Journal of Cancer Metastasis and Treatment

Review

Open Access

Thermal ablation of metastatic disease to the musculoskeletal system

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How to cite this article: Xia E, Huang AJ. Thermal ablation of metastatic disease to the musculoskeletal system. *J Cancer Metastasis Treat* 2023;9:36. https://dx.doi.org/10.20517/2394-4722.2023.26

Received: 23 Mar 2023 First Decision: 7 Jun 2023 Revised: 30 Jul 2023 Accepted: 8 Oct 2023 Published: 1 Nov 2023

Academic Editors: Santiago A Lozano-Calderon, Christos A. Papadimitriou Copy Editor: Fangling Lan Production Editor: Fangling Lan

Abstract

A variety of indications have been published regarding the use of percutaneous thermal ablation for treating tumors of the musculoskeletal system, including bone and soft tissue lesions, benign and malignant lesions, and primary and metastatic tumors. In the appropriately selected patient, the advantages of percutaneous thermal ablation include decreased morbidity, decreased cost, and shorter hospitalization stays compared to surgery. The number of different thermal ablation modalities is increasing, and each modality has its advantages and disadvantages. Studies directly comparing the effectiveness of the various thermal ablation modalities are sparse, however, so the choice of ablation modality often depends on availability, user preference, and local expertise. Although the list of uses for percutaneous thermal ablation is ever-expanding, in this article, we will discuss the two most well-established indications, which are palliation of pain attributed to bone and soft tissue metastases and local control of oligometastatic disease. Numerous clinical trials have shown percutaneous thermal ablation to be an effective method of palliating pain due to bone and soft tissue metastases and of achieving local control in the setting of oligometastatic disease with low rates of complication.

Keywords: Musculoskeletal intervention, radiofrequency ablation, cryoablation, image-guided, metastatic disease



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INTRODUCTION

Percutaneous thermal ablation is a minimally invasive treatment in which one or more specialized needles - ablation probes - are inserted into a target lesion(s) using image guidance. These ablation probes are attached to a device that delivers lethal thermal energy to a zone around the tip of the ablation probe known as the ablation zone. The size and shape of the ablation zone are determined by the size of the active tip of the ablation probe and the type of thermal energy being delivered, such as radiofrequency ablation versus cryoablation. Multiple ablation probes can often be used simultaneously to craft customized ablation zones that conform to the size and shape of the lesion being treated. In the appropriately selected patient, advantages of percutaneous thermal ablation include decreased morbidity, decreased cost, and shorter hospitalization stays compared to surgery^[1].

A variety of indications have been published regarding the use of percutaneous thermal ablation for treating tumors of the musculoskeletal system. In this review, we will focus on the two most well-established indications: palliation of painful bone and soft tissue metastases, and local control of oligometastatic disease. Other published indications include treatment of benign tumors (specifically, osteoid osteoma^[1,2], chondroblastoma^[3,4], osteoblastoma^[5-7], extra-abdominal desmoid tumor^[8-13], and giant cell tumor^[14,15]) and, more recently, treatment of abdominal wall endometriosis^[13,16,17].

INDICATIONS FOR THERMAL ABLATION

Palliation of painful bone and soft tissue metastases

In patients with breast, prostate, and lung cancer, up to 85% have musculoskeletal metastases at the time of death^[18], and approximately 50%-80% have painful metastases^[19,20]. Radiation therapy is the standard treatment for these symptomatic lesions; however, the pain can be resistant to or recur after treatment, with only approximately one-third of patients able to experience long-lasting pain relief^[21,22]. Analgesics (opioid and non-opioid), osteoclast inhibitors (e.g., bisphosphonates, denosumab), and systemic anticancer therapy (chemotherapy, targeted therapies, hormone therapy) also play important roles in the treatment of painful musculoskeletal metastases. Surgery is typically reserved for lesions associated with pathologic fracture, mechanical spinal instability, or epidural spinal cord compression^[23].

Over the past two decades, clinical trials have shown percutaneous thermal ablation to be an effective, safe, and durable method of pain palliation for bone and soft tissue metastases. This treatment has emerged as an important therapeutic option for patients with persistent or recurrent localized pain from bone and soft tissue metastases who are not candidates for surgery or reirradiation. Determining whether thermal ablation is appropriate, however, requires a multidisciplinary team approach involving medical oncology, radiation oncology, orthopedic oncology, and interventional radiology. Patients selected for ablation should have at least moderate pain (defined as 4 or more on a standardized 10-point pain scale) related to a limited number of metastases seen on cross-sectional imaging that correlate to the site(s) of pain on physical examination^[24]. For patients with at most mild pain (0-3 on a standardized 10-point pain scale), analgesics may be more beneficial than ablation.

