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SCIENTIFIC ARTICLE

Image-guided cryoablation for the treatment of painful musculoskeletal metastatic disease: a single-center experience

J. David Prologo · Matthew Passalacqua · Indravadan Patel · Nathan Bohnert · David J. Corn

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Abstract
Purpose The role of image-guided thermal ablation techniques for the nonoperative local management of painful osseous metastatic disease has expanded during recent years, and several advantages of cryoablation in this setting have emerged. The purpose of this study is to retrospectively evaluate and report a single-center experience of CT-guided percutaneous cryoablation in the setting of painful musculoskeletal metastatic disease.
Methods This study was approved by the institutional review board and is compliant with the Health Insurance Portability and Accountability Act. Electronic medical records of all patients who underwent percutaneous image-guided palliative cryoablation at our institution were reviewed (n=61). An intent-to-treat analysis was performed. Records were reviewed for demographic data and anatomical data, primary tumor type, procedure details, and outcome—including change in analgesic requirements (expressed as morphine equivalent dosages), pain scores (utilizing the clinically implemented visual analog scale), subsequent therapies (including radiation and/or surgery), and complications during the 24 h following the procedure and at 3 months. Patients were excluded (n=7) if data were not retrospectively identifiable at the defined time points.
Results Fifty-four tumors were ablated in 50 patients. There were statistically significant decreases in the median VAS score and narcotic usage at both 24 h and 3 months (p<0.000). Six patients (11 %) incurred complications related to their therapy. Two patients had no relief at 24 h, of which both reported worsened pain at 3 months. One patient had initial relief but symptom recurrence at 3 months. Four patients went on to have radiation therapy of the ablation site at some point following the procedure.
Conclusions CT-guided cryoablation is a safe, effective, reproducible procedural option for the nonoperative local treatment of painful musculoskeletal metastatic disease.

Keywords Percutaneous Cryoablation · Musculoskeletal Intervention

J. D. Prologo (✉)
Emory University Hospital, Department of Radiology and Imaging Sciences, Division of Interventional Radiology and Image-Guided Medicine, 1364 Clifton Road, NE Suite D112, Atlanta GA 30322, USA
e-mail: jdprologo@hotmail.com

M. Passalacqua · I. Patel · N. Bohnert
Department of Radiology, University Hospitals Case Medical Center, 11,100 Euclid Avenue, Cleveland, OH 44106, USA

M. Passalacqua
e-mail: Matthew.passalacqua@uhhospitals.org

I. Patel
e-mail: Indravadan.patel2@uhhospitals.org

N. Bohnert
e-mail: Nathan.bohnert@uhhospitals.org

D. J. Corn
Departments of Radiology and Biomedical Engineering, University Hospitals Case Medical Center, Cleveland, OH, USA
e-mail: Djc26@case.edu

Introduction

Pain from neoplastic involvement of bone is a major cause of morbidity in cancer patients [1–6]. The role of interventional radiology in the management of these patients has evolved over recent years [7–10], as have the techniques of thermal ablation [11–22]. Specifically, image-guided percutaneous cryoablation is emerging as a safe, efficacious, and durable therapy for the palliation of painful musculoskeletal metastatic disease [13, 19–21, 23–30].

Advantages of cryoablation when compared to radiofrequency or microwave ablation are direct visualization of the ablation zone, decreased intraprocedural and postprocedural pain, and the ability to utilize multiple probes in variable configurations to create tailored additive overlapping ablation zones [13, 23, 26, 31, 32].

The purpose of this study is to retrospectively evaluate and report a single-center experience of CT-guided percutaneous cryoablation in the setting of painful musculoskeletal metastatic disease.

Materials and methods

Data collection

This study was approved by the institutional review board and is compliant with the Health Insurance Portability and Accountability Act. Electronic medical records of all patients who underwent percutaneous image-guided palliative cryoablation at our institution were reviewed (n=61). An intent-to-treat analysis was performed. Records were reviewed for demographic data and anatomical data, primary tumor type, procedure details, and outcome—including change in analgesic requirements (expressed as morphine equivalent dosages), pain scores (utilizing the clinically implemented visual analog scale), subsequent therapies (including radiation and/or surgery), and complications during the 24 h following the procedure and at 3 months. Patients were excluded (n=7) if data were not retrospectively identifiable at the defined time points. The “3-month” follow-up translated objectively to 80 ± 17.7 days.

