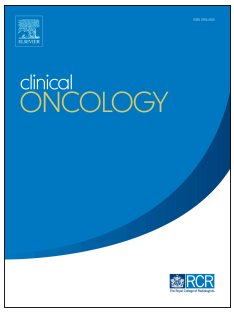

Differential Response of Pelvic Bone Marrow FDG Uptake in Patients Receiving Concurrent Chemoradiotherapy

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Differential Response of Pelvic Bone Marrow FDG Uptake in Patients Receiving Concurrent Chemoradiotherapy

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Abstract

Irradiation of pelvic bone marrow (PBM) at the level of the typical low dose bath of IMRT delivery (10-20Gy) is associated with increased risk of haematological toxicity, particularly when combined with concurrent chemotherapy. Whilst sparing of the whole of PBM at 10-20Gy dose level is unachievable, it is known that PBM is divided into hematopoietically active and inactive regions that are identifiable based on threshold uptake of [^{18}F]-fluorodeoxyglucose seen on PET-CT. In published studies to date, the definition of active PBM widely used is that of a standard uptake value (SUV) greater than the mean SUV of whole PBM prior to commencement of chemoradiation. These studies include those looking at developing an atlas-based approach to contouring of active PBM. Using baseline and mid-treatment [^{18}F]-fluorodeoxyglucose PET scans acquired as part of a prospective clinical trial we seek to determine the suitability of current definition of active bone marrow as representative of differential underlying cell physiology. Active and inactive PBM was contoured on baseline PET-CT and using deformable registration mapped onto mid-treatment PET-CT. Volumes were cropped to exclude definitive bone, voxel SUV extracted and change between scans calculated. Change was compared using Mann-Whitney U testing. Active and inactive PBM were shown to response differentially to concurrent chemoradiotherapy. Median absolute response of active PBM for all patients was -0.25 g/ml, whilst median inactive PBM response was -0.02 g/ml. Significantly, inactive PBM median absolute response has been shown as near zero with a relatively unskewed distribution (0.12). This would support the definition of active PBM as FDG uptake greater than mean of the whole structure as being representative of underlying cell physiology. This work would support the development of atlas-based approaches published in literature to contouring of active PBM based on the current definition as being suitable.

Keywords: FDG uptake, Bone Marrow Response, Chemoradiation

Original Article

Differential Response of Pelvic Bone Marrow Fluorodeoxyglucose Uptake in Patients Receiving Concurrent Chemoradiotherapy

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Abstract
Aims: Irradiation of pelvic bone marrow (PBM) at the level of the typical low dose bath of intensity-modulated radiotherapy delivery (10–20 Gy) is associated with an increased risk of haematological toxicity, particularly when combined with concurrent chemotherapy. Although sparing of the whole of the PBM at a 10–20 Gy dose level is unachievable, it is known that PBM is divided into haematopoietically active and inactive regions that are identifiable based on the threshold uptake of [^{18}F]-fluorodeoxyglucose (FDG) seen on positron emission tomography-computed tomography (PET-CT). In published studies to date, the definition of active PBM widely used is that of a standardised uptake value (SUV) greater than the mean SUV of the whole PBM prior to the start of chemoradiation. These studies include those looking at developing an atlas-based approach to contouring active PBM. Using baseline and mid-treatment FDG PET scans acquired as part of a prospective clinical trial we sought to determine the suitability of the current definition of active bone marrow as representative of differential underlying cell physiology.
Materials and methods: Active and inactive PBM were contoured on baseline PET-CT and using deformable registration mapped onto mid-treatment PET-CT. Volumes were cropped to exclude definitive bone, voxel SUV extracted and the change between scans calculated. Change was compared using Mann–Whitney U testing.
Results: Active and inactive PBM were shown to respond differentially to concurrent chemoradiotherapy. The median absolute response of active PBM for all patients was –0.25 g/ml, whereas the median inactive PBM response was –0.02 g/ml. Significantly, the inactive PBM median absolute response was shown to be near zero with a relatively unskewed distribution (0.12).
Conclusions: These results would support the definition of active PBM as FDG uptake greater than the mean of the whole structure as being representative of underlying cell physiology. This work would support the development of atlas-based approaches published in the literature to contour active PBM based on the current definition as being suitable.

