Painful Metastases Involving Bone: Percutaneous Image-guided Cryoablation—Prospective Trial Interim Analysis[1]

Matthew R. Callstrom, MD, PhD
Thomas D. Atwell, MD
J. William Charboneau, MD
Michael A. Farrell, MD
Matthew P. Goetz, MD
Joseph Rubin, MD
Jeff A. Sloan, PhD
Paul J. Novotny, MS
Timothy J. Welch, MD
Timothy P. Maus, MD
Gilbert Y. Wong, MD
Kathy J. Brown, BS

Purpose: To prospectively determine the safety and effectiveness of percutaneous cryoablation for the reduction of pain, improvement in the activities of daily life, and reduction in the use of analgesic medications for patients with painful metastatic lesions involving bone.

Materials and Methods: This study was compliant with HIPAA and was approved by the institutional review board. Written informed consent was obtained. During 18 months, 14 patients (eight men, six women; age range, 21–72 years; mean age, 54 years) with one or two painful metastatic lesions involving bone, with a score of 4 or greater out of 10 for worst pain in a 24-hour period, and who did not respond to or refused conventional radiation treatment or chemotherapy were treated with percutaneous cryoablation. Patient response was measured with the Brief Pain Inventory, and analgesic use was recorded before and after the procedure at days 1 and 4, weekly for 4 weeks, and then every other week for a total of 6 months. Complications were monitored. Analysis of the primary end points was undertaken with paired comparison procedures by using paired *t* tests across individual time points supplemented with repeated measures analysis of variance.

Results: Treated lesions were 1–11 cm in diameter. Before cryoablation, the mean score for worst pain in a 24-hour period was 6.7 of 10; the score decreased to 3.8 ($P = .003$) 4 weeks after treatment. Mean pain interference with activities of daily living was 5.5 of 10 before treatment and decreased to 3.2 ($P = .004$) 4 weeks after treatment. All eight (100%) patients (exact 95% binomial confidence interval: 63%, 100%) for whom narcotics were prescribed prior to the procedure reported a reduction in these medications after cryoablation. No serious complications were observed.

Conclusion: Percutaneous cryoablation is a safe and effective method for palliation of pain due to metastatic disease involving bone.

[1] From the Departments of Diagnostic Radiology (M.R.C., T.D.A., J.W.C., M.A.F., T.J.W., T.P.M., K.J.B.), Oncology (M.P.G., J.R.), Biostatistics (J.A.S., P.J.N.), and Anesthesiology (G.Y.W.), Mayo Clinic, 200 First St SW, Rochester, MN 55905. Received July 25, 2005; revision requested September 29; revision received October 28; accepted November 17; final version accepted February 1, 2006. Supported in part by a grant from Endocare, Irvine, Calif. **Address correspondence to** M.R.C. (e-mail: *callstrom.matthew@mayo.edu*).

Current conventional treatments for patients with painful bone 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, metastatic skeletal disease is often refractory to standard chemotherapy or hormonal therapy. Surgery, which is usually reserved for impending fracture, is not always an option when patients have advanced disease and poor functional status. Radiopharmaceuticals, which have known benefit in patients with diffuse painful metastases involving bone, are not considered standard of care for patients with isolated, painful lesions. For many patients with painful metastatic disease, systemic analgesics remain the only alternative treatment option.

Investigators have explored several alternative strategies for the treatment of painful metastatic disease; these involve the use of percutaneous image-guided methods to deliver tissue ablative devices into focal metastatic lesions: ethanol (1), laser-induced interstitial thermotherapy (2), percutaneous radiofrequency (RF) ablation (3–5), and, most recently, cryoablation (6). Of these methods, RF ablation has been evaluated in a multicenter study that demonstrated RF ablation substantially reduces pain in patients with bone pain that is refractory to standard treatments (7). Although RF ablation is effective in reducing patients' pain, it has important limitations including the inability to depict the ablation margin with computed tomographic (CT) monitoring (it is possible with magnetic resonance [MR] imaging but often impractical), pain associated with the procedure, frequent increased pain during the immediate period after treatment, and a period of weeks before substantial pain reduction is achieved. In contrast to RF ablation, cryoablation results in formation of an ice ball, which defines the limits of the ablation zone and is readily identified with CT.

Cryoablation has been used extensively to successfully treat neoplasms in different organs, including the prostate, kidney, liver, lung, breast, and uterus (8–17). First-generation devices were limited to intraoperative use because of the large diameters of the devices, the use of liquid nitrogen for tissue cooling, and the lack of well-insulated probes. Newly developed percutaneous cryoprobes are based on delivery of argon gas through a segmentally insulated probe and rapid expansion of the gas in the sealed probe tip, which results in rapid cooling that reaches −100°C within a few seconds. Active thawing of the ice ball is achieved by actively instilling helium gas instead of argon gas into the cryoprobes.

The purpose of our single-center study was to prospectively determine the safety and effectiveness of percutaneous cryoablation for the reduction of pain, improvement in the activities of daily life, and reduction in the use of analgesic medications for patients with painful metastatic lesions involving bone.

Advances in Knowledge

- To our knowledge, ours is the first prospective clinical study of the use of percutaneous cryoablation of painful metastatic disease involving bone.
- Percutaneous cryoablation provides safe, effective, and durable pain palliation for patients with focal pain due to osteolytic metastases.
- Percutaneous cryoablation of painful metastases results in improved activities of daily life.

Materials and Methods

The manufacturer of the cryoablation probes (Endocare, Irvine, Calif) provided financial support for this study. The authors had control of the data and information submitted for publication.