Cryoablation procedures

All procedures were performed with CT guidance. Patients were positioned to maximize safe access to the tumors. Anesthesia consultation was dependent on patient comorbidities, ability to position on the table, and predicted tolerance of the procedure. Overall, the great majority (49/54, 91 %) of procedures were performed with formal anesthesia sedation management, though only 10/54 (19 %) patients were intubated.

In all cases, cryoprobes from Galil (Arden Hills, MN) were used, ranging in size from 13 to 17 G, with predicted ablation zones ranging from 2 cm × 1 cm–3.5 cm × 2 cm (Fig. 1). Probe selection and number varied according to lesion characteristics (Fig. 2). Specifically, the bone or soft tissue interface with the neoplastic lesion was targeted for inclusion in the predicted lethal zone. Each lesion underwent two 10–5-min freeze-thaw intervals, with images obtained at 8 min into the freeze cycle each time. There were no probe manipulations between cycles. No ancillary techniques were employed to protect adjacent structures or improve lesion accessibility.

Outcome variables

The primary outcome variables analyzed were pain relief, opioid usage, and complication rate. Pain relief was evaluated by compiling the patient’s initial report of pain, pain report at 24 h, and at 3-month follow-up. The initial and 24-h reports were documented by the operator (for inpatients and outpatients). The 3-month follow-up responses were gleaned from medical records of outpatient visits to primary care doctors and oncologists. Patient narcotic usage was documented as part of routine clinical, preprocedural, post procedure, and follow-up consultations and visits. The drugs were converted to morphine equivalent values using established tables [23, 33, 34]. Complications were identified and classified according to the SIR classification system for complications by outcome [14].

Statistical analysis

Pain relief and opioid usage were evaluated for median differences using the Wilcoxon signed-rank test. In order to analyze the non-normal data distribution (Fig. 3) appropriately, results are reported as median±absolute deviation (as opposed to

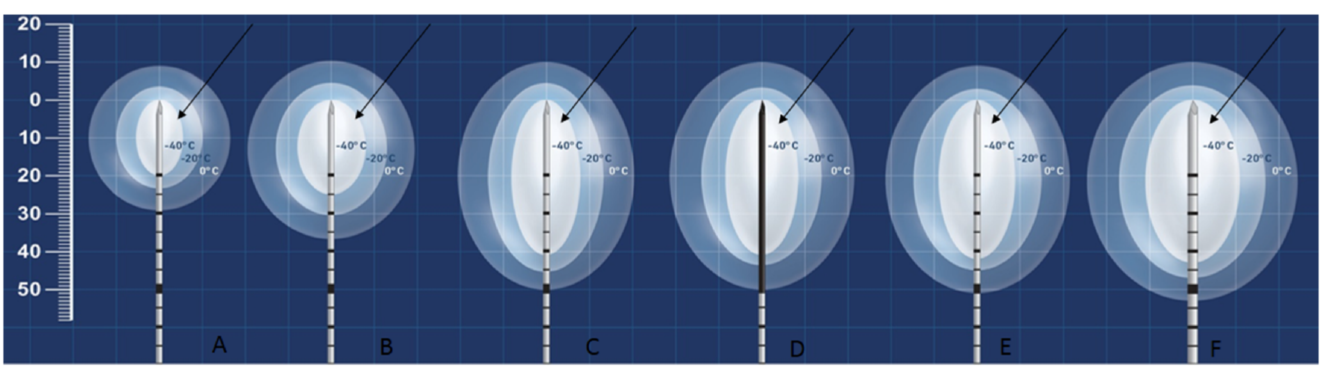

Fig. 1 Range of isotherm maps for cryoablation probes used during the study period. The temperature ranges closest to the probes (*arrows*) are the predicted lethal zones. Probes A-E are 17 G; probe F is 13 G