Lesions best suited for percutaneous thermal ablation include those that are osteolytic, mixed osteolytic/ osteoblastic, or those that have a prominent soft tissue component. Purely osteoblastic lesions may also be targeted, but they can be technically challenging to access in the presence of intact bone. The junction between the metastasis and the bone (the "bone-tumor interface") is felt to be the primary source of pain, so in order to palliate pain effectively, ablation probes should be positioned with a primary focus towards ablating the bone-tumor interface and not necessarily the center or even the entirety of the lesion [Figure 1]^[24]. The metastatic lesion should be accessible percutaneously and should be safely distanced



Figure 1. 63-year-old female with stage IV renal cell carcinoma. (A) Axial CT image through the pelvis shows a large destructive lytic metastasis involving the posterior aspect of the left hip resulting in severe pain (circle). (B) Axial CT image during cryoablation of the left hip metastasis for pain palliation shows one of multiple cryoablation probes inserted into the lesion using a posterior approach (arrow). The ovoid low attenuation ablation zone is visible (arrowheads) and covers the bone-tumor interface.

(10 mm or more) from critical structures, which include the central nervous system, peripheral motor nerves, major vessels, skin, bowel, and bladder. Insulation techniques using fluid (hydrodisplacement, iatrogenic joint effusion), balloons, or gas may be used to protect nearby organs [Figure 2]^[25,26]. Skin warming may be used during cryoablation, and skin cooling may be used during radiofrequency ablation, using hot packs or ice packs, respectively, to minimize the risk of thermal injury.

Successful pain palliation following percutaneous thermal ablation of bone and soft tissue metastases has been well demonstrated across multiple studies^[27-42]. A 2019 systematic review of 11 papers (3 on radiofrequency, 2 on cryoablation, 1 on microwave, and 5 on focused ultrasound) showed mean pain reduction ranging from 26% to 91% at 4 weeks and 16% to 95% at 12 weeks, with all techniques achieving pain relief after 1 and 3 months in 91% and 95% of patients, respectively^[41]. More recently, the MOTION trial (Multicenter Study of Cryoablation for Palliation of Painful Bone Metastases), which included 66 patients, showed mean pain reduction by 2 points (on a 10-point scale) by week 1 and 2.61 points by week 8, with improved quality of life, stabilized opioid doses, and maintained functional status over 6 months^[50]. The OPuS One Study, which included 100 patients treated for bone metastases using radiofrequency ablation, showed rapid (within 3 days) and statistically significant pain improvement, with sustained long-term relief through 6 months^[40].

There are no randomized controlled trials comparing the different thermal ablation approaches for the management of symptomatic bone and soft tissue metastases. Some studies have suggested cryoablation to be superior to radiofrequency ablation in achieving decreased opioid requirements, shorter hospital stays, and complete pain response^[43,44]. The choice of ablation modality, however, depends on multiple factors, including availability, user preference, and local expertise.

Local tumor control (oligometastatic disease)

Oligometastatic disease (5 or fewer metastases) is a state in which patients may still be cured with focal therapy, which, although aggressive, avoids or postpones the potential side effects of systemic therapy, including chemotherapy, hormonal therapy, immunotherapy, or other targeted pharmacologic therapies. In patients with limited bone and soft tissue metastases, percutaneous thermal ablation may be used to achieve local tumor control or even disease remission^[23,45,46]. Surgical resection, though used to treat limited



Figure 2. 49-year-old female with stage IV breast cancer. (A) Coronal maximum intensity projection image from FDG PET study shows extensive FDG-avid osseous metastases throughout the spine, pelvis, and ribs. FDG activity in the renal collecting systems, urinary bladder, gastrointestinal tract, and brain is normal. (B) Axial fused FDG PET-CT image of the chest shows an FDG-avid metastasis in the sternum resulting in severe pain (circle). There is a subtle pathologic fracture obscured by the FDG activity. The lesion lies less than 1 cm away from the skin surface. (C) Axial CT image during radiofrequency ablation of the sternal metastasis for pain palliation shows the radiofrequency probe within the lesion (dotted arrow). Because of close proximity of the lesion and the planned radiofrequency ablation zone to the skin surface, a spinal needle was inserted into the subcutaneous tissues anterior to the sternum (solid arrow), and hydrodisplacement was performed to displace the skin away from the sternal metastasis and the ablation zone (*). (D) Follow-up axial fused FDG PET-CT image following treatment shows marked decrease in FDG activity (circle), with residual FDG activity due to the healing pathologic fracture. The patient experienced a moderate reduction in her presenting pain.

metastases in other locations such as liver, lung, and kidney, is much less common for musculoskeletal metastases due to the morbidity of resection and the potential for functional loss^[45]. Stereotactic body radiotherapy (SBRT) has been increasingly used to treat oligometastatic bone disease^[47].

