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Real-Time Magnetic Resonance Guided Focused Ultrasound for Painful Bone Metastases

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TITLE:

Real-Time Magnetic Resonance Guided Focused Ultrasound for Painful Bone Metastases

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KEYWORDS:

bone metastases, cancer pain, focused ultrasound, magnetic resonance-guided focused ultrasound, quality assurance, thermal ablation

SUMMARY:

Magnetic resonance could offer real-time monitoring of the position and temperature of focused ultrasound in thermal ablation for painful bone metastases, regardless of cancer type or previous local treatments. Our innovative method of quality assurance could facilitate the application of this effective and safe treatment.

ABSTRACT:

Bones are one of the most common sites of cancer metastasis, which usually causes pain and impairs quality of life. Radiation therapy combined with opioids is the standard treatment for painful bone metastases. This treatment achieves effective pain control in 60−74% of patients, but limited treatment choices with limited benefits are available for recurrent or residual painful bone metastases after radiotherapy. More than 40% of patients still experience moderate to severe bone pain after reirradiation. Magnetic resonance-guided focused ultrasound (MRgFUS) combines high-intensity focused ultrasound, which achieves thermal ablation of bone metastases and subsequent pain reduction, with real-time magnetic resonance (MR) thermometry to monitor the temperature of anatomic MR images, with an accuracy of 1 °C, spatial resolution of 1 mm, and temporal resolution within 3 s. As well as being increasingly used clinically for controlling metastatic bone pain, the use of MRgFUS for other diseases has also been tested. However, the use of MR software as a thermometer is the only technique available to verify the accuracy of the software and assure energy delivery. Here, we describe an efficient method of quality assurance we developed for thermal detection and energy delivery before each MRgFUS treatment and also propose a modified workflow to expedite the treatment course as well as to reduce patients' pain during the procedure.

INTRODUCTION:

Bones are one of the most common sites of cancer metastasis, which usually causes pain and impairs quality of life. Radiation therapy (RT) combined with opioids is the standard treatment for painful bone metastases. This treatment achieves effective pain control in 60−74% of patients[1]. However, limited treatment choices are available for recurrent or residual metastatic bone pain after RT. Reirradiation, surgical intervention, percutaneous cryoablation, or radiofrequency ablation and increased doses of systemic opioids and analgesics are options with limited indications and usually with side effects. Moreover, these secondary treatments have yielded unsatisfactory results: more than 40% of patients continue to experience moderate to severe bone pain after reirradiation[2].

High-intensity focused ultrasound systems integrate ultrasounds from multiple angles into one spot, transferring acoustic energy at ablative temperatures of more than 65 °C[3]. This noninvasive technique has been used for thermal ablation at various sites and for various types of lesions[4,5]. Generally, focused ultrasound systems generate acoustic energy at frequencies of 200 kHz–4 MHz[6,7], producing an intensity in the focal point on the order of 100–10,000 W/cm^2. At these energy levels, the focused ultrasound beams trigger a rise in cell temperature over the treated volume of tissue. The temperature rise varies according to the tissue absorption coefficient, predicted using Arrhenius analysis or the Sapareto–Dewey isoeffect thermal dose relationship.

To achieve better control and a more rapid temperature increase, focal volumes of 0.2–5 mm^3 are suggested for each sonication. Therefore, the ablation of larger areas requires tiling of multiple sonications to cover a large volume and to create homogeneous thermal damage. In addition to causing damage as a result of thermal effects, focused ultrasound also creates microbubbles because of physical factors such as rectified diffusion in the treated area. When the size of microbubbles reaches a cutoff, they eventually implode, causing microshock waves and affecting surrounding tissues. This parallel nonthermal effect also contributes to tissue injury and tumor necrosis.

Unlike other image guidance techniques, such as ultrasound imaging, magnetic resonance (MR) imaging provides a three-dimensional image of anatomy with clear resolution images of soft tissue and quantitative temperature monitoring. The mapping software of quantitative MR thermometry can calculate the thermal change in degrees Celsius and then superimpose the respective locations onto the anatomic MR images[8]. By detecting the proton resonance frequency shift in water hydrogen, which corresponds to approximately 0.01 ppm per degree Celsius, the temperature-sensitive MR sequence can control energy deposition, with an accuracy of 1 °C for measurement of thermal changes, a spatial resolution of 1 mm, and a temporal resolution within 3 s[9,10]. With this extended software, the MR device could provide diagnostic images and also detect thermal changes within seconds, mapping these onto the anatomical images during the whole treatment course. Despite the development of such an innovative technique, few articles describe qualitative security during each treatment course. Here we aim to share our protocol and experiences with MRgFUS.

PROTOCOL:

Taipei Medical University Joint Institutional Review Board approval was obtained for this study.

NOTE: The same protocol, validated in Kao et al.[11], has been used to treat 138 cases between 2015 and 2019. The inclusion criteria for treatment enrollment were 1) the presence of a solitary distinguishable painful bone metastasis; 2) no administration of previous local therapy to the targeted bone lesion; and 3) the ability to access the targeted bone lesion with MRgFUS (**Table of Materials**). Patients with impending pathological fractures were excluded. Detailed materials and devices are listed in the **Table of Materials**.

