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Abbreviations:
BPI = Brief Pain Inventory
RF = radio frequency

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Painful Metastases Involving Bone: Feasibility of Percutaneous CT- and US-guided Radio-frequency Ablation[1]

PURPOSE: To determine the safety and efficacy of radio-frequency (RF) ablation for pain reduction, quality of life improvement, and analgesics use reduction in patients with skeletal metastases.

MATERIALS AND METHODS: Over 10 months, 12 adult patients with a single painful osteolytic metastasis in whom radiation therapy or chemotherapy had failed and who reported severe pain (pain score ≥ 4 [scale of 0–10]) over a 24-hour period were treated with percutaneous imaging-guided RF ablation with a multitined electrode while under general anesthesia. Patient pain was measured with a Brief Pain Inventory 1 day after the procedure, every week for 1 month, and thereafter every other week (total follow-up, 6 months). Patient analgesics use was also recorded at these follow-up intervals. Follow-up contrast material–enhanced computed tomography was performed 1 week after the procedure. Complications were monitored. Analysis of the primary end point was undertaken with paired comparison procedures.

RESULTS: Lesion size was 1–11 cm. Before RF ablation, mean worst pain score in a 24-hour period in 12 patients was 8.0 (range, 6–10). At 4 weeks after treatment, mean worst pain decreased to 3.1 ($P = .001$). Mean pain before treatment was 6.5 and decreased to 1.8 ($P < .001$) 4 weeks after treatment. Mean pain interference in general activity decreased from 6.6 to 2.7 ($P = .002$) 4 weeks after treatment. Eight of 10 patients using analgesics reported reduced use at some time after RF ablation. No serious complications were observed.

CONCLUSION: RF ablation of painful osteolytic metastases is safe, and the relief of pain is substantial.

Pain management in terminally ill patients with metastases involving bone can be challenging. Conventional therapeutic options for pain control include radiation therapy and/or chemotherapy, surgery, and the use of opioid and other analgesics (1). Despite these measures, the quality of life for these patients is often poor because of intolerable pain. Reasons for failure of traditional therapies to control pain include the following: *(a)* Radiation therapy may not be an option because of radiation insensitivity of the neoplasm or limitations of radiation dose to normal structures, *(b)* further chemotherapy may not be beneficial because of poor therapeutic response or toxicity of the chemotherapeutic agent, and *(c)* intolerable analgesic-related side effects may develop with increasing analgesic doses. Failure of these therapies to provide adequate pain relief may markedly decrease quality of life for these patients.

Percutaneous image-guided therapy of metastatic neoplasms involving bone may offer an alternative to conventional therapies for pain control. Gangi et al (2) described the use of computed tomography (CT)-guided percutaneous administration of 95% ethanol for the palliation of pain from 27 metastatic bone lesions in 25 patients previously treated

with radiation therapy and/or chemotherapy. A single dose of ethanol was used in 16 lesions, while two doses were used in 10 lesions and three doses were used in one lesion. The response of patients to this treatment was assessed in terms of reduction in use of analgesic medicines 48 hours and 2 weeks after therapy. Complete pain relief was achieved in four patients; and very good but incomplete relief (75% reduction in analgesic medicine), in 11 patients. Seven patients experienced little or no relief with the treatment.

Percutaneous radio-frequency (RF) ablation has been studied extensively for the treatment of primary and metastatic disease involving the liver (3–5). Rosenthal et al (6–8) have reported the use of RF ablation for treatment for osteoid osteomas, a therapy now commonly used in primary treatment for this skeletally based lesion. In preliminary reports, Dupuy and Gevargez and co-workers (9–11) found that RF ablation may provide a new method for palliation of painful skeletal metastases. Although these investigators have reported preliminary findings with the use of RF ablation for pain palliation resulting from metastatic lesions, there are no peer-reviewed reports, to our knowledge, that describe this new therapy.

The purpose of this study was to determine the safety and efficacy of RF ablation for reduction of pain, improvement in quality of life, and reduction of the use of analgesic medications by patients with skeletal metastatic disease.

MATERIALS AND METHODS

Over 10 months, from October 2000 through August 2001, 19 patients with severe pain from metastatic lesions involving bone that were refractory to radiation therapy, chemotherapy, surgery, or analgesic medicines or, alternatively, who had refused to undergo these standard therapies were considered for enrollment in the study. Only patients with a pain score of 4 or higher 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.

Patients included in the study had pain resulting from no more than two sites of metastatic disease. Any patients undergoing chemotherapy or radiation therapy had completed these therapies more than 3 weeks prior to entrance into the study. Other entry criteria included age of at least 18 years, ability to give written consent, and life expectancy of greater than 2 months. Patients with lesions within 1 cm of the spinal cord, brain, aorta, inferior vena cava, bowel, or bladder and patients with impending fracture at the potential ablation site were not eligible for this study. Seven patients did not meet the inclusion criteria or were excluded from the study, including three patients with metastatic lesions within 1 cm of the spinal cord or major nerves. Two patients gave a pain score of less than 4, one patient could not reliably participate in answering the Brief Pain Inventory (BPI), and one patient elected not to participate when the therapy was offered. The remaining 12 patients were treated with RF ablation. Informed consent was obtained from all patients included in this study, and the protocol was approved by the institutional review board.

CT-guided procedures and post-RF ablation examinations were performed with a HiSpeed CT/i system (GE Medical Systems, Milwaukee, Wis) equipped with SmartView interventional fluoroscopic hardware. An intermittent CT-fluoroscopic technique (120 kVp, 10–40 mA) was used for needle placement and deployment. Electrode deployment positioning was confirmed by using 3–5-mm section thickness with a standard CT technique (120 kVp, ≈240 mA). Postprocessing of CT images was accomplished with commercial three-dimensional software (Vitrea; Vital Images, Plymouth, Minn). Ultrasonography (US)-guided needle placement and deployment were performed by using a Sequoia system (Acuson, Mountain View, Calif).

Pretreatment Patient Assessment

Prior to RF ablation, each patient was assessed by using the BPI (12,13), a validated visual-analogue scale for assessment of patient pain, and the use of analgesic medicine was recorded. In the BPI, patients are asked to rate their worst pain in 24 hours, least pain in 24 hours, and average pain, with allowed responses ranging from 0 to 10 (0 = no pain, 10 = pain as bad as can be imagined). Relief of pain through the use of pain treatments or medications is scored on a scale of 0% (no relief) to 100% (complete relief). Pain interference with daily living is evaluated with questions concerning general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life, also 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 count and prothrombin time were obtained within 24 hours of the procedure. If no previous histologic or cytologic proof of the patient's malignancy had been obtained, a percutaneous biopsy was performed prior to treatment. A radiation oncology consultation was offered to the patient prior to entry into the study if not already completed. CT, magnetic resonance, and US images, acquired within 4 weeks of entry into 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., J.W.C., B.D.L., T.J.W., M.A.F.) prior to entry into the study. All patients underwent physical examination immediately prior to treatment to determine the site or sites of focal pain. Each patient's history of chemotherapy and radiation therapy was recorded.

