Journal of Nuclear Medicine, published on August 26, 2019 as doi:10.2967/jnumed.119.232926

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

Eric Laffon [1,2,3 *], Henri de Clermont [1], Roger Marthan [1,2,3].

[1] CHU de Bordeaux - F-33000 Bordeaux, France.

[2] Univ. Bordeaux, Centre de Recherche Cardio-Thoracique de Bordeaux, F-33000 Bordeaux, France.

[3] INSERM U-1045, Centre de Recherche Cardio-Thoracique de Bordeaux F-33000 Bordeaux, France.

*Correspondence to Dr Eric Laffon, Service de Médecine Nucléaire, Hôpital du Haut-Lévèque, avenue de Magellan, 33604 PESSAC, France.
Telephone: +33557656838; elaffon@u-bordeaux.fr

TO THE EDITOR: In prostate-cancer patients investigated with ^{18}F-DCFPyL, a second generation ^{18}F-labeled PSMA 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 two-tissue compartment model, whereas the standardized uptake value (SUV), normalized either to body weight or lean-body mass, showed a poor SUV-Ki correlation (R^2 = 0.96 versus R^2 = 0.47 and 0.60, respectively; Figure 3 and Table 3).

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 since 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 (by

using the WebPlotDigitizer software) to calculate AUC from trapezoidal integration and, hence, to calculate t_s. Since image-based TBR was assessed by Jansen et al. at 105–110 min post-injection, when t is 107.5 min, t_s is then estimated to be 204 min that 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, in order 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 since $TBR(t) = C_T(t)/C_p(t)$ ($= SUV_{tumor}/SUV_{blood}$), 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 by 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, owing to decay correction, the SUV apparently rises during the first two hours post-injection (assuming irreversible trapping), whereas the TBR actually rises with time (Figure 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

1. Jansen BHE, Yaqub M, Voortman J et al. Simplified Methods for Quantification of 18F-DCFPyL Uptake in Patients with Prostate Cancer. *J Nucl Med.* 2019 Apr 18. pii: jnumed.119.227520. doi: 10.2967/jnumed.119.227520. [Epub ahead of print].

2. Patlak CS, Blasberg RG, Fenstermacher JD. Graphical evaluation of blood-to brain transfer constants from multiple-time uptake data. *J Cereb Blood Flow Metab.* 1983;3:1–7.

3. Laffon E, Milpied N, Marthan R. Measurement uncertainty of lesion and reference mediastinum standardized uptake value in lung cancer. *Nucl Med Commun.* 2017;38:509–514.
4. Laffon E, Marthan R. The total amount of uptake may affect the input function: a theoretic approach about ^{18}F-FDG PET imaging. *Nucl Med Biol*. 2015;42:724–727.