As with palliation of painful metastatic disease, percutaneous thermal ablation may be used in select patients with oligometastatic disease [Figure 3]. The criteria for choosing patients for ablation of oligometastatic disease are not well established and, like palliation of painful bone and soft tissue metastatic disease, should involve a multidisciplinary team approach. Patients who are not candidates for radiation therapy, patients with lesions unresponsive to radiation therapy, or patients with lesions that have developed in previously irradiated fields may be good candidates for percutaneous thermal ablation^[45]. Unlike ablation for palliation of painful bone and soft tissue metastatic disease, which targets the bone-tumor interface, ablating to achieve durable local tumor control with minimal risk of residual or recurrent disease requires creating an ablation zone that encompasses the entire lesion plus a margin [Figure 4]^[1]. Therefore, the target lesions should be located 10 mm or more from critical structures^[46]. Additionally, lesions with large intratumoral vessels should be avoided, as the vessels can act as a thermal sink and dissipate the heat or cold away from the ablation zone, thus limiting the effectiveness of the ablation^[19].



Figure 3. 47-year-old female with sacral chordoma. (A) Sagittal T1-weighted, (B) sagittal short tau inversion recovery (STIR), and (C) axial T2-weighted images of the lumbar spine show a marrow-replacing lesion in the L2 vertebral body, detected during routine imaging surveillance of the entire spine, consistent with metastatic disease (*). No other lesions were detected. Biopsy of the lesion revealed metastatic chordoma. The patient was asymptomatic from this lesion and presented for radiofrequency ablation of oligometastatic disease. (D) Prone axial CT image during radiofrequency ablation of the L2 lesion shows 2 radiofrequency probes inserted into the lesion using a bipedicular approach (arrows). Because of the midline location of the lesion within the vertebral body, a bipedicular approach was needed to ensure maximum ablative coverage of the lesion.

Case series, most using cryoablation, have shown variable rates of tumor control for bone and soft tissue oligometastatic disease, ranging from 36% to 97%^[46,48,49]. One series of 46 patients with 49 bone metastases (37 treated with cryoablation, 12 treated with radiofrequency) showed a local progression-free survival of 76.8% at 1 year and 71.7% at 2 years, irrespective of tumor histology, with bone metastases greater than 2 cm in size showing higher rates of local tumor progression^[48]. In another single institution study examining musculoskeletal oligometastatic disease treated with cryoablation, local control was achieved in 45 of 52 tumors (87%) at a median follow-up of 21 months^[49]. Just as with palliation of painful bone and soft tissue metastases, there are no randomized trials comparing the efficacy of the different thermal ablation modalities with respect to local tumor control for the management of oligometastatic disease.

MODALITIES OF THERMAL ABLATION

There are several ablation modalities in clinical use, but the two principal ablation modalities to date for bone and soft tissue metastases are radiofrequency ablation and cryoablation. For all image-guided ablation modalities, the patient is brought to the procedure room and positioned on the imaging table in a way that permits a safe trajectory from the skin surface to the lesion(s). CT is the most commonly used method of image guidance, but ultrasound and even MRI can be utilized under the appropriate circumstances.



Figure 4. 36-year-old female with stage IV leiomyosarcoma. Axial (A) T1-weighted, (B) T2-weighted fat-suppressed, and (C) T1-weighted fat-suppressed gadolinium-enhanced MR images of the pelvis show a low T1 signal intensity, high T2 signal intensity, enhancing lesion in the left gluteus maximus detected during routine imaging surveillance, consistent with metastatic disease (*). No other lesions were detected. The patient was asymptomatic from this lesion and presented for cryoablation of presumed oligometastatic disease. (D) Axial CT image during cryoablation of the left gluteus maximus lesion shows a cryoablation probe inserted into the lesion (solid arrow). The ovoid low attenuation ablation zone is visible (arrowheads) and covers the entire lesion with an approximately 1 cm margin. Because of close proximity of the ablation zone to the skin surface, a spinal needle was inserted into the lesion and the ablation zone (yellow *).