Treatment Procedure

All patients were treated during general anesthesia. Dispersive grounding pads were typically attached to the patient's thighs with two monitoring temperature electrodes (Mon-a-therm, model 4070 with series 700 thermistor; Mallinckrodt Medical, St Louis, Mo) placed on the corners of the leading edges (nearest the ablation location) of both grounding pads. The grounding pads were left exposed to air, with continuous monitoring of the underlying skin temperature. When the grounding pads were placed on the lower extremities, cloth material was placed between the patient's thighs to prevent skin contact. If the skin temperature reached 39°C, dry cold packs were applied over the grounding pads.

After sterile preparation, an electrode (Starburst XL; RITA Medical Systems, Mountain View, Calif) was introduced through a skin nick by one or more of the participating radiologists (M.R.C., J.W.C., B.D.L., T.J.W., M.A.F.). CT (nine patients), US (two patients), or both CT and US (one patient) guidance was used for the insertion. The insulated needle tip was placed into the lesion to be treated; the electrodes were advanced through the soft-tissue portion of the lesion until no further advancement was possible owing to placement of the electrode tips against the soft-tissue–bone interface. The electrode tip position was confirmed at CT or US.

The Starburst XL is a 14-gauge, 6.4-F

needle with an active electrode trocar tip and nine electrodes spread in a ball-like fashion. This model generates up to a 5-cm-diameter zone of necrosis. The diameter of electrode deployment is controlled by the length of exposed electrode. The deployment diameter, as determined with 1-cm scale markings on the needle handle, was recorded for each RF ablation. This electrode system contains integrated thermocouples for continuous temperature monitoring of the ablated tissue. The energy deposited by the electrode was controlled with a generator (model 1500; RITA Medical Systems) that provides 460-kHz frequency with a maximum power of 150 W. Once the target temperature of 100°C was achieved, this temperature was maintained by means of automatic adjustment of the RF energy deposition by the generator for a minimum of 5 minutes, with a goal of 5–15 minutes.

A single ablation was performed for lesions of 3 cm in diameter or smaller. For larger (>5-cm) lesions, the lesion was systematically treated with multiple 3–5-cm deployments of the electrode. For these larger lesions, the entire lesion was not completely treated; rather, ablation treatments were focused on the margin of the lesion involving bone, with the goal of treating the soft-tissue–bone interface. For each patient treated, lesion location, size of each treated lesion, number and diameter of each electrode deployment, and corresponding time at target temperature were recorded. Total RF ablation and anesthesia times were also recorded for each patient treated.

After ablation, the electrodes were withdrawn into the insulated needle and the needle was then removed. Approximately 10 mL of 0.25% bupivacaine (Marcaine; Abbott Laboratories, North Chicago, Ill) was injected into the deep soft tissues immediately after removal of the electrode. Immediate postprocedural pain was treated with intravenous administration of fentanyl (Abbott Laboratories) and 1 mg/mL of midazolam (Versed; American Pharmaceutical Partners, Los Angeles, Calif). If pain persisted beyond the first 1–2 hours after treatment, the patient was treated with orally administered morphine.

Posttreatment Patient Assessment and CT Examination

Patients were evaluated for severity and influence of pain on their lives by using the BPI (12,13). The patients completed the BPI with the assistance of a study coordinator the day after treatment. The BPI was also completed weekly by means of 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 treated lesion. Analgesic use was also recorded during each of these interviews.

Each patient underwent contrast material–enhanced (iohexol, [Omnipaque 300]; Nycomed, Princeton, NJ) CT of the treated region 1 week after RF ablation. This examination of the ablated region was performed 1 week after treatment for three reasons: *(a)* to evaluate the change in appearance of the ablated region, *(b)* to provide a baseline study for subsequent CT examinations and potential RF ablation re-treatment, and *(c)* to capture possible late post-RF therapy complications.

Statistical Methods

Design and procedures.—This study was a single-arm, paired-comparison, observational study with patients serving as their own controls. There was an initial efficacy observation period of 8 weeks, based on the assumption that the effect of ablation would be observed within 8 weeks of the procedure. There was a supplementary observation period of an additional 4 months to assess duration of effect among those patients who reported successful pain reduction in the initial 8 weeks.

Primary end points were the worst pain and average amount of pain, constructed from the weekly pain scores on the visual-analogue scale (score of 0–10). A secondary end point was the percentage of patients who were able to reduce analgesic medications.

The accrual goal was 30 patients. An interim analysis was planned once 15 patients provided evaluable data to determine the preliminary effectiveness, because this number of patients would provide 80% power for detection of a difference of 2 units on average. This interim evaluation was also planned to be used in consideration of stopping the trial early if no patients derived benefit from RF ablation. The interim analysis was performed in 12 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 2 units on average and *(b)* a 3-month period without additional patient enrollment was encountered.

Statistical analysis.—Analysis of the primary end point was undertaken by means of 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 CIs, of the proportion of patients who experienced a decrease of at least 3 points on the pain scale from the pretreatment level. Similar comparisons were performed by using the additional questions regarding quality of life contained in the BPI. Differences with $P \leq .05$ were considered statistically significant.

Missing values were handled in a number of ways, including complete-case analysis and imputation according to the nearest neighbor; mean value; last value; and worst-value-carried-forward approaches (14,15). Multiple approaches were used so that the sensitivity of results to alteration in imputation assumptions could be assessed.

RESULTS

General

The eight men and four women in this study ranged in age from 56 to 75 years (mean, 65 years ± 5 [SD]) (Table). Four patients completed the 24-week follow-up. Three patients died during the course of the study, 4, 7, and 13 weeks after therapy; their deaths were unrelated to the RF ablation. One patient withdrew from the study 8 weeks after therapy. One patient suffered a stroke 18 weeks after RF ablation treatment and was no longer able to complete the BPI. Three patients remained in the study with 10, 16, and 16 weeks of follow-up beyond their RF ablation treatment date.

All treated lesions were osteolytic, with a combination of bone destruction and a soft-tissue mass. These metastatic bone lesions included those in four patients with renal cell carcinomas; in four with colorectal carcinomas; and in one each with melanoma, small cell lung carcinoma, endometrial carcinoma, and transitional cell carcinoma of the bladder. Four lesions involved the iliac bone; two involved the sacrum; and one each involved the pubic symphysis, vertebral body and rib, body wall with liver and overlying rib, rib, tibia, and talus. A single lesion was treated in each patient. The size of the treated lesion ranged from

