Solitary Painful Osseous Metastases: Correlation of Imaging Features with Pain Palliation after Radiofrequency Ablation—A Multicenter American College of Radiology Imaging Network Study¹

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Purpose:

To identify the correlation of pre- and postablation imaging features with pain relief, pain intensity, and patient mood after radiofrequency (RF) ablation of solitary painful osseous metastases.

Materials and Methods:

This prospective, multicenter group trial was approved by each institutional review board. Participants were enrolled between November 1, 2001, and April 6, 2006. Written informed consent was obtained from all subjects, and patient confidentiality protocols were followed in compliance with HIPAA. Computed tomography (CT)-guided RF ablation and contrast material-enhanced 1-month follow-up CT and/or magnetic resonance imaging were performed in 49 subjects (24 men, 25 women; age range, 34–83 years) with a confirmed malignant solitary bone lesion of maximum dimension of 8 cm or smaller that was causing intractable pain. Pain intensity and patient mood were measured before and after RF ablation. Tumor imaging features were recorded. Unadjusted and adjusted linear mixed-effects models, with a random intercept for each subject, were used to model patient mood, pain relief, and pain intensity scores at three times after ablation as a function of each tumor characteristic.

Results:

Decreased postablation tumor pain correlated with preablation tumor volume ($P = .02$) and pathologic fracture ($P = .01$), while pain relief correlated with pathologic fracture ($P = .03$) and percentage of bone-tumor interface (BTI) ablated ($P = .02$). Conversely, presence of an irregular rim after ablation ($P = .02$) and rim thickness ($P = .01$) correlated with increased pain. There was no evidence in this study that RF ablation of larger tumor percentage or larger volume leads to better pain relief or decreased pain ($P > .05$).

Conclusion:

Existing pathologic fracture and smaller tumor size appear to be predictive parameters of success when selecting patients for palliative RF ablation of painful solitary osseous metastases. Successful palliation also appears to be related to the percentage of BTI ablated.

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Bone is the third most common site of metastasis, and metastases from almost all primary anatomic cancer sites have been identified in bone at autopsy (1). Pain from osseous metastases remains refractory to treatment in many cases, despite a persistent attempt to develop a method of reliable analgesia over the past 40 years (2–9). Recent comprehensive reviews detail the current understanding of bone cancer pain pathophysiology (10,11), as well as the pharmacologic, hormonal, radiotherapeutic, radiopharmaceutical, and interventional treatment options currently used to treat such pain (12). The effectiveness and safety of image-guided percutaneous radiofrequency (RF) ablation as a treatment option for painful osseous metastases has been established (9,13–15), but the imaging features associated with successful palliation have not been reported. The purpose of this study was to identify the correlation of pre- and postablation imaging features with pain relief, pain intensity, and patient mood after RF ablation of solitary painful osseous metastases.

Materials and Methods

Study Design

This prospective study was performed as part of a cooperative, multicenter, group

Advances in Knowledge

- Radiofrequency (RF) ablation reduces absolute pain from solitary painful osseous metastases, with pain reduction proportional to decreasing tumor size ($P < .01$); also, in patients with pathologic fracture, it reduces absolute pain ($P = .01$) and leads to subjective patient pain relief, as measured on a visual analog scale ($P = .03$).
- RF ablation leads to better pain relief from solitary painful osseous metastases, as a larger proportion of the bone-tumor interface (BTI) is ablated ($P = .02$).
- There is no evidence in this study that either ablation volume or percentage of tumor ablated is related to reduction of pain from a solitary osseous metastasis ($P > .05$).

trial of the American College of Radiology Imaging Network (ACRIN). The study was approved by each institutional review board, and written informed consent was obtained from all subjects according to institutional and federal guidelines. Patient confidentiality protocols were followed in compliance with the Health Insurance Portability and Accountability Act.

Sixty-six participants were enrolled at nine study sites (range, 1–27 participants per site) between November 1, 2001, and April 6, 2006. Participant demographics are provided in Table 1. One radiologist investigator was located at each site and had performed at least 10 RF ablation procedures and 10 computed tomography (CT)-guided biopsy procedures prior to study commencement. The RF generator and perfusion pump (CC-1; Covidien, Boulder, Colo) and a single 17-gauge electrode or cluster electrode, both from the same manufacturer (Cool-tip; Covidien), with variable lengths (15 cm and 20 cm) and tip exposure of 1–3 mm for the single electrode and 2.5 cm for the cluster electrode were used for all RF ablation procedures. Each investigator had performed at least one prior ablation with the Covidien device used in this protocol.