Patients

Institutional review board approval and informed consent were obtained. During an 18-month period from December 2003 through May 2005, 24 patients who had substantial pain from metastatic lesion(s) involving bone (either arising from a bone metastasis or from a lesion abutting bone which causes periosteal reaction) and whose lesions were refractory to radiation therapy, chemotherapy, surgery, or analgesic medicines were considered for enrollment in our Health Insurance Portability and Accountability Act–compliant study. Alternatively, those who refused these standard therapies also were considered for enrollment. Only patients with substantial pain as indicated by a score of ≥4 on a scale of 0–10 for the question "Please rate your pain by circling the one number that best describes your worst pain over the past 24 hours" were included in the study (18,19). Patients included in the study had pain resulting from no more than two sites of metastatic disease. The number of lesions was limited to no more than two in order to make it easier for the patients to rate their response to treatment. Only patients who had completed chemotherapy or radiation treatment more than 3 weeks prior to cryoablation treatment were included in the study. All patients were older than 18 years, were able to give written consent, and had a life expectancy of greater than 2 months. The portions of lesions within 0.5 cm of the spinal cord, brain, aorta, inferior vena cava, bowel, or bladder were not treated. Patients with impending fractures at the

Published online
10.1148/radiol.2412051247

Radiology 2006; 241:572–580

Abbreviations:
BPI = Brief Pain Inventory
CI = confidence interval
RF = radiofrequency

Author contributions:
Guarantor of integrity of entire study, M.R.C.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, M.R.C., T.D.A., M.P.G., G.Y.W.; clinical studies, M.R.C., T.D.A., J.W.C., J.R., T.J.W., T.P.M., K.J.B.; statistical analysis, M.R.C., J.A.S., P.J.N.; and manuscript editing, M.R.C., T.D.A., J.W.C., M.A.F., M.P.G., J.R., J.A.S., P.J.N., T.J.W., G.Y.W.

See Materials and Methods for pertinent disclosures.

potential ablation site were not eligible for this study.

Ten patients did not meet the inclusion criteria or were excluded from the study. Of these 10 patients, three patients had metastatic lesions in weight-bearing bones at risk for fracture, had a treatment plan that involved subsequent cementoplasty of the same lesion, or both. Five patients planned to continue or definitely were continuing chemotherapy after cryoablation treatment. Two additional patients were enrolled for treatment; however, one patient was excluded prior to treatment because treatment planning included cementoplasty of the target lesion and one patient was excluded prior to treatment because the third-party payer refused to cover treatment. The remaining 14 patients (eight men, six women; age, 21–72 years; mean age ± [standard deviation], 54 years ± 16) were treated with cryoablation.

Image Guidance

CT-guided procedures were performed by experienced interventional radiologists (M.R.C., T.D.A., J.W.C., M.A.F., T.J.W., and T.P.M. with 4, 4, 24, 5, 20, and 20 years of experience, respectively), and postcryoablation examinations were performed with a CT scanning system (HiSpeed CT/i; GE Healthcare, Milwaukee, Wis) equipped with interventional fluoroscopic hardware (SmartView; GE Healthcare). CT examinations were performed with contrast material (iohexol, Omnipaque 300; GE Healthcare). An intermittent CT-fluoroscopic technique (120 kVp, 10–40 mA) was used for CT-guided cryoprobe placement. MR imaging was performed with a 1.5-T clinical imager (Signa; GE Healthcare), with standard pulse sequences and contrast material (Omniscan; GE Healthcare). Both CT and MR postcryoablation images were examined by authors (M.R.C., T.D.A., J.W.C., and M.A.F.) to determine the extent of ablation and to evaluate for possible complications. Cryoprobe placement was performed with ultrasonographic (US) guidance (Sequoia; Acuson, Mountain View, Calif). Cryoprobe positioning was confirmed by using a 2.5–5.0-mm section thickness with a standard CT technique (120 kVp, approximately 240 mA). Postprocessing of CT images was performed with commercial three-dimensional software (Vitrea; Vital Images, Plymouth, Minn).

When the bowel was within 1 cm of the target lesion, a 7- or 15-cm-long, 19-gauge (5-F) catheter (Yueh; Cook, Bloomington, Ind) with an open tip and side holes was used for hydrodisplacement of the bowel by administering sterile normal saline (20). Esophageal dilation balloons (CRE Wireguided, 180 cm; Boston Scientific, Natick, Mass) were also placed percutaneously with US guidance to displace the bowel when it was within 1 cm of the target lesion. A 13-gauge bone biopsy set (Osteo-Site Murphy Diamond Bevel M2; Cook) was used to access lesions through areas of intact bone.

Pretreatment Patient Assessment

Prior to therapy with cryoablation, each patient was assessed with the Brief Pain Inventory (BPI)-Short Form (18,19), which is a validated visual analog scale for assessment of patient pain, and use of analgesic medicine was recorded. The BPI questionnaire asks patients to rate their worst pain in 24 hours, least pain in 24 hours, and average pain with responses from 0 to 10 (0, no pain; 10, pain as bad as you can imagine). Relief of pain through the use of pain treatments or medications is scored on a 0%–100% scale (0%, no relief; 100%, complete relief). Pain interference with activities of daily living was evaluated with questions concerning general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life on a 0–10 scale (0, no interference; 10, completely interferes). Each patient was asked to answer these questions with respect to the lesion that was to be treated.

A complete blood cell count and prothrombin time were obtained between the same day and 14 days prior to the procedure and within 24 hours after the procedure. If no previous histologic or cytologic proof of a lesion's malignancy had been obtained, a percutaneous biopsy was performed prior to treatment. A radiation oncologic consultation was offered to the patient prior to entry into the study if not already completed. Available CT, MR, and US images acquired within the 4 weeks prior to the study were evaluated for eligibility (pain from one or two metastatic lesions) and lesion accessibility by one or more of the participating radiologists (M.R.C., T.D.A., J.W.C., M.A.F., T.J.W., T.P.M.) prior to entry into the study. All patients were physically examined by the radiologist performing the procedure immediately prior to treatment to determine the site or sites of focal pain. Each patient's history of previous chemotherapy and radiation therapy was recorded.

