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Radiofrequency Ablation for the Palliative Treatment of Bone Metastases: Outcomes from the Multicenter OsteoCool Tumor Ablation Post-Market Study (OPuS One Study) in 100 Patients

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ABSTRACT

Purpose: To evaluate the effectiveness of radiofrequency (RF) ablation as measured by change in worst pain score from baseline to 3 mo after RF ablation for the palliative treatment of painful bone metastases.

Materials and Methods: One hundred patients (mean age, 64.6 y) underwent RF ablation for metastatic bone disease and were followed up to 6 mo. Subjects' pain and quality of life were measured before RF ablation and postoperatively by using the Brief Pain Index and European Quality of Life questionnaires. Opioid agent use and device-, procedure-, and/or therapy-related adverse events (AEs) were collected.

Results: Eighty-seven patients were treated for tumors involving the thoracolumbar spine and 13 for tumors located in the pelvis and/or sacrum. All ablations were technically successful, and 97% were followed by cementoplasty. Mean worst pain score decreased from 8.2 ± 1.7 at baseline to 3.5 ± 3.2 at 6 mo (n = 22; $P < 0.0001$ for all visits). Subjects experienced significant improvement for all visits in average pain ($P < .0001$), pain interference ($P < .0001$), and quality of life ($P < .003$). Four AEs were reported, of which 2 resulted in hospitalization for pneumonia and respiratory failure. All 30 deaths reported during the study were attributed to the underlying malignancy and not related to the study procedure.

Conclusions: Results from this study show rapid (within 3 d) and statistically significant pain improvement with sustained long-term relief through 6 mo in patients treated with RF ablation for metastatic bone disease.

ABBREVIATIONS

AE = adverse event, BPI = Brief Pain Inventory, PMMA = polymethyl methacrylate, RF = radiofrequency

Current estimates report bone metastatic involvement in 60%–84% of cases in the presence of an underlying neoplastic process, which can lead to morbidities (1). Patients in whom bone metastases develop may experience pain, fracture, or neurologic injury. The annual health care burden for the treatment of malignancy-related bone-related complications is estimated at $12.6 billion (1). With the growing incidence of cancer cases combined with the prolonged survival of patients as a result of effective chemotherapy and targeted therapies, the prevalence of patients with bone metastases is increasing (2).

The primary goals of the treatment of bone metastases is pain relief, reduction of delayed skeletal or neurologic events, preservation of daily function, and optimization of quality of life. Although first-line therapy usually consists of bisphosphonates or targeted bone agents, external-beam radiation therapy is considered the standard of care for symptomatic patients; however, pain relief often is not immediate and may take as long as 4–6 weeks to be fully effective (3). Stereotactic body radiation therapy has demonstrated higher rates of palliation, ranging from 50% to 85%, but is associated with fracture rates as high as 11%–39% (4–7). Surgical treatments such as vertebrectomy, spinal reconstruction with cages, pedicle screw internal fixation, Harrington-type acetabular reconstruction, or other types of invasive therapies are available to assist with pain relief and strengthen skeletal integrity; however, these are associated with prolonged recovery time, increased infection rates, and high morbidity and mortality rates (8,9). In addition, these invasive procedures can delay radiation therapy or other systemic therapies (10).

Minimally invasive ablation procedures with kyphoplasty and polymethyl methacrylate (PMMA) augmentation have been shown in randomized controlled studies to achieve marked reduction in back pain and improvement in quality of life with a decrease in opioid agent use (11). More recently, several small observational studies of percutaneous radiofrequency (RF) ablation have demonstrated pain relief (8,12–16), mood and pain intensity improvements (13), and decreased opioid agent use (12,16). The clinical goal of RF ablation in vertebral metastases is primarily pain reduction and tumor cavitation before stabilization (17,18). Recent multidisciplinary treatment guidelines have outlined a treatment paradigm whereby RF ablation may be considered in conjunction with other therapies (19).

The purpose of this prospective, nonrandomized, multicenter study was to evaluate the effectiveness of skeletal RF ablation to demonstrate rapid (within 3 d) and sustained pain improvement in patients with painful bone metastases. This study provides the results in this cohort of patients.