Safety and effectiveness have been reported previously (15). Our study was performed by one of the investigating radiologists (D.E.D.) and by a medical student radiology researcher (J.P.G.). The data were controlled by ACRIN, and the investigators were blinded to the data.

Enrollment Criteria

Subject selection was performed as reported previously by Dupuy et al (15).

Implications for Patient Care

- RF ablation of solitary painful bone metastases for palliation should be prioritized in patients with existing pathologic fractures and smaller tumors.
- RF probe placement for palliative ablation of solitary painful bone metastases should be targeted for maximum possible ablation of the BTI.

Briefly, participants were required to have histologically or cytologically confirmed malignant disease and a single bone lesion of maximum dimension of 8 cm or smaller. The bone lesion was required to have features of metastatic disease (a new lesion with evidence of osteoblastic, osteolytic, or mixed changes), cause persistent and intractable pain despite active treatment with narcotics, and be eligible for RF ablation with a percutaneous CT-guided approach. Patients had to be cognitively intact.

Treatment with bisphosphonates or radiation therapy (radionuclide or external beam) was not a reason for study exclusion, but participants could not have undergone radiation treatment within 30 days of RF ablation or have been scheduled for concurrent treatment with external-beam radiation or radioisotopes. Bisphosphonates were allowed because they are standard treatment for certain primary cancers to prevent bone osteolysis and thus may help to maintain the hydroxyapatite matrix and prevent pathologic fracture in the setting of thermal bone injury secondary to tumor ablation. Radiation therapy was allowed after 30 days so that patients who were not

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Abbreviations:

ACRIN = American College of Radiology Imaging Network

BTI = bone-tumor interface

RF = radiofrequency

Author contributions:

Guarantors of integrity of entire study, J.P.G., E.K., D.E.D.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, J.P.G., D.E.D.; clinical studies, J.P.G., D.E.D.; experimental studies, D.E.D.; statistical analysis, M.J.L., E.K.; and manuscript editing, all authors

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Conflicts of interest are listed at the end of this article.

responsive to ablation could receive alternate palliative treatment.

Chemotherapy was not allowed within 14 days prior to or after the RF ablation procedure so that chemotherapy-related effects on subject mood and pain would not confound procedure-related mood and pain changes. Chemotherapy was allowed after 14 days because it tends not to improve cancer pain and would not confound tumor pain data.

Adequate 1-month follow-up images were required for inclusion in this imaging assessment study, but, given the high mortality rates and limited number of patients with 3-month follow-up images, 3-month images were not required for inclusion.

Methods of Tumor Ablation and Follow-up Imaging

RF ablation and follow-up imaging were performed at nine study sites by nine experienced radiologists (one at each site), as reported previously by Dupuy et al (15), the pertinent aspects of which are concisely reported again here. Per the study protocol, tumors at least 4 cm in greatest dimension were treated with a cluster RF electrode, while tumors smaller than 4 cm were treated with a single RF electrode. When possible, the electrode was inserted parallel to the longitudinal axis of the tumor, and the tip of the electrode was positioned against the deepest margin of the tumor. Conscious sedation (with midazolam and fentanyl [Abbott Laboratories, North Chicago, Ill]) was the preferred method of anesthesia; however, general endotracheal anesthesia was permitted when tumors were not located within 3 cm of a major neurovascular bundle, when deemed clinically appropriate by the site investigator.

