Comparing imaging changes and pain response in patients with intra- or extra-osseous bone metastases treated palliatively with magnetic resonance guided high intensity focused ultrasound (MRgHIFU)

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Conflicts of Interest

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Abstract

Purpose: To compare imaging changes and pain relief in patients with intra- vs. extra-osseous bone metastases treated palliatively with magnetic resonance guided high intensity focused ultrasound (MRgHIFU).

Materials and Methods: 21 patients were treated prospectively with MRgHIFU at 3 centers. Intra-procedural thermal changes measured on proton resonance frequency shift thermometry (PRFS), and Gadolinium T1-weighted (Gd-T1W) image appearances after treatment, were compared for intra- and extra-osseous metastases. Pain scores and analgesic use documented before, and up to 90 days after treatment, were used to classify response, and were compared between intra- and extra-osseous groups. Gd-T1W changes were compared between responders and non-responders in each group.

Results: Thermal dose volumes were significantly larger in the extra-osseous group (p=0.039). Tumor diameter did not change after treatment in either group. At Day 30, Gd-T1W images showed focal non-enhancement in 7/9 patients with intra-osseous tumors; in patients with extra-osseous tumors, changes were heterogeneous.

Cohort reductions in worst pain scores were seen for both groups, but differences from baseline at Days 14, 30, 60 and 90 were only significant for the intra-osseous group (p=0.027, p=0.013, p=0.012, p=0.027 respectively). By Day 30, 67% (6/9) patients with intra-osseous tumors were classified as responders, for patients with extra-osseous tumors response rate was 33% (4/12). In neither group was pain response indicated by non-enhancement on Gd-T1W.

Conclusion: Intra-osseous tumors showed focal non-enhancement by Day 30, and patients had better pain response to MRgHIFU than those with extra-osseous tumors. In this small cohort, post-treatment imaging was not informative of treatment efficacy.

Introduction

High Intensity Focused Ultrasound (HIFU) is emerging as a credible option for palliating pain from bone metastases(1, 2), a common cause of cancer-related morbidity(3). Studies have evaluated the safety and efficacy of HIFU in radiation refractory and radiation naïve populations, and shown significant improvements in pain, with a low rate of treatment-related adverse events(4-9). The mechanism of action may be thermal denervation of the periosteum(2), exploiting cortical bone's high acoustic absorption and low thermal conduction, so that targeting it results in energy deposition at the periosteal surface(10). This strategy therefore, may be ineffective for extra-osseous metastases, where the lack of a cortical barrier may mean that ablative energy is transmitted directly into the tumor and misses involved periosteal nerves. Whilst the cortical integrity of treated tumors has been noted in a few prior studies(6, 9), pain response to HIFU in patients with intra- or extra-osseous bone metastases critically remains unexplored.

HIFU treatments may be guided by MR imaging (MRgHIFU), which allows accurate depiction of the target and surrounding anatomy. MRI based temperature measurement using a proton resonance frequency shift (PRFS) technique is used to monitor treatments(11, 12), where thermal data are displayed as color overlays superimposed on anatomical images. Raising tissue temperature to ≥56^{o}C for only a few seconds is considered to be ablative(13). After treatment, Gadolinium enhanced T1-weighted (Gd-T1W) imaging can show non-perfused regions indicative of tissue ablation(14). It may also be used to assess outcomes after treatment (6), but the significance of the non-perfused volume (NPV) in relation to dose delivered, or to treatment response, is

unclear(8, 15). The purpose of this study was to compare imaging changes during and after treatment in patients with intra- versus extra-osseous bone metastases treated palliatively with MRgHIFU. Any changes were related to longitudinal changes in pain scores over 90 days.

Materials and Methods

Study Population

This study interrogated an exploratory end-point in 21 patients with a dominant painful bone metastasis participating in a prospective, single arm study (NCT01586273)(16). They were treated with MRgHIFU at one of 3 centers, after approval from Institutional review boards (REC number: 12/LO/0424, IRB code: 2013-04-050). Patients were provided with a study information sheet, prior to giving their written informed consent for treatment. All had a proven diagnosis of bony metastatic disease arising from a primary solid tumor, and a dominant painful metastasis of numerical rating scale (NRS) ≥4/10. Eligibility was determined at screening using criteria provided in **Table 1**. Patient and tumor characteristics are provided in **Table 2,** and classified as either intra-osseous (cortex intact), or extra-osseous (cortical breach).

Baseline Assessments

Pre-treatment baseline vital signs and body temperature were recorded, and target metastasis NRS pain score documented in a case report form (CRF). Global pain was assessed using the Brief Pain Inventory short form (BPI-SF) (17). Analgesic use in the 24 hours prior to treatment was also recorded.

Treatment delivery

Treatments were delivered using a Sonalleve HIFU device (Profound Medical, Ontario, Canada) with patients positioned within a 3T or 1.5T MR scanner (Philips Healthcare, Best, The Netherlands). A dampened Aquaflex gel-pad (Parker Laboratories Inc., Fairfield, NJ, USA) ensured optimal acoustic contact between their skin and the HIFU device.

After patients were sedated, MRgHIFU treatments were planned on a patient and tumor-specific basis using a series of volumetric treatment 'cells' of 4, 8 or 12 mm diameter(18). For intra-osseous tumors, cells were centered on the cortical surface; for extra-osseous tumors, additional cells were positioned within its soft tissue component.

Intra-procedural MR Imaging

T1W Imaging

3D T1W imaging was acquired over the full extent of the treatment region to confirm that the target metastasis lay within the targeting range of the transducer, and to allow treatment planning. If patients moved during treatments, the 3D T1W imaging was re-acquired to confirm the new patient position, and allow the location of prior sonications to be mapped to the new position.

PRFS Thermometry

PRFS thermometry was obtained at 3 s intervals before, during, and after each sonication to evaluate temperature change in overlying muscle (intra-osseous group) and within tumor (extra-osseous group). Sonications were terminated if

heating was excessive, occurred outside the target region, or if patient movement compromised targeting accuracy. After each sonication, PRFS data were reviewed to evaluate the magnitude and extent of thermal change, and determined the cooling times required to reduce the risk of unwanted heat build up in surrounding tissues.

Gd-T1W imaging

On completion of treatments, and after administration of 0.2 ml/kg body weight Gd contrast agent, 3D fat suppressed Gd-T1W images were obtained. Summary parameters for all sequences are shown in Table E1.

Post treatment assessments

After treatment, patients' pain scores for the treated metastasis were recorded in the CRF. For 30 days after treatment, patients completed a daily diary to record their worst pain score from the treated metastasis, and their analgesic consumption. They also completed the BPI-SF at home on Days 7 and 14 after treatment, and at Day 30 when they attended a follow-up appointment to complete the CRF and undergo MRI. All investigations were repeated on Days 60 and 90 where possible. Any adverse events (AEs) that occurred after recruitment to the study were reported, in accordance with study and institutional requirements.

Data analysis

Treatment delivery parameters

The number, diameter and total volume of treatment cells for each patient were recorded. The duration and power of each sonication was noted; their product provided the applied acoustic energy of each sonication, whose sum for all delivered sonications provided the total acoustic energy for the treatment. Treatment time was measured from first exposure to last.

Thermal changes were measured on PRFS by estimating thermal dose volume, calculated as the product of 3 orthogonal maximum dimensions of the 240 equivalent minutes (EM) at 43^{o}C dose contour(12, 19) (**Figure 1**). The sum of thermal dose volumes for all sonications was the estimate of total thermal dose volume for each patient (V_{240EM}). In addition, the maximum temperature recorded in the target region during each sonication was used to calculate the mean maximum temperature (T_M) from all sonications, for each patient.

