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Reversibility of ^{68}Ga-FAPI-2 trapping might prove an asset for PET quantitative imaging

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TO THE EDITOR:

In a recent paper Giesel et al. analyzed the tissue biodistribution and preliminary dosimetry of two 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 post-injection, and an almost equal uptake in comparison with ^{18}F-FDG. However, from 1 to 3 h post-injection, in contrast to ^{68}Ga-FAPI-4 that 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 standard uptake value (SUVmax) at 10–60–180 min post-injection in 2 patients with metastasized breast cancer, respectively *(1)*. Since the two tracers have rapid clearance from blood, we assume their input function (IF) has become negligible at 60, and, a fortiori, at 180 min post-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}; Equation (3) in reference *(3)*). For sake

of clarity, let us assume an IF mono-exponential 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 SUVmax, can be approximated from 60 to 180 min post-injection, by:

$$A_T(t) \approx Ki \times A_P(t=0) \times \exp(- k_B \times t)/(\alpha - k_B) \quad (1)$$

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 post-injection in Figure 2 with a mono-exponentially 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, since (i) only two time points were analyzed and (ii) only one 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 multi-exponentially 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 upon 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.

REFERENCES

1. Giesel FL, Kratochwil C, Lindner T et al. ^{68}Ga-FAPI PET/CT: Biodistribution and Preliminary Dosimetry Estimate of 2 DOTA-Containing FAP-Targeting Agents in Patients with Various Cancers. *J Nucl Med.* 2019;60:386–392.

2. Kratochwil C, Flechsig P, Lindner T et al. ^{68}Ga-FAPI PET/CT: Tracer Uptake in 28 Different Kinds of Cancer. *J Nucl Med.* 2019;60:801–805.

3. Laffon E, Allard M, Marthan R, Ducassou D. A method to quantify at late imaging a release rate of ^{18}F-FDG in tissues. *C R Biol.* 2005;328:767–772.
4. Laffon E, Adhoute X, de Clermont H, Marthan R. Is liver SUV stable over time in ^{18}F-FDG PET imaging? *J. Nucl. Med. Technol.* 2011;39:258–263.