Lesion Characteristics and Treatment in 12 Patients

Patient No./ Age (y)/Sex	Primary Neoplasm	Treatment Location	Lesion Size (cm)*	Deployment Diameter (cm)	Time at Target Temperature (min)	Total RF Time (min)	Total Procedure Time (min)
1/57/M	Renal	Ilium	5.5 × 4.4 × 4.3	3, 3, 2, 3, 3	5, 5, 5, 5, 5	56	150
2/59/M	Melanoma	Tibia	1.3 × 1.4 × 1.3	2, 2, 3, 3	10, 10, 10, 10	50	135
3/65/M	Lung	Rib, body wall and liver	6.3 × 4.3 × 8.3	4, 3, 3, 3, 5, 3	15, 10, 10, 10, 25, 10	95	187
4/68/M	Colorectal	Sacrum	10.0 × 10.8 × 7.0	4, 4, 4, 4, 4, 4, 4 and 4, 4, 4, 4, 4, 4, 4†	10, 8, 5, 5, 5, 5, 5 and 5, 5, 5, 5, 5, 5, 5†	60 63	180 120
5/68/F	Colorectal	Rib	2.1 × 1.0 × 1.8	1, 1	5, 5	16	120
6/67/F	Endometrial	Pubic symphysis	3.5 × 3.9 × 2.9	3, 3, 3, 5	7, 7, 10, 20	54	150
7/66/M	Bladder	Ilium	3.5 × 6.4 × 6.3	3, 3, 4, 2, 4, 5	10, 3,‡ 10, 4, 15, 10	51	150
8/65/M	Renal	Ilium	5.0 × 3.0 × 5.0	3, 3, 3, 3	5, 5, 5, 5	30	150
9/75/F	Colorectal	Vertebral body and rib	4.0 × 8.0 × 4.0	2, 2, 3	5, 5, 7	27	90
10/68/F	Colorectal	Sacrum	5.0 × 8.0 × 3.0	2, 3, 4, 4, 3	5, 5, 5, 5, 5	36	135
11/66/M	Renal	Ilium	10.0 × 7.5 × 9.1	3, 5, 5, 5	3,‡ 8, 8, 8	41	105
12/56/M	Renal	Talus	3.1 × 2.6 × 3.5	3, 3	8, 8	32	75

* Data are craniocaudal by right-to-left by anteroposterior dimensions.
† Large lesion treated at two sessions 6 weeks apart.
‡ Treatment aborted due to suboptimal electrode placement.

1 cm in smallest dimension in a rib to approximately 11 cm in a lesion contained in the sacrum (Table). One patient with a large lesion was treated in two sessions 6 weeks apart, while the remaining 11 patients were treated in a single session. Time maintained at the target temperature for each electrode deployment is shown in the Table. The range of electrode deployments for the RF ablation procedure was 2–7 (mean, 4.5 deployments ± 1.6). The range for total ablation time was 16–95 minutes (mean, 47 minutes ± 20). The total anesthesia time required for the procedure ranged from 90 to 187 minutes (mean, 134 minutes ± 32).

Five of 12 patients (42%) underwent both chemotherapy and radiation therapy prior to treatment with RF ablation. Four of 12 patients (33%) underwent radiation therapy without chemotherapy. Of these four patients, two refused chemotherapy and two did not undergo prior chemotherapy because of no evidence of metastatic disease at the time of the initial diagnosis and surgical resection of the primary neoplasm. Three of 12 patients (25%) underwent chemotherapy and no prior radiation therapy. One of these three patients did not undergo radiation therapy because of adjacent involvement of the liver, and two patients chose RF ablation rather than radiation therapy. Ten of 12 patients (83%) were concurrently being treated with oral analgesic medications for their pain. The remaining two of 12 patients (17%) refused oral analgesic medications.

For each patient, contrast-enhanced CT scans obtained 1 week after treatment showed an area of nonenhancing low-attenuating tissue, consistent with necrosis, that corresponded to the placement and deployed diameter of the RF ablation electrode. CT scans also showed that no major complications resulted from RF ablation in these 12 patients. However, the first patient treated received a second-degree burn along the leading edge of one of the grounding pads. After this event, skin temperature measurements along the leading edges of the grounding pads were performed, and no further grounding-pad burns were observed throughout this study. Although specific skin temperatures along the leading edges of the grounding pads were not recorded, skin surface temperatures of 39°C–40°C were observed deep to the grounding pads during treatment in several patients. These elevated skin temperatures were treated by applying dry cold packs to the grounding pads.

In addition, because of severe pain at the RF ablation site after the procedure, nine of 12 patients required intravenous administration of analgesic medications in the immediate postprocedure recovery period and over the course of the following 8–10 hours. One of these nine patients was further treated with administration of bupivacaine and fentanyl through an epidural catheter for a period of 24 hours, after which the catheter was removed and the patient's pain was managed with oral analgesic medications. This same patient also developed pneumonitis within 2 days of the procedure, presumably due to aspiration of stomach contents while under general anesthesia. Three of 12 patients experienced persistent pain beyond the immediate post-treatment recovery period, and their treatment was converted to oral analgesic medications by the following morning, when they were discharged from the hospital.

Individual and Averaged Responses of Pain to RF Ablation

The primary method used to determine the response of patients with these painful metastatic lesions to the RF ablation treatment was the BPI (12,13). The frequency of missing data was minimal. No patients had missing values at baseline or day 1. Only one patient had a missing value at week 4. This patient entered the hospice at week 4 and died the following week. Sensitivity and intention-to-treat analyses adjusted for this missing value did not change the results.

As shown in Figure 1, all patients experienced a decrease in worst pain ("Please rate your pain by circling the one number that best describes your worst pain over the past 24 hours") over the course of the follow-up period. The mean patient response for worst pain prior to RF treatment was 8.0. At 1, 4, 6, and 8 weeks after treatment, this mean response decreased to 4.6 ($P < .012$), 3.1 ($P = .001$), 3.1 ($P = .002$), and 2.4 ($P < .004$), respectively (Fig 1, top). From baseline to week 4, nine of 11 patients (82%; exact binomial CI: 48%, 98%) experienced at least a three-point decrease in worst pain. Over the course of the protocol, 11 of the 12

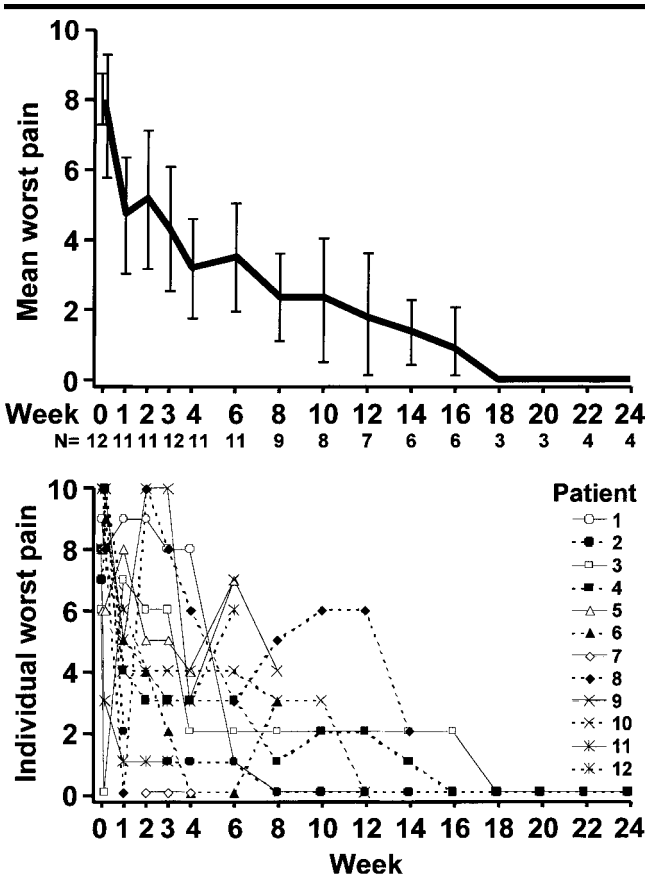

Figure 1. Graphs show worst pain over 24 hours for patients treated with RF ablation, as measured with the BPI. Data for week 0 represent the baseline (pretreatment) measurement. Top: Mean responses for all patients. Error bars = 95% CIs, *N* = number of patients completing BPI at each time point. Bottom: Individual responses for each patient.

