



MR Guided Focused Ultrasound for the Palliation of Bone Metastases: Clinical Procedures and Outcome

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Abstract

Purpose: The purpose of this paper is to report our initial clinical experience with MR Guided Focused Ultrasound (MRgFUS) for the palliative treatment of bone metastases with a focus on patient treatment workflow and Quality Assurance (QA) procedures to ensure the safe and effective operation of MRgFUS.

Methods: In addition to the monthly, annual QA and Preventive Maintenance (PM), pre-treatment machine QA was performed one week before and on the day prior to patient treatment to test the machine hardware, imaging and treatment software and patient safety devices. The geometrical ultrasound focal spot between the planning focal spot and treatment focal spot was registered with an acoustic phantom using MR thermometry. The QA procedures were verified through patient treatments. Seven patients (recruited in the multicenter Phase III clinical trial, BM004) with scapula, humeral head, sacrum, ilium, pubic ramus and acetabular bone metastases were treated using a FDA approved clinical focused ultrasound system under MR guidance. Patients were treated with a frequency of 1 MHz; acoustic power of $32W \pm 4.0W$ to $96W \pm 11W$ with a duration of 20-30 seconds for each sonication resulting in an energy of $628J \pm 78J$ to $1859J \pm 338J$. MR phase images were used to monitor the temperature changes at focal spots in real-time. Based on the temperature feedback, the acoustic power can be adjusted to reach designed temperatures ($\geq 60^\circ C$) for individual sonications. The effectiveness of the treatment was evaluated by pain score using the visual analog scale (0-10VAS).

Results: Our data showed that all seven patients tolerated the MRgFUS treatment well. No skin toxicity or other complications were observed during or after treatment. The patient pain rating was significantly reduced from 8.0 ± 1.1 before treatment to 4.7 ± 3.0 , 3.0 ± 1.5 , 3.2 ± 2.8 and 3.4 ± 1.5 at one day, one month, two months and three months after treatment, respectively.

Conclusions: Our clinical data suggests that with appropriate treatment and QA procedures, MRgFUS is a safe and effective treatment modality for the noninvasive palliation of bone metastases.

Keywords: Quality assurance; MR guided focused ultrasound; Bone metastases

Introduction

High Intensity Focused Ultrasound (HIFU or FUS) is a completely non-invasive treatment modality. This technique has long been known to offer “trackless lesioning” and has been identified as an “ideal surgical tool” for many years but only in the past decade with high quality methods using medical imaging, has it become a practical option in clinical treatment [1]. This high quality image technique not only provides accurate target delineation and ultrasound beam placement but also enables real-time assessment of treatment effects during the treatment procedure.

FUS has been developed for tissue ablation using the continuous ultrasound mode to treat both benign and malignant diseases, such as patients with uterine fibroids, Benign Prostatic Hyperplasia (BPH), prostate cancer, renal tumors, hepatic tumors, breast cancer, brain tumors and for palliative treatment of bone metastases to relieve pain, etc. [2-11]. Current imaging modalities being used for treatment guidance include ultrasound and MR imaging [12,13].

FUS has also been investigated to enhance local drug (or enhancement agent) delivery using the pulsed mode in animal models for chemotherapy, gene therapy, immunotherapy and radiation therapy [12,14-20].

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A clinical phase III study (*BM004 ExAblate*) to evaluate the effectiveness and safety of ExAblate treatment of metastatic bone tumors for the palliation of pain in patients who are not candidates for radiation therapy has been completed successfully [21]. The goal of the treatment is to relieve the pain from the bone metastases and the principle of the treatment is to ablate the adjacent periosteum of the bone which is the sensory origin of the pain. Based on the success of this clinical trial, MR guided high intensity focused ultrasound (MRgFUS) for palliative treatment of bone metastases was approved for routine clinical practice by the United States Food and Drug Administration (FDA) in October, 2012.