Treatment Procedure

All patients were treated after the administration of general anesthetic (Ultane; Abbott Laboratories, Abbott Park, Ill). After sterile preparation, one or more cryoprobes (Perc-17, Perc-22, and Perc-24; Endocare) were introduced through a skin nick with CT (nine patients) or both CT and US (five patients) guidance by one or more of the participating radiologists (M.R.C., T.D.A., J.W.C., M.A.F., T.J.W., T.P.M.). The cryoprobes were placed into the lesion to be treated in a parallel arrangement approximately 2 cm apart and for complete coverage of the soft-tissue–bone interface. Additional cryoprobes were also placed within 1 cm of the tumor margin to provide adequate coverage along the periphery of the lesion. Cryoprobe positioning was confirmed with CT imaging.

The Perc-24 cryoprobe is a sealed 2.4-mm-diameter (13-gauge [7.2-F]) needle that generates an ice ball measuring up to 3.7 cm in diameter and up to 5.7 cm along the probe shaft. Rapid freezing of tissue with these cryoprobes is based on rapid expansion of argon gas in a sealed probe with a distal uninsulated portion. This process results in rapid cooling that reaches −100°C within a few seconds. Active thawing of the ice ball is achieved by actively instilling helium gas into the cryoprobes instead of argon gas. The system (Cryocare Surgical System; Endocare) allows the independent

operation of up to eight cryoprobes at a time. The diameter of the ice ball generated can be controlled by the rate of gas delivered to the probe.

A single cryoprobe was placed for lesions 3 cm or less in diameter. For larger lesions, two to seven additional cryoprobes were systematically placed with US and CT guidance. For lesions >5 cm in diameter, the entire lesion was not completely treated; rather, ablation treatments were focused on the margin of the lesion involving bone to treat the soft-tissue–bone interface. A single freeze-thaw-freeze cycle was performed for each lesion, and a time frame of 10 minutes, 8 minutes, and 10 minutes, respectively, was intended for the cycle. Shorter or longer times were used for the freezing portions of the cycle, which depended on the adequacy of coverage of the lesion and the proximity of adjacent critical structures. Unenhanced CT imaging (with body window [400 HU] and level [40 HU] settings) was performed approximately every 2 minutes throughout the freezing portions of the cycle to monitor the growth of the ice ball. For each patient who was treated, the lesion location, size of each treated lesion, number and diameter of cryoprobes used, and corresponding freeze-thaw-freeze times were recorded. Total cryoablation procedure time and total time in the CT suite were also recorded for each patient who was treated.

After completion of the final freeze of the cryoablation procedure, the cryoprobes were warmed with active heating by using helium gas until the temperature reached >20°C. The cryoprobes were then withdrawn. Immediate pain after the procedure was typically treated with intravenous fentanyl (Sublimaze; Abbott Laboratories) and midazolam (Versed; American Pharmaceutical Partners, Los Angeles, Calif). If pain persisted or was not adequately treated, oral analgesics or a patient-controlled analgesic unit was used and dose titrated to adequate pain relief. If pain persisted beyond the first 12–24 hours after treatment, the patient's intravenous analgesic requirement was converted to oral analgesics. Pain medication use immediately after the procedure and throughout the hospital stay was recorded for each patient who was treated.

Patient Assessment after Treatment and CT or MR Imaging

Patients were evaluated for pain severity and influence of pain on activities of daily living by using the BPI-Short Form (18,19). The patients completed the BPI questionnaire with the assistance of a study coordinator the day after the treatment. One study coordinator (K.J.B.) was used for all interviews. The BPI questionnaire was also completed 4 days after the procedure, weekly during a telephone interview with a study coordinator for the following 4 weeks, and every 2 weeks thereafter for a total of 6 months. The patients were not given a copy of the BPI, and no prior responses were available for review at subsequent interviews in order to ensure accuracy and minimize bias. Each patient was asked to answer these questions with respect to the lesion that was treated. Analgesic use was also recorded during each of these interviews.

Each patient underwent contrast material–enhanced CT or MR imaging of the treated region 4–6 weeks after the treatment. MR imaging was performed in patients with allergies to iodine-based contrast material; CT imaging was performed in all other patients. This examination of the ablated region was performed for three reasons: *(a)* to evaluate the change in appearance of the ablated region, *(b)* to provide a baseline examination for subsequent CT or MR imaging and potential cryoablation retreatment, and *(c)* to capture possible late post-cryoablation complications.

Statistical Methods

Design and procedures.—The initial efficacy observation period was 8 weeks on the assumption that the effect of the ablation would be observed within 8 weeks of the procedure. We used a supplementary observational period of 4 additional months to assess duration of effect among those patients who experienced successful pain reduction within the 8-week initial period.

Primary end points were the worst pain in 24 hours and average amount of pain constructed from the weekly BPI scores on a visual analog scale with a score of 0–10 (18,19). A secondary end point was the percentage of patients who were able to reduce use of analgesic medications.

The accrual goal for the study was 30 patients. An interim analysis was planned once 15 patients provided evaluative data to determine the preliminary effectiveness, because this number of patients would have provided 80% power to detect a difference of two units (on a 0–10 scale for worst pain in 24 hours) on average. This interim evaluation was also planned to be used in consideration of stopping the trial early if no patients derived benefit from cryoablation treatment. The interim analysis was performed with 14 patients, rather than 15, for two reasons: *(a)* ongoing evaluation of the data suggested that the effect of the treatment was more profound than a change in two units on average and *(b)* a 2-month period without additional patient enrollment was encountered.

Statistical analysis.—Analysis of the primary end points was undertaken with paired comparison procedures. This involved paired *t* tests across individual time points supplemented by repeated measures analysis of variance. The end points were further examined by constructing an estimate, with associated confidence intervals (CIs), of the proportion of patients who experienced a drop of at least three points on the pain scale from that at the pretreatment level. Similar comparisons were performed by using the additional BPI questions regarding quality of life. Findings with $P \leq .02$ were considered to indicate a statistically significant difference.

Missing values were addressed in various ways, including complete-case analysis and imputation according to the nearest neighbor, mean value, last value, and worst-value-carried-forward approaches (21,22). Multiple approaches were used so that the sensitivity of results to alteration in imputation assumptions could be assessed. Statistical analysis was performed with dedicated software (SAS, version 8.0, 1999; SAS Institute, Cary, NC).

