CLINICAL STUDY

Percutaneous Image-Guided Cryoablation of Musculoskeletal Metastases: Pain Palliation and Local Tumor Control

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ABSTRACT

Purpose: To evaluate the safety and effectiveness of cryoablation of musculoskeletal metastases in terms of achieving pain palliation and local tumor control.

Materials and Methods: A retrospective review was performed of 92 musculoskeletal metastases in 56 patients treated with percutaneous image-guided cryoablation. Mean age of the cohort was 53.9 y ± 15.1, and cohort included 48% (27/56) men. Median tumor volume was 13.0 cm^3 (range, 0.5–577.2 cm^3). Indications for treatment included pain palliation (41%; 38/92), local tumor control (15%; 14/92), or both (43%; 40/92). Concurrent cementoplasty was performed after 28% (26/92) of treatments.

Results: In 78 tumors treated for pain palliation, median pain score before treatment was 8.0. Decreased median pain scores were reported 1 day (6.0; $P < .001$, n = 62), 1 week (5.0; $P < .001$, n = 70), 1 month (5.0; $P < .001$, n = 63), and 3 months (4.5; $P = .01$, n = 28) after treatment. The median pain score at 6-month follow-up was 7.5 ($P = .33$, n = 11). Radiographic local tumor control rates were 90% (37/41) at 3 months, 86% (32/37) at 6 months, and 79% (26/33) at 12 months after treatment. The procedural complication rate was 4.3% (4/92). The 3 major complications included 2 cases of hemothorax and 1 transient foot drop.

Conclusions: Cryoablation is an effective treatment for palliating painful musculoskeletal metastases and achieving local tumor control.

ABBREVIATIONS

IQR = interquartile range, NRS = Numeric Rating Scale, PET = positron emission tomography

Bone is the third most common site of metastatic disease; up to 85% of patients with breast, prostate, and lung cancer are found to have bone metastases at autopsy (1,2). Symptomatic patients most commonly present with pain caused by biochemical stimulation of periosteal and endosteal nociceptors, tumor mass effect, or associated pathologic fracture (2–4). In these cases, the goal of therapy is rapid and durable pain relief (5). There is also preliminary evidence that cryoablation of asymptomatic or minimally symptomatic musculoskeletal metastases may prolong survival of patients with oligometastatic disease (6).

Radiation therapy is the standard of care for palliation of metastatic bone pain, but it has important limitations. First, certain tumor histologies respond poorly to radiation therapy, particularly renal cell carcinoma, melanoma, and sarcoma (7–9). Second, radiation therapy may be limited by the cumulative tolerance of nearby radiosensitive organs, such as the spinal cord or bowel. Third, some patients may not respond until 4–6 weeks after therapy, which is suboptimal for patients

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with short life expectancies (10). Finally, radiation therapy excludes patients from certain systemic chemotherapy clinical trials.

Percutaneous cryoablation is a locally directed palliative therapeutic option for pain palliation and local tumor control of musculoskeletal metastases when radiation therapy is ineffective or contraindicated. Concurrent cementoplasty is often performed after ablation of bones with associated or at imminent risk of pathologic fracture (5). Advantages of cryoablation over heat-based ablation modalities include the ability to visualize the ablation zone in soft tissues on computed tomography (CT), less procedural pain, and the ability to cover a larger area and tailor the configuration of the ablation zone using multiple ablation probes (11–14). Previous case series have shown decreased pain scores up to 24 weeks after cryoablation of musculoskeletal metastases with complication rates of 2%–11% (11,15), and 1 study reported a musculoskeletal metastasis local control rate of 87% at a median follow-up of 21 months after cryoablation (6). However, these encouraging initial results must be replicated. The purpose of this study was to evaluate the safety and effectiveness of percutaneous image-guided cryoablation of musculoskeletal metastases in terms of achieving pain palliation and local tumor control.

MATERIALS AND METHODS

Institutional review board approval was obtained to retrospectively review a single-center institutional database for all percutaneous image-guided musculoskeletal cryoablation procedures performed between April 2012 and July 2015. Informed consent was waived for retrospective study participation. During the study period, 92 musculoskeletal metastases in 56 patients were treated with percutaneous cryoablation. Patients were selected for cryoablation by a multidisciplinary team of medical, radiation, surgical, and interventional oncologists. Procedures were performed for pain palliation only (41%; 38 of 92), local tumor control only (15%; 14 of 92), or both pain palliation and local tumor control (43%; 40 of 92). Goals of therapy were determined in a multidisciplinary fashion based on patient age, performance status, and tumor burden according to the Metastatic Spine Disease Multidisciplinary Working Group algorithms (5). Patients underwent physical examination before treatment to determine whether the sites of focal pain correlated with the presence of tumor. Treated patients had contraindications to radiation therapy, had malignancies that previously demonstrated radiation resistance, or were being treated with systemic chemotherapy regimens that would have been interrupted by radiation therapy.

