Prognostic and predictive factors for clinical and radiographic responses in patients with painful bone metastasis treated with magnetic resonance-guided focused ultrasound surgery

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**ABSTRACT**

**Background:** Magnetic resonance-guided focused ultrasound surgery (MRgFUS) is an alternative local therapy for patients with painful bone metastasis. However, little is known about the prognostic and predictive factors of MRgFUS in treating bone metastasis.

**Materials and methods:** This retrospective study analyzed the performance status, treated site, pretreatment pain score, pretreatment tumor volume and lesion coverage volume factor (CVF) of 31 patients who underwent MRgFUS. A numerical rating scale for pain was used at the same time to assess the clinical response. Radiographic responses were evaluated using a modified version of The University of Texas MD Anderson Cancer Center criteria and reference to the MR imaging or computed tomography scans obtained 3 months after treatment. Univariate and multivariate logistic regression analyses were conducted to examine the effect of variables on clinical and radiographic responses.

**Results:** The overall clinical response rate was 83.9% and radiographic response rate was 67.7%. Multivariate logistic regression analysis revealed that the better pretreatment Karnofsky performance status (KPS) (odds ratio: 1.220, 95% confidence interval (CI): 1.033–1.440; \( p = 0.019 \)) was significantly associated with a more positive clinical response, and that the lesion CVF (odds ratio: 1.183, 95% CI: 1.029–1.183; \( p = 0.0055 \)) was an independent prognostic factor for radiographic responses. The radiographic response of patients with lesion CVF \( \geq 70\% \) and CVF \( < 70\% \) were 91.7% and 52.6%, respectively (\( p = 0.0235 \)).

**Conclusion:** The pretreatment KPS was an independent prognostic factor for clinical responses, and lesion CVF was an independent prognostic factor for radiographic responses.

**Introduction**

Bone metastasis commonly causes pain and other serious symptoms that are detrimental to the quality of life in patients, and it occurs in approximately 30% of all cancer patients [1]. The incidence of bone metastasis varies significantly depending on the primary tumor [2]. Most patients with bone metastasis experience some level of pain, and more than one half of them experience severe pain. Thus, pain control can significantly improve their quality of life [3].

Conventional radiotherapy (RT) has been reported to be an effective treatment method for patients with painful bone metastasis, and pain relief occurs in 60–80% of patients [4,5], and 27% of patients experience pain recurrence [6]. According to preliminary evidence, high-intensity focused ultrasound hyperthermia, which heats targeted lesions to temperatures of 65–85°C, was conceptually designed for bone pain palliation primarily through thermally induced cell death of the treated bone tumor and immediate periosteal denervation [7,8].

By integrating real-time magnetic resonance imaging (MRI) with high-intensity focused ultrasound hyperthermia, MR-guided focused ultrasound surgery (MRgFUS) allows the
continual monitoring of treatment sites and temperature mapping through MR thermometry, thus providing accurate and precise treatment for pain resulting from bone metastasis [9–11]. MRgFUS is an alternative noninvasive treatment for patients with bone metastasis refractory to RT [8,12–14], with response rates ranging from 64% to 76% [8,12,15]. MRgFUS yields a similar overall treatment response rate but faster pain relief compared with conventional RT, and can serve as a first-line treatment for painful bone metastasis in selected patients [15].

However, little is known regarding the prognostic and predictive factors of MRgFUS for bone metastasis. In this retrospective study, we analyzed clinical and radiographic responses in patients with painful bone metastasis who were treated using MRgFUS. Moreover, because there is no practical parameter to predict the radiographic response after MRgFUS, we used the concept of coverage volume factor (CVF), a useful parameter for evaluating the tumor coverage in radiosurgery [16,17].