Results

General

Four patients were followed up for at least 24 weeks. Three patients died during the first 24 weeks of the study (4, 14, and 15 weeks after the procedure) of causes unrelated to the cryoablation treatment. Two patients were excluded from further follow-up—one at 3 weeks and one at 4 weeks—because of the need for further chemotherapy, one patient was excluded from further follow-up because of the need for radiation therapy, and one patient was excluded from further follow-up because of the need for repeat cryoablation of the same painful lesion. At that time, the remaining three patients remained in the study at 6, 14, and 20 weeks of follow-up beyond their cryoablation treatment date.

All treated lesions involved bone with osteolytic bone destruction (Table) (patients 1, 3–8, 10–14) or periosteal reaction and a soft-tissue mass (patients 2 and 9). A single lesion was treated in 10 patients, and two lesions were treated in four patients. Metastatic lesions involving the ribs ($n = 5$), chest wall ($n = 3$), clavicle ($n = 2$), sacrum ($n = 2$), iliac bone ($n = 2$), femur, scapula, vertebral lamina, and acetabulum were treated. These metastatic bone lesions included three renal cell carcinomas, two rectal carcinomas, two paragangliomas, and a non–small cell lung carcinoma, a squamous cell carcinoma, an ovarian carcinoma, a medullary thyroid carcinoma, an adrenal cortical carcinoma, a melanoma, and a desmoid tumor. Treated lesion sizes ranged from 1.0 cm in diameter in a rib and in the chest wall to approximately 11.0 cm in diameter in the sacrum (Table). All patients were treated during a single session. The number of cryoprobes used for the ablation procedure ranged from one to seven (mean, 2.8 cryoprobes ± 1.6). The total cryoablation procedure time ranged from 83 to 280 minutes (mean, 139 minutes ± 53). The total time required in the CT suite for the procedure ranged from 125 to 320 minutes (mean, 185 minutes ± 56).

Four (29%) of 14 patients underwent both chemotherapy and radiation therapy prior to treatment with cryoablation. Three (21%) of 14 patients underwent radiation therapy but not chemotherapy. Two (14%) of 14 patients underwent chemotherapy but not radiation therapy. Five (36%) of 14 patients did not undergo either chemotherapy or radiation therapy. Ten (71%) of 14 patients were currently taking oral analgesic medications for pain; eight (80%) of these 10 patients were taking opioid analgesic medications. The remaining four (29%) of 14 patients refused oral analgesic medications or had not taken these medications in the 24-hour period prior to the cryoablation procedure.

Postprocedural pain control was managed with patient-controlled opioid analgesia in five (36%) of 14 patients during the immediate postprocedural recovery period. No patients required placement of an epidural catheter during the immediate postprocedural recovery period or during their hospitalization.

Complications

There were no major complications associated with the procedures. For each patient, contrast-enhanced CT or MR imaging at 4–6 weeks after the procedure showed an area of unenhanced

Characteristics of Patients, Treated Lesions, and Cryoablation Procedures

Patient No.	Age (y)/ Sex	Primary Neoplasm Location or Type	Lesion No.	Treatment Location	Lesion Size (cm)			Cryoprobes Used		Procedure Time (min)			Total Procedure Time (min)	Total Room Time (min)
					Craniocaudal	Right to Left	Anteroposterior	No.	Diameter (mm)	First Freeze	Thaw	Second Freeze		
1	44/F	Paraganglioma	1	Clavicle	4.0	4.0	1.8	2	2.2	10	10	15	123	192
2	53/F	Ovary	1	Ilium	3.1	3.1	3.1	2	2.4	8	5	8	107	127
3	72/M	Kidney	1	Rib	4.0	6.2	4.4	4	2.4	10	9	10	87	142
4	60/F	Squamous cell	1	Rib	7.0	4.2	4.4	2	2.4	10	5	7	218	256
			2	Rib	8.5	9.0	6.1	3	2.4	12	5	7	· · ·	· · ·
5	72/M	Lung	1	Lamina	2.2	2.8	2.2	3	2.2	4	10	1	135	190
			2	Acetabulum	2.0	1.4	2.0	2	2.2	10	5	10	· · ·	· · ·
6	21/M	Desmoid	1	Chest wall	5.8	9.1	6.4	4	2.4	10	7	21	150	232
7	42/M	Thyroid	1	Ilium	2.4	2.0	3.7	2	2.4	12	5	15	111	173
8	67/F	Adrenal gland	1	Rib	7.0	3.6	7.0	3	2.4	13	10	10	147	160
9	55/M	Melanoma	1	Chest wall	3.0	3.1	2.3	1	2.4	12	10	10	83	125
			2	Chest wall	1.0	1.0	1.0	1	2.2	4	4	2	· · ·	· · ·
10	31/F	Paraganglioma	1	Scapula	3.0	2.3	3.7	3	2.4	10	7	10	280	320
			2	Rib	1.0	1.0	1.0	1	2.4	8	4	5	· · ·	· · ·
11	45/F	Rectum	1	Sacrum	4.0	9.0	4.0	5	2.4	12	7	11	120	180
12	47/M	Rectum	1	Sacrum	11.0	8.5	10.2	7	2.4	12	11	10	165	219
13	68/M	Renum	1	Clavicle	5.0	6.1	5.2	2	2.4	12	8	16	106	135
14	72/M	Renum	1	Femur	5.3	3.4	3.4	3	2.4	10	5	10	115	145

low-attenuating tissue, consistent with necrosis, corresponding to the placement of the cryoablation probes. These cross-sectional images depicted no major complications that resulted from the procedure in these 14 patients.

Effect of Cryoablation on Patient Pain

The primary method used to determine the effect of cryoablation on painful metastatic lesions was the BPI (18,19). The frequency of missing data was minimal. One patient had a value missing for day 1 because the patient was moved to an intensive care unit as a result of a persistent, high level of pain that was unchanged after the cryoablation procedure. The first four patients had values missing for day 4 because the initial protocol design did not include a patient interview for that day. One additional patient had a value missing for day 4. Only one patient had a missing value at week 1. Sensitivity and intent-to-treat analyses to adjust for missing values did not change the results.

