Original Article

Urinary cytokines/chemokines after magnetic resonance-guided high intensity focused ultrasound for palliative treatment of painful bone metastases

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Background: Pain is experienced by 50–75% of patients with bone metastases, representing a major source of morbidity amongst cancer patients. Magnetic resonance-guided high intensity focused ultrasound (MRgHIFU) is a new, non-invasive, outpatient treatment modality for painful bone metastases. The aim of this study was to analyze urinary cytokines/chemokines pattern after MRgHIFU for palliative treatment of painful bone metastases. The findings were compared to the cytokines/chemokines pattern post single 8 Gy fraction radiation from our previous study.

Methods: Urine samples were collected from patients with painful bone metastases 3 days before and 2 days after treatment with MRgHIFU. Each urine sample was tested for pro-inflammatory cytokines and anti-inflammatory cytokines. Patients received teaching on how to collect urine samples on their own. The Millipore Milliplex 42-Plex Cytokine/Chemokine Kit™ was used to measure urinary levels of a panel of cytokines/chemokines.

Results: Ten patients were enrolled for the study. The following 15 cytokines were above the level of detection (LOD) in at least 50% of patients at both pre MRgHIFU and post MRgHIFU: EGF, eotaxin, Fit-3 ligand, fractalkine, G-CSF, GRO, IFNα2, IL-1ra, IL-8, IP-10, MCP-1, PDGF-AA, RANTES, sIL-2Rα, and VEGF. Nine urinary cytokines significantly decreased post MRgHIFU, namely, eotaxin, GRO, IL-8, IL-13, IP-10, MCP-1, MIP-1β, RANTES, and sIL-2Rα. In addition, there were significant differences between post MRgHIFU and post-8 Gy fraction radiation in most urinary cytokines.

Conclusions: Nine urinary cytokines significantly reduced post-MRgHIFU in patients with painful bone metastases. The significance of cytokines/chemokines pattern for palliative treatment of painful bone metastases is still unknown.

Keywords: Bone metastases; cytokines/chemokines; magnetic resonance-guided high intensity focused ultrasound (MRgHIFU); palliative treatment

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Introduction

Bone metastases are common among patients with advanced cancer and have been reported in up to 85% of cancer patients at autopsy (1). Pain is experienced by 50–75% of patients with bone metastases, representing a major source of morbidity amongst cancer patients (2).

External beam radiotherapy is the current standard treatment for patients with painful uncomplicated bone metastases (3). The overall pain response rate to external beam radiotherapy is approximately 60% (4). Radiotherapy re-treatment is limited by cumulative doses delivered to sensitive structures. Although cumulative effects do not limit other ablative techniques such as cryotherapy and percutaneous radiofrequency ablation, these techniques are invasive with risk of complications.

Magnetic resonance-guided high intensity focused ultrasound (MRgHIFU) is a new, non-invasive, outpatient treatment modality for painful bone metastases (5). It consists of a specially designed transducer that is used to focus a beam of ultrasound energy into a small volume at a specific target site in the body. The focused beam produces therapeutic hyperthermia in the target field (ablation is achieved when target tissue temperatures reach more than 57 ℃), only harmlessly affecting the immediately surrounding tissue. Magnetic resonance (MR) imaging is used for two main purposes:

(I) Focus the ultrasound beam on the target field in the bone (the metastatic lesion and adjacent periosteum containing the nerves and vasculature for the tumor);

(II) Perform real-time thermal mapping at and around the target.

The mechanism of action of pain response is thought to be thermal periosteal denervation and/or thermal ablation of the tumor mass that diminishes pressure on the surrounding tissue (6-8). In addition, decrease in circulating immunosuppressive cytokines after MRgHIFU treatment is also thought to play a role in the overall reduction in pain response (9).

In this study, we aimed to analyze urinary cytokines/chemokines pattern after MRgHIFU for palliative treatment of painful bone metastases. The findings were compared to the cytokines/chemokines pattern post single 8 Gy fraction radiation from our previous study.

Methods

This was a single centre study that was conducted at Odette Cancer Centre (OCC), Sunnybrook Health Sciences Centre (SHSC)-Toronto, Canada. Ethics approval was obtained from the Research Ethics Board at SHSC. Patients with bone metastases who were planned to be treated with MRgHIFU were approached. Inclusion criteria included patient age ≥18 years, ability to give informed consent, patient weight <140 kg, radiologic evidence of bone metastases from any solid tumor, ability of patient to characterize pain specifically at the site of interest (target lesion) with pain score of ≥4 on a 0–10 point scale irrespective of medications, target lesion accessible for MRgHIFU procedure with maximum dimension ≤8 cm, target lesion as uncomplicated (i.e., no fracture/spinal cord compression/cauda equina syndrome/soft tissue component), target lesion visible by non-contrast MRI imaging, interface between bone and skin ≥1 cm from surface, ability to communicate sensation during MRgHIFU treatment, and MRgHIFU treatment date ≥2 weeks from most recent treatment of primary tumor or any chemotherapy.

We excluded patients with prior radiotherapy, surgery, ablative therapy, or other local therapy to target lesion, unable to characterize pain specifically at the site of interest, pregnant or nursing woman, target lesion as complicated (i.e., presence of one of fracture/spinal cord compression/cauda equina syndrome/soft tissue component). Target lesion <1 cm from nerve bundles/bladder/bowel, in contact with hollow viscera, and/or located in skull, spine (excluding sacrum which is allowed) or sternum were excluded. We also excluded the presence of scar along proposed MRgHIFU beam path, orthopaedic implant along proposed MRgHIFU beam path or at site of target lesion, serious cardiovascular, neurological, renal or hematological chronic disease, presence of active infection, inability of patient to tolerate required stationary position during treatment, and patients with allergy to MRI contrast agent or sedation.

Participating patients meeting the inclusion criteria were enrolled and informed consent was obtained. Urine samples were collected from patients with painful bone metastases 3 days before and 2 days after treatment with MRgHIFU. Patients received teaching on how to collect urine samples on their own. We decided to use the least invasive method to measure urinary cytokines/chemokines due to the underlying medical situation for our palliative patients. The Millipore Milliplex 42-Plex Cytokine/Chemokine Kit™ was used to measure urinary levels of a panel of cytokines/chemokines. Each urine sample was tested for pro-inflammatory cytokines and anti-inflammatory cytokines. In

Table 1 Demographic and primary cancer site of subjects

ID	Gender (F = female, M = male)	Age (years)	Primary cancer site
1	F	61	Breast
2	M	77	Prostate
3	F	45	Breast
4	M	72	Neuroendocrine
5	F	68	Liver
6	M	78	Esophagus
7	F	69	Pancreas
8	M	42	Lung
9	M	62	Orbit
10	M	71	Prostate

each urine sample we measured EGF, eotaxin, FGF-2, Flt-3 ligand, fractalkine, G-CSF, GM-CSF, GRO, INFα2, INFγ, IL-1ra, IL-1α, IL-1β, IL-2, sIL-2Rα, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12(p40), IL-12(p70), IL-13, IL-15, IL-17, IP-10, MCP-1, MCP-3, MDC, MIP-1α, MIP-1β, PDGF-AA, PDGF-AB/BB, RANTES, sCD40L, TGFα, TNFα, TNFβ and VEGF as well as markers of bone turnover (N-telopeptides).