Since it is a new treatment technique, detailed clinical Quality Assurance (QA) procedures and treatment workflow are not available in the literature to our knowledge. Appropriate QA procedures play an important role in the success of MRgFUS treatment for both safety and effectiveness. The purpose of this paper is to describe our clinical experience with MRgFUS for the palliation of bone metastases with a focus on treatment workflow and QA procedures through patient treatments based on our 7 patients recruited for the BM004 clinical trial and 15 patients treated after FDA approval for clinical treatment using a FDA approved clinical HIFU treatment system.

Methods and Materials

MRgFUS treatment system

The clinical focused ultrasound treatment system (ExAblate 2000 - Insightec) was used in this study. The HIFU treatment system is approved by FDA for the treatment of uterus fibroids and bone metastases clinically. The MR (1.5T) scanner (GE medical system) was used for MR guidance in target delineation, treatment planning, ultrasound beam placement, and temperature measurement during treatment using MR thermometry. The main components of the system include the patient treatment table, operator console and the equipment cabinet.

Patient treatment table, ultrasound transducer and positioning system: The patient treatment table is a modified SIGNA MRI Table. It is detachable and can be docked to a GE 1.5T/3T MR scanner in the same way that the standard MR table docks: it is connected with a single quick-connect socket. A phased array transducer with 208 elements is housed in a sealed degassed water bath in the patient treatment table and is connected to an electronic motion system controlled by a computer (Figure 1). The transducer can be moved in X Y directions (but cannot be moved up and down). It can also be tilted relative to its neutral position, parallel with the Table. The focal length of the transducer is 16cm (for each element, not using electronic steering). However, since the transducer is a phased array transducer, the phases of each element can be changed to create a new focus and therefore steer the focal length range from 6cm to 22cm away from the transducer. The focal size can be varied depending on the size and depth of the focal volume to be treated, ranging from 1mm diameter x 8mm length to 10mm diameter x 45mm length. The operating frequency is around 1MHz ranging from 0.95MHz to 1.35MHz. For bone treatment, the frequency used is typically 1MHz. The equipment cabinet is located adjacent to the MR control room. It contains a main power switch along with electrical components.

Operator console: The console is located in the control room next to the MR workstation. It includes a flat panel display, keyboard, and mouse and stop-sonication button. It controls the entire treatment process by the physician.

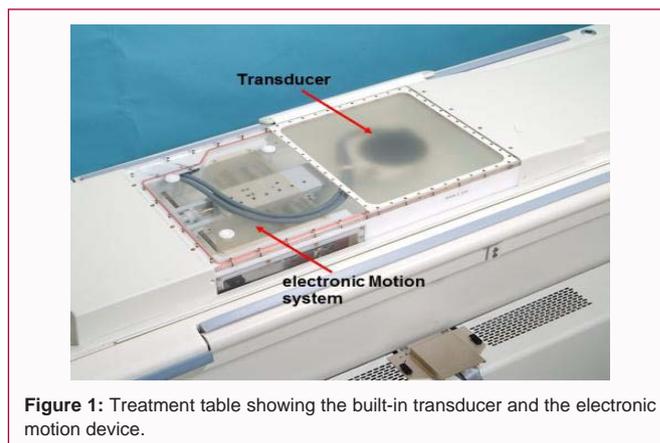


Figure 1: Treatment table showing the built-in transducer and the electronic motion device.

The treatment console is used for 1) image fusion, 2) target delineation, 3) treatment planning, 4) controlling both the therapeutic table (transducer motion and energy delivery), and the MR scanner, 5) assessment of the treatment by analyzing and displaying each energy delivery outcome in real-time including thermal feedback using MR thermometry and for thermal dose with color overlay on the treated spots.

Safety devices: Safety devices include a sonication lamp, which is installed in a prominent position on the MRI scanner and lights up during treatment sonication, and three stop-sonication switches, which instantaneously stop the delivery of ultrasound energy to the patient for emergency. One is held by the patient who is instructed to squeeze it in case of sudden discomfort or for an emergency; another is mounted on the scanner for use by staff in the treatment room; and the third switch is installed in the FUS operator console in the control room.