Key words: Bone marrow response; chemoradiation; FDG uptake

Introduction (A head)

Irradiation of pelvic bone marrow (PBM) is associated with an increased risk of haematological toxicity, particularly when combined with concurrent chemotherapy. The precise radiation dose at which significant toxicity risk is incurred is unknown, but studies have shown an association with the volume of PBM receiving a relatively modest 10–20 Gy (whole treatment course dose) when delivered with concurrent chemotherapy [1,2]. This is the typical low dose bath received by PBM with standard intensity-modulated radiotherapy (IMRT) delivery. Indeed a UK audit of patients receiving concurrent chemoradiotherapy for anal cancer reported haematological toxicity grade 3 or greater of 18% using IMRT [3]. Although sparing of the whole of the PBM at the 10–20 Gy dose level is unachievable, and in fact undesirable given the probable impact on dose conformity to target structures or sparing of other equally critical organs at risk (OAR), studies have shown blood count nadir to correlate more strongly with smaller substructures of PBM [1,4]. In addition to smaller subregions of PBM being identified as more closely correlated with the suppression of blood cell count, it is known that PBM itself is not homogeneous and is divided into haematopoietically active and inactive regions. These regions have been shown to be identifiable on [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) [5]. Reference to these gross regions as bone marrow is a simplification of bone anatomy, which is not simply split between compact bone and marrow, but a more complex mix of compact bone, marrow and, for example, trabecular bone. Nonetheless, defining these structures provides a practical approach to limiting toxicity risk in PBM irradiation and studies have identified the potential for some degree of active PBM-targeted sparing to limit toxicity risk without unacceptable compromises to target dose conformality or other OAR sparing [6]. However, the precise link between standardised uptake value (SUV) and whether PBM can be considered haematopoietically active or not is unclear, with somewhat contradicting studies. Indeed, although a reduction in SUV with concurrent chemoradiation is apparent [7], it has been shown that there is both an increased association of regions of active PBM with haematological toxicity and that there is no increased association with haematological toxicity [8,9]. In published studies to date, the definition of active PBM widely used is that of a SUV greater than the average, most typically the mean of each patient, SUV of the whole PBM prior to the start of chemoradiation [7–11]. These include studies looking at atlas-based model approaches for contouring of active PBM [12,13]. This definition, although a reasonable hypothesis, is largely an arbitrarily chosen one and there is a lack of evidence that it is truly representative of underlying active/inactive bone marrow cell physiology.

In this study we sought to determine if the current definition of active PBM used is representative of underlying cell physiology through analysis of the response of SUV in PBM in a mid-treatment PET-CT scan relative to baseline PET-CT in a patient population receiving chemoradiation for anal cancer as part of an exploratory endpoint in a prospective observational study.

Materials and Methods (A head)

Patient Selection and Imaging (B head)

Patients were identified from the [AQ1] trial. In brief, the [AQ1] trial was a prospective observational single-centre study evaluating the role of functional imaging during radical concurrent chemoradiation in anal cancer patients. Eligibility criteria included confirmed invasive primary squamous carcinoma of the anus, stage T2N0 or greater, did not have a prosthetic hip and were radiotherapy naive. Patients underwent PET-CT at two time points: baseline (prior to chemoradiation) and at fraction 8–10 of treatment (week 2 scan). All patients had PET-CT scans on either a GE Discovery 690 or a 710 PET-CT scanner. Patients were injected with 4 MBq/kg bodyweight up to a protocol maximum of 600 MBq and scanned a minimum of 60 min post-injection. Local institution routinely clinically used PET acquisition and reconstruction parameters were used in this study. Images were reconstructed with CT for attenuation correction, manufacturer scatter correction and with a Bayesian penalised reconstruction algorithm using a previously optimised beta value of 400 [14,15]. Scans were reconstructed at 3.75 mm slice thickness with 2.7 mm pixel size (256 × 256 matrix size) and a 4 min PET acquisition time per bed position. Patients were scanned 'eyes to thighs' so had a variable number of PET bed positions depending on the height of the patient. The spatial resolution of the PET scanner is about 5 mm [16]. Both PET-CT scanners were subjected to regular quality assurance, including SUV calibration, and were matched in terms of image quality and quantification with identical image reconstruction settings. Excluding radiotherapy, trial imaging procedure doses totalled 96 mSv, of which 53 mSv was in addition to routine standard of care. All elements of the trial, including additional imaging and associated additional radiation doses, were approved by the local institution ethics board.