Procedural sedation or anesthesia is administered by the appropriate personnel with the goal of providing maximum comfort with no patient motion during a procedure which can last up to several hours for large or multiple lesions. After preliminary images are acquired to localize the tumor and identify a site and trajectory for probe placement, ablation probes are advanced sterilely into the target under image guidance. Ablation probes can be inserted directly into the lesion if it is composed of soft tissue, but they cannot be inserted directly into bone since they do not have cutting or drilling surfaces. In this situation, the lesion must first be accessed using separate cannulas or drills, after which the ablation probes can be inserted coaxially through the auxiliary instruments into the lesion. The generator to which the ablation probes are attached is then activated to allow the ablation probes to achieve target ablation temperatures and maintain them for a specified duration according to published ablation protocols, which vary according to ablation probes and any accompanying instruments are removed. When hemostasis is achieved and wounds are dressed, the patient is transferred to the recovery room before being discharged back to the wards if the ablation is performed on an inpatient basis or to home or other facilities if the ablation is performed on an outpatient basis. Individual ablation modalities are discussed in greater detail in the following sections.

Radiofrequency ablation

Radiofrequency ablation (RFA) uses high-frequency alternating electric current to generate ionic agitation and frictional heating within target tissue, resulting in denaturing of proteins, damage to cell membranes, and ultimately cell death. There are monopolar and bipolar RFA systems. In monopolar RFA systems, each ablation probe contains a single electrode, which produces an elliptical zone of heating; thermal conduction expands the ablation zone into surrounding tissue, with temperature dropping precipitously as the distance from the probe tip increases^[19]. Monopolar RFA systems require the use of grounding pads to complete the circuit through the body. In bipolar RFA systems, energy flows between two electrodes, which eliminates the need for grounding pads and creates a more focused ablation area^[42]. Cell death occurs instantly at temperatures above 60 °C and within minutes at temperatures between 50 °C and 60 °C. Because of the insulating effects of cortical bone, RFA is less favored for blastic metastases^[50]. Ablation zones cannot be visualized by CT or ultrasound but may be estimated using temperature-sensitive MR pulse sequences; however, it is impractical to perform all RFA procedures using MRI guidance^[51]. Some RFA systems can accommodate multiple ablation probes, which allows the creation of larger ablation zones with some limited ability to customize their shape.

RFA may also be combined with cementoplasty to stabilize axial load-bearing bones (such as spine and acetabulum) and decrease the risk of pathologic fracture. Cementoplasty, which involves percutaneous instillation of polymethylmethacrylate cement into bone, may be performed immediately after heat-based ablation^[46]. Studies have shown that cementoplasty of skeletal metastases, performed alone or in combination with percutaneous thermal ablation, results in pain palliation^[1].

Potential risks of RFA include postablation syndrome (malaise and fatigue caused by the release of cytokines from tumoral cell death), a paradoxical increase in pain in the first week following the procedure, and subsequent fracture^[19]. The risk of thermal injury to adjacent structures, including skin burns^[1], may be minimized by careful probe positioning and insulation techniques.

Cryoablation

Cryoablation uses pressurized room-temperature argon gas delivered through an insulated probe. Rapid expansion of gas at the non-insulated probe tip causes rapid cooling, with temperatures reaching -100 °C within a few seconds. This results in the formation of a low-attenuation ice ball, which can be easily visualized on noncontrast CT or MRI. The ice ball contains both intracellular and extracellular ice. Intracellular ice causes mechanical shear injury to the cells. Extracellular ice dehydrates the cells and damages the cell membrane and cellular enzymes. These mechanisms occur simultaneously and result in cell death. The size of the ice ball depends on the length of the probe tip, the diameter of the cryoprobe, and the duration of freezing. Most cryoablation systems allow the simultaneous use of multiple ablation probes, placed 1.5-2 cm apart, to provide the best geometric coverage of the tumor. For bone and soft tissue metastases, a standard freeze-thaw-freeze cycle of 10-5-10 min is performed for each lesion, with intermittent imaging obtained typically every 2-3 min to monitor ice ball formation and ensure safe distancing from any nearby critical structures. Complete cell death is achieved at temperatures below -40 °C^[19]. The visible edge of the ice ball represents 0 °C, with reliable cell death occurring 3-5 mm deep to this margin^[1,51]. This margin must be considered when planning cryoablation treatments, especially when treating oligometastatic disease for a potential cure. Many cryoablation systems also allow helium gas to be delivered through the cryoprobe for active thawing, which allows for rapid removal of the probes and potentially cauterization of the needle track ("track ablation").