Patient treatment protocol

Study Protocol BM004, a randomized phase III trial, was a multicenter, single-blinded, randomized study to evaluate the efficacy and safety of treatment for metastatic bone tumors using the ExAblate for the palliation of pain in patients who have failed radiation or who were not candidates for or refused radiation therapy [21]. Patients randomized in the sham group received no acoustic power during the treatment. Three weeks after the treatment the patient was entered in the treatment group. A total of 148 patients were recruited for the study in the U.S. and internationally.

Safety was evaluated by assessing the incidence and severity of device-related complications from the first treatment day through the 3-month post-treatment time point. Effectiveness of the treatment was evaluated based on treated patients who experienced at least a 2-point improvement from baseline on a numeric rating scale NRS (0-10) at the treated site without an increase in medications.

Treatment team

The treatment team at Fox Chase Cancer Center (FCCC) for this study included one radiation oncologist, one project coordinator; two registered nurses (advanced cardiovascular life support certified), one medical physicist and one board certified MR technologist. Each person performed a specific role in the study. The radiation oncologist was responsible for recruitment of patients, performing treatment planning, patient treatment and the follow-ups after treatment. The project coordinator was responsible for coordinating patient treatment with the treatment team, patient and study sponsor

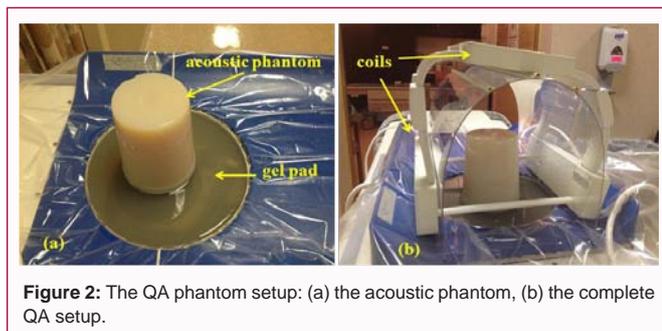


Figure 2: The QA phantom setup: (a) the acoustic phantom, (b) the complete QA setup.

(Insightec) and also for maintaining the treatment records. Two registered nurses were responsible for working with the operating physician to provide an appropriate level of sedation and continuous monitoring of vital signs (pulse, blood pressure, oxygen saturation) with MRI compatible equipment. One nurse remained with the patient in the treatment room for the entire treatment time. The medical physicist was responsible for treatment QA (machine calibrations including the hardware, software and all safety devices). The MR technologist worked with the physicist for patient treatment setup and was also responsible for performing MR images before, during and after treatment.

Machine calibrations

Daily QA (DQA): In order to allow the vendor to have adequate time to correct potential problems from QA without delaying the patient's scheduled treatment, we performed DQA at least one week prior to the patient's treatment.

Mechanical check: 1) To reboot the MR scanner, 2) to dock the HIFU treatment table to the MR scanner and check the mechanical movements for table in and out; up and down positions, 3) attach the coupler cable to the treatment table, 4) turn on the HIFU workstation and log into the computer, 5) connect the pelvic coil to the MR scanner, and 6) set up the landmark for MR scan.

QA phantom set up: A gel pad was placed on the treatment table in line with the transducer. Degassed water was used for the interface between the treatment table and the gel pad for the acoustic coupling. Care was taken to eliminate air bubbles between the interfaces. The gel pad is used not only for supporting the acoustic phantom but also as a medium for ultrasound transmission. The acoustic phantom was placed on top of the gel pad (Figure 2). The phantom was manufactured by ATS Labs, Inc. (Bridgeport, CT) with acoustic properties similar to those of human soft tissue (the attenuation coefficient = $0.503 \text{ dB cm}^{-1} \text{ MHz}^{-1}$; speed of sound = 1538 MPS; estimated specific heat = 2.684 cal/g) except for without the property of thermal conductivity due to lack of blood flow. The acoustic phantom is not used for patient tissue calibration. It is used for mechanical calibration and software for the end to end test. The phantom was used for identifying the geometrical treatment focal spot by temperature elevation during the sonication. The effective treatment focal spot was registered with the template focal spot in the planning software (see below). The verification of the focal spot position in patients is achieved using low-energy subtherapeutic sonications and MR thermometry.