Statistical analysis

Descriptive analysis was conducted for pre-MRgHIFU, post-MRgHIFU, and MRgHIFU changes for each urinary cytokines using mean, standard deviation (SD), median, interquartile (Q1, Q3), and ranges in all patients. To compare pre-MRgHIFU and post-MRgHIFU cytokines levels in all patients and in patients with positive pain response, Wilcoxon signed rank test (non-parametric) was used. Two-sided P value <0.05 was considered statistically significant. For each individual patient, a list was performed for those urinary cytokines which significantly decreased post-MRgHIFU levels. Heat maps were conducted for 42 cytokine variables in all patients with pre-MRgHIFU and post-MRgHIFU. Box plots of significant urinary cytokines levels between pre-MRgHIFU and post-MRgHIFU were generated.

Similar descriptive analysis was also conducted for post-MRgHIFU (n=10) and post-radiation (n=28) for each "original" urinary, and Wilcoxon rank-sum test (non-parametric) to compare post-MRgHIFU and post-radiation cytokines levels. Kruskal-Wallis test (non-parametric) was used to compare patients from three groups: post-MRgHIFU, post-8 Gy fraction radiation with pain flare, and post-8 Gy fraction radiation with no pain flare for each urinary cytokine. All analyses were conducted using statistical analysis software (SAS version 9.4 for Windows).

Results

Ten patients were enrolled for the study from February 2011 to March 2012. They included four females and six males with a median age of 68.5 years with painful bone metastases from various primary tumors. Primary tumor sites included breast, prostate, pancreas, esophagus, orbit, lung, liver, and neuroendocrine. *Table 1* summarizes the demographics of our patient population.

The following 15 cytokines were above the level of detection (LOD) in at least 50% of patients at both pre-MRgHIFU and post-MRgHIFU: EGF, eotaxin, Fit-3 ligand, fractalkine, G-CSF, GRO, IFNα2, IL-1ra, IL-8, IP-10, MCP-1, PDGF-AA, RANTES, sIL-2Rα, and VEGF. The heat map (*Figure 1*) demonstrates the changes in urinary cytokines pre-MRgHIFU and post-MRgHIFU. Nine urinary cytokines significantly decreased post-MRgHIFU, namely, eotaxin, GRO, IL-8, IL-13, IP-10, MCP-1, MIP-1β, RANTES, and sIL-2Rα (*Table 2*). *Table 3* shows the nine urinary cytokines that significantly decreased post-MRgHIFU for each individual patient. Some patients showed a greater decrease in most cytokines post-MRgHIFU, e.g., patient ID =1, 3, 7, and 8. *Figure 2* demonstrates boxplots for the selected nine cytokines; using original urinary cytokine levels at pre- and post-MRgHIFU treatment in all patients.

In our previous cytokines study with post-8 Gy fraction radiation treatment, we had 28 patients with days 1–5 post-8 Gy fraction radiation treatment for each urinary cytokines (10). When comparing the differences in urinary cytokines between post-MRgHIFU and post-8 Gy fraction radiation, there were significant difference between post-MRgHIFU and post-8 Gy fraction radiation on all urinary cytokines, except for FGF-2, IL-3, IL-6, IL-7, IL-8, IL-12(p40), IL-12(p70), IL-15, IL-17, MCP-1, MDC, MIP-1β, PDGF-AA, PDGF-AB/BB, sIL-2Rα, and TGFα. Patients with post-MRgHIFU are more likely to have higher cytokines on EGF, Eotaxin, Fit-3 ligand, fractalkine, G-CSF, GRO, IFNα2, IL-1β, IL-1ra, IP-10, M1P-1α, RANTES, and sCD40L, comparing to those with post-8 Gy fraction radiation. However, patients with post-MRgHIFU have

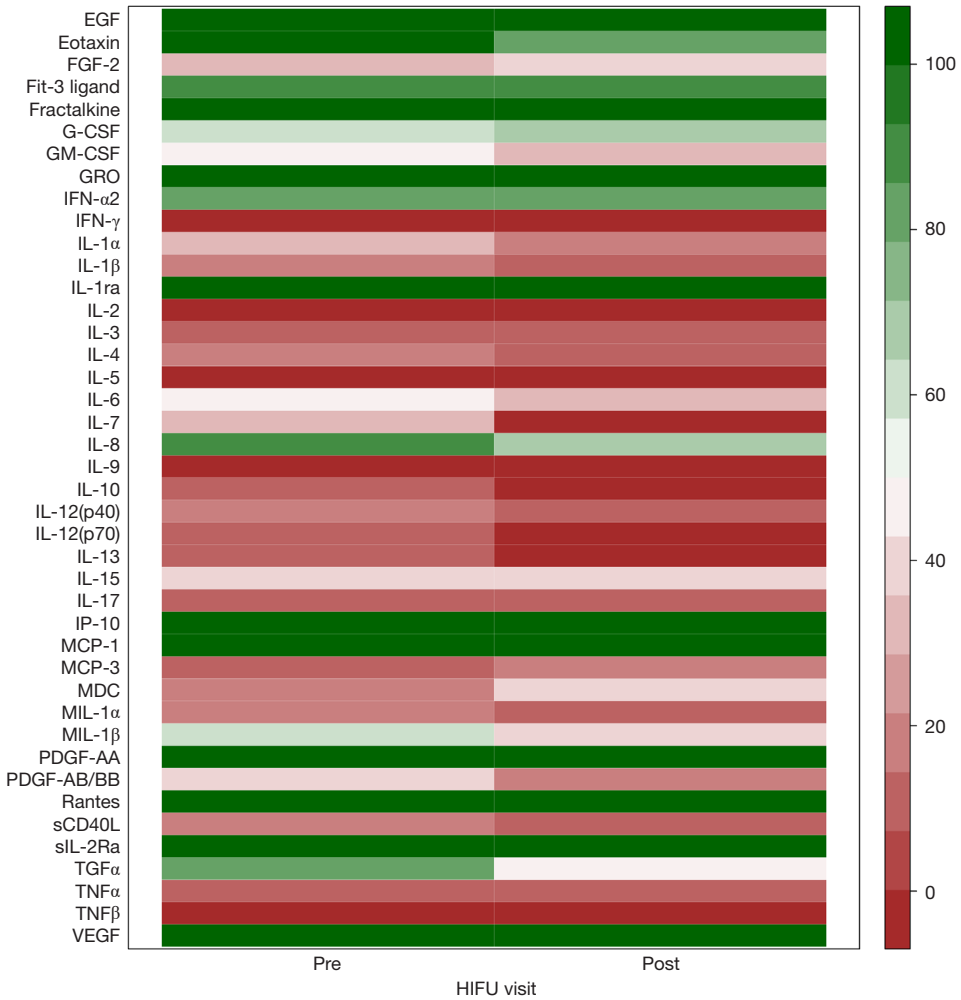

Figure 1 The following heat map shows the percentage of patients with data more than the limits of detection (LOD, 3.2) for each cytokine levels (using original values). Red indicates if 0% of patients with data > LOD, and green indicates if 100% of patients with data > LOD.

significant lower cytokines on GM-CSF, IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-9, IL-10, IL-13, MCP-3, TNFα, TNFβ, and VEGF, comparing to those with post-8 Gy fraction radiation.