The mean age of the cohort was 53.9 years ± 15.1, and the cohort comprised 48% (27 of 56) men and 52% (29 of 56) women. Tumor locations and primary histologies are listed in Tables 1 and 2. The median tumor volume was 13.0 cm^3 (range, 0.5–577.2 cm^3), which was estimated by multiplying the greatest anteroposterior, transverse, and craniocaudal dimensions of each tumor. Of tumors, 54% (50 of 92) were lytic, 6.5% (6 of 92) were blastic, 22% (20 of 92) were mixed lytic and blastic, and 17% (16 of 92) were normal radiographic bone density. Four tumors (4.3%; 4 of 92) were treated with cryoablation for recurrent pain after radiation therapy. In these cases, the shortest time interval between radiation and

Table 1. Anatomic Locations of Metastases Treated with Cryoablation

Location	Number (%)
Scapula	5 (5.5)
Humerus	2 (2.2)
Ribs	11 (12)
Sternum	1 (1.1)
Clavicle	1 (1.1)
Spine	9 (9.8)
Thoracic	3 (3.3)
Lumbar	6 (6.5)
Sacrum	7 (7.6)
Coccyx	2 (2.2)
Pelvis	42 (46)
Ilium	24 (26)
Acetabulum	9 (9.8)
Pubic rami	5 (5.4)
Ischial tuberosity	4 (4.3)
Tibia	1 (1.1)
Calcaneus	1 (1.1)
Soft tissues	10 (11)
Chest wall	6 (6.5)
Abdominal wall	1 (1.1)
Gluteal muscles	1 (1.1)
Thigh	1 (1.1)
Pelvis	1 (1.1)
Total	92

Table 2. Primary Tumor Histologies of Metastases Treated with Cryoablation

Histology	Number (%)
Non–small cell lung cancer	24 (26)
Sarcoma	19 (21)
Papillary thyroid	12 (13)
Breast adenocarcinoma	9 (9.8)
Renal cell carcinoma	6 (6.5)
Malignant peripheral nerve sheath tumor	6 (6.5)
Epithelioid hemangioendothelioma	6 (6.5)
Gastrointestinal adenocarcinoma	5 (5.4)
Pancreatic adenocarcinoma	3 (3.2)
Hemangiopericytoma	1 (1.1)
Head and neck squamous cell carcinoma	1 (1.1)
Total	92

cryoablation therapy was 23 weeks. There were 26 patients (48%; 26 of 54) with oligometastatic disease, defined as ≤ 5 metastases at the time of cryoablation therapy.

Cryoablation Systems

Procedures were performed with the Endocare Cryocare System (HealthTronics, Austin, Texas) (39%; 36 of 92), or the Visual-ICE Cryoablation System (Galil Medical Inc, Arden Hills, Minnesota) (61%; 56 of 92). Both systems operate on the Joule-Thomson effect using circulating inert argon. Active tissue thawing is mediated by circulating inert helium through the system. Endocare cryoprobes included the Perc-15 and Perc-17, both of which are 15 cm in length and 1.7 mm in diameter. Galil cryoprobes included the IceRod 1.5 series, IceEdge 2.4 series, and IceSphere 1.5 series, which are 17.5 cm in length and 1.5–2.4 mm in diameter.

Cryoablation Procedure

All patients were treated in a single session. Of the 56 treatment sessions, 91% (51 of 56) were performed with conscious sedation, and 8.9% (5 of 56) were performed with general anesthesia. Conscious sedation was achieved with intravenous midazolam and fentanyl and monitored by a trained nurse. The median conscious sedation time—defined as the time between the first and last doses of intravenous midazolam—was 240 minutes (interquartile range [IQR], 163–422 min). The median doses of intravenous midazolam and fentanyl were 13 mg (IQR, 8–17 mg) and 550 μg (IQR, 356–1,000 μg), respectively. CT guidance was used for 94.6% (53 of 56) of procedures, and fluoroscopy was used for the remaining 5.4% (3 of 56). The median dose length product of the CT–guided procedures was 2,027 mGy-cm (IQR, 1,361–2,724 mGy-cm).

