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Magnetic Resonance–Guided Focused Ultrasound for Patients With Painful Bone Metastases: Phase III Trial Results

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Background Pain due to bone metastases is a common cause of cancer-related morbidity, with few options available for patients refractory to medical therapies and who do not respond to radiation therapy. This study assessed the safety and efficacy of magnetic resonance-guided focused ultrasound surgery (MRgFUS), a noninvasive method of thermal tissue ablation for palliation of pain due to bone metastases.

Methods Patients with painful bone metastases were randomly assigned 3:1 to receive MRgFUS sonication or placebo. The primary endpoint was improvement in self-reported pain score without increase of pain medication 3 months after treatment and was analyzed by Fisher's exact test. Components of the response composite, Numerical Rating Scale for pain (NRS) and morphine equivalent daily dose intake, were analyzed by *t* test and Wilcoxon rank-sum test, respectively. Brief Pain Inventory (BPI-QoL), a measure of functional interference of pain on quality of life, was compared between MRgFUS and placebo by *t* test. Statistical tests were two-sided.

Results One hundred forty-seven subjects were enrolled, with 112 and 35 randomly assigned to MRgFUS and placebo treatments, respectively. Response rate for the primary endpoint was 64.3% in the MRgFUS arm and 20.0% in the placebo arm ($P < .001$). MRgFUS was also superior to placebo at 3 months on the secondary endpoints assessing worst score NRS ($P < .001$) and the BPI-QoL ($P < .001$). The most common treatment-related adverse event (AE) was sonication pain, which occurred in 32.1% of MRgFUS patients. Two patients had pathological fractures, one patient had third-degree skin burn, and one patient suffered from neuropathy. Overall 60.3% of all AEs resolved on the treatment day.

Conclusions This multicenter phase III trial demonstrated that MRgFUS is a safe and effective, noninvasive treatment for alleviating pain resulting from bone metastases in patients that have failed standard treatments.

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Bone metastases are common in patients with advanced cancer and are the greatest contributor to cancer-related pain, often severely affecting quality of life (1,2). Many patients with advanced cancer are undertreated for pain (3,4). Radiation therapy (RT), together with systemic therapies and analgesics, is the standard of care for localized metastatic bone pain, although up to two-thirds of patients have residual pain after RT (5,6), leaving them with limited treatment options. These include reirradiation, which results in temporary pain reduction in some patients (7), surgical intervention (8), and percutaneous cryoablation (9). More effective systemic therapies are prolonging survival of cancer patients with metastatic disease, resulting in an increased need for alternative therapies for painful bone metastases.

Focused ultrasound is a noninvasive technique that delivers acoustic energy to heat lesions focally to ablative temperatures

of more than 65°C. The combination of focused ultrasound with magnetic resonance (MR) imaging enables physicians to perform precise localized tumor tissue ablation, while using MR thermometry for real-time temperature monitoring (10,11). Preliminary clinical studies on the use of MR-guided focused ultrasound surgery (MRgFUS) for palliation of painful bone metastases demonstrated excellent response rates and safety (12–14).

We report here results of a randomized controlled trial to evaluate safety and efficacy of MRgFUS for treating bone metastases in patients with persistent or recurrent pain after RT, or who were otherwise not candidates for RT, or who declined RT. The primary objective was to evaluate pain reduction after MRgFUS. The secondary objectives of the study included assessment of the treatment's impact on pain-related interference with patient functioning and treatment-related toxicity.

Methods

Patient Characteristics

Patients were enrolled between July 2008 and May 2012 at 17 centers across the United States, Canada, Israel, Italy, and Russia. Patients were aged at least 18 years with life expectancy equal to or greater than 3 months and had bone metastases 1) that were painful despite previous RT; 2) were otherwise unsuitable for RT (eg, because of prior definitive high-dose treatment to the area of pain); or 3) who declined RT. Targeted tumors were device accessible, located in ribs, extremities (excluding joints), pelvis, shoulders, or posterior aspects of spinal vertebra below L2. Patients with up to 5 painful lesions were eligible; however the single treated lesion had to cause at least 2 points greater pain on the Numerical Rating Scale (NRS) than any other lesion. Eligible tumors had a worst pain NRS score equal to or greater than 4 despite pretreatment optimization of pain medication (15,16). Bone metastasis had to be visible by noncontrast MR imaging, be at least 1 cm from skin and major nerve bundles with Mirel's fracture risk score less than or equal to 7. Patients needing surgical stabilization or with clinically significant comorbidities were excluded. Patients provided written informed consent.