1. Pretreatment consultation and CT-simulation for treatment spot

1.1. Evaluation of patients indicated for MRgFUS

1.1.1. Assess patient suitability for MRgFUS in treating metastatic bone pain. Explain the procedure and related information to the patient and family. Record daily analgesic medication and pain score before and after medication.

1.1.2. Have a radiation oncologist and radiologist locate the lesion and nearby anatomy based on pretreatment computed tomography (CT) or magnetic resonance imaging (MRI) scans.

NOTE: Spinal metastasis is excluded because of possible injury to the spinal cord or cauda equina. Lesions in the trunk should be treated dorsally rather than ventrally in order to prevent injury to major vessels and organs.

1.2. Confirm the treatment spot by CT simulation 1 day before MRgFUS.

1.2.1. Position the patient in a supine, head-first position on the couch and perform a helical CT scan (120 kV, 400 mAs/slice) over the treating area with a 3 mm slice thickness. Adjust and tilt the patient's position, in the center of the couch, to locate the lesion.

1.2.2. Place a CT marker, 1 cm lead wire, on the skin surface, vertically closest to the lesion, and conduct a helical CT scan (120 kV, 400 mAs/slice) again to confirm the position of the patient and the location of the CT marker. Mark the location of the CT marker with a marker pen and take a picture of the patient's position.

NOTE: Precise confirmation of the treatment spot and position before MRgFUS can facilitate the positioning process during MRgFUS.

2. Patient preparation for MRgFUS on treatment day

2.1. Verify the patient's identity according to photo identification. Verify that the patient removed all metal objects and magnetic devices prior to the scan.

2.2. Prescribe local and systemic analgesics before treatment.

2.2.1. At 1 h before the scheduled treatment time, apply lidocaine cream on the marked skin, with a radius of 10 cm. Remove the cream carefully 10 min before treatment.

2.2.2. At 30 min before treatment, intravenously drip 5 mg of dexamethasone with 50 mL of normal saline for 10 min and 30 mg of ketorolac with 50 mL of normal saline for 10 min. Set the peripheral intravenous line on either hand, forearm, leg, or foot on the side opposite to the lesion.

2.3. Check the patient's vital signs (heart rate, blood pressure, respiratory rate, and blood saturation) 5 min before sending the patient out for treatment.

3. Daily quality assurance (DQA) before MRgFUS

3.1. DQA setup

3.1.1. Replace the diagnostic couch with the MRgFUS couch with a focused ultrasound transducer and connect the couch to the system.

NOTE: The staff must remove all metal objects and electric devices, including rings, watches, pens, mobile phones, or magnetic ID cards, before entering the MRI room.

3.1.2. Apply ultrasound transmission gel (~1 mm thickness) and degassed water on the surface panel of the focused ultrasound transducer.

NOTE: Be careful not to scratch the plastic panel during this process.

3.1.3. Carefully cover the panel with plastic drape, avoiding any folds of the drape over the panel area. Add degassed water to a level as high as the MR coil on the couch.

NOTE: Be careful not to make any gas bubbles between the panel, transmission gel, the drape, and degassed water.

3.1.4. Slowly and carefully place the gel pad on the panel without creating any gas bubbles during the process. Place the DQA phantom on the gel pad without creating any gas bubbles.

3.1.5. Place the MR coil on the couch and connect the coil to the MRI device. Press **Landmark** on the MRI control panel and align the red laser to the black stripe on the coil. Then, press **Advanced to Scan** on the MRI control panel.

3.2. DQA prescan

3.2.1. Click **Idle** on the MRI system to create a new MR scan. Enter DQA as patient's name and enter 50 kg for body weight. Choose **Supine** and **Feet First** as scanning parameters.

3.2.2. Choose scanning protocol as **ExAblate – Plan – Bone**. Then click **Save Series** | **Download** | **Scan**. Check scanning images on the monitor to check for any gas bubbles.

NOTE: If any gas bubbles are found, set up the DQA once more to remove them.

3.3. DQA procedure

3.3.1. Click **Bone Tumors** on the MRgFUS system and click **Calibrate** to start the DQA. Click **MR Scan** and confirm that the exam number is the same as in the MRI system.

3.3.2. Adjust the position of the transducer in the axial and sagittal images in order to let the sonication field cover the phantom. Click **Load** to load MRI images. Then click **Sag** | **Select All** to select all images. Click **Ax** | **Select All** again.

3.3.3. Click **Draw** to define the sonication area. Click **Skin Line** to contour the surface between the phantom and gel pad. Click **Copy** to copy the skin lines to all sagittal and axial slices of images. Then adjust and confirm the skin line is correct in each image.

3.3.4. Click **Treating Area** to contour the treatment area in the phantom for three continuous slices. Click **Protocol** to choose **Bone 15** and then click **Apply**. Click **Fiducial** and choose a spot in the phantom as a reference point.