Preprocedural nonenhanced and/or contrast material-enhanced CT and/or fluoroscopic CT was performed, along with follow-up contrast-enhanced CT and/or magnetic resonance (MR) imaging at 1 and 3 months. For contrast-enhanced CT, an appropriate field of view was chosen to include at least the entire affected region after acquisition of digital scout localizer images. CT images were obtained with 120 kVp, 230 mA, and 5-mm-thick collimation 1 minute

Table 1

Cohort Selection and Characteristics

Parameter	Datum
No. of enrolled participants	66
No. of ineligible participants	6
No. with primary bone cancer	2
No. with chemotherapy administered within 14 days of RF ablation	2
No. with ibuprofen taken within 24 h of RF ablation	1
No. with radiation to the RF ablation site administered within 30 d of RF ablation	1
No. of participants that did not complete RF ablation or pain assessment questionnaire	11
RF ablation not performed, as patient was medically unstable	3
RF ablation stopped for intractable pain	1
RF ablation stopped due to electrocardiogram changes	1
No. of participants who underwent RF ablation	49
No. who did not complete enough imaging for study	14
No. who had no follow-up images	1
No. who had no contrast-enhanced 1-mo images	9
No. who had only 3-mo images	2
No. who had images of uninterpretable quality	1
No. who had follow-up images with inadequate anatomic coverage	1
No. who did not complete adequate pain assessment follow-up for study	3
No. of participants who had initial images, 1-mo contrast-enhanced follow-up images, and corresponding pain scores	32
No. who had both contrast-enhanced 1- and 3-mo images	18
No. who had only contrast-enhanced 1-mo images	13
No. who had 1-mo images with and 3-mo images without contrast enhancement	1
No. of men	24
No. of women	25
Median age of all participants (y)*	62 (34–83)
Median age of men (y)*	59 (44–83)
Median age of women (y)*	66 (34–80)
Primary cancer location†	
No. with prostate cancer	2 (4)
No. with breast cancer	3 (6)
No. with lung cancer	16 (33)
No. with colon cancer	9 (18)
No. with kidney cancer	9 (18)
No. with other cancers	10 (20)
Cancers classified according to tumor region†	
No. with cancers in pelvis	20 (41)
No. with cancers in spine	6 (12)
No. with cancers in chest wall	17 (35)
No. with cancers in an extremity	6 (12)

* Numbers in parentheses are ranges.

† Numbers in parentheses are percentages.

after the intravenous infusion of 130 mL of 60% nonionic iodinated contrast medium (Omnipaque; GE Healthcare, Shanghai, China) by using a power injector (Medrad, Indianola, Pa) at the rate of 1 mL/sec. The CT sections were acquired in standard bone (eg, window width, 2000 HU; window level, 350 HU)

and soft-tissue (eg, window width, 500 HU; window level, 50 HU) windows. Dilute oral contrast material (750 mL) was administered 3 to 4 hours prior to all follow-up imaging when a metastasis was known to be located near hollow viscera. MR imaging was performed with a rapid low-spatial-resolution localizer sequence

Figure 1: CT images acquired in an 80-year-old woman with a solitary painful thoracic spine metastasis. **(a–c)** Axial contrast-enhanced supine CT images acquired in soft-tissue windows. **(a)** Preablation scan shows $4.2 \times 6.0 \times 6.0$ -cm mass (arrows); **(b)** 1-month follow-up scan shows ablation zone (arrows) and reactive tissue rim (arrowheads); **(c)** 3-month follow-up scan shows complete ablation (arrows) with evidence of contraction. **(d, e)** Axial contrast-enhanced supine 8-year follow-up CT scans (obtained after study completion) show **(d)** complete ablation (arrows) with further contraction and radiation fibrosis (arrowheads) in soft-tissue windows and **(e)** dysmorphic bone changes with tumor mineralization (arrows) in bone windows.

used to identify the region of interest. Axial and longitudinal T1-weighted sequences (repetition time msec/echo time msec, 300–600/10–20) were performed before and at least 5 minutes after the intravenous administration of 10 mL of gadolinium-based contrast material. A local coil was used for extremity imaging, and a body coil was used for imaging of the pelvis, hip, chest wall, and spine. Fat saturation was performed for the T1-weighted gadolinium-enhanced images. The section thickness was no wider than 5 mm, with no more than a 1-mm gap between sections. Axial and longitudinal fast spin-echo T2-weighted images (2000–3000/30–80) were also obtained.

The number of phase-encoding steps was 192–256, with at least two excitations for both T1- and T2-weighted images. Individual sites were allowed to perform short inversion time inversion-recovery sequences instead of T2-weighted imaging for extremities.