None of our patients reported pain flare post-MRgHIFU treatment. We compared post-MRgHIFU from the current study with pain flare or no pain flare from our previous post-8 Gy fraction radiation study on each cytokine. Patients who reported pain flare post-radiation are more likely to have lower urinary cytokines levels for; EGF, Eotaxin, Fractalkine, GRO, IFNα2, IL-1α, IL-1β, IL-1ra, IP-10, RANTES, and sCD40L, compared to post-MRgHIFU patients. On the other hand, patients with no reported pain flare post-radiation are more likely to have significantly lower levels of Fit-3 Ligand cytokines compared to post-MRgHIFU. For other significant cytokines such as GM-CSF, IFN-γ, IL-4, IL-5, IL-9, IL-10, IL-13, MCP-3, TNFα, and TNFβ, post-radiation patients with pain flare are more likely to have higher cytokine values compared to post-MRgHIFU patients (*Table 4*).

In patients who had a positive pain response post-MRgHIFU, we correlated the patterns of cytokines post-MRgHIFU with pain response (5). We found no significant decrease in the cytokine patterns and pain response. We then compared cytokines level pre- and post-MRgHIFU in patients with positive pain response and found significant cytokine levels decreases in namely, GRO, IFN-γ, IP-10, IL-13, MCP-1, and RANTES (*Table 5*).

Table 2 Wilcoxon signed rank test to compare post-MRgHIFU with pre-MRgHIFU for each urinary cytokines in all patients (N=10)

Urinary cytokines	Pre-HIFU	Post-HIFU	HIFU change (post-pre)	Wilcoxon signed rank P value
EGF				0.9219
Mean ± SD	52,395.771±79,783.133	31,372.685±35,367.680	–21,023.086±76,199.091	
Median (Q1, Q3)	23,762.53 (14,423.68, 50,236.45)	15,806.57 (10,706.21, 39,979.66)	782.86 (–15,993.05, 8,791.88)	
Range	3,707.0, 271,362.0	5,194.6, 122,231.6	–216,194.3, 71,995.2	
Eotaxin				0.0039*
Mean ± SD	40.840±45.772	9.011±5.055	–31.830±45.134	
Median (Q1, Q3)	21.68 (14.00, 35.50)	8.95 (4.50, 10.46)	–13.35 (–28.27, –6.54)	
Range	5.5, 144.0	3.2, 19.6	–136.7, 2.5	
FGF-2				0.3750
Mean ± SD	11.238±14.299	7.521±6.493	–3.716±10.792	
Median (Q1, Q3)	3.20 (3.20, 15.10)	3.20 (3.20, 11.74)	0.00 (–3.35, 0.00)	
Range	3.2, 37.5	3.2, 22.1	–28.9, 10.3	
Fit-3 ligand				0.1309
Mean ± SD	37.007±42.542	13.451±8.205	–23.557±39.800	
Median (Q1, Q3)	14.59 (8.29, 58.24)	11.56 (6.80, 18.35)	–7.65 (–48.84, 0.47)	
Range	2.7, 124.6	3.2, 27.7	–110.8, 12.3	
Fractalkine				0.9999
Mean ± SD	119.334±110.747	107.713±52.364	–11.621±112.510	
Median (Q1, Q3)	92.47 (47.13, 134.86)	118.36 (53.06, 148.41)	–7.85 (–51.36, 29.18)	
Range	31.9, 408.3	41.7, 192.4	–267.1, 160.5	
G-CSF				0.4922
Mean ± SD	21.193±36.301	6.105±3.381	–15.088±35.411	
Median (Q1, Q3)	5.30 (1.79, 8.72)	5.92 (3.18, 7.73)	1.21 (–0.29, 2.09)	
Range	1.1, 97.7	1.5, 11.6	–86.2, 3.9	
GM-CSF				0.1934
Mean ± SD	3.304±1.481	2.536±1.744	–0.768±1.504	
Median (Q1, Q3)	3.01 (2.06, 4.97)	1.89 (1.19, 3.40)	–0.81 (–1.54, 0.84)	
Range	1.3, 5.2	1.0, 6.1	–3.6, 1.1	
GRO				0.0020*
Mean ± SD	167.744±227.803	70.570±116.768	–97.174±156.374	
Median (Q1, Q3)	70.66 (25.84, 160.89)	28.89 (13.65, 61.82)	–25.35 (–98.52, –8.58)	
Range	12.0, 638.8	8.9, 393.1	–488.4, –3.0	

Table 2 (*continued*)

Table 2 (*continued*)

Urinary cytokines	Pre-HIFU	Post-HIFU	HIFU change (post-pre)	Wilcoxon signed rank P value
IFNα2				0.4922
Mean ± SD	9.305±6.816	7.739±3.924	−1.566±6.486	
Median (Q1, Q3)	7.61 (4.91, 11.83)	9.20 (4.08, 10.74)	−1.38 (−2.00, 1.88)	
Range	1.3, 22.2	1.7, 12.9	−14.4, 7.9	
IFN-γ				0.2324
Mean ± SD	0.881±0.756	0.621±0.411	−0.260±0.844	
Median (Q1, Q3)	0.59 (0.40, 0.96)	0.54 (0.40, 0.68)	−0.09 (−0.38, −0.09)	
Range	0.1, 2.3	0.3, 1.7	−1.7, 1.1	
IL-1α				0.8457
Mean ± SD	8.443±13.502	5.719±8.625	−2.724±10.880	
Median (Q1, Q3)	2.10 (0.63, 7.49)	1.80 (1.22, 3.20)	0.22 (−2.70, 1.83)	
Range	0.4, 38.5	0.4, 23.4	−27.0, 12.9	
IL-1β				0.7344
Mean ± SD	2.312±4.640	4.132±12.068	1.820±8.399	
Median (Q1, Q3)	0.28 (0.15, 0.34)	0.31 (0.20, 0.49)	−0.00 (−0.04, 0.33)	
Range	0.1, 13.7	0.1, 38.5	−7.4, 24.8	
IL-1ra				0.6250
Mean ± SD	929.234±1,410.274	545.219±863.350	−384.015±1,352.077	
Median (Q1, Q3)	210.15 (145.47, 1,359.54)	95.89 (35.12, 487.21)	−73.39 (−110.35, 269.83)	
Range	22.6, 4,527.7	12.0, 2,501.2	−4,116.5, 608.6	
IL-2				0.8750
Mean ± SD	2.328±1.415	2.284±1.476	−0.044±1.466	
Median (Q1, Q3)	3.20 (0.72, 3.20)	3.20 (0.22, 3.20)	0.00 (−0.09, 0.00)	
Range	0.0, 3.2	0.0, 3.2	−3.0, 3.2	
IL-3				0.8125
Mean ± SD	2.854±2.039	3.051±1.123	0.197±2.025	
Median (Q1, Q3)	3.20 (1.70, 3.20)	3.20 (3.20, 3.20)	0.00 (0.00, 1.50)	
Range	0.1, 7.4	0.2, 4.7	−3.0, 3.1	
IL-4				0.2754
Mean ± SD	3.102±3.057	1.882±1.191	−1.221±2.837	
Median (Q1, Q3)	1.83 (1.12, 3.20)	2.11 (1.09, 3.20)	−0.88 (−2.11, 0.89)	
Range	0.4, 9.1	0.2, 3.3	−6.8, 2.8	

