Kinetic Analysis of ^{18}F-FLT PET in Lung Tumors

TO THE EDITOR: The recent interesting and highly relevant article by Brockenbrough et al. (*1*) includes a significant methodologic misconception and mistake regarding PET measurements of tissue radiotracer uptake. On page 1183, column 1, final paragraph, the authors state "K_{FLT} was not partial-volume–corrected because it represents a net movement over time of ^{18}F-FLT through tissue compartments, with all time frames equally affected by partial-volume effect, and these are accounted for by the method defining the region of interest (full width at half maximum)."

The region-of-interest technique used to obtain tumor time–activity curves (lower threshold = 50% of maximum voxel standardized uptake value) could not have compensated for the partial-volume effect (*2*). Uncorrected partial-volume effect would have introduced negative errors in measurements of standardized uptake value over time. Those errors would have varied from tumor to tumor within and among patients.

The flux parameter K_{FLT} (units of mL/min/g of tissue) is the clearance of 3′-deoxy-3′-^{18}F-fluorothymidine (^{18}F-FLT) from blood into ^{18}F-FLT nucleotides within the tissue included in the region of interest. In terms of model rate coefficients, $K_{FLT} = K_1k_3/(k_2 + k_3)$. A straightforward examination of the differential equations for the kinetic model and that relating the PET signal to the model (*3*) shows that any error in measured standardized uptake value produces a proportional error in K_1. Since the kinetic parameters are correlated, that error would also propagate from K_1 to the other model parameters (*3*).

Accurate absolute image quantitation is no less essential for kinetic modeling than for static uptake measurements. To the extent that partial-volume effect varied among tumors, failure to correct for it may obscure the authors' analyses of relationships between K_{FLT} and tumor thymidine kinase-1 or Ki-67 (Fig. 5; Tables 4 and 5).

Partial-volume correction for tumor images large enough to demonstrate irregular shapes or heterogeneous image intensity is a difficult and as yet unsolved problem (*4*). Although it may not have been feasible for the authors to make such corrections, they should have acknowledged the problem and its potential impact on their findings.

REFERENCES

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REPLY: We appreciate the opportunity to reply to Dr. Bading's letter about our recent publication (*1*). We agree that the sentence quoted by Dr. Bading—"K_{FLT} was not partial-volume–corrected because it represents a net movement over time of ^{18}F-FLT through tissue compartments, with all time frames equally affected by partial-volume effect, and these are accounted for by the method defining the region of interest (full width at half maximum)."—could be construed as misleading. We have always regarded partial-volume effects as an important limiting factor in any quantitative PET study. We have actually emphasized using partial-volume correction solutions in all our prior publications on static PET of lung cancer with ^{18}F-FDG or 3′-deoxy-3′-^{18}F-fluorothymidine (^{18}F-FLT) (*2–6*) and have promoted its importance.

In the present study, our static measures of ^{18}F-FLT maximum standardized uptake value were all partial-volume–corrected according to methods we have described and validated (*5,6*). However, the measures of ^{18}F-FLT flux derived from dynamic ^{18}F-FLT PET that we reported were not partial-volume–corrected. Like static images, individual images of a dynamic PET dataset are affected by partial-volume effects for lesions that are small compared with the reconstructed resolution of the scan. However, contrary to static PET images, for which we have been able to design a first-order correction method (*6*), we have not been able to correct dynamic datasets for partial-volume effects. The correction used for static standardized uptake value is based on maximum pixel standardized uptake value, which we have found to be superior to methods based on an average standardized uptake value (*6*). However, because dynamic image bins are short (ranging from 10 s to 10 min) compared with a late static image (30-min-long sum of data acquired from 60 to 90 min after ^{18}F-FLT injection), they are intrinsically noisy. Using a maximal pixel approach within a lung nodule or mass in a set of dynamic images would result in, first, possible selection of different pixel locations from one time frame to the next because of noise and not physiologic differences and, second, amplification of the image noise by time derivatives when solving the compartment model. To minimize this difficulty presented by image noise, we elected to use an approach in which pixels within 50% of the maximum pixel value are selected on a late static summed image (60- to 90-min summed image). This results in the definition of a region of interest that was then applied to each individual image frame of the dynamic dataset for the purpose of compartment modeling and evaluation of the flux constant K_{FLT}. However, although it overcomes noise problems in the dynamic image data, this approach leads to regions of interest of variable shape across lesions. We

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