Study Design

This was a randomized, placebo-controlled, single-blind, multicenter, pivotal trial of MRgFUS in the palliation of pain from bone metastases. Subjects were blinded to treatment arm, as were all personnel in contact with the patient with the exception of key members of the treatment team, including those typically responsible for follow-up assessments. The study complied with institutional review board/independent ethics committees and the US Food and Drug Administration, informed consent regulations, International Committee on Harmonization of Good Clinical Practice Guidelines, the Declaration of Helsinki, and local regulations. ClinicalTrials.gov Identifier: NCT00656305.

Before randomization, persistent moderate to severe pain despite optimization of other interventions for pain, including medications, was documented. Patients were randomly assigned 3:1 to MRgFUS or placebo treatment, which was identical to MRgFUS but with sonication power off. The 3:1 imbalance in randomization was chosen to minimize ethical concerns with placebo treatment in this patient population. A separate randomization database on the clinical server for the study was created. Unbeknownst to investigators, a randomization schedule was computer generated in blocks of eight by site with seven blocks set aside per site. Each block of eight had six ExAblate treatments and two placebo treatment assignments in random order. Randomization was performed by the principal investigator at each site who had a log-in username and password to this part of the system for the purpose of randomization. To ensure transparency, a careful count and track was maintained of all subjects being screened/randomized/treated with an electronic log for completeness and US Food and Drug Administration study investigational device exemption approval requirements. Safety was assessed throughout the trial, and efficacy was evaluated after treatment at 1 day, 3 days, and 2 weeks by phone and at 1 week and 1, 2, and 3 months by follow-up visit.

Treatment Procedure

Patients received sedation and analgesia ranging from local anesthesia plus conscious sedation up to general anesthesia according to

local site standards. Treatment was performed using the ExAblate MRgFUS system (InSightec, Tirat Carmel, Israel). Patients were positioned on the MRgFUS table with the targeted tumor centered above the ultrasound transducer, with positioning and clear ultrasound pathway verified by MR imaging (standard T2-weighted fat-saturated images). Images were loaded to the ExAblate workstation, and the target area was marked by the treating physician. A patient-specific treatment plan was generated covering the targeted lesion optimizing the number of sonications, location, and energy levels to avoid damage to nontargeted tissue. After verifying correct positioning using low-energy subtherapeutic sonications, treatment began at full energy, reaching ablation temperatures of 65°C to 85°C. During each sonication, real-time MR thermometry and anatomical images were acquired. At treatment completion, T1-weighted contrast-enhanced MR images were acquired (Figure 1). Patients randomized to placebo underwent the same procedure as those receiving MRgFUS treatment but without energy deposition. All patients were queried immediately after treatment on whether they thought they had received MRgFUS or placebo treatment. The procedure was usually performed on an outpatient basis.

Efficacy and Safety Endpoints

Primary efficacy was assessed at 3 months by composite endpoint of change from baseline in worst NRS pain score (0–10 scale) and morphine equivalent daily dose (MEDD) intake according to previously established standards and endpoints as published by the International Bone Metastases Consensus Working Party (17). Specifically, a patient whose worst NRS decreased by at least two points and whose MEDD intake did not increase by more than 25% from baseline to 3 months was considered a responder; otherwise, the patient was considered a nonresponder. The consensus meeting of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials defined these measures as appropriate to assess treatment impact on pain (18). Secondary endpoints included change from baseline to 3 months in NRS and MEDD considered individually and change in the Brief Pain Inventory (BPI-QoL), an assessment of functional interference related to pain (19). Safety endpoints were treatment-related adverse events (AEs).

Statistical Methods

Analyses were done using SAS version 9.2 (SAS Institute, Cary, NC). Accrual targets were 111 and 37 subjects, respectively, for the MRgFUS and placebo arms to provide 80% power, assuming 60% and 25% response rates in MRgFUS and placebo, respectively, allowing for 20% dropout. Power computation was based on a two-group continuity corrected χ^2 test with one-sided alpha of 0.05. At the same time, all statistical tests were done with two-sided alpha of 0.05. The primary hypothesis was that response rate at 3 months after MRgFUS would be statistically significantly higher than that after placebo. Primary and secondary endpoints were tested at 3 months, with graphic representation provided over the full study course and post hoc comparisons between arms done at individual time points. All analyses were conducted on the modified intent-to-treat population of subjects receiving at least one MRgFUS or placebo sonication. Missing values were imputed using the last observation carried forward method. Unless noted otherwise, descriptive statistics in the text refer to mean \pm standard deviation.