End-to-end test: Successful completion of the end-to-end test indicated that all parts including the mechanical hardware, MR scanner, MR coils, and treatment software have passed QA. For the end-to-end test, a 3-plane localization of MR sequence was performed.

The images were carefully checked for any gas bubbles between the interfaces. The images were loaded to the FUS workstation. The position of the transducer from the images was calibrated to the contour of the transducer from the treatment software. The effective treatment focal spot was registered in 3 imaging planes using MR thermometry. Finally, all of the safety devices (described as above) were tested.

Preventive maintenance (PM): A Preventive Maintenance (PM) program was developed for both quality and safety control. PM is performed by a trained engineer from the vendor. The quality control checks may include items such as alignment light, coils, patch update, large volume shim, eddy current class, coherent noise, SNR and spike noise etc. while the safety control checks may include oxygen monitor operation, patient blower & filter, patient table, pneumatic patient alert system and magnet rundown unit. A PM procedure is performed every 6 months in the Radiation Oncology Department of FCCC.

Patient preparation and treatment setup

On the day of the treatment, each patient reported to the clinic in the Department of Radiation Oncology 2 hours before treatment for preparation, including removal of the skin hair (if any) in the treatment area, placement of the intravenous line and Foley catheter and application of anti-thrombotic compression devices. The patient was also sent to Interventional Radiology for a periosteal injection consisting of bupivacaine and epinephrine into the region of the desired treatment target under fluoroscopic imaging guidance.

A pelvic MR coil (23cm circular hollow in the center) was placed and secured on the treatment Table. A plastic sheet was placed on the Table. The interface between the treatment Table and the plastic sheet was coupled using acoustic gel and degassed water. The edges of the plastic sheet were secured on the coil frame using medical plastic tape so that it appeared comparable to a large plastic bowl. A 2cm thick gel pad was placed on the plastic sheet with degassed water for an acoustic coupling. The degassed water was filled to a few mm above the gel pad.

The ideal position for patient setup is to have the treatment target in line with the center of the transducer. In order to save time for patient setup, a temporary skin marker indicating the position relative to the target was created using the guidance of diagnostic CT images. The patient was laid on the gel pad in contact with the degassed water. The skin marker related to the treatment site was positioned in line with the center of the transducer. Initially, a localization scan (axial, sagittal and coronal) was performed. From the MR images, the interfaces between the treatment table and gel pad, the gel pad and patient's skin were carefully checked for gas bubbles (Figure 3).

Treatment procedures

The patient was treated under conscious sedation. A registered nurse was with the patient in the MR room for the entire treatment procedure working with the physician to provide an appropriate level of sedation. Continuous monitoring of vital signs (pulse, blood pressure, and oxygen saturation) was implemented by the nurse with MRI compatible equipment.

Prior to treatment, patient CT images were loaded onto the MR console. The patient was instructed to hold a panic button for emergency purposes during treatment. Both axial and sagittal T2-weight MR scans were performed. Both MR and CT images were

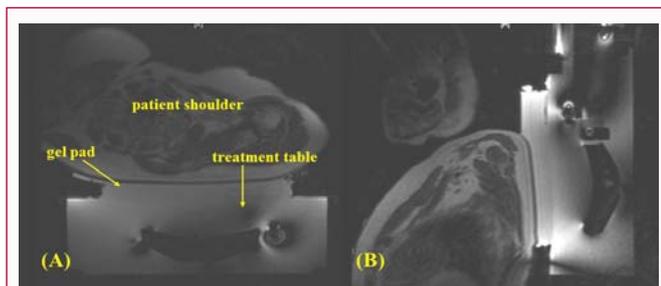


Figure 3: MR image showing the patient setup: (a) an axial view and (b) a sagittal view.