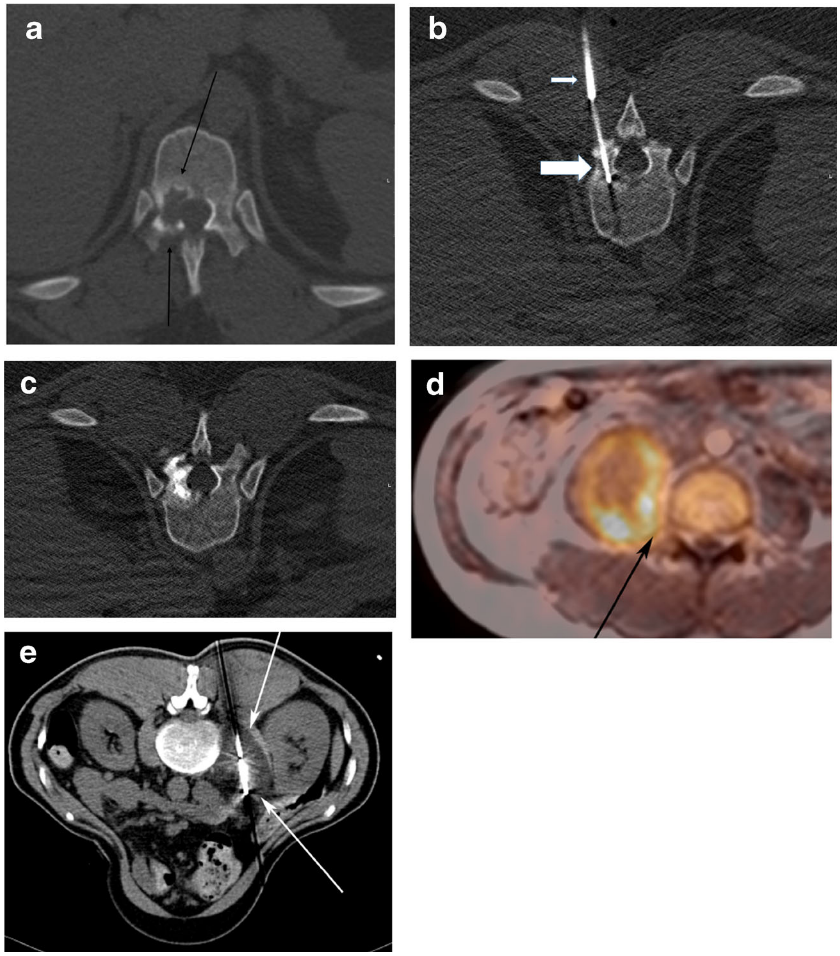

Fig. 2 Ablation images demonstrating the range of approaches. **a** Single axial CT image at the level of T10 in a 47-year-old female with breast cancer and focal back pain demonstrates a 1 × 2-cm lytic pedicle lesion (*arrows*) corresponding to her symptoms. **b** Through a co-axial anchor (*small arrow*), a 17 G cryoablation probe ["B" from Fig. 1 (*small arrow*)] was advanced across the lesion and freeze-thaw cycles undertaken. **c** The next morning, the patient had polymethylmethacralate instilled to the ablation bed under combination CT/fluoroscopic guidance. **d** Single axial PET-MR image in a 61-year-old male with metastatic sarcoma and L4 radiculopathy demonstrating FDG activity superimposed on an underlying 12-cm mass lesion in the right psoas muscle (*arrow*). **e** Single axial image obtained during the cryoablation demonstrating the iceball created by probe "E" from Fig. 1 reaching to the periphery of the mass in the region of the exiting nerve root (*arrows*). **f** Additional image from the same patient shows a second, similar probe superiorly—demonstrating the iceball margins (*arrows*) in relation to the mass and the need for additional probes

means, the former being resistant to outliers). All computations were performed using Stata Statistical Software, Release 12 (StataCorp LP, College Station, TX). For all statistical analyses, an alpha of 0.05 was used.