3.4. DQA planning

3.4.1. Click **Plan** | **Verify** to proceed. Click **Add Sonication** to add one spot for sonication within the phantom. Confirm that the sonication field is within the phantom in each sagittal and axial slice.

3.4.2. Set the scan parameters: direction = **Coronal** and number slice = **5** with preset energy output. Click **Sonication** to start.

3.5. Calibration

3.5.1. After sonication, monitoring the MRgFUS system shows the temperature images. Confirm the heating spot and click **Center** to mark the spot. Use the mouse to check the heating spot and other, different spots to compare the thermal curve to locate artifacts or background signals.

3.5.2. The system shows adjustments for transducer location in millimeters in 3 axials. Click **Accept** and then click **Back** to perform the sonication again with a 20% increase in energy. Confirm that the 2nd adjustment is within 1 mm and click **Reject**.

3.5.3. Set scan parameter: direction = **Axial** and number slice = **5** with preset energy output. Make axial adjustments as described in steps 3.5.1 and 3.5.2. Click **Exit** to leave DQA and remove the phantom.

4. Patient positioning and pretreatment MR scanning

4.1. Patient positioning

4.1.1. Position the patient on the MRgFUS couch in the same position as the previous simulation in step 1.2. Align the mark on the skin with the center of the gel pad.

4.1.2. Secure the patient to the couch using a safety belt and teach the patient how to use the emergency button. Set the finger pulse oximeter on one index finger.

4.1.3. Place the MR coil on the couch and align the coil. Then press **Advanced to Scan** on the MRI control panel.

4.2. Pretreatment MR scanning

4.2.1. Create a new MR scan and enter the patient's information. Choose **Supine** and **Feet First** as the scanning parameters and the scanning protocol as **ExAblate – Plan – Bone**.

4.2.2. Acquire three-plane T2 images, then click **View Edit** to confirm the scanning area. Click **Save** | **Download** | **Auto PreScan**. Confirm the scanning area after prescan and then click **Scan**.

4.3. Confirm the lesion and patient position.

4.3.1. Reconfirm the lesion, MR scanning field, and patient position.

NOTE: The MR scanning field should be over the treatment area and cover the ultrasound transducer.

4.3.2. Examine any gas bubbles between skin surface and gel pad. Reposition the patient if any gas bubbles are present.

5. Treatment contouring and planning

5.1. Import MR images.

5.1.1. Click **Bone Tumors** on the MRgFUS system. Click **Contouring** | **MR scan** and confirm that the exam number is the same as in the MRI system.

5.1.2. Click **Load** to load MRI images collected in step 4.2. Click **Sag** | **Select All**. Then click **Ax** | **Select All** again.

5.2. Contouring

5.2.1. Click **Draw** to define the sonication area. Click **Skin Line** to contour the skin surface. Click **Copy** to copy the skin lines to all sagittal and axial slices of the images. Adjust and confirm that the skin line is correct in each image.

NOTE: The skin line must be contoured on each MR image slice with the ultrasound transducer.

5.2.2. Click **Bone** to contour the bone surface. Click **Block** to contour vital organs, such as nerves, vessels, or bowels, to prevent sonication through these areas. Click **Fiducial** and choose a spot near the lesion as a reference point.

5.3. Planning

5.3.1. Click **Plan** | **Verify** to proceed after all contouring is completed. Review treatment planning and adjust the sonication if needed.

NOTE: The pathway of sonication should be from the transducer to the lesion through the skin surface.

6. Verification and treatment

6.1. Analgesics and sedation

6.1.1. At 10 min before verification and treatment, intravenously drip 25 mg of meperidine and 7.5 mg of midazolam with 50 mL of normal saline for 10 min.

6.1.2. Intravenously drip 7.5 mg of morphine with 50 mL of normal saline for 10 min at an interval of 30 min if the patient complains of pain during the treatment course.

NOTE: A physician may adjust analgesics and sedation medication according to clinical conditions.

6.1.3. Periodically check the pulse and oximeter between sonication.

NOTE: If the patient is very nervous or requires accompaniment, a nurse or staff member may stay inside during sonication. MR and ultrasound do not cause radiation nor harm to other personnel nearby.

6.2. Verification

6.2.1. Choose one sonication with preset parameters and click **Sonication** to start. Monitor the temperature rise and thermal curve of the heating spot as well as the reference spot to check for artifacts or background signals. Increase the energy output and repeat the sonication to the same spot.

6.2.2. Repeat the sonication to the same spot until the temperature is over 65 °C to reach thermal ablation.

NOTE: Different people with different body mass, different locations, and different tissues would have various energy absorptions and thermal changes. Using lower energy for verification is necessary.

NOTE: Repeatedly heating the same spot or a nearby area in a short time may influence MR

thermometry. Therefore, allow the system to pause if the sonication intervals are too close.

6.3. Treatment

6.3.1. Click **Sonication** to start the treatment with the verified energy output described in step 6.2.

6.3.2. Monitor the temperature rise and thermal curve of the heating spot and repeat the sonication with increasing energy output until the temperature is over 65 °C. Complete all sonication for the treatment area.