Table 2 (*continued*)

Table 2 (*continued*)

Urinary cytokines	Pre-HIFU	Post-HIFU	HIFU change (post-pre)	Wilcoxon signed rank P value
Il-5				0.8203
Mean ± SD	0.166±0.262	0.434±0.977	0.267±1.007	
Median (Q1, Q3)	0.07 (0.05, 0.11)	0.13 (0.05, 0.20)	0.01 (–0.03, 0.09)	
Range	0.0, 0.9	0.0, 3.2	–0.5, 3.1	
IL-6				0.9999
Mean ± SD	5.519±5.763	6.573±9.923	1.054±11.693	
Median (Q1, Q3)	3.73 (0.90, 8.49)	3.20 (2.12, 6.07)	1.84 (–6.37, 2.83)	
Range	0.4, 17.1	0.6, 33.8	–12.5, 29.6	
IL-7				0.6250
Mean ± SD	3.519±1.211	3.112±0.280	–0.407±1.445	
Median (Q1, Q3)	3.20 (3.20, 3.37)	3.20 (3.20, 3.20)	0.00 (–0.17, 0.00)	
Range	1.6, 6.3	2.3, 3.2	–4.0, 1.6	
IL-8				0.0098*
Mean ± SD	143.936±319.985	57.850±152.564	–86.086±172.323	
Median (Q1, Q3)	14.20 (3.34, 123.18)	8.39 (2.03, 22.79)	–6.27 (–96.72, –1.33)	
Range	2.9, 1,034.7	1.6, 491.3	–543.4, 1.9	
IL-9	10	10	10	0.2754
Mean ± SD	1.408±0.567	1.258±0.479	–0.150±0.452	
Median (Q1, Q3)	1.22 (1.03, 1.59)	1.04 (0.93, 1.42)	–0.08 (–0.36, 0.02)	
Range	1.0, 2.9	0.8, 2.3	–1.1, 0.6	
IL-10				0.2500
Mean ± SD	1.053±1.109	0.744±0.438	–0.309±0.849	
Median (Q1, Q3)	0.65 (0.56, 1.07)	0.60 (0.42, 0.78)	–0.04 (–0.36, 0.04)	
Range	0.3, 4.1	0.4, 1.7	–2.4, 0.8	
IL-12(p40)				0.6250
Mean ± SD	4.252±4.430	3.306±0.989	–0.946±3.668	
Median (Q1, Q3)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	0.00 (–1.52, 0.00)	
Range	0.6, 16.1	1.7, 5.8	–10.4, 2.6	
IL-12(p70)				0.9999
Mean ± SD	3.085±0.755	3.029±0.539	–0.055±1.123	
Median (Q1, Q3)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	0.00 (0.00, 0.00)	
Range	1.1, 4.1	1.5, 3.2	–2.6, 2.1	

Table 2 (*continued*)

Table 2 (*continued*)

Urinary cytokines	Pre-HIFU	Post-HIFU	HIFU change (post-pre)	Wilcoxon signed rank P value
IL-13				0.0488*
Mean ± SD	1.211±1.229	0.599±0.455	−0.612±0.908	
Median (Q1, Q3)	0.80 (0.44, 1.48)	0.46 (0.27, 0.90)	−0.48 (−0.77, −0.10)	
Range	0.3, 4.3	0.1, 1.6	−2.6, 0.4	
IL-15				0.9219
Mean ± SD	4.465±5.585	3.398±2.565	−1.066±4.074	
Median (Q1, Q3)	1.94 (0.99, 4.19)	2.64 (1.60, 3.93)	0.03 (−0.63, 0.90)	
Range	0.7, 17.4	1.0, 9.3	−8.8, 3.2	
IL-17				0.2500
Mean ± SD	4.307±4.443	3.165±2.496	−1.142±2.797	
Median (Q1, Q3)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	0.00 (−3.15, 0.00)	
Range	0.7, 16.8	0.0, 9.2	−7.6, 2.5	
IP-10				0.0020*
Mean ± SD	776.687±14,25.422	65.141±40.691	−711.546±1,430.818	
Median (Q1, Q3)	293.62 (51.38, 694.94)	63.82 (31.08, 107.40)	−208.86 (−583.71, −10.87)	
Range	34.6, 4722.6	8.1, 116.3	−4,691.6, −0.5	
MCP-1				0.0273*
Mean ± SD	1,267.257±924.755	690.759±566.813	−576.498±705.692	
Median (Q1, Q3)	767.92 (694.10, 2,246.24)	396.57 (298.05, 1,013.05)	−390.07 (−1,157.33, −113.16)	
Range	247.9, 2,816.9	134.7, 1,912.9	−1,803.9, 466.1	
MCP-3				0.9999
Mean ± SD	3.858±2.121	3.668±0.994	−0.190±1.526	
Median (Q1, Q3)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	0.00 (0.00, 0.00)	
Range	3.1, 9.9	3.2, 5.8	−4.1, 2.1	
MDC				0.8125
Mean ± SD	29.344±77.533	15.522±31.847	−13.822±46.256	
Median (Q1, Q3)	3.20 (3.20, 3.20)	3.20 (3.20, 9.58)	0.00 (0.00, 3.21)	
Range	3.2, 249.6	3.2, 105.5	−144.1, 11.3	
MIP-1α				0.1250
Mean ± SD	11.064±24.037	5.282±8.895	−5.783±15.235	
Median (Q1, Q3)	3.20 (3.20, 3.20)	3.20 (1.76, 3.20)	0.00 (−2.50, 0.00)	
Range	1.7, 79.4	0.7, 30.4	−48.9, 0.1	