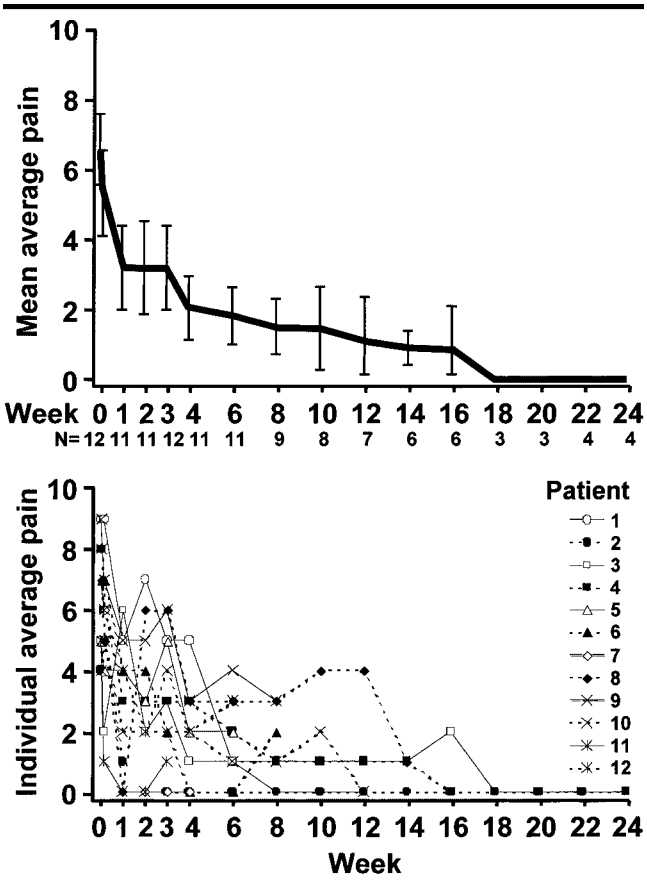

Figure 2. Graphs show average pain for patients treated with RF ablation, as measured with the BPI. Data for week 0 represent the baseline (pretreatment) measurement. Top: Mean responses for all patients. Error bars = 95% CIs, *N* = number of patients completing the BPI. Bottom: Individual responses for each patient.

patients (92%; exact binomial 95% CI: 62%, 99%) reported at least a three-point decrease in worst pain over the previous 24 hours. Four of 12 patients (33%) experienced increased or no improvement in worst pain in a 24-hour period the day after RF ablation. Three of 12 patients (25%) reported increased or no improvement in worst pain 1 week after RF ablation (Fig 1, bottom). Notably, one of these patients (patient 2, Table) had early relief of pain but participated in an athletic event 1 day after the RF ablation procedure and then reported a BPI score of 10 for worst pain. This same patient reported scores of 2 or less for the remainder of follow-up. As shown in Figure 1, bottom, individual patient responses varied over the course of follow-up, with a gradual downward trend for all patients.

Response to average pain before and after RF ablation ("Please rate your pain by circling the one number that best describes your pain on the average") is shown in Figure 2. The mean patient response for average pain prior to RF treatment was 6.5. At 1, 4, 6, and 8 weeks after treatment, this mean response decreased to 3.1 ($P < .003$), 1.8 ($P < .001$), 1.5 ($P = .001$), and 1.4 ($P < .004$), respectively (Fig 2, top). From baseline to week 4, 11 of 12 patients (92%; exact binomial CI: 48%, 98%) experienced at least a three-point decrease in average pain. Over the course of the protocol, all 12 patients (100%, exact binomial 95% CI: 62%, 100%) reported at least a three-point decrease in average pain. As was seen for individual responses for worst pain, the corresponding individual responses for average pain also varied over the course of follow-up, with a gradual downward trend for all patients, as shown in Figure 2, bottom.

A mean score for interference of pain in activities of daily living before and after RF ablation treatment ("Please circle the one number that describes how, during the past 24 hours, pain has interfered with your. . . activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life") is shown in Figure 3, top. Before treatment, the mean score for interference of pain in activities of daily living was 6.6. At 1, 4, 6, and 8 weeks after treatment, this mean response decreased to 4.2 ($P = .023$), 2.7 ($P = .002$), 2.2 ($P = .001$), and 1.8 ($P < .004$), respectively. The mean corresponding individual responses to these questions are shown in Figure 3, bottom. Four weeks after RF ablation, six of 11 patients (55%; exact binomial 95% CI: 23%, 83%) experienced at least a three-point reduction in mean score for interference of pain in activities of daily living. Over the course of the follow-up period, 11 of 12 patients (92%; exact binomial 95% CI: 62%, 99%) experienced at least a three-point reduction in mean score for interference of pain in activities of daily living.

The mean score for how pain treatments or medications provided relief from pain ("In the past 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received") is shown in

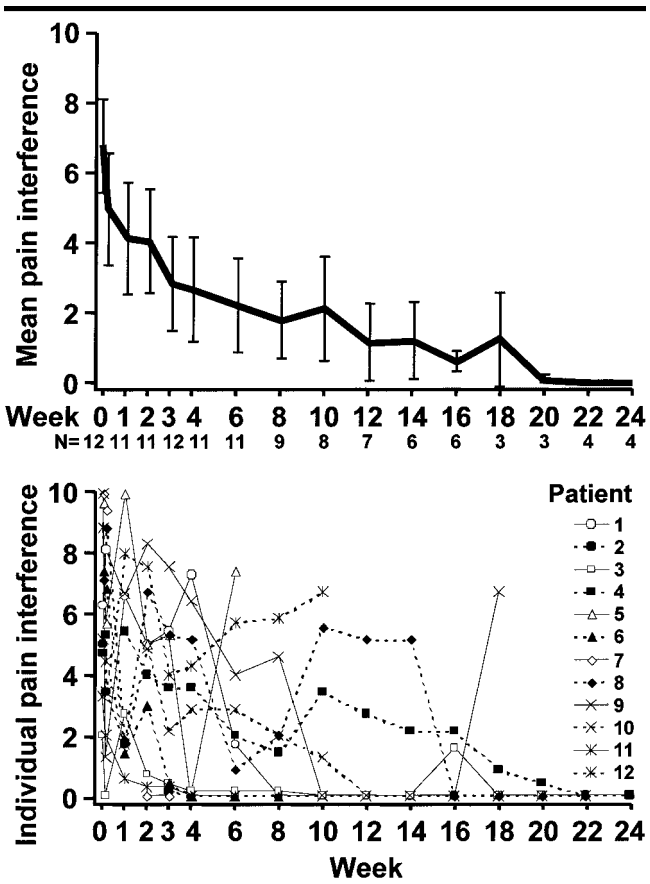

Figure 3. Graphs show interference of pain in daily activities for patients treated with RF ablation. Data for week 0 represent the baseline (pretreatment) measurement. Top: Mean responses for all patients. Error bars = 95% CIs, *N* = number of patients completing the BPI. Bottom: Individual responses for each patient.