7. Post-treatment evaluation

7.1. Post-treatment MR scanning

7.1.1. Conduct post-MRgFUS scanning with all series as in steps 4.2 and 4.3.

7.1.2. Inject intravenous contrast medium at a rate of 4−5 mL/s and conduct a contrasted MR scanning as step 7.1.1.

NOTE: The volume of contrast is based on body weight (i.e., 0.2 mL per 1 kg).

7.2. Evaluate treatment/thermal effect from post-treatment MRI. Repeat the sonication if the thermal ablation does not treat the whole lesion.

REPRESENTATIVE RESULTS:

A 68-year-old male patient was diagnosed with hepatocellular carcinoma (HCC) in October 2012. He received a left lobectomy on October 18, 2012, and pathology reported an 8.8 cm HCC. After operation, he experienced lower back pain and soreness, and an MRI on November 2, 2012 revealed a large metastatic mass involving the left sacrum, ilium, and gluteal soft tissue. Because of tumor compression and pain reaching 6 points on the visual analogue scale (VAS), he received RT with 45 Gy in 15 fractions in November 2012, and systemic therapy for metastatic HCC was also prescribed. Six months later, the pelvic metastatic tumor progressed and pain recurred, reaching 7 points on the VAS. A second RT with 25 Gy in 10 fractions in June 2013 and a third RT with 25 Gy in 10 fractions in November 2013 were arranged to treat the progressing tumor. The pain subsided for another 4 months but then recurred, reaching 7 points on the VAS in May 2014.

Because irradiation had previously been administered three times in the same location, MRgFUS was the only treatment option. For a huge pelvic mass over the left side of the pelvis, the treatment on May 27, 2014 used nine sonications of 2987.56 ± 1083.98 J, heating the tumor up to 61.78 ± 7.11 °C in each 20 s sonication (**Figure 1**). Using CTCAE version 4.0, a Grade 1 skin burn with minimal symptoms was noted, but no intervention was required. The patient's pain level dropped to 4 points on the VAS, which allowed analgesic dosages to be reduced for over 3 months.

However, due to the failure of systemic medication, the residual mass progressed again and caused moderate to severe pain, intermittently reaching 8 points on the VAS 5 months after his first MRgFUS treatment. In the absence of alternatives, the second MRgFUS treatment (**Figure 2**) was arranged on January 11, 2015 for the same bone metastasis. The treatment plan used 5 sonications with 1638.60 ± 210.67 J, heating the tumor to 64.40 ± 6.31 °C in each 20 s sonication. No adverse effect was noted on this occasion. The patient's pain level decreased to 4 points on the VAS within 1 day, and he was continuously maintained at a level of <4 points on the VAS for over 3 months. He passed away 7 months after the second MRgFUS.

FIGURE LEGENDS:

Figure 1: MR image in the 1st treatment. (**A**) Upper left image shows T2 fat-saturation before treatment and upper right image (**B**) shows T1 with contrast. The red arrowhead indicates the metastatic tumor over left sacroiliac joint. The lower image (**C**) is the monitoring image during the treatment, with the left side showing the current sonication spot and the right side showing the energy output and temperature of the sonication spot.

Figure 2: MRgFUS system showing in the 2nd treatment. System screen showing the intraprocedural MR images and controls (**A**), the thermal map after sonication (**B**), and a graph of the calculated temperature elevation during the sonication (**C**). T_{max} = maximum temperature.

Figure 3: Temperature-time curve of MR thermometry and thermoelectric couple.

DISCUSSION:

Several studies have demonstrated that MRgFUS is safe and efficient for controlling pain from recurrent or residual bone metastases after RT[12,13]. For 64.3–72.0% of patients, metastatic bone pain persists after RT and opioids. Studies have also determined MRgFUS has limited toxicity and a tolerable treatment course.

MRgFUS received approval for use in metastatic bone pain in 2011 by the Conformité Européenne and in 2012 by the U.S. Food and Drug Administration. As well as being increasingly used clinically for controlling metastatic bone pain, MRgFUS has also been investigated for use in other diseases, such as prostate cancer, breast cancer, and essential tremor[9]. However, use of MR software as a thermometer is the only technique available to verify the accuracy of the software and the safety of the device, which generates a focused ultrasound and delivers energy. Therefore, we demonstrated a treatment course using MRgFUS to treat bone metastases and also investigated an efficient method of providing quality assurance for thermal detection and energy delivery prior to each treatment. In this article, we propose modifications to the workflow currently recommended, which with the help of computed tomography simulation before treatment, could expedite the treatment course and also reduce patient suffering and pain during the procedure.