The mean patient response for worst pain in 24 hours prior to cryoablation treatment was 6.7 of 10. At 1, 4, 6, and 8 weeks after treatment, this mean response dropped to 5.8 (P = .236), 3.8 (P = .0003), 2.5 (P = .001), and 3.4 (P = .007), respectively (Fig 1, top). From baseline to week 4, seven (64%) of 11 patients (exact binomial CI: 31%, 89%) experienced at least a three-point decrease in worst pain. During the follow-up period of 24 weeks, 12 (86%) of 14 patients (exact 95% binomial CI: 57%, 98%) reported at least a three-point drop in worst pain during the past 24-hour period. Additionally, we evaluated the pain scores of patients during the immediate postprocedural period and at week 1. Eight (62%) of 13 patients experienced an increase or no improvement in their worst pain in the 24-hour period after cryoablation. Eight (62%) of 13 patients reported an increase or no improvement in their worst pain 1 week after cryoablation (Fig 1, bottom). Individual patient responses varied during the course of the follow-up period; a gradual downward trend occurred for most patients.

The mean patient response for average pain prior to cryoablation treat-

Figures 1, 2

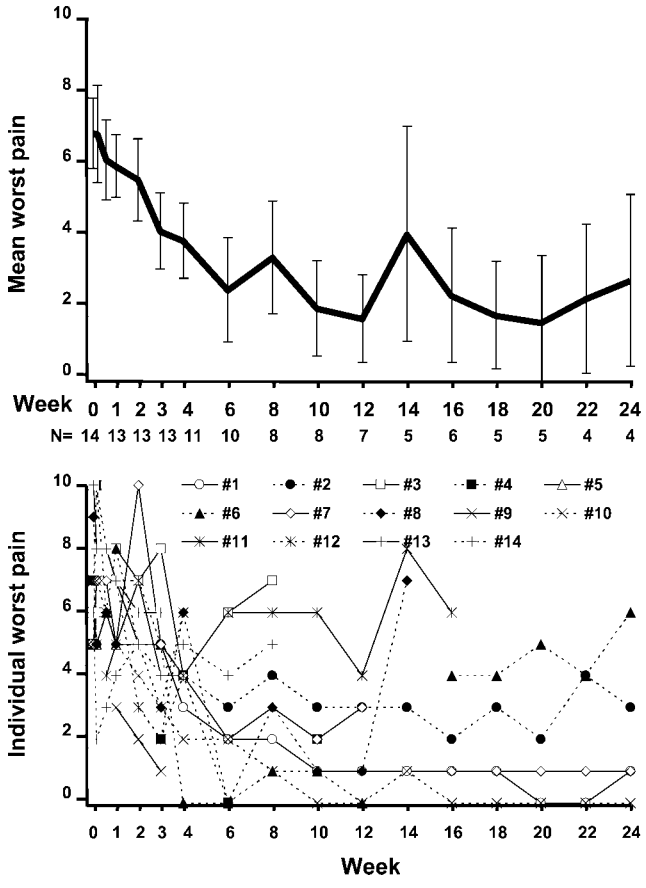

Figure 1: Graphs show worst pain during 24 hours for 14 patients treated with cryoablation, as measured with BPI. Top: Mean responses for all patients (error bars = 95% CIs, N = number of patients who completed BPI questionnaire). Bottom: Individual responses for each patient. Week 0 is response prior to treatment.

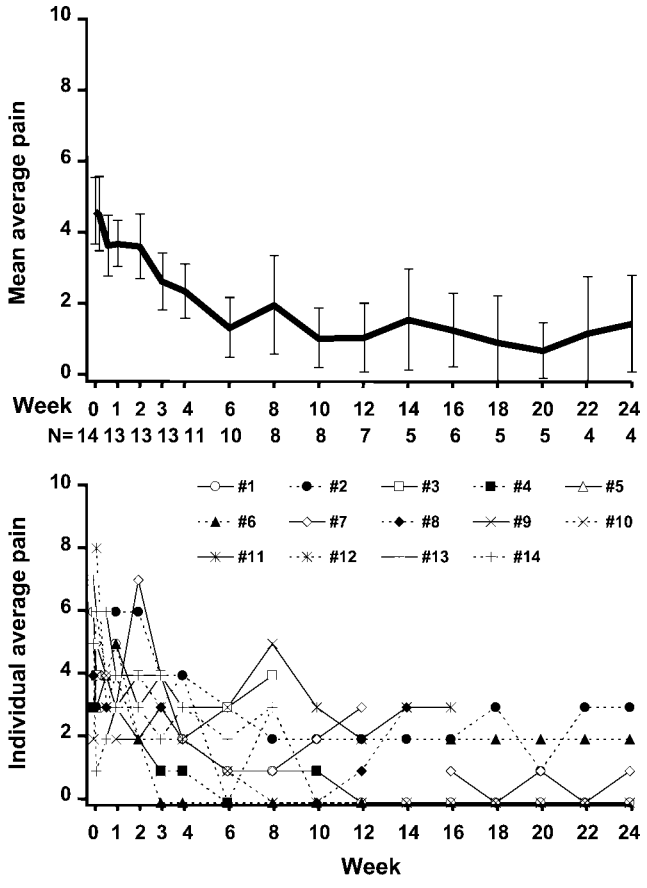

Figure 2: Graphs show average pain for patients treated with cryoablation, as measured with BPI. Top: Mean responses for all patients (error bars = 95% CIs, N = number of patients who completed BPI questionnaire). Bottom: Individual responses for each patient. Week 0 is response prior to treatment.

