Magnetic resonance guided focused ultrasound surgery (MRgFUS) of bone metastases: From primary pain palliation to local tumor control

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Magnetic Resonance guided Focused Ultrasound Surgery (MRgFUS) of Bone Metastases: from Primary Pain Palliation to Local Tumor Control

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Abstract. Purpose: To evaluate the clinical performance of MRgFUS in primary pain palliation of painful bone metastases and in local tumor control. Materials and Methods: We enrolled 26 consecutive patients (female/male 12/14; age: 64.7±7.5yrs) with painful bone metastases. Before and 3 months after MRgFUS treatment pain severity and pain interference scores were assessed according to Brief Pain Inventory-Quality of Life (BPI-QoL) criteria and patients underwent both CT and MRI. Local tumor control was evaluated according to lesion size, density and perfusion at CT, dynamic contrast enhancement at MRI (Discovery 750HD, GE; Gd-Bopta, Bracco) and metabolic activity at PET or scintigraphy. Patients were classified as responders or non-responders. Results: No treatment-related adverse events were recorded during the study. As statistically significant difference between baseline and follow-up values for both pain severity and pain interference scores was observed ($p<0.05$). Increased bone density was observed in 9/26 (34.6%) patients. Non-Perfused Volume values ranged between 20% and 92%. There was no difference in NPV values between responders and non-responders (46.7±24.2% [25 – 90 %] vs. 45±24.9% [20 – 93 %]; p=0.7). In 6 patients (5 prostate and 1 breast primary cancer) there was nearly absence of metabolic activity after treatment (mean SUV=1.2). Conclusion: MRgFUS can be safely and effectively used as the primary treatment for pain palliation in patients with painful bone metastases; moreover our experience demonstrated also a potential role for the MRgFUS in local tumor control.

INTRODUCTION

Bone is the third most common organ for distant tumor metastases, after lung and liver [1]. Patients suffering from bone metastases often require treatment because of pain, immobility, pathologic fractures [2]. Conventional therapies for bone metastases include surgery, chemotherapy and various forms of percutaneous ablation. The success rate of combined treatment is often adequate, but a significant percentage of patients do not benefit from symptom relief, or they face symptom recurrence in the short term [3]. Magnetic Resonance-guided Focused Ultrasound (MRgFUS) is a non-invasive thermal ablation modality that combines the ablative properties of high intensity focused ultrasound with MR imaging for target definition and real-time guidance and monitoring [4]. The aim of this study was to determine the preliminary feasibility, safety, and clinical efficacy of MRgFUS for treatment of painful bone metastasis.

MATERIALS AND METHODS

Pre-procedure

The study was approved by the local Ethics Committee and written informed consent was obtained from all patients. 26 consecutive patients (12 female and 14 mal) with painful bone metastases were enrolled. Patient characteristics

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were summarized in table 1. In order to confirm the diagnosis and the treatment feasibility, all patients underwent unhenanced CT scan (Somatom Sensation 64-MDCT, Siemens, Erlangen – Germany, 120 kV, 200 mAp, detector configuration: 64 x 0.6, slice thickness 1 mm, reconstruction interval 1 mm) and MRI (3T unit, Discovery 750, GE Healthcare, Milwaukee, WI, USA) with dynamic contrast enhancement sequences (DCE-MRI, Gd-Bopta, Bracco). No confirmatory biopsy was necessary before MRgFUS ablation, but in case of doubtful diagnosis were required a third diagnostic modalities (PET/CT, scintigraphy).

Table 1: Characteristics of patients

Study population (n=26)	
Age:	
- Range, (mean)	37-82, (63,6)
Metastasis type, n(%)	
- Osteolytic	11(42,3)
- Sclerotic	8(30,7)
- Mixed	7(27,0)
Metastasis location, n(%)	
- Non-axial skeleton	12(46,1)
- Axial skeleton	14(53,9)
Metastase number, n(%)	
- Single lesion	4(15,3)
- Multiple lesions	22(84,7)
Primary Tumor, n(%)	
- Lung	7(26,9)
- Breast	6(23,1)
- Prostate	4(15,4)
- Colon	3(11,5)
- Others	6(23,1)

Inclusion are reported in table 2 and exclusion criteria are reported in table 3. The target lesions close to joints, tendons, tendon sheats, or neurovascular bundles were individually evaluated for accessibility.

Table 2

MRgFUS inclusion criteria
- Karnofsky performance status scale ≥ 60%;
- Known primary malignancy;
- Bone metastases confirmed by two or more imaging modalities;
- MRgFUS treatment feasibility assessed at preliminary MR planning examination;
- VAS scale ≥ 4

Table 3

MRgFUS exclusion criteria:
- Life expectancy shorter than follow up timeline;
- General contraindication to MR imaging and/or gadolinium-based contrast agents (including chronic renal failure);
- Controindication general anesthesia or regional anesthesia;
- Vertebral location of skeletal metastases:
- Previous radiotherapy on the target site;

Procedure

All procedures were performed by a single physician (A.N., 8 years of experience in musculoskeletal interventional radiology) with a focused ultrasound phased-array treatment system (ExAblate 2100, InSightec, Tirat Carmel, Israel) integrated within the 3T MRI scanner. The patients were anesthetized (deep sedation, epidural, or general anesthesia) to avoid movement and ensure pain management. Treatment planning starts with acquisition of T2-w images to target lesion. The operator manually draws tumor margins. Treatment started after verifying the correct target, with a sub-therapeutic sonication. Each sonication ablates an area between 2 to 6 cm^2 (fig.1).

