MR-guided Focused Ultrasound (MRgFUS) Ablation for the Treatment of Nonspinal Osteoid Osteoma
A Prospective Multicenter Evaluation

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Background: Magnetic resonance-guided focused ultrasound (MRgFUS) is a novel imaging-guided surgical technique that allows the performance of noninvasive and radiation-free ablation. Presently, computed tomography (CT)-guided radiofrequency ablation, a minimally invasive percutaneous technique, is the standard for treating symptomatic osteoid osteomas. The purpose of this study was to evaluate the use of MRgFUS ablation for the treatment of nonspinal osteoid osteomas in terms of technical success, complications, and clinical success through one year of follow-up.

Methods: In this prospective multicenter study, thirty consecutive patients with a nonspinal osteoid osteoma were enrolled between May 2010 and April 2012 at three different university centers; twenty-nine of the patients were treated with use of MRgFUS. Lesions had been previously diagnosed on the basis of imaging, including dynamic contrast-enhanced MR. The mean number of sonications and energy deposition were determined. Technical success was evaluated through an assessment of complications immediately after treatment. Clinical success was determined on the basis of pain reduction as measured with a visual analog scale (VAS), recurrence, and long-term complications through twelve months.

Results: Technical success of MRgFUS was observed for all twenty-nine patients. The mean number of sonications (and standard deviation) was 7 ± 3, and the mean delivered acoustic energy was 1180 ± 736 J. At the twelve-month follow-up, complete clinical success was observed in twenty-six (90%) of the twenty-nine patients (95% confidence interval [CI] = 84 to 95; mean VAS, 0 ± 0 points). Partial success was observed in three (10%) of the twenty-nine patients (95% CI = 5 to 16; mean VAS score, 5 ± 0 points); two of these patients subsequently underwent CT-guided radiofrequency ablation, and one underwent open surgery. Pain score values showed a significant reduction (p < 0.001) between baseline (mean VAS score, 8 ± 1 points) and post treatment (mean VAS score, 1 ± 2 points). No complications were observed.

Conclusions: MRgFUS may be an effective and safe alternative approach in the treatment of nonspinal osteoid osteoma. A complete clinical success rate of 90% was demonstrated without adverse events. MRgFUS is totally noninvasive and eliminates radiation exposure.

Level of Evidence: Therapeutic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Peer Review: This article was reviewed by the Editor-in-Chief and one Deputy Editor, and it underwent blinded review by two or more outside experts. The Deputy Editor reviewed each revision of the article, and it underwent a final review by the Editor-in-Chief prior to publication. Final corrections and clarifications occurred during one or more exchanges between the author(s) and copyeditors.

A n osteoid osteoma is a benign, painful musculoskeletal tumor that usually occurs in young males¹. Bergstrand, in 1930, was the first to describe this entity¹, and Jaffe later characterized it in a small case series³. A typical feature is a nidus on radiograph⁴, and clinically, pain is often worse at night. Pain is initially managed with the use of

Disclosure: None of the authors received payments or services, either directly or indirectly (i.e., via his or her institution), from a third party in support of any aspect of this work. None of the authors, or their institution(s), have had any financial relationship, in the thirty-six months prior to submission of this work, with any entity in the biomedical arena that could be perceived to influence or have the potential to influence what is written in this work. Also, no author has had any other relationships, or has engaged in any other activities, that could be perceived to influence or have the potential to influence what is written in this work. The complete Disclosures of Potential Conflicts of Interest submitted by authors are always provided with the online version of the article.

salicylates or other nonsteroidal anti-inflammatory drugs (NSAIDs).

The standard of care in the United States is computed tomography (CT)-guided radiofrequency ablation, a minimally invasive percutaneous procedure, with clinical success rates ranging between 85% and 98%. Operative approaches may include traditional open surgery for nidus removal or a minimally invasive percutaneous intervention guided by nuclear medicine study (radionuclide-guided excision) or CT (excision or laser coagulation).

