João Passos, Hipólito Nzwalo, Joana Marques, Ana Azevedo, Sofia Nunes, and Duarte Salgado

Neurology Department, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon, Portugal (J. P., J. M., A. A., D. S.); Biomedical Science and Medicine Department, Universidade do Algarve, Algarve, Portugal (H. N.); Paediatric Department (S. N.) and Paediatric Neuro-Oncology Unit, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon, Portugal (D. S.)

Corresponding Author: Hipólito Nzwalo, M.D., MSc, Universidade do Algarve Faro, Algarve Portugal (nzwalo@gmail.com; hipolito.nzwalo@gmail.com).

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Response to "Cognitive function, cerebral microbleeds, radiotherapy, and bevacizumab in survivors of paediatric brain tumors"

We thank the authors for their reply to our article. We agree that it is of utmost importance to disentangle the complex determinants of microvasculopathy development as well as the determinants of potential regression in this vulnerable population of pediatric brain tumor patients. We find that their demonstration that radiation-induced cerebral microbleeds (CMBs) can progress to cavernomas to be an important observation. Although this was not a specific end point of our study, we did note that one patient in our cohort had a CMB that developed into a cavernous malformation. We have previously reported that cavernous malformations are common in survivors of pediatric brain tumors who received radiation and can present on a spectrum of histological features.[1] It is our goal to continue to follow this cohort of patients to observe the natural history of these lesions.

Regarding the use of bevacizumab, we acknowledge that the population who received this drug may have been unique. However, there was no significant difference in tumor type or rate of tumor recurrence between patients who developed CMBs and those who did not (Table 1).[2] Post-hoc analysis of patients who received bevacizumab demonstrates that the rate of recurrence between patients who received bevacizumab and those who did not was not statistically different (36% and 20%, $P = .145$), though patients with high- or low-grade gliomas were more likely to receive bevacizumab (67% versus less than 10% for all other tumor types, $P = .004$). Interestingly, others have shown that administration of the anti-angiogenic drug enzastaurin with cranial radiation therapy was associated with decreased rate of additional CMB formation in adults. The underlying etiology for this was hypothesized to be a potential radioprotective effect of the anti-angiogenic therapy on microvasculature by decreasing capillary permeability and cytokine release.[3]

Determining the role specifically of bevacizumab on CMB development was not the focus of our study, and given that we had only 14 patients who received bevacizumab, more numbers are needed to further study the effect of bevacizumab on CMB development and potential evolution.

Erika Roddy and Sabine Mueller

University of California San Francisco, San Francisco, California (E.R., S.M.)

Corresponding Author: Sabine Mueller, M.D., Ph.D., University of San Francisco, California, San Francisco, CA USA (sabine.mueller@ucsf.edu).

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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.

Francesco Cicone, Norbert Galldiks, Giuseppe Minniti, Christian P. Filss, Francesco Scopinaro, John O. Prior, Nathalie L. Albert, and Karl-Josef Langen

Nuclear Medicine and Molecular Imaging Department, Lausanne University Hospital, Lausanne, Switzerland