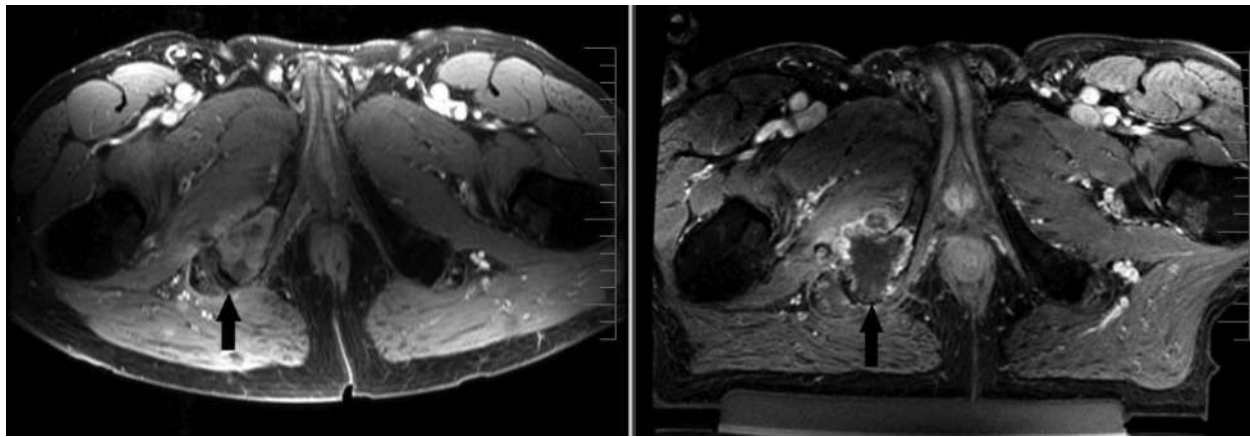


Figure 1. Day of treatment pre- and post-procedure magnetic resonance (MR) imaging. Axial T1-weighted contrast-enhanced MR images demonstrating a right ischial metastasis (**black arrow**) before treatment (**left**) and immediately after magnetic resonance-guided focused ultrasound surgery (MRgFUS) treatment (**right**). The post-treatment image shows nonenhancement of the lesion, which was targeted from a posterior approach. Each **hash mark** on the scale bars represents 1 cm.

Five patients enrolled in the study twice for different painful lesions, a protocol violation with potential to bias outcome. Consequently, data from second participation were excluded from the modified intent-to-treat population. The primary endpoint response was analyzed by Fisher's exact test. Components of the response composite, NRS and MEDD intake, were analyzed by *t* test and Wilcoxon rank-sum test, respectively. BPI-QoL was compared between MRgFUS and placebo by *t* test. To investigate the imbalance between groups that emerged in sex and prior RT (see Results section), despite random assignment, we conducted analyses of covariance for each of the four efficacy endpoints where the effect of interest was the covariable \times group interaction, which if statistically significant would indicate that MRgFUS's effect is not uniform over sex and/or prior RT.

Results

One hundred ninety-seven patients consented to participate. Forty-five were screen failures before treatment. Five cases of second participation were also excluded, as noted. Thus, our data consist of 147 patients treated once with MRgFUS or placebo; of these, 112 were randomly assigned to MRgFUS and 35 to placebo. [Figure 2](#) shows patient disposition by study arm. Notably, analysis inclusive of second participation data yielded results virtually identical to these reported here.

Patient demographics, baseline characteristics, and prior treatments for both arms are presented in [Table 1](#). MRgFUS and placebo groups were similar, although differing statistically significantly in sex ($P = .009$) with more females in the placebo arm and a greater proportion in the treatment arm having received prior radiation ($P = .03$) to the targeted lesion. We have no ready explanation for either of these differences, save to note that randomization was not stratified by baseline variables. Given the large number of variables measured, statistically significant differences could be expected by chance alone. The possible effect of these differences on treatment outcome is reported below and was assessed by analyses of covariance accounting for possible dependency, as described in the Statistical Methods section.