In our internal investigation, we found the focus error (FE) between the sonication focus and the spot with the highest temperature in the phantom was 1.73 ± 1.21 mm in the right–left (RL) axial, 0.95 ± 0.82 mm in the superior–inferior (SI) axial, and 0.31 ± 0.63 in the anterior–posterior (AP) axes before data quality assurance (DQA). After DQA, FE was significantly reduced to 0.43 ± 0.34 in the RL axial and 0.11 ± 0.22 in the SI axial, with $p < 0.01$ (pair t test). Our investigation suggested that DQA improves FE by up to 1 mm, with a 95% confidence interval, resulting in an FE of less than 0.5 mm in the SI and AP axes. Furthermore, we also verified the MR thermometry of MRgFUS with an MR-compatible thermoelectric couple (TEC) within a phantom to detect thermal changes. The result suggested that the thermal curve and temperature detection followed the same trend (**Figure 3**). The small temperature difference between MR thermometry and TEC contributed to quality assurance. Because the TEC is small and the metallic component interferes with image resolution, contouring the exact position of the TEC was difficult. Additional modification of the TEC in the phantom to improve thermal mapping and detection requires further investigation.

In conclusion, MRgFUS appears to be an effective, instant, and safe palliative treatment in patients with metastatic bone pain, especially for recurrent or residual pain. Demand and use for the treatment have been rapidly growing, but quality assurance and improvements to the treatment workflow have been rarely discussed in studies. Here, we describe our procedure and study results for DQA, indicating the value of DQA before each treatment. Using CT simulation before MRgFUS could facilitate workflow and reduce patients' suffering and pain during the procedure.

ACKNOWLEDGMENTS:

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DISCLOSURES:

The authors have nothing to disclose.

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Figure 1

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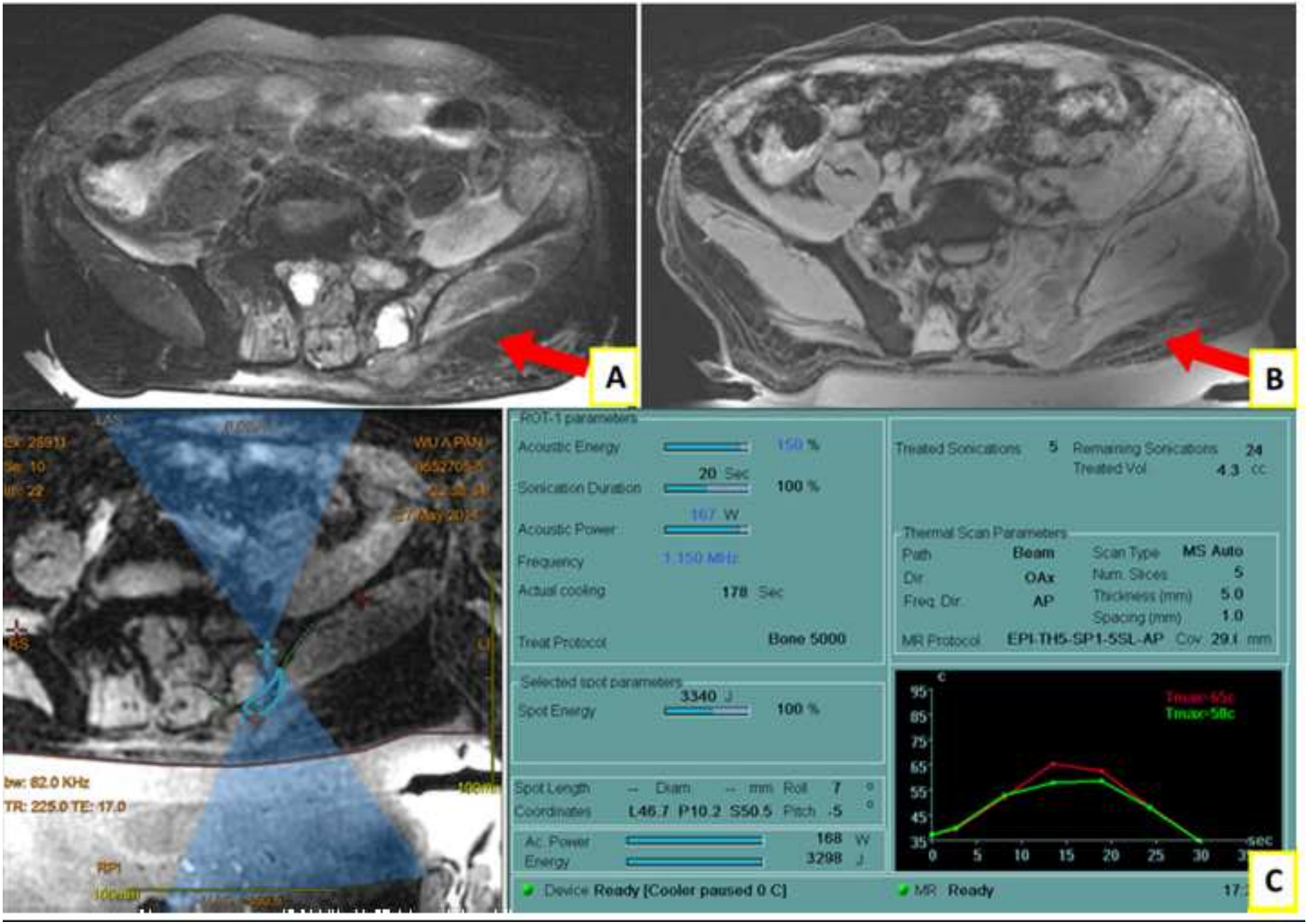

