Simplified Methods for Quantification of ^{18}F -Fluoromethylcholine Uptake: Is $\text{SUV}_{\text{AUC,PP}}$ Actually an SUV?

TO THE EDITOR: Verwer et al. (1) recently presented a study aimed at validating the use of simplified methods for quantification of ^{18}F -fluoromethylcholine uptake in a routine clinical setting of prostate cancer patients. The authors nicely demonstrated that ^{18}F -fluoromethylcholine uptake should be quantified using full kinetic modeling involving a single-tissue-compartment model with irreversible trapping and a blood volume parameter, in combination with a metabolite-corrected plasma input function based on invasive arterial blood sampling. The authors proposed—as a noninvasive simplified method based on 2 consecutive static PET scans—the use of the ratio ($\text{SUV}_{\text{AUC,PP}}$) of lesion activity concentrations ($A_L(t)$, assessed 30–40 min after injection) normalized to the area under the curve of the metabolite-corrected plasma input function (AUC_{PP} , computed over 0–30 min after injection). This ratio provided an excellent correlation to the uptake rate constant of the full kinetic modeling (Fig. 6C; $\text{SUV}_{\text{AUC,PP}} = 14.54 \times K_1 + 0.02$; $R^2 = 0.91$) (1).

We would like to point out that the slope of the fit reveals a discrepancy of 14.54 between $\text{SUV}_{\text{AUC,PP}}$ and K_1 , whereas $\text{SUV}_{\text{AUC,PP}}$ should be considered as a noninvasive surrogate for K_1 and a slope around 1 should be expected. Indeed, as previously shown by Patlak (2), $K_1 = A_L(t)/\text{AUC}_{\text{PP}}$, which is actually the $\text{SUV}_{\text{AUC,PP}}$ definition. Therefore, corrections to the $\text{SUV}_{\text{AUC,PP}}$ outcomes reported by Verwer et al. may be proposed for a better comparison with K_1 . For this comparison, an analytic expression for AUC_{PP} and hence for $\text{SUV}_{\text{AUC,PP}}$, as simple as possible, is needed to clarify the unit of each parameter. Let us assume that the metabolite-corrected plasma input function monoexponentially decays with a (decay-corrected) time constant α : then $\text{AUC}_{\text{PP}} = A_0/\alpha \times [1 - \exp(-\alpha T)]$, with $T = 30$ min and A_0 the initial (virtual) metabolite-corrected plasma activity concentration (3). AUC_{PP} is the total number of disintegrations per milliliter (of blood) that have occurred over the time range 0– T ; A_0 is expressed in Bq/mL, that is, number of disintegrations per second and per milliliter; $[1 - \exp(-\alpha T)]$ has no dimension; α is expressed in s^{-1} because A_0 involves becquerels (i.e., equivalent to s^{-1}). Finally, $\text{SUV}_{\text{AUC,PP}}$ is expressed in s^{-1} because of the $A_L(t)$ unit, which is Bq/mL. To consistently compare $\text{SUV}_{\text{AUC,PP}}$ and K_1 , we suggest that 2 corrective factors should be applied. First, because in current practice $A_L(t)$ is usually expressed in kBq/mL rather than in Bq/mL, A_0 should then be expressed in kBq/mL instead of in MBq/mL, as indicated in Figure 6C (and in Supplemental Fig. 2C) (1): the corrective factor is 1/1,000. Second, because K_1 is usually expressed in min^{-1} rather than in s^{-1} (the axis units in Fig. 6C and supplemental Fig. 2C are not clearly indicated), the corrective factor is 60. As a result, we suggest that the $\text{SUV}_{\text{AUC,PP}}$ outcomes reported by Verwer et al. should be multiplied by a corrective factor of 60/1,000, leading to a further slope of 0.87 instead of 14.54 in Figure 6C.

In conclusion, Verwer et al. convincingly demonstrated that, instead of SUV, $\text{SUV}_{\text{AUC,PP}}$ could be used in current clinical practice to noninvasively quantify ^{18}F -fluoromethylcholine uptake in prostate cancer patients. We further suggest that $\text{SUV}_{\text{AUC,PP}}$ is actually an uptake rate constant rather than an SUV (usually expressed in min^{-1} and g/mL, respectively) and that the above-proposed correction strengthens its relevance.