Cryoprobe placement was determined by the interventional radiologist based on tumor size and location and therapeutic intent. Multiple cryoprobes were placed 10–15 mm apart with the goal of producing a contiguous ice ball that encompassed the planned treatment volume. The median number of cryoablation probes used to treat a single tumor was 2 (range, 1–20). When treating with only palliative intent, the goal was to include all bone-tumor and soft tissue–tumor interfaces in the ablation zone. When the intent of therapy was local tumor control, the goal was to produce an ablation zone that completely encompassed the gross tumor volume plus an ablative margin of 5–10 mm (16). The ablative margin was assumed to be approximately 5 mm inside the margin of the visible hypoattenuating ice ball evaluated at 40 HU with a window width of 400 HU on nonenhanced CT (**Fig 1a–g**) (17). Technical success of treatment with the intent of achieving local tumor control was defined as complete tumor coverage with the ablation zone (18). Each ablation included at least 2 freeze cycles separated by an active thaw. Intraprocedural ablation imaging was generally performed at 5- and 10-minute intervals during the freeze cycles, although monitoring was performed at intervals of 2 minutes when ablation was close to sensitive structures.

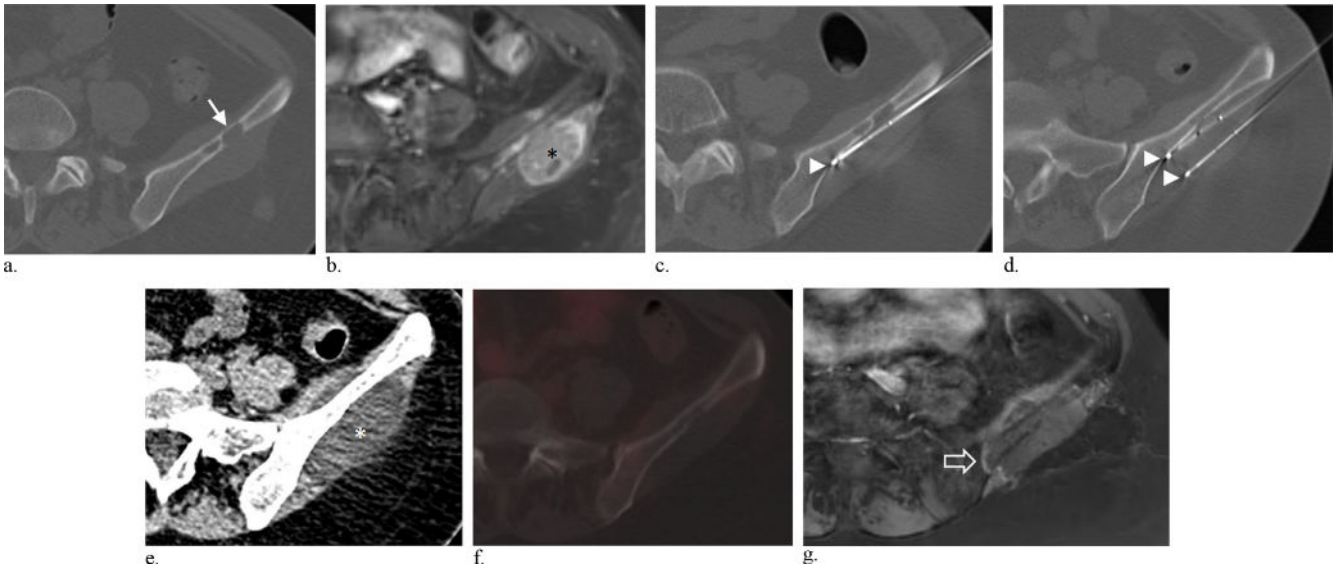

Figure 1. A 52-year-old woman with metastatic leiomyosarcoma and severe left buttock and leg pain that was minimally relieved with oral opioid pain medications. Axial CT with bone windowing **(a)** and T1-weighted MR imaging after contrast administration with fat suppression **(b)** show a lytic lesion in the left iliac wing (arrow) with an enhancing soft tissue component (black asterisk). Axial CT images with bone windowing **(c, d)** show multiple cryoprobes positioned along the posterior wall of the iliac crest (arrowheads). Axial CT image with soft tissue windowing **(e)** shows the resulting ice ball enveloping the tumor (white asterisk). The patient experienced near-complete pain relief after the procedure. Axial 18-fluorodeoxyglucose PET/CT **(f)** performed 16 weeks after cryoablation shows no uptake in the treated metastasis. Axial T1-weighted MR imaging after contrast administration with fat suppression **(g)** performed 30 weeks after treatment shows a thin rim of enhancing granulation tissue at the margin of the ablation zone (block arrow) and no residual enhancing tumor.

