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doi:10.1093/neuonc/now255

Comment on Hatzoglou et al: Dynamic contrast-enhanced MRI perfusion versus ^{18}FDG PET/CT in differentiating brain tumor progression from radiation injury

We read with great interest the paper by Hatzoglou et al, recently published in *Neuro-Oncology*,[1] concerning the discrimination between progressive disease and radiotherapy-induced changes in brain tumors, which is a clinical challenge of paramount importance. To address this diagnostic problem, the authors compared dynamic contrast enhanced (DCE) MRI and fluorine-18-fluorodeoxyglucose (FDG) PET/CT in a total of 53 patients with primary brain tumors (n = 29) or brain metastases (n = 26). They found that the DCE MRI–derived plasma volume ratio (Vp_{ratio}) and transfer coefficient ratio (K^{trans}_{ratio}), as well as the FDG PET–derived standardized uptake value ratio (SUV_{ratio}) were useful in distinguishing between progression and radiation injury, both in the overall cohort and in the 2 main subgroups (primary and secondary brain tumors). They concluded, however, that DCE MRI–derived Vp_{ratio} was the "most robust" predictor of progression after showing a trend toward higher performances for Vp_{ratio} with respect to SUV_{ratio} (sensitivity and specificity = 92% and 77% vs 68% and 82%; AUC = 0.87 vs 0.75, P = .061, for Vp_{ratio} and SUV_{ratio}, respectively).

Perfusion-weighted MRI and FDG PET are widely available imaging modalities which have proven to be useful to complement standard MRI in this setting. However, we would like to emphasize that, in the last decade, PET using radiolabeled amino acids has developed as a powerful diagnostic tool in brain tumor diagnostics. Recently, the Response Assessment in Neuro-Oncology (RANO) working group and the European Association for Neuro-Oncology (EANO) have published their recommendations for the clinical use of PET imaging in gliomas in *Neuro-Oncology*.[2] These recommendations clearly favor amino acid PET over FDG PET and claim the superiority of amino acid PET over standard MRI in several clinical scenarios, including the differentiation of glioma recurrence from treatment-induced changes. To the best of our knowledge, no such level of evidence and consensus has been reached with regard to perfusion-weighted MRI in this field. The fact that amino acid PET is widely used in centers that have full access to the spectrum of functional and molecular MRI techniques emphasizes the value of amino acid PET beyond these alternative MRI methods.[3] These important aspects are not mentioned in the paper by Hatzoglou et al and should be disclosed to the readers.

Fewer data are available on the implementation of amino acid PET in brain metastases and no specific recommendations have been published so far. Nonetheless, the results of a direct comparison between perfusion-weighted MRI and 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (FDOPA) PET demonstrated a higher accuracy of amino acid PET in classifying indeterminate enlarging brain metastases after radiation treatment.[4] Additionally, further studies have confirmed the high accuracy of different amino acid PET tracers in this setting, although no comparison with advanced MRI techniques was included.[5,6] In single centers, combined MRI and amino acid PET criteria are already being clinically used for this problem solving.[7]

Finally, we would also like to remark that Hatzoglou et al have probably compared DCE MRI with an underpowered FDG PET technique, as a single time point PET has already shown to be less accurate than dual time point acquisitions in the same setting.[8]

In conclusion, we agree that the results of Hatzoglou et al are valuable, since it is the largest, albeit heterogeneous prospective series providing a comparison between DCE MRI and FDG PET/CT in differentiating brain tumor progression from radiation injury after cranial irradiation. However, the emerging role of amino acid PET imaging in this field is not adequately addressed and needs to be disclosed to the readers.

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"Comment on Hatzoglou et al.: Dynamic contrast-enhanced MRI perfusion vs 18FDG PET/CT in differentiating brain tumor progression from radiation injury"-Reply

We thank Cicone et al. for their interest and excellent commentary on our article.[1] We agree with the authors and the recently proposed RANO/EANO recommendations[2] that amino acid PET offers several clear advantages over FDG PET including superior lesion discrimination against low background uptake and nondependence upon breakdown of the blood-brain barrier.

The intent of our paper was to directly compare 2 FDA-approved, widely available and commonly performed techniques: FDG PET and MRI perfusion. Despite the limitations of FDG and the growing popularity of alternative radiotracers, FDG remains the workhorse of PET imaging and is the only FDA-approved radiotracer in the United States. And, despite the limitations of MRI, there is no practical substitute for the high-resolution structural details it provides; despite the limitations of MRI, patients will continue to require MRI scans at diagnosis and at follow-up for the foreseeable future. There are many logistical advantages to obtaining functional data at the same session as perfusion, diffusion, and/or spectroscopic imaging.

As indicated by Cicone et al. in their letter, there are currently few data directly comparing the latest MRI and PET technologies. In 42 patients with 50 brain metastases, their previous work nicely described the superior accuracy of F-DOPA PET (91.3%) over relative cerebral blood volume (rCBV) (75.6%).[3] rCBV is derived from T2* dynamic contrast susceptibility (DSC) images, which represent the most commonly used MRI brain perfusion technique. There are limitations to DSC perfusion, however, including degradation by susceptibility artifacts (from blood, air, bone, metal) and need for T1 leakage corrections with either contrast preloading or post hoc analysis (eg, γ-variate curve fitting). Since 2011, Memorial Sloan Kettering Cancer Center has been performing the newer T1 dynamic contrast enhanced (DCE) perfusion. DCE has several important theoretical advantages including higher spatial and temporal resolution, permeability measurements, and insensitivity to susceptibility artifacts; practical applications have demonstrated superior performance over DSC in evaluating gliomas and treatment-related changes.[4,5]

There is no doubt that amino acids and other novel radiotracers are gaining importance for evaluating treatment-related changes vs tumor progression and other common neuro-oncological issues. Indeed, in our own practice, we offer several non-FDG radiotracers including 18F-Cho, 18F-Glu, 89Zr-J591 PSMA, and 124I-PUAD. For