Results

Patients and procedures

The demographic, anatomical, primary tumor type, and inclusion criteria distribution of the included patients are delineated in Table 1. One procedure was aborted because of inability to traverse the lesion. The remaining ablations were all technically successful with no immediate complications. Fifty-four tumors were ablated in 50 patients. Three patients had two sites ablated on different days. Eighteen of the ablated patients had cementoplasty performed as part of the procedure. Two of the cementoplasty patients had a 2-day procedure with polymethylmethacralate being instilled on the 2nd day.

Response to pain

There were statistically significant decreases in the median VAS score and narcotic usage at both 24 h and 3 months (Table 2). The median VAS score of all patients reported prior to their procedures was 8±1. At 24 h and 3 months post procedure, the median VAS score decreased to 3±1 (p<0.000), where it remained at 3 months post procedure. Median VAS score at 3 months was significantly lower than

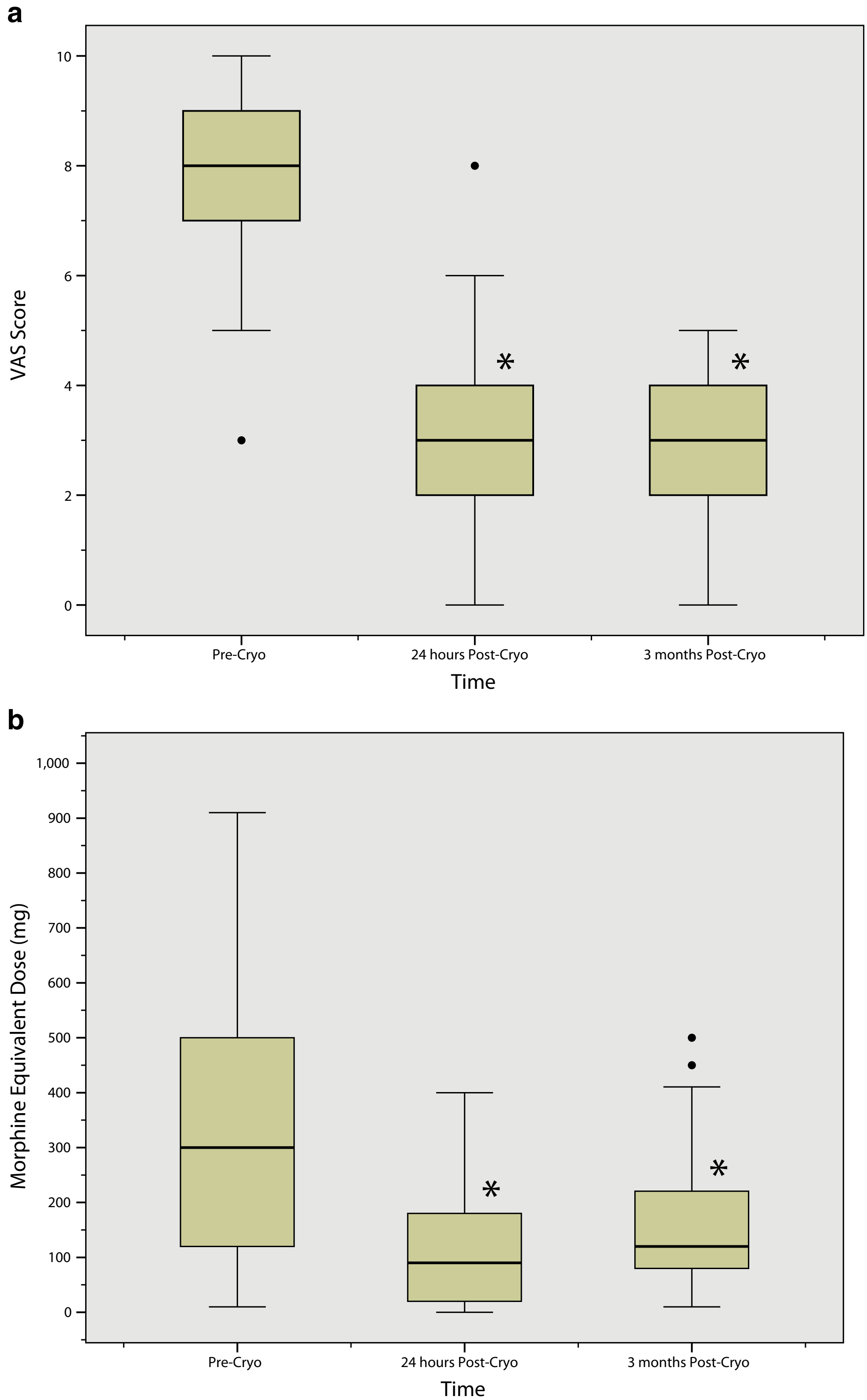

Fig. 3 Distribution of study population VAS scores **a** and narcotic usage **b** at the study time points

prior to the procedure ($p<0.000$). Median narcotic usage, expressed as morphine equivalent (the amount of narcotics taken in 24 h, expressed as a morphine equivalent), was 340± 180 mg prior to the procedure. Morphine equivalent values

Table 1 Demographic data, inclusion criteria, tumor type, and anatomical data for patients undergoing percutaneous CT-guided cryoablation for painful musculoskeletal metastatic disease

Inclusion criteria category[1]	Age range, sex, inpatient vs. outpatient	Sex	Inpatient vs. outpatient	Tumor size range	Osseous anatomical locations	Soft tissue anatomical locations	Primary