The maximum durations of the freeze and thaw cycles were 10 minutes and 8 minutes, respectively, but the duration of the freezing portion of the ablation cycle was adjusted on the basis of the adequacy of lesion coverage and the proximity of adjacent critical structures to the margin hypoattenuating ice ball on interval imaging. When treating large tumors, the deeper portion of the tumor was often ablated initially, after which the cryoprobes were retracted to ablate the more superficial portion.

Cementoplasty was performed during the same treatment session if the patient reported mechanical pain or there was a preexisting or imminent risk of pathologic fracture. The ice ball was actively thawed after the second freeze cycle, and approximately 1 hour was allowed to elapse before cement was instilled into the ablation cavity with the StabiliT System (DFINE, Inc, San Jose, California) under fluoroscopy or CT fluoroscopy through the same percutaneous cannulas used for ablation. An active thaw was performed before cementoplasty to allow for more even cement distribution.

Periprocedural Monitoring

Thermal protection techniques were employed during the treatment of 27 tumors (29%; 27 of 92), including hydrodissection (3.3%; 3 of 92), pneumodissection (20%; 18 of 92), or a combination of both (6.5%; 6 of 92) (Table 3). Hydrodissection and pneumodissection were performed by injection of carbon dioxide and warmed 5% dextrose in water, respectively, through an additional percutaneous 18- to 22-gauge needle (Fig 2a, b). The goal of hydrodissection or pneumodissection was to create as much separation as possible between the tumor and the at-risk structure. Intraprocedural motor and somatosensory evoked potential monitoring was used during the 5 treatment sessions (8.9%; 5 of 56) performed with general anesthesia, including the treatment of 4 metastases located in the thoracic spine or paraspinal soft tissues in close proximity to the spinal cord and nerve roots and 1 axillary metastasis in close proximity to the brachial plexus. Cutaneous thermal protection consisted of a surface application of warm saline solution in all cases.

Table 3. Anatomic Locations of Metastases for which Thermal Protection Techniques Were Used during Cryoablation

Location	Hydrodissection	Pneumodissection	Both
Scapula	—	1	—
Lumbar spine	2	—	—
Sacrum	—	1	1
Coccyx	—	1	—
Ilium	—	—	2
Acetabulum	—	1	1
Pubic rami	—	2	—
Ischial tuberosity	—	2	—
Tibia	1	—	—
Chest wall	—	7	2
Abdominal wall	—	1	—
Thigh	—	1	—
Pelvis	—	1	—
Total	3	18	6

Patients were clinically evaluated 1 hour after each procedure for evidence of acute complications, such as hematoma formation or neurologic injury. Five patients (8.9%; 5 of 56) were admitted for overnight observation after the procedure or were inpatients at the time of treatment. Procedural complications were documented according to the Society of Interventional Radiology (SIR) classification (19).

Assessment of Pain Relief

Worst pain before treatment and 1 day, 1 week, 1 month, 3 months, and 6 months after treatment was measured using the Numeric Rating Scale (NRS), a validated self-reporting 10-point scale (20). Worst pain before treatment was assessed on the day of treatment by a musculoskeletal radiology nurse coordinator. Pain scores were obtained after treatment via in-person or telephone interviews with the same nurse coordinator. Follow-up pain scores were not obtained at the specified time points because patients could not be reached by telephone, died or entered hospice, or were lost to follow-up (Table 4).

Assessment of Technical Efficacy

Follow-up tumor imaging included CT in 79% (73 of 92) of cases, magnetic resonance (MR) imaging in 45% (41 of 92) of cases, and combined positron emission tomography (PET)/CT in 36% (33 of 92) of cases. All follow-up imaging was performed for clinical reasons at the request of the referring oncologist. Initial follow-up imaging was evaluated for residual unablated tumor. Subsequent follow-up imaging was evaluated for local tumor progression, defined as (*a*) increased osteolysis or increased soft tissue tumor component on CT, (*b*) increased enhancing tissue on MR imaging, or (*c*) persistent 18-fluorodeoxyglucose uptake on PET/CT. To serve as an internal control, cross-sectional imaging performed after treatment was also reviewed for evidence of systemic disease progression, including enlargement of visceral or intracranial metastases or osseous metastases that were not ablated. Follow-up imaging was not obtained at the specified time points because the patients were doing well clinically with no local symptoms to warrant imaging, died or entered hospice, or were lost to follow-up (Table 5).