Materials and methods

Patient eligibility

We retrospectively reviewed the electronic medical records of patients with bone metastasis who had received MRgFUS between 1 December 2014, and 30 November 2017, at Taipei Medical University Hospital, Taiwan. The inclusion criteria were as follows: (1) presence of distinguishable painful bone metastasis with a score of ≥4 on the 11-point numerical rating scale (NRS), with 0 indicating no pain and 10 indicating the worst pain imaginable [18], irrespective of pain medication; (2) MRgFUS as the primary local therapy for painful bone metastasis; (3) an unchanged schedule of systemic treatment, including chemotherapy, hormonal therapy, targeted therapy and bone-targeted agent for 2 weeks before and 3 months after MRgFUS and (4) imaging follow-up prior to and 3 months after MRgFUS with contrast-enhanced MRI or computed tomography (CT). The exclusion criteria were local therapy prior to or within 3 months after MRgFUS.

This study was approved by the Taipei Medical University-Joint Institutional Review Board. At our institute, the treatment strategy of patients diagnosed with bone metastasis is discussed at the tumor board by a multidisciplinary cancer team. MRgFUS was recommended to patients with (1) a solitary distinguishable and painful bone metastasis, (2) in whom the targeted bone lesion could be accessed with MRgFUS [14,15,19] and (3) a Karnofsky performance status (KPS) of ≥60 before the intervention. Patients with a Mirels score [20] of >7, indicating an impending pathological fracture, were unsuitable for MRgFUS.

Before MRgFUS, each patient underwent a clinical examination to confirm the origin of pain to be in the target lesion and to exclude any other possible causes for the pain. Furthermore, we performed CT simulations to localize the targeted bone lesion with optimal patient positioning before both treatments and then repeated the positions on the treatment couch to avoid repositioning and facilitate treatment delivery.

MRgFUS treatment

The MRgFUS procedure began with the acquisition of a series of MR images over the targeted area by using a 1.5 Tesla MR scanner (Signa HDxt, GE Healthcare, Waukesha, WI, USA). The standard imaging protocol included T1- and T2-weighted sequences acquired through variable orientations with and without spectral fat suppression. After lesion localization, meperidine and midazolam were administered for conscious sedation intravenously, followed by the practice guidelines specified by the American Society of Anesthesiologists [21]. Physicians identified symptomatic bone lesions by viewing MR images on the workstation of the Exablate 2000 system (InSightec Ltd., Haifa, Israel). They defined the regions of treatment, contouring skin, bone cortex and marked ‘risky’ areas (e.g., regions with extensive scarring and neurovascular bundles). The system then automatically generated a treatment plan instructing the device to avoid these risky areas.

After verification of the treatment plan determined using the planning software, and any modification thereof, therapeutic high-intensity focused ultrasound was delivered to the region for treatment with real-time temperature monitoring using MRI. This energy delivery (sonication) process was repeated at multiple adjacent points to cover the entire target volume. Additional intravenous morphine was administered during treatment depending on intraprocedural pain.

After treatment, contrast-enhanced MRI was used to assess the effects of thermal ablation [8]. For prophylaxis of local inflammation, corticosteroids and nonsteroidal anti-inflammatory drugs were administered. In order to confirm that the ablation had been confined to the target tissue and that no substantial damage had been incurred by the tissue surrounding the target lesion, Contrast-enhanced T1-weighted sequences were acquired to evaluate both changes in lesion vascularization and the integrity of the adjacent tissues at the end of each treatment.

Assessment of treatment efficacy

Clinical response

The clinical response was assessed using the criteria provided by the International Consensus on Palliative Radiotherapy Endpoints for Future Clinical Trials in Bone Metastases [22]. A complete response (CR) indicated the reduction of pain to 0 on the NRS at the treatment site without a concomitant increase in the morphine-equivalent daily dose. A partial response (PR) indicated pain reduction of ≥2 points on the NRS at the treatment site without an increase in the morphine-equivalent daily dose or a reduction of ≥25% in the morphine-equivalent daily dose from baseline without an increase in the pain score on the NRS.

After treatment, all patients were scheduled to undergo follow-up clinical examinations 1 and 2 weeks; and 1, 2 and 3 months after the MRgFUS for clinical evaluation of pain control. Two experienced radiation oncologists independently evaluated the clinical response related to MRgFUS 3 months after treatment. Patients who exhibited a CR or PR were classified as responders, and the others were classified as nonresponders.
We documented treatment-related adverse events, which were identified in accordance with the Common Terminology Criteria for Adverse Events, version 4.03 [23].

