Dynamic amino-acid PET in neuro-oncology: a prognostic tool becomes essential

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Amino-acid PET imaging is an efficient complementary tool to MRI for the assessment of gliomas, principally for high-grade gliomas [1] and is now recommended by the Response Assessment in Neuro-Oncology Group (RANO) [2]. ¹¹C-methyl-L-methionine (¹¹C-MET), O-2-¹⁸F-fluoroethyl-L-tyrosine (¹⁸F-FET) and 3,4-dihydroxy-6-¹⁸F-fluoro-L-phenylalanine (¹⁸F-FDopa) are the three main amino-acid radiotracers used in neuro-oncology PET imaging, with most published studies based on ¹⁸F-FET [1–3]. Most nuclear medicine centres only analyse static acquisitions of amino-acid PET imaging. These static acquisitions have proven effective for diagnosing gliomas and for defining the extent of tumour involvement and are particularly useful for treatment planning [4–9]. The European guidelines nevertheless introduced dynamic amino-acid PET utility for the assessment of gliomas [3] and numerous publications on dynamic amino-acid PET imaging also report that this approach yields additional information about tumour biology. Although amino-acid PET imaging primarily detects the expression of L-amino-acid transporters (LAT) in gliomas, additional dynamic parameters may reveal characteristics relating to perfusion and therefore identify features of tumour neovascularization [10].

Several studies initially investigated dynamic analyses in gliomas using ¹⁸F-FET [11], then ¹⁸F-FDopa [12] and even ¹¹C-MET [13], notwithstanding the short radioactive period of the ¹¹C radio-isotope. Dynamic analysis is based

on the assumption that aggressive gliomas (i.e. high-grade gliomas and/or IDH-wildtype gliomas) have high tracer uptake within the first few minutes post-injection (wash-in), followed by a decrease in the uptake curve (wash-out), while less aggressive gliomas (i.e. low-grade gliomas and/or IDH-mutant gliomas) typically show a slow increase in amino-acid uptake with the highest values observed during later time frames. As initially suggested by Pöpperl et al. [11], the washout observed in high-grade gliomas might be indicative of micro vessel density and LAT expression but also of disruption of the blood–brain barrier. To date, amino-acid PET dynamic analysis studies have contributed to position dynamic analysis as an essential component of glioma prognostic information and as a useful complementary tool to static images. The prognostic information for glioma kinetic amino PET analysis can be obtained from a scan of only 30–40 min [14]. This represents a significant reduction in the acquisition time normally required for dynamic PET, which had previously restricted the wider application of the analysis in clinical practice. Dynamic PET studies predominantly focus on two parameters extracted from the tumour volume of interest, namely, the time-to-peak (TTP), which represents the time from the beginning of the injection to the maximum SUV, and the slope, which is typically a linear regression of the late phase of the time-activity curve (TAC).

Most of the prognostic information from molecular parameters, which is included in the WHO 2016 classification of gliomas [15], is derived from dynamic PET parameters. It has become crucial to non-invasively determine glioma molecular parameters, such as IDH mutation status, since they are associated with better patient outcome [15]. Irrespectively of whether dynamic parameters are based on ¹⁸F-FET [16, 17] or ¹⁸F-FDopa PET imaging [12], they predict the presence of an IDH mutation at the initial diagnosis with accuracies ranging from 72 to 79% [12, 16, 17]. Static parameters were unable to provide IDH mutation status or provided lower performances. In addition, the prognostic value of dynamic parameters persists even when taking

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into account PET textural features [18, 19], numerous other quantitative features derived from static images. Indeed, the Zaragori et al. radiomics study reports an accuracy of 74% for predicting IDH mutations, with the TTP dynamic feature accounting for 35.5% of this predictive value [19]. Dynamic amino-acid PET parameters are even able to identify different patient outcomes within the same histologically defined group [20–22]. For example, although lower tumour-to-background ratios in static images and longer median TTP in dynamic images were both associated with better glioma outcomes, only TTP was specifically associated with better outcomes in the IDH-mutant astrocytoma group [23]. Longer TTP values also identified increased PFS within the IDH-wildtype glioma group, whereas none of the static parameters considered was associated with PFS [24]. TTP is also an independent predictor of OS in this IDH-wildtype population [24].