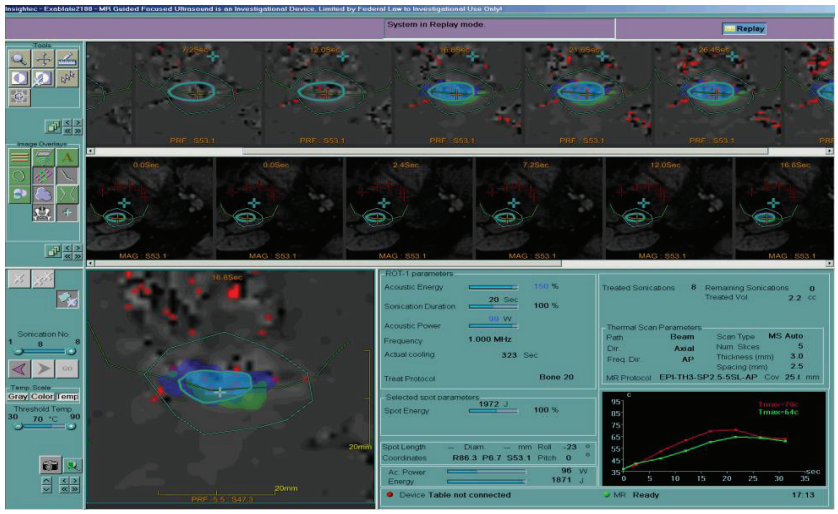

FIGURE 1. MR thermal maps

Although MR thermal maps cannot be measured directly within the bone tissue (as a result of the low MR signal from the cortical zone), heating due to conductive processes from the bone surface within the adjacent soft tissue is considered adequate for treatment monitoring [5]. Immediately after treatment, patients were examined and questioned for any adverse events and for 1-2 hours prior to discharge.

Post-procedure

Clinical evaluation of pain intensity was performed in all patients before and 3 months after treatment, by using visual analog scale (VAS), ranged from 0 (none) to 10 (severe) and Brief Pain Inventory-Quality of Life (BPIQOL), ranged the patients were then asked to complete a 10-point scale questionnaire in which the number 1 corresponded to the absence of pain and the number 10 corresponded to the worst experienced pain [6,7]. According to International Bone Metastases Working Party guidelines [8], partial response was defined as a decrease of at least 2 points in the VAS score without an increase in pain medication or a decrease of 25% in pain medication without an increase in the reported VAS score; complete response to treatment was defined as a score of 0 on the VAS without an increase in pain medication. From other hand, no response was defined as a no changes in VAS. The imaging evaluation was conducted by using computed tomography (CT) and routinary MR exam with also dynamic ce-MR sequences (DCE-MRI) at baseline and at 3 months post-treatment. DCE-MRI sequences were performed to evaluate the presence of a coagulative necrosis and the corresponding not-perfused volume (NVP) within ablated area.

RESULTS

No treatment- or anesthesia-related complications were observed during or after MRgFUS. Treatment was carried out using a variable sonications number (mean 4±1.8) with a mean energy deposition of 866 ± 211 J. Each sonication had a duration of about 20 seconds. According to International guidelines, 18 (69.2%) patients were classified as complete clinical responders, 7 (26.9%) as partial responders and only one (3.9%) was classified as non-responder. As an additional method to evaluate treatment efficacy we used Brief Pain Inventory—Quality of

Life (BPIQOL) criteria. From clinical point of view, pain severity score changed significantly from a baseline average of 7.1 ± 2.08 (4–10) to 1 ± 1.1 (0–3) at 3 months' follow-up. In particular, at the end of the protocol, 19 of 26 (73.0 %) patients reported a 0 score for pain severity without medication intake, consisting of a complete response to treatment. From an imaging point of view, CT examinations performed at 3 months of follow-up revealed an increase of bone density with restoration of the cortical border in 9 of 26 (34.6%) patients [FIG.2].