**Radiographic response**

All recruited patients underwent contrast-enhanced CT or MRI before and 3 months after treatment to assess the radiographic response of target bone lesions.

Bone metastases are typically located in irregularly shaped bones and are difficult to measure with rulers. The response criteria specific to bone metastases have been developed at the University of Texas MD Anderson Cancer Center (MDA criteria) [24] that can be used to assess the therapeutic response in various types of bone metastases.

The original MDA criteria utilized CT, MRI, radiography, and skeletal scintigraphy, whereas in our study, we used the modified MDA criteria (Table 1) to evaluate local treatment response of MRgFUS using CT or MRI [24,25]. The reason for this was that these two imaging methods were characterized as the most accurate radiological evaluation tools, especially for the evaluation of a single lesion, such as was the case for the efficacy evaluation conducted in this study.

One radiation oncologist and one radiologist independently evaluated the MRI or CT images at the 3-month follow-up after each treatment. Patients who exhibited CR or PR were classified as responders and the remaining as nonresponders.

**CVF.** After treatment, contrast-enhanced T1-weighted sequences were used to evaluate the treatment response. Contrast-enhanced images were used to quantify the nonperfused volume—the volume of cancer tissue enhanced at the baseline that did not exhibit contrast uptake after treatment.

To investigate the associations between tumor coverage, clinical response and radiographic response after MRgFUS, we assessed the lesion CVF, the index of which signified the volume percentage of the lesion that had undergone thermal necrosis change, as indicated by the nonperfused volume within the targeted lesion [16,17]. To evaluate the lesion CVF, the MR images were uploaded onto the Pinnacle 9.8 treatment planning system (Philips Medical Systems, Madison, WI) and fused with simulation CT images. We contoured both the pretreatment tumor volume and the thermal ablation area within targeted lesion evaluated from the pretreatment and posttreatment MR imaging, respectively. The lesion CVF equation was as follows:

\[
\text{Lesion CVF} = \frac{\text{Thermal Ablative Tumor Volume}}{\text{Pretreatment Tumor Volume}} \times 100\%
\]

| Table 1. Modified MDA criteria. |
|---------------------------------|
| **Patient characteristics**     |
| Complete response                |
| Partial response                 |
| Progressive disease             |
| Stable disease                  |
| **Definition**                   |
| Complete sclerotic fill-in of lytic lesions on CT, normalization of bone density on CT or normalization of signal intensity on MRI with contrast Development of a sclerotic rim or partial sclerotic fill-in of lytic lesions on CT, osteoblastic-flare-interval visualization of lesions with sclerotic rims or new sclerotic lesions alongside the presentation of other PR signs in the absence of progressive bone disease, a decrease of \( \geq 50\% \) in measurable lesions on CT or MRI, or a subjective decrease of \( \geq 50\% \) in the size of ill-defined lesions on CT or MRI | 25% increase in the size of measurable lesions on CT or MRI or \( >25\% \) subjective increase in the size of ill-defined lesions on CT or MRI | No change, either \( <25\% \) increase or \( <50\% \) decrease in the size of measurable lesions, or either \( <25\% \) subjective increase or \( <50\% \) subjective decrease in the size of ill-defined lesions |

**Statistical analysis**

Categorical data were presented as number (percentage) and ordinal and continuous data were reported as median ± standard deviation or median (range). Univariate and multivariate logistic regression analyses were conducted to examine the effect of variables on clinical and radiographic responses. The scheme of the multivariate regression models was as follows: a series of univariate (unadjusted) regression analyses were performed, and variables with \( p < 0.1 \) in the univariate analyses were included in the multivariate stepwise logistic regression analyses. Statistical significance was defined as two-sided. A comparison of the categorical variables in the response and nonresponse groups regarding the clinical and radiographic responses of patients who had received MRgFUS was performed using a chi-squared test. Actuarial tumor local control was calculated by using the Kaplan-Meier method. All statistical analyses were performed using Python 2.7 with the SciPy module version 0.14.0 and StatsModels version 0.8.0.