Table 2 (*continued*)

Table 2 (*continued*)

Urinary cytokines	Pre-HIFU	Post-HIFU	HIFU change (post-pre)	Wilcoxon signed rank P value
MIP-1β				0.0273*
Mean ± SD	10.252±13.710	3.585±3.619	−6.667±10.481	
Median (Q1, Q3)	3.54 (2.12, 11.22)	2.86 (0.75, 5.26)	−2.17 (−5.98, 0.00)	
Range	1.6, 42.8	0.4, 12.2	−30.7, 0.9	
PDGF-AA				0.1602
Mean ± SD	62.974±58.974	37.790±50.899	−25.184±75.781	
Median (Q1, Q3)	44.06 (20.35, 80.05)	24.41 (6.19, 40.14)	−21.77 (−44.13, 1.68)	
Range	4.5, 191.1	4.6, 174.9	−173.1, 124.7	
PDGF-AB_BB				0.2188
Mean ± SD	8.987±11.009	3.502±0.864	−5.485±10.341	
Median (Q1, Q3)	3.20 (3.20, 9.45)	3.20 (3.20, 3.20)	0.00 (−6.25, 0.00)	
Range	2.6, 34.2	3.2, 5.9	−28.2, 0.6	
RANTES				0.0020*
Mean ± SD	31.952±24.609	10.813±5.953	−21.139±20.643	
Median (Q1, Q3)	26.88 (17.26, 32.88)	8.83 (5.40, 16.76)	−17.45 (−24.15, −6.81)	
Range	8.4, 94.2	3.9, 20.3	−73.9, −3.0	
sCD40L				0.4688
Mean ± SD	8.417±18.120	3.609±4.772	−4.808±13.653	
Median (Q1, Q3)	3.20 (1.02, 3.20)	3.20 (1.02, 3.20)	0.00 (−2.18, 0.71)	
Range	0.3, 59.7	0.3, 16.7	−42.9, 2.2	
sIL_2Rα				0.0020*
Mean ± SD	1,298.182±808.665	716.354±563.325	−581.828±490.465	
Median (Q1, Q3)	1,256.91 (640.72, 1,685.31)	528.15 (242.74, 1,058.40)	−528.42 (−854.05, −242.22)	
Range	266.5, 2,771.2	166.6, 1,814.1	−1,628.7, −23.8	
TGFα				0.0645
Mean ± SD	7.859±6.140	4.873±2.880	−2.986±5.568	
Median (Q1, Q3)	5.43 (4.02, 12.96)	3.87 (2.92, 6.55)	−1.48 (−4.82, −0.37)	
Range	2.1, 21.6	1.7, 10.7	−15.1, 5.6	
TNFα				0.9023
Mean ± SD	1.600±1.809	1.378±0.980	−0.223±0.917	
Median (Q1, Q3)	0.97 (0.93, 1.25)	0.97 (0.94, 1.08)	0.00 (−0.15, 0.09)	
Range	0.9, 6.7	0.9, 4.0	−2.7, 0.7	

Table 2 (*continued*)

Table 2 (*continued*)

Urinary cytokines	Pre-HIFU	Post-HIFU	HIFU change (post-pre)	Wilcoxon signed rank P value
TNFβ				0.3008
Mean ± SD	0.543±0.455	0.405±0.249	–0.138±0.269	
Median (Q1, Q3)	0.35 (0.28, 0.71)	0.35 (0.20, 0.49)	–0.04 (–0.15, 0.00)	
Range	0.2, 1.7	0.1, 1.0	–0.7, 0.1	
VEGF				0.4922
Mean ± SD	48.382±39.797	33.191±5.434	–15.191±42.137	
Median (Q1, Q3)	36.89 (32.18, 42.27)	32.16 (28.79, 34.31)	–6.56 (–9.09, 8.23)	
Range	26.1, 160.2	27.5, 45.1	–131.7, 12.9	

*, P value <0.05 was considered statistically significant.

Table 3 The nine urinary cytokines that significantly decreased post-MRgHIFU for each individual patient

PID	Eotaxin	GRO	IL-13	IL-8	IP-10	MCP-1	MIP-1β	RANTES	sIL-2Rα
1	–28.267	–37.764	–0.117	–14.307	–583.714	–1,803.892	–5.952	–18.774	–854.053
2	–10.803	–64.094	–0.105	–96.715	–43.248	–438.661	–0.660	–21.418	–582.665
3	–90.282	–488.404	–0.575	–190.829	–842.361	–333.356	–20.230	–31.875	–242.220
4	–9.406	–3.049	–0.705	–1.313	–25.958	–473.933	–1.536	–6.813	–474.166
5	–6.541	–9.609	0.280	–6.384	–0.476	–41.021	0.229	–6.116	–58.361
6	–16.604	–3.068	0.425	–6.161	–9.711	466.109	0.938	–9.246	–245.701
7	–15.904	–245.709	–2.649	–543.414	–4,691.551	–341.481	–30.679	–73.859	–23.784
8	–6.227	–12.937	–1.517	1.894	–374.477	–1,528.245	–2.797	–16.120	–957.086
9	–136.725	–98.522	–0.774	–2.293	–533.089	–1,157.335	–5.978	–24.150	–1,628.698
10	2.461	–8.582	–0.388	–1.333	–10.869	–113.162	0.000	–3.024	–751.547

Discussion

The aim of this study was to analyze urinary cytokines/chemokines pattern after MRgHIFU for palliative treatment of painful bone metastases. The results showed that nine urinary cytokines significantly decreased post-MRgHIFU. They include; Eotaxin, GRO, IL-8, IL-13, IP-10, MCP-1, MIP-1β, RANTES, and sIL-2Rα. It is thought that MRgHIFU can decrease tumor-secreted immunosuppressive cytokine production; in addition it has a direct tumor destruction activity (9). These changes may reduce the effect of tumor-induced immunosuppression, and renew antitumor immunity after MRgHIFU in cancer patients.

Cytokines play a significant role in pain initiation and maintenance (10). Cytokines may be either pro- or anti-inflammatory; they are mainly produced by macrophages, neutrophils, and epithelial cells. Cytokines are mainly involved in the processes of angiogenesis, inflammation, wound healing, and tumorigenesis. They can down-regulate and inhibit the immune system of the host, contributing to the growth and progression of tumor (11-15).