Magnetic resonance-guided focused ultrasound (MRgFUS) ablation is a novel noninvasive interventional technique that uses high acoustic energy for targeted tissue ablation under MR guidance with real-time thermal monitoring. An understanding of basic concepts related to focused ultrasound therapy and MR imaging (MRI) is necessary with respect to this combined approach.

Ultrasound waves are acoustic pressure waves. Their frequency range starts at 16 kHz, the limit of human hearing, and extends into the megahertz range. Propagation of ultrasound waves into human tissue follows two physical behaviors, reflection and absorption. Reflection of low-energy ultrasound waves (1 to 20 MHz) is the basis of conventional diagnostic ultrasound. Absorption predominates in high-intensity focused ultrasound therapy, when high-power ultrasound waves are focused on a single point. Focused ultrasound therapeutic action is characterized by two mechanisms, the conversion of mechanical energy into heat and cavitation. Normally when an ultrasound beam propagates through tissues, heat generated from energy deposition is negligible and dissipates rapidly. When high-intensity waves are focused, heating exceeds cooling, and tissue temperature rises. Thermal toxicity along with irreversible cell death and coagulative necrosis occurs if the focal temperature is raised >56°C for at least one second, as occurs in focused ultrasound therapy. Acoustic cavitation is more unpredictable and is due to a combination of thermal injury and mechanical stress, also resulting in cell necrosis.

MRI adds to focused ultrasound therapy the advantages of lesion localization and temperature monitoring. Lesion localization is achieved through the intrinsic high tissue contrast of MRI, while temperature monitoring is achieved with the use of specific MRI sequences performed in real time during the ablation.

Recently, MRgFUS has been described as an alternative therapy for symptomatic osteoid osteomas. A prospective small-series exploratory study that included six patients demonstrated a good clinical success rate without major complications.

To our knowledge, no prospective multicenter evaluation of MRgFUS for the treatment of osteoma has been performed. Therefore, the purpose of our study was to evaluate the technical success of the treatment of nonspinal, painful osteoid osteomas in a larger patient group at different centers with the use of MRgFUS, to assess complications, and measure clinical success through one year of follow-up.

Materials and Methods

This prospective multicenter cohort study followed the recommendations defined within the IDEAL (Idea, Development, Exploration, Assessment, and Long-term study) guidelines for assessing innovation in surgery (Stage II)21,22. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were also used in the reporting of this observational study.23

Institutional review board permission was obtained at each center. Written informed consent for the interventional procedure along with permission to analyze personal data was obtained from each enrolled subject.

Patient Population and Inclusion Criteria

An a priori power analysis was performed to determine the sample size with the intention of giving our study a statistical power of 90%, adopting an alpha level of 0.05. The sample-size determination reflected the primary end point: MRgFUS treatment should be clinically relevant in terms of pain palliation for a symptomatic nonspinal osteoid osteoma. As compared with CT-guided radiofrequency ablation, which has an average success rate of around 90%,24,25 an average rate of 80% response to treatment with use of MRgFUS was considered acceptable in this study. The minimum sample size was determined to be twenty-four patients. Allowing for a 10% dropout rate, we chose a sample size of twenty-seven patients who had a diagnosis of osteoid osteoma based on imaging.

From May 2010 to April 2012, thirty consecutive patients (twenty-one male and nine female patients) who ranged in age from ten to forty-seven years old (mean age [and standard deviation], 25 ± 16 years) were recruited at three orthopaedic referral centers. Treatment with MRgFUS was proposed as a totally noninvasive, alternative technique to CT-guided radiofrequency ablation or open surgery. Study inclusion criteria were a clinical diagnosis of osteoid osteoma followed by positive imaging. The clinical diagnosis was based in part on nocturnal pain that was unrelated to physical activity or trauma and that was relieved by NSAIDs (a pain score of ≥3 points as measured with a visual analog scale [VAS]). Positive imaging included radiographs and CT and MRI scans demonstrating typical features. MR evaluation included dynamic contrast-enhanced MR (Gd-BOPTA; Bracco, Milan, Italy). The final diagnosis was determined by consensus, without biopsy, by two fellowship-trained musculoskeletal radiologists per center who had at least five years of experience (D.G., A.N., A.C., L.M.G., A.B., and M.B.). Exclusion criteria were general contraindication to MRI and a vertebral location of the lesion. Claustrophobia was not an absolute exclusion criterion.

