Palliation of Painful Bone Metastases: The "Rizzoli" Experience

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Purpose

The improvement of survival in cancer patients due to the increasing longevity of the population and the progress of treatments of primary tumors is enhancing the incidence of distant metastasis such as bone metastasis. Pain represents the main symptom in patients affected by bone metastasis and this causes a significant impairment of quality of life [1].

Hence the development of strategies to improve quality of life is fundamental and represents a major clinical challenge.

Current treatment options for bone metastases consist of systemic therapy (analgesic treatment-opioid and non-opioid, hormonal therapy, bisphosphonates, radio pharmaceuticals, and chemotherapy) and local treatments (different radiotherapy regimens, kypho/vertebroplasty, surgical resection, surgical stabilisation and more recently laser ablation and radiofrequency percutaneous ablation) [1-2]. Unfortunately, most of these therapies do not achieve long-lasting efficacy, frequently cause side effects (i.e. toxicity and myelosuppressive effect of radiotherapy) or need chronic and/or combined administration [3].

Recently, a new technique, magnetic resonance guided focused ultrasound surgery (MRgFUS), has been proposed with a potential in pain palliation of bone metastases, characterized by several advantages (no ionizing radiation, lack of cumulative dose, treatment might be repeated as many times as needed, fast pain relief, contraindications limited to magnetic resonance and general fitness to anaesthesia) [4]. MRgFUS is a completely noninvasive technique that uses focused ultrasound to ablate target tissues, and MRI to plan the treatment and monitor energy deposition and temperature in real time. Since the periosteum is considered to be the major source of pain in patients with bone metastasis, applying acoustic energy on the bone surface will result in bone cortex heating, indirectly ablating the adjacent periosteum and tumour tissue [4].

To date, 5 prospective cohort studies of MRgFUS for painful bone metastases have been published, obtaining good results in pain palliation [5-9].

The aim of this work is to evaluate the clinical outcome of patients affected by painful bone metastases and submitted to MRgFUS at the "Rizzoli" Orthopaedic Institute (Bologna, Italy).
Methods and Materials

From November 2012 to March 2015, patients affected by oncological diseases with metastatic spread to bone and one painful bone lesion were prospectively enrolled for MRgFUS treatment with the aim of pain palliation. Exclusion criteria were general contraindications to MR imaging and/or to anaesthesiological procedures planned for the patient; metastasis location at skull or spine with the exception of lesions affecting spinous or transverse processes only; large scar at skin or deeper soft tissue potentially included in the planned path of the ultrasound beam; a distance skin - lesion (target) < 1 cm.

All patients were clinically examined (pain assessment) by using a 10-point visual analogue scale (VAS) at baseline with a 1-, 3-, 6-, and 12-month follow-up.

Each patient underwent MRI (1.5 T, Signa HDxt, GE Healthcare, Milwaukee, Wis, USA) immediately before MRgFUS in order to localize the lesion and plan the treatment. The standard imaging protocol included T1-weighted and T2-weighted sequences acquired with variable orientations with and without spectral fat suppression.

The patients were treated under conscious deep sedation, local anaesthesia, nerve block, epidural anaesthesia, or general anaesthesia depending on lesion location, physical fitness of patients, and anaesthesiology indication.

MRgFUS was performed with a focused ultrasound phased-array treatment system (ExAblate 2100; InSightec, Haifa, Israel) integrated with the 1.5 T MR imager.

Immediately after the treatment, the patients were examined and questioned for any adverse events (i.e. skin burns).

Type of primary tumors, presence of other metastatic lesions, size and site of the treated lesion, and previous treatments performed (such as radiotherapy, chemotherapy, embolization) were recorded, as well as the technical parameters and the time of treatment.

The efficacy of treatment was evaluated on the basis of International Consensus on Palliative Radiotherapy Endpoints for Clinical Trials in Bone Metastases (IBMCW - 2012 update; Fig. 1) [10].

Data are reported as mean, median and standard deviation (± s.d.). T-Test was used to calculate the statistical significance between VAS score at baseline and during the follow-up. Mann-Whitney, ANOVA and logistic regression were used to test the correlations among the efficacy of MRgFUS and the features of the lesions and type of primary cancer.
Fig. 1: Criteria to evaluate the treatment efficacy for pain palliation established by the International Consensus on Palliative Radiotherapy Endpoints for Clinical Trials in Bone Metastases.

Results

90 secondary bone lesions affecting 64 patients (36 males, 28 females; 60.7± 10.7 years-old) were treated, with different primary cancers: breast (27-30.0%), kidney (17-18.9%), lung (8-8.8%), colorectal (10-11.0%), prostate (9-10.1%), thyroid (9-10.1%), stomach (2-2.3%), liver (4-4.4%), bladder (2-2.3%), uterus (2-2.3%), soft-tissue sarcoma (3-3.3%), and Ewing sarcoma (1-1.1%) (Fig. 2). The lesions were located at: pelvis (65-71.1%); femur (8-8.8%); knee (1-1.1%); tibia (1-1.1%); ribs (4-4.4%); humerus (4-4.4%); spine (2-2.3%); scapula (3-3.3%); calcaneus (2-2.3%) (Fig. 3).

Table 1 shows the main features of lesions, the type of anesthesia and the employed technical parameters.

84 lesions were evaluated after 1 month (93.3%), while 61 lesions reached the 3-month (67.7%), 42 the 6-month (46.6%) and 21 the 12-month (23.3%) after MRgFUS. On a lesion-based approach, VAS score at baseline was 5.3 ± 2.7 (median 6). This decreased to 2.7 ± 2.3 (median 2) (#% = -40.9%) at 1 month, and to 2.4 ± 2.3 (median 2), 2.1 ± 2.4 (median 1), and 1.8 ± 2.1 (median 1) after 3, 6 and 12 months respectively (#VAS % vs. baseline: -50.7%, -41.7% and -57.4%) (p=0.001) (Fig. 4). A statistically significant difference between baseline and all follow-up time points was observed for pain severity (p=0.001).

In 73.8% of cases a favorable response was documented at 1 month (complete response: 23/84-27.4%; partial response: 39/84-46.4%); in 70.4% at 3 months (complete response: 19/61-31.1%; partial response: 24/61-39.3%); in 71.4% at 6 months (complete response: 14/42-33.3%; partial response: 16/42-38.1%) and 12 months (complete response: 4/21-19.0%; partial response: 11/21-52.4%). 5.9% of cases (5/84) experienced a worsening of pain severity at 1 month after MRgFUS; 9.8% (6/61) at 3 months, 9.5% (4/42) at 6 months and 14.3% (3/21) at 12 months. No pain relief was observed in 20.2% (17/84), 19.7% (12/61), 19.0% (8/42) and 14.3% (3/21) at 1, 3, 6 and 12 months, respectively (Fig. 5).

Only two adverse events were observed (one case of acute prostatitis and one case of second degree skin burn).

The response to treatment was independent from the type, size and site of lesion, the presence/absence of interrupted bone cortex, and the type of primary cancer.
Fig. 2: Site of primary tumors (of treated bone lesions).

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Fig. 3: Skeletal site of treated lesions.

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Table 1

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**Fig. 4:** Box plot: VAS score (pain severity) at baseline and during the follow-up period.

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**Fig. 5:** Response to treatment at 1, 3, 6 and 12 months. Blue - favorable responses (complete and partial response); red - unfavorable response (pain progression); green - no response (indeterminate response).

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Conclusion

MRgFUS is a valid therapeutic option for patients affected by painful bone metastasis. MRgFUS can be effectively adopted for the treatment of bone metastases and can be performed safely and with a high rate of pain relief.
References


