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PERSPECTIVE

Percutaneous ablation for bone and soft tissue metastases—why cryoablation?

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Introduction

Image-guided percutaneous thermal ablation has been developed into an effective method to help treat patients with bone and soft tissue tumors, including both benign and metastatic disease. Indeed, during the past few decades, many new ablation technologies have been developed and applied to this clinical problem, including cryoablation, radiofrequency ablation (RFA), microwave ablation, laser interstitial thermal therapy (LITT), and focused ultrasound therapy. While these are all minimally invasive methods to destroy abnormal tissue, the technologies vary in the type of energy delivered, image guidance methods, treatment monitoring, and patient experience with each procedure. These differences become important in the ability to derive palliation of pain, achieve complete local control of the tumor when necessary, and avoid complications.

Cryoablation has a long history of successful treatment of neoplasms in several organs, including prostate, kidney, liver, and lung. Cryoablation has also recently emerged as an exceptional method for treatment of metastatic disease involving bone and soft tissue outside of liver and lung [1]. The rationale for using cryoablation for this clinical need is based on its ability to treat often complex metastatic disease effectively, while preserving adjacent normal critical tissue. Careful monitoring of the cryoablation margin is possible, due to the visibility of the ice ball on computed tomography (CT), which is a key advantage of cryoablation over other methods. While cryoablation has only recently been applied to this clinical problem, RFA has been the most studied and is the most commonly performed ablation method for disease involving the skeletal system. In fact, RFA has emerged as the gold standard for treatment of osteoid osteomas [2–5]. As different ablative technologies have been applied to the treatment of patients with metastatic disease, a rational approach to the treatment of these patients is possible and may be understood on the basis of the goals of the treatment and adjacency of important normal structures. This article highlights some of the advantages of the use of cryoablation for treatment of metastatic disease involving bone and soft tissue over the other ablation technologies and summarizes the data supporting the effectiveness of cryoablation for treatment of metastatic bone and soft tissue tumors.

The clinical problem

Bone and soft tissue metastases are a common problem in oncology patients. Up to 85% of patients with breast, prostate and lung cancer have bone metastases at the time of death [6]. Complications due to skeletal metastases, including intractable pain, fracture, and decreased mobility, can reduce performance status and quality of life [6, 7]. In addition, these complications can lead to depression and anxiety [6].

Many patients with bone and soft tissue metastases have a remitting course of their disease and, as a result, will require intermittent treatment for metastases over the course of several years. The use of minimally invasive therapies for these patients is important to maintain quality of life. At the same time, achieving local control of disease with these therapies is necessary, to avoid repeat treatment of a given tumor. Therefore, these minimally invasive therapies must also allow complete treatment of often-times complex

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tumors, while avoiding complications due to injury of adjacent normal critical tissues.

Standard therapies

Current treatments for painful bone and soft tissue metastases are primarily palliative and include localized therapies (radiation and surgery), systemic therapies (chemotherapy, hormonal therapy, radiopharmaceuticals, and bisphosphonates) and analgesics (opioids and nonsteroidal anti-inflammatory drugs). Unfortunately, painful metastatic skeletal disease in this patient population is often refractory to these therapies. External beam radiation therapy (RT) is the current standard of care for cancer patients with localized bone pain. In a prospective trial of 1,016 patients, conducted by the Radiation Therapy Oncology Group (RTOG), RT resulted in complete relief in 53% and partial relief in 83% of patients, achieved after a period of 4–12 weeks [8]. Pain relief from RT is often transient, with recurrence of pain in 57% of patients at a median of 15 weeks after completion of RT [8]. 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.

Surgery is typically not an option for patients with multifocal metastatic disease and, rather, is reserved for patients with a recent or impending fracture in a weight-bearing bone. Moreover, surgery may not be an option in debilitated patients with poor functional status and advanced disease. For patients with oligometastatic disease, surgery may be offered, but the uncertain prognosis and often long recovery time for these patients makes minimally invasive alternative treatments attractive. Chemotherapy is typically ineffective to alleviate pain from bone and soft tissue metastases and rarely results in remission, although bisphosphonates sometimes provide pain relief in certain painful metastases. For many patients with painful metastatic disease, systemic 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 ablation

Because of the limitations of these therapies, investigators have explored several minimally invasive therapies for the treatment of painful metastatic disease, which promise effective, durable, and repeatable therapy for relief of pain in these patients. Of these methods, RFA has been evaluated most carefully. A multi-center study found that RFA significantly reduces pain in patients with pain due to metastatic disease that was refractory to standard treatments [9–11]. A total of 59/62 patients (95%) experienced a clinically significant drop in pain (≥2 point drop in worst pain in a 24 h period). Although RFA is effective in reducing pain, it has significant limitations, including: (1) inability to visualize the ablation margin with CT or ultrasound monitoring (possible but impracticable with magnetic resonance (MR) thermal mapping); (2) need for multiple, sequential, overlapping ablation sessions; (3) significant pain during and immediately following the procedure.

