

rectum with a diverting colostomy. The patient had reduced bladder function that he described as difficulty with initiation of voiding and incomplete emptying of his bladder. Because there was the desire to retain the patient's bladder function, the lesion was treated in two stages, 6 weeks apart, with a total of 14 electrode deployments, with the initial treatments focused on the caudal aspect of the sacrum. Figures 10C and D show two of the seven RF ablation

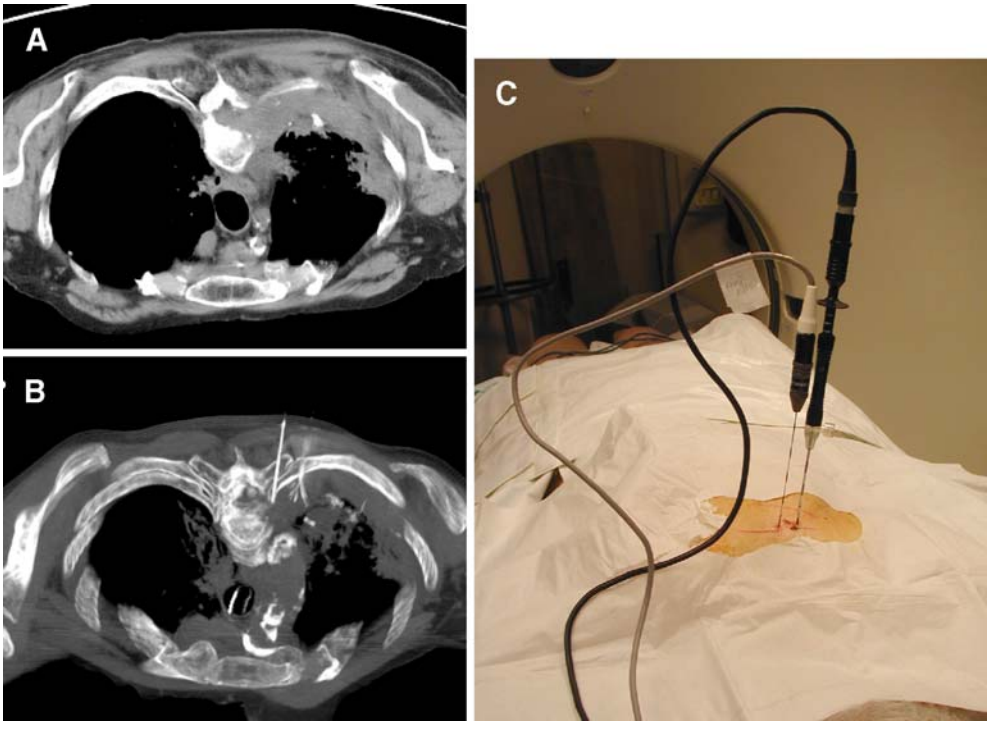

Fig. 11 Metastatic colorectal carcinoma involving rib, vertebral body and pleural surface. **A** Prone CT demonstrates osteolytic destruction of the lateral portion of the vertebral body, with associated soft-tissue mass anterior to the rib. **B** Prone CT scan shows the passive thermocouple probe placed near the vertebral body pedicle with the RF electrode deployed laterally in the metastatic lesion. Ablation was discontinued when the temperature at the passive thermocouple reached 40°C. **C** Photograph of the RF ablation electrode in place, with adjacent thermocouple located medially. The patient's pain had decreased from 10/10 to 3/10 4 weeks after the treatment

electrodes at the first stage of the treatment. Following the initial treatment, the patient was able to sit in bed the same day and described 3/10 pain in the treated region 4 weeks following the procedure. Because of the patient's desire for greater pain relief, and with the understanding that further RF ablation could lead to loss of bladder function, we treated the superior portion of the lesion up to the level of the S2 neural foramina. Within 4 weeks, his pain had decreased to 0/10 at the treated region, and, fortunately, his bladder function was not disturbed by the treatment.