Imaging changes after treatment

T1W images were used to estimate any changes in tumor diameter from baseline. Gd-T1W images were used to measure NPV, by drawing regions of interest (ROIs) on the immediate post-treatment and Day 30/60/90 images. The total NPV was calculated from the product of totaled ROI areas and slice thickness. Where no focal NPV was identified, changes were classified as Grade 1 change (ill-defined expansion of non-perfused regions) or Grade 2 change (definite increase in non-perfusion, or reduction in contrast enhancement).

Treatment Response

CRF and diary (local) and BPI-SF (global) pain scores at all post-treatment time-points were compared with baseline (pre-treatment) scores. The Pain Severity Index and the Pain Interference Index were also calculated from the BPI-SF(17). A change in analgesic requirement after treatment was assessed from the patient diaries and the CRF.

Treatment response was classified using established criteria(20). Complete response (CR) was defined as a BPI-SF worst pain score of zero, without increase in analgesic intake. Partial response (PR) was defined as a reduction of ≥2 points in worst pain, without analgesic increase; or analgesic reduction of ≥25%, without increase in worst pain. Pain progression (PP) was an increase of ≥2 points in worst pain, without analgesic decrease; or analgesic increase of ≥25%, with worst pain ≤1 point above baseline. No response (NR) applied to all other cases. The < or ≥25% change in analgesia was determined by calculating the change in morphine equivalent daily dose (MEDD) (21); for non-opioid medication where MEDD could not be calculated, the magnitude of dose reduction was established through comparison with pre-treatment dose. Patients were classified as responders (CR or PR) or non-responders (NR or PP) at Days 7, 14, 30, 60 and 90 after treatment.

Adverse Events

AEs were classified in accordance with the Clinical Practice Guidelines of the Society of Interventional Radiology(22). They were further categorized as definitely/probably/possibly/unlikely device-related (from MRgHIFU treatment), study-related (from study procedures), or unrelated to treatment.

Statistical Analyses

Statistical analyses were performed using GraphPad Prism software (Version 7, San Diego, USA). D'Agostino & Pearson tests for normality were used to select parametric or non-parametric tests. A value of $p<0.05$ was chosen as the criterion for statistical significance.

Baseline patient and tumor characteristics, and treatment delivery parameters for intra- and extra-osseous groups, were compared using two-tailed tests for unrelated samples; where data were normally distributed, unpaired t-tests were used; where they were not, Mann-Whitney tests were used. For each group, post treatment changes in pain scores (CRF, diary and BPI-SF) were compared using paired t-tests, and a Bonferroni correction for multiple comparisons.

After treatment, any difference in tumor diameter from baseline was compared using paired t-tests for the intra-osseous data, and a Wilcoxon matched-pairs signed rank test for the non-normally distributed extra-osseous data. Any change in NPV from immediately after treatment to Day 30 was compared using paired t-tests after log-transformation of these non-normally distributed data. The log-transformed post treatment NPV data were also compared with log-transformed intra-procedural V_{240EM} data using Pearson's correlations. Any differences in imaging features between intra- and extra-osseous responders and non-responders were described qualitatively because the sample sizes of these sub-groups were too small to justify the use of statistical tests.

Results

Patients and Treatments

Figure 2 shows the number of treated patients who completed follow-up. **Table 3** gives differences in delivered treatment and PRFS-measured thermal parameters between patients with intra-osseous (n=9) and extra-osseous (n=12) tumors. Although treatments appeared more extensive in the extra-osseous group, differences between groups were only significant in the number of delivered sonications and the measured thermal dose volume (V_{240EM}).

Imaging changes after treatment

For both intra- and extra-osseous tumors, mean maximum diameter measured on unenhanced T1W imaging was stable after treatment, with no significant difference from baseline at any post treatment time-point (**Table 3**).

Intra-osseous Group

A non-perfused volume was recognized immediately after treatment on Gd-T1W images in 8 of 9 patients with intra-osseous tumors. In 5/9 (56%), this was seen as a rind of non-enhancing tissue on either side of the osseous cortex, with a surrounding rim of enhancement at the proximal border of the un-enhanced rind. In 3 tumors, ill-defined regions of non-perfusion were seen, and no contrast enhancement was evident in one. By Day 30 after treatment, a clear

focal region of non-enhancement was present in 7/9 patients (78%) (**Figure 3**) that persisted at Day 60 and 90 in those with follow up.

NPV measured immediately after treatment in 7/9 patients (mean±SD: 5.5±9.9 ml, range: 0.1-27.3 ml) showed a strong and significant correlation with V_{240EM} measured during treatments (r=0.87, p=0.011). The NPV did not change significantly from immediately post treatment to Day 30, (mean±SD: 5.7±8.8 ml, range: 1.0-25.3 ml, p=0.25).

Extra-osseous Group

All 12 extra-osseous tumors were heterogeneous, with patchy regions of contrast enhancement and non-perfused regions of presumed necrosis on images acquired prior to the treatment day. These showed no visibly identifiable change on the post-treatment scan in 7/12 patients (58%); in 2 there was Grade 1 change, and in 3 there was Grade 2 change. By Day 30 after treatment, there was some evolution of image appearances in the 9 patients with imaging data: 2 still showed no change from baseline, 4 had Grade 1 change, 2 had Grade 2 change, and 1 had a re-establishment of pre-treatment enhancement, after Grade 1 change had been seen immediately post treatment.

Response to Treatment

Pain scores recorded on the CRF for the treated tumor in both groups showed reduction (**Figure 4a,b**), but differences from baseline at Days 30, 60 and 90 were only significant for the intra-osseous Group (p=0.012, p=0.029, p=0.042 respectively). The same pattern was seen from pain scores recorded in the BPI-

SF, with significant reductions in worst pain, pain severity index and pain interference index at every time-point from Day 14 after treatment only for the intra-osseous Group (**Figure 5a-f**). The daily worst pain scores recorded in the patient diaries also showed much earlier onset of pain relief in the intra- vs. extra-osseous group, with a >2-point improvement reported 1 day after treatment, and 22 days after treatment, respectively (**Figure 6a,b**).

6/9 intra-osseous patients (67%) were classified as responders at Day 30, compared to 4/12 in the extra-osseous group (33%). The latter also had a higher withdrawal rate from the study, with only 50% achieving Day 90 follow-up, compared to 70% of intra-osseous patients (**Figure 7)**. For both groups of patients, there was no clear difference in Gd-T1W imaging changes after treatment in those classified as responders or non-responders at Day 30.

Adverse Events (AEs)

There were no treatment related serious adverse events (SAEs) reported in the 21 patients. Of 5 AEs related/possibly related to treatment in 4 patients, 4 were reports of pain after treatment in intra-osseous patients, and one of temporary numbness of the buttock after treatment of a sacral metastasis in an extra-osseous patient. There were no fractures or skin burns after treatment, although Day 30 imaging indicated possible thermal injury to adjacent subcutaneous fat tissues in one extra-osseous patient. As expected in this population, the rate of AEs unrelated to treatment was higher (42 AEs in 14 patients, mainly relating to progression of underlying disease).