I. Patients with limited painful metastatic disease in whom conventional tx has failed or been declined. n=47	33–91	28 F, 15 M	19IP, 24OP	1.7 cm–18 cm	Pelvic bones (16), Skull base (2), Upper extremity (6), Sternum (3), Tibia (2), Foot (2), pedicle (2), chest wall (1)	Masticator Space (2), Pterygopalatine fissure (1), Psoas muscle (1), Iliacus muscle (1), Gluteus musculature (2), obturator muscle (1), chest wall (2), neck soft tissue (3)	Breast (10), renal cell (7), squamous cell (4), lung (9), sarcoma (7), melanoma (8), mucoepidermoid (1), prostate (1)
II. Patients at risk for further morbidity related to progression of their lesion. n=4	67–88	3 F, 1 M	4IP	2.5 cm–7 cm	Femur [2 (pending fracture)], iliac bone [1 (pending fracture)]	Retropharyngeal space [1 (pending airway compromise)]	Breast (2), renal cell (1), squamous cell (1)
III. Patients with limited metastatic disease who are not surgical candidates n=3	72–88	0 F, 3 M	3IP	4.5 cm–12 cm	Upper extremity (2)	Pelvic ST mass (1)	Renal cell (2), colon (1)
IV. Patients with systemically symptomatic metastatic disease n=0							

[1] Clinical criteria for image-guided ablation of metastatic disease involving bone and soft tissue beyond the liver and lung, as per the JVIR Research Reporting Standards for Image-guided Ablation of Bone and Soft Tissue Tumors

Table 2 Responses to pain outcome variables before, 24 h, and 3 months post procedure. Values are expressed as median ± absolute deviation

	Preprocedure	Post procedure (24 h)	3 months
Median VAS	8±1	3±1	3±2
p Value	X	$p<0.000$	$p<0.000$
24 h morphine equivalent (mg)	304±180	90±70	120±70
p Value	X	$p<0.000$	$p<0.000$

decreased to 85±70 mg ($p<0.000$) 24 h after the procedure and at 3 months had increased to 130±70 mg ($p<0.000$). At 3 months post procedure, morphine equivalent values remained significantly lower than prior to the procedure ($p<0.000$).

Two patients had no relief at 24 h, of which both reported worsened pain at 3 months. One patient had initial relief but symptom recurrence at 3 months (Fig. 4). Four patients went on to have radiation therapy of the ablation site at some point following the procedure. Of these, one was planned as a complementary therapy for a very large lesion, and three sought additional therapy for continued pain.