Figure 2

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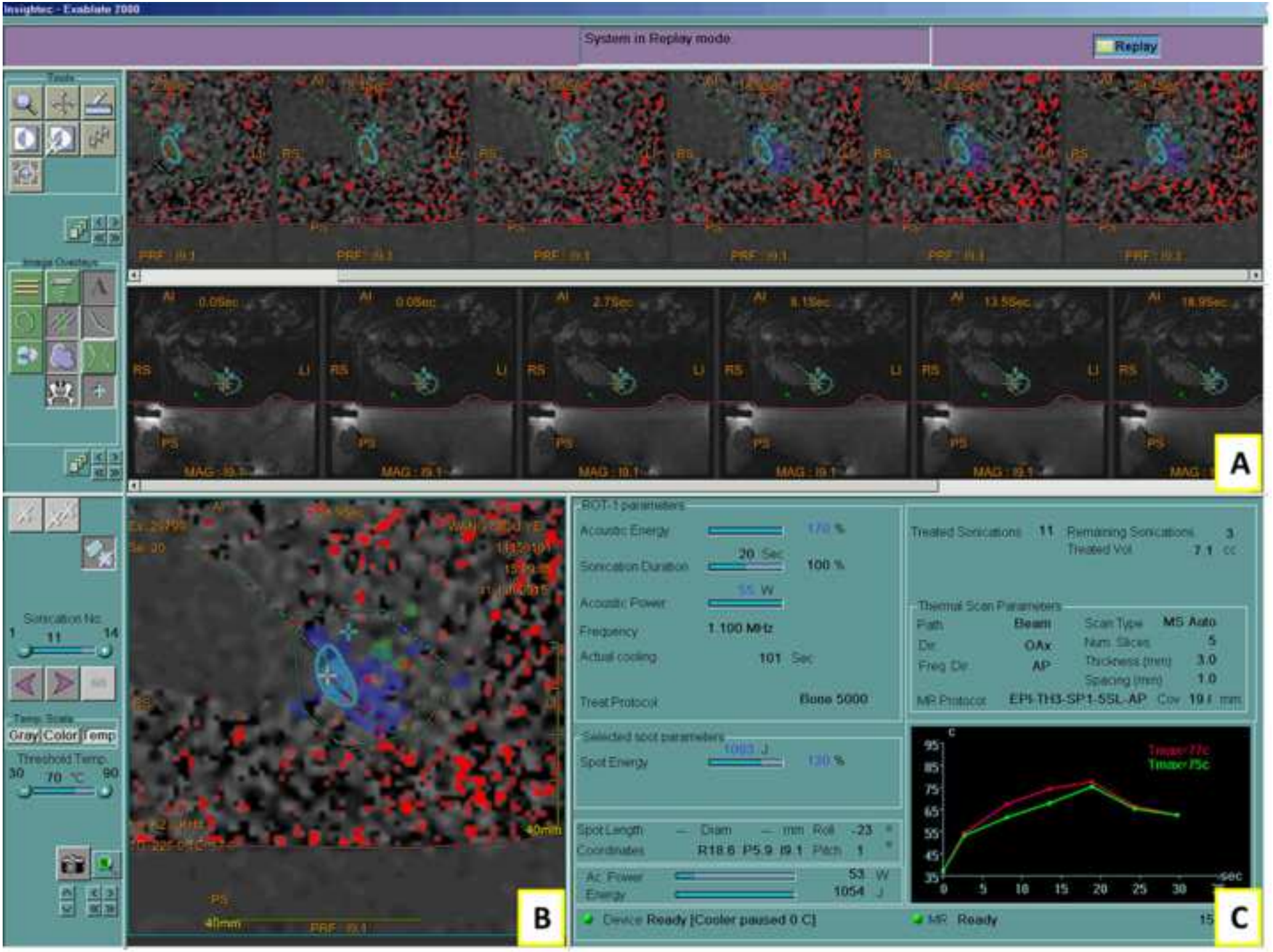
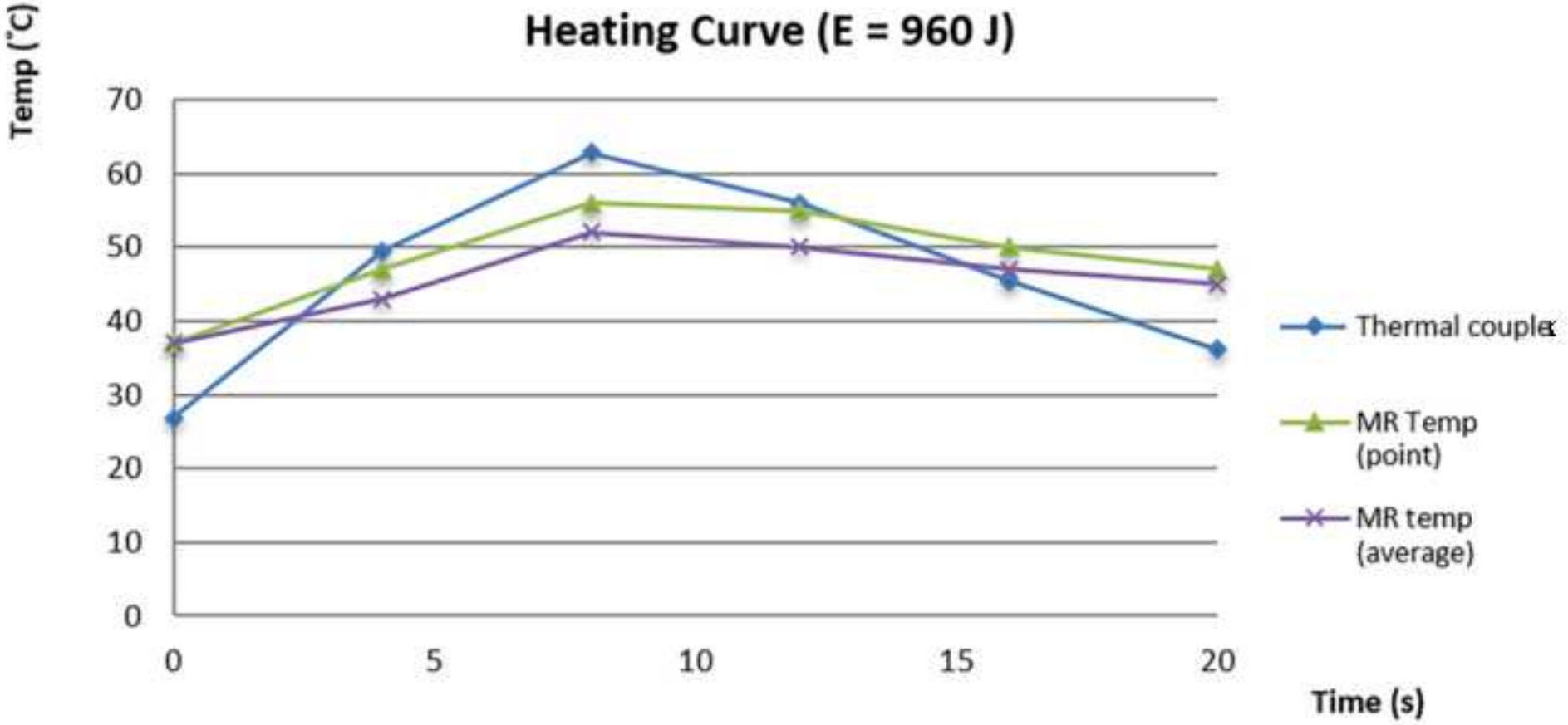


