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PERCUTANEOUS IMAGE - GUIDED CRYOABLATION OF PAINFUL METASTASES INVOLVING BONE: MULTICENTER TRIAL

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Abstract

PURPOSE—To describe the results of a single-arm multicenter clinical trial using image-guided percutaneous cryoablation for the palliation of painful metastatic tumors involving bone.

METHOD/MATERIALS—Over a 44-month period, 61 adult patients with one or two painful bone metastases with 4/10 worst pain in a 24-hour period who had failed or refused conventional treatment were treated with percutaneous image-guided cryoablation. Patient pain and quality of life was measured using the Brief Pain Inventory (BPI) prior to treatment, 1 and 4 days after the procedure, weekly for 4 weeks and every 2 weeks thereafter for a total of 6 months. Patient analgesic use was also recorded at these same follow-up intervals. Complications were monitored. Analysis of the primary endpoint was undertaken via paired comparison procedures.

RESULTS—A total of 69 treated tumors ranged in size from 1–11 cm. Prior to cryoablation, the mean score for worst pain in a 24 h period was 7.1/10 with a range of 4–10/10. One, 4, 8, and 24 weeks after treatment, the mean score for worst pain in a 24 hour period decreased to 5.1/10 ($p < 0.0001$), 4.0/10 ($p < 0.0001$), 3.6/10 ($p < 0.0001$), and 1.4/10 ($p < 0.0001$), respectively. One of 61 (2%) patients had a major complication with osteomyelitis at the site of ablation.

CONCLUSION—Percutaneous cryoablation is a safe, effective and durable method for palliation of pain due to metastatic disease involving bone.

Keywords

Palliation; Image-guided; Cryoablation; Metastases; Skeletal

INTRODUCTION

The bony skeleton is the most common metastatic site from cancer after lungs and liver, with prostate, breast, lung, kidney, and thyroid malignancies accounting for approximately 80% of skeletal metastases. Of the patients that develop skeletal metastases, approximately 50% of patients will develop poorly controlled pain during the course of their disease.^{1–4} Unfortunately, it is often difficult to achieve adequate pain relief and the quality of life for these patients is poor. Current standard of care treatments for patients that develop painful bone metastases are primarily palliative. For focal palliative pain treatment, external beam radiation and surgery are most commonly offered, while for diffuse metastases a systemic approach is utilized including chemotherapy, hormonal therapy, radiopharmaceuticals, and bisphosphonates.

Because many patients fail to derive adequate pain relief despite utilization of current conventional therapies, multiple minimally invasive focal therapies have been explored as new strategies for the palliation of painful metastatic disease. Of these methods, radiofrequency ablation (RF ablation) has been most thoroughly evaluated with results from two multicenter studies demonstrating significantly reduced focal pain in patients that are unresponsive to standard treatments.^{5, 6} Although effective at reducing patient's pain, RF ablation has a critical limitation, which is the non-visualization of the ablation margin with CT monitoring. In contrast to RF ablation, the ablation zone of cryoablation is readily identified with CT imaging as a low attenuation ice-ball beyond which tissues are safe from thermal injury.⁷ Another advantage of cryoablation relative to RF ablation is that patients treated with cryoablation do not experience increased pain during the procedure or in the immediate post-treatment period.⁸

The purpose of this prospective multicenter study was to determine the safety and efficacy of percutaneous cryoablation for the reduction of pain, improvement in the quality of life and the reduction in the use of analgesic medications for patients with painful metastatic tumors involving bone.

MATERIALS AND METHODS

Following IRB approval and Health Insurance Portability and Accountability Act compliance, informed consent was obtained from a total of 65 patients with moderate to severe pain for percutaneous cryoablation of 1 or 2 metastatic tumors involving and/or abutting bone. Over an initial 18-month period from December 2003 through May 2005, 14 patients were enrolled at a single institution.⁹ Subsequently through September 2007 (44 months in total), an additional 22 patients were enrolled at the same institution as well as 29 patients at 7 additional institutions in the United States. All patients had received optimized radiation therapy, chemotherapy, surgery and/or analgesic medicines, or were considered to be poor candidates for conventional therapy by the referring medical team, or the patients had refused these standard therapies. Only patients with pain as indicated by a score of 4 on a scale of 0-10 over the prior 24 hours were included in the study.^{10, 11} For those patients that had received chemotherapy or radiation therapy prior to treatment, these therapies were completed more than 3 weeks prior to inclusion in the study. All patients were 18 years old, were able to give written consent, and had a life expectancy of greater than 2 months. Tumors with 0.5 cm of the spinal cord and brain, were not treated. Patients with impending fractures at the potential ablation site were not eligible for this study as determined using the Mirels Classification scheme.^{12, 13} Following enrollment, one patient was excluded because cementoplasty was also necessary, one patient was excluded prior to treatment because of refusal of a third party payer for treatment coverage, one patient was excluded because the target tumor became partially sclerotic and was considered no longer technically feasible, and one patient was excluded because the target tumor became infected. The remaining 61 patients were treated with percutaneous cryoablation.