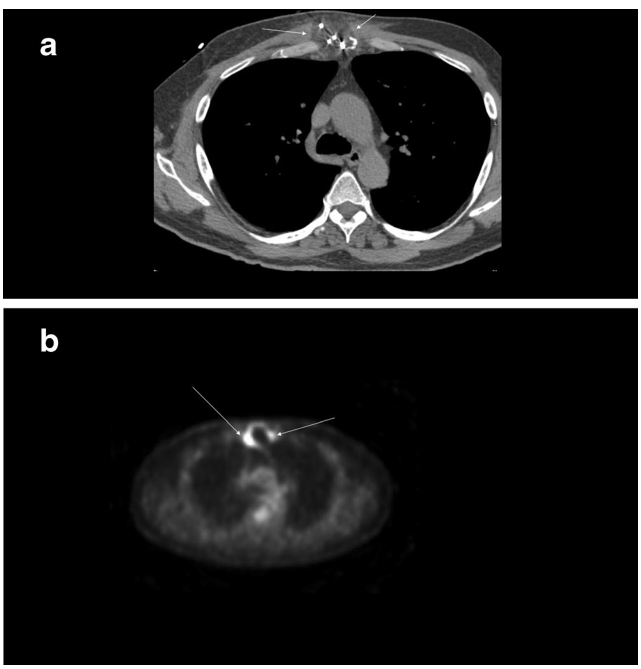

Fig. 4 Images from a patient with symptomatic recurrence at 3 months. **a** Single axial CT taken during an ablation in a 61-year-old male with painful metastatic lung cancer involving the sternum demonstrates four cryoprobes ("D" from Fig. 1) and the associated ice ball (arrows). The patient had initial relief of his symptoms reflected as a reported VAS decrease from 10 to 2. **b** Single axial PET image obtained 3 months later demonstrates abnormal activity at the periphery of the ablation bed (arrows) corresponding to the patient's recurrent symptoms, interpreted as either recurrence or initial "underablation"

Complications

Six patients (11 %) incurred complications related to their therapy [21, 28]. Two of these were minor (A) and consisted of symptomatic osteocartilaginous damage beyond the lesion, which resolved. Four were major [C (n=1) and D (n=3)]: two complete femoral fractures following ablation and cementoplasty of proximal lytic lesions and two transient neuropathies resulting from damage to adjacent nerves during the ablation—one suprascapular nerve involvement during a supraclavicular metastatic lymph node ablation with associated denervation changes on MR and one sciatic nerve involvement during an intragluteal metastatic melanoma deposit ablation (Table 3).

Discussion

Up to 85 % of patients with primary cancers have bone metastases, and half of these will develop intractable pain related to their osseous lesion [1–4]. Pain from neoplastic involvement of bone results from (1) osteoclast-mediated proton sensitization of the sensory fibers at the mineralized bone-tumor interface, (2) sensitization or activation of sensory nerve fibers by products directly produced in tumor and tumor stromal cells, and (3) distortion of mechano-sensitive fibers following normal mechanical stress because of loss of tensile strength in the bone due to cancer [5, 6].

Management options for treatment of symptomatic bone metastases include systemic and local interventions. Bisphosphonates, radionuclides, and chemotherapy are systemically administered in select patients for palliation [7, 35, 36], and systemic analgesic use is well established in cancer pain [37, 38]. The current standard of care for local treatment

Table 3 Complications

Minor complications	
A. No therapy. No consequence	
B. Nominal therapy, no consequence, includes overnight admission for observation only	N=2 Two symptomatic osteocartilaginous injuries outside the targeted lesion
Major complications	
C. Require therapy, minor hospitalization (<48 h)	N=1 Peri-ablational neuropathy
D. Require major therapy, unplanned increase in the level of care, prolonged hospitalization (>48 h)	N=3 Two proximal femoral fractures, one peri-ablational neuropathy
E. Permanent adverse sequelae	
F. Death	

of extra-spinal metastases is external beam radiation therapy [39–43]. Indications for operative local management include fractures, immobilization, and pain refractory to radiation therapy [44]. The role of image-guided thermal ablation techniques for the nonoperative local management of painful osseous metastatic disease has expanded during recent years [7–13, 19, 20, 23–29].

