

LETTER TO THE EDITOR

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# Reproducibility of 18F-fluoromisonidazole intratumour distribution in non-small cell lung cancer; methodological issues to avoid mismanagement of the patients

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I was interested to read the paper by Grkovski M and colleagues published in the Dec 2016 issue of *EJNMMI Res* [1]. They aimed to assess the reproducibility of 18F-fluoromisonidazole (FMISO) positron emission tomography (PET) as a non-invasive, quantitative imaging technique, spatiotemporal intratumour distribution in patients with non-small cell lung cancer (NSCLC) [1]. The Pearson correlation coefficient  $r$  was calculated for mean standardized uptake values (SUV) within investigated volumes of interest and for voxels within tumour volumes ( $r_{TV}$ ). The reproducibility of FMISO voxelwise distribution, SUV- and tumour-to-blood ratio (TBR)-derived indices was assessed using correlation and Bland-Altman analyses [1]. Although they correctly used Bland-Altman, they reported Pearson's correlation  $r$  which in reproducibility (precision, repeatability, reliability, or interchangeability) is one of the common mistakes [2–6]. Pearson's correlation  $r$  only assesses the linearity between two continuous variables. Any shift in the location and/or scale of the regression line which leads to non-reproducibility cannot be detected by this correlation coefficient [2–6]. Therefore, for quantitative variables, Intra Class Correlation Coefficient single measure is the best statistical test to evaluate reproducibility [2–6].

Based on their results, the  $SUV_{max}$ ,  $SUV_{mean}$ ,  $TBR_{max}$  and  $TBR_{mean}$  were highly correlated ( $r \geq 0.87$ ,  $p < 0.001$ ) and were reproducible to within 10–15% [1]. It is good

to know that in reliability analysis, individual based approach should be considered instead of global average which Pearson's correlation  $r$  cannot do. It means we can simply get strongly positive and significant Pearson  $r$  ( $r = 0.95$ ,  $p$  value  $< 0.001$ ) with no reproducibility at all. Moreover, statistically significant should not be considered in reproducibility analysis [2–6]. They concluded high reproducibility of FMISO intratumour distribution in NSCLC patients, facilitating its use in determining the topology of the hypoxic tumour sub-volumes for dose escalation, in patient stratification strategies for hypoxia-targeted therapies, and in monitoring response to therapeutic interventions. Such conclusion may be a misleading message due to inappropriate use of statistical test to assess reproducibility. Briefly, for reliability analysis, appropriate tests should be applied; otherwise, misdiagnosis and mismanagement of the patients cannot be avoided.

#### Competing interests

The author declares that he has no competing interests.

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