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EDITORIAL

Editorial commentary to "^{18}F-Fluorocholine PET uptake correlates with pathologic evidence of recurrent tumor after stereotactic radiosurgery for brain metastases" by Grkovski and colleagues

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Dear Editor,

We read with great interest the paper of Grkovski et al. recently published in the *European Journal of Nuclear Medicine and Molecular Imaging* [1] investigating ^{18}F-fluorocholine (^{18}F-FCH) PET in patients with progressive brain metastases previously treated by stereotactic radiosurgery (SRS) and scheduled for surgical resection. Previous publications showed that changes in size and enhancement at magnetic resonance imaging (MRI) are not reliable features to distinguish between recurrence and radionecrosis [2–4]. In addition, advanced MRI sequences such as perfusion-weighted imaging, diffusion-weighted imaging, spectroscopy, and PET using ^{18}F-FDG and radiolabeled amino acids can improve the accuracy in this setting [3]. Yet, iconographic diagnosis remains challenging. Finally, SRS is nowadays used in many centers as an alternative to surgery to treat brain metastases and showed comparable outcome in terms of local control [4, 5]. In addition, SRS showed to provide a better control of irradiated metastases compared with whole brain radiotherapy [6] with a lower rate of side effects on neurocognitive function and on quality of life [7]. Therefore, imaging follow-up will certainly be more frequently faced with this issue that deserves further research.

The prospective study presented by Grkovski and colleagues is interesting as ^{18}F-FCH PET/CT has not yet been tested to differentiate response from progression of brain metastases treated by radiotherapy. More importantly and thanks to collaboration with neurosurgeons, authors pointed out a significant correlation between ^{18}F-FCH uptake and not only the percentage of viable tumor but also inflammation and reactive gliosis quantified by the pathologist. Radiolabeled choline uptake in inflammation was previously reported [8, 9], demonstrated in rat models [10, 11] and might be responsible for a limited specificity of ^{18}F-FCH to differentiate viable tumor from post-radiation processes, including radionecrosis [12, 13]. In this study, quantification of ^{18}F-FCH uptake revealed higher tracer uptake in the presence of tumor than in the absence of tumor, though with SUV overlap. Indeed, multiple confounding factors may potentially influence ^{18}F-FCH uptake including: (a) the primary cancer (melanoma, lung, breast, sarcoma, colorectal, testicular, ovarian, renal, and endocrine) which brings heterogeneity in terms of biological properties; (b) the SRS parameters (classical single-fraction versus multi-fraction treatment and the total absorbed dose, both having an impact on the amount of inflammation and radiation necrosis risk [14]); and finally (c) systemic treatments, including corticosteroids and immunotherapy. Not all these variables are specified in the work of Grkovski et al. [1].

Using pharmacokinetic modeling, authors showed no added value of a dynamic acquisition over a late static acquisition performed 40 min after the injection of ^{18}F-FCH, facilitating both image acquisition process and image analyses. Moreover, in a series of 24 patients with various brain lesions, Mertens et al. suggested that ^{18}F-fluoromethylcholine PET images might be performed even earlier within minutes after the tracer injection, although this study included only one metastasis and 2 radionecroses [12].

Finally, one objective of this study was to correlate the ^{18}F-FCH lesion uptake with patient survival related to progression of brain metastases after treatment. The authors concluded that a higher uptake of ^{18}F-FCH portends worse prognosis. This conclusion is, in our opinion, to take with great caution for

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several reasons: (a) the very small population size, (b) the variety of primitive neoplasia with variable aggressiveness and prognosis, (c) the non-significant *P* value of 0.068 at a time when many scientists would like to drastically raise the threshold of significance due to plenty of false-positive and non-replicable results in the literature [15], and (d) the bias generated by the introduction in the survival analysis of 2 patients without pathologic recurrence at the time of surgery (patients number 4 and 8) with less likely risk to die from the progression of a brain lesion if it is not neoplastic. Given the small size of the population and the relatively low ^{18}F-FCH uptake of these two lesions, it certainly influenced the results and it would be interesting to test the prognostic value of ^{18}F-FCH uptake in the group of tumor recurrences. Furthermore, additional information with potential role in disease progression and survival are neither mentioned in the paper nor considered in the survival analysis, e.g., SRS characteristics (fractions, dose, isodose surface), initial volume of metastases, complete or incomplete surgical resection of the recurrent lesions, and subsequent systemic treatments.

In conclusion, ^{18}F-FCH PET might not be accurate for the distinction between recurrent brain metastasis and post-radiation changes, especially in the presence of inflammation after SRS. Further prospective clinical trials, in larger populations, are needed to evaluate ^{18}F-FCH PET as a complimentary tool to standard multiparametric MR imaging in this setting. Eventually, development of quantitative and automatic imaging signal analyses, using radiomics and artificial intelligence, will certainly help refining diagnostic and prognostic value of combined imaging techniques [16, 17].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of informed consent This article does not contain any studies with human participants or animals performed by any of the authors.

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