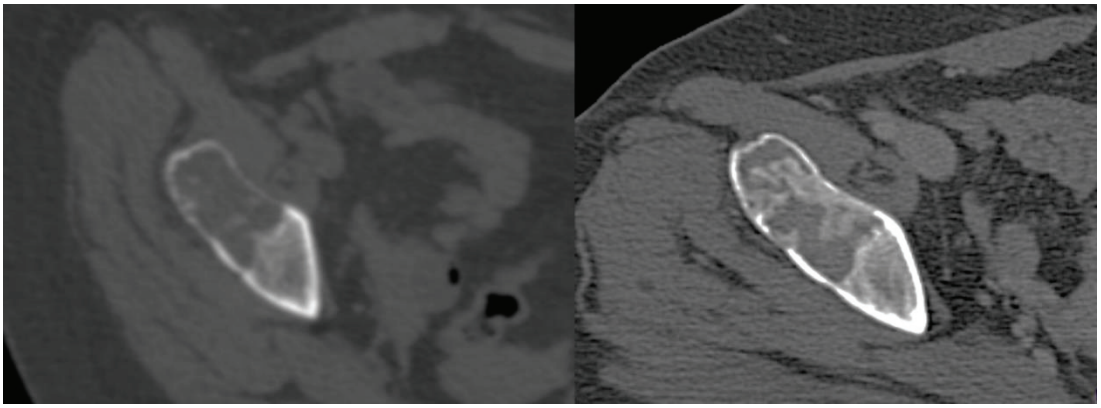

FIGURE 2. Increase bone density at 3 months CT-follow-up

At the MR-follow-up, Non-Perfused Volume values ranged between 20% and 92% [FIG.3] ; there was no difference in NPV values between our groups (46.7±24.2% [25 – 90 %] vs. 45±24.9% [20 – 93 %]; p=0.7).

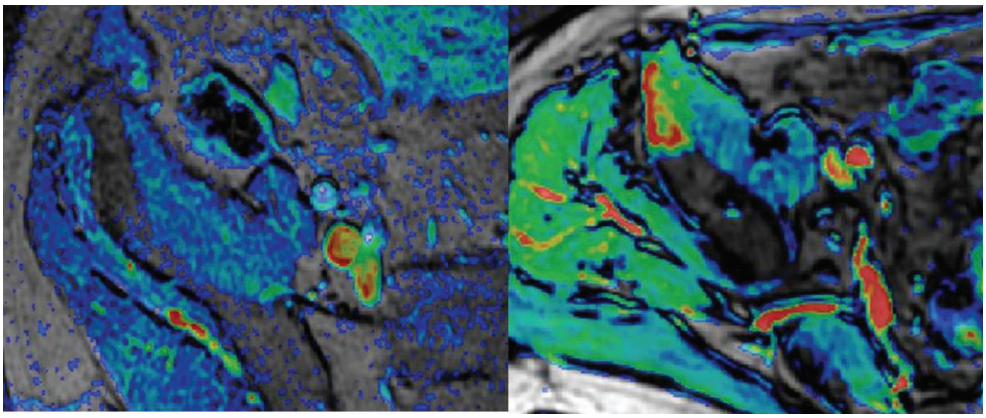

FIGURE 3. To NPV at 3 months MR-follow-

Moreover, in 6 patients (5 prostate and 1 breast primary cancer) there was nearly absence of metabolic activity after treatment (mean SUV=1.2).

DISCUSSION

Pain palliation is one of most important factors influencing quality of life in patients with bone metastases [8]. Currently standard reference treatment for localized painful bone metastases is EBRT [9]. Response rates range from 50 to 90%, and complete response rates range from 10 to 50% [10, 11]. Our study shown that MRgFUS is a safe and feasibility modality for pain palliation in skeletal painful metastases with complete clinical success achieved in 18 of 26 treated patients (72,2%). These results in symptoms relief are similar to what reported in literature for other therapies [12, 13]. Beyond our study, Gianfelice et al [3] treated 11 patients with painful bone metastases, reporting progressive pain decrease during 3-month follow-up. Another multicenter study, performed by Liberman [14], followed up 39 patients with bone metastases treated with MRgFUS, demonstrated significant

reductions in pain scores. The proposed mechanism for MRgFUS-induced pain palliation is the thermal lesion of periosteal pain receptors; however, the coexistent ablation of the tumor mass may diminish the pressure on adjacent healthy tissues, contributing to pain palliation [15]. We also noted that treated bone responded with a variable degree of de novo mineralization, cortical thickening, and morphology rearrangement. Notably, bone regrowth was not linked to NPV extension. One possible explanation is that the use of high energy (up to 6677 J) can, in parallel with tumor necrosis, determine quiescent osteoblastic cell death, thereby impeding the de novo bone production. Even if performed in a limited population, the absence of adverse events in our study suggests the use of this treatment option as a viable noninvasive alternative to standard pain palliation treatments, including EBRT, for the primary treatment of painful bone metastases. In this regard, although current guidelines [16] do not consider the safety profile of EBRT to be unacceptable in patients with painful bone metastases, EBRT-related acute and long-term adverse effects (eg, skin and gastrointestinal reactions, loss of nerve function and bone marrow damage) can occur in up to 3% of cases. In this study, none of these adverse effects occurred in the patients who underwent the MRgFUS treatment. Our study has several limitations: first, sample size was relatively small; another relevant limitation is represented by the absence of a control group. Finally, histological evidence was not available to assess and validate tissue modification after treatment. In conclusion, MRgFUS can be safely and effectively used as the primary treatment for pain palliation in patients with painful bone metastases; our results indicated also a positive trend to bone rearrangement after treatments. Moreover our experience demonstrated a potential role for the MRgFUS in local tumor control.

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