MATERIALS AND METHODS

One hundred six patients were enrolled at 14 global investigational centers between October 2017 and March 2019 in the OsteoCool Tumor Ablation Post-Market (OPuS One) Study. The study is projected to enroll a maximum of 250 patients as long as 12 months after RF ablation. After enrollment, 6 subjects discontinued participation before undergoing RF ablation (Fig 1). The present document reports the results in the first 100 subjects treated with RF ablation. The present institutional review board/ethics committee–approved prospective study (*clinicaltrials.gov* identifier, NCT 03249584) was conducted in compliance with federal Health Insurance Portability and Accountability Act regulations. All patients included were at least 18 years of age with metastatic tumors of the thoracic and/or lumbar vertebral body/bodies, periacetabulum, iliac crest, and/or sacrum and were candidates for RF ablation per the labeled indications. Exclusion criteria included pure osteoblastic tumors, worst pain rated as < 4 on a scale from 1 to 10 in the past 24 hours, more than 2 painful sites requiring treatment, or Karnofsky performance score < 40 at enrollment. Included subjects had osteolytic bone metastases confirmed by imaging or biopsy per physician discretion. All procedures were considered technically successful if RF ablation was delivered to the targeted tumor.

A total of 134 ablations were performed under imaging guidance in the 100 patients. Sixty-eight patients (68%) had a single target site treated with RF ablation, and 32 (32%) had multiple sites treated. For those treated in the thoracic and lumbar vertebrae, the majority (85%) of RF ablation approaches were bilateral. Although not required per protocol, PMMA augmentation was performed in the majority of cases (97%; 130 of 134). No patients underwent additional RF ablation procedures during the follow-up period. Table 1 demonstrates patient characteristics and Table 2 reflects details of the ablation procedures.

Patient outcomes including pain, pain interference, and quality of life were collected in a total of 94, 89, 64, 46, and 22 patients at 3 days, 1 week, 1 month, 3 months, and 6 months, respectively. A total of 40 patients discontinued study participation after RF ablation treatment but before the 6-month follow-up, with 2 additional discontinuations after 6 months. The reasons for discontinuation included 30 deaths (71%), 9 voluntary patient withdrawals of consent (21%), 2 losses to follow-up (5%), and 1 discontinuation upon biopsy diagnosis of nonmalignant bone tumor (1%). Chemotherapy (43%), steroids (39%), and osteoporosis medications (38%) were reported as the most frequent treatments after RF ablation.

RF Ablation Procedure

Ablation of the targeted tumor(s) was performed with the OsteoCool RF Ablation System (Sofamor Danek/Medtronic, Dublin, Ireland). The system consists of an RF generator, peristaltic pump, and the connector hub, which provides 2 channels for the use of the ablation probes and 2 channels for the use of the optional independent thermocouples. The bipolar ablation probe is a coaxial, bipolar technology that provides localized tumor ablation and automatically adjusts the power to maintain the RF heating within the desired treatment range. The active tip of the RF ablation probe is internally cooled with circulating sterile water in a closed-loop system. RF energy heats the tissue while circulating
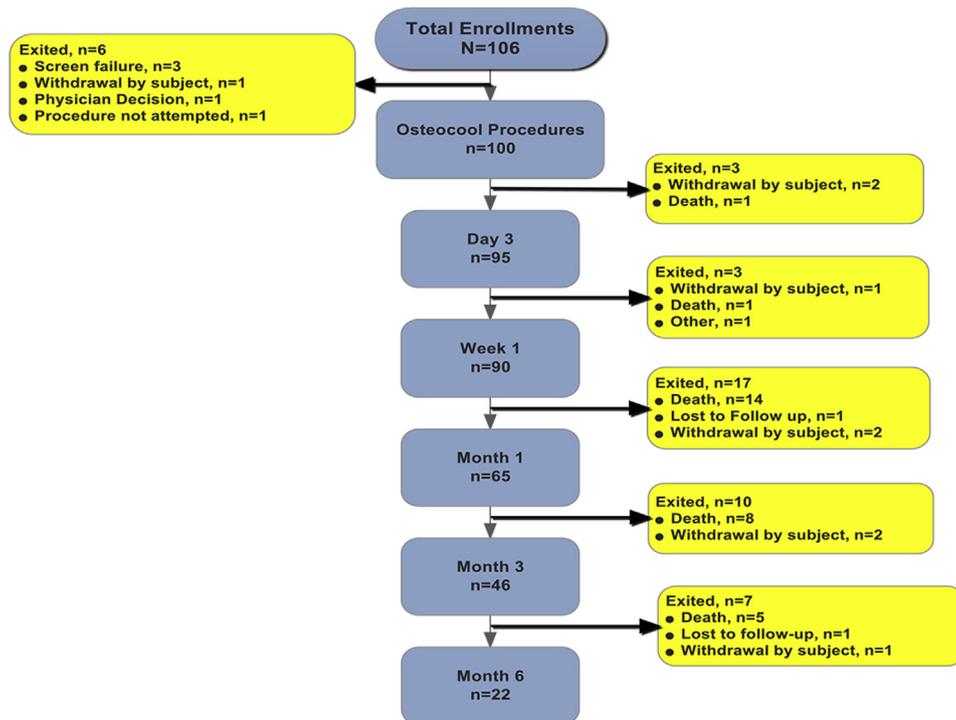
Figure 1. Study flow. The differences between counts at a visit and the next visit may not equate to the discontinued count because of subjects who were still actively being followed at the time of manuscript preparation.

