Quantification of ^{18}F-DCFPyL Uptake: TBR Versus Patlak's Analysis

TO THE EDITOR: In prostate-cancer patients investigated with ^{18}F-DCFPyL, a second-generation ^{18}F-labeled prostate-specific membrane antigen ligand, Jansen et al. have recently validated the image-based tumor-to-blood ratio (TBR) as an optimal trade-off between a reliable surrogate for the net influx rate of the tracer versus simplicity of its assessment (*1*). The image-based TBR (blood-mL.tumor-mL^{-1}) can be obtained from any standard whole-body acquisition as the mean tumor–activity concentration ($C_T(t)$; kBq.mL^{-1}) to the time-matched blood–activity concentration ($C_p(t)$; kBq.mL^{-1}) within the ascending aorta. A high correlation coefficient was found between TBR and net-influx-rate constant (Ki; mL. min^{-1}.mL^{-1}) obtained from a reversible 2-tissue-compartment model, whereas the SUV, normalized either to body weight or lean-body mass, showed a poor SUV-Ki correlation (R^2 = 0.96 vs. 0.47 and 0.60, respectively; Figure 3 and Table 3 in Jansen et al. (*1*)).

We believe that the comparison between either whole-blood or image-based TBR proposed by Jansen et al. and Patlak's graphical analysis may be fruitful because the former is actually the *y*-axis of the latter. For $t > t^*$ and irreversible trapping, Patlak's basic equation is indeed: $TBR(t) = C_T(t)/C_p(t) = Ki \times AUC(t)/C_p(t) + V_b$ (*2*). AUC(t) is the time integral of $C_p(t)$ and V_b the fraction of free ^{18}F-DCFPyL in blood and interstitial volume (mL.mL^{-1}). The ratio $AUC(t)/C_p(t)$ is the so-called stretched time (t_s; min), and then writing $TBR(t) = Ki \times t_s + V_b$ leads to further comment on Figure 3B by Jansen et al. that shows TBR versus Ki (*1*). The linear slope of Figure 3B (R^2 = 0.96) is actually an average value of t_s that is specific to Jansen et al.'s study. To support this assertion, blood data can be extracted from Figure 1 (using the WebPlotDigitizer software) to calculate AUC from trapezoidal integration and, hence, to calculate t_s. Because image-based TBR was assessed by Jansen et al. at 105–110 min after injection, when t is 107.5 min, t_s is then estimated to be 204 min, which is consistent with the 222-min slope for the TBR-Ki correlation reported in Table 3 (*1*). Thus, such a crucial role of t_s in the TBR-Ki correlation and, hence, that of real time t, stresses Jansen et al.'s recommendation for harmonizing injection-acquisition time delay, scanning direction, and whole-body scan duration, to reliably compare TBRs between centers. Furthermore, the authors acknowledged that TBR repeatability should be investigated for treatment-response assessment. We suggest that TBR repeatability should take into account repeatability of both tumor- and blood-activity concentration because $TBR(t) = C_T(t)/C_p(t)$ ($= SUV_{tumor}/SUV_{blood}$), as demonstrated with SUV in lung cancer patients investigated with ^{18}F-FDG (*3*). Despite this increased repeatability percentage, blood normalization involved in the TBR makes it a much better surrogate for Ki than the SUV, because the latter is significantly affected by the difference in the blood–activity concentration between patients, depending on the total tumor burden, as illustrated in Figure 4 in Jansen et al. (*1,4*). This SUV feature involving TBR may be simply summarized as: $SUV_{tumor}(t) = TBR(t) \times SUV_{blood}(t) \propto TBR(t) \times C_p(t)$. Finally, let us note that, because of decay correction, the SUV apparently rises during the first 2 h after injection (assuming irreversible trapping), whereas the TBR actually rises with time (Fig. 3A), furthermore justifying Jansen et al.'s recommendation (*1*).

In conclusion, we are convinced that the image-based TBR can reliably assess ^{18}F-DCFPyL uptake in prostate cancer metastases, thus opening up possible tumor characterization and treatment-response assessment. We suggest that the TBR may be considered a simplified Patlak's analysis that is adapted to daily clinical practice (i.e., to standard whole-body acquisition without the need for invasive blood sampling). In this connection, we suggest that reporting the correlation between TBR and Patlak's Ki might be of interest.

REFERENCES

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Reply: Quantification of ^{18}F-DCFPyL Uptake: TBR Versus Patlak's Analysis

REPLY: We thank Drs. Laffon, de Clermont, and Marthan for their positive letter on our paper (*1,2*). They effectively argue that the tumor-to-blood ratio (TBR) can be seen as a simplification of a Patlak's analysis—which in turn should be seen as a simplification of full pharmacokinetic analysis (based on nonlinear regression analysis with arterial blood sampling as input function). As suggested by Laffon et al., we have provided the correlation between Patlak's K_i (net-influx-rate constant) and our proposed image-based TBR (Fig. 1) (*2*). Indeed, a good correlation was observed (R^2 = 0.91), supporting the suggestion of Laffon et al. that TBR could be considered as a surrogate for Patlak's analysis that is suitable for daily clinical practice.

Overall, our study and the letter by Laffon et al. (*1,2*) emphasize the need for technical validation of simplified metrics to quantify tracer uptake of novel tracers. In particular, our study demonstrated that SUV, normalized to injected activity over body weight, is not a