Treatment (B head)

Radiotherapy (C head)

Patients were treated using seven- to nine-field IMRT or coplanar volumetric modulated arc therapy in 28 fractions using simultaneous integrated boost. Delineation of the radiotherapy target and OAR structures was as per UK guidance [17]. In summary, gross anal tumour plus a 2.5 cm margin received either 53.2–61.6 Gy (if T3 and T4) or 41.4–50.4 Gy in 23–28 fractions (if T2); the involved nodes plus a 2 cm margin received 50.4 Gy and the prophylactic nodes (plus a 0.5–1 cm margin) received 34.5–40 Gy in 23–28 fractions. A constraint was placed on femoral head dose (dose to 50% less than 30 Gy, dose to 35% less than 40 Gy and dose to 5% less than 44 Gy), but the dose to other pelvic bone structures was unconstrained.

Chemotherapy (C head)

Patients fit enough to receive concurrent chemotherapy had 12 mg/m^2 mitomycin on day 1 and 825 mg/m^2 capecitabine twice daily on days 1–28 on radiotherapy days only. Capecitabine was withheld with thrombocytopenia grade 2 or neutropenia grade 3 or any grade 3 non-haematological toxicity considered related to capecitabine, until it resolved to grade 1 and was then restarted at the same dose or at a reduced dose.

Bone Marrow Delineation (B head)

PBM was delineated using the external surface of bone, i.e. not the low density region within the bone but the entire bone structure, as in previously published work by Mell *et al.* [2,4]. Contouring was carried out in Eclipse radiotherapy treatment planning software (Varian, Palo Alto, CA, USA). However, analysis for the purposes of this study consisted of PBM as a whole structure rather than the substructures of iliac, lumbosacral and lower pelvis bone marrow described by Mell *et al.* [2,4] and shown in Figure 1.

Figure 1 here

Analysis (B head)

PET-CT and associated PBM structures were exported from Eclipse and imported into Mirada (Mirada Medical, Oxford, UK). The CT component of mid-treatment scans was registered to the CT of the baseline scan using deformable registration software [AQ1]. The resulting image registration was qualitatively reviewed by an experienced medical physicist for suitable registration of pelvic bone structures. Mid-treatment PET scans were transformed to match the baseline using the transformation matrix of the CT component. Analysis of corresponding PET images consisted exclusively of SUV calculated using patient bodyweight. Voxel SUV of PBM seen in PET scans (g/ml) was extracted as .csv files and analysed using a custom script developed in Julia programming language. Bone marrow was tested for normality using Anderson-Darling normality testing. Active bone marrow was defined in two separate analyses using a threshold of SUV greater than the mean and median SUV seen in PBM at baseline for each individual patient. A further analysis was also carried out using a factor of 0.8, 0.9, 1.1 and 1.2 applied to the median SUV at baseline to determine if evidence could support an improvement in threshold value used to define active bone marrow. All defined active and inactive PBM voxels were subsequently cropped to having corresponding CT HU <250 to exclude definitive bone. Lastly, the change in uptake was calculated for active and inactive PBM as the absolute and percentage change.

Results (A head)

In total, 26 patients were enrolled in the study. Twelve patients had evaluable whole-body week 2 scans encompassing the whole of the PBM; the remaining patients either had a scan range limited to the primary tumour or did not receive a second PET-CT scan. The patient scan bodyweight mean was 72 kg (52–103 kg). Table 1 shows the mean and median of SUV of whole PBM structure for each patient at baseline. PBM SUV failed normality testing but mean and median values were similar, with a maximum difference of 0.11 g/ml. Figure 1 shows an example of contoured bone marrow and regions of active bone marrow within it for a typical patient (note: the contouring of substructures of PBM described by Mell *et al.* [2,4] is shown to aid the interpretation of the relative positioning of active bone marrow for the reader, but analysis consisted of PBM as a whole structure). On initial inspection of the voxel response histogram, significant outliers were shown to be present. Outliers were subsequently removed using a pragmatic cut-off threshold of six times greater than the interquartile range when pooling the sample population voxel response values, after which data were deemed not reasonably thought to be associated with the distribution. Outliers represented significantly less than 0.1% of data and were probably the result of high bladder