Statistical Analysis

For patients with NRS pain score ≥ 4 before treatment, the Mann-Whitney *U* test was used to compare pain scores before and after treatment. The Mann-Whitney *U*

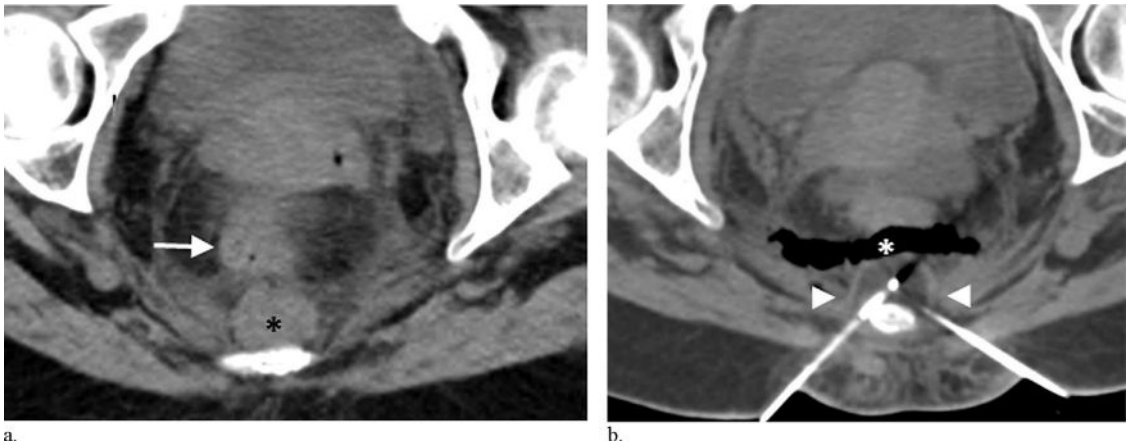

Figure 2. A 45-year-old woman with metastatic non–small cell lung cancer and severe low back pain requiring hospital admission for pain control. On physical examination, her pain was localized to the coccyx. Axial CT image **(a)** shows a soft tissue mass immediately anterior to the coccyx (black asterisk), in close proximity to the rectosigmoid colon (arrow). Axial CT image **(b)** after a 22-gauge needle has been used to inject carbon dioxide (white asterisk) into the fat plane between the mass and the colon, separating the 2 structures. Two cryoprobes have been placed on either side of the coccyx and an ice ball has formed that envelops the tumor (arrowheads). The patient reported nearly complete pain relief immediately after the procedure.

Table 4. Treatments without Follow-up Pain Scores at Each Time Point and the Reasons Pain Scores Were Not Obtained

Time Point	Unable to Contact	Death/Hospice	Lost to Follow-up	Total
1 d	16	—	—	16 (21)
1 week	5	2	1	8 (10)
1 month	11	4	—	15 (15)
3 months	18	29	3	50 (64)
6 months	25	35	7	67 (86)

Note–Values in parentheses are percentages of the total number of treatments performed for pain palliation (n = 78).

Table 5. Treatments without Follow-up Imaging at Each Time Point and the Reasons Imaging Was Not Obtained

Time Point	No Symptoms to Warrant Imaging	Death/Hospice	Lost to Follow-up	Total
3 months	4	9	—	13
6 months	3	—	1	4
12 months	3	1	—	4

test was used because the Shapiro test confirmed that the pain scores were non-normally distributed. Additionally, univariate analysis was performed with clinically significant pain palliation (reduction in NRS pain score $\geq$ 2 points) at 1 week and 1 month as the dependent, binary variables. Independent variables tested included patient age and sex, tumor location and histology, lesion bone quality (lytic, blastic, mixed lytic and blastic, or normal), tumor volume, goal of therapy (pain palliation or both pain palliation and local tumor control), NRS pain score before treatment (dichotomized as $\geq$ 8 or $<$ 8), previous radiation therapy, whether concurrent cementoplasty was performed, whether the procedure was technically successful, and duration of local tumor control. Variables that were significantly included in the univariate models were included in a multivariable model. A similar analysis was performed with duration of local tumor control as the dependent, continuous variable. P values $<$ .05 were considered statistically significant.

RESULTS

Palliative Efficacy

Pain palliation results are summarized in Table 6. There were 78 treatments performed for pain palliation, with median pain score of 8.0. Decreased median pain scores were reported 1 day (6.0; $P < .001$, n = 62), 1 week (5.0; $P < .001$, n = 70), 1 month (5.0; $P < .001$, n = 63), and 3 months (4.5; $P = .01$, n = 28) after treatment. The median pain score at 6 months was 7.5 ($P = .33$, n = 11). Pain scores 6 months after treatment were documented for 7 patients who underwent cryoablation of 11

Table 6. Pain Scores before and after the Procedure

		NRS		
	Number (%)	Median	IQR	*P* Value
Before treatment	78	8.0	6.0–9.0	—
After treatment				
1 d	62 (79)	6.0	4.0–8.0	< .001
1 week	70 (90)	5.0	3.5–7.0	< .001
1 month	63 (81)	5.0	3.0–8.0	< .001
3 months	28 (36)	4.5	4.0–7.0	.01
6 months	11 (14)	7.5	5.5–8.0	.33