water moderates the temperature in close proximity to the active tip to minimize charring. The ablation volume and time are determined based on the probe tip size.

All procedures were performed with computed tomography (16%) or fluoroscopic guidance (84%) under moderate sedation (30%), monitored anesthesia care (18%), or general anesthesia (52%) per the institution's standard of care. The target tumors were accessed by using an 8- or 10-gauge introducer cannula. In the thoracolumbar spine, the vertebral bodies were accessed via a transpedicular or parapedicular approach. The ablation probe lengths were predetermined and placed through the access cannula. The RF ablation protocol was performed by using the preset manufacturer algorithm. At the completion of RF ablation, PMMA, if used, was injected through the same bone access cannula.

Clinical Follow-up

Relevant cancer medical history and demographic information was collected before the procedure. Patients completed validated questionnaires to measure their pain, function, and quality of life. The Brief Pain Inventory (BPI) short form is a 12-item self-administered questionnaire used to evaluate the severity of a patient's pain and the impact of this pain on the patient's daily functioning. For the purpose of this analysis, a minimal clinically important difference in pain, as measured by the BPI, was defined by a ≥ 2-point change from baseline to postprocedural follow-up (20). The European Quality of Life–Five Dimensions is a standardized measure of patients' health status widely used as a validated tool to determine health-related quality of life (21).

Follow-up assessments occurred after the ablation procedure, 3 days, 1 week, and 1, 3, and 6 months after the procedure. Device-, therapy-, and/or procedure-related adverse events (AEs) were collected through the follow-up period.

Study Population

Patient demographic and baseline characteristics are presented in Table 1. A majority of the patients were female (56%; 56 of 100), and the mean age was 64.6 years (range, 30–89 y). The most common histology of the underlying primary tumor was adenocarcinoma; lung (25%) and breast (21%) were reported as the most common primary cancer. Eighty-seven subjects (87%) were treated for tumors involving the thoracolumbar spine, and 13 subjects (13%) were treated for tumors located in the pelvis and/or sacrum. Seventy-one percent of patients (71 of 100) reported concurrent treatments at baseline. Of these treatments, steroids, chemotherapy, and osteoporosis medications were reported most often. At the baseline visit, 95 patients (95%) reported not currently receiving radiation at the targeted tumor; only 5 patients (5%) reported undergoing radiation in the target area previously.

Statistical Analysis

The primary objective was to achieve significant pain improvement, from baseline to 3 months, in patients treated with RF ablation for spinal metastases involving the thoracic and/or lumbar vertebral body/bodies. A minimum sample

Table 1. Patient and Tumor Characteristics

Characteristic	Value
No. of patients	100
Sex	
Female	56 (56)
Male	44 (44)
Age (y)	
Mean	64.6
Range	30–89
Primary cancer	
Lung	25 (25)
Breast	21 (21)
Kidney	10 (10)
Prostate	6 (6)
Colon, rectosigmoid	5 (5)
Liver	4 (4)
Lymph node	3 (3)
Endometrium	2 (2)
Pancreas	2 (2)
Skin	2 (2)
Bone	1 (1)
Gastrointestinal system	1 (1)
Thyroid	1 (1)
Noncancerous*	1 (1)
Other	16 (16)
Metastatic tumor location	
Thoracic	44 (44)
Lumbar	33 (33)
Lumbar and thoracic	10 (10)
Periacetabulum	4 (4)
Sacrum	3 (3)
Lumbar and iliac crest	2 (2)
Iliac crest	1 (1)
Sacrum and iliac crest	1 (1)
Lumbar and sacrum	1 (1)
Thoracic and sacrum	1 (1)
Current treatments at baseline[†]	
0	29 (29)
1	28 (28)
2	31 (31)
3/4	12 (12)
Type of treatment at baseline	
Osteoporosis medications	33 (33)
Chemotherapy	33 (33)
Steroids	29 (29)
Radiation treatment at baseline	
Yes	5 (5)
No	95 (95)