uptake overlapping with PBM structure at the interfaces of the bladder and PBM. The absolute and percentage responses of active and inactive PBM excluding outliers are shown in Table 1 using the threshold of mean SUV. All patients showed a statistically significant difference in response expressed in absolute terms. The mean volume of definitive bone was 43% (33–56%) of whole PBM; active bone marrow and inactive bone marrow after cropping for definitive bone represented 30% (25–34%) and 27% (19–34%), respectively. Active bone marrow represented 51% of bone marrow when excluding definitive bone from the total. The median absolute response of active PBM for all patients was –0.25 g/ml (–19.5%), whereas the median inactive PBM response was –0.02 g/ml (–4.0%). The skewness of the absolute active PBM response was –0.37, whereas it was 0.12 for inactive bone marrow. A histogram of response of active and inactive PBM, both absolute and percentage change, is shown in Figure 2. The absolute inactive response was seen with the relatively, in comparison with active PBM, unskewed distribution with a definitive peak about zero. A histogram of the absolute responses of all PBM combined is shown in Supplementary Figure S1.

Figure 2 here

Supplementary Table S1 shows the absolute and percentage responses of active and inactive PBM defined using factors of 0.8, 0.9, 1.1 and 1.2 applied to the median SUV at baseline for active bone marrow threshold. Active bone marrow represented 74–35% of bone marrow when excluding definitive bone from the total. The median absolute response of active PBM for all patients was –0.19 to –0.34 g/ml (–16.1 to –22.4%), whereas the median inactive PBM response was 0.00 to –0.05 g/ml (–0.1 to –6.7%).

Discussion (A head)

This prospective study looked to determine if the current definition of active bone marrow, as that greater than the mean SUV of the whole PBM structure, is representative of underlying cell physiology. We investigated this through analysis of the response of PBM in SUV in a mid-treatment PET-CT scan relative to the baseline scan. To our knowledge this has not been previously reported. Validation of the definition of active PBM is important when considering targeted sparing of active PBM or in attempting to identify those patients likely to experience acute haematological toxicity from concurrent chemoradiation or indeed chemotherapy/radiation given in isolation. Validation is also a key requirement as part of increasing efforts to streamline contouring of active bone marrow through atlas-based approaches and integrate targeted sparing into clinical practice more routinely. Using the current definition, a differential response of active versus inactive PBM was found with a sample population inactive PBM having a near zero median response (0.2 g/ml) across a population of patients and a relatively unskewed distribution. Active PBM in contrast showed a reduction in SUV and a significant negative skew in the distribution of pixel response values. It may be the case that active bone marrow included a degree of inactive bone marrow and that the definition of truly haematopoietically active PBM is higher or lower than the current definition. Indeed, further analysis suggested that a lower threshold of 0.8 times the median SUV of PBM at baseline resulted in an inactive absolute bone marrow response of 0.00 and a percentage change of –0.1%. However, the distribution of active versus inactive bone marrow is unclear, i.e. is active bone marrow homogeneously

localised with a definitive boundary or is some form of variable concentration present, within a definitive boundary or otherwise. It should also be noted that using this lower threshold active bone marrow represented a much larger percentage of total bone marrow at 74% when looking across the sample population. Notwithstanding this, cluster analysis or similar, combined with a range of active bone marrow threshold values, would be of merit for further investigation. However, for all current practical clinical purposes, this paper is in support of the current definition of active bone marrow as that greater than the mean or median of SUV of PBM being an appropriate practical definition for clinical use.

The main limitation of this work was the relatively small sample size and single institution data. Additionally, the patient population was limited to anal cancer as an available study population within a wider local anal cancer trial involving baseline and mid-treatment PET at a local institution. Although there is no reason to think underlying cell physiology is different, validation of the results presented here in a different disease site, e.g. cervical cancer, would be of merit to supporting the finding. A further limitation was that although the sample population of inactive PBM showed a near zero median response, it should be noted that individuals within the sample did not, as seen in Table 1. Subsequently, the suitability of the current definition of active PBM to any one individual will be variable. It should also be noted that this study sought only to provide a form of practical validation for a widely used, both in research and clinical practice, definition of active PBM. This study had limited scope to address whether improvements on this definition could be made. Discussion points around incorporating the impact of image noise and other limitations of PET imaging in better modelling/analysis of active PBM are also doubtless valid. Finally, it should be noted that for practical purposes, underlying cell physiology has been inferred from SUV in this study. Although reasonable in the context, this study subsequently does not represent a direct study of cell physiology using a biopsy that may provide better understanding. It should also be noted that an inflammation response to radiotherapy may affect tracer uptake. However, at treatment fraction 8–10 inflammation is probably minimal; a previous study looked at suppression seen in unirradiated spine at a mid-treatment scan and concluded that no suppression was seen, suggesting the response is caused by the direct effect of chemoradiation on PBM [7]. Blood count and radiotherapy dose data for the patient population used in this analysis can be seen in a prior publication [AQ2].