Discussion

This study demonstrates significant differences in pain relief for patients with intra- vs. extra-osseous bone metastases treated palliatively with MRgHIFU. The improvements in pain scores for the treated tumor (measured from the CRF) and in global pain (measured from the BPI-SF) seen in both groups showed a significant change from baseline at Days 14/30/60/90 only in patients with intra-osseous tumors. This was reflected in the patient diaries, which showed that changes occurred much earlier, with clinically relevant and important improvements(23, 24) being seen within 1 day of treatment. The rapid onset of improvement in patients with painful intra-osseous tumors constitutes a major advantage of the HIFU technique, but appears harder to achieve in patients with extra-osseous tumors.

The 67% response rate for the intra-osseous patients at Day 30 is comparable with other studies that have included heterogeneous populations(4-7, 9, 25). Furthermore, of the 3 intra-osseous non-responders at Day 30, one had achieved response by Day 60 (sustained at Day 90) whilst the 2 remaining patients had each reported 5 and 3 point reductions in focal pain at the treated site at Day 60, but both also required >25% increase in analgesia for worsening pain in other regions, and were therefore classified as non-responders.

The lower 33% response rate for the extra-osseous patients at Day 30 did not improve at later follow-up. Of the 3 patients classified as non-responders at Day 90, 2 only ever experienced a 1-point reduction in pain score, without a change in analgesia, whilst 1 patient had both increased pain scores and increased analgesia, making all 3 true non-responders. The high rate of withdrawal from

the study (50% by Day 90) because of disease progression is testament to the fact that these were patients with end-stage disease. Consequently, there were numerous adverse events unrelated to treatment reported in this group.

If HIFU thermally denervates the periosteum(2, 26), it is unsurprising that better response rates were seen in the intra-osseous group. Furthermore, as the treatments delivered to patients with the larger extra-osseous tumors were not significantly more extensive than those delivered to the smaller intra-osseous tumors, an insufficient proportion of the soft tissue tumors may have been targeted to elicit a response, either from a de-bulking effect, or from alterations in the release of pro-inflammatory signaling molecules(26, 27). A larger relative extent of thermal dose volume may be needed to achieve pain control in these soft tissue tumors. Whilst more aggressive treatments are technically feasible, they also risk a greater rate of adverse events. However, the aim of achieving local tumor control, as well as pain palliation, has already been highlighted as a research priority for MRgHIFU of painful bone metastases(1).

In the intra-osseous patients, thermal neurolysis was probably achieved, given clear regions of focal non-enhancement (NPV) were seen immediately after treatment in 5/9 patients, and by Day 30 in 7/9 cases. The NPV was significantly correlated with thermal dose volumes (V_{240EM}), but did not translate to an indication of treatment response. The small sample size, or the potential confounding effects of response classification may explain this. Alternatively, it may be that periosteal ablation is achieved regardless of visible soft tissue damage. This re-inforces previous studies where NPV was unrelated to pain score(15), and did not differ between responders and non-responders(8).

These results suggest that post treatment imaging, even using contrast-enhanced techniques, may not be informative about treatment efficacy for pain palliation of bone metastases. It can also only play a very limited role in ensuring patient safety, given that the opportunity to modify treatments has passed. It might serve a purpose in early recognition of complications, e.g. a large immediate post treatment NPV involving adjacent muscle in 1 intra-osseous patient could have prompted pro-active, early referral for physiotherapy to reduce muscle stiffness. However, this could also have been recognized during treatment because of the high intra-procedural V_{240EM}. Thus PRFS data may potentially help flag the likelihood of collateral tissue damage at a time when treatments could still be modified or curtailed. Removing the requirement for post treatment imaging assessments would reduce the burden of imaging appointments on patients, and spare them repeat administrations of contrast agents at a time when use of these agents is increasingly scrutinized. It would also reduce the resource requirement for institutions delivering these treatments.

The main limitation of this study was the small sample size in each group, caused by difficulties in recruiting sufficient suitable patients within a reasonable timescale, and high rates of study withdrawal. A potential source of bias in the findings was that the patients in each group were not matched, and the extra-osseous patients may have had more advanced disease. Response relative to ablative thermal dose per tumor volume and length of destroyed cortex needs to be established in these patients. There was also no mechanism for separating analgesic use for pain in a target tumor from pain in non-target regions, potentially confounding response assessment in some cases. In addition, the

estimated V_{240EM} was only an approximation of thermal dose volume, chosen because it could be quickly and easily obtained on the Sonalleve console as treatments progress. More accurate and robust methods for calculating thermal dose volume after treatment completion already exist, and could potentially be made available in a more timely fashion.

This study documents differences in MRgHIFU treatments delivered to patients with intra- and extra-osseous bone metastases. Response rates for patients with intra-osseous tumors were considerably better than for those with extra-osseous ones, who may require more aggressive treatments to achieve pain control. Imaging changes differed between the groups, but did not indicate treatment response. Follow-up scanning after treatment might therefore only be required for assessing disease progression or adverse events, rather than for monitoring on-going treatment efficacy.

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Tables and Figures

Table 1: Eligibility Criteria

Inclusion criteria	Exclusion criteria
Prior to enrolment:	
Adult ≥18 years,	Metastasis is from primary bone tumor, lymphoma, myeloma or leukemia
Patient capable of communication and informed consent	Communication barrier present
Weight < 140 kg	Patient enrolled in conflicting clinical study
Radiologic evidence of bone metastases from any solid tumor	Pain related to target metastasis mainly due to fracture, impending fracture, or to spinal cord compression
Dominant painful bone metastasis (NRS≥4), either refractory to standard of care treatment, or standard of care contra-indicated or refused by patient	Target tumor located in skull, spine (excluding sacrum), or ribs and sternum (unless exposure to lung can be avoided)
Patient has been on stable pain medication for ≥1 week before proposed HIFU treatment	Need for surgical stabilization in case of impending fracture (lytic tumor in weight-bearing bone larger than 50% of bone diameter)
Pain localized to target metastasis, or referred pain arising from it	Pregnancy
Patient has ≤3 painful bone metastases	Prior surgery or minimally invasive treatment of target tumor
Planned HIFU treatment date ≥4 weeks from last local treatment of target metastasis	Clinically relevant medical history that could compromise patient safety
At screening:	
Intended target metastasis accessible for HIFU	Contra-indications to MRI, MR contrast media, or to sedation
Target tumor diameter ≤8cm	Scar along proposed beam path
Intended target tumor visible by non-contrast enhanced MR imaging	Internal or external fixation device along proposed beam path, or at target
Distance between tumor and skin ≥1cm	Patient unable to tolerate required position for treatment
	Target tumor <3cm from critical structure along proposed beam path, or <1cm orthogonal to beam path
	Target in contact with hollow viscera

Table 1: Eligibility criteria: initial criteria refer to patients' suitability for enrolment in the trial, before consent for screening investigations. After screening to confirm patients' suitability for treatment, further eligibility criteria were applied prior to their inclusion.