Note–Values in parentheses are percentages.
*Determined by biopsy after radiofrequency ablation.
[†]Before radiofrequency ablation.

size of 35 subjects completing the 3-month BPI worst pain assessment was required to demonstrate an improvement of ≥ 2 points. The results also include an expanded analysis

Table 2. Tumor Radiofrequency Procedure Characteristics

Characteristic	Value
Imaging guidance	
CT	16 (16)
Fluoroscopy	84 (84)
Anesthesia	
General	52 (52)
Local conscious sedation	30 (30)
Monitored anesthesia care	18 (18)
Procedure time (h)	
Mean	1.1
Range	0.3–3.1
Ablation sites per subject	
1 site	68 (68)
2 sites	30 (30)
3 sites*	2 (2)
Approach per ablation (134 ablations)	
Vertebral ablation	120
Bilateral (2 probes)	102 (85)
Unilateral (1 probe)	18 (15)
Other locations	14
1 probe	3 (21)
2 probes	7 (50)
3 probes	2 (14)
4 probes	2 (14)
Cement augmentation	
Yes	130 (97)
No	4 (3)
Technical success	134 (100)

Note–Values in parentheses are percentages.
*Deviations documented for treating 3 sites.

cohort by including subjects treated for metastatic tumors in the periacetabulum, iliac crest, and/or sacrum.

Change from baseline was tested: a Shapiro–Wilk test P value ≤ .05 prompted the use of a Wilcoxon signed-rank test; otherwise, a paired t test was used. For serial results over time, if any visit showed a Shapiro–Wilk P value ≤ .05, a Wilcoxon test was applied to all visits. The primary objective was examined for significance at the 0.05 level; remaining additional measures were examined at 0.0025 following post-hoc Bonferroni adjustment. Primary objective sensitivity analyses included the use of multiple imputation and last observation carried forward. SAS software (version 9.4; SAS, Cary, North Carolina) was used for all analyses.

The trial was designed by the principal investigators (S.B, J.L.) and the sponsor (Medtronic). The data were collected by the individual sites and analyzed by the sponsor. The first and last authors prepared the first draft, which was then reviewed and edited by the other coauthors.

RESULTS

Outcomes

Following RF ablation, patients experienced significant improvement in worst pain, average pain, pain interference,

Table 3. Clinical Outcomes Scores at Baseline through 6-Month Follow-up

Characteristic	Baseline (n = 100)	Day 3 (n = 94)	Week 1 (n = 89)	Month 1 (n = 64)	Month 3 (n = 46)	Month 6 (n = 22)
BPI worst pain						
Mean score ± SD	8.2 ± 1.7	5.6 ± 2.7	4.7 ± 2.9	3.9 ± 3.0	3.7 ± 2.9	3.5 ± 3.2
Median	8.0	5.0	5.0	4.0	3.0	3.0
P value (Wilcoxon)	–	< .0001	< .0001	< .0001	< .0001	< .0001
95% CI of change	–	–3.1 to –1.9	–3.9 to –2.7	–4.7 to –3.1	–5.1 to –3.1	–6.2 to –3.5
Subjects with ≥ 2-point change (%)	–	59	66	75	83	86
BPI average pain						
Mean score ± SD	6.0 ± 2.1	4.0 ± 2.3	3.3 ± 2.3	2.8 ± 2.2	2.8 ± 2.4	2.9 ± 2.5
Median	6.0	4.0	4.0	3.0	3.0	3.0
P value (Wilcoxon)	–	< .0001	< .0001	< .0001	< .0001	< .0001
95% CI of change	–	–2.5 to –1.4	–3.3 to –2.1	–3.4 to –2.1	–3.6 to –2.1	–4.4 to –2.1
Subjects with ≥ 2-point change (%)	–	51	62	67	74	77
BPI pain interference score						
Mean score ± SD	6.1 ± 2.3	4.1 ± 2.8	3.1 ± 2.7	2.9 ± 2.5	2.8 ± 2.7	2.5 ± 2.5
Median	6.0	3.9	2.4	2.6	2.1	1.3
P value (t test)	–	< .0001	< .0001	< .0001	< .0001	< .0001
95% CI of change	–	–2.4 to –1.4	–3.5 to –2.3	–3.5 to –2.2	–3.9 to –2.1	–4.7 to –2.6
EQ-5D index						
Mean score ± SD	0.48 ± 0.32	0.58 ± 0.33	0.64 ± 0.28	0.69 ± 0.21	0.66 ± 0.26	0.69 ± 0.24
Median	0.59	0.69	0.70	0.71	0.70	0.69
P value (Wilcoxon)	–	.0018	< .0001	< .0001	.0021	.0006
95% CI of change	–	0.03–0.15	0.10–0.21	0.10–0.24	0.05–0.25	0.09–0.34