### TABLE I Osteoid Osteoma Location and Size

<table>
<thead>
<tr>
<th>Location</th>
<th>Total No. (%)</th>
<th>Femur (no.)</th>
<th>Tibia (no.)</th>
<th>Hand (no.)</th>
<th>Ankle (no.)</th>
<th>Elbow (no.)</th>
<th>Nidus Size* (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subperiosteal</td>
<td>5 (17%)</td>
<td>2</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>7 ± 2 (5-9)</td>
</tr>
<tr>
<td>Intracortical</td>
<td>18 (62%)</td>
<td>12</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>7 ± 2 (4-10)</td>
</tr>
<tr>
<td>Endosteal</td>
<td>3 (10%)</td>
<td>1</td>
<td>NA</td>
<td>2</td>
<td>2</td>
<td>8 ± 1 (7-9)</td>
<td></td>
</tr>
<tr>
<td>Medullary</td>
<td>3 (10%)</td>
<td>2</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
<td>5 ± 1 (4-6)</td>
<td></td>
</tr>
</tbody>
</table>

*Values are presented as the mean and standard deviation with the range in parentheses. NA = not applicable.
The presence of superficial soft-tissue scarring, intra-articular lesion location, lesion proximity to ligaments or tendons, and the presence of neurovascular bundles were individually evaluated with use of MRI prior to treatment.

**MRgFUS Treatment**

General anesthesia was administered in patients who were under sixteen years of age; otherwise, an epidural block or peripheral block was used, depending on the location of the lesion. One musculoskeletal radiologist per center trained in MRgFUS (A.N., A.C., and A.B.) performed the procedures with the use of either a 3.0-T or a 1.5-T MR unit (Discovery MR750 or MR450; GE Medical Systems, Milwaukee, Wisconsin). Each unit incorporates an ExAblate 2100 MR-guided focused ultrasound system (InSightec, Tirat Carmel, Israel). Lesion localization was achieved with the use of nonenhanced T1 and T2-weighted MR sequences, with and without fat saturation, to allow accurate treatment planning. Because high-intensity ultrasound waves generate focal-tissue heating, if reflecting structures such as scars, ligaments, and tendons, or air are interposed between the beam origin and target lesion, thermal damage to structures located along the planned ultrasound trajectory may occur. In those cases, reflection obstructs wave transmission, and thermal damage and skin burns may result. Approaching the cortical bone surface with a perpendicular trajectory may reduce beam reflection. To avoid beam-deflecting structures, we approximated the shortest trajectory between the skin and the osteoid osteoma (Fig. 1). With the use of the ExAblate treatment planning software, we performed manual segmentation, which consisted of manually drawing a region of interest around the target area (nidus) and the contouring regions to be avoided (Fig. 2).

Treatment then consisted of a series of sonifications. The term “sonifications” relates to the act of applying sound waves to agitate matter and is used in our case to describe each energy deposition (ablation) into the nidus. A low-energy sonification, consisting of a preliminary heating test, was performed to verify the correct position of the target area (nidus) and preceded full-energy, twenty-second ablations. With the use of specific MR sequences, real-time thermometric maps were acquired and evaluated during each ablation. The treatment end point was to quantify energy deposition into the nidus, reaching a minimum of 60°C. A critical 65°C temperature threshold for ablation was set at the level of the perilesional tissues adjacent to the target area. Real-time thermal control was performed. The number of sonifications and the amount of energy delivered for the treatment of each patient were recorded (Fig. 2).