Table 2: Patient and tumor characteristics

	Intra-osseous Group	Extra-osseous Group
Patients		
n (%)	9 (43%)	12 (57%)
Sex	3 male (33%)	8 male (67%)
	6 female (67%)	4 female (33%)
Age (years)	52.6±9.6	58.1±11.3
Primary tumor site		
Breast	6 (67%)	2 (17%)
Liver	-	4 (33%)
Lung	1 (11%)	3 (25%)
Renal	1 (11%)	2 (17%)
Colorectal	-	1 (8%)
Eccrine	1 (11%)	-
MRgHIFU Treatment Site		
Pelvis	5 (56%)	8 (67%)
Ribs	2 (22%)	1 (8%)
Humerus	1 (11%)	1 (8%)
Femur	1 (11%)	1 (8%)
Sacrum	-	1 (8%)
Prior EBRT to target metastasis	9 (100%)	12 (100%)
8 Gy 1#	3 (33%)	2 (17%)
20 Gy 5#	2 (22%)	1 (8%)
30 Gy 10#	3 (33%)	1 (8%)
High dose >30 Gy, or multiple treatments	1 (11%)	8 (67%)
Responder to prior EBRT? (CR or PR)	3 (33%)	6 (50%)
Baseline pain from target metastasis		
NRS 4-6: Moderate pain	3 (33%)	5 (42%)
NRS 7-10: Severe pain	6 (67%)	7 (58%)

Table 2: Characteristics of n=21 patients treated with MRgHIFU, all of whom had received prior radiotherapy to the target tumor**. NB:** Intra-osseous lesions had intact bone cortex along the entire length of the tumor, with no visible periosteal involvement; extra-osseous lesions had clear cortical breach with visible periosteal involvement with tumor. EBRT= external beam radiotherapy, CR=complete response, PR=partial response.

Table 3: Differences in treatment parameters and tumor diameter between groups.

	Intra-osseous Group	Extra-osseous Group	Difference
Delivered treatment parameters			
Depth of target (mm)	35.9±17.1	36.9±16.3	p=0.9
n sonications	15±5	29±15	**p=0.022**
Use of 12 mm diameter cells	1 patient	4 patients	
Treatment volume (ml)	12.1±13.3	16.4±12.0	p=0.21
Treatment time (minutes)	70.6±28.2	89.4±42.0	p=0.25
Mean power per sonication (W)	69.8±29.9	85.2±46.8	p=0.41
Total energy of treatment (kJ)	23.5±16.8	51.9±49.3	p=0.17
Measured thermal parameters			
V_{240EM} (ml)	5.4±9.9 range: 0.3-31.2	13.9±19.1 range: 2.4-62.7	**p=0.039**
T_M (^oC)	62.2±5.9	60.6±4.7	p=0.51
Tumor Diameter			
At baseline (mm)	38.9±12.8	55.7±14.9	**p=0.012**
Significance of change in lesion diameter from baseline (*)			
At Day 30	p=0.83	p=0.13	
At Day 60	p=0.96	p=0.47	
At Day 90	p=0.34	p=0.63	

Table 3: Differences in characteristics and treatment parameters for patients with intra- versus extra-osseous tumors. Baseline tumor diameter, and the lack of significant change after treatment are also indicated (*p-values uncorrected for multiple time-point comparisons). Unless otherwise specified, values provided are mean±standard deviation (SD) values.

Supplementary Table E1

Parameter	T1W	PRFS	Gd-T1W
TR (ms)	3.5	25	5.4
TE (ms)	2.3	16	2.6
FA (°)	7	18	12
Fat suppression	-	ProSet	SPAIR
Frequency offset (Hz)	-	-	220
EPI/TFE factor	-	11	18
Voxel size (mm^3)	1.25 x 1.75 x 1.25	2.1 x 2.1 x 7.0	1.5 x 1.5 x 3.0
FOV (mm)	240 x 320 x 140	400 x 300 x 7 each stack	220 x 220 x 105
NSA	2	2	1
Number slices	112	4	70
Scan duration min:sec	* 2:30 - 3:10	$ 0:03	1:55

Supplementary Table E1: Summary of acquired sequence parameters at one site using a 3T Achieva system. Comparable sequence parameters were implemented at the other 2 sites, one of which used a 3T system and the other used a 1.5T system. **NB**: * Scan duration was influenced by the amount of oversampling required to avoid wrap artefacts, $ Images updated every 3 s (dynamic scan time); total acquisition time was determined by number of frames of imaging (dynamics) acquired.

Figure 1

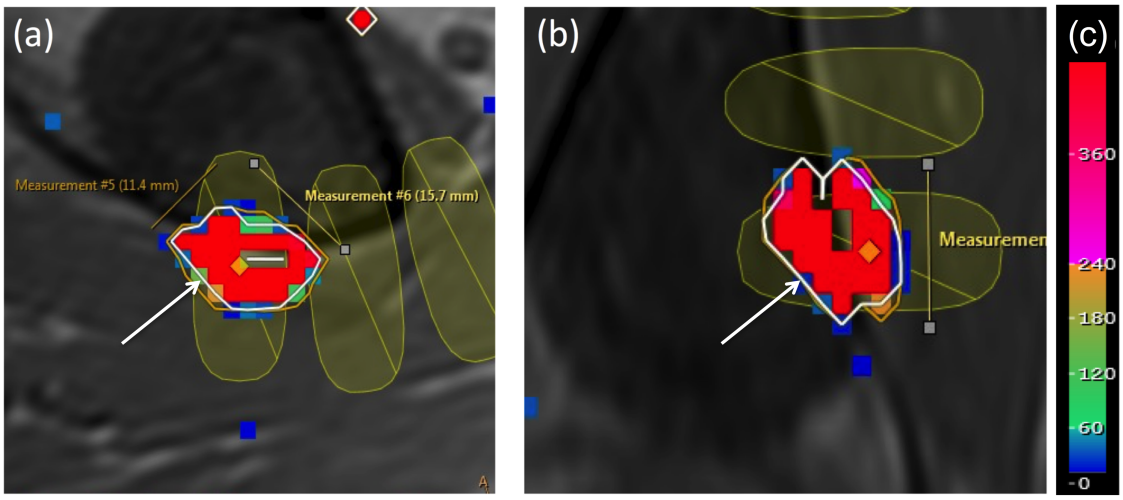


Figure 1: V_{240EM} estimates overlaid on T1W imaging acquired for treatment planning in a patient with an intra-osseous tumor. The white line (arrowed) represents the 240EM at 43°C thermal dose contour in (a) the axial, and (b) the coronal planes. The colored pixels (scale given in c) show the thermal dose in equivalent minutes (EM) within this contour. The product of the 3 largest orthogonal dimensions of the 240EM contour was used to estimate the thermal dose volume of each sonication. The total of these volumes was recorded as the total thermal dose volume (V_{240EM}) for each patient. **NB:** the orange contour represents the 30EM thermal dose contour, and the yellow ellipses show the positions of planned cells.

Figure 2

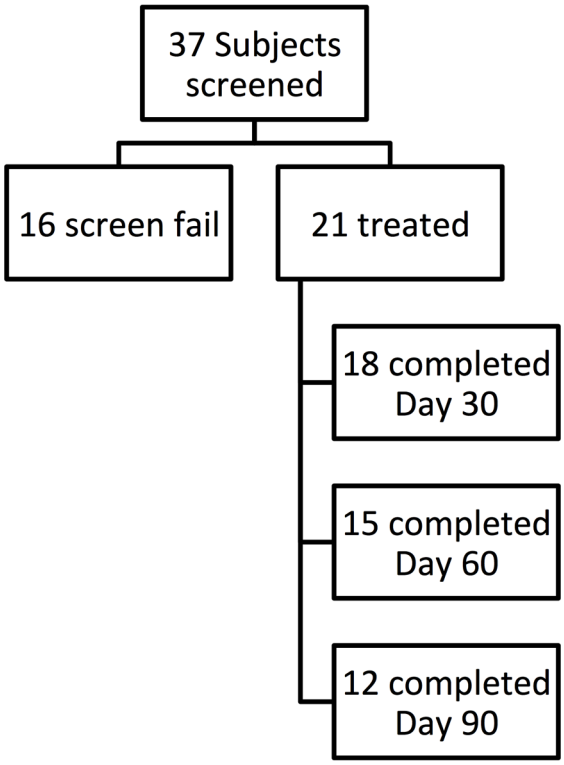


Figure 2: Numbers of patients initially enrolled in the study and who subsequently progressed to treatment and attended for follow-up. Of the 9 patients who failed to complete Day 90 follow-up, 5 were withdrawn from the study due to adverse events unrelated to treatment, 3 were referred to other interventions (radiotherapy), and 2 chose to withdraw from the study due to declining health.