Safety and Tolerability

Sixty-three AEs were reported ([Table 2](#)); the most common was pain during sonication at the time of treatment experienced by 32.1% of MRgFUS patients, with 6.2%, 10.7%, and 15.2% reporting mild, moderate, and severe pain, respectively. The majority of AEs (60.3%) were transient and resolved on the treatment day, with an additional 14.3% resolving within 1 week. Five patients randomized to MRgFUS did not complete the full complement of planned sonications, three (2.7%) because of pain during treatment and two who complained of the length of treatment. Average sonication time was 83 ± 43 minutes and time inside the scanner was 176 ± 57 minutes. Among adverse events lasting more than 1 week, the most clinically significant were a third-degree skin burn that resolved within 2 months associated with noncompliance with treatment guidelines (target < 1 cm from skin) and fractures in two patients (1.8%), one outside the treatment location. The fracture rate compares favorably with the fracture risk associated with RT (5). Four AEs possibly related to treatment did not resolve by the end of the study: one was the patient with a delayed pathological fracture distant to the treated lesion. A second patient reported neuropathy, expressed as hip flexor weakness, and a third patient reported post-treatment fatigue. A fourth patient reported mild skin numbness.

In the placebo arm, a single AE of positional pain due to lying in the same position for an extended period occurred and resolved within 2 days. There were no unanticipated adverse device effects for subjects in either arm.

Efficacy

Blinding of placebo patients was highly effective. The proportion of subjects immediately upon completion of the study treatment believing they received actual treatment in the placebo arm did not statistically significantly differ from that in the MRgFUS arm (88.6% and 90.2%, respectively).

The study met its primary endpoint, with 72 of 112 (64.3%) responders in the MRgFUS arm and 7 of 35 (20.0%) responders in the placebo arm at 3 months ($P < .001$). In the MRgFUS arm, 23.2% of participants had a complete response (worst NRS