After treatment, patients were monitored for six hours and evaluated for potential thermal skin necrosis and skin burns. Patients who received general anesthesia were hospitalized for twenty-four hours; the others were outpatients.

**Data Analysis**

Lesion size and location were recorded prior to treatment following the classification scheme of Kayser et al.20.

**Technical Success**

The immediate postprocedural outcome was evaluated to detect procedure-related problems. Each patient was examined in the recovery room. The procedure site was evaluated for swelling, thermal skin necrosis, and skin burns. Neurovascular integrity was clinically assessed. A brief (twenty-four hour) course of analgesics (NSAIDs) was administered to reduce pain and discomfort from perilesional edema in the ablated area.

**Pain-Score Assessment and Clinical Follow-up**

Patients were asked to fill out a ten-point VAS pain diary prior to MRgFUS treatment and underwent a complete clinical evaluation at one, six, and twelve months following treatment that included an assessment of residual pain (VAS score) and complications. If the patient had a pain score of 0 at one month after treatment and no recurrent symptoms and was stable at one year of follow-up, the clinical response was considered complete. Otherwise, the response was considered partial if the patient had a reduction in pain score of at least 2 points at one month. If, in a two-week postprocedure interval, the patient presented the same symptoms that occurred before treatment, the response was considered a recurrence. The statistical difference between VAS scores at baseline and at the one year follow-up was evaluated with the use of the paired t test.

Perilesional bone-marrow edema (as seen on T2-weighted MRI with fat saturation) and nidus appearance and vascularization (as seen on dynamic contrast-enhanced T1-weighted MRI) was evaluated at twelve months by one reader at each center (D.G., A.C., and A.B.).
After treatment, nonstrenuous activity for one week was recommended to decrease weight on areas exposed to thermal ablation.

Data analysis was performed with use of SPSS Statistics 20.0 (IBM, Armonk, New York).

**Source of Funding**
This study was funded by the Italian National Health System.

**Results**

**Study Cohort and MRgFUS Treatment**
One patient was excluded from the study because of the inability to undergo the MRgFUS procedure due to obesity, making him unable to fit in the gantry. A total of twenty-nine patients, each presenting with a single osteoid osteoma, were...
treated with use of MRgFUS and completed the twelve-month follow-up evaluation.

Pretreatment imaging (radiographs, CT, and MR) allowed localization and characterization of five subperiosteal lesions (17%), eighteen intracortical lesions (62%), three endosteal lesions (10%), and three medullary lesions (10%). Lesions were located in the femur in seventeen of twenty-nine patients; the tibia in seven patients; the hand (the metacarpal and intermediate phalanx) in two patients; the ankle (talus) in two; and the elbow (olecranon) in one. Four nidi (those in the hands and tali) were located <1 cm from the skin surface. The mean nidus size was 7 ± 2 mm (range, 4 to 10 mm) (Table I). General anesthesia was administered to four patients; epidural block, twenty patients; and peripheral block, five patients. The mean duration of the procedure was forty minutes (range, fifteen to ninety-five minutes). The mean effective treatment time was 13 ± 5 minutes (range, five to twenty-five minutes).

The mean number of sonifications was 7 ± 3 (range, one to twelve sonifications) with a mean delivered energy of 1180 ± 736 J (range, 416 to 3645 J) (Table II). No complications related to treatment or anesthesia were reported. No thermal