The prognostic value of dynamic imaging is also useful for assessing low-grade gliomas, particularly those imaged without any contrast enhancement on MRI. Low-grade gliomas diagnosed in this manner may indeed harbour high-grade entities or exhibit poor prognostic molecular characteristics which may induce rapid progression [25] and must therefore be detected as early as possible. Decreasing time-activity curves from the kinetic analysis of newly diagnosed low-grade gliomas were highly prognostic for shorter progression-free survival periods and reduced times to malignant transformation [26]. Moreover, among the suspected low-grade gliomas identified by MRI, kinetic analysis of ^{18}F -FET uptake detected the presence of high-grade gliomas with 95% sensitivity [27]. These high-grade gliomas would have been missed by the conventional static analysis [27]. These results were recently confirmed in a cohort of gliomas initially diagnosed by MRI without any contrast enhancement. A 5-year follow-up in 98 gadolinium-negative gliomas reveals that increasing, mixed and decreasing TACs were associated with a 85%, 47% and 19% overall survival, respectively [28].

The prognostic information obtained at initial diagnosis is nevertheless more complicated to apply to glioma recurrences. The prognostic value of static parameters for this particular indication appears to be higher than prognostic values exclusively determined from dynamic parameters [29, 30].

The Li et al. publication [31], in the current issue of *EJNMMI*, confirms the high prognostic value of dynamic amino-acid PET parameters at the initial diagnosis by focusing on a specific molecular parameter included in the new cIMPACT-NOW future central nervous system tumour classification [32], the telomerase reverse transcriptase promoter (TERTp) mutation. TERTp mutations in IDH-wildtype gliomas are reported to be associated with poor overall survival [33]. In addition to confirming the prognostic value of dynamic

PET acquisitions, Li et al. also provide a novel approach for studying dynamic parameters [31]. Instead of using volumes of interest to extract dynamic parameters of the tumour area, these authors use a voxel-wise analysis. They report that TTP dynamic parametric images non-invasively predict TERTp mutations with an accuracy of 85% [31]. This foreshadows the novel insights that could be applied to further develop the promise of dynamic acquisitions.

There have been previous reports of voxel-wise analysis in dynamic acquisitions of amino-acid PET imaging in gliomas [34–36]. But the Li et al. study differs from these previous investigations because it evaluates the textural features of TTP parametric images, i.e. by attributing one value of TTP per voxel in the tumour area [31]. This allows to evaluate the heterogeneity of dynamic images and is a similar approach to that used to investigate textural features in static images [18, 19], i.e. SUV parametric images. The same authors previously reported no significant predictive value of dynamic parameters for identifying TERTp mutations in newly diagnosed gliomas by using an approach based on volume of interest [37]. Since almost all dynamic PET studies are based on a volume of interest approach, the latest Li et al. study therefore paves the way to improve predictive performances more generally [31]. The voxel-wise analysis, however, requires kinetic parameters to be fitted, which necessitates long computation times and increases the impact of data noise. In addition, patients' movements must be corrected with great precision to ensure that each voxel is aligned during the whole acquisition. These potential limitations need to be resolved before this type of analysis can be implemented more widely. Another issue to overcome in PET dynamic analysis is to ensure that simplified dynamic models based on time-activity curves of SUV parametric images are representative of tumour metabolism of the amino-acid PET radiotracer. This is the case for the non-metabolized ^{18}F -FET radiotracer [38], but is yet to be investigated for the intracellular metabolized radiotracers ^{18}F -FDopa [39, 40] and ^{11}C -MET [36]. Indeed, the fitting of direct kinetic parameters using compartmental models requires the user to provide an input function, which can either be measured invasively from arterial blood samples or extracted from large vessels appearing in the image [36, 41]. These two requirements are very onerous processes in clinical routine practice. Validated and easy-clinically transposable kinetic models will therefore need to be developed for each radiotracer to accurately define brain tumour amino-acid metabolism to allow this approach to be adapted to the clinic.

The latest Li et al. paper [31] and an appraisal of the current literature make a strong case for the widespread use of amino-acid dynamic PET, in all nuclear medicine centres for neuro-oncology imaging, given its high prognostic value. Novel insights in dynamic analyses should help to further

enhance amino-acid dynamic PET diagnostic performances to better reflect the heterogeneity of gliomas.

Declarations

Ethics approval Institutional Review Board approval was not required because the paper is an editorial.

Consent to participate Not applicable.

Conflict of interest The authors declare no competing interests.

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