Conclusions (A head)

Active and inactive PBM have been shown to respond differentially to concurrent chemoradiotherapy. Significantly, the sample population inactive PBM median absolute response has been shown as near zero with a relatively unskewed distribution. This would support the definition of active PBM as FDG uptake greater than the mean or median of the whole structure as being representative of underlying cell physiology.

Conflicts of interest

The authors report no conflicts of interest

Acknowledgement

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Author contributions

MR is the guarantor of integrity of the entire study. MR, RM and MAH were responsible for study concepts and design. MR, MAH and DMcG carried out the literature research. MR, RM, K-YC and CJ were responsible for the clinical studies. MR was responsible for the experimental studies/data analysis and the statistical analysis. MR and MAH prepared the manuscript. MR, MAH and DMcG edited the manuscript.

Appendix A. Supplementary data

[AQ3]Supplementary data to this article can be found online at

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Fig 1. The distribution of active bone marrow (red) in a typical patient within pelvic bone marrow. To aid visual interpretation, the whole pelvic bone marrow structure has been separated into iliac (yellow), lower pelvis (cyan) and lumbosacral bone (blue), but the analysis consisted of the pelvic bone marrow structure as a whole.

Fig 2. Frequency histograms of absolute voxel uptake absolute difference (g/ml) (left) and percentage change (right) seen in mid-treatment positron emission tomography relative to baseline in active (blue) and inactive (orange) bone marrow combined across all 12 patients.

Table 1
Summary of absolute voxel uptake change (g/ml) and percentage change of active and inactive bone marrow for individual patients at mid-treatment scan relative to baseline

Patient	1	2	3	4	5	6	7	8	9	10	11	12
Mean of baseline pelvic bone marrow (median)	1.20 (1.17)	1.14 (1.1)	1.12 (1.07)	0.94 (0.94)	0.73 (0.72)	1.35 (1.32)	1.06 (0.99)	0.82 (0.82)	1.30 (1.27)	1.39 (1.32)	1.09 (1.05)	1.64 (1.53)
Active bone marrow response												
Median (%)	–0.45 (–29.9)	–0.32 (–22.2)	–0.53 (–36.3)	0.02 (2.0)	–0.12 (–11.6)	–0.44 (–24.9)	–0.12 (–9.2)	–0.20 (–19.8)	–0.23 (–14.1)	–0.52 (–28.8)	–0.15 (–10.7)	–0.70 (–31.2)
First quartile	–0.63	–0.51	–0.72	–0.13	–0.25	–0.68	–0.30	–0.32	–0.43	–0.78	–0.32	–0.95
Third quartile	–0.26	–0.10	–0.36	0.19	0.02	–0.19	0.06	–0.06	–0.01	–0.29	0.02	–0.44
Inactive bone marrow response												
Median (%)	–0.15 (–18.1)	–0.07 (–9.2)	–0.15 (–17.8)	0.04 (6.0)	0.01 (2.3)	–0.06 (–6.4)	0.02 (3.6)	–0.02 (–4.7)	–0.02 (–1.7)	–0.07 (–6.9)	0.09 (10.7)	–0.19 (–16.1)
First quartile	–0.28	–0.20	–0.26	–0.06	–0.07	–0.22	–0.09	–0.11	–0.17	–0.25	–0.04	–0.36
Third quartile	–0.02	0.07	–0.03	0.15	0.09	0.10	0.15	0.06	0.15	0.12	0.22	–0.02

Author queries

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AQ1 Please provide the missing information
AQ2 Please provide reference
AQ3 Please update web address once known