RF ablation of painful paraspinal lesions

RF ablation of painful paraspinal metastatic lesions is also possible. Extreme caution must be used when metastatic lesions have destroyed the vertebral body with resultant loss of the insulative effect of the adjacent bone [51]. Figure 11A shows a CT scan of a large metastatic colorectal carcinoma lesion involving a rib, vertebral body and pleural surface. So that thermal damage to the spinal cord could be avoided, a passive thermocouple was placed along the lateral aspect of the destroyed pedicle (Fig. 11B,C). Subsequently, the lesion was treated with three electrode deployments along the involved rib. With the electrode deployed in the nearest paraspinal location (Fig. 8D), treatment was discontinued when the passive thermocouple reached 40°C. This patient reported a reduction in pain from 10/10 prior to the treatment to 3/10 4 weeks after the RF ablation procedure.

Pain assessment and follow-up

Patients' pain was the primary endpoint in the clinical trial and was measured with the BPI. All patients were interviewed with the BPI just prior to the procedure, the day following the treatment, weekly for 1 month, and then every 2 weeks for the second month through the six-month follow-up. Each patient was asked to answer the questions with respect to the lesion that was treated.

The type of malignancy, size, and location of the lesions that were treated are summarized in Table 1. The majority of lesions treated were renal and colorectal metastases, with breast and lung also commonly treated. The most common sites of tumor involvement were in the pelvis, sacrum, ribs, and vertebrae. Treated lesions were osteolytic, with the exception of those of two patients who had mixed osteolytic/osteoblastic lesions. The size of the treated lesion ranged from 1 cm in a rib to approximately 18 cm in the paraspinal region. The median number of ablations per lesion was 3.0 (range 1–14) with an average time per ablation of 11.7 min (range 1.1–52.5 min). The mean total ablation time was 42.2 min (range 8.0–218.9 min).

Table 1 Characteristics of patients treated with RFA in a multicenter trial

Characteristic		
Number of patients	62	
Female	22	35%
Male	40	65%
Age	Median	Range
	64 years	28–88 years
Tumor type (number)		
Renal CA	14	
Colorectal CA	12	
Lung CA	4	
Breast	4	
Sarcoma	3	
Other	25	
Tumor size (largest diameter)	6.3 cm	Range
		1.0–18.0 cm
Tumor location		
Pelvis	19	
Sacrum	12	
Rib	6	
Vertebrae	4	
Other	21	
Prior radiation to treated site	44	71%
Concurrent opioid analgesics	52	84%

Pain response to RF ablation

A total of 59/62 patients (95%) experienced a drop in pain that was considered clinically significant when a predefined validated endpoint (≥2 point drop in worst pain in a 24 h period) was utilized [61]. Patients experienced highly significant reductions in worst pain, average pain, and pain interference, and significant improvements in pain relief after RFA of painful metastases involving bone (Fig. 12). Significant decreases were seen, beginning at week 1 and extending to week 24 for all pain parameters (Table 2). Prior to RFA treatment, the mean score for worst pain in a 24 h period was 7.7/10, with a range of 4–10/10. Four, 12, and 24 weeks after treatment, mean worst pain had decreased to 4.9, 3.5, and 2.4, respectively. These changes in worst pain over a 24 h period equate to 36%, 55%, and 69% decreases at weeks 4, 12, and 24, respectively. Average pain prior to treatment was 5.6, which decreased to 3.2 at 4 weeks, 2.4 at 12 weeks, and 1.8 at 24 weeks. These changes in average pain over a 24 h period equate to 43%, 57%, and 68% decreases at weeks 4, 12, and 24 weeks, respectively. Mean pain interference decreased from 6.6 at baseline to 4.1 at week 4, 3.2 at week 12, and 1.3 at week 24. These changes in mean pain interference over a 24 h period equate to 38%, 52%, and 80% decreases at weeks 4, 12, and 24 weeks, respectively. Pain relief from