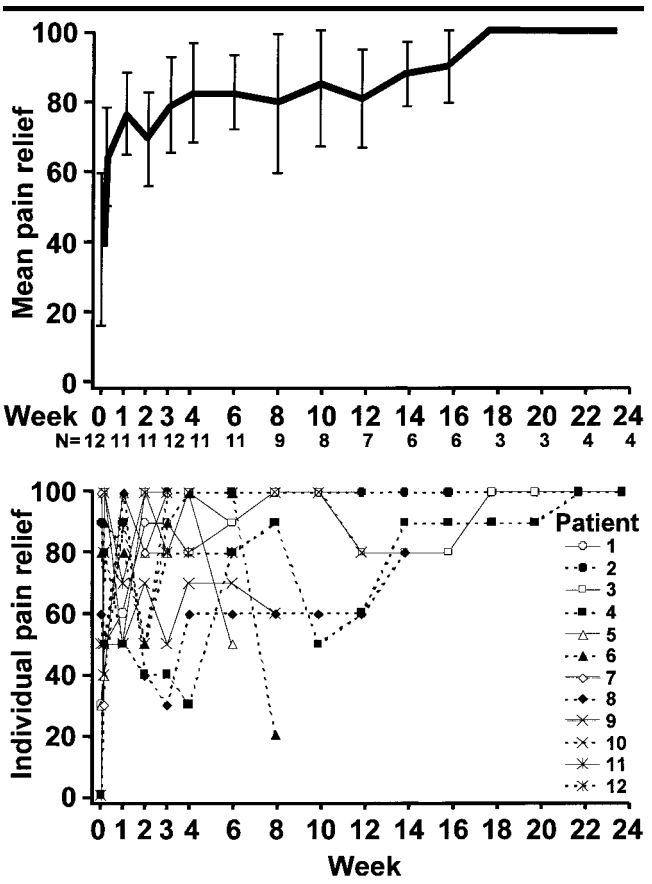

Figure 4. Graphs show relief due to pain treatments or medications in patients treated with RF ablation. Data for week 0 represent the baseline (pretreatment) measurement. Top: Mean responses for all patients. Error bars = 95% CIs, *N* = number of patients completing the BPI. Bottom: Individual responses for each patient.

Figure 4, top. The average relief from pain provided by treatments or medications prior to RF ablation was 37%. At 1, 4, 6, and 8 weeks after treatment, this average response increased to 76% ($P < .004$), 84% ($P = .002$), 83% ($P = .002$), and 79% ($P < .047$), respectively. As shown in Figure 4, bottom, individual patient responses varied over the course of the follow-up period, with a gradual trend toward improved pain relief from pain medications and treatments for all patients.

A secondary measure of response of pain after RF ablation was the change in each patient's use of analgesic medications. Over the course of the follow-up period, eight of 10 patients (80%; exact binomial 95% CI: 43%, 95%) reported a reduction in the use of analgesic medication at some time after RF ablation. The remaining two patients were not using analgesic medications at the time of entry into the study. Four weeks after RF ablation, three of nine patients (33%; exact binomial 95% CI: 7%, 70%) reported

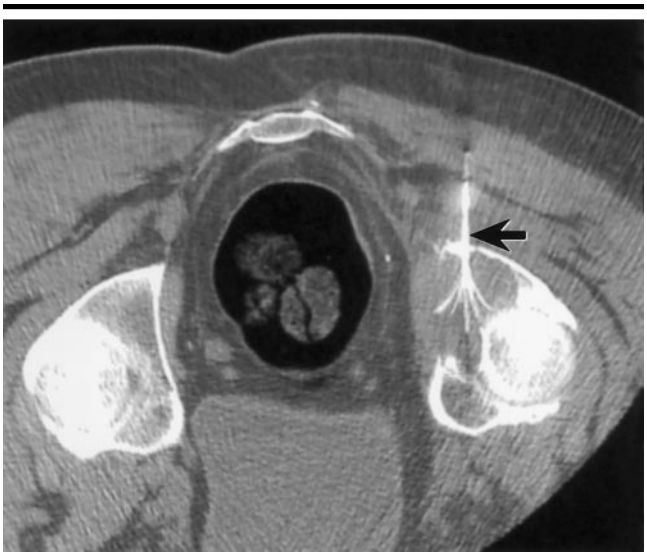

Figure 5. Patient 1. Transverse CT image obtained at the level of the acetabuli with the patient prone. A percutaneously placed RF electrode (arrow) was deployed in an osseous and soft-tissue renal cell carcinoma metastatic lesion involving the medial and posterior wall of the left acetabulum. Before RF ablation, the patient's average pain score 8. At 4, 6, and 8 weeks after RF ablation, the average pain score was 5, 1, and 0, respectively. The patient died 6 weeks after 6-month follow-up, with no pain at the treated site.