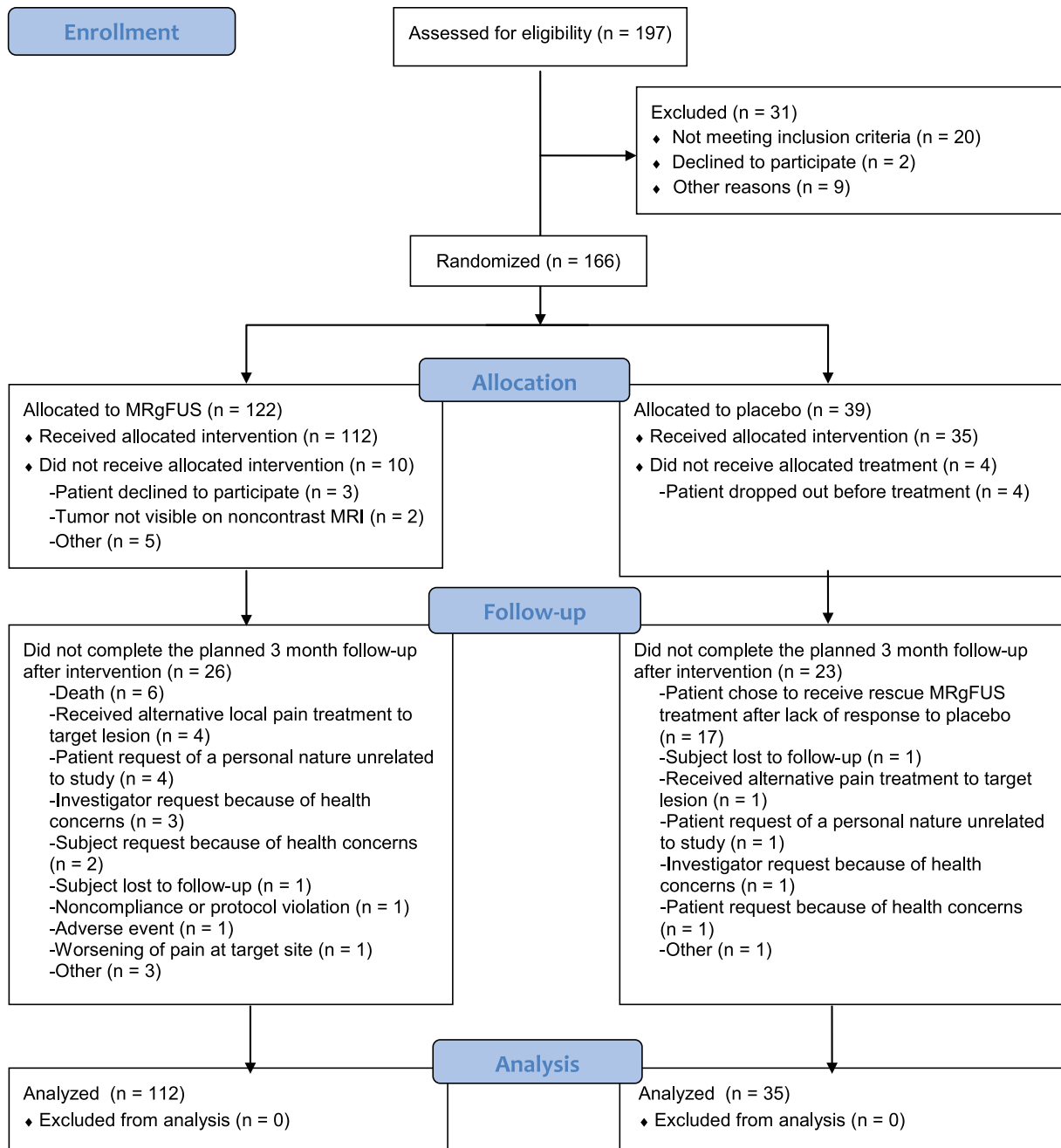


Figure 2. CONSORT 2010 flow diagram: magnetic resonance-guided focused ultrasound surgery (MRgFUS) vs placebo for pain palliation of bone metastasis. MRI = magnetic resonance imaging.

of 0 by trial's end), and in the placebo arm, 5.7% had a complete response. Figure 3 represents responder rates over time, with post hoc analyses indicating by day 3 there was statistically significantly more pain relief for MRgFUS patients ($P = .02$). The statistically significant difference between the groups was maintained at every subsequent time point throughout the trial.

Of placebo subjects, 65.7% did not complete the intended 3-month follow-up, a much larger proportion than seen in the MRgFUS arm. This difference was largely because of lack of response to placebo treatment. Seventeen of these 23 (74%) placebo patients dropped out after requesting rescue treatment during the designated 3-month follow-up. Results were similarly

statistically significant after excluding dropout groups and comparing only subjects completing the trial. Although response to rescue treatment was not included in the primary efficacy analysis, notably 70.7% of placebo crossover subjects experienced a statistically significant pain response per protocol definition.

Individual examination of the two secondary endpoints making up the composite primary endpoint at 3 months showed 1) a statistically significant difference in change from baseline in worst NRS, with mean reduction of 3.6 ± 3.1 in the MRgFUS group and 0.7 ± 2.4 in the placebo group ($P < .001$) (Figure 4A), and 2) a trend toward statistically significant change from baseline in pain medication (Figure 4B). Twenty-seven percent and 14% of responders

Table 1. Patient characteristics*

Parameter	MRgFUS (n = 112; 76%)	Placebo (n = 35; 24%)
Age, y, Median (range)	61.7 (19.1–83.6)	59.7 (29.7–83.2)
Sex, No. (%)		
Male	51 (45.5)	7 (20.0)
Female	61 (54.5)	28 (80.0)
KPS score, Median (range)	80 (60–90)	80 (60–100)
NRS worst pain score, Median (range)	7 (4–10)	7 (4–10)
MEDD, Median (range)	0.80 (0–323.3)	0.48 (0–840)
BPI-QoL overall score, Mean ± SD	5.6 ± 2.0	5.2 ± 2.3
Target lesion volume, cm ³ , Median (range)	75.4 (0.4–1341.2)	62.8 (1.8–2345.8)
Time from initial diagnosis of the targeted bone metastasis, y, Median (range)	0.6 (0–12.2)	0.4 (0–6.9)
Time from initial diagnosis of the primary cancer, y, Median (range)	2.4 (0–22.1)	2.9 (0.1–21.0)
Primary cancer type, No. (%)		
Breast	34 (30.4)	19 (54.3)
Prostate	15 (13.4)	2 (5.7)
Kidney	9 (8.0)	2 (5.7)
Lung	17 (15.2)	4 (11.4)
Missing	2 (1.8)	0 (0.0)
Other	35 (31.2)	8 (22.9)
Target lesion type, No. (%)		
Osteoblastic	25 (22.3)	6 (17.1)
Osteolytic	59 (52.7)	21 (60.0)
Mixed	27 (24.1)	8 (22.9)
Unknown	1 (0.9)	0 (0.0)
Target lesion location, No. (%)		
Pelvis	70 (62.5)	19 (54.3)
Sacrum and coccyx	12 (10.7)	6 (17.1)
Rib and sternum	16 (14.3)	6 (17.1)
Extremities	7 (6.3)	3 (8.6)
Scapula	7 (6.3)	1 (2.9)
No. of distinguishable painful lesions, No. (%)		
1	89 (79.5)	26 (74.3)
2	17 (15.2)	6 (17.1)
3	3 (2.7)	3 (8.6)
4	3 (2.7)	0 (0.0)
Prior radiation therapy, No. (%)		
Prior radiation to the targeted lesion	49 (43.8)	9 (25.7)
Prior radiation not to the targeted lesion	14 (12.5)	2 (5.7)
No prior radiation	46 (41.1)	24 (68.6)
Missing	3 (2.7)	0 (0.0)
Chemotherapy, No. (%)		
Yes	23 (20.5)	10 (28.6)
No	86 (76.8)	25 (71.4)
Missing	3 (2.7)	0 (0.0)
Hormone therapy, No. (%)		
Yes	16 (14.3)	4 (11.4)
No	93 (83.0)	31 (88.6)
Missing	3 (2.7)	0 (0.0)
Bisphosphonates, No. (%)		
Yes	46 (41.1)	19 (54.3)
No	63 (56.3)	16 (45.7)
Missing	3 (2.7)	0 (0.0)