Methods of Imaging Assessments

On preprocedural images, maximum tumor size was measured in the anteroposterior, transverse, and craniocaudal directions. Tumor volume was calculated with a prolate ellipse equation as the product of the anteroposterior, transverse, and craniocaudal measurements and 0.52, the ellipsoid volume

conversion factor. The bone-tumor interface (BTI) was measured in two ways: For tumors in bones with relatively large radii, such as in vertebrae, the ilium, and the ischium, the longest linear measurement of bone involvement in the anteroposterior, transverse, and craniocaudal directions was used; for tumors in bones with relatively small radii, such as ribs, the BTI was calculated with the Pythagorean theorem by approximating the bone curve in the axial plane and measuring the craniocaudal bone involvement. Distances to major neurovascular bundles (arteries larger than 3 mm in diameter) within 2 cm were measured, and pathologic fractures were noted.

On 1- and 3-month follow-up images (Figs 1, 2), maximum tumor size was measured in the anteroposterior,

transverse, and craniocaudal planes. Areas of rim enhancement, which could indicate either residual tumor or inflammatory response, and areas of ablation were included in these measurements. Tumor volume and BTI were calculated as described earlier, distances to major neurovascular bundles within 2 cm were measured, and pathologic fractures were noted. In addition, for images obtained with contrast material, maximum ablation zone size was measured in the anteroposterior, transverse, and craniocaudal directions. Ablation zone volume was calculated in the same manner as tumor volume, as described earlier. Percentage of tumor ablated was calculated as the ratio of ablation zone volume to tumor volume. Percentage of BTI covered was assessed visually as 0%–24%, 25%–49%, 50%–74%, 75%–99%, or 100%, and a binary cutoff of 75% or greater (“yes” or “no”) was used in our models. Whenever an enhancing rim was present, its maximum width was measured, and it was noted whether the rim was regular, with the same diameter circumferentially in all planes, or irregular. It was also noted if the ablation zone encompassed previously identified nearby neurovascular bundles. General tumor progression and tumor progression at the BTI were both assessed visually as either present or absent. Pain assessment was measured before and after RF ablation by using a visual analog scale (16), as reported previously by Dupuy et al (15).

All images and imaging findings were reviewed independently by a researcher (J.P.G.), with more than 3 years of cross-sectional radiology research experience, and by a board-certified radiologist (D.E.D.), with more than 20 years of experience.

Statistical Analysis

Patient-perceived pain relief relative to preablation pain level, tumor pain intensity, and mood were measured each day for days 1–14 and at roughly 1 and 3 months after RF ablation with a visual analog scale (16), as reported previously by Dupuy et al (15). Pain was also measured on a scale of one to eight by using

Figure 2

Figure 2: Images in a 70-year-old man with a painful metastasis in the right ilium. **(a)** Axial contrast-enhanced supine CT scan acquired in soft-tissue windows shows $3.6 \times 5.1 \times 5.6$ -cm mass (arrows) less than 2.0 cm from the internal iliac neurovascular bundle (arrowheads). **(b)** Axial fluoroscopic CT scan obtained during RF ablation shows a cluster RF electrode (arrow) placed appropriately in the mass. **(c)** Axial contrast-enhanced 1-month follow-up supine CT scan obtained in soft-tissue windows shows the ablation zone at the BTI (arrow) and tumor progression (arrowheads). **(d)** Axial contrast-enhanced 3-month follow-up CT scan obtained in soft-tissue windows shows the ablation zone at the BTI and tumor progression (arrowheads).

a modified Memorial Pain Assessment Card, but those data were not used in our analysis for the present study to maintain consistency in the outcome measurement scales. Because the primary outcomes were palliation measurements at 1 and 3 months after RF ablation and because of strong correlations

between an individual's measurements on days 1–14, each subject's outcomes between days 1 and 14 were averaged and treated as one time. Patient mood, pain relief, and pain intensity at time 1 (mean of days 1–14), time 2 (month 1), and time 3 (month 3) were fit on each pre-RF ablation variable. Mood, pain

relief, and pain intensity at time 2 and time 3 were fit on each post-RF ablation variable, adjusting for time 1 outcome.