Figures 3, 4

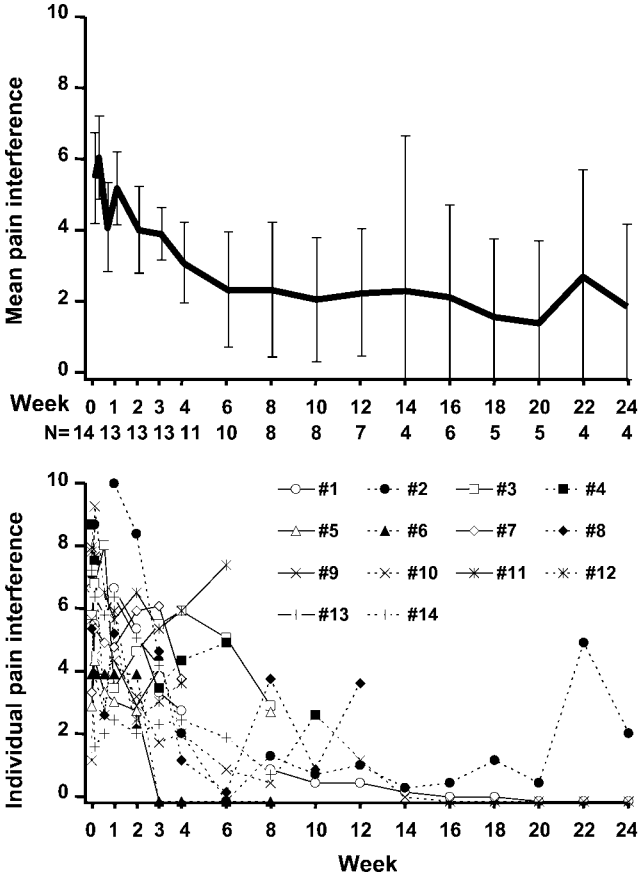

Figure 3: Graphs show pain interference for patients treated with cryoablation, as measured with BPI. Top: Mean responses for all patients (error bars = 95% CIs, *N* = number of patients who completed BPI questionnaire). Bottom: Individual responses for each patient. Week 0 is response prior to treatment.

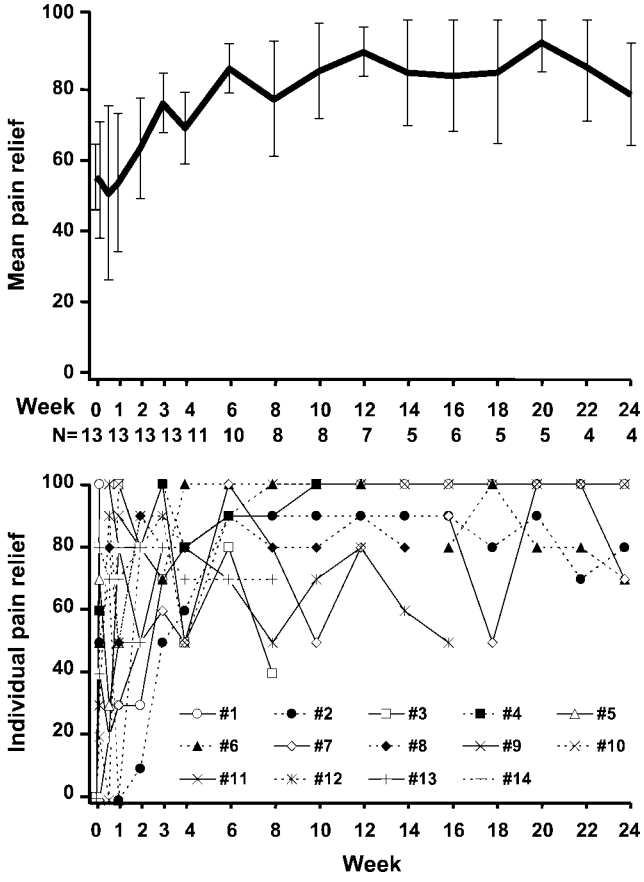

Figure 4: Graphs show relief from pain treatments or medications for patients treated with cryoablation, as measured with BPI. Top: Mean responses for all patients (error bars = 95% CIs, *N* = number of patients who completed BPI questionnaire). Bottom: Individual responses for each patient. Week 0 is response prior to treatment.

ment was 4.5 of 10; at 1, 4, 6, and 8 weeks after treatment, this mean response dropped to 3.6 ($P = .089$), 2.4 ($P = .003$), 1.4 ($P = .0002$), and 2.0 ($P = .008$), respectively (Fig 2, top). From baseline to week 4, four (36%) of 11 patients (exact binomial CI: 11%, 69%) experienced at least a three-point decrease in average pain. During the course of the follow-up period of 24 weeks, 11 (79%) of 14 patients (exact 95% binomial CI: 49%, 95%) reported at least a three-point drop in average pain. As was seen for individual responses to worst pain, the individual corresponding responses for average pain (Fig 2, bottom) also varied during the follow-up period; a gradual downward trend occurred for most patients.

The mean score for interference of pain on activities of daily living (Fig 3, top) prior to cryoablation treatment was 5.5 of 10; 1, 4, 6, and 8 weeks after treatment, this mean response dropped to 5.2 ($P = .954$), 3.2 ($P = .004$), 2.4 ($P = .002$), and 2.4 ($P = .013$), respectively. Four weeks after the cryoablation treatment, five (45%) of 11 patients (exact 95% binomial CI: 17%, 77%) experienced at least a three-point reduction in mean score for interference of pain on activities of daily living. During the follow-up period, six (43%) of 14 patients (exact 95% binomial CI: 18%, 71%) experienced at least a three-point reduction in mean score for interference of pain on activities of daily living.

The average relief from pain provided by using treatments or medications prior to cryoablation treatment was 57%; 1, 4, 6, and 8 weeks after treatment, this averaged response was 56% ($P = .916$), 71% ($P = .206$), 87% ($P = .005$), and 79% ($P = .310$), respectively. Individual patient responses varied during the follow-up period; a gradual improving trend of pain relief from pain medications and treatments occurred for most patients (Fig 4).