**Results**

**Clinical characteristics**

According to the electronic medical records, 96 patients underwent MRgFUS between 1 December 2014, and 30 November 2017, at Taipei Medical University Hospital, Taiwan. After applying the inclusion and exclusion criteria, 31 patients were enrolled for analysis; their clinical characteristics are listed in Table 2.

Among the 31 patients, the median age was 60 years (range, 36–78 years), 18 (58.06%) were men and 13 were (41.94%) women, the median pretreatment KPS was 80 (range, 70–90), and the mean pretreatment pain score was 5.55 ± 1.76. We listed the median age, sex distribution, primary cancer type, pretreatment NRS pain score and treatment site as well as the pretreatment KPS and size of the targeted lesion. All MRgFUS-treated patients underwent a single procedure for a targeted bone lesion in the size range of 2.2–85.6 cm³. Overall, 71.0% experienced moderate pain (NRS pain score 4–6) and 29.0% experienced severe pain (NRS pain score 7–10). Most treatment sites were in the pelvic bone (27/31, 87.1%), and a few in the ribcage (4/31, 12.9%). The median sonication time was 38 min (range, 21–94 min).

**Assessment of treatment efficacy**

**Clinical response**

Follow-ups were conducted on all recruited patients with bone metastasis for at least 3 months after treatment. Of the
Table 2. Clinicodemographic characteristics of MRgFUS-treated patients with bone metastasis.

| Patient characteristics                          | 31 patients |
|--------------------------------------------------|-------------|
| Number of patients                               | 31          |
| Age, median [range], years                       | 60 [36–78]  |
| Gender (no. [%])                                 |             |
| Male                                             | 18 (58.1%)  |
| Female                                           | 13 (41.9%)  |
| Pretreatment KPS, median [range]                 | 80 [70–90]  |
| Primary cancer (no. [%])                         |             |
| Breast                                           | 11 (35.5%)  |
| Prostate                                         | 5 (16.1%)   |
| Non-small-cell lung                              | 5 (16.1%)   |
| Renal pelvis transitional cell carcinoma         | 2 (6.5%)    |
| Cervical                                         | 1 (3.2%)    |
| Nasopharyngeal                                   | 1 (3.2%)    |
| Multiple myeloma                                 | 1 (3.2%)    |
| Osteogenic sarcoma                               | 1 (3.2%)    |
| Colorectal                                       | 1 (3.2%)    |
| Thymic                                           | 1 (3.2%)    |
| Renal cell carcinoma                             | 1 (3.2%)    |
| Cholangiocarcinoma                               | 1 (3.2%)    |
| Treated site                                     |             |
| Pelvis                                           | 27 (87.1%)  |
| Rib cage                                         | 4 (12.9%)   |
| Pretreatment pain score (NRS)                    |             |
| Mean ± STD [range]                               | 5.55 ± 1.76 [4–9] |
| 4–6                                              | 22          |
| 7–10                                             | 9           |

KPS: Karnofsky performance status.

31 patients, 15 demonstrated CR and 11 exhibited PR (overall clinical response rate, 83.9%). The remaining patients either experienced no change in pain control (n = 4) or progression of their disease (n = 1).

Radiographic response

In accordance with the modified MDA criteria, CR was observed in 2 of the 31 patients (6.5%), PR in 19 (61.3%), SD in 9 (29.0%) and PD in 1 (3.2%). The overall radiographic response rate was 67.7%. The 1-year local control rate of the treated bone tumor was 57.0%.

Prognostic factors associated with clinical and radiographic responses

Table 3 presents the analyses of clinical characteristics in predicting clinical responses to MRgFUS. Univariate analysis revealed that the pretreatment pain score (p = 0.062) and pretreatment KPS (p = 0.019) were reliable predictors of clinical responses, but the pretreatment pain score was excluded after the multivariate analysis (p = 0.393), leaving only pretreatment KPS. We discerned no correlation between clinical response and age, treatment site, pretreatment tumor volume or tumor coverage.