Figure 3

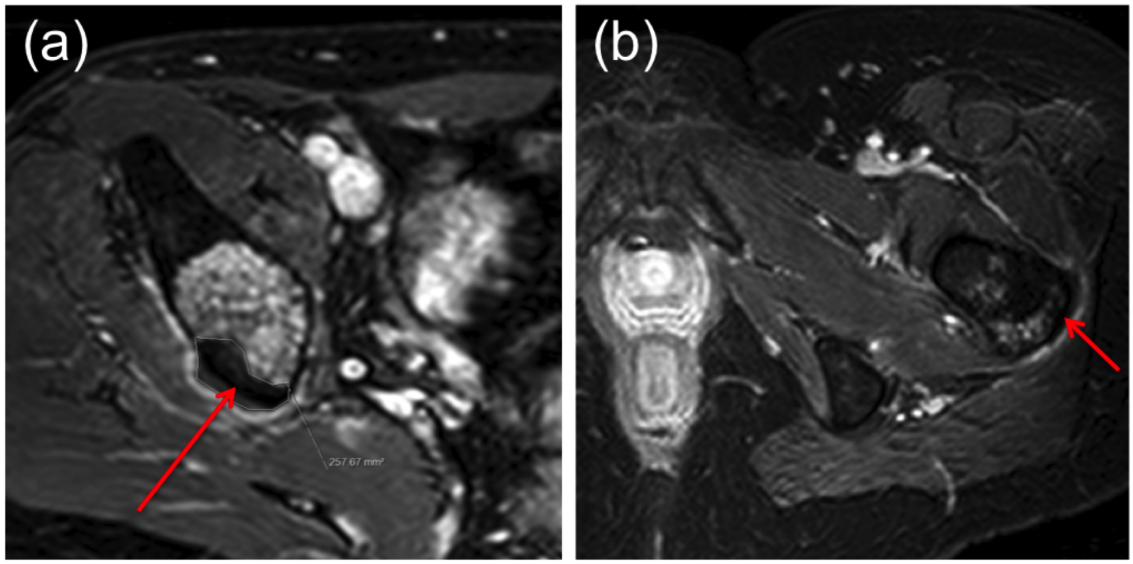


Figure 3: Example Gd-T1W image appearances 30 days after treatment. A clear focal region of non-enhancement (arrowed) was seen either side of the bony cortex for intra-osseous tumors, shown in (a) a 36 year old male with metastatic lung cancer, and (b) a 45 year old female with metastatic breast cancer. In both cases, a thin rim of enhancing tissue was also seen at the proximal border of the region of non-enhancement.