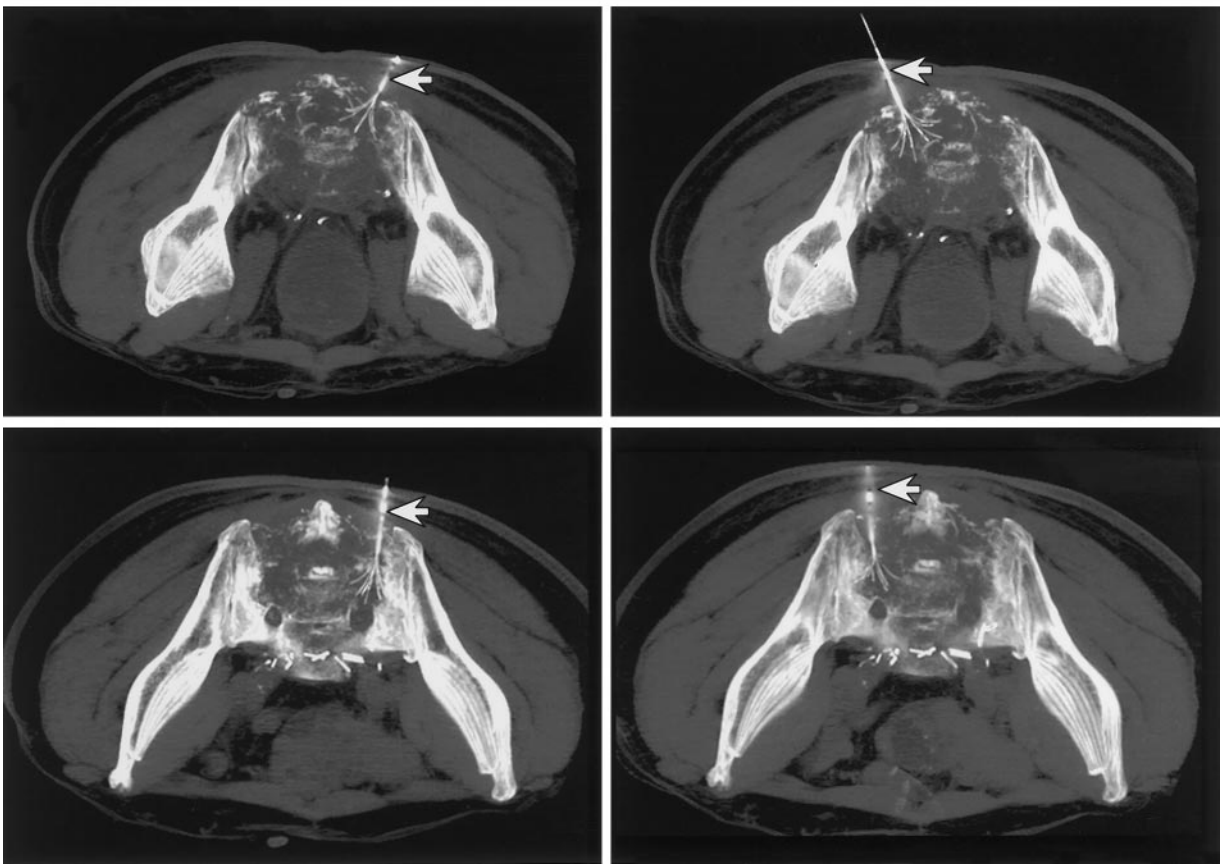

Figure 6. Patient 4. Transverse three-dimensional volume CT images obtained at the level of the sacrum with the patient prone show four of 14 percutaneously placed RF electrode deployments (arrows) in an osseous and soft-tissue colorectal carcinoma metastatic lesion diffusely involving the sacrum. Before RF ablation, the average pain score was 8. At 4, 6, and 8 weeks after ablation, the average pain score was 3, 2, and 1, respectively. At 6 months after ablation, the reported average pain score was 0.

a reduction in the use of pain medications. One patient did not participate in the 4-week follow-up interview.

RF Electrode Placement and Deployment in Individual Cases

The number of ablations that were performed varied for each patient and was dependent on the size, shape, and location of the metastatic lesion, with the intent to ablate all metastatic tissue in contact with bone.

One patient who was treated had an approximately 4.5-cm-diameter metastatic renal cell carcinoma lesion to the ilium involving the medial and posterior aspects of the left acetabulum with extension to the left hip joint surface (patient 1, Fig 5). To avoid ablation of the joint surface, five separate RF ablations were performed with electrode diameter deployments of 2 and 3 cm. Once the target temperature of 100°C was achieved, this temperature was maintained for 5 minutes for each separate deployment.

For treatment of larger lesions, multiple separate ablations were performed with the electrode deployment diameter determined by the volume of metastatic lesion to be treated and by the proximity of adjacent critical structures. Treatment of an approximately 11-cm colorectal carcinoma metastatic lesion diffusely involving the sacrum involved a total of 14 separate RF ablations performed during 2 separate days, 6 weeks apart (patient 4, Fig 6). All RF ablations were performed with an electrode diameter of 4 cm. The first and second ablations were maintained at the target temperature of 100°C for 10 and 8 minutes, respectively. Because the target temperature was reached quickly in these ablations (approximately 2 minutes) and because of the large volume of lesion, the target temperature was maintained for 5 minutes for each of the remaining RF ablations.

All patients were examined before RF ablation to determine focal site(s) of pain. The location of the most intense pain was used to guide therapy. One patient in the study had widespread metastatic renal cell carcinoma involvement of the left iliac bone in the region of the acetabulum. At examination, we found that most of the patient's pain corresponded to a metastatic implant in the soft tissues of the left gluteal musculature. Therefore, the metastatic lesions involving the iliac bone, as well as the implant in the soft tissues, were treated with RF ablation with three 5-cm electrode deployments in the involved iliac bone and one 3-cm deployment in the involved gluteal musculature (patient 11, Fig 7).

CT guidance was primarily used for percutaneous placement of the RF electrode. However, for patients with lesions primarily involving soft tissue rather than bone, US was used rather than CT for electrode placement and deployment. For example, a patient with small cell carcinoma of the lung metastatic to the lateral aspect of the right lobe of the liver, the adjacent body wall and overlying rib

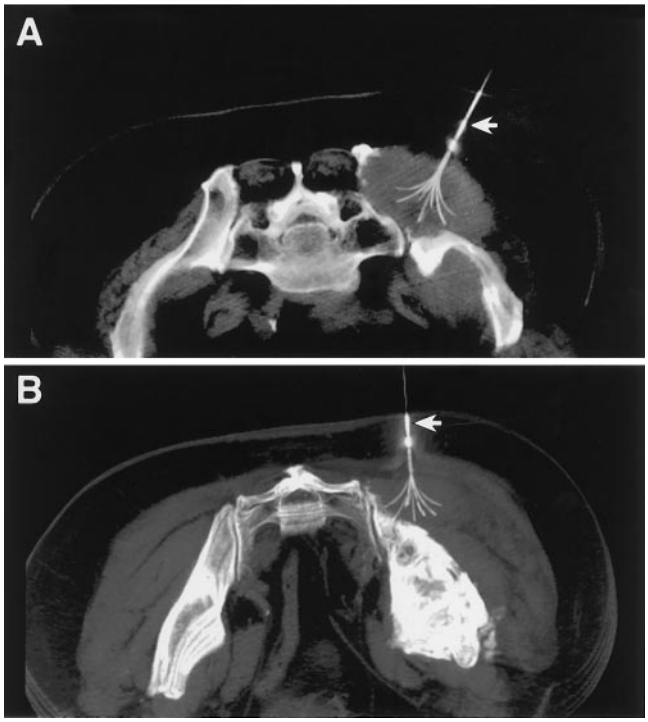

Figure 7. Patient 11. Transverse three-dimensional volume CT images obtained at the level of the sacrum with the patient prone show a percutaneously placed RF electrode (arrows) deployed in an osseous and soft-tissue renal cell carcinoma metastatic lesion diffusely involving the left iliac bone *(A)* and in a soft-tissue lesion involving gluteal musculature of the left buttock *(B).* The soft-tissue lesion corresponded to the site of patient's greatest pain. Before RF ablation, the average pain score was 5. At both 4 and 6 weeks after ablation, the average score was 0. This patient died 7 weeks after RF ablation, with no pain at the treated site.