Pretreatment Patient Assessment

Prior to therapy with cryoablation, the effect of focal painful metastatic disease was assessed by the use of the Brief Pain Inventory-Short Form (BPI), a validated visual analogue scale for assessment of patient pain and quality of life, and analgesic medicine usage was also recorded.^{10, 11} Each patient was instructed to specifically respond to the BPI questions with respect to the focal painful metastasis that was to be treated.

Patients were physically examined by the participating radiologist prior to treatment to determine whether the site or sites of focal pain correlated with available imaging including computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound imaging, which was obtained within 4 weeks of entry into the study. A percutaneous biopsy was performed if metastatic disease was not previously documented. A complete blood count and prothrombin time were obtained within 2 weeks of the ablation procedure. Each patient's history of previous chemotherapy and radiation therapy was recorded. Complications were recorded throughout the follow-up period and classified via Common Terminology Criteria for Adverse Events (CTCAE v 4.03).¹⁴

Treatment Procedure

Patients were treated under general anesthesia or moderate sedation according to the proceduralist's discretion. Protocol guidelines included treatment of masses larger than 8 cm

in diameter in two sessions on sequential days while masses smaller than 8 cm in diameter could be treated in a single session. Following sterile preparation, one or more Endocare Perc-17, Perc-22 or Perc-24 cryoprobes (Healthtronics/Endocare, Inc., Irvine, CA) were directly inserted, introduced through a skin nick under CT-guidance (49 patients), or both CT and ultrasound (12 patients) guidance. Hydrodissection was utilized to displace immediately adjacent bowel, bladder and dermis from the target tumor.¹⁵ Cryoprobe positioning was confirmed by CT imaging. A freeze-passive thaw-freeze cycle was performed for each tumor treated with a goal of 10 minutes – 8 minutes – 10 minutes, respectively for the cycle. Non-contrast CT imaging was performed approximately every 2-5 minutes throughout the freezing portions of the cycle, and displayed with body window width and level settings (W400 HU, L40 HU), to monitor the location and dimensions of the ice-ball coverage. Figure 1 shows one patient's CT imaging obtained during the treatment of a metastasis in the medial head of the left clavicle. For each patient that was treated, the tumor location, size of each treated tumor, number and diameter of cryoprobes utilized, and corresponding freeze-passive thaw-freeze times were recorded. Total cryoablation procedure time and total time in the CT suite were also recorded for each patient that was treated.

Post treatment Patient Assessment

Patients were evaluated for response to treatment by using the Brief Pain Inventory-Short Form (BPI) a validated visual analog assessment of patient pain.^{10, 11} Patients completed the BPI questionnaire with respect to the focal painful metastasis with the assistance of a study coordinator the day following the treatment. Each patient was asked to answer these questions with respect to the tumor that was treated. If two metastases were treated, a single response was recorded for the most painful of the two treated areas. The questionnaire was also completed 4 days and then weekly by telephone interview with one centralized study coordinator, for the following 4 weeks and every 2 weeks thereafter for a total of 6 months. Patients were not given a copy of the BPI and prior responses were not available to the patient for review on subsequent interviews in order to ensure accuracy and minimize bias. Analgesic use, reported by the patient, was also recorded during each of these interviews. No additional supportive care was offered as a part of this treatment. If a patient received other focal therapy to the treated tumor or initiated new chemotherapy during the follow-up period, no further data was collected.