Table 4 presents the analyses of clinical characteristics in predicting radiographic responses to MRgFUS. The analyses revealed that lesion CVF (hazard ratio: 1.183, 95% confidence interval: 1.029–1.183; p = 0.0055) was an independent prognostic factor for radiographic responses, according to the modified MDA criteria. No significant associations were discerned between radiographic response and sex, pretreatment pain score, treatment site or pretreatment KPS. The lesion CVF was further divided into two groups—CVF ≥ 70% and CVF < 70%—comprising 12 and 19 patients, respectively; their radiographic response was 91.7% and 52.6%, respectively (p = 0.0235).

Outcome and toxicity

During the MRgFUS procedure, grade 2 procedure-related pain was reported by 4 (12.9%) of the 31 patients who required temporary treatment interruption and additional intravenous morphine administration. One patient (3.2%) required repositioning due to the motion of the treatment site. No adverse events higher than grade 2 were documented for the MRgFUS-treated patients during the 3-month follow-up period.

Discussion

This study analyzed the predictive and prognostic factors of MRgFUS for primary pain palliation therapy in bone metastases. We found that higher pretreatment KPS was associated with greater pain reduction and that higher lesion CVF was correlated with superior radiographic response.

MRgFUS has emerged as an alternative treatment modality for pain relief in patients with bone metastasis [9–11]. MRgFUS can result in rapid pain relief within 3 days, with a 72% clinical response rate after 3 months [8]. One randomized controlled study found a superior response rate in the MRgFUS arm compared with a placebo arm (64.3% vs. 20.0%, p < 0.001) for patients who failed to previous RT at the 3-month follow-up [14]. Furthermore, a matched-pair design study compared the therapeutic effects of MRgFUS with those of conventional RT as first-line local treatment and found a higher MRgFUS response rate 1 week after treatment (71% vs. 26%, p = 0.0009) and a similar clinical response rate at the 3-month follow-up [15]. In the literature, the clinical response rate after MRgFUS ranged from 64% to 76% [8,12,15]. Consistent with these findings, we demonstrated a comparative overall clinical response rate of 83.9% at 3 months after MRgFUS; moreover, no adverse events higher than grade 2, according to the Common Terminology Criteria for Adverse Events 4.03 [23], were reported.

To our knowledge, this is the first study to investigate the prognostic and predictive factors for clinical and radiographic responses in patients undergoing MRgFUS. Similar to the palliation of painful bone metastases treated by RT, pretreatment KPS was a prognostic factor for clinical response. A nonrandomized single-center study of 205 patients examined the effects of total dose and pretreatment performance status on pain response, and found lower clinical response rates and worse performance status in patients receiving lower doses [26]. One prospective study including 956 patients also showed that good performance status is one of the baseline predictors for better pain response [27]. In our study, the lower pretreatment KPS was associated with an inferior clinical response rate (OR = 1.220, p = 0.019). Among patients with KPS ≥ 80 and KPS < 80, there was no statistically significant difference in the mean CVF (67.2% vs. 56.1%, p = 0.313) and median sonication time (45.7 min vs. 38.0 min,
Table 3. Univariate and multivariate analyses of clinical characteristics for the prediction of clinical responses to MRgFUS.

| Characteristics                        | Univariate analysis |                | p-value | Multivariable analyses |                | p-value |
|----------------------------------------|---------------------|----------------|---------|------------------------|----------------|---------|
| Age, median [range], years              | 1.002               | 0.921–1.090    | 0.965   |                        |                |         |
| Gender (male vs. female)                | 2.052               | 3.974–1.06     | 0.967   |                        |                |         |
| Primary cancer (breast and prostate vs. others) | 1.750               | 0.249–12.279   | 0.573   |                        |                |         |
| Pretreatment KPS, median [range]        | 1.220               | 1.033–1.440    | 0.019*  | 1.220                  | 1.033–1.440    | 0.019*  |
| Pretreatment pain score (NRS)           | 0.585               | 0.333–1.027    | 0.062** |                        | 0.737          | 3.664–1.483 | 0.393  |
| Pretreatment tumor volume               | 0.974               | 0.930–1.020    | 0.260   |                        |                |         |
| Coverage volume factor                  | 0.804               | 0.007–98.400   | 0.929   |                        |                |         |

OR: odds ratio; CI: confidence interval; KPS: Karnofsky performance status.
*p for significant difference.
**p for linear trend.