Note–95% CIs are the 95% 2-sided CIs for the change from baseline.
BPI = Brief Pain Inventory; CI = confidence interval EQ-5D = European Quality of Life–Five Dimensions.

and quality of life. Before RF ablation, the mean score for worst pain was 8.2 (Table 3). After ablation, worst pain significantly improved, with mean scores decreasing to 5.6, 4.7, 3.9, 3.7, and 3.5 at 3 days, 1 week, 1 month, 3 months, and 6 months, respectively ($P < .0001$ for all visits; Fig 2). More than half of patients (59%) experienced immediate improvement, reporting a ≥ 2-point change in worst pain at the targeted treatment site(s) 3 days after ablation. Worst pain continued to improve, with approximately 75%, 83%, and 86% of patients reporting ≥ 2-point improvement at the 1-, 3-, and 6-month visits, respectively. The vertebral-treated subject subgroup included in the primary objective experienced a mean improvement in worst pain from 7.8 at baseline to 3.6 at 3 months ($P < .0001$; Table 4). To assess any impact of dropout on this result, 2 preplanned sensitivity analyses were performed. These confirmed that the change in pain from baseline to 3 months is robust to missing data, as the analyses demonstrated results consistent with those of only subjects with complete data.

Decreases in average pain were also observed. Before RF ablation, patients reported an average pain score of 6.0 (mean). Average pain score improved, with means reported as 4.0, 3.3, 2.8, 2.8, and 2.9 at 3 days, 1 week, 1 month, 3 months, and 6 months, respectively ($P < .0001$ for all visits). Three days after ablation, 51% of patients were considered to have a clinically relevant change in average

pain. This increased to 67% after 1 month and further increased to 77% at the 6-month visit.

Quality of life and pain interference with patient's functionality was also assessed before and after the procedure. The mean European Quality of Life index was 0.48 at baseline. Following RF ablation, it improved to 0.58, 0.64, 0.69, 0.66, and 0.69 at 3 days, 1 week, 1 month, 3 months, and 6 months, respectively, corresponding to respective mean changes (improvements) from baseline of +0.09, +0.15, +0.17, +0.15, and +0.21 ($P ≤ .003$ for all visits). The degree of pain interference with patient functionality per BPI showed improvement, with the mean degree of interference decreasing consistently over time after ablation from baseline (6.1) to 4.1, 3.1, 2.9, 2.8, and 2.5 at the respective scheduled follow-up visits ($P < .0001$ for all visits). Eighty-four subjects (84%) did not report receiving any radiation treatments at the targeted area after RF ablation. Data were collected on transdermal and/or oral narcotic agents taken 24 hours before each visit. Data were then converted into morphine equivalent dose. Mean oral morphine equivalent 24-hour dose for all treated subjects at baseline was 61.0 mg, and it decreased to 50.4 mg at the 3-month visit.