Note–The second column denotes the number of tumors for which follow-up pain scores were obtained at each time point. IQR = interquartile range; NRS = numeric rating scale.

metastases; 4 of these patients had decreased pain scores 6 months after treatment, each of whom had a single treated metastasis. The first patient with recurrent pain 6 months after cryoablation of bilateral iliac epithelioid hemangioendothelioma metastases also had metastases in the sacrum, both acetabula, right inferior pubic ramus, and right femoral head. The second patient had recurrent pain 6 months after cryoablation of sacral and bilateral iliac non–small cell lung cancer metastases. The third patient had recurrent pain 6 months after cryoablation of a right iliac breast cancer metastasis but also had contralateral iliac and sacral metastases as well as severe sacroiliitis that was palliated with multiple intra-articular steroid injections.

In univariate analysis, an at least 2-point reduction in pre-procedure NRS pain score at 1 week after treatment was associated with an NRS pain score before treatment of $\geq$ 8 ($P < .001$), shorter duration of local tumor control ($P < .008$), and pain palliation alone as the goal of therapy ($P = .018$). In multivariable analysis, only NRS pain score before treatment of $\geq$ 8 ($P = .015$) and shorter duration of local tumor control ($P = .032$) remained as significant predictors of pain relief at 1 week. In univariate analysis, the only significant predictor of an at least 2-point reduction in the pre-procedure NRS pain score at 1 month after treatment was an NRS pain score before treatment of $\geq$ 8 ($P = .043$). Tumor volume, lesion bone quality, concurrent cementoplasty, and prior radiation therapy were not significant predictors of pain palliation at 1 week or 4 weeks after treatment.

Technical Success and Efficacy

Of the 54 tumors (59%; 54 of 92) treated with the intent of local tumor control, technical success was achieved in 96% (52 of 54) of cases. In 1 case, total ablation of an infiltrative left axillary soft tissue mass could not be achieved because it was abutting the brachial plexus. The other case was a 294-cm^3 hemangiopericytoma chest wall metastasis with marked vascularity that created a "cool sink" that prevented formation of a sufficiently large ice ball around the tumor.

Technical efficacy results are summarized in Figure 3. Residual unablated tumor was identified on initial follow-up imaging in 7.4% (4 of 54) of cases. The locations and histologies of these tumors included the ribs (malignant peripheral nerve sheath tumor), sacrum (papillary thyroid), ilium (sarcoma), and acetabulum (non–small cell lung cancer). No additional cases of local tumor progression were documented within 3 months of cryoablation. Follow-up imaging demonstrating local tumor control at least 3 months after cryoablation was available for an additional 37 tumors. The overall radiographic local tumor control rate at 3 months was 90% (37 of 41). Including only cases in which additional imaging demonstrated progression of systemic metastatic disease, the 3-month radiographic local tumor control rate was 88% (29 of 33). One additional tumor (an iliac sarcoma metastasis) demonstrated local tumor progression 3–6 months after cryoablation. Follow-up imaging demonstrating local tumor control at least 6 months after cryoablation was available for an additional 32 tumors. The overall radiographic local tumor control rate at 6 months was 86% (32 of 37). Including only cases in which additional imaging demonstrated progression of systemic metastatic disease, the 6-month radiographic local tumor control rate was 86% (32 of 37). Two additional cases of local tumor progression—an acetabular sarcoma and a malignant peripheral nerve sheath tumor rib metastasis—were documented 6–12 months after cryoablation. Follow-up imaging demonstrating local tumor control at least 12 months after cryoablation was available for an additional 26 tumors. The overall radiographic local tumor control rate at 12 months was 79% (26 of 33). Imaging demonstrated progression of systemic metastatic disease in all these cases. In univariate analysis, duration of systemic disease control ($P < .001$) was the only positive predictor of local tumor control.

The cryoablation complication rate was 4.3% (4 of 92). A minimally displaced pathologic rib fracture after cryoablation of an epithelioid hemangioendothelioma metastasis was diagnosed radiographically but did not require additional therapy or affect the patient's activities of daily living. This was classified as a minor complication (grade A). The 3 major complications included 2 cases of hemothorax requiring chest tube placement after treatment of chest wall tumors (grade D) and 1 case of foot drop after treatment of an acetabular tumor that resolved over 5 weeks (grade C).