Figure 4

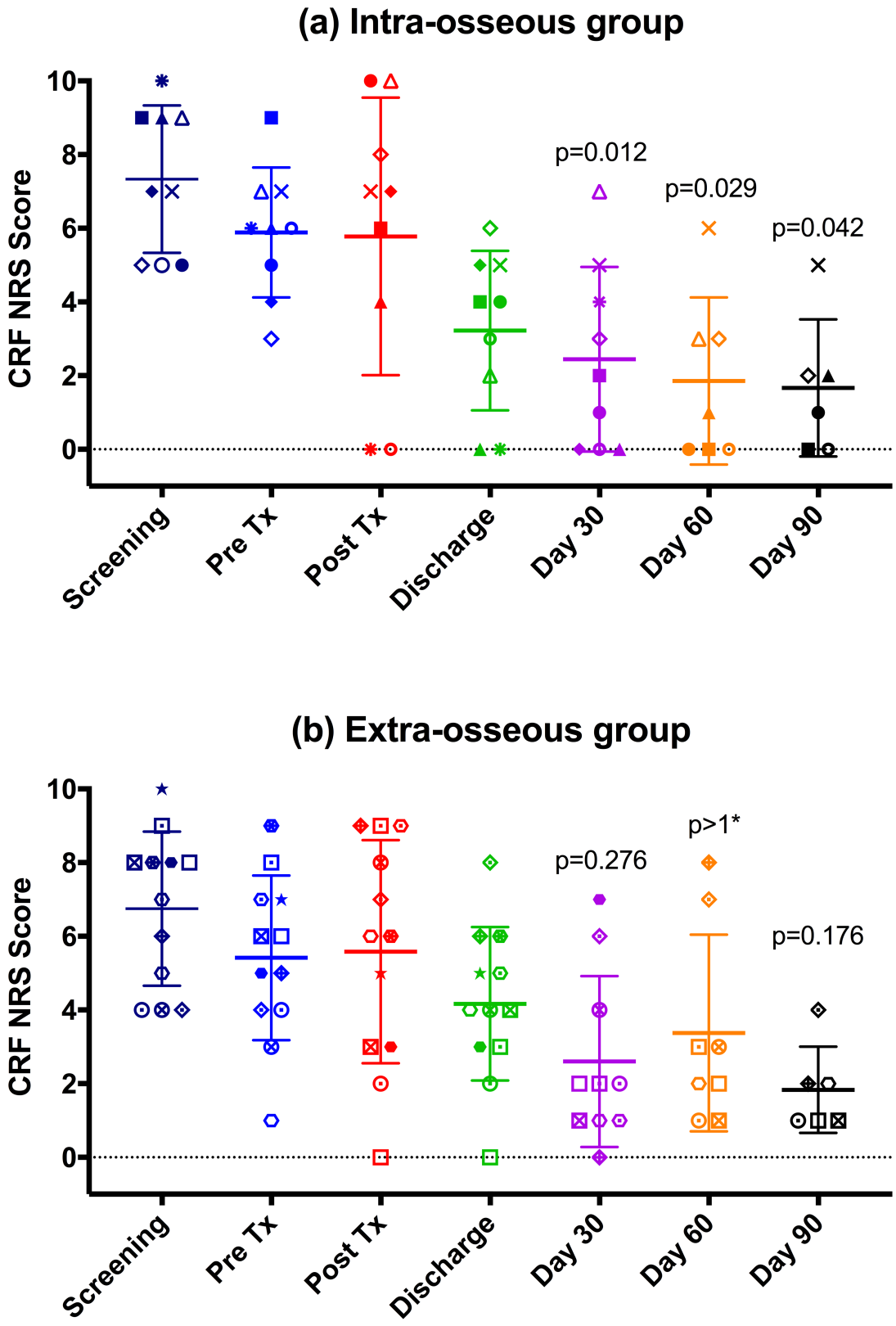
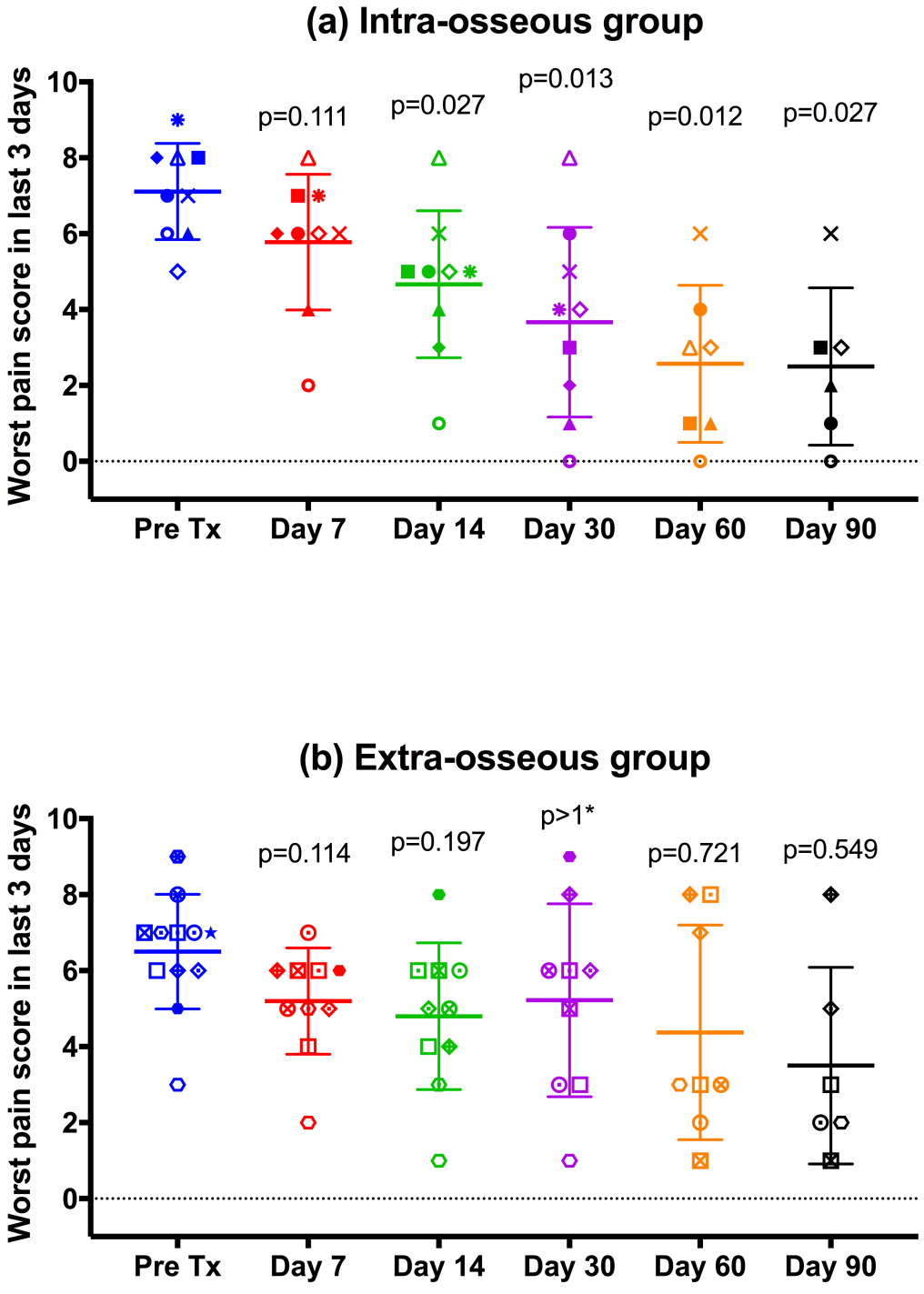
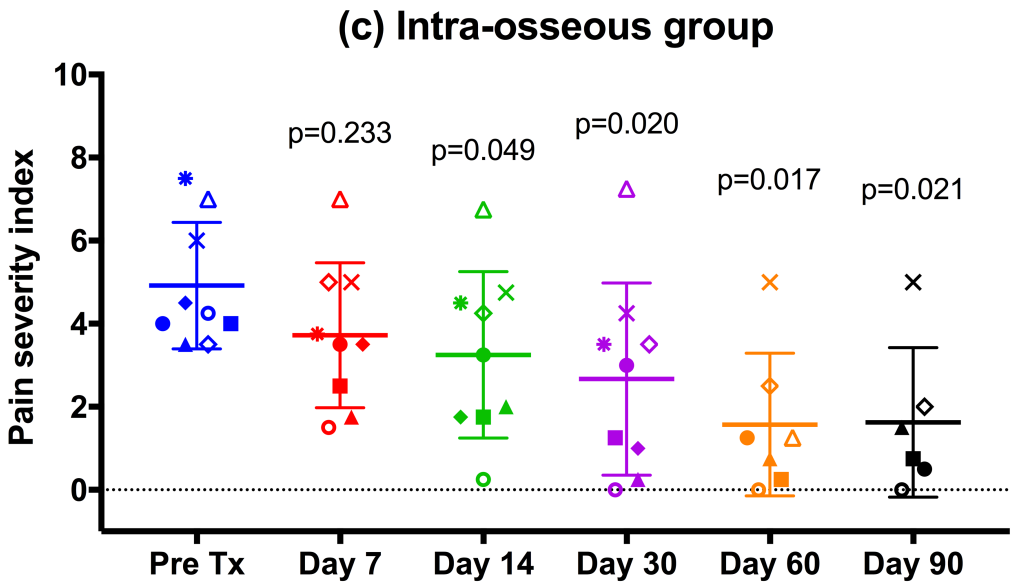
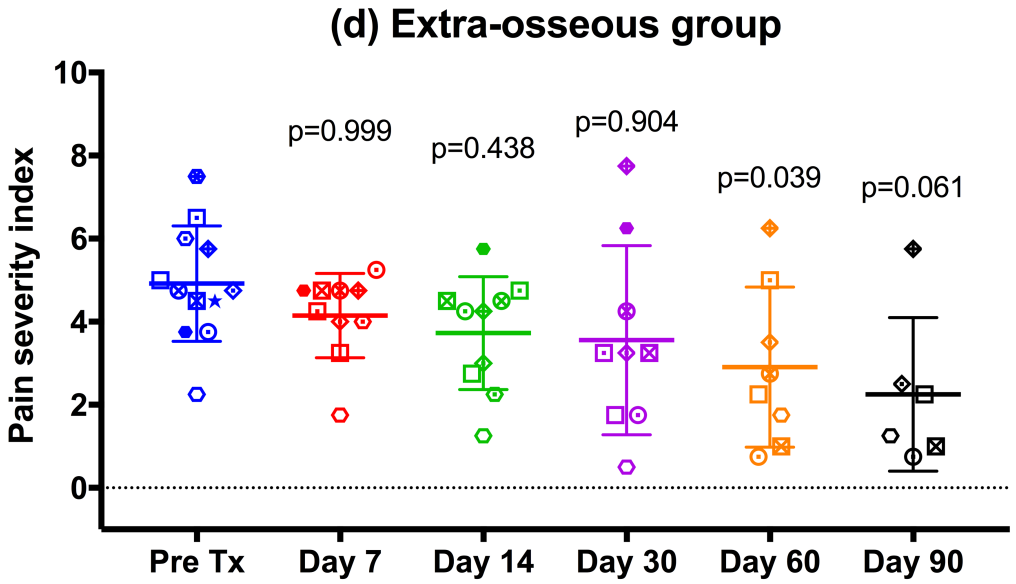

(a) Intra-osseous group
CRF NRS Score
10
8
6
4
2
0
p=0.012
p=0.029
p=0.042
Screening
Pre Tx
Post Tx
Discharge
Day 30
Day 60
Day 90
(b) Extra-osseous group
CRF NRS Score
10
8
6
4
2
0
p=0.276
p>1*
p=0.176
Screening
Pre Tx
Post Tx
Discharge
Day 30
Day 60
Day 90

Figure 4: Pain scores recorded in the CRF for the treated tumor for (a) 9 patients in the intra-osseous group and (b) 12 patients in the extra-osseous group. In each graphic, the horizontal lines show the mean±SD scores, and a discrete marker shape is used to show the individual score for each patient at each time-point. At Days 30, 60 and 90 after treatment, scores were significantly lower than pre-treatment (Pre Tx) for the intra-osseous group, but not for the extra-osseous group. The displayed p-values have been corrected for multiple comparisons; p>1* indicates that the uncorrected p-value was already >0.34.