Four AEs were reported, of which 2 resulted in hospitalization for pneumonia and respiratory failure, respectively. Thirty deaths were reported during the course of the study, with 29 through the 6-month visit. All deaths were
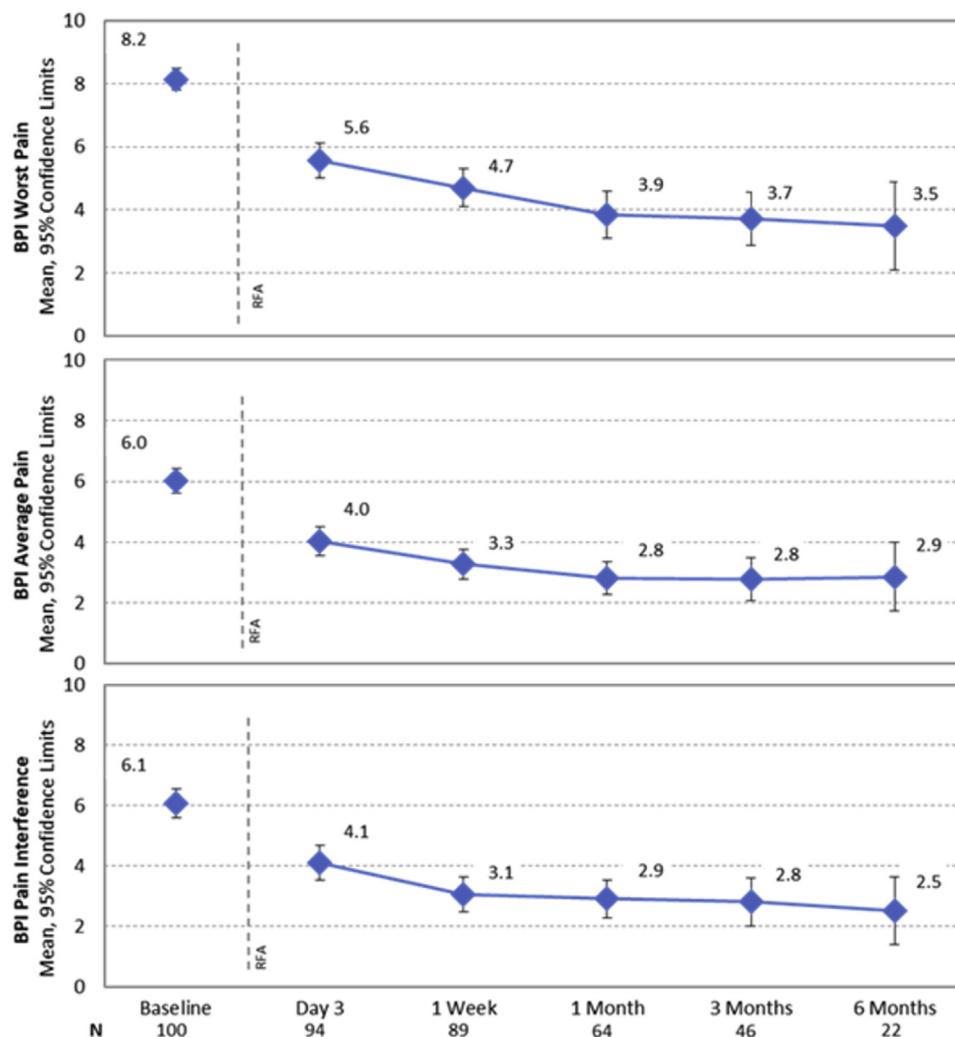
Figure 2. BPI scores for worst pain, average pain, and pain interference. Change from baseline is significant at all time points ($P < .0001$) for all 3 measures.

classified by the clinical events committee and investigator to be attributed to underlying malignancy and not related to RF ablation.

DISCUSSION

The primary analysis of the prospective OPuS One Study shows rapid and significant pain improvement at 3 days after RF ablation and sustained significant long-term relief through 6 months in patients with metastatic bone disease treated in real-world settings. The results also show significantly improved quality of life and significantly increased function in patients with painful bone metastasis. The rapid and sustained pain-relief results after treatment with the RF ablation system were clinically impactful given the advanced disease state of this cohort of patients.

Three days after the ablation procedure, more than half of patients experienced clinically relevant improvement with a minimum 2-point decrease in worst pain score. Patients continued to have substantial pain improvement, with

approximately 75% experiencing clinically relevant improvement at 1 month and more than 85% at 6 months. Average pain also showed consistent significant improvement over time. Quality of life and the degree of pain interference with daily activities improved significantly compared with before ablation.