Figure 3



Name of Material/ Equipment	Company
1L degasseed water pouch	InSightec
CT scan	Philips
EXABLATE	InSightec
Gel Pad ASSY	InSightec
MR scan	GE
MRI contrast	Guerbet
Patient accessory kit	InSightec
Patient plastic drape	InSightec
Pelvic RF coil	GE
phantom	ATS Labs ATS Labs Inc
ultrasound transmission gel	InSightec

Catalog Number	Comments/Description
ASM001480	for good ultrasound beam transmission
Brilliance Big Bore 16 Slice CT, 7387	Acquire CT images for positioning
EXABLATE 2000	System for non-invasive tumor ablation through Focal Ult
SET999014	Transmission gel pad for single Body treatment.
HDxT	Acquire MR images for contouring and planning
Dotarem	Enhance MR for acquiring images
SET000016	clinical applications single use treatment kit
DTP000067	Cover the panel of ultrasound transducer. Deposible, hygi
ASM000956	Enhance MR for acquiring images
Model TxS-100	for calibration
SET000885	gel for calibration prior MR-guided FUS treatment

rasound (FUS) treatment under Magnetic Resonance (MR) guidance

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Changes to be made by the author(s):

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Well received and revised the manuscript.

The language and grammar in the manuscript has been edited by Wallace Academic Editing.

2. Title: Please revise to avoid the use of punctuation (colon, dash, etc.).

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3. Keywords: Please provide at least 6 keywords or phrases.

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4. 1.1.2: Please describe how.

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6. Discussion: As we are a methods-based journal, please discuss critical steps in the protocol, modifications and troubleshooting of the method, and limitations of the method.

Thanks for the comment!

We propose modifications to the workflow currently recommended, which—with the help of computed tomography simulation before treatment—could expedite the treatment course and also reduce patient suffering and pain during the procedure. We also investigated an efficient method for providing quality assurance for thermal detection and energy delivery prior to each treatment. However, additional modification of TEC in the phantom to improve thermal mapping and detection merits further investigation. We have revised the discussion to strengthen the importance of our study.

7. For in-text references, the corresponding reference numbers should appear as superscripts after the appropriate statement(s) in the text (before punctuation but after closed parenthesis).