Patient	1	2	3	4	5	6	7	8	9	10	11	12
Mean of baseline PBM (median)	1.20 (1.17)	1.14 (1.1)	1.12 (1.07)	0.94 (0.94)	0.73 (0.72)	1.35 (1.32)	1.06 (0.99)	0.82 (0.82)	1.30 (1.27)	1.39 (1.32)	1.09 (1.05)	1.64 (1.53)
Active BM response												
Median (%)	-0.45 (-29.9)	-0.32 (-22.2)	-0.53 (-36.3)	0.02 (2.0)	-0.12 (-11.6)	-0.44 (-24.9)	-0.12 (-9.2)	-0.20 (-19.8)	-0.23 (-14.1)	-0.52 (-28.8)	-0.15 (-10.7)	-0.70 (-31.2)
1st Quartile	-0.63	-0.51	-0.72	-0.13	-0.25	-0.68	-0.30	-0.32	-0.43	-0.78	-0.32	-0.95
3rd Quartile	-0.26	-0.10	-0.36	0.19	0.02	-0.19	0.06	-0.06	-0.01	-0.29	0.02	-0.44
Inactive BM response												
Median (%)	-0.15 (-18.1)	-0.07 (-9.2)	-0.15 (-17.8)	0.04 (6.0)	0.01 (2.3)	-0.06 (-6.4)	0.02 (3.6)	-0.02 (-4.7)	-0.02 (-1.7)	-0.07 (-6.9)	0.09 (10.7)	-0.19 (-16.1)
1st Quartile	-0.28	-0.20	-0.26	-0.06	-0.07	-0.22	-0.09	-0.11	-0.17	-0.25	-0.04	-0.36
3rd Quartile	-0.02	0.07	-0.03	0.15	0.09	0.10	0.15	0.06	0.15	0.12	0.22	-0.02

Table One: Summary of absolute voxel uptake change (g/ml) and percentage change of active and inactive bone marrow for individual patients at mid-treatment scan relative to baseline.

Highlights

- Differential suppression of bone marrow FDG uptake during chemoradiation
- Non-active bone marrow FDG uptake shown to have a median response near zero
- Active bone marrow definition appropriately representing underlying cell physiology