MRgHIFU ablation causes direct destruction of tumor cells. This is thought to occur by activation of antitumor responses in the host following the ablation (16,17). As a result, this effect potentially allows the host immune system to control micro-metastases and decrease tumor recurrence

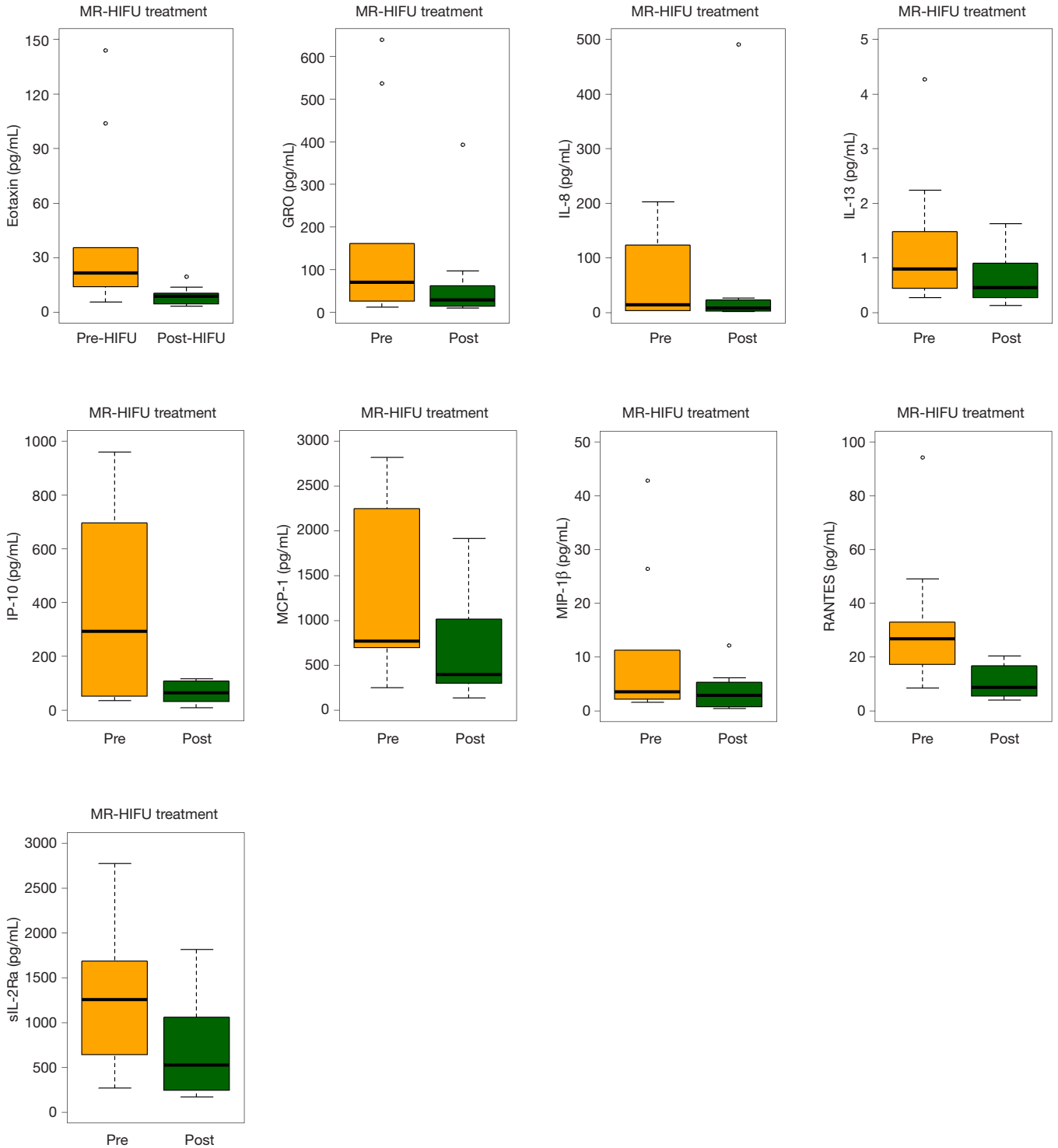

Figure 2 Boxplots for nine significant urinary cytokines between pre- and post-magnetic resonance-guided high intensity focused ultrasound (MRgHIFU) in all patients. Yellow indicates patients with Pre-MRgHIFU treatment, and green indicates patients with post-MRgHIFU treatment.

Table 4 Kruskal-Wallis nonparametric test to compare post-MRgHIFU, post radiation with pain flare, and post radiation with no pain flare for each urinary cytokine

Urinary cytokines	Post-HIFU (N=10)	No pain flare post-radiation (N=17)	Pain flare post-radiation (N=11)	Kruskal-Wallis P value
EGF				0.0006*
Mean ± SD	31,372.685±35,367.680	5,944.942±4,131.156	6,654.298±34,85.800	
Median (Q1, Q3)	15,806.57 (10,706.21, 39,979.66)	4,866.49 (2,462.89, 10,092.24)	6,606.85 (3,522.96, 8,757.71)	
Range	5,194.6, 122,231.6	1,021.4, 13,286.1	2,564.9, 14,363.8	
Eotaxin				0.0322*
Mean ± SD	9.011±5.055	7.889±12.731	6.025±8.630	
Median (Q1, Q3)	8.95 (4.50, 10.46)	3.20 (3.20, 5.00)	3.20 (3.20, 3.50)	
Range	3.2, 19.6	3.2, 55.5	3.2, 32.0	
FGF-2				0.6037
Mean ± SD	7.521±6.493	3.757±0.747	3.785±0.650	
Median (Q1, Q3)	3.20 (3.20, 11.74)	3.20 (3.20, 3.89)	3.57 (3.20, 4.39)	
Range	3.2, 22.1	3.2, 5.6	3.2, 4.8	
Fit-3 ligand				0.0042*
Mean ± SD	13.451±8.205	3.945±1.279	12.746±17.738	
Median (Q1, Q3)	11.56 (6.80, 18.35)	3.55 (3.20, 3.78)	5.13 (3.33, 10.49)	
Range	3.2, 27.7	3.2, 7.5	3.2, 61.0	
Fractalkine				0.0020*
Mean ± SD	107.713±52.364	34.828±45.455	35.082±38.142	
Median (Q1, Q3)	118.36 (53.06, 148.41)	18.18 (5.51, 43.42)	16.25 (13.21, 47.67)	
Range	41.7, 192.4	3.2, 184.5	3.2, 127.9	
G-CSF				0.0783
Mean ± SD	6.105±3.381	3.248±0.236	3.204±0.012	
Median (Q1, Q3)	5.92 (3.18, 7.73)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	
Range	1.5, 11.6	3.1, 4.2	3.2, 3.2	
GM-CSF				0.0321*
Mean ± SD	2.536±1.744	5.751±7.570	3.833±1.119	
Median (Q1, Q3)	1.89 (1.19, 3.40)	3.20 (3.20, 5.26)	3.20 (3.20, 4.42)	
Range	1.0, 6.1	3.0, 34.8	3.1, 6.8	
GRO				0.0311*
Mean ± SD	70.570±116.768	64.702±202.788	16.438±12.870	
Median (Q1, Q3)	28.89 (13.65, 61.82)	6.56 (4.20, 28.93)	12.68 (5.05, 22.00)	
Range	8.9, 393.1	2.9, 847.2	3.2, 44.5	

Table 4 (*continued*)