![Fig. 3](https://example.com/fig3.png)  
Images of an eleven-year-old boy (same patient as seen in Fig. 2) treated for a painful tibial osteoid osteoma, including a radiograph (Fig. 3-A), pretreatment CT image (Fig. 3-B), pretreatment contrast-enhanced T1-weighted MR map (Fig. 3-C), pretreatment T2-weighted MR image with fat saturation (Fig. 3-D), T2-weighted MR image with fat saturation acquired twelve months after treatment (Fig. 3-E), and contrast-enhanced T1-weighted MR map acquired at twelve months after treatment (Fig. 3-F). Note the typical imaging features of an osteoid osteoma (Figs. 3-A, 3-B, and 3-D). Nidus hyperemia was present before treatment (Fig. 3-C, arrow) and absent at twelve months (Fig. 3-F). Similarly, a marked reduction of bone-marrow edema at the twelve-month follow-up was observed (Fig. 3-E). Immediately after treatment, the patient reported a VAS pain score of 0 and was stable at the time of follow-up. RAI indicates the perfusion color map scale.
The mean VAS score for pain at baseline was 8 ± 1 points (range, 5 to 10 points). The VAS pain score improved in all patients. Twenty-six of twenty-nine patients had a mean VAS pain score of 0 one month after treatment, and pain relief was stable until the final follow-up. Three of twenty-nine patients had a partial response, with a mean score of 5 ± 0 points that went unchanged during follow-up (mean baseline VAS, 8 ± 0 points). Follow-up evaluations demonstrated a decrease in pain symptoms in all patients, with a mean score of 1 ± 2 points at one, six, and twelve months (see Appendix). The paired t-test demonstrated a significant difference between VAS scores at baseline and at the one-month follow-up (p < 0.001), while no significant differences were observed between one, six, and twelve-month follow-up evaluations. An overall rate of 90% complete clinical success (twenty-six of the twenty-nine patients; 95% confidence interval [CI] = 84 to 95; mean VAS, 0 ± 0 points) and 10% partial success (three of the twenty-nine patients; 95% CI = 5 to 16; mean VAS: 5 ± 0 points) was observed (see Appendix).

At baseline, patients were taking between 400 mg and 2500 mg of NSAIDs as needed. For patients who had complete clinical success at the time of follow-up, drug intake was discontinued immediately following treatment. Anti-inflammatory therapy for pain management was continued until the end of the study for partially successful cases (three of twenty-nine), although a drug dose reduced to half was adequate for managing pain. After the twelve-month follow-up, partially successful cases underwent CT-guided radiofrequency ablation (two of three patients) or open surgery (one of three patients).

At the twelve-month imaging evaluation, a marked reduction in perilesional bone-marrow edema (T2-weighted imaging with fat saturation) along with a marked reduction in nidus vascularization (contrast-enhanced T1-weighted imaging and dynamic maps) was noted for all patients presenting complete clinical success (Fig. 3; see also Appendix). No substantial changes were observed on follow-up imaging in cases that resulted in partial clinical success.

**Clinical Success Rate and Follow-up**

The mean VAS score for pain at baseline was 8 ± 1 points (range, 5 to 10 points). The VAS pain score improved in all patients. Twenty-six of twenty-nine patients had a mean VAS pain score of 0 one month after treatment, and pain relief was stable until the final follow-up. Three of twenty-nine patients had a partial response, with a mean score of 5 ± 0 points that went unchanged during follow-up (mean baseline VAS, 8 ± 0 points). Follow-up evaluations demonstrated a decrease in pain symptoms in all patients, with a mean score of 1 ± 2 points at one, six, and twelve months (see Appendix). The paired t-test demonstrated a significant difference between VAS scores at baseline and at the one-month follow-up (p < 0.001), while no significant differences were observed between one, six, and twelve-month follow-up evaluations. An overall rate of 90% complete clinical success (twenty-six of the twenty-nine patients; 95% confidence interval [CI] = 84 to 95; mean VAS, 0 ± 0 points) and 10% partial success (three of the twenty-nine patients; 95% CI = 5 to 16; mean VAS: 5 ± 0 points) was observed (see Appendix).

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The absence of skin burns, thermal skin necrosis, and complications and the positive clinical results in our series demonstrate the substantial ablation accuracy and high safety profile of MRgFUS, delivered through imaging guidance and real-time thermometry. Partial treatment encountered with CT-guided radiofrequency ablation relative to inaccurate needle positioning\(^1\) could also potentially be avoided.