There are several advantages of cryoablation over RFA. Firstly, the ablation zone is visible on cross-sectional imaging and therefore can be monitored in real time during the treatment. This allows for greater confidence and safety in treating tumor margins, especially when operating near critical structures. Secondly, multiple cryoprobes, typically more than 2, may be placed simultaneously, which permits the creation of larger ablation zones with more customizable shapes. Thirdly, the ice ball penetrates deeply into bone, allowing effective treatment of osteoblastic metastases, whereas RF energy penetrates poorly into sclerotic bone. Lastly, cryoablation patients experience less pain during the immediate posttreatment period compared to RFA^[43,44], possibly because the freezing temperatures achieved during treatment may provide a degree of anesthesia (cryoanalgesia)^[50]. Disadvantages of cryoablation include greater procedural time and increased cost compared to RFA^[51]. The lack of an insulating effect of cortical bone on cryoablation can lead to a deeper propagation of ice through the bone, which can be a disadvantage when ablating near the spinal canal.

Cryoablation of bone and soft tissue metastases has been shown to be very safe, with low rates of complications^[52,53]. A large retrospective case series including 239 patients and 320 bone tumors showed a major complication rate of 2.5%, with pathologic fracture being the most common complication (1.2%). Other major complications included tumor seeding, arterial bleeding, ablation site infection, and severe hypotension, each occurring in one of 320 procedures (0.3%). Risk factors for major complications included: the use of 3 cryoprobes, patient age > 70 years, and cryoablation of long bones. Minor complications included post-procedural pain, temporary paresthesia, and peripheral neuropathy. The total complication rate was $9.1\%^{[s2]}$. Postablation syndrome, described above in the section on RFA, can also occur after cryoablation.

Cryoablation may also be combined with cementoplasty to decrease the risk of pathologic fracture. To improve filling of the tumor cavity, cementoplasty is most often done one day or more after cryoablation to allow for adequate tissue thawing and necrosis^[54].

Microwave ablation

Microwave ablation (MWA) relies on electromagnetic energy transmitted through antennae in a microwave probe to force water molecules to oscillate, generating heat. Unlike RF energy, microwaves can propagate through materials with low or zero conductivity, resulting in larger and more uniform ablation zones. This property also makes MWA relatively immune to heat sink effects and well-suited for treating tumors with high water content (e.g., large vascular tumors). MWA can achieve cell death temperatures faster than other ablation techniques^[50].

A systematic review evaluating MWA protocol, safety, and efficacy in treating bone tumors, which included seven non-comparative studies and 269 malignant bone tumors, showed that MWA was effective at achieving pain relief at 4-6 months^[55]. The authors concluded that although MWA appeared safe, further studies are needed, as there is large heterogeneity in ablation protocols, and more evidence is needed.

Microwave ablation may also be combined with cementoplasty to alleviate pain and reduce the risk of pathologic fracture^[56].

Focused ultrasound and laser ablation

Focused ultrasound is a relatively newer and completely non-invasive thermal ablation technique in which high-intensity ultrasound waves are focused on a small target area (usually under MR thermometry guidance), resulting in tissue heating and cell death. Focused ultrasound has been shown to be effective in

palliating painful bone metastases^[39,57,58].

Laser ablation is another heat-based thermal ablation technique in which infrared energy delivered through laser fibers causes precisely targeted tissue coagulation/cell death. The use of laser ablation in the musculoskeletal system has largely been limited to the treatment of benign lesions (e.g., osteoid osteoma, vascular malformations)^[50].

Intraoperative ablation

Thermal ablation may also be performed intraoperatively as an adjunct/adjuvant treatment technique to improve surgical margins. Intraoperative thermal ablation has already been described in the treatment of non-musculoskeletal tumors (e.g., liver^[59], lung^[60], and brain^[61]). The underlying principles may also be applied in the treatment of musculoskeletal tumors.