REFERENCES

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REPLY: We would like to thank Laffon and coworkers for their interest in our paper (1), as well as for their valuable comments and for giving us the opportunity to further clarify our results.

In our paper we aimed to find a simplified method for quantification of ^{18}F -fluoromethylcholine uptake. The most common simplified metric to quantify tracer uptake is the standardized uptake value (SUV), which represents tracer concentration at a certain time normalized to injected activity and a factor representing distribution volume (e.g., weight, lean body mass, or body surface area). This normalization is used as a surrogate for the integrated availability of the radiotracer to the tumor.

One of the aims of full kinetic analysis is to identify and validate these simplified methods or normalization factors. In our study, we found that commonly used normalization factors such as injected activity per weight, lean body mass, or body surface area were not appropriate surrogates for the integrated availability of the radiotracer to the tumor, that is, the integral of the input function. Therefore, we proposed a dual-scan procedure in which the first scan is used to directly measure this integral, which is then used to normalize tracer uptake measured in the second scan. We would argue that the unit of the normalization factor does not qualify or disqualify the simplified measure from being termed an SUV, since commonly used normalization factors such as body weight or body surface area also yield SUV in different units.

Nevertheless, the authors are correct in their observation that we have not consistently used the same units in nominators and denominators of the relevant equations and we could have been

more transparent on the units of the variables used in the paper. K_1 is indeed expressed in $\text{mL}\cdot\text{cm}^{-3}\cdot\text{min}^{-1}$ (essentially, min^{-1}), tissue activity concentration is in $\text{kBq}\cdot\text{mL}^{-1}$, and AUC is in $\text{MBq}\cdot\text{s}\cdot\text{mL}^{-1}$ (i.e., 10^6 disintegrations/mL), which makes the unit of SUV_{AUC} 10^{-3} s^{-1} . We have chosen these units so that the order of magnitude of the resulting values would be comparable to the commonly used SUV parameter. In this way, there would be a more intuitive understanding of high and low tracer uptake by the presented $\text{SUV}_{\text{AUC,PP}}$ data for all those readers who are used to SUV data. Of course, strictly speaking, the authors are correct with respect to using units consistently.

As the authors note, $\text{SUV}_{\text{AUC,PP}}$ can also be treated as a surrogate direct estimation of the rate constant K_1 . Indeed, for a single-tissue-compartment irreversible model (1T1k) with negligible blood volume fraction, $K_1 = \text{SUV}_{\text{AUC,PP}}$ by definition. We agree with the authors that if $\text{SUV}_{\text{AUC,PP}}$ is to be used in this way, it is important to use comparable units, which can indeed be achieved by applying the correction factor of 60/1,000 as indicated by the authors.

We would like to point out, however, that in the paper, K_1 was derived with blood volume correction ($1\text{T1k} + V_B$), whereas $\text{SUV}_{\text{AUC,PP}}$ was not. Therefore, the definition $\text{SUV}_{\text{AUC,PP}} = K_1$ will not hold and should be replaced with $\text{SUV}_{\text{AUC,PP}} = V_B \frac{\int_0^t C_{\text{WB}}}{C_{\text{pdt}}} + (1 - V_B)K_1$,

where C_{WB} is the whole-blood activity concentration, C_{p} is the metabolite-corrected activity concentration in plasma, and V_B is the blood volume parameter. We believe V_B to be responsible for part of the underestimation observed for SUV_{AUC} compared with

K_1 . We would also like to point out that in the paper, $\text{SUV}_{\text{AUC,PP}}$ (and K_1) represents a surrogate measure for K_i , that is, a combination of K_1 , k_2 , and k_3 , and should not be viewed as a simple rate constant.

Despite the confusion regarding units, we hope we have shown that commonly used SUV metrics cannot be applied to quantify ^{18}F -fluoromethylcholine uptake reliably and that normalization of tracer uptake by the integral of the input function (as a surrogate of K_i) is, in our opinion, the best simplified approach.

REFERENCE

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Erratum

In the article “Significant Therapeutic Efficacy with Combined Radioimmunotherapy and Cetuximab in Preclinical Models of Colorectal Cancer,” by Vassileva et al. (*J Nucl Med.* 2015;56:1239–1245), Author Jane Kinghorn of the Translational Research Office, University College London, was mistakenly mentioned in the Acknowledgments instead of the byline. The authors regret the error.