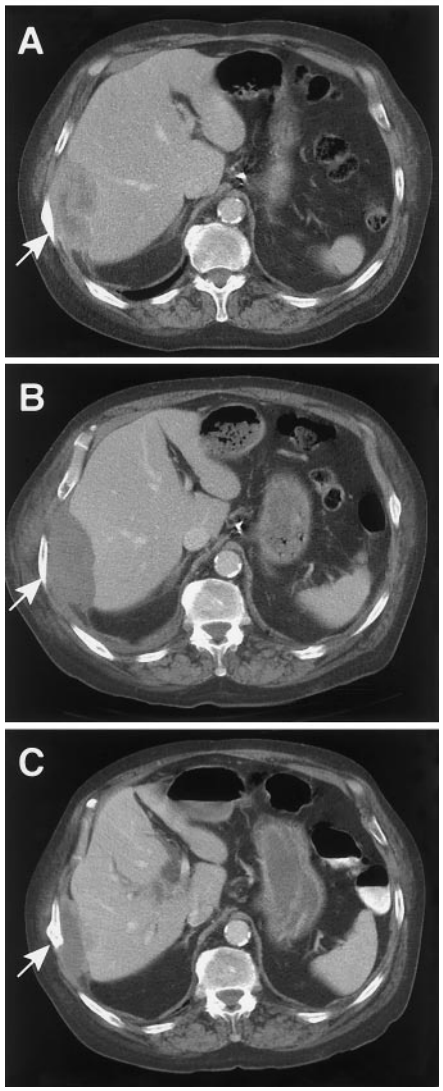

Figure 8. Patient 3. Transverse contrast-enhanced CT images with patient supine show metastatic small cell lung carcinoma lesion (arrows) involving a rib, body wall, and underlying liver. *A,* Immediately before RF ablation, the mass shows partial enhancement. *B,* At 1 week after ablation, the mass is hypovascular, which is consistent with necrosis. *C,* At 12 weeks after ablation, the necrotic mass shows interval decrease in size. Before ablation, the average pain score was 5. At 4, 6, and 8 weeks after ablation, the average pain score was 1. At 6 months after ablation, the reported average pain score was 0.

was readily depicted with US. Placement of the electrode was achieved with US guidance, which allowed safe deployment of the electrode and prevented ablation of the nearby diaphragm and lung (patient 3, Fig 8).

We performed only one RF ablation of a lesion involving a vertebral body and paravertebral soft tissues. This metastatic colorectal carcinoma involved the lateral aspect of the vertebral body, as well as the adjacent rib and pleural surface (patient 9, Fig 9). This RF ablation was performed with the patient's understanding and consent that the underlying intercostal nerve would be destroyed. To protect the spinal cord from thermal injury, the most medial RF treatment (2-cm-diameter deployment, 5 minutes at target temperature) was performed after placement of a thermocouple near the adjacent vertebral body pedicle (Fig 9). The osteolytic soft-tissue component involving the vertebral body was not treated. As is shown in Figure 9, contrast-enhanced CT images obtained 1 week after treatment depicted a low-attenuating lesion that was generated in the location of the RF electrode needle deployment. No neurologic injury, beyond the expected intercostal nerve destruction, resulted from this RF ablation.

DISCUSSION

Approximately 40% of patients with cancer develop metastatic disease; of these patients, 50% have poorly controlled pain (13,16–22). Achieving adequate pain control is often difficult, and, as a result, quality of life for these patients is poor. Various therapies, including chemotherapy, hormonal therapy, localized irradiation, systemic radioisotope therapy, and surgery, may be used in an attempt to provide palliative pain relief. Some patients fail to derive satisfactory pain relief with these therapies, and relief, when achieved, may not occur until 4–12 weeks after the initiation of the treatment. When these methods are not possible or are not effective, analgesic medications remain as the only current alternative therapy.

We chose to report the response in these 12 patients with painful skeletal metastatic disease treated with RF ablation with a minimum follow-up of 10 weeks for all participating patients (two patients died within this time period at 4 and 7 weeks; one patient withdrew from the study at 8 weeks). Although the study

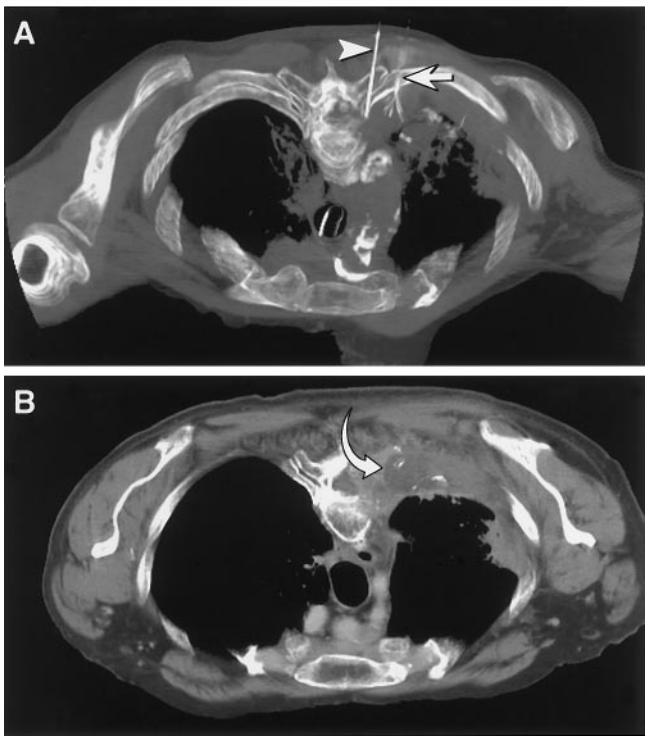

Figure 9. Patient 9. Transverse CT images obtained with the patient prone. *A,* Three-dimensional volume unenhanced image shows RF electrode (arrow) placed into a colorectal carcinoma metastatic lesion involving a vertebral body, rib, and adjacent pleural surface, with a thermocouple (arrowhead) placed in the region of the lateral margin of a largely destroyed left pedicle. *B,* Contrast-enhanced image of the same region, obtained 1 week after RF ablation, demonstrates a low-attenuating area (arrow), consistent with necrosis, in the paravertebral soft tissues, corresponding to the ablated region. Before ablation, the average pain score was 9. At 4, 6, and 8 weeks after ablation, the average pain score was 3, 4, and 3, respectively. At latest follow-up (16 weeks after ablation), the reported average pain score was 0.

was designed for an interim evaluation after treatment in 15 patients, this design was based on detection of a difference of 2 points with 80% power in the response to RF treatment, as scored with the BPI. Because we observed profound responses to the RF ablation and because of a 3-month period with no additional patient enrollment, we elected to perform the interim analysis at this stage.