* Characteristics are provided for all patients in the group, where five patients are counted twice because of repeated enrollment. BPI-QoL = Brief Pain Inventory; KPS = Karnofsky performance status; MEDD = morphine equivalent daily dose; MRgFUS = magnetic resonance-guided focused ultrasound surgery; NRS = Numerical Rating Scale.

discontinued and 17% and 0% of responders reduced medication usage in the MRgFUS and placebo arms, respectively. Change in BPI-QoL from baseline at 3 months with MRgFUS was 2.4 points superior to that with placebo ($P < .001$). [Figure 4C](#) presents BPI-QoL data over time by arm. Post hoc analyses showed a statistically

significant difference on BPI-QoL between MRgFUS and placebo was maintained from day 3 onwards ($P = .03$ at day 3).

As noted, MRgFUS and placebo arms statistically significantly differed on the baseline parameters of sex and prior RT. Analyses of covariance for sex and prior RT separately for each of the four

efficacy endpoints showed that the interaction term was not statistically significant in any of eight models. Moreover, results for MRgFUS were better than placebo for all endpoints for both men and women, as well as for patients with or without prior RT to target lesion/or nontarget lesions.

Discussion

There are a number of approaches to palliation of pain due to osseous metastases. However, additional strategies to address this pervasive problem are needed, as evidenced by patients who participated on this trial who had moderate to severe pain despite optimization of other interventions, including narcotics, documented before study participation. Radiation therapy is widely used but does not provide desired relief for a clinically significant number of patients (5,6,20,21,22). At other times, RT may be contraindicated, as for instance because

Table 2. Frequency of magnetic resonance-guided focused ultrasound surgery patients experiencing device-related adverse events*

Adverse event	MRgFUS (n = 112; 76.2%)	Sham (n = 35; 23.8%)
	No. (%)	No. (%)
Any adverse events	51 (45.5)	1 (2.9)
Sonication pain†	36 (32.1)	0 (0.0)
Position pain‡	9 (8.0)	1 (2.9)
Postprocedure pain	5 (4.5)	0 (0.0)
Fatigue	2 (1.8)	0 (0.0)
Neuropathy: leg	2 (1.8)	0 (0.0)
Fracture	2 (1.8)	0 (0.0)
Skin burn	2 (1.8)	0 (0.0)
Blood in urine	1 (0.9)	0 (0.0)
Fever	1 (0.9)	0 (0.0)
Myositis	1 (0.9)	0 (0.0)
Numbness	1 (0.9)	0 (0.0)
Skin rash	1 (0.9)	0 (0.0)

* MRgFUS = magnetic resonance-guided focused ultrasound surgery.

† Two patients had sonication pain twice. In the above table, this adverse event is counted once for each subject.

‡ There was one adverse event in the placebo group, position pain, which resolved the day after placebo treatment.

of prior definitive high-dose treatment to the area of pain. Effective pain palliation in RT failures has been reported in several small series treated with percutaneous radiofrequency ablation or cryoablation but these methods are invasive and limited mainly to lytic lesions (23,24,25). MRgFUS has additional advantages that may positively influence safety and effectiveness compared with other ablative therapies. These include high-resolution imaging of the targeted tumor and nontargeted normal anatomy, intraprocedural MR thermometry accurate within approximately 2° to verify adequate temperatures to achieve ablation while respecting normal tissue tolerances, and immediate post-treatment validation of the extent of ablation.