A secondary measure of the effect of cryoablation treatment on pain was the

change in each patient's use of analgesic medications. Ten (71%) of 14 patients reported the use of analgesic medications prior to the procedure. The remaining four patients entered the study without the use of analgesic medications. Eight (80%) of the 10 patients who reported the use of analgesic medications were using opioid medications. No statistically significant change in morphine-equivalent dose was observed on average for these eight patients during the follow-up period. *P* values were .61, .14, .22, and .38 at weeks 1, 4, 8, and 12, respectively. During the follow-up period, however, all eight (100%) patients who were prescribed narcotics (exact 95% binomial CI: 63%, 100%) reported a 6%–100% reduction in the use of opioid analgesic medication some time after cryoablation. Four weeks after the cryoablation treatment, all six (100%) patients (exact 95% binomial CI: 54%, 100%) reported a reduction in the use of narcotic pain medications. Two (50%) of four patients (exact 95% CI: 5%, 85%) who were not receiving analgesics at baseline reported opioid analgesic use at week 4. Two patients did not complete the 4-week follow-up interview; one patient died and one patient was removed from the study because of initiation of chemotherapy.

Discussion

External-beam radiation therapy is the standard of care for patients with localized bone pain. An extensive review of radiation therapy for the palliation of painful bone metastases found complete pain relief at 1 month in 25% of patients and at least 50% relief in 41% of patients at some time during the trials (23). In a large prospective trial of 1016 patients conducted by the Radiation Therapy Oncology Group, radiation therapy resulted in complete relief in 53% and partial relief in 83% of the patients studied (24). Steenland and colleagues (25) found the median time to a two-point reduction in pain in those who did respond to therapy was 3 weeks; however, approximately 35% of these patients did not obtain relief until 5–20 weeks after treatment. Comparison of our patient response scores after cryoablation to data reported after the treatment of patients with radiation therapy is difficult because the methods for measuring patient pain response after radiation therapy do not correspond directly to those of the BPI used for this study, and the number of patients in this study is small. Cryoablation can result in substantial pain reduction, however, as shown with a 43% mean reduction in worst pain at 4 weeks which is considered to be clinically important (26). Patients also reported pain relief 4 weeks after cryoablation that ranged from 50% to 100%, which compares favorably with the reported radiation therapy response.

Unfortunately, pain relief from radiation therapy is often transient. The Radiation Therapy Oncology Group study found recurrence of pain in 57% of patients at a median of 15 weeks after completion of radiation therapy (24). Steenland and colleagues (25) found that of those who initially experienced pain relief, 49% experienced a return to the initial pain score or higher in a median time of 8–36 weeks (overall median, 20–24 weeks) as a function of the type of tumor treated. Furthermore, patients who have recurrent pain at a metastatic site previously irradiated may not be eligible for further radiation therapy because of limitations in normal tissue tolerance. Whereas return of pain after radiation therapy is common, the patients treated with cryoablation in our study appeared to have durable pain relief; four (80%) of five patients reported excellent pain control in the treated lesion during the 24-week follow-up period. One patient reported transiently increased pain scores at the 24-week follow-up interview but during the following 6 months reported worst pain scores of 0–3 of 10, which indicates durable pain control. A randomized prospective trial comparing cryoablation with radiation therapy would be necessary to determine the relative effect of these treatments on patients' pain.

The patients who were treated in our study have substantial pain from metastatic skeletal disease; however, this group is heterogeneous with respect to size, location, and neoplasm type that was treated. Rectal and renal cell carcinomas were the most frequently treated tumor types in this study. Notably absent are breast and prostate cancers, which are relatively common cancers and are cancers that often metastasize to the bone. Patients with prostate cancer most typically have sclerotic lesions and often have widely metastatic disease when they have pain. It is possible that cryoablation would be amenable to certain patients with sclerotic prostate metastases that are focally painful, because the ice ball is able to penetrate deeply into bone whereas RF ablation penetrates poorly into bone. It would be important to test the safety of this procedure, however, before practice could be recommended. Patients with breast cancer and metastatic skeletal disease often have lesions amenable to percutaneous ablation such as osteolytic or mixed sclerotic and osteolytic lesions, but these patients were not represented in this study.

We found that cryoablation of skeletal metastases is a time-consuming procedure. On average, the total time for positioning the patient, placing the cryoprobes, conducting the freeze-thaw-freeze portion of the treatment, rewarming the cryoprobes, removing the cryoprobes, and securing the skin insertion sites was 2 hours 19 minutes. The total time in the CT suite for the procedure averaged 3 hours 5 minutes. This additional 46 minutes in the CT suite was the result of administration of general anesthetic, which included induction and extubation of the patients in the CT suite. The overall time for the procedure could be substantially reduced with the use of conscious sedation rather than general anesthetic. Despite the use of only a single freeze-thaw-freeze cycle and the average use of 2.8 cryoprobes for the procedure, the time necessary for this procedure is greater than that necessary for the RF ablation procedure of similar patients. In a prior study of RF ablation, the average ablation time was 46 minutes, the average time in the CT suite was 2 hours 14 minutes, and the aver-

age number of electrode needle placements was 4.5 (4).

Cryoablation treatments require more time than does RF ablation for several reasons. Although RF ablation of painful lesions often requires multiple overlapping ablations, the time necessary for each separate RF ablation is short (5–10 minutes). By necessity, a typical cryoablation treatment requires 25–30 minutes for the freeze-thaw-freeze cycle and an additional 10 minutes for cryoprobe warming prior to withdrawal. Depiction of the RF ablation margin is not possible with CT; depiction of the ice ball from cryoablation, however, is readily achieved. As a result, additional time was often used in this study to maximize the ablation margin with several freeze cycles that extended beyond 10 minutes. Additionally, because it is possible to shape the ice ball by using strategic placement of two or more cryoprobes, greater time was used in the cryoprobe placement portion of the procedure. We believe that the overall time required for cryoablation could be reduced with the use of conscious sedation rather than general anesthetic, which is required with RF ablation.