Two linear mixed-effects models (17) were considered, both with random subject-specific intercepts to account for within-subject correlation. The first model adjusts for imaging feature and time only, while the second allows the addition of fixed effects for Eastern Cooperative Oncology Group score, narcotics level, ablation site, and patient age (hereafter referred to as tumor and patient characteristics), all previously found to be significant with these outcomes (15). Because the intent of this study was to evaluate the relationship between the outcomes and imaging features, investigating the changes in scores over time (ie, time effect) was not a main focus. In the linear mixed-effects models, time was included as a categorical covariate, with fixed effects for times 1, 2, and 3 by using a first-order autoregressive covariance structure. The small sample size requires that a simpler covariance structure be used here, although we note that with uneven time intervals, other options may be preferred. Other models were attempted, including ones that treat time as being continuous, with linear and quadratic terms for time with an unstructured correlation structure. However, the maximum likelihood iteration for these models did not converge, probably because of the small sample size.

Use of spaghetti plots and the Akaike information criterion statistic led us to choose a first-order autoregressive covariance structure for mood and pain relief scores and an unstructured matrix for pain intensity scores. The significance level was set at .05. All statistical analyses were conducted by using software (SAS, version 9.3; SAS Institute, Cary, NC).

Results

Table 2 shows the estimated coefficients (and standard errors) of the estimated effect of pre-RF ablation features on pain outcomes, several of which correlate significantly with improved mood, pain relief, and pain intensity. Tumor volume correlates significantly with

decreased pain ($P < .01$) in that greater pain relief tends to be achieved as tumor size decreases. Preablation pathologic fracture correlated significantly with pain relief ($P = .03$) and with decreased pain ($P = .01$ with and $P = .03$ without adjustment for tumor and patient characteristics). Ablation of tumors that had a border within 2 cm of a major neurovascular bundle correlated significantly with improved mood after ablation ($P = .02$). Ablation of tumors with a border within 2 cm of a major neurovascular bundle also appeared to possibly correlate positively with pain relief ($P = .08$). The distance between the metastases and a major neurovascular bundle was close enough to be measured in 20 subjects. Among those subjects, increases in distance from the neurovascular bundle are associated with significantly improved mood ($P = .02$) and decreased pain ($P = .01$) after adjustment for tumor and patient characteristics.

Table 3 shows the estimated coefficients (and standard errors) of the estimated effect of 1-month post-RF ablation features on pain outcomes. Percentage of BTI ablated correlated significantly with pain relief ($P = .04$ with and $P = .02$ without adjustment for tumor and patient characteristics), in that greater pain relief tended to be achieved with higher percentage of BTI ablation. Presence of a rim correlated significantly with improved mood ($P = .04$), while rim thickness correlated significantly with worsened mood ($P = .03$), and presence of an irregular rim correlated significantly with increased pain ($P = .03$ without and $P = .02$ with adjustments for tumor and patient characteristics). Progression of tumor correlated significantly with improved mood ($P = .01$).

Discussion

The percutaneous thermal ablation of bone metastases has developed only over the past decade and, while very little has been published to date, the limited available data are promising. The safety and effectiveness of RF ablation for the palliation of painful bone metastases has been demonstrated

in two multicenter studies, one with 43 participants from nine sites in the United States and Europe (13), and another, a precursor to our study, with 66 participants from nine sites in the United States (15). In a more recent multicenter clinical trial (18) of 61 subjects with one or two painful bone metastases, the researchers demonstrated the safety and effectiveness of cryoablation for the palliation of painful bone metastases. Cryoablation has also recently been shown to be safe and effective in the treatment of limited musculoskeletal metastases for local tumor control and short-term complete remission (19). Additional case studies and small series have been published and are addressed in a comprehensive review by Rosenthal and Callstrom (20). To our knowledge, only safety and effectiveness data have been published to date, and the present study is the first to address the association of imaging features with palliative outcomes. These data are important not only for improved patient selection, but also for procedural planning, both of which are essential for optimization of clinical outcomes.

Our study results suggest that several preablation imaging features may be used as predictive parameters of success when selecting patients for palliative RF ablation of painful solitary osseous metastases. Our study findings also suggest, through the analysis of postablation imaging features, that certain procedural strategies may increase effectiveness and improve outcomes of palliative RF ablation.