External-beam radiation therapy is the current standard of care for the treatment of bone metastases. Although radiation therapy is noninvasive, it has several important limitations (22). Pain relief with external-beam radiation therapy can take as long as 4–6 weeks after treatment completion, and pain response rates are estimated at 60% (3,23). Although the use of stereotactic body radiation therapy has increased, especially in oligometastatic disease, radiation-induced vertebral compression fractures are reported in 11%–39% of cases (24). Because of tissue tolerance, there is also a potential inability to repeat radiation therapy at the same site if the pain persists (12). The present study is unique, as the majority of patients reported no previous radiation at the treated site at baseline. Given the radiation-

Table 4. Primary Objective: Change in Worst Pain at 3 Months for Vertebral Subjects

Analysis Method	N	Mean		Change		P Value (*t* test)
		Baseline	Month 3	Mean	95% CI	
Primary (completers)	42	7.8	3.6	–4.1	–5.2 to –3.1	< .0001
Sensitivity analyses (including imputation)						
Multiple imputation	69	8.1	3.8	–4.4	–5.3 to –3.5	< .0001
LOCF	69	8.1	4.3	–3.8	–4.7 to –3.0	< .0001

Note–Subject count included in the sensitivity analyses is less than the total treated because some subjects were treated outside of the vertebral body/bodies or had inadequate follow-up (< 3 mo since treatment) at the time of primary objective assessment.
CI = confidence interval; LOCF = last observation carried forward.

naivety of this cohort of patients at baseline, the results indicate that the effects of pain relief can be attributed to the study procedure. Forty-six percent of patients had metastatic lung or breast cancer, which is typically radiation-sensitive, but patients in this study experienced clinically impactful pain relief quickly, within 3 days after RF ablation. Other RF ablation studies were limited in their evaluation of pain response by the confounding variable of previous radiation treatment ([16],[25]). In addition, in the present study, only 16% of patients received radiation at the ablation site after RF ablation.

No postprocedural fractures at the ablation site(s) were reported in this study, suggesting that RF ablation with PMMA augmentation can address biologic pain while protecting against future mechanical failures. This study did not have any symptomatic PMMA leakage complications that have been previously reported in other studies ([26]). Four AEs were reported, with 2 resulting in hospitalization for pneumonia and respiratory failure, respectively. All 30 deaths reported during the study were classified by the independent clinical events committee and investigators as not related to the RF ablation procedure, therapy, or device and attributed to the natural progression of the disease.

The limitations of the present study include the difficulty to discern the impact of RF ablation alone as a result of the use of PMMA augmentation. The study of Berenson et al ([11]) previously demonstrated that kyphoplasty alone can improve pain control in patients with cancer with painful compression fractures at 1 month and maybe as early as 1 week. The potential combined benefit of tumor ablation for biologic pain and prevention of delayed skeletal events with the administration of PMMA for mechanical stabilization and mechanical pain was likely complementary. This becomes more important in the patient population of the present study, given that the inclusion criteria included predominantly axial weight-loading bones, thoracolumbar spine, and periacetabular locations, where mechanical stabilization is crucial. For those reasons, it is unlikely that these 2 therapies will ever be studied separately in the same prospective trial. Additionally, the use of only oral and transdermal narcotic agents was collected; intravenous administration of narcotic agents was not collected, which could confound the study results. In the authors' opinion,

given that intravenous narcotic agents are more likely to be given in an inpatient setting and follow-up was predominantly on an outpatient basis, this might suggest that the pain reduction could have actually been underestimated. Finally, the high mortality rate in this cohort (30%, with 16 of 30 dying before the 1-mo visit) implies that RF ablation was provided as palliative treatment at the end of the care continuum, with more severe symptoms, rather than earlier in therapy, when recurrence or disease progression may be more likely. The high mortality rate in the present cohort (30%) is comparable to the high mortality rate previously reported (> 20% at 6 mo) for patients undergoing surgical treatment for cancer-associated compression fractures ([11]).

In conclusion, considering the rapid and long-lasting significant pain relief and high degree of safety shown in the present study, RF ablation of axial skeletal metastases is a viable treatment option. As suggested by more recent multidisciplinary guidelines, RF ablation with cementoplasty has become one of the ideal treatment modalities that may be performed alone or in combination with radiation therapy in the treatment of metastatic bone disease. Consideration of this therapy sooner in the care continuum to maximize its palliative benefits in metastatic bone disease is a potential future direction. Other future studies could be targeted to imaging-based local tumor control assessment, comparison of tumor reduction with and without adjunctive external-beam radiation therapy, and potential for reduction in fractures versus radiation therapy alone.

ACKNOWLEDGMENTS

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