Statistical Methods

Design and Procedures—This study was a single arm observational study using patients as their own controls. Primary endpoints were the worst pain and average pain scores on a visual-analogue scale using a score of 0-10. A secondary endpoint was the percentage of patients who were able to reduce analgesic medications following treatment. The accrual goal for the study was 65 patients. An interim analysis was performed once 15 patients provided evaluable data to determine the preliminary effectiveness, as this number of patients would provide 80% power to detect a difference of 2 units on average.⁹

Statistical Analysis—Analysis of the primary endpoint was undertaken via paired comparison procedures. This involved paired t-tests across individual time points supplemented by repeated measures analysis of variance. The endpoints were further

examined by constructing an estimate, with associated confidence intervals, of the proportion of patients who experienced a drop of at least 3 points on the pain scale from the pre-treatment level. Similar comparisons were performed using the additional questions regarding quality of life contained in the BPI. Findings with p-values of less than or equal to 0.05 are considered statistically significant. As confirmatory analyses, each endpoint was also tested using a Wilcoxon test instead of a t-test.

Missing values were handled by complete-case analysis and imputation via the nearest neighbor; mean value, last value, and worst value carried forward approaches.^{16, 17} Multiple approaches were used so that the sensitivity of results to alteration in imputation assumptions could be assessed. Results were robust across different imputation sensitivity analyses despite missing values for the primary endpoint of change in worst pain from baseline to week 8. All of the imputation strategies resulted in no significant changes in the primary endpoint results.

RESULTS

General

The patient demographics and tumor characteristics are contained in Table 1. All treated tumors abutted bone or were osteolytic or mixed osteolytic and sclerotic with a combination of bone destruction and a soft tissue mass. Single tumors were treated in 53 patients and two tumors were treated in 8 patients for a total of 69 tumors. A majority of patients received radiation to the treated site and had failed to achieve pain relief prior to entry into the trial. However, 23 of 61 patients (38%) patients had not received radiation prior to treatment and a total 13 of 61 patients (21%) had received neither radiation treatment nor chemotherapy prior to cryoablation treatment.

Sixty-seven of 69 (97%) tumors were treated in a single session while two masses larger than 8 cm were treated in 2 sessions on successive days. The average time for the treatment was similar at the host and expansion institutions (Table 2). The vast majority of procedures were performed with general anesthesia at the host institution although both general anesthesia and conscious sedation were employed nearly equally at the expansion sites.

Post-procedure pain control was managed with patient-controlled intravenous opioid analgesia for 12 of 61 patients (20%) in the immediate post-treatment recovery period. No patients required placement of an epidural catheter in the immediate post-procedure recovery period or during their hospitalization. Hospitalization length of stay averaged 1.5 days with a range from 0-6 days. Hospitalization beyond one day following the procedure was related to management of pain.

There was one major complication amongst the 61 patients (2%) treated with cryoablation that was associated with the procedure which developed two weeks after treatment that involved development of an infection in the treated area which was subsequently treated with intravenous antibiotics and surgery. No instances of moderate or severe complication due to injury of major motor nerves, bowel or bladder were recorded.

Responses of Patient's Pain to Cryoablation

The frequency of missing data in the follow-up period was small. A total of 599 of 649 (92%) possible phone interviews were conducted with completion of the BPI over the 24-week follow-up period. Sensitivity and intent-to-treat analyses adjusting for these missing values did not change the results. During the 24-week follow-up period drop-out from the study was due to patient death (21), initiation of new chemotherapy (12), initiation of radiation therapy (2), retreatment with cryoablation (2), refusal to participate further (7) and due to a complication (1). Table 3 contains the patient's responses to worst and average pain in the previous 24 hours as well as change in quality of life and pain relief from the cryoablation treatment and other medications. Figure 2 shows the successful treatment of a painful metastatic paraganglioma contained in a left rib with durable response to treatment throughout the follow-up period. Patient pain score responses were reduced over the follow-up period with high statistical significance and were similar at the participating sites (Figure 3A). Patient worst pain scores did not change significantly from a score of 7.1/10 at baseline to 7.0/10 at the day one interview. The mean morphine equivalent 24-hour doses of 113 mg at baseline and 99 mg in first 24 hours following the procedure were not significantly different ($p = 0.6329$). From baseline to week 1, 30 of 61 patients (49%) reported at least a 2-point decrease in worst pain with 24 of 61 patients (30%) reporting at least a 3-point drop in worst pain. Additionally, 46 of 61 patients (75%) reported 90% or higher pain relief at some time in the follow-up period. Of the patients that were followed for a minimum of 8 weeks, 5 of 35 patients (14%, exact 95% confidence interval of 5 – 30%) had recurrent worst pain that was equal to or greater than the worst pain prior to cryoablation treatment during the follow-up period that occurred at weeks 8, 12, 14, 20, and 24. Thirty-eight of 61 patients (62%) had completed radiation treatment to the tumor treated with cryoablation. There was no significant difference in pain scores for patients that had or had not received radiation prior to cryoablation treatment and there was no significant difference in pain scores throughout the follow-up period. Comparison of pain scores for patients that were lost to follow-up, and those that initiated new chemotherapy, and were also subsequently lost to follow-up, with all other patients at the available corresponding time points, found no significant difference in response to therapy. The two patients that had radiation therapy following the cryoablation treatment had pain scores at or above the pain scores reported on entry to the study.