The pathophysiology of bone tumor pain is only partially understood and appears to be multifactorial. Proton stimulation of nociceptors due to an acidic microenvironment created by increased osteoclast activity and tumor cell lysis is a likely component (21). Hyperalgesia and allodynia appear to be caused by tumor and/or macrophage release of nociceptive factors, including bradykinin, adenosine triphosphate, and nerve growth factor (21–24). There may be a neuropathic component from the destruction of distal processes of sensory fibers that innervate tumor-replaced mineralized bone and marrow

Table 2

Relationship between Preablation Features and Visual Analog Pain Outcomes by Using Linear Mixed-Effects Models

Feature	Patient Mood		Pain Relief		Pain Intensity	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Tumor volume	−0.01 (0.03)	−0.02 (0.03)	−0.02 (0.04)	−0.05 (0.04)	0.08 (0.04)*	0.10 (0.04)†
BTI	0.51 (0.77)	0.21 (0.84)	0.02 (0.99)	−1.46 (1.04)	0.89 (0.99)	1.70 (1.03)
Pathologic fracture (yes vs no)	−0.25 (4.52)	−1.41 (4.66)	12.45 (5.49)‡	11.21 (5.63)*	−14.03 (5.36)‡	−12.60 (5.51)‡
Within 2 cm of a neurovascular bundle (yes vs no)	5.78 (4.20)	12.35 (5.14)‡	1.22 (5.45)	11.95 (6.65)*	−6.05 (5.35)	−8.61 (6.86)
Distance to neurovascular bundle	12.10 (6.30)*	16.35 (5.82)‡	6.20 (8.80)	14.08 (7.60)*	−6.07 (5.60)	−8.35 (2.41)†

Note.—Data are coefficients for each preablation feature, and numbers in parentheses are standard errors. Model 1 is adjusted for time and pre-RF ablation score; model 2 is adjusted for time, pre-RF ablation score, and tumor and patient characteristics. BTI and distance to neurovascular bundle were measured in centimeters.

* P value was between .05 and .1.

† P value was less than .01.

‡ P value was between .01 and .05.

Table 3

Relationship between Postablation Features and Visual Analog Pain Outcomes by Using Linear Mixed-Effects Models

Feature	Patient Mood		Pain Relief		Pain Intensity	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Ablation volume	0.11 (0.08)	0.07 (0.09)	0.15 (0.10)	0.13 (0.11)	0.10 (0.09)	0.06 (0.10)
Percentage of tumor ablated	−0.11 (0.11)	−0.21 (0.11)*	−0.01 (0.14)	−0.04 (0.14)	−0.03 (0.12)	−0.12 (0.12)
75% of the BTI ablated (yes vs no)	6.40 (6.47)	1.57 (7.96)	22.20 (9.01)†	22.97 (8.88)†	8.46 (8.81)	4.95 (8.55)
Rim presence (yes vs no)	9.52 (7.11)	13.49 (6.29)†	4.37 (8.92)	7.77 (8.31)	11.33 (7.43)	12.71 (6.88)*
Rim thickness (mm)	−6.09 (2.68)†	−3.69 (3.23)	−5.16 (4.06)	−6.44 (5.59)	4.24 (2.45)*	1.13 (1.68)
Rim enhancement (yes vs no)	6.03 (6.97)	10.62 (6.26)	3.57 (8.73)	7.98 (8.27)	6.92 (7.51)	9.73 (6.81)
Rim irregular (yes vs no)	5.01 (7.15)	10.33 (6.44)	0.77 (8.59)	2.93 (8.08)	14.82 (6.74)*	15.83 (5.96)†
Within 2 cm of a neurovascular bundle (yes vs no)	−0.84 (9.99)	−7.67 (12.10)	−1.41 (12.22)	−9.90 (14.40)	−14.10 (10.74)*	−10.77 (14.58)
Tumor progression (yes vs no)	5.55 (6.74)	18.61 (6.51)†	6.62 (8.45)	13.51 (9.11)	5.16 (7.53)	12.57 (8.43)
BTI tumor progression (yes vs no)	−9.16 (8.03)	−2.05 (9.53)	5.59 (10.49)	11.32 (12.36)	2.92 (9.10)	16.27 (10.87)

Note.—Data are coefficients for each postablation feature, and numbers in parentheses are standard errors. Model 1 was adjusted for time, pre-RF ablation score, and pain outcome at time 1; model 2 was adjusted for time, pre-RF ablation score, tumor and patient characteristics, and pain outcome at time 1.