We found that, on average, patients derived benefit from the RF ablation treatment within 1 week, with decreases of 3.4, 3.4, and 2.4 points for worst pain in 24 hours, average pain, and pain interference, respectively. Reported pain relief with pain treatments and medications increased from 37% to 76% 1 week after treatment. A few patients reported increased or no improvement in their pain in the 1st weeks after RF ablation. Anecdotally, these patients stated that the pain they felt after the procedure was different from their typical pain. This subset of patients was treated in the same manner as patients who had more immediate relief of pain. We found no significant correlation of time for onset of pain relief in these patients with size, depth, or location of the treated lesion or with level of baseline average or worst pain in 24 hours. Importantly, all of these patients experienced improvement in their pain over the course of follow-up. The patients who were treated in this study had in common severe pain from metastatic skeletal disease; however, this group was heterogeneous with respect to size, location, and type of neoplasm that was treated. It is possible that with increased numbers of treated patients, we will develop an understanding of how different groups of patients will respond to the RF ablation treatment.

The patients in this study showed greater benefit from RF ablation with time, reporting mean decreases of 4.9, 4.7, and 3.9 points for their worst pain in 24 hours, average pain, and pain interference, respectively, 4 weeks after treatment. Pain relief with pain treatments and medications also improved to 84% 4 weeks after treatment. In addition to providing pain relief, RF ablation resulted in improved quality of life with decreased interference from pain in the activities of daily living. Importantly, 83% of patients reported that they had 100% relief from pain at some point after RF ablation. Three patients died during the observation period, at 4, 7, and 13 weeks after therapy. One patient died 6 weeks after 6-month follow-up. Three of these four patients were free of pain from the treated lesions at the time of death. The fourth patient entered the study with scores for average and worst pain in 24 hours of 7 and 8, respectively. This patient reported no pain after 4 weeks and, just prior to death, reported scores of 2 and 3 for average and worst pain in 24 hours, respectively.

The designed follow-up period for this study was 6 months, a period that we believed was clearly sufficient to demonstrate usefulness if the benefit derived had this duration. Although only 4 patients had completed 6 months of follow-up at the time this article was written, all four reported no pain at the sites treated with RF ablation at the 6-month follow-up interview. Continued follow-up in the remaining patients is warranted. In addition, extension of the follow-up period beyond 6 months would be useful to help determine the longevity of the RF ablation treatment.

Radiation therapy is the standard of care for palliative treatment of pain due to focal metastatic lesions involving bone. This therapy may be administered in a single dose; however, most radiation therapy schedules in the United States involve daily treatments over 2–3 weeks. Janjan (23) reported that the time required to derive maximal benefit following radiation therapy for solitary and multiple metastases, as defined in terms of cessation of analgesic medications, is usually 12–20 weeks, with 29%–70% of patients achieving relief in 2–4 weeks and 53%–84% achieving relief in 4–12 weeks. Although these results are not directly comparable to ours, the time to achieve a benefit from radiation therapy may be more prolonged than the time to achieve symptom relief in patients treated with RF ablation. We expect that RF ablation will provide an alternative treatment for palliation of painful metastatic lesions that are resistant to radiation and in cases where further radiation

therapy is not possible because of limitations of dose to normal structures. It is also possible that RF ablation will play an adjunctive role to the use of radiation therapy for palliation of painful metastatic lesions. Prospective comparison studies of RF ablation and radiation therapy may be useful to help distinguish the relative benefits of these therapies for palliation of painful metastatic lesions.

Our results suggest that RF ablation is a safe procedure for treatment of metastatic lesions involving bone. A contrast-enhanced CT study was obtained 1 week after the treatment, to exclude late hemorrhage, infection, and involvement of adjacent organs. Because no major complications were found in these 12 patients, we believe that this examination is unnecessary as a component of this treatment. Notably, one patient experienced a second-degree skin burn at the grounding-pad site; further burns were prevented through careful monitoring of skin temperature deep to the grounding pads, and, when elevated temperatures were observed, improved ventilation and applications of dry cold packs adequately reduced the skin temperature. A second patient developed pneumonia 2 days after the procedure, most likely related to aspiration during general anesthesia. This complication was not considered to be due to unique patient positioning or related specifically to the RF ablation procedure. Although there were no major complications in patients treated in this study, careful selection of lesions and electrode placement are important to avoid inadvertent ablation of critical structures such as spinal cord, major nerves, bowel, and bladder.

The lesions that were treated in this study were predominantly osteolytic with an associated soft-tissue component. In all cases, electrodes were readily deployed into the osteolytic and soft-tissue component of the metastatic lesion. When deployed, the electrode maintained its symmetric shape with typical deployment of the electrode tips at the interface between bone and soft tissue. We expect that this technique may apply only to these types of metastatic lesions, and we suspect that deployment of electrodes into osteoblastic lesions would be difficult.

The mechanism of action responsible for decreased pain at the metastatic site after RF ablation is unclear. Our approach focused on ablation of neoplastic tissue adjacent to involved bone. Although a substantial fraction of the metastatic tissue was treated, it is possible that more extensive, or possibly more focal, treatment would provide better pain relief. Several possible mechanisms responsible for decreased pain include *(a)* physical destruction of adjacent sensory nerve fibers involving the periosteum and cortex of bone, inhibiting pain transmission; *(b)* mechanical decompression of tumor volume, decreasing stimulation of sensory nerve fibers; *(c)* destruction of tumor cells that produce nerve-stimulating cytokines (tumor necrosis factor–α, interleukins, and others), which may sensitize nerve fibers and affect pain transmission; and *(d)* inhibition of osteoclast activity, which may cause pain (24–26). It is possible that with a clearer understanding of the mechanisms responsible for pain generation, combination therapies of RF ablation with chemotherapeutic agents (27), bisphosphonates (28,29), antiosteoclast activity agents (25), or radiation therapy would provide a greater, possibly synergistic, effect.

This study involved the use of a single multitined type of RF electrode. It is possible that other configurations of electrodes may provide the same, or potentially greater, benefit. We believe that the parameters used for the various ablations resulted in adequate tissue destruction, based on the low-attenuation changes in ablated tissue (consistent with tissue necrosis) on 1-week follow-up contrast-enhanced CT images. However, optimization of RF ablation parameters with increases or decreases in deployment diameter and time maintained at the target temperature may provide greater benefit.

A factor of concern with this therapy is the time currently necessary for the RF ablation treatment, particularly for large lesions. We found that these treatments require an average of 2 hours 14 minutes of anesthesia time with the patient in the CT suite; a substantial component of the time necessary for the procedure was an average of 47 minutes of ablation time. Optimization of RF electrode energy deposition and corresponding improvements in grounding-pad design may allow a decrease in the amount of time necessary for this procedure, with a corresponding decrease in procedure time. Additionally, all patients in this study were treated while under general anesthesia; it is possible that the use of regional anesthesia or conscious sedation methods would reduce the time necessary for the procedure.

We treated one lesion involving the talus that had a potential risk of fracture after RF ablation. Although this patient had not experienced a fracture to date after the RF procedure, it is possible that a combination of RF ablation followed by the use of bone cement may be important in stabilization of impending fractures resulting from metastatic disease.

These results demonstrate that RF ablation provides a potential alternative method for palliation of painful osteolytic metastatic lesions; the procedure is safe, and the pain relief is substantial. Importantly, the quality of life for these patients is improved with this therapy.

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