Over the course of the follow-up period of 24 weeks, 42 of 61 patients (69%) reported at least a two-point drop in average pain (Figure 3B). Of the patients that were followed for a minimum of 8 weeks, 2 of 32 patients (6%, exact 95% confidence interval of 1 – 21%) had recurrent average pain that was equal to or greater than the average pain prior to cryoablation treatment that occurred at week 8 for both patients. Over the course of the follow-up period, 41 of 61 patients (67%) experienced at least a two-point reduction in mean score for interference of pain on activities of daily living (Figure 3C). Patients also reported improved overall pain relief from the cryoablation procedure and other medications although these data were not statistically significant until week 8 (Figure 3D).

A secondary measure of response of pain to cryoablation was the change in each patient's use of opioid analgesic medications. Patient's opioid analgesic use, converted to the

morphine equivalent dose, is contained in Table 3. Forty-seven of 61 (77%) patients reported the use of opioid analgesics prior to the cryoablation procedure. Of the patients that reported the use of opioid analgesics prior to the procedure, 39 of 47 (83%, exact 95% confidence interval of 69 to 92%) reported a reduction in the use of opioid analgesic medications and 19 of 47 (40%, exact 95% confidence interval of 26 to 56%) reported no opioid analgesic medications at some time following the cryoablation procedure. Patients also reported similar opioid analgesic use in the days immediately following treatment. Morphine equivalent dose change from baseline did not reach statistical significance throughout the follow-up period.

DISCUSSION

We report highly significant reductions in pain scores and improvement in quality of life for patients with focal painful metastases following percutaneous cryoablation treatment. This cohort of patients reported profound reductions in pain scores with 75% (46 of 61 patients) achieving 90% or higher pain relief at some point in the follow-up period. The reduction in pain was durable with only 14% (5 of 35 patients) reporting recurrent worst pain that was equal to or greater than the worst pain prior to treatment during the follow-up period. These results were reproduced by multiple proceduralists at multiple centers, which suggests that this procedure can be successfully utilized in other centers for patients with focal painful metastases.

In this trial, 62% (38 of 61 patients) had received external beam radiation therapy prior to cryoablation treatment. Importantly, there was no significant difference in patient pain response to the cryoablation treatment comparing patients with or without prior radiation therapy. Direct comparison of patient response scores following cryoablation to data reported from the treatment of patients with external beam radiation therapy is difficult as the this group of patients is likely different than those treated with radiation therapy and the methods for measuring patient pain response following external beam radiation therapy do not correspond directly with the Brief Pain Inventory used for this study. A trial conducted by the Radiation Therapy Oncology Group (RTOG) including 1,016 patients found complete pain relief in 53% of patients and partial relief in 83% with a mean duration of response of 12 and 20 weeks in these two groups, respectively.¹⁸ The cryoablation treatment results in rapid significant pain reduction with 49% (30 of 61 patients) reporting a 2 point mean reduction in worst pain in 1 week which compares favorably with the median of 3 weeks to a 2 point reduction following radiation therapy.^{19, 20} A recent meta-analysis review of 25 randomized trials comparing single and multiple fraction external beam radiation therapy schedules for palliation of painful bone metastases noted similar duration of response for the single and multiple fraction treatments with median duration of response ranging from 12-28 weeks.²¹ Duration of response following cryoablation compares favorably with radiation therapy as a treatment option with 14% reporting equal or greater pain than the initial pain score throughout the follow-up period of 24 weeks.

The etiology of bone cancer pain is multifactorial including (1) osteoclast mediated bone remodeling, (2) loss of mechanical strength of the affected bone and corresponding activation of mechanosensitive sensory nerves, and (3) production of nerve stimulating

tumor derived products (cytokines, vasoactive peptides, growth factors, and others).^{22–24} Goblirsch has suggested that reduced tumor burden and reduced osteolysis are important for decreased pain following radiation therapy.²⁵ The mechanism of action resulting in reduced pain following cryoablation has not been studied but is likely similar. The time to onset of pain relief is likely related to differential rates of cell death following radiation therapy and cryoablation and the incidence of recurrent pain following these two treatments is likely a function of residual tumor and regrowth at the treated site.