Clinical trials of MRgFUS, based on the clinical trial database (www.clinicaltrials.gov), include studies on prostate cancer, breast cancer, and brain tumors in addition to bone metastases. This is the first completed phase III study of MRgFUS in oncology. MRgFUS is a well-established therapeutic platform that has been used to treat more than 10 000 patients with an excellent safety and efficacy profile. Phase I/II trials have yielded preliminary data suggesting that MRgFUS may be a safe and effective treatment for painful bone tumors (12,13,14). Although the mechanism of action has not been definitively determined, preliminary studies indicate that, in addition to periosteal denervation, tumor debulking may also play a clinically significant role in symptom relief (12,13,26).

This phase III trial is the first randomized study to demonstrate a role for MRgFUS in the treatment of cancer-related bone pain. The results of this randomized placebo-controlled study support the findings of previous studies with this technology. Response to MRgFUS was typically rapid, with about two-thirds of responses seen within days after treatment. Additionally, 47% of the patients treated by MRgFUS reduced (21%) or completely stopped (26%) their MEDD consumption. Bone pain is the primary factor negatively influencing quality of life for many patients with disseminated cancer (27). Impact of MRgFUS on patient functioning, which often influences quality of life, is an important additional finding of the study. The reduction of functional interference from pain in the MRgFUS arm evaluated by BPI-QoL is clinically significant, rapid, and durable, whereas placebo patients showed no statistically or clinically significant change. MRgFUS thus contributes to the well-being of patients.

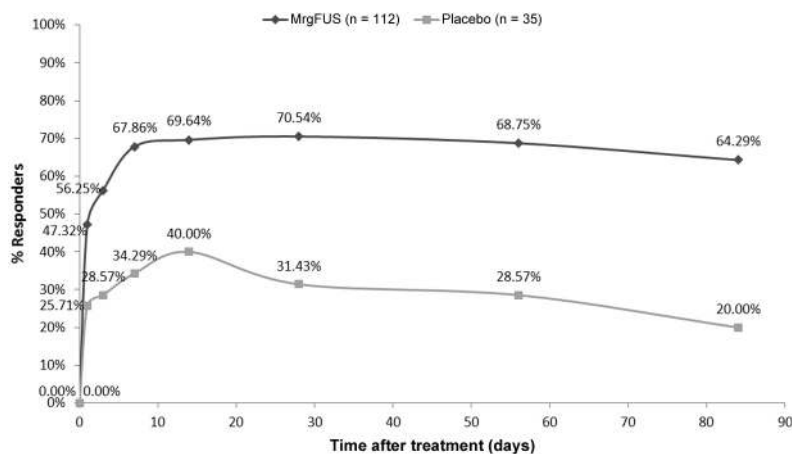


Figure 3. Treatment response per the primary endpoint. Response is defined as a decrease in Numerical Rating Scale for pain (NRS) score by at least 2 points and morphine equivalent daily dose (MEDD) intake that did not increase by more than 25% from baseline. MRgFUS = magnetic resonance-guided focused ultrasound surgery.