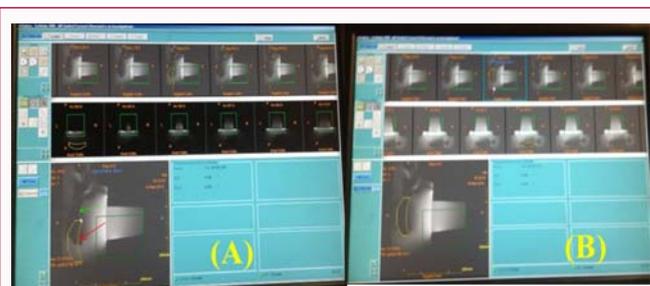


Figure 5: MR images showing the transducer before (a) and after (b) the calibration.

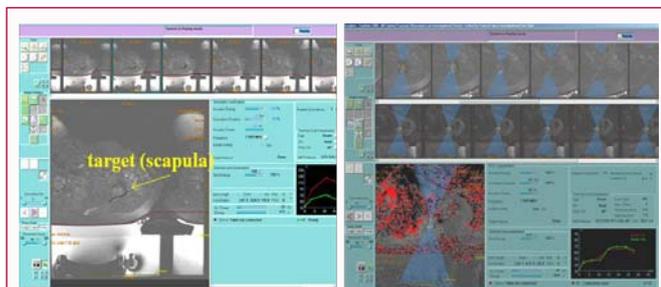


Figure 4: A screenshot demonstrating (a) real-time treatment planning, and (b) treatment monitoring with MR thermometry.

loaded to the HIFU treatment station. CT and MR fusion was performed using built-in software. The target outlining and treatment planning were performed by the treatment physician in real-time.

Patients were treated with a frequency of 1 MHz; acoustic power of $32\text{W} \pm 4.0\text{W}$ to $96\text{W} \pm 11\text{W}$ and energy of $628\text{J} \pm 78\text{J}$ to $1859\text{J} \pm 338\text{J}$ for 20-30 seconds for each sonication. Temperature changes (in the soft tissues immediately adjacent to the treated bone target) were monitored in real-time using MR thermometry with the proton resonant frequency shift method. Based on the temperature feedback, the acoustic power was adjusted to reach the desired temperature ($\geq 60^\circ\text{C}$) for each individual sonication. Figure 4 demonstrates real-time MR guidance for FUS treatment. Patients were followed up to 3 months after treatment based on the study protocol.

Results and Discussion

QA

Pre-treatment QA plays an important role in performing the MRgFUS treatment safely and effectively. Figure 5 shows the registration of the transducer position between the physical transducer and the transducer contour from the treatment software using MR guidance. In our practice, in order to avoid the possibility of cancellation of patient treatment due to treatment machine malfunctions, pre-machine QA (a few days before) is necessary. For example, we found that during the pre-treatment QA for one of the seven patient treatments, the transducer could not be returned to the home position; therefore, we informed the vendor without delaying the patient's treatment. The "new" QA procedure translated into non-cancellation of treatments.

Figure 6 demonstrates an example of the gas bubbles trapped between the interfaces, which must be removed before the sonication treatment. During the patient setup, we carefully removed all gas bubbles and further checked this through MRI imaging. We believe that with the clinical treatment protocol (treatment target is $>1\text{cm}$ from the skin surface), skin toxicities should not occur unless gas

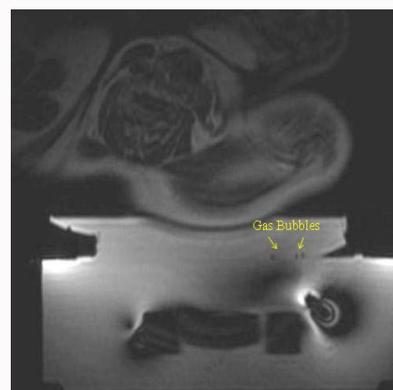


Figure 6: MR image showing the gas bubbles near the interfaces between the treatment table and the gel pad.

bubbles exist between the interfaces of the skin and the gel pad.