Table 4. Univariate and multivariate analyses of clinical characteristics for the prediction of radiographic response to MRgFUS.

| Characteristics                        | Univariate analysis |                | p-value | Multivariable analyses |                | p-value |
|----------------------------------------|---------------------|----------------|---------|------------------------|----------------|---------|
| Age, median [range], years              | 0.958               | 0.893–1.028    | 0.234   |                        |                |         |
| Gender (male or female)                 | 1.625               | 0.355–7.434    | 0.531   |                        |                |         |
| Primary cancer (breast and prostate vs. others) | 2.000               | 0.432–9.256    | 0.375   |                        |                |         |
| Pretreatment KPS, median [range]        | 0.663               | 0.874–1.089    | 0.663   |                        |                |         |
| Pretreatment pain score (NRS)           | 1.198               | 0.753–1.908    | 0.446   |                        |                |         |
| Pretreatment tumor volume               | 0.972               | 0.933–1.012    | 0.171   |                        |                |         |
| Coverage volume factor                  | 1.183               | 1.029–1.183    | 0.006*  | 1.183                  | 1.029–1.183    | 0.006*  |

OR: odds ratio; CI: confidence interval; KPS: Karnofsky performance status.
*p for significant difference.

In an analysis of randomized controlled trials from the Dutch Bone Metastasis Study database, KPS and breast or prostate cancer as the primary cancer type are also predictive of a better clinical response [27]. In our study, there was no significant difference in clinical response between prostate cancer or breast cancer and other cancer types (OR = 1.750, p = 0.573). Similar to the reports of higher response rates corresponding to lower initial pain scores regarding the palliation of painful bone metastases by RT [5], in our study, univariate analysis indicated a trend of association between lower initial NRS scores and more favorable clinical response. However, further studies are required to confirm the correlation between clinical response and the initial pain score. Based on our results, there was no statistically significant difference between the lesion CVF and the clinical response to MRgFUS. A possible explanation is that the pain-relieving effect after MRgFUS can result not only from thermal necrosis of the targeted bone lesion but also from periosteal denervation, and different strategies focusing on immediate pain palliation or durable tumor control can be tailored depending on the treatment goal of patients suffering from bone metastases [12].

We also analyzed radiographic responses based on the modified MDA criteria, and CR or PR was found in 21 of the 31 patients (67.7%) who had not received previous RT to the targeted bone lesions. Napoli et al. investigated 18 patients who had received MRgFUS and reported a radiographic response rate of 33.3% (6/18), including CR and PR, in accordance with the MDA criteria [12]. Furthermore, our retrospective analysis demonstrated that the lesion CVF was an independent prognostic factor for the radiographic response rate in patients who had received MRgFUS. CVF has been proven to be a useful parameter for evaluating the tumor coverage of radiosurgery [16,17]. It represents the lesion volume covered by thermal necrosis change, as defined by the nonperfused volume (NPV) within the target [16,17]. More recently, the effectiveness of MRgFUS for local control for various types of tumors, such as uterine fibroids, breast cancer and prostate cancer, has been investigated. In patients with uterine fibroids, a higher ratio of NPV has been correlated with a higher treatment success rate [28]. Our results revealed that a higher lesion CVF was associated with significantly more favorable radiographic responses (OR = 1.183, p = 0.006), which represents local control of the tumor, with at least 70% being recommended to provide a radiographic response rate of >90%. A greater lesion CVF represents more effective thermal necrosis of the treated bone tumor, which indicates the potential role of CVF for evaluating local tumor control after MRgFUS.

The main limitations of the current study were the relatively small sample size and the retrospective design. However, we found that patients with better performance status were more likely to benefit from MRgFUS because of greater possibility of clinical pain relief. Higher lesion CVF is an independent factor for predicting superior radiographic response in terms of favorable local tumor control. These factors are helpful for optimizing the treatment outcome of MRgFUS in treating painful bone metastasis. Future large-scale prospective studies are required to validate our findings.

Disclosure statement
No potential conflict of interest was reported by the authors.

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