Table 4 (*continued*)

Urinary cytokines	Post-HIFU (N=10)	No pain flare post-radiation (N=17)	Pain flare post-radiation (N=11)	Kruskal-Wallis P value
IFNα2				0.0193*
Mean ± SD	7.739±3.924	3.819±2.478	3.303±0.179	
Median (Q1, Q3)	9.20 (4.08, 10.74)	3.20 (3.20, 3.20)	3.20 (3.20, 3.53)	
Range	1.7, 12.9	3.2, 13.4	3.2, 3.6	
IFN-γ				<0.0001*
Mean ± SD	0.621±0.411	3.200±0.000	3.200±0.000	
Median (Q1, Q3)	0.54 (0.40, 0.68)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	
Range	0.3, 1.7	3.2, 3.2	3.2, 3.2	
IL-1α				0.0417*
Mean ± SD	5.719±8.625	10.772±31.102	3.255±0.182	
Median (Q1, Q3)	1.80 (1.22, 3.20)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	
Range	0.4, 23.4	3.2, 131.5	3.2, 3.8	
IL-1β				<0.0001*
Mean ± SD	4.132±12.068	3.199±0.005	3.200±0.000	
Median (Q1, Q3)	0.31 (0.20, 0.49)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	
Range	0.1, 38.5	3.2, 3.2	3.2, 3.2	
IL-1Ra				<0.0001*
Mean ± SD	545.219±863.350	40.616±148.520	11.173±22.111	
Median (Q1, Q3)	95.89 (35.12, 487.21)	3.20 (3.20, 3.78)	3.20 (3.20, 7.02)	
Range	12.0, 2501.2	3.2, 616.8	3.2, 77.2	
IL-2				0.0513
Mean ± SD	2.284±1.476	3.200±0.000	3.200±0.000	
Median (Q1, Q3)	3.20 (0.22, 3.20)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	
Range	0.0, 3.2	3.2, 3.2	3.2, 3.2	
IL-3				0.8363
Mean ± SD	3.051±1.123	3.200±0.000	3.200±0.000	
Median (Q1, Q3)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	
Range	0.2, 4.7	3.2, 3.2	3.2, 3.2	
IL-4				<0.0001*
Mean ± SD	1.882±1.191	5.818±1.620	5.013±1.827	
Median (Q1, Q3)	2.11 (1.09, 3.20)	5.72 (4.35, 7.18)	4.59 (3.69, 5.63)	
Range	0.2, 3.3	3.2, 8.8	3.2, 8.9	

Table 4 (*continued*)

Table 4 (*continued*)

Urinary cytokines	Post-HIFU (N=10)	No pain flare post-radiation (N=17)	Pain flare post-radiation (N=11)	Kruskal-Wallis P value
IL-5				<0.0001*
Mean ± SD	0.434±0.977	3.200±0.000	3.200±0.000	
Median (Q1, Q3)	0.13 (0.05, 0.20)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	
Range	0.0, 3.2	3.2, 3.2	3.2, 3.2	
IL-6				0.6919
Mean ± SD	6.573±9.923	3.860±1.215	4.567±3.632	
Median (Q1, Q3)	3.20 (2.12, 6.07)	3.20 (3.20, 3.82)	3.20 (3.20, 3.71)	
Range	0.6, 33.8	3.2, 7.0	3.2, 15.3	
IL-7				0.2224
Mean ± SD	3.112±0.280	4.490±5.221	3.227±0.089	
Median (Q1, Q3)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	
Range	2.3, 3.2	3.2, 24.7	3.2, 3.5	
IL-8				0.3830
Mean ± SD	57.850±152.564	167.835±630.943	8.340±9.191	
Median (Q1, Q3)	8.39 (2.03, 22.79)	8.22 (5.61, 12.22)	4.21 (3.20, 11.36)	
Range	1.6, 491.3	3.2, 2615.0	3.1, 33.8	
IL-9				<0.0001*
Mean ± SD	1.258±0.479	3.199±0.005	3.217±0.056	
Median (Q1, Q3)	1.04 (0.93, 1.42)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	
Range	0.8, 2.3	3.2, 3.2	3.2, 3.4	
IL-10				<0.0001*
Mean ± SD	0.744±0.438	3.201±0.003	3.200±0.000	
Median (Q1, Q3)	0.60 (0.42, 0.78)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	
Range	0.4, 1.7	3.2, 3.2	3.2, 3.2	
IL-12(p40)				0.4467
Mean ± SD	3.306±0.989	3.233±0.136	3.180±0.047	
Median (Q1, Q3)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	
Range	1.7, 5.8	3.2, 3.8	3.1, 3.2	
IL-12(p70)				0.5800
Mean ± SD	3.029±0.539	3.200±0.000	3.200±0.000	
Median (Q1, Q3)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	
Range	1.5, 3.2	3.2, 3.2	3.2, 3.2	

Table 4 (*continued*)

Table 4 (*continued*)

Urinary cytokines	Post-HIFU (N=10)	No pain flare post-radiation (N=17)	Pain flare post-radiation (N=11)	Kruskal-Wallis P value
IL-13				<0.0001*
Mean ± SD	0.599±0.455	3.200±0.000	3.193±0.022	
Median (Q1, Q3)	0.46 (0.27, 0.90)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	
Range	0.1, 1.6	3.2, 3.2	3.1, 3.2	
IL-15				0.3030
Mean ± SD	3.398±2.565	3.220±0.104	3.907±1.639	
Median (Q1, Q3)	2.64 (1.60, 3.93)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	
Range	1.0, 9.3	3.1, 3.6	3.2, 8.1	
IL-17				0.7303
Mean ± SD	3.165±2.496	3.200±0.000	3.200±0.000	
Median (Q1, Q3)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	
Range	0.0, 9.2	3.2, 3.2	3.2, 3.2	
IP-10				0.0143*
Mean ± SD	65.141±40.691	24.315±31.433	32.727±28.537	
Median (Q1, Q3)	63.82 (31.08, 107.40)	8.00 (3.40, 36.14)	29.54 (3.83, 41.65)	
Range	8.1, 116.3	3.2, 103.3	3.2, 93.1	
MCP-1				0.1992
Mean ± SD	690.759±566.813	384.229±387.093	850.391±900.241	
Median (Q1, Q3)	396.57 (298.05, 1,013.05)	220.85 (137.85, 496.39)	418.55 (106.65, 1,696.54)	
Range	134.7, 1,912.9	58.9, 1,558.6	59.0, 2,581.3	
MCP-3				0.0157*
Mean ± SD	3.668±0.994	3.794±0.631	4.608±1.409	
Median (Q1, Q3)	3.20 (3.20, 3.20)	3.68 (3.20, 4.04)	3.99 (3.56, 5.27)	
Range	3.2, 5.8	3.2, 5.1	3.2, 7.6	
MDC				0.7057
Mean ± SD	15.522±31.847	5.239±1.380	5.298±1.508	
Median (Q1, Q3)	3.20 (3.20, 9.58)	4.86 (4.44, 5.75)	5.66 (4.00, 7.03)	
Range	3.2, 105.5	3.2, 8.1	3.2, 7.5	
MIP-1α				0.0571
Mean ± SD	5.282±8.895	4.045±1.217	3.701±0.914	
Median (Q1, Q3)	3.20 (1.76, 3.20)	3.20 (3.20, 5.16)	3.20 (3.20, 4.23)	
Range	0.7, 30.4	3.2, 7.3	3.2, 5.5	

