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Reversibility of ^{68}Ga-FAPI-2 Trapping Might Prove an Asset for PET Quantitative Imaging

TO THE EDITOR: In a recent paper, Giesel et al. analyzed the tissue biodistribution and preliminary dosimetry of 2 quinoline-based PET tracers that act as fibroblast activation protein (FAP) inhibitors, namely, ^{68}Ga-FAPI-2 and ^{68}Ga-FAPI-4 (*1*). The authors reported a fast clearance via the kidneys, a low tracer uptake in normal organs, equal tumor-to-background contrast ratios at 1 h after injection, and an almost equal uptake in comparison with ^{18}F-FDG. However, from 1 to 3 h after injection, in contrast to ^{68}Ga-FAPI-4, which displayed a prolonged tumor retention (25% washout), ^{68}Ga-FAPI-2 tumor uptake decreased by 75%, thus reflecting release of the tracer from the malignant tissue. This difference explains why a companion paper by Kratochwil et al. used ^{68}Ga-FAPI-4 for identifying the most promising indications for future application (*2*).

We suggest that ^{68}Ga-FAPI-2 trapping reversibility, evidenced by a decrease in tumor uptake observed at late imaging, might prove an asset for PET quantitative imaging. Figure 2, by Giesel et al., shows ^{68}Ga-FAPI-2 and ^{68}Ga-FAPI-4 maximal SUV (SUV_{max}) at 10, 60, and 180 min after injection in 2 patients with metastasized breast cancer, respectively (*1*). Because the 2 tracers have rapid clearance from blood, we assume their input function (IF) has become negligible at 60, and, a fortiori, at 180 min after injection. Thus, a previously published method designed for ^{18}F-FDG may be adapted to ^{68}Ga-FAPI-2 and ^{68}Ga-FAPI-4 for assessing their release rate k_B (in min^{-1}; Eq. 3 in Laffon et al. (*3*)). For the sake of clarity, let us assume an IF monoexponential decay with decay-corrected time constant α and initial amplitude $A_P(t = 0)$ (in min^{-1} and $kBq.mL^{-1}$, respectively). The decay-corrected tissue activity concentration related to trapped tracer (in kBq/mL), which is proportional to SUV_{max}, can be approximated from 60 to 180 min after injection, by:

$$A_T(t) \approx Ki \times A_P(t = 0) \times \exp(-k_B \times t)/(\alpha - k_B), \qquad \text{Eq. 1}$$

where Ki is the uptake rate constant of the tracer (in $mL.min^{-1}.mL^{-1}$). Fitting the outer extreme metastasis data (extracted with the WebPlotDigitizer software) at 60 and 180 min after injection in Figure 2 with a monoexponentially decaying function leads to the following range for k_B: 0.01435–0.01439 and 0.00129–0.00212 min^{-1} for ^{68}Ga-FAPI-2 and ^{68}Ga-FAPI-4, respectively. For comparison, k_B for ^{18}F-FDG trapping in the normal human liver has been estimated to be 0.00650 min^{-1} on average (*4*). It is noteworthy that, because only 2 time points were analyzed and only 1 patient per tracer was examined in Figure 2 by Giesel et al., the assessment of k_B measurement uncertainty is out of the scope of the current paper (*1*). Therefore, additionally to SUV, we suggest that one could take advantage of the significant ^{68}Ga-FAPI-2 trapping reversibility to better characterize tumors by means of calculating k_B. Furthermore, the above-proposed fitting of k_B might be easily performed at the voxel level, thus allowing parametric imaging of tracer release. Finally, let us note that a multiexponentially decaying IF does not alter the current line of argument.

To conclude, ^{68}Ga-FAPI PET/CT is a promising new diagnostic method for imaging various cancers that overexpress FAP (*1*). We suggest that the choice between ^{68}Ga-FAPI-2 and ^{68}Ga-FAPI-4 should not be only based on the criterion of reversible versus irreversible (or nearly) trapping of the tracer, even if the latter is an indubitable advantage for a theranostic purpose. Indeed, one could also take advantage of the significant trapping reversibility of ^{68}Ga-FAPI-2 to better characterize malignant tissues. Furthermore, we suggest that performing both uptake and release quantitation of ^{68}Ga-FAPI-2 trapping might be an innovative tool for assessing the response to treatment.

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