DISCUSSION

Over the past two decades, percutaneous thermal ablation has emerged as an effective and promising tool for treating metastatic disease in bone and soft tissue. It is typically performed on an outpatient basis with relatively short recovery times and low complication rates and can be performed either alone or in conjunction with surgery, radiation, or systemic therapy. Since there are few guidelines prescribing which lesions should be treated with thermal ablation, deciding which patients will benefit from this treatment requires thoughtful multidisciplinary discussion amongst the patient's medical oncologist, radiation oncologist, orthopedic oncologist, and interventional radiologist. The two most studied and well-established indications are palliation of painful metastases and local control/cure of oligometastatic disease. The choice of ablation modality depends on lesion character, size, and location, as well as user preference, experience, and equipment availability. There are no randomized controlled trials showing one ablation modality to be superior to another. Thus, the decision on which modality to use lies with the interventionalist, and the advantages and disadvantages of each should be considered.

It is the authors' experience that the main factor influencing the choice of ablation modality is lesion size. Larger lesions are better suited to cryoablation, since individual cryoablation probes can generate ablation zones up to 6 cm × 4 cm × 4 cm, and some cryoablation systems can accommodate up to 20 probes simultaneously, allowing the possibility of creating very large ablation zones. By contrast, the largest ablation zones generated by RFA probes are on the order of 3 cm \times 2 cm \times 2 cm, and since RFA systems typically accommodate only up to two probes simultaneously, using an RFA system to create an ablation zone of comparable size to a multi-cryoablation probe ablation zone would require repositioning the RFA probes within the target multiple times to perform multiple serial ablations, which could be prohibitively time-consuming. On the other hand, the minimum ablation zone size of an RFA system is approximately 1 cm, whereas the minimum ablation zone size of a cryoablation system is approximately 2 cm. RFA may therefore be better suited for small lesions in tight spaces near critical structures, such as in the posterior elements of the spine. Additionally, the insulating effect of cortical bone that makes RFA disadvantageous for treating blastic metastases is actually advantageous when treating spine lesions, since an intact cortex can form a somewhat protective barrier between the ablation zone and the nearby spinal cord or exiting nerve root. For lesions approximately 2-3 cm in size, other factors become more important, such as whether the lesion is in bone or soft tissue, whether there is a desire to combine the ablation with cementoplasty, procedure cost and time, etc. These and other considerations, which were already discussed in greater detail within the respective modality sections above, are summarized in Table 1.

	Radiofrequency ablation	Cryoablation	
Ablation zone visible?	No	Yes for soft tissue, not typically for bone	
Lesion size	Good for lesions < 3 cm, not well-suited for lesions > 5 cm	Good for lesions > 5 cm, not well-suited for lesions < 1 cm	
Lytic vs. blastic lesions	Not as effective for blastic lesions	No difference between lytic and blastic lesions	
Spine lesions	Intact cortex can protect against damage to adjacent structures, e.g. nerve and spinal cord	Intact cortex is not protective against damage to adjacent structures	
Combine with cementoplasty?	Can be performed at the same time	Best if delayed by 1-2 days	
Ablation time	< 15 min	At least 25 min for standard musculoskeletal ablation protocol	
Procedure cost	Generally shorter procedure room time, fewer probes needed, each less expensive	Generally longer procedure room time, more probes needed for large lesions, each more expensive	
Post-procedure pain	Variable, usually mild	Variable, usually less than RFA due to cryoanalgesia	

Table 1. Summar	y of the main difference	es between radiofreque	ncy ablation and cryoablation
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Clinical trials have shown thermal ablation to be effective in achieving palliation of painful metastases; results have been more variable when trying to achieve local control for oligometastatic disease. In most series, the proportion of subjects being treated with sarcoma metastases is very small, so it is unknown whether this variability can be attributed to differences in tissue type. However, since the cell death mechanisms induced by thermal ablation do not act upon the DNA machinery of the cell, it seems unlikely that the resistance mechanisms that occur with chemotherapy and radiation therapy and certain tissue types will apply to thermal ablation.

CONCLUSION

The use of percutaneous thermal ablation is ever expanding, and thermal ablation should be considered and offered to patients when discussing treatment options, particularly with respect to palliation of painful bone and soft tissue metastases and local control of oligometastatic disease. Because of the dearth of randomized controlled studies, there are many unanswered and incompletely answered questions that are worthy of pursuit and additional study. As more clinicians incorporate this tool into their arsenal, more data could lead to new indications and more established guidelines for effective use.

DECLARATIONS

Authors' contributions

Literature search, manuscript writing: Xia E Conceptualization, manuscript writing, manuscript review and editing, figures and tables: Huang AJ

Availability of data and materials

Not applicable.

Financial support and sponsorship None.

Conflicts of interest Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate Not applicable.

Consent for publication

Not applicable.

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