Journal of Nuclear Medicine, published on June 15, 2017 as doi:10.2967/jnumed.117.195461

Reply: Repeatability of Quantitative Whole Body 18F-FDG PET/CT Uptake Measures in NSCLC Patients: Dynamic versus Test-Retest Design.

Reply: Need for Glucose Correction for 18F-FDG PET Influenced by Glucose Sensitivities to Types of Tissue and Random Factors

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We thank Dr. Laffon, Dr. Marthan and Dr. Thie for their response on our paper (*1*). In this study we tried to comprehensively investigate the repeatability of various whole body ^{18}F-FDG uptake metrics and assess the influence of several correction methods to normalize ^{18}F-FDG uptake.

In their letter Dr. Laffon and Marthan discuss the advantages and disadvantages of a dynamic and test-retest study design for the assessment of ^{18}F-FDG repeatability. We fully agree that measurement uncertainty of all quantitative PET metrics should be determined. As stated a dynamic design may be particularly suitable when assessing the role of statistical noise on variability of individual PET/CT systems. Yet, we would like to emphasis that a test-retest study is needed for assessment of repeatability in response evaluation setting where patient are scanned at different occasions. A true test-retest design is the closest approximation of the clinical conditions met during response assessment and includes all sources of variability encountered in clinical practice, such as variability in injected activity, uptake time, physiological status, patient (re-)positioning, breathing induced artefacts. These results can be used to determine thresholds that are able to differentiate metabolic response and progression from intrinsic measurement variability of quantitative uptake metrics after start of treatment.

We also want to point out that differences in ^{18}F-FDG uptake measures due to variation in uptake time are caused by differences in ^{18}F-FDG kinetics at 60 and 90 min post injection and not physical decay of ^{18}F (*2*). Omitting physical decay correction to correct for differences in uptake time between two scans falsely assumes that ^{18}F decay and ^{18}F-FDG kinetics are proportional. This uptake time correction method should therefore not be used in longitudinal setting because of physiological variations in ^{18}F-FDG kinetics.

In addition, we assessed the effect of several ^{18}F-FDG uptake normalization methods, including one for glucose correction, on repeatability. In the current cohort all plasma glucose levels (4.5 – 7.1 mmol/L) were well within recommended the range and showed a low interscan variability (≤2.2 mmol/L) (*3*). The influence of competing endogenous glucose on ^{18}F-FDG uptake metrics was thus likely to be limited. However, by correcting tumor uptake for glucose correction a potential source of measurement variability is also introduced. This is supported by the finding that the median differences of repeated glucose level measurements in the same patient, using a calibrated device was 0.2 mmol/L (0–0.8 mmol/L) in this study. We would therefore suggest that glucose correction should be not be performed if glucose levels are

within the reference range as also noted by Dr. Thie in his letter. We would like to encourage Dr. Thie and colleague's to study the influence of other (more complex) glucose correction methods on repeatability of ^{18}F-FDG uptake metrics in a cohort with a higher variability in plasma glucose levels. This of particular interest for metastatic diseases as a wide variety of tissues can be affected.

REFERENCES

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