In our study, lesion size did not change treatment. The sonicated volume, irrespective of the osteoid osteoma size, was planned in advance and the ablation coverage of the targeted area was achieved in a single session. The number of sonifications differed among patients because our treatment end point was to quantify energy deposition into the nidus, reaching a minimum of 60°C and visually monitoring results through MRI. Recovery from treatment was uncomplicated and related to general anesthesia (when administered).

The potential reduction in complications and hospitalization time from the use of MRgFUS may also mean a decrease in overall costs, although we did not perform a specific cost analysis for MRgFUS compared with other treatment approaches.

While 10% of the patients (three of twenty-nine) in our study had a partial benefit from treatment, their pain decreased after treatment. However, partial clinical success should be regarded as treatment failure. Initial thought had been directed to extending treatment to cover the entire periosteum as well as the nidus for the potential pain-relief effect on periosteal neurolysis. As a result, in one of our patients with an exuberant periosteal thickening (a femoral osteoid osteoma), energy deposition into the nidus may have been less than desirable (see Appendix). In this case, a partial clinical effect at the twelve-month follow-up evaluation was observed and successful open surgery was performed. We believe that, especially if a large sclerotic reaction is present, in order to thermally reach the nidus, it may be necessary to use higher energies at lower frequencies and focus treatment to the nidus rather than...
peri­lesional areas (peri­osteum). This case was of pivotal im­por­tance to our learn­ing curve.

In another case, we treated a distal tibial osteoid osteoma located at the level of the inter­osseous crest. The lesion appeared to be difficult for the ultrasound beam to access during the procedure, and this likely caused partial treatment. After the completion of one-year follow-up, the patient underwent successful treatment with CT-guided radiofrequency ablation (Fig. 4). This patient had declined to be retreated with MRgFUS.

Partial clinical success was also observed for a patient with a cortical femoral osteoid osteoma. During the MRgFUS treatment, this patient became uncomfortable and could not stay in one position. Slight movement during treatment may have been the cause of the partial success. Although MRgFUS may be repeated over time, this patient chose to be retreated with CT-guided radiofrequency ablation. In our series, no patient was retreated with use of MRgFUS during the follow-up period.

Based on our experience, an accurate evaluation of lesion location and ultrasound beam trajectory is necessary when planning treatment to allow adequate energy deposition into the nidus. A comfortable patient position to achieve immobility is also necessary. CT-guided radiofrequency ablation may be preferred if this criterion cannot be achieved.

This study had some limitations. Although a power analysis was performed, a larger study population would have been preferable.

Core biopsy was not performed before treatment, and the diagnosis was made on the basis of clinical evaluation and typical features shown on imaging. Core biopsy for osteoid osteoma is not mandatory at our centers.

We did not include spinal lesions in our study for safety reasons. A small number of these lesions were studied in a previous report by Rosenthal et al. (three of 263 patients) but, to our knowledge, treatment of spinal lesions with MRgFUS has never been reported.

As mentioned previously, a cost analysis was not performed. This would be desirable in order to compare MRgFUS with other techniques.

The results of this study suggest that MRgFUS may favorably compare with CT-guided radiofrequency ablation in terms of treatment success for accessible nonspinal osteoid osteomas. Noninvasiveness is a major advantage of this technique, and MRgFUS may be considered an alternative treatment strategy to CT-guided radiofrequency ablation in selected cases.

In conclusion, the results of this prospective multicenter study suggest that MRgFUS may be considered an effective and safe alternative approach for the interventional management of nonspinal osteoid osteoma. This study demonstrated a complete clinical success rate of 90% without adverse events.

Appendix

A table showing mean VAS pain scores at baseline and at the twelve-month follow-up and images from two cases are available with the online version of this article as a data supplement at jbjs.org.

References