Several different image-guided ablation strategies have been studied as treatments for painful bone metastases including ethanol,²⁶ laser-induced interstitial thermotherapy,²⁷ magnetic resonance guided focused ultrasound^{28, 29}, and RF ablation.^{5, 6, 30, 31} Of these focal treatment methods, RF ablation has been the most studied and widely used. Two prospective clinical trials, with similar cohorts of patients to this trial, have studied RF ablation for treatment of painful metastatic disease.^{5, 6} These trials found that RF ablation provides significant and durable pain relief for patients that have failed conventional therapies with similar outcomes to the data presented in this report. In the trial data reported by Goetz et al., pain scores for worst pain using the BPI were 7.9/10 prior to treatment and 1, 4, 8, and 24 weeks following RF ablation treatment were reduced to 5.8, 4.5, 3.0 and 1.4/10, respectively. The corresponding values for this trial were 7.1/10 prior to treatment and 1, 4, 8, and 24 weeks following cryoablation treatment pain scores were 5.1, 4.0, 3.6, and 1.4/10, respectively.

Even though clinical outcomes may be similar following RF ablation, cryoablation can be performed confidently in close proximity to critical structures due to visibility of the ice-ball with noncontrast CT imaging. In this study, the major complication rate was 2% (1 of 61 patients) with the one complication due to an infection in the treatment area. No patients suffered an injury to a major motor nerve or reported neuropathic pain following the procedure. Although the complication rate using RF ablation for treatment of painful metastases is low, 2 of 55 (4%) of patients suffered neurologic injuries in a clinical trial.⁶ Despite the relatively low risk of major complications as reported in this study, careful selection of suitable patients for treatment, and intermittent monitoring of the ice-ball with CT imaging is necessary to avoid injury of adjacent critical structures. In addition, pain management following cryoablation is more readily accomplished than RF ablation as the treatment is not painful.⁸

Limitations of this study include that this cohort of patients is a subset of patients that present with focal painful metastatic tumors. This group of patients is heterogeneous with respect to size, location and type of neoplasms that were treated. Although vertebrae and the femur are common sites of metastasis, only two patients with these sites of disease were included in this trial likely due to preferred treatment of these patients with radiation therapy or surgery.³² Although breast and prostate carcinomas are the most common skeletal metastases, the most common metastases treated in this study were from lung, renal and colorectal neoplasms. Breast and prostate carcinomas are commonly osteoblastic and only those patients with an osteolytic component were included in this trial. In addition, this study utilized cryoprobes and a controller from one manufacturer. It is expected that other cryoprobe systems would work equally well in the treatment of these patients. The data

captured by the Brief Pain Inventory was with respect to the treated tumor and the incidence of new metastatic disease was not captured. Opioid narcotic medication use during the follow-up period did not reach statistical significance possibly due to the progression of disease. The patients included in this study are a subset of patients that are included in multiple radiation treatment trials and, as a result, comparison of the effectiveness of cryoablation with radiation therapy is limited and a prospective randomized trial of these two treatments would be necessary to allow a direct measure of their relative efficacy. Although there was no significant difference in the response to cryoablation for patients that had received radiation therapy prior to entry to the study, it is possible that a larger study would demonstrate a benefit from combination treatment.

This single-arm prospective multicenter clinical trial found that cryoablation is a safe, effective and durable treatment for patients with painful metastatic skeletal tumors that have failed or refused standard therapies. This study also found that the quality of life is improved for these patients following cryoablation treatment.

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Condensed Abstract

Single-arm multicenter trial of the use of percutaneous cryoablation for palliation of focal painful metastatic tumors involving bone was conducted using the Brief Pain Inventory as a measure for treatment response. This image-guided treatment is a safe, effective and durable method for palliation of pain due to metastatic disease involving bone.

FIGURE 1.

A) Noncontrast CT image of the upper chest with bone windows demonstrates an osteolytic metastasis in the medial head of the right clavicle (arrows). A cryoprobe (arrow head) is placed in the metastasis.