It is possible to demonstrate the RF ablation margin with magnetic resonance imaging (MRI), but the MRI environment is often impracticable in most clinical practices. Although it is possible to use up to three RFA probes simultaneously, treating bone and soft tissue metastases is often limited by adjacent normal critical structures, requiring caution. Treating a tumor which cannot be adequately covered with three probes requires multiple overlapping ablations. These overlaps are subject to potential incomplete tumor ablation at the margins of the overlapping treatments. Furthermore, the RFA procedure may be associated with significant pain, and patients frequently have increased pain in the immediate post-treatment period, requiring a period of weeks before significant pain reduction is achieved.

Percutaneous cryoablation technology

First-generation cryoablation devices were restricted to intraoperative use because of their large diameters, the use of liquid nitrogen for tissue cooling, and the lack of well-insulated probes to prevent collateral damage. Current-generation percutaneous cryoprobes deliver room temperature argon gas through a sealed, segmentally insulated probe. Rapid expansion of the gas in the sealed distal cryoprobe results in rapid cooling (Joule–Thompson effect), reaching −100°C at the probe tip within a few seconds. Smaller diameter probes (1.2–2.4 mm or approximately 11–17 gauge) and insulation along their shafts allow the percutaneous use of these devices. Active thawing is achieved by the infusion of helium gas into the cryoprobes, instead of argon gas. The size of the ablation zone, or ice ball, generated can be controlled and depends upon the diameter of the cryoprobe, the length of the uninsulated tip, and the time of freezing. A single cryoprobe typically provides an oblong ice ball of approximately 3.5 cm diameter. Multiple cryoprobes (up to 25) may be used simultaneously with current cryoablation systems.

Percutaneous cryoablation technique

Cryoablation of bone and soft tissue tumors may be performed with the patient under moderate conscious sedation or general anesthesia. Cryoprobes may be placed in the geometric configuration that provides best coverage of the tumor, with particular attention being paid to the treatment of the bone–tumor interface while avoiding adjacent critical structures. Owing to the oblong shape of the ice that is generated, cryoprobes are most often placed in parallel along the long axis of the tumor. In general, when multiple probes are used, they are placed approximately 2 cm apart within the tumor and 1 cm from the outer tumor margin. Ultrasound imaging may be used to guide probe placement in superficial lesions or those with a significant soft tissue component. As in RFA, ultrasound is limited as a tool for monitoring the ablation zone in cryoablation; the superficial margin of ice ball produces an impenetrable acoustic shadow.

A single freeze–thaw–freeze cycle is performed for each lesion, with a goal treatment time of 10–5–10 min, respectively. Shorter or longer freeze times may be used, depending on the adequacy of lesion coverage by the ice and the proximity of adjacent critical structures. Monitoring may be performed as frequently as every 2 min with limited noncontrast CT, although the ablation zone may also be seen with MRI. The ablation zone is identified as a well-marginated low attenuation region along the distal shaft of the cryoprobe (Fig. 1). The outer edge of the ice, as seen on body window and level settings (W400, L40) corresponds to 0°C, with cell death reliably occurring 3 mm deep near the edge. The probes are then actively thawed for 10–15 min until they reach approximately +25°C, at which point they may be removed.

Appropriate patient and lesion selection

For painful bone and soft tissue metastases: (1) patients should report moderate to severe pain that is at least 4 on a 10-point scale for worst pain in a 24 h period. It is difficult to improve upon mild pain with ablation, and, typically, the pain of these patients can be well managed with oral administration of analgesics. (2) Secondly, patients should have pain localized to one or two sites with corresponding abnormalities on cross-sectional imaging. Patients with diffuse painful skeletal metastases are better served with systemic therapies rather than a focal approach. Furthermore, it is difficult to locate the source of a patient's pain satisfactorily when numerous lesions are present. (3) Lesions should be osteolytic, mixed osteolytic–osteoblastic, or primarily soft tissue in composition. Osteoblastic lesions, which are often multifocal when present, may also be treated but require a bone biopsy device or a bone drill. (4) Finally, the target lesion must be accessible percutaneously and be sufficiently distant from the spinal cord, major motor nerves, brain, artery of Adamkiewicz, bowel, or bladder. The required margin of safety depends on the ability to visualize adjacent critical structures, the use of techniques to displace normal tissues, the use of thermal protection and monitoring devices, and the experience of the interventional radiologist.