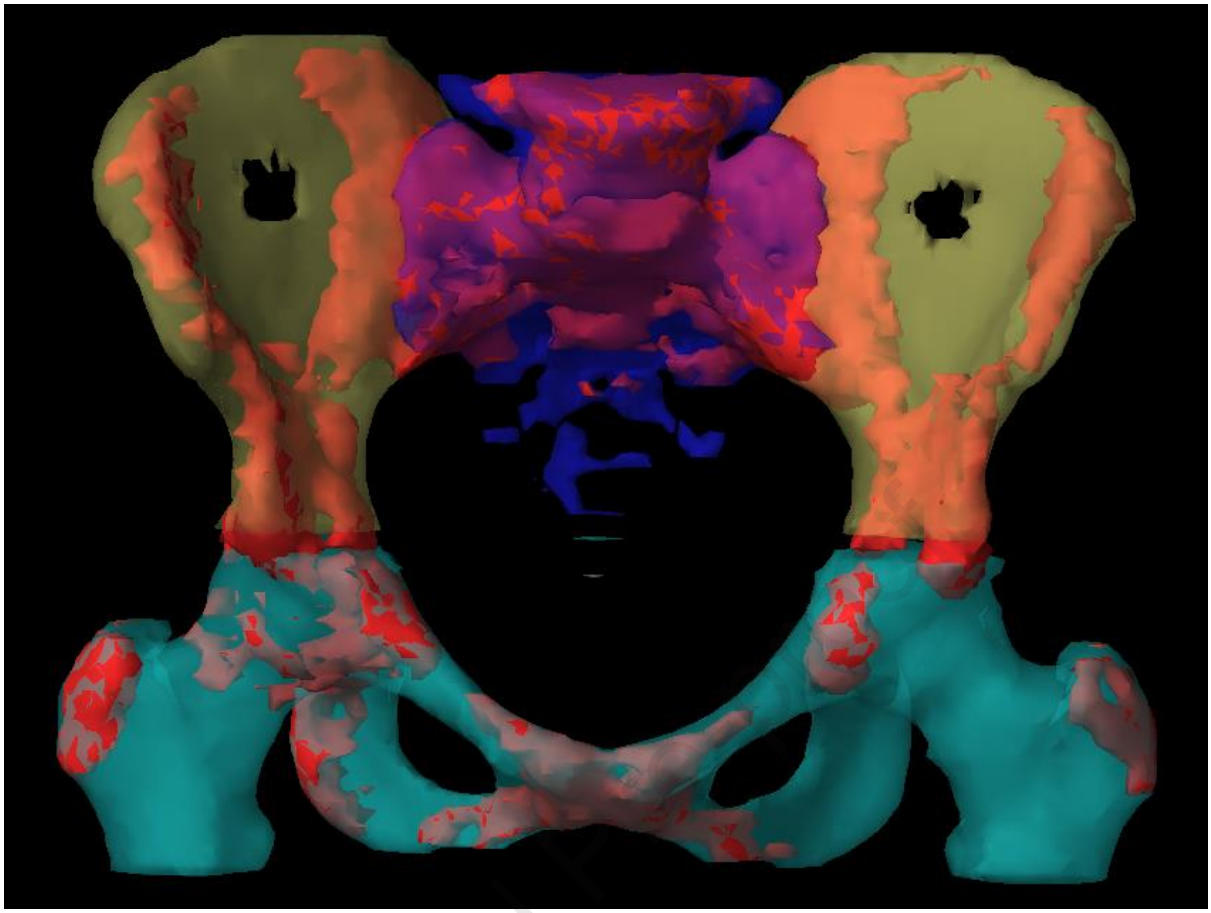

Figure One: The distribution of active bone marrow (red) in a typical patient within pelvic bone marrow. To aid visual interpretation the whole pelvic bone marrow structure has been separated into iliac (yellow), lower pelvis (cyan) and lumbosacral bone (blue), but analysis consisted of pelvic bone marrow structure as a whole.

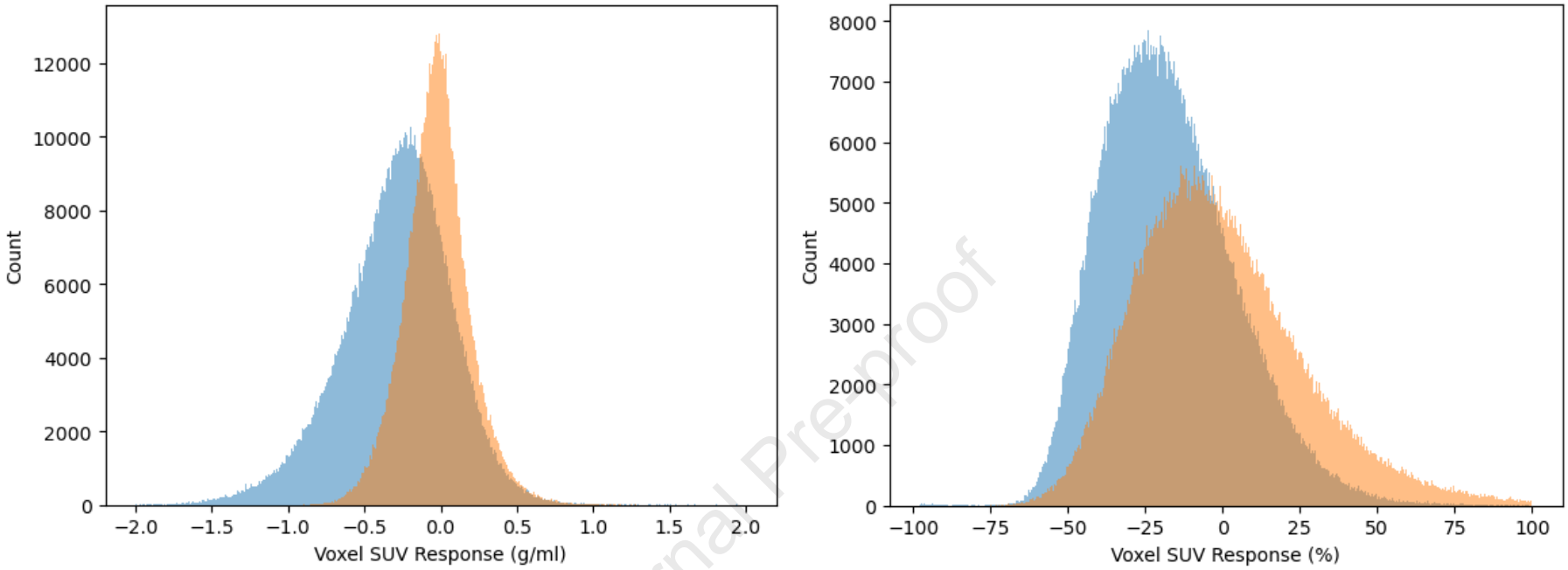

Figure Two: frequency histograms of absolute voxel uptake absolute difference (g/ml) (left) and percentage change (right) seen in mid-treatment PET relative to baseline in active (blue) and inactive (orange) combined across all 12 patients.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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