B) Noncontrast CT image of the upper chest with body windows demonstrates an ice-ball, visible as a low-attenuation area about the cryoprobe with 0 °C at the ice-ball tissue boundary, extending beyond the margin of the clavicle and the osteolytic metastasis (arrows).

FIGURE 2.

Treatment of a painful metastatic paraganglioma contained in a rib. Prior to treatment, the patient had 5/10 worst pain which was reduced to 2/10 by week 4 and 0/10 by week 8. Patient reported 0/10 pain at latest follow-up of 24 weeks. A) Contrast-enhanced CT image of the upper abdomen with body windows demonstrates an enhancing osteolytic metastasis in the left 10th rib (arrow).

B) Noncontrast CT image of the upper abdomen with bone windows demonstrates a cryoprobe (arrow) placed in the metastasis

C) Noncontrast CT image of the upper abdomen with body windows demonstrates an ice-ball, visible as a low-attenuation area (arrow heads) extending beyond the margin of the target tumor.

D) Contrast-enhanced CT image of the upper abdomen with body windows performed following the ablation procedure shows no residual enhancement of the mass contained in the left 10th rib (arrow).

FIGURE 3.

Mean BPI scores over time for patients treated with percutaneous cryoablation for (A) worst pain, (B) average pain, (C) pain interference, and (D) pain relief. Error bars represent the 95% confidence intervals. N=the number of patients completing BPI at each time point.

Table 1**Patient and Tumor Characteristics**

Characteristic	Value
No. of patients (female/male)	22/39
Mean age, y ($\pm$ SD)	61 (14)
Range	21–95
Previous RT	38/61 (62%)
Previous chemotherapy	32/61 (52%)
Previous RT and chemotherapy	22/61 (36%)
No previous RT	23/61 (38%)
No previous RT or chemotherapy	13/61 (21%)
Opioid analgesics at presentation	47/61 (77%)
Tumor type histology (N = 61)	
Lung	16 (31%)
Renal	10 (20%)
Colorectal	7 (14%)
Melanoma	4 (8%)
Prostate	4 (8%)
Squamous cell (non-lung)	3 (6%)
Transitional cell	2 (4%)
Paraganglioma	2 (4%)
Breast	2 (4%)
Other (1 each)	11 (22%)
Tumor location (N = 69)	
Rib/chest wall	33 (48%)
Iliac/ischium/pubis bones	20 (29%)
Scapula/clavicle/sternum	7 (10%)
Sacrum	5 (7%)
Extremity	2 (3%)
Vertebral body	1 (1%)
Mastoid	1 (1%)
Mean tumor diameter, cm ($\pm$ SD)	4.8 (2.4)
Tumor diameter range, cm	1–11
Patients with 1 tumor	53/61 (87%)
Patients with 2 tumors	8/61 (13%)

Abbreviations: RT, radiotherapy; SD, standard deviation.

Table 2**Tumor Cryoablation Treatment**

Characteristic	Value
Treatment time (min, range)	129 (50–210)
Room time (min, range)	165 (88–280)
Guidance method	
CT alone	51/61 (84%)
US alone	2/61 (3%)
CT/US combination	8/61(13%)
Number of cryoprobes	3.4 ($\pm$ 1.8, range 1–8)
Freeze-thaw-freeze (min)	10.3-7.6-9.4
Anesthesia	
General	46/61 (75%)
Moderate conscious sedation	15/61 (25%)

Abbreviations: CT, computed tomography; US, ultrasound.

Table 3
Brief Pain Inventory-Short Form Mean Pain Scores at Baseline and Following Cryoablation Treatment

	Baseline (N = 61)	Week 1 (N = 57)	Week 4 (N = 49)	Week 8 (N = 35)	Week 24 (N = 16)
Worst pain (0–10)					
Score	7.1	5.1	4.0	3.6	1.4
<i>P</i>		<.0001	<.0001	<.0001	<.0001
Average pain (0–10)					
Score	4.7	3.5	2.6	2.1	0.9
<i>P</i>		.0003	<.0001	<.0001	<.0001
Pain interference (0–10)					
Score	5.2	3.8	2.9	2.1	1.1
<i>P</i>		.0004	<.0001	<.0001	<.0001
Pain relief (0–100)					
Score	57	62	67	80	88
<i>P</i>		.2708	.1178	.0003	.0056
Morphine-equivalent 24-hour dose (mg)					
Dose	113	76	96	130	29
<i>P</i>		.6526	.2138	.6365	.7952