* P value was between .05 and .1.

† P value was between .01 and .05.

(24,25). It is also postulated that mechanical stress and fracture trigger mechanosensitive sensory fibers (10), potentially in the relatively highly innervated periosteum. Most notable is that cancer-induced pain is a distinct entity, with different neurochemical findings in the dorsal and ventral horns than those of pain from inflammatory and neuropathic processes, possibly caused by spinal astrocyte hypertrophy (26). Cancer-induced pain creates a hyperexcitable state within the spine that appears to be related to dorsal horn neuron changes not seen in inflammation or neuropathy (27).

Given the apparent multifactorial nature of bone cancer pain, it is not surprising that individual pharmaceutical and radiopharmaceutical interventions are of limited utility. One of the highlights of RF ablation may be that it can break multiple cancer-pain pathways. In an early feasibility study for RF ablation treatment of bone pain, it was hypothesized that mechanisms leading to successful analgesia include ablation of nerves in the periosteum and cortex, decompression of nerves resulting from tumor volume reduction, destruction of cytokine-secreting tumor cells, and inhibition of osteoclast activity (9).

Given the lack of correlation between ablation volume and outcomes in this study, along with the scientific evidence for extratumoral genesis of pain, decompression of nerves resulting from volume reduction is not a likely component of RF ablation effectiveness in larger tumors but may be involved in smaller tumors, as was shown previously (15). Ablation of nerves in the periosteum, cortex, and bone marrow may play a role, particularly in eliminating the neuropathic pain component caused by tumor-induced injury of sensory fibers, but such ablation could also be expected to produce a component of

neuropathic pain itself. Given the apparent role of cytokine-induced hyperalgesia and allodynia, RF ablation denaturation of cytokines and destruction of cytokine-producing tumor cells and macrophages would eliminate a cause of nociceptor excitement and is a likely component of RF ablation analgesia. Similarly, destruction of acid-producing osteoclasts and tumor cells with reduction in the acidity of the microenvironment is also a likely component. Given these proposed mechanisms of analgesia, it is curious that ablation volume does not correlate with outcomes in this study, but the lack of correlation may be attributable to the general lack of intratumoral nerve fibers, a hypothesis supported by the correlation of both percentage of BTI ablated and preablation pathologic fracture with postablation pain relief, which suggests that pain primarily originates in the region of destroyed bone. A postmortem study on the assessment of the dorsal and ventral horn neurochemistry of patients who had undergone successful palliative RF ablation for solitary bone metastasis would be of great interest in assessing whether RF ablation may reverse the hyperexcitable and hyperanalgesic state induced by bone cancer pain.

There were several limitations to this study, primarily related to sample size. As RF ablation for palliation of pain related to osseous metastases was experimental, only 66 participants were enrolled. The analyzed sample was further reduced to 32 because many of the participating subjects had terminal disseminated disease that resulted in death prior to study completion, because comorbidities in several patients resulted in an inability to administer intravenous contrast material, and because of other unforeseeable complications in care. This percentage of patient dropout is not unusual for palliative studies and is similar to that of other published studies of metastatic bone pain palliation (13,28), and it limited our statistical power. In addition, because of the small sample size, the distribution of tumor biology may not be representative of the general population with osseous

metastases, which possibly affects the generalizability of this study. The heterogeneity of primary tumor biology may also affect our results, and the results may vary according to tumor type. Finally, even though the image reviews were blinded to patient outcomes, the images in this study were reviewed by one board-certified radiologist and a radiology researcher, as opposed to two board-certified radiologists. Further studies are recommended to increase power and generalizability.

In summary, existing pathologic fracture and smaller tumor size appear to be predictive parameters of success when selecting patients for palliative RF ablation of painful solitary osseous metastases. Moreover, successful analgesia appears to be related to the percentage of the BTI ablated and not to the overall ablation volume. Not surprisingly, tumors that advance at the ablation site are not associated with adequate analgesia. We thus recommend prioritizing treatment for patients with existing pathologic fractures and smaller tumors, with RF electrode placement targeted for maximum possible ablation of the BTI.

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