The evolution of these ablative procedures has been toward cryotherapy. The foundation for this evolution was established through key papers demonstrating the safety and efficacy of image-guided radiofrequency ablation for the palliation of painful musculoskeletal metastatic disease [17, 18]. Over time, cryoablation appeared in descriptive papers, review articles, and comprehensive reviews [12, 19, 25, 45–47] and afforded several advantages—including direct visualization of the ablation zone, decreased intraprocedural and postprocedural pain, and the ability to utilize multiple probes in variable configurations to create tailored additive overlapping ablation zones [13, 23, 26, 31, 32].

In 2011, Thacker et al. showed in a retrospective review of 58 patients, divided as 36 cryoablation and 22 radiofrequency ablation, that those who underwent cryoablation for painful musculoskeletal metastatic disease had significantly less short-term analgesic requirement and shorter hospital stays than those who underwent radiofrequency ablation [23].

Subsequently, Callstrom et al. reported the results of a multicenter prospective single-arm trial of 61 patients who underwent image-guided cryoablation for the palliation of painful osseous metastases [26]. Patients had significant decreases in pain and subjective improvements in quality of life at 1, 4, 8, and 24 weeks following the procedure as reflected through Brief Pain Inventory scores, with only one patient incurring a major complication. Similarly, Masala et al. demonstrated symptomatic relief (through VAS scores) following CT-guided cryoablation for painful osseous metastases that correlated positively with post-procedure radiopharmaceutical activity on PET-CT [30].

In the spine, Masala et al. retrospectively described safety and efficacy—through reduced pain (VAS scores) and disability (ODI)—of cryoablation combined with cementoplasty for the palliation of painful vertebral metastases that was at least equivalent to vertebroplasty alone [27]. Although primary, Kurup et al. also reported local control of recurrent sacrococcygeal tumors with cryoablation [28], and recent reports have begun to link cryoablation to systemic inflammatory responses [48–56], as well as suggest potential benefits for patients who undergo cryoablation of metastatic disease [29, 57, 58].

The cytotoxic effects of cryoablation are mediated through the formation of intracellular ice crystals during probe-mediated temperature manipulation. The crystals cause denaturation of proteins and shearing of intracellular structures, including cell membrane rupture. A liquid gas, commonly argon, is used to rapidly cool the tip of the cryoprobe, forming an enlarging ice-ball over time followed by a “thawing” phase, commonly achieved with helium gas, resulting in an osmotic gradient [59]. This causes water to rush into, swell and then burst the tumor cell, eventually leading to cell hypoxia via indirect ischemic injury [60].

To our knowledge, this is the first-single center review describing cryoablation as the exclusive thermal ablation modality for the treatment of painful musculoskeletal metastatic disease to follow the prospective multicenter study put forth by Callstrom et al. The number of patients in this study is similar to that enrolled in the prospective single-arm study. The patient demographics, tumor types, and inclusion criteria are comparable as well. In the present study, patients experienced significant palliation as reflected by decreased VAS scores and narcotic usage—consistent with previously published results. The overall complication rate reported here is slightly higher than in previous reports, but is all inclusive. When only major complications are considered, our rate is similar to previously published results (7 %). Three patients in our series clearly did not benefit from the procedure; two never experienced pain relief and one had recurrence at the periphery of the ablation bed. Upon detailed review, the two patients who had no relief had very large lesions.

This study is limited by its retrospective methodology. It is further limited by the variability of our second follow-up point. That is, there was a fairly large deviation from the mean when considering the population for “3-month” follow-up. Finally, it is limited by the utilization of VAS scores for pain relief vs. the more inclusive Brief Pain Inventory.

Our safety and efficacy results are commensurate with published studies of image-guided cryoablation in the setting of painful musculoskeletal metastatic disease and may have contributory value in establishing the reproducibility of these procedures for palliation. A prospective randomized study of this therapy vs. the historical standard of care radiation therapy will be valuable going forward.

Conflict of interest The primary author of this manuscript has consulted on behalf of Galil in the past (2012).

Disclosure Have provided paid consultation in the past for Galil Medical.

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