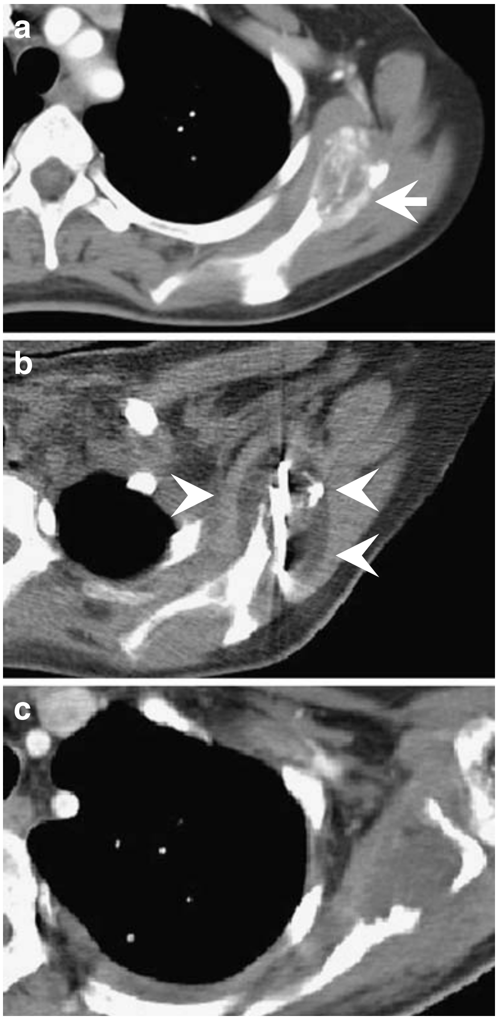

Fig. 1 CT axial images at the level of the scapula. **a** Enhancing osteolytic paraganglioma metastasis involving the scapula (*arrow*). **b** Two percutaneously placed cryoprobes in the soft tissue lesion with an ice ball encompassing the tumor (*arrowheads*). **c** Contrast-enhanced CT 3 months following ablation showing no enhancement in the treated area. Prior to cryoablation, the worst pain was 5/10. Four weeks, 8 weeks and 24 weeks after cryoablation, the worst pain was 2/10, 1/10, and 0/10, respectively

Advantages of cryoablation over other ablation methods

Both heat-based therapies and cryoablation provide safe, effective, and durable results in the treatment of bone and soft tissue metastases. Moreover, these treatments are repeatable, as needed in cases of recurrent pain or pain in new metastatic bone or soft tissue lesions. However, cryoablation affords several distinct advantages over these other methods in the treatment of metastatic disease involving bone and soft tissue.

Most importantly, the ablation zone generated with cryoablation is readily monitored during the procedure with intermittent noncontrast CT or MR imaging. In contrast, the ablation zone for RFA is not visible with CT monitoring. While the ablation zone for RFA may be estimated with temperature-sensitive MRI pulse sequences, it is often impracticable in most clinical practices to perform RF procedures in the MRI environment. With clear demonstration of the treatment margin, tumors may be treated confidently and with greater safety in relative proximity to (or while sparing) adjacent critical structures, such as large nerves, bowel, or bladder. Tumors may be treated aggressively, which is particularly important for those patients with slowly progressive limited metastatic disease, in whom local control may be achieved with cryoablation. The inability to see the ablation margin with RFA may lead to incomplete tumor ablation in regions near critical structures, leading to failure in achieving local control or, potentially, the need for multiple treatment sessions. These limitations are important, as the use of heat-based therapies adjacent to critical structures may be restricted or performed suboptimally in order to avoid complications, leading to potentially reduced immediate effectiveness and long-term durability of treatment. Without visualization of the ablation margin, and with the goal of local tumor control for patients with limited slowly progressive metastatic disease, it may not be possible to achieve complete ablation of their focal disease, or they may require repeated RF ablation if local control is to be achieved.

A second advantage of cryoablation systems is the opportunity to use multiple (up to 25) cryoprobes simultaneously, which allows the generation of large ice balls (>8 cm diameter) and the ability to shape the ablation zone through varied geometry of probe placement to match the shape of the target lesion. Importantly, synchronous ablation with several cryoprobes eliminates possible residual disease at the ablation interfaces that exist when one is performing the overlapping ablations required when treating large lesions with RFA [12].