Figure 7 is the registration of the treatment focal spot to the treatment planning focal spot in 3 dimensions demonstrating real-time closed loop quality assurance procedure.

Patient treatment parameters and treatment outcomes

The principle of bone palliative treatment is to use FUS to ablate the adjacent periosteum, which is the sensory origin of the pain. The benefits of MRgFUS for palliation of pain in bone metastases, generally include a single treatment session, a non-invasive treatment procedure, nonionizing therapy, and fast pain relief. Table 1 summarizes the information for seven treated patients including the primary tumor, treated site, treatment parameters, the total number of sonications and the temperature reached in the treated target.

On average, the temperatures from MR thermometry in the target ranged from 62°C to 77°C with a standard deviation of $\pm 7^\circ\text{C}$ -12°C . All 7 patients tolerated the MRgFUS treatment well including 15 additional patients treated after the system received FDA approval. No device-related severe adverse events were recorded for any of the patients. There were no skin toxicities or other complications identified. Figure 8 represents a picture taken immediately following HIFU treatment demonstrating no skin toxicity from the treatments.

Our data showed that the numerical pain scale was significantly reduced from 8.0 ± 1.1 before treatment to 4.7 ± 3.0 , 3.0 ± 1.5 , 3.2 ± 2.8 and 3.4 ± 1.5 at one day, one month, two months and three month intervals after treatment, respectively (Figure 9). Based on the clinical trial protocol, responders were defined as a decreased VAS pain score of 2 points without a 25% increase in narcotic pain medication. The average VAS pain score from our study was reduced from 8.0 prior to treatment to 3.4 at 3 months post-treatment (a 4.6 point decrease).

Table 1: Patient information and summary of HIFU treatment parameters.

Pt#	Primary tumor	Treatment site	Sonications Acoustic	Acoustic Power(W)	Energy (J)	Durationslp or sonication(S)	T(°C)
1	breast	LT scapula	6	34 ± 4.0	628 ± 78	20 ± 0	62 ± 11
2	prostate	RT scapula	17	21 ± 4.0	628 ± 99	30 ± 0	66 ± 9
3	breast	RT humeral head	9	42 ± 3.0	1005 ± 114	24 ± 3	77 ± 7
4	breast	Sacrum	18	79 ± 11.0	1607 ± 178	20 ± 0	69± 7
5	colon	RT Ilium	17	96 ± 11.0	1859 ± 338	20 ± 0	73 ± 11
6	kidney	Pubic ramus	13	62 ± 15.0	1240 ± 293	20 ± 0	69 ± 12
7	breast	LT acetabular	12	78 ± 32.0	1605 ± 611	20 ± 0	65± 7

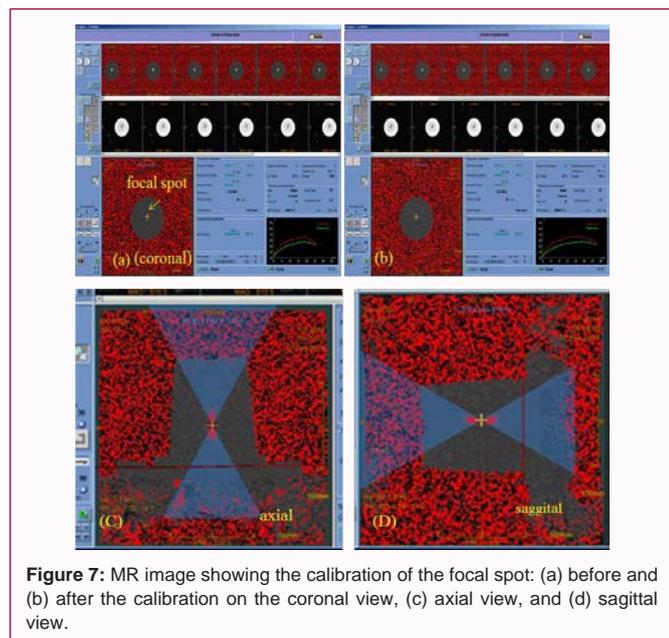


Figure 7: MR image showing the calibration of the focal spot: (a) before and (b) after the calibration on the coronal view, (c) axial view, and (d) sagittal view.