Figure 5


(a) Intra-osseous group
Worst pain score in last 3 days
10
8
6
4
2
0
p=0.111
p=0.027
p=0.013
p=0.012
p=0.027
Pre Tx
Day 7
Day 14
Day 30
Day 60
Day 90
(b) Extra-osseous group
Worst pain score in last 3 days
10
8
6
4
2
0
p=0.114
p=0.197
p>1*
p=0.721
p=0.549
Pre Tx
Day 7
Day 14
Day 30
Day 60
Day 90


(c) Intra-osseous group
Pain severity index
10
8
6
4
2
0
p=0.233
p=0.049
p=0.020
p=0.017
p=0.021
Pre Tx
Day 7
Day 14
Day 30
Day 60
Day 90


(d) Extra-osseous group
Pain severity index
10
8
6
4
2
0
p=0.999
p=0.438
p=0.904
p=0.039
p=0.061
Pre Tx
Day 7
Day 14
Day 30
Day 60
Day 90

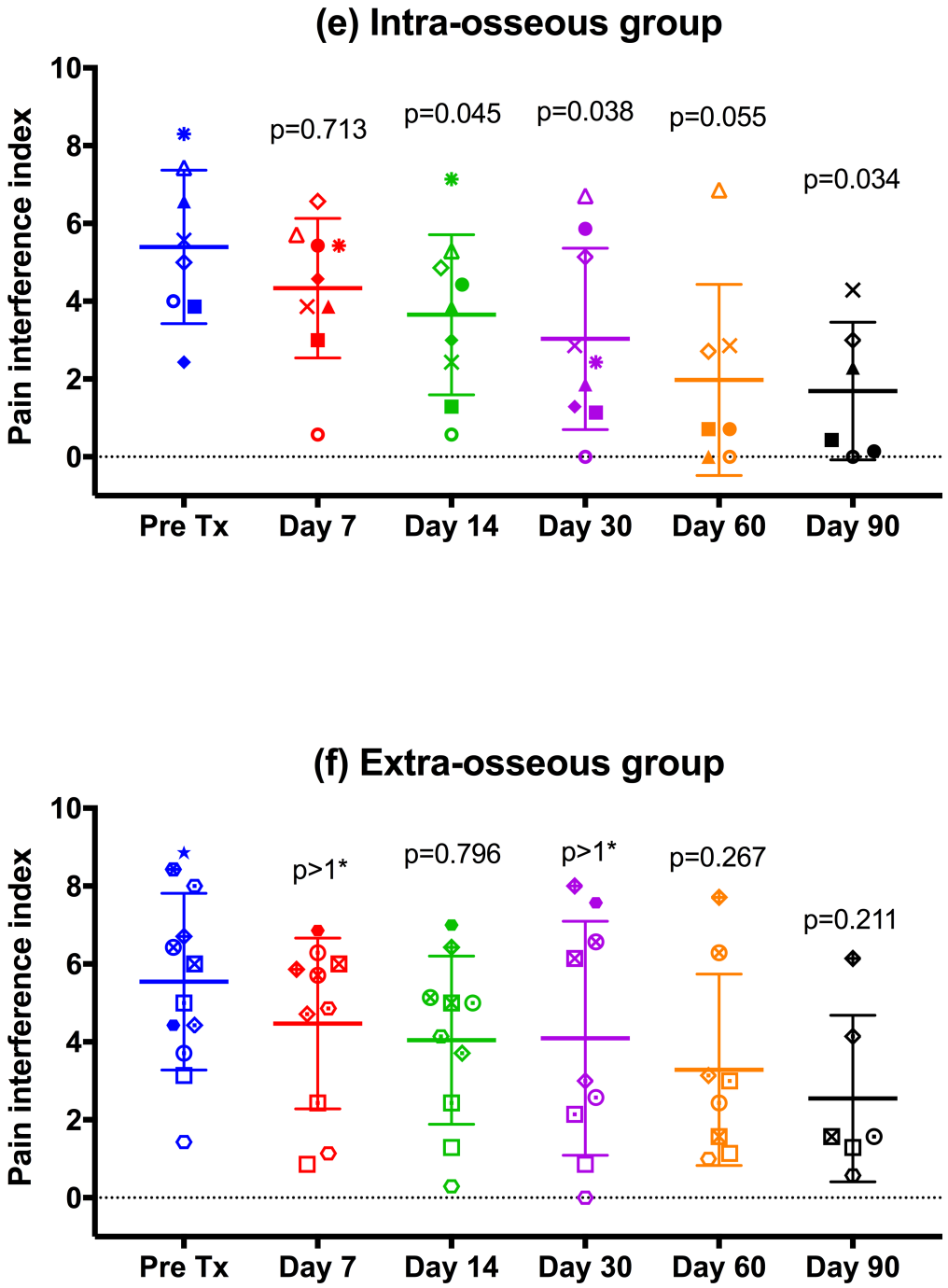
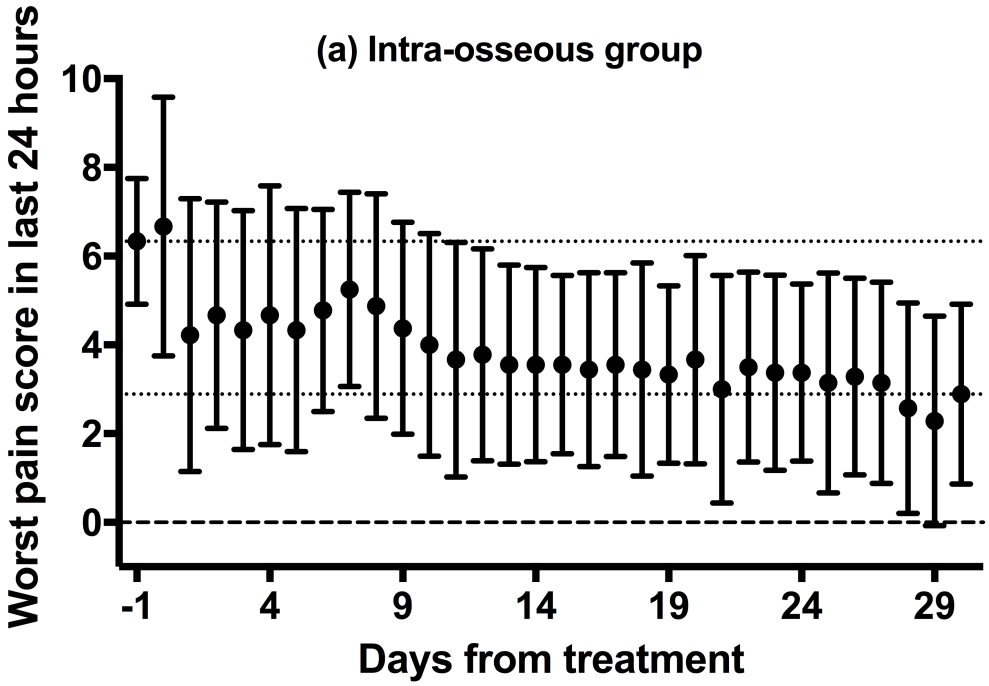


Figure 5: BPI-SF pain metrics for (a,c,e) intra-osseous and (b,d,f) extra-osseous groups. Worst pain, pain severity index, and pain interference index were all significantly improved from Day 14 after treatment for the intra-osseous group, but not for the extra-osseous group. Horizontal lines show the mean±SD

scores, and the discrete marker shapes show individual scores for each patient. Displayed p-values have been corrected for multiple comparisons; p>1* indicates that the uncorrected p-value was >0.20.