It is possible to treat metastatic lesions in close proximity to critical normal structures, and techniques that include varied patient positioning and injection of sterile fluid or gas to displace adjacent normal structures are used to increase the safety of the procedure. Cryoablation allows the additional option of tissue displacement with catheter-guided balloons, which is not possible with heat-based methods, due to the thermal limitations of these devices.

Furthermore, although osteoblastic metastases are less commonly treated with cryoablation for reasons previously mentioned, the ice ball is able to penetrate deeply into bone, whereas radiofrequency energy poorly penetrates into bone. When isolated, a painful osteoblastic metastasis could, therefore, be treated with cryoablation.

Another potential advantage of cryoablation relative to heat-based ablation is that cryoablation is well tolerated by patients under conscious sedation, and they do not experience increased pain in the immediate post-treatment period. In contrast, RFA patients frequently experience significant pain in the immediate post-procedural period, although this may be controlled with regional anesthesia, such as epidural or spinal blockade, or general anesthesia.

Effective pain palliation with percutaneous cryoablation

The recently published interim results of our single-center prospective clinical trial using cryoablation to treat painful metastatic disease are encouraging. Fourteen patients with painful metastatic disease involving bone were treated by percutaneous cryoablation. They had one or two painful lesions causing ≥4/10 pain in a 24 h period. On the Cleeland brief pain inventory [13, 14], the mean score for worst pain in a 24 h period decreased from 6.7/10 to 3.8/10 over 4 weeks. All patients who had been prescribed narcotics prior to the procedure reported a reduction in these medications (eight out of eight). No serious complication was seen. Pain relief from cryoablation appeared to be durable, with four of five patients (80%) reporting excellent pain control in the treated area during the 24-week follow-up period.

Comparison of patients' response scores following cryoablation with data reported from the treatment of patients with RT is difficult, as the methods for measuring patients' pain response following RT do not correspond directly, and the number of patients in this study was small. However, cryoablation resulted in significant pain reduction, with a 43% mean reduction in worst pain in 4 weeks, which is considered to be clinically significant [15]. Patients' reported pain relief 4 weeks following cryoablation ranged from 50–100%, which compared favorably with the reported RT response.

These findings suggest that cryoablation is a safe and effective treatment for the palliation of painful metastatic lesions that are refractory to standard therapies. Prospective comparison studies of cryoablation and radiation therapy or radiofrequency ablation may be useful to distinguish the relative benefits of these therapies for palliation of painful metastatic lesions.

Disadvantages of cryoablation

Cryoablation of skeletal metastases is a more time-consuming procedure than RFA. In the prospective cryoablation trial, the total time for positioning the patient, placement of cryoprobes, the freeze–thaw–freeze portion of the treatment, re-warming of the cryoprobes, removal of the cryoprobes and securing the skin insertion sites averaged

2 h and 19 min. The total time in the CT suite for the procedure averaged 3 h and 5 min. Despite the use of only a single freeze–thaw–freeze cycle with the average use of 2.8 cryoprobes for the procedure, the time necessary for this procedure was greater than that necessary for the treatment of similar patients with RFA. In a prior study using RFA, the average ablation time was 46 min, with an average of 2 h and 14 min in the CT suite and an average of 4.5 electrode needle placements [10].

There are several reasons why cryoablation requires more time than RFA. Although RFA of painful lesions often requires multiple overlapping ablations, the time necessary for each separate RF ablation is short (5–10 min). These relatively short RFA treatment times for painful metastases is because the therapy is focused on the ablation of the bone–tumor interface and the treatment is not expected to result in complete local control. The RFA electrodes must be carefully placed in the targeted tumor to achieve the desired tumor ablation while avoiding injury of normal critical adjacent tissues, as the ablation margin is only estimated and is not visualized with ultrasound (US) or CT. Since the ablation zone is readily visualized with cryoablation, additional time is often used to maximize the ablation margin with freeze cycles extending beyond 10 min. Additionally, because it is possible to shape the ice ball by strategic placement of two or more cryoprobes, greater time may be used in the cryoprobe placement portion of the procedure compared to RFA.

Percutaneous cryoablation may also be more expensive than RFA. An effort to achieve local control, which is possible with cryoablation, often leads to the use of multiple probes, increasing the cost beyond that of RFA when a single device is used.

Conclusion

Percutaneous cryoablation is a promising treatment alternative that offers several advantages over conventional palliative treatments. This minimally invasive image-guided treatment also offers advantages over other ablation technologies, because it gives one the ability to readily monitor and control the ablation margin, making it an excellent treatment option for patients with oligometastatic disease.

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