DISCUSSION

The present study adds to the growing number of case series showing that cryoablation of musculoskeletal metastases is safe and produces rapid and durable pain relief (11,15,21,22). In a previous multicenter prospective study, Callstrom et al (15) treated 61 patients with 69

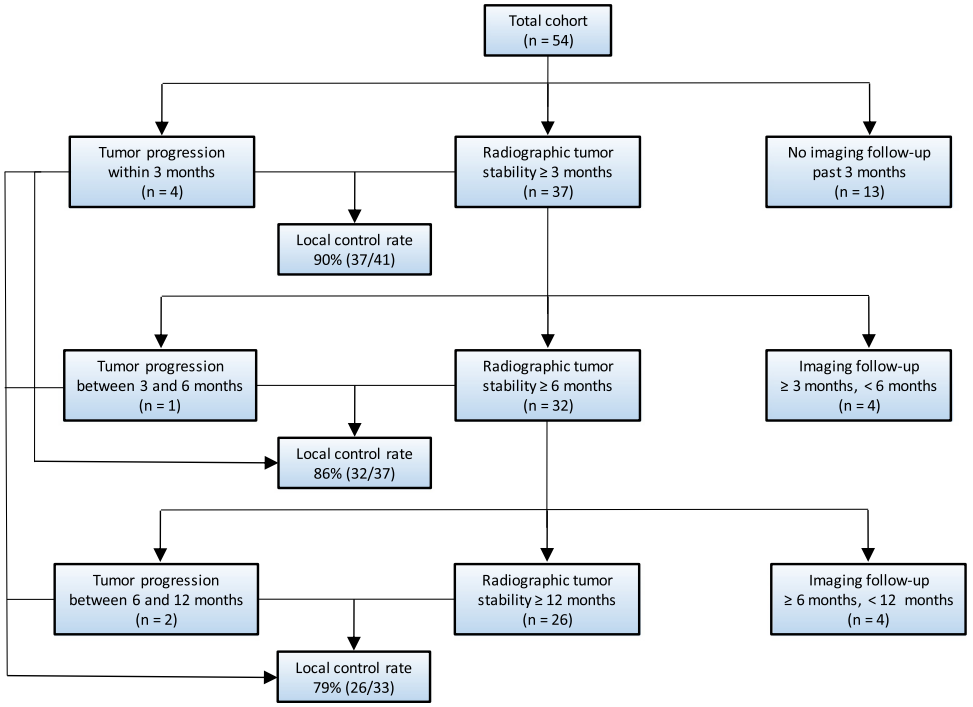

Figure 3. Flowchart summarizing overall radiographic local tumor control results at 3-month, 6-month, 9-month, and 1-year follow-up imaging evaluations.

bone metastases with percutaneous cryoablation. The mean score for worst pain in a 24-hour period before treatment was 7.1 (10-point scale; range, 4–10). At 1-, 4-, 8-, and 24-week follow-up examinations, mean pain scores decreased to 5.1, 4.0, 3.6, and 1.4 ($P < .001$ at all time points). In a subsequent single-center retrospective study by Prologo et al (11), cryoablation of 54 painful tumors was performed in 50 patients. The median visual analogue scale pain score before treatment was 8 ± 1 (10-point scale). Patients reported decreased pain scores of 3 ± 1 at 24 hours after treatment and 3 ± 2 at 3 months after treatment ($P < .001$ at both time points). Both of these studies included various primary tumor histologies and locations. The present study similarly shows clinically significant pain relief 1 day and up to 3 months after treatment. No reduction in median pain score at 6 months was demonstrated, although pain scores at this time point were recorded for only 7 patients with 11 treated metastases. In this group, 4 patients with a single treated metastasis all reported decreased pain scores, whereas 3 patients with 7 treated metastases reported unchanged or increased pain scores, raising the median pain score. The latter 3 patients all had both treated and untreated pelvic metastases, and 1 patient also had sacroiliitis. The pain scores of these patients may have been confounded by an inability to discriminate between multiple potential sources of pain in close anatomic proximity.

Selection of patients for palliative cryoablation therapy requires accurate assessment of the potential benefits and risks of the procedure. An NRS pain score before treatment of ≥ 8 was associated with a higher likelihood of pain relief at both 1 week and 4 weeks after treatment—an intuitive and encouraging result. A shorter duration of local tumor control was also associated with pain relief 1 week after treatment, which can be explained only by the presence of a covariate not represented in our multivariable model. The most likely explanation is that biologic tumor aggressiveness correlates with both a rapid palliative response to treatment and a shorter duration of local tumor control. The mechanisms of cryoablation-induced pain relief are not completely understood but are likely related to decreased tumor burden (15,23). Cryoablation causes tumor necrosis through several mechanisms, including cellular swelling and dehydration, intracellular ice formation, coagulative necrosis, free radical release and apoptosis in response to biochemical stress, and stimulated immunologic targeting of tumor cells (24,25). More aggressive tumors may be more susceptible to these mechanisms of cryoablation-induced cell death initially, but any residual tumor would then be expected to progress rapidly, resulting in shorter duration of local tumor control. Tumor histology was included in the statistical model and was not associated with likelihood of pain relief, but histology is an imperfect surrogate for biologic behavior. Additionally, the relatively small numbers of each tumor histology limits the statistical power to detect an association between histology and pain relief.