Our study had several limitations. First, we used cryoprobes and a controller from one manufacturer. Other cryoprobe designs may work equally well, or possibly better, in the treatment of these patients. Second, the parameters used for the cryoablation were based on depiction of the ice ball encompassing the targeted bone–soft-tissue interface, which indicates complete treatment of the tumor, when technically feasible. It is possible that better pain relief would be achieved on average if a greater portion of the larger metastatic lesions had been treated. Finally, no patients at risk for fracture of a weight-bearing bone (>50% cortical bone loss) were treated. All patients who were at risk for fracture of a weight-bearing bone were treated outside of the study by using cryoablation followed with application of bone cement. It is possible that this subset of patients would have had a different response to the treatment than did the group of patients included in this study.

Our findings suggest that cryoablation is a safe and effective treatment for the palliation of painful metastatic lesions that are refractory to standard therapies. Most important, the activities of daily living for these patients are improved with this therapy. Prospective comparison studies of cryoablation and radiation therapy may be useful to distinguish the relative benefits of these therapies for palliation of painful metastatic lesions.

Acknowledgments: We thank Patty Wehrs, BSN, and Cindy Dockter, BSN, for their assistance with the coordination necessary for the cryoablation procedure, with the cryoablation procedure, and with the necessary follow-up with the patients in this study. We also thank Bryce Bergene, BS, for his expert graphics assistance with the figures included in this article.

References

1. Gangi A, Kastler B, Klinkert A, Dietemann JL. Injection of alcohol into bone metastases under CT guidance. J Comput Assist Tomogr 1994;18:932–935.
2. Gröenemeyer DH, Schirp S, Gevargez A. Image-guided percutaneous thermal ablation of bone tumors. Acad Radiol 2002;9:467–477.
3. Dupuy DE, Safran H, Mayo-Smith WW, Goldberg SN. Radiofrequency ablation of painful osseous metastatic disease [abstract]. Radiology 1998;209(P):389.
4. Callstrom MR, Charboneau JW, Goetz MP, et al. Painful metastases involving bone: feasibility of percutaneous CT- and US-guided radiofrequency ablation. Radiology 2002; 224:87–97.
5. Goetz MP, Callstrom MR, Charboneau JW, et al. Percutaneous image-guided radiofrequency ablation of painful metastases involving bone: a multicenter study. J Clin Oncol 2004;22:300–306.
6. Beland MD, Dupuy DE, Mayo-Smith WW. Percutaneous cryoablation of symptomatic extraabdominal metastatic disease: preliminary results. AJR Am J Roentgenol 2005;184: 926–930.
7. Goetz M, Rubin J, Callstrom M, et al. Percutaneous US and CT-guided radiofrequency ablation of painful metastases involving bone. Presented at the annual meeting of the American Society of Clinical Oncology, San Diego, Calif, May 18–21, 2002; 1544.
8. Bahn DK, Lee F, Badalament R, Kumar A, Greski J, Chernick M. Targeted cryoablation of the prostate: 7-year outcomes in the primary treatment of prostate cancer. Urology 2002;60:3–11.
9. Shingleton WB, Sewell PE Jr. Percutaneous renal tumor cryoablation with magnetic resonance imaging guidance. J Urol 2001;165: 773–776.
10. Desai MM, Gill IS. Current status of cryoablation and radiofrequency ablation in the management of renal tumors. Curr Opin Urol 2002;12:387–393.
11. Gill IS, Remer EM, Hasan WA, et al. Renal cryoablation: outcome at 3 years. J Urol 2005;173:1903–1907.
12. Zhou XD, Tang ZY. Cryotherapy for primary liver cancer. Semin Surg Oncol 1998;14:171–174.
13. Kerkar S, Carlin AM, Sohn RL, et al. Long-term follow up and prognostic factors for cryotherapy of malignant liver tumors. Surgery 2004;136:770–779.
14. Wang H, Littrup PJ, Duan Y, Zhang Y, Feng H, Nie Z. Thoracic masses treated with percutaneous cryotherapy: initial experience with more than 200 procedures. Radiology 2005;235:289–298.
15. Kaufman CS, Bachman B, Littrup PJ, et al. Cryoablation treatment of benign breast lesions with 12-month follow-up. Am J Surg 2004;188:340–348.
16. Littrup PJ, Freeman-Gibb L, Andea A, et al. Cryotherapy for breast fibroadenomas. Radiology 2005;234:63–72.
17. Cowan BD, Sewell PE, Howard JC, Arriola RM, Robinette LG. Interventional magnetic resonance imaging cryotherapy of uterine fibroid tumors: preliminary observation. Am J Obstet Gynecol 2002;186:1183–1187.
18. Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with metastatic cancer. N Engl J Med 1994;330:592–596.
19. Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. Pain 1983;17:197–210.
20. Farrell MA, Charboneau JW, Callstrom MR, Reading CC, Engen DE, Blute ML. Paranephric water instillation: a technique to prevent bowel injury during percutaneous renal radiofrequency ablation. AJR Am J Roentgenol 2003;181:1315–1317.
21. Fairclough DL, Peterson HF, Cella D, Bonomi P. Comparison of several model-based methods for analysing incomplete quality of life data in cancer clinical trials. Stat Med 1998; 17:781–796.
22. Fairclough DL. Summary measures and statistics for comparison of quality of life in a clinical trial of cancer therapy. Stat Med 1997;16:1197–1209.
23. McQuay H, Collins S, Carroll D, Moore R. Radiotherapy for the palliation of painful bone metastases. Cochrane Database Syst Rev. 1999;3:CD001793. *http://www.update-software.com/abstracts/ab001793.htm.* Accessed August 8, 2000.
24. Tong D, Gillick L, Hendrickson FR. The palliation of symptomatic osseous metastases: final results of the study by the Radiation Therapy Oncology Group. Cancer 1982;50:893–899.
25. Steenland E, Leer JW, van Houwelingen H, et al. The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. Radiother Oncol 1999;52:101–109.
26. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001; 94:149–158.