Figure 8: A photo of a patient showing no skin damage immediately after the MRgFUS treatment.

Our results are consistent with those reported by other participating centers. Liberman “et al”. [7] showed that the average VAS score was reduced from 5.9 prior to treatment to 1.8 at 3 months post-treatment (a 4.1 point decrease). Gianfelice “et al”. [4] reported that all patients showed a progressive decrease in pain in the treated regions. VAS scores averaged 6.0 before treatment and decreased to 0.5 at 3 months (decrease in pain score, 92%; P <0.01) without any adverse events. Catane “et al”. [21] also reported a prolonged improvement in pain score and/or reduced analgesic dosage without any severe adverse events.

Thermal feedback with MR thermometry using the proton resonant frequency shift method [23] in bone treatment is a challenge since bone produces weak signals on MRI due to the low water content of bone cortex. Therefore, the temperature increase inside the bone tissue cannot be directly measured. The reliable temperature measurements were obtained from soft tissue adjacent to the treated

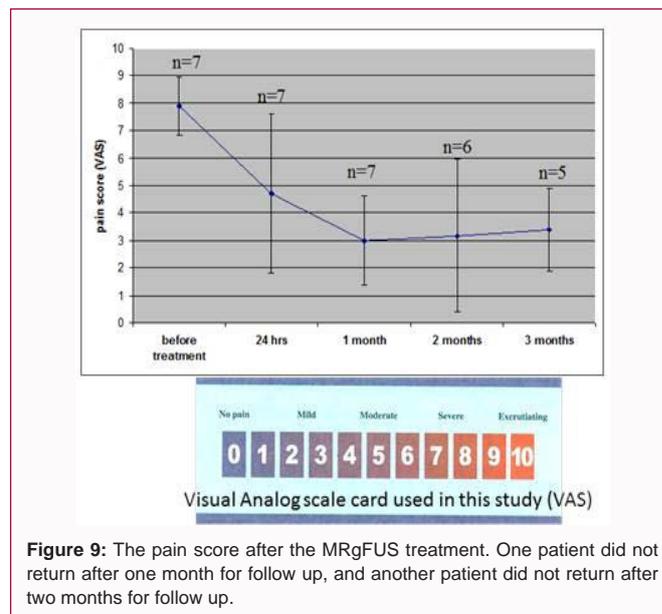


Figure 9: The pain score after the MRgFUS treatment. One patient did not return after one month for follow up, and another patient did not return after two months for follow up.

bone. The treatment system embedded software calculates the temperature elevation providing temperature mapping on the phase images, which exhibited some noises inside bone, fatty areas, and near interfaces between tissues, etc. Therefore, it is a challenge for the operator to manually select the real heating area accurately by drawing a polygon. Only the thermal dose [24] inside the drawn polygon will be collected for treatment reference. However, the outcome of the treatment is very effective and significant from our clinical experience and the studies from other institutions, as mentioned above [21].

The significance of this work is not only to report the favorable clinical outcome of MRgFUS bone palliation that is consistent with those reported but more importantly to demonstrate practical QA procedures which is essential for its safe and effective operation. The QA procedures and the clinical workflow described in this paper would be of assistance to other institutions in gaining clinical experience using the same treatment systems.

The limitation of this study was a small patient population. However, we also mentioned an additional 15 patients treated after the system received FDA approval. These 15 patients did not show device-related severe adverse events either. Another limitation was the short follow up of the study. The original study design considered most patients enrolled in this study to be terminal patients. A longer follow up will be considered in our future studies.

Conclusion

In this work, the clinical workflow and practical QA procedures have been described for the palliative treatment of metastatic bone

patients using the clinical MRgFUS system. Our data suggests that with careful execution of the QA procedures MRgFUS is a safe, effective and noninvasive treatment modality for metastatic bone palliation.

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