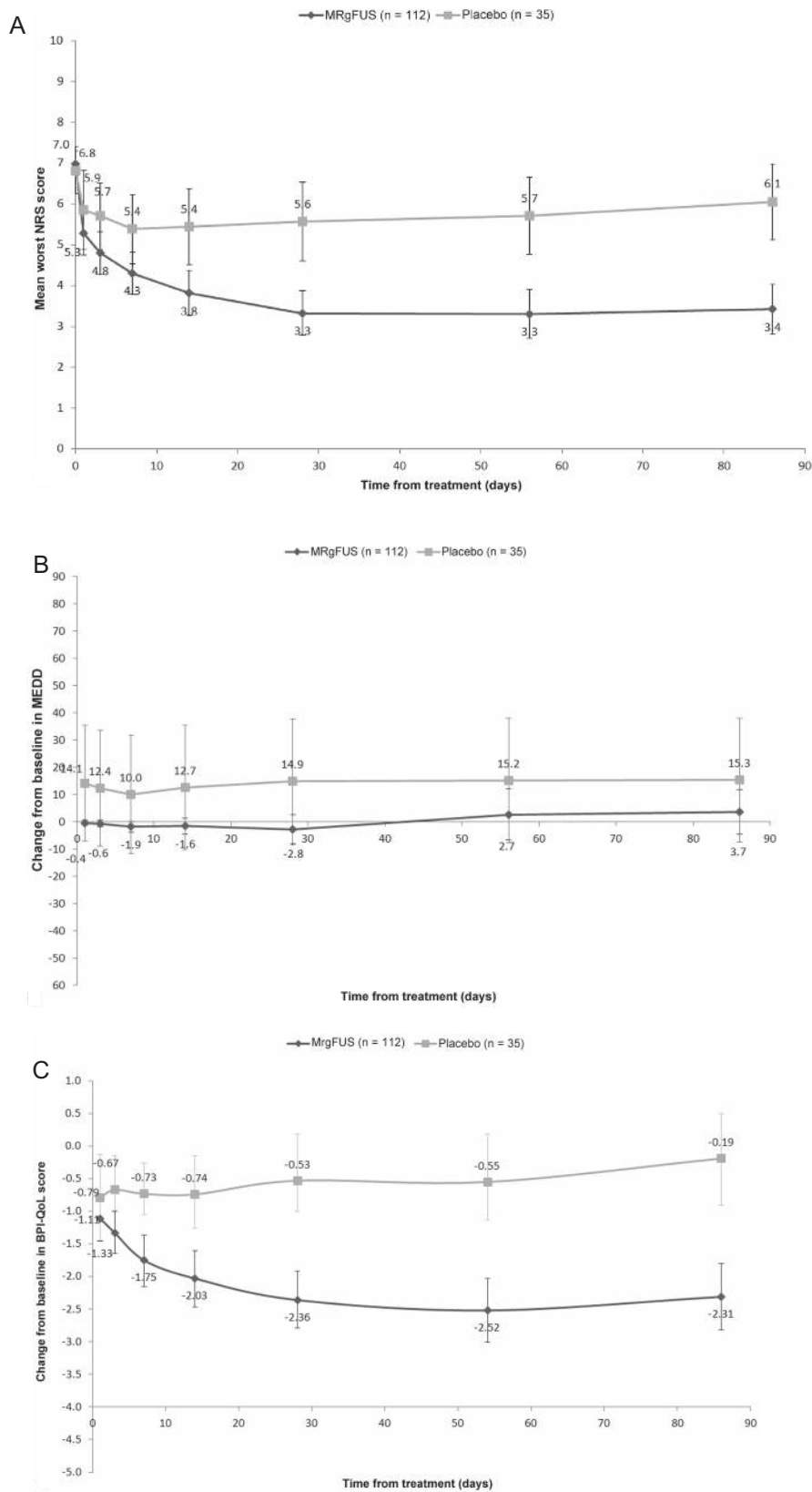


Figure 4. Additional response parameters. **A**) Numerical Rating Scale (NRS) for pain score: mean change in worst NRS for pain score over the 3-month evaluation period is shown. **B**) Morphine Equivalent Daily Dose (MEDD) intake: change from baseline in MEDD intake over the 3-month evaluation period is shown. **C**) Brief Pain Inventory–Quality of Life (BPI-QoL): change in BPI-QoL score over the 3-month evaluation period is shown. The 95% confidence intervals are shown in each diagram. MRgFUS = magnetic resonance-guided focused ultrasound surgery.

The overall safety profile of the MRgFUS treatment is favorable, with good tolerability and AEs that are both relatively minor in the context of patients' disease and of generally limited duration. The most frequent treatment side effect in this study was procedure-related pain, which can be mitigated by tailoring sedation to minimize pain experienced during the treatment. The relationship between MRgFUS treatment parameters, including mode of sedation, safety, and overall efficacy, are beyond the scope of this report and will be reported separately. Only one third-degree skin burn (0.9%) and two post-treatment fractures (1.8%) occurred. These results compare well with the complication rate of RT.

Potential weaknesses in this study are use of the last observation carried forward method for imputation of missing data, double enrollment of five patients, and difference in sex and prior RT between study arms. To address concern about overestimated precision with the last observation carried forward method, multiple imputation of missing endpoint data was performed, as well as a sensitivity analysis that included worst case imputation where all missing values in the placebo arm were imputed responders and all missing values in MRgFUS were imputed as nonresponders. Even in this "worst case" scenario, the statistically significant difference between groups in favor of MRgFUS was maintained ($P = .01$), supporting the robustness of the reported results. Five patients were enrolled twice, and therefore, because of potential bias, the outcomes from the second enrollment were excluded from analysis. Notably, assessment of outcomes including these five cases had no impact on study conclusions. Finally the imbalances in the treatment arms despite randomization were addressed by demonstrating that neither sex nor prior RT interacted with study treatment.

In conclusion, MRgFUS provides durable pain relief and improved function in patients who failed radiation or those who are not candidates for or declined radiation. Given the impact of these clinically significant results, coupled with a favorable side effect profile, MRgFUS should be considered a viable treatment option for painful bone metastases. Further studies are required to assess the role of MRgFUS in patients with bone metastases as first-line therapy.

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