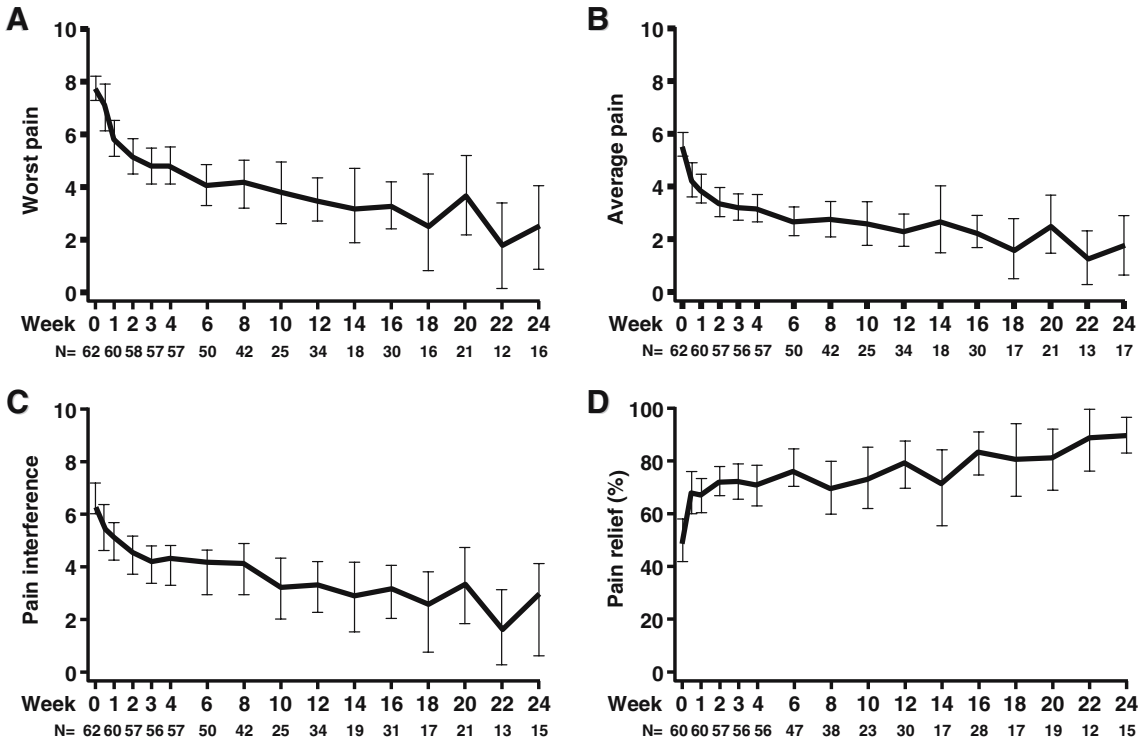

Fig. 12 Mean BPI pain scores over time for patients treated with RFA. **A** Worst pain; **B**) average pain; **C** interference of pain in daily activities; **D** pain relief from RFA and medications. *Error bars* represent the 95% confidence intervals. *N* number of patients completing BPI at each time point

treatments or medication improved from 50% (0–100%) at baseline to 71% at 4 weeks, 79% at 12 weeks, and 90% at 24 weeks. Two patients, whose pain responded to initial RFA, required retreatment after a recurrence of pain (≥4/10 worst pain) at week 8 and week 16, respectively. Both patients had significant drops in worst pain (≥4 point drop) following retreatment.