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Reviewers' comments:
Reviewer #1:
The authors did not response to my questions in the previous review process.
In the introduction, the importance of the problem to be investigated is not described.
Thanks for the comment! We aim to share our experiences on using such innovative treatment technique. We have modified the introduction to help readers understand.
Hard to understand "transferring acoustic energy to ablation temperature"
Thanks for the comment!
Focused ultrasound systems produce acoustic energy by using a piezoelectric transducer that operates at frequencies of 200 kHz–4 MHz, producing an intensity in the focal volume on the order of 100–10,000 W/cm2, a peak compression pressure of up to 70 MPa, and a peak rarefactional pressure of up to 20 MPa. At these energy levels, the interaction between the focused ultrasound beams and biologic tissue results in a rise of cell temperature over the treated volume of tissue. The increased cell temperature leads to coagulative necrosis at a thermal range of 65°–85°C.
What's "intra-cellular heat change"? I think it is thermal conduction of the biological material.
Thanks for the comment!
It means a rise of cell temperature over the treated volume of tissue. As mentioned above, the interaction between the focused ultrasound beams and biologic tissue results in a rise of cell temperature over the treated volume of tissue. We will revised the manuscript to help readers understand the meaning.
Concept of bubble cavitation is wrong, not induced by the number of microbubbles
Thanks for the comment! The nonlinear oscillation of a microbubble subjected to an acoustic pressure was analyzed by numerically solving the Rayleigh-Plesset equation. When the size of the microbubbles reaches a critical cutoff, they eventually implode, producing microshock waves capable of damaging surrounding tissues. We will revised the sentence for better accuracy.
Referrence:
M. Susani, S. Madersbacher, C. Kratzik, L. Vingers, and M.Marberger, “Morphology

of tissue destruction induced by focused ultrasound," Eur. Urol., vol. 23, Suppl. 1, pp. 34–38, 1993.

N. A. Watkin, S. B. Morris, I. H. Rivens, and G. R. ter Haar, "High-intensity focused ultrasound ablation of the kidney in a large animal model," J. Endourol., vol. 11, no. 3, pp. 191–196, 1997.

Only one patient is included in this study so the robustness of the proposed approach cannot be validated.

We have treated 138 cases between 2015 and 2019 using the same protocol.

In 2016, we have published an article to validate this protocol. we measured sonication-induced temperature change in a homogenous phantom before and after Daily Quality Assurance (DQA) procedure performed in thirty-one treatment sessions. And DQA procedure effectively decrease FE (Pre-DQA group: 1.73±0.43 mm, DQA group: 0.43±0.12 mm, p-value＜0.01).

Referrence:

https://tmu.pure.elsevier.com/en/publications/position-stability-analysis-of-a-clinical-mri-guided-focused-ultr

Have the authors considered the thermos-viscous effects at the tip of thermocouple?

Thanks for the comment! This study aims to demonstrate a protocol for better accuracy while a lot of basic research is still conducted. We aim to use the heat clinically to kill cancer cells. Whether there is another way to cause cell damage beyond heat is still under investigated. After all, we have treated many patients successfully and we aim to demonstrated this procedure with quality assurance.

Line 37-38 very hard to understand this sentence

Thanks for the comment!

It means there is limited ever none treatment choices when bone metastases progresses after radiotherapy. We have revised this sentence for better understanding.

Line 46-47 hard to understand "use thermometer to verify the accuracy of the software"

Thanks for the comment! MR Thermometry was the only way to verify the accuracy of the software. However we develop an efficient method of quality assurance to conduct quality assurance. We have revised this sentence for better understanding.

Line 69 at the focal point not in the focal volume

Thanks for the comment and we have revised the sentence.

Line 71 focal volume instead of focal area

Thanks for the comment and we have revised the sentence.

Line 74 "mm" is not the unit for volume

Thanks for the comment and we have revised the sentence.

Line 84 temporal resolution of 3 s is not real-time

Thanks for the comment! We have revised this sentence for accuracy.

Reviewer #2:

Manuscript Summary:

The paper still presents some critical weaknesses.

Major Concerns:

The aim of the paper is not clearly stated in the introduction.

Thanks for the comment! We aim to share our experiences on using such innovative treatment technique. We have modified the introduction to help readers understand.

The protocol is described for a specific software but the name of the software is not shown.

Thanks for the comment and we have added the software in the material and method.

Please list all the names of the technical equipment (softwares, MRgfUS machine, etc...) used in the M&M section.

Thanks for the comment and we have added the software in the manuscript.

The type of statistical analysis used needs to be clarified.

We have treated 138 cases between 2015 and 2019 using the same protocol.

In 2016, we have published an article to validate this protocol. we measured sonication-induced temperature change in a homogenous phantom before and after Daily Quality Assurance (DQA) procedure performed in thirty-one treatment sessions. And DQA procedure effectively decrease FE (Pre-DQA group: 1.73±0.43 mm, DQA group: 0.43±0.12 mm, p-value＜0.01, pair t test).

Referrence:

https://tmu.pure.elsevier.com/en/publications/position-stability-analysis-of-a-clinical-mri-guided-focused-ultr

Minor Concerns:

English needs to be improved.

Thanks for the comment! The language and grammar in the manuscript has been edited by Wallace Academic Editing.