Figure 6


(a) Intra-osseous group
Worst pain score in last 24 hours
10
8
6
4
2
0
-1
4
9
14
19
24
29
Days from treatment

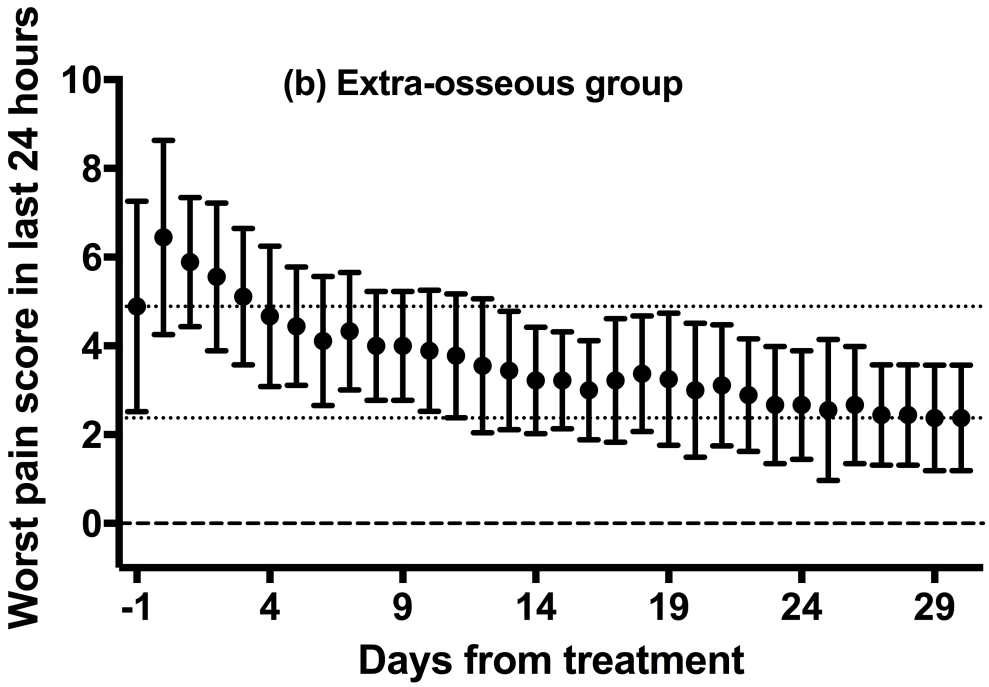

(b) Extra-osseous group
Worst pain score in last 24 hours
10
8
6
4
2
0
-1
4
9
14
19
24
29
Days from treatment

Figure 6: Mean±SD 24-hour worst pain scores recorded in the patient diaries for (a) the intra-osseous group and (b) the extra-osseous group. Day -1 was the score recorded on the treatment day before treatment, whilst Day 0 was the score recorded on the same day after treatment. The dotted lines show the mean pre-treatment and Day 30 scores. A >2-point improvement in pre-treatment scores was seen 1 day after treatment for the intra-osseous group, but not until Day 22 for the extra-osseous group. The pre-treatment score for the extra-osseous group appears artificially low in comparison with baseline CRF and BPI-SF scores. However, even if the post-treatment score had been used as the baseline, scores improved more gradually in this group, compared to the intra-osseous patients.

Figure 7

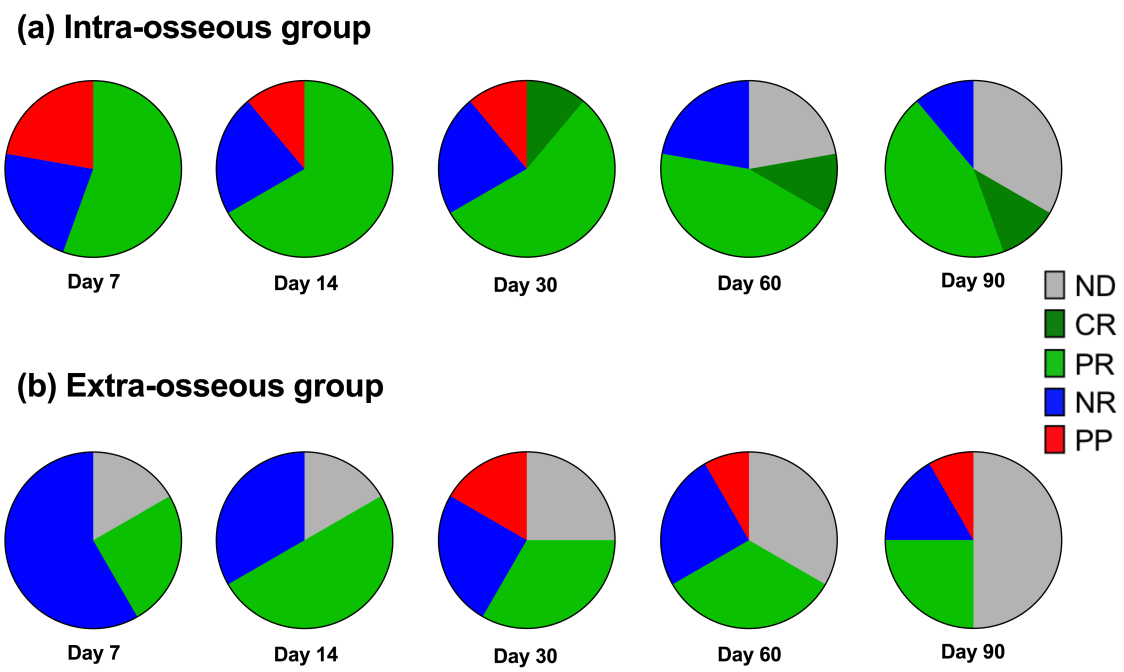


Figure 7: Treatment response classification for (a) intra-osseous and (b) extra-osseous groups. The proportion classified as responders at each time-point is shown by the dark and light green segments, which indicate a complete response (CR), or a partial response (PR) respectively. The non-responders are shown in blue (NR: no response), and in red (PP: pain progression). The grey segments show the patients who did not have follow-up data at each time-point (ND: no data). These show higher response rates for the intra-osseous group at every time-point, even though 2 patients initially had a flare of increased pain (which subsequently resolved). More of the intra-osseous group completed follow-up compared to the extra-osseous group (where 2 patients did not complete Day 7, and 50% were withdrawn by Day 90).