Opioid use was recorded for each patient and converted into morphine equivalents using standardized conversions [61]. Following RFA, opioid requirements peaked at week 1 (Table 2). At week 4, although opioid requirements were not statistically different from baseline, a trend towards decreasing requirements was seen. By weeks 8 and 12, significant reductions in opioid usage were seen. Increases in opioid usage were seen at week 24, although the corresponding pain scores did not increase at that time. These increases in analgesic requirements likely reflect pain resulting from other sites, as pain scores that were

Table 2 Number of patients, BPI mean pain scores, and opioid requirements at baseline and following RFA

Parameter	Baseline	Day 1	Week 1	Week 4	Week 8	Week 12	Week 24
Number	62	47[a]	60	57	42	34	17
Worst pain	7.7	7.0	5.8	4.9	4.1	3.5	2.4
(0–10)		*P*=0.1330	*P*<0.0001	*P*<0.0001	*P*<0.0001	*P*<0.0001	*P*=0.0001
Average pain	5.6	4.3	3.9	3.2	2.8	2.4	1.8
(0–10)		*P*<0.0001	*P*<0.0001	*P*<0.0001	*P*<0.0001	*P*<0.0001	*P*=0.0001
Pain interference	6.6	5.5	5.0	4.1	3.9	3.2	1.3
(0–10)		*P*=0.0053	*P*=0.0001	*P*<0.0001	*P*<0.0001	*P*<0.0001	*P*=0.0013
Pain relief	50	68	67	71	70	79	90
(0–100)		*P*=0.0004	*P*<0.0001	*P*<0.0001	*P*=0.0002	*P*<0.0001	*P*=0.0011
Morphine equivalent dose	66.0	220.0	90.8	84.0	27.5	98.4	44.0
(MED)		*P*=0.05	*P*=0.01	*P*=0.02	*P*=0.27	*P*=0.74	*P*=0.62

P values are signed-rank tests of the null hypothesis that the difference in the current time period minus the baseline value is equal to zero
[a]US cohort only

collected with the BPI were specific to the site that was treated by RFA. Most patients that were included in this study had progression of their metastatic disease over the follow-up period.

Significant adverse events following the procedure were noted in 4/62 (6.5%) patients. One patient developed an acetabular fracture 6 weeks following RFA of a breast cancer metastasis, with significant involvement of the ilium, ischium and acetabulum. The patient required open reduction and fixation of the acetabulum. In the absence of RFA, this fracture would have likely occurred. It is not known whether RFA treatment of this lesion shortened or lengthened the time to fracture. Three patients developed worsening of tumor–cutaneous fistulas within 1–2 weeks of the procedure. These patients had in common a central necrotic metastatic colorectal lesion in the presacral space abutting the sacrum. They all had received prior radiation therapy. The site of the fistula was not along the probe placement tract in any of the affected patients. Approximately 20 other patients were treated for metastatic disease in the low pelvis or perineum and did not develop tumor–cutaneous fistulas as a result of the treatment. This complication can most likely be avoided by careful examination of the perineum prior to ablation. If a fistula is present, RFA of these lesions should not be performed or the patient should be advised that the treatment may result in exacerbation of the fistula.

A minor adverse event occurred in 1/62 patients (1.6%), who developed a second-degree skin burn at the grounding-pad site. This burn resolved with conservative therapy. As a result of this skin burn, all further RF ablations were monitored with skin temperature thermometers. Cold-packs were placed over the grounding pads when skin temperatures exceeded 38°C. One patient developed transient bowel and bladder incontinence following RFA of a previously irradiated leiomyosarcoma metastasis involving the upper sacrum.

Percutaneous RFA is the most studied of the ablative methods. However, the results of this multicenter trial can likely be extended to the use of other ablative methods. This is important, as centers have different experiences and comfort with the use of other ablative methods. It is important, also, because the application of these methods for a particular lesion may favor one of the methods because of anatomical location or adjacency of other critical structures. For example, ablation of a lesion adjacent to the spine requires careful monitoring of the ablation zone during the procedure. This is more easily achieved by cryoablation in a CT or MRI suite, or possibly the use of LITT or RF in an MRI suite, where the ablation margin can be monitored while the ablation is being performed.

Summary

Percutaneous ablation techniques are important treatment alternatives for managing pain due to bony metastatic disease. Significant pain reduction is possible in patients who have failed to achieve benefit from conventional therapies that include chemotherapy and external beam radiation. Importantly, the pain reduction that is achieved is durable.

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