Table 4 (*continued*)

Table 4 (*continued*)

Urinary cytokines	Post-HIFU (N=10)	No pain flare post-radiation (N=17)	Pain flare post-radiation (N=11)	Kruskal-Wallis P value
MIP-1β				0.3878
Mean ± SD	3.585±3.619	4.318±2.072	4.618±2.604	
Median (Q1, Q3)	2.86 (0.75, 5.26)	3.61 (3.20, 4.02)	3.64 (3.20, 3.84)	
Range	0.4, 12.2	3.2, 10.8	3.1, 10.2	
PDGF-AA				0.2518
Mean ± SD	37.790±50.899	41.585±31.504	67.627±58.206	
Median (Q1, Q3)	24.41 (6.19, 40.14)	39.52 (14.95, 56.57)	53.41 (24.01, 132.64)	
Range	4.6, 174.9	3.2, 116.9	3.2, 182.5	
PDGF-AB_BB				0.7338
Mean ± SD	3.502±0.864	4.177±2.030	3.453±0.501	
Median (Q1, Q3)	3.20 (3.20, 3.20)	3.20 (3.20, 3.48)	3.20 (3.20, 3.48)	
Range	3.2, 5.9	3.2, 9.3	3.2, 4.8	
RANTES				0.0008*
Mean ± SD	10.813±5.953	4.530±2.415	4.292±1.413	
Median (Q1, Q3)	8.83 (5.40, 16.76)	3.20 (3.20, 4.52)	3.66 (3.20, 4.90)	
Range	3.9, 20.3	3.1, 10.1	3.2, 7.7	
sCD40L				0.0243*
Mean ± SD	3.609±4.772	3.296±0.355	3.261±0.112	
Median (Q1, Q3)	3.20 (1.02, 3.20)	3.20 (3.20, 3.20)	3.20 (3.20, 3.37)	
Range	0.3, 16.7	3.2, 4.7	3.2, 3.5	
sIL-2Ra				0.4258
Mean ± SD	716.354±563.325	505.154±514.868	799.829±688.601	
Median (Q1, Q3)	528.15 (242.74, 1,058.40)	295.47 (195.31, 545.00)	634.69 (198.24, 1,333.43)	
Range	166.6, 1,814.1	3.2, 1,835.3	53.6, 1,924.8	
TGFα				0.1698
Mean ± SD	4.873±2.880	5.136±2.063	8.438±6.285	
Median (Q1, Q3)	3.87 (2.92, 6.55)	4.51 (3.69, 6.05)	6.16 (3.33, 10.64)	
Range	1.7, 10.7	3.1, 10.2	3.2, 24.3	
TNFα				<0.0001*
Mean ± SD	1.378±0.980	3.200±0.000	3.200±0.000	
Median (Q1, Q3)	0.97 (0.94, 1.08)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	
Range	0.9, 4.0	3.2, 3.2	3.2, 3.2	

Table 4 (*continued*)

Table 4 (*continued*)

Urinary cytokines	Post-HIFU (N=10)	No pain flare post-radiation (N=17)	Pain flare post-radiation (N=11)	Kruskal-Wallis P value
TNFβ				<0.0001*
Mean ± SD	0.405±0.249	3.200±0.000	3.200±0.000	
Median (Q1, Q3)	0.35 (0.20, 0.49)	3.20 (3.20, 3.20)	3.20 (3.20, 3.20)	
Range	0.1, 1.0	3.2, 3.2	3.2, 3.2	
VEGF				0.0859
Mean ± SD	33.191±5.434	39.293±7.761	36.978±7.223	
Median (Q1, Q3)	32.16 (28.79, 34.31)	37.38 (33.43, 44.82)	35.39 (30.41, 44.58)	
Range	27.5, 45.1	27.8, 55.9	28.8, 51.0	

*, P value < 0.05 was considered statistically significant.

Table 5 Cytokines levels pre- and post-MRgHIFU in patients with positive pain response

Urinary cytokines (pre-HIFU-post-HIFU)	Wilcoxon signed-rank test P value
EGF	0.8438
Eotaxin	0.0625
FGF-2	0.5000
Fit-3 ligand	0.0625
Fractalkine	0.8438
G-CSF	0.5625
GM-CSF	0.2188
GRO	0.0313
IFNα2	0.3125
IFN-γ	0.0313
IL-1α	0.9999
IL-1β	0.4375
IL-1ra	0.8438
IL-2	0.9999
IL-3	0.5000
IL-4	0.8438
Il-5	0.8125
IL-6	0.8438
IL-7	0.5000
IL-8	0.1563
IL-9	0.2188
IL-10	0.3125
IL-12-p40	0.9999
IL-12-p70	0.9999
IL-13	0.0313
IL-15	0.8438
IL-17	0.5000
IP-10	0.0313
MCP-1	0.0313
MCP-3	0.9999
MDC	0.9999
MIP-1α	0.5000
MIP-1β	0.0625
PDGF-AA	0.0625
PDGF-AB_BB	0.2500
RANTES	0.0313
sCD40L	0.7500
sIL-2Rα	0.0313
TGFα	0.0625
TNFα	0.6875
TNFβ	0.1250
VEGF	0.2188

Table 5 (*continued*)

Table 5 (*continued*)

at the local site following MRgHIFU treatment.

When comparing the urinary cytokines/chemokines pattern between post-MRgHIFU and post-8 Gy fraction radiation, we found significant differences between the cytokines pattern and no correlation could be made between the patterns seen in both treatment modalities (10).

Our study is not without any limitations; the most notable is our small sample size. Many of our enrolled patients were very sick with widespread metastatic disease. The clinical benefit of the decrease in cytokines post-MRgHIFU was not evaluated. The next step is to conduct a randomized clinical trial to assess the clinical significance of the changes in cytokines/chemokines pattern in patients with painful bone metastases.

In conclusion, our study showed that nine urinary cytokines significantly reduced post-MRgHIFU in patients with painful bone metastases. The significance of cytokines/chemokines pattern for palliative treatment of painful bone metastases is still unknown. Further research is required to confirm the possible correlation between decreased cytokines/chemokines pattern post-MRgHIFU with pain response in patients with painful bone metastases.

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None.

Footnote

Conflicts of Interest: Charles Mougenot is employed by Philips Healthcare. The other authors have no conflicts of interest to declare.

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