Several important variables were not predictive of pain relief at 1 week or 1 month after therapy. First, pain

relief was not associated with tumor volume, which highlights the ability to use multiple cryoablation probes to form contiguous ice balls around even large tumors, up to 577.2 mL in this series. Second, bone lesion quality was not associated with pain relief, again demonstrating that cryoablation is not limited by the intrinsically higher impedance of sclerotic bone (26,27). Finally, 4 tumors (4.3%; 4/92) in this cohort were treated with radiation therapy before cryoablation, and concurrent cementoplasty was performed as part of 28% (26 of 92) of treatments, both of which are possible confounders of pain relief; however, neither of these variables was associated with pain relief at either time point.

The local control rates achieved in this and previous studies support the use of cryoablation for this indication (6,28,29). McMenomy et al (6) previously reported a local control rate of 87% (45 of 52) at a median follow-up of 21 months after cryoablation of metastases from various tumor histologies. The present study similarly showed a 1-year radiographic local control rate of 79% (26 of 33) despite progression of metastases at other sites. The only variable associated with local tumor control was duration of systemic disease control, likely indicating that more biologically aggressive tumors progress more rapidly despite both locally directed and systemic therapy. However, as with pain palliation, duration of local tumor control was not associated with tumor volume, bone lesion quality, previous radiation therapy, or concurrent cementoplasty. In the palliative setting, the goal of local tumor control is to achieve more durable pain relief. However, there is also growing evidence that outcomes of patients with oligometastatic disease (generally defined as $\leq$ 5 metastases) may be improved by eradicating all clinically detectable sites of disease with locally directed therapy (6,30–32).

The safety profile of musculoskeletal cryoablation in this and previous case series is acceptable, especially given the invasiveness of surgical alternatives (6,11,15,28,29). In the study by Callstrom et al (15), 1 patient developed osteomyelitis at the ablation site, resulting in a major complication rate of 2% (1 of 54). Prologo et al (11) reported a complication rate of 11% (6 of 54) with 4 major complications including 2 femoral fractures after treatment of proximal lytic metastases, suprascapular neuropathy after supraclavicular lymph node ablation, and sciatic neuropathy after treatment of an intragluteal melanoma deposit. The present study had a complication rate of 4.3%. However, 2 of 13 patients treated for paraspinal chest wall lesions developed a hemothorax, resulting in a complication rate of 15% (2 of 13) for tumors in this location. In contrast to ablation-related nerve injuries, little can be done to mitigate the risk of hemothorax, and patients should be informed that the risk of this complication may be higher when treating paraspinal tumors.

This study has important limitations. First, pain scores are inherently subjective and may be confounded by pain medication usage, which was not routinely recorded in this study, and the status of other sites of metastatic disease and other medical conditions. For example, the 5 patients (8.9%; 5 of 56) who were hospitalized after ablation therapy may have received increased pain medications that artificially lowered their pain scores measured 1 day hours after treatment. Moreover, reliance on pain scores does not account for other quality-of-life indicators, such as functional disability. Second, pain scores after treatment were not obtained in many patients. The most common reason was that the patient died or entered hospice, as is expected in a cohort of patients with metastatic disease. However, many patients could not be reached for pain score assessment or were lost to follow-up entirely, which potentially biased the rates of pain palliation. Third, duration of local tumor control was not based on a standardized imaging follow-up schedule. As a result, duration of local tumor control was overestimated for patients with residual or recurrent tumor and underestimated for patients with local tumor control. This may have also led to underestimation of local tumor control rates because imaging is not clinically warranted in patients without symptoms of local tumor progression.

In conclusion, the present study adds to the growing number of case series demonstrating the safety and efficacy of treating musculoskeletal metastases with percutaneous cryoablation. Clinically significant pain relief was demonstrated 1 week after treatment and persisted up to 3 months, and radiographic local tumor control was achieved in 79% (26 of 33) of tumors 1 year after treatment despite progression of metastases at other sites. The complication rate of 4.3% (4 of 92) in this study is acceptable given the lack of alternative therapeutic options for these patients. However, a 15% (2 of 13) incidence of hemothorax should be considered when treating chest wall tumors.

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