Application of PET-MRI in pseudo progression versus true progression in High Grade Gliomas: A new avenue!

Sir,

Enlarging or new lesions frequently appear on magnetic resonance imaging (MRI) after concurrent administration of radiotherapy (RT) and temozolamide (TMZ) in high grade glioma (HGG) patients and in most of such cases, the observed radiologic changes are not due to true disease progression, but a result of a postradiation inflammatory state called pseudo progression (PP).[1] In the absence of definitive radiologic criteria or histopathological (HP) diagnosis, such a situation presents a diagnostic dilemma.[1]

Currently, there are no definitive radiologic criteria to differentiate between true progression (TP) and PP. The response criteria developed by the Response Assessment in Neuro-Oncology (RANO) Working Group state that the apparent radiologic progression can be considered TP within 12 weeks of completion of chemo RT only if new lesions have appeared outside the radiation field or if pathology confirmation has been obtained.[2] HP might assist in making the differentiation, but it can be challenging, because specimens may contain viable tumor, necrosis, and/or edema.[3]

Over the past 20 years, positron emission tomography (PET) and MRI systems have evolved slowly but steadily. The most important step toward the establishment of PET as a clinically viable tool was the introduction of combined PET/computerized tomography (CT) in 1998 by David Townsend and Ronald Nutt.[4] Clinical MRI evolved toward higher fields, faster imaging sequences, and whole-body imaging capabilities. Especially for brain imaging, 3-Tesla MRI is now the standard.[5]

PET with ^{18}F-Fluoro deoxy glucose (FDG) has become an essential imaging modality in oncology for diagnosing, staging, and predicting prognosis. However, its utility remains limited in neuro oncology because of the high rate of physiologic glucose metabolism in normal brain tissue. However, compared with standard ^{18}F-FDG PET studies, quantitative dual-time-point ^{18}F-FDG PET can improve sensitivity for the identification and volume delineation of HGG.[6]

PET and MRI provide complementary information in the study of the human brain. Simultaneously acquired data allows the spatial and temporal correlation of the measured signals, creating opportunities impossible to realize using stand-alone instruments.[7]

We discuss the case of a young female where PET-MRI proved an able adjunct in diagnosing an active disease in the background of PP.

A 26-year-old young female with glioblastoma multiforme (GBM) presented after a previous irradiation for a grade II astrocytoma. She had complaints of gradually worsening left hemiparesis, incontinence, headache, and seizures. The patient's Karnofsky performance score (KPS) was 60.

Patient was diagnosed with a right fronto-temporal (FT) glioma in 2010 [Figure 1]. She was operated upon in June 2010. The postoperative HP was grade II astrocytoma with focal areas of high MIB-1 labeling index. Patient underwent RT to a total dose of 5400 centigray (cGy) till August 2010. A post-RT MRI done in November 2010 was suggestive of residual change in right FT lobes with no other abnormality [Figure 2].

She was apparently alright for 2 years with serial follow up imaging when she started having complaint of dull headache. A contrast MR was performed and was presumed as a PP and patient was treated with medical decompressive therapy. However, the patient did not respond to it and instead developed further neurological deterioration. She then underwent a whole body F-18 FDG PET-MRI scan in January 2013. Simultaneous MRI PET study of brain was done 45 minutes after intravenous administration of 9.0 milli Curie of F-18 FDG. In addition, proton MRI of brain was done before and after administration of 10 ml IV gadolinium contrast OMNISCAN (Gadodiamide) with T1, T2W and FLAIR sequences using matrix coil. MR-based attenuation correction was done based on Dixon sequences. Postacquisition data analysis was done using syngoVIA MR engine with multimodal image fusion [Figures 3-5], which revealed an enhancing lesion in inferolateral relation to the margins of the postoperative cavity along with an enhancing necrotic lesion seen in anteromedial relation to the operated bed showing mild diffuse tracer uptake. However, the mildly enhancing lesion with bulkiness seen posterior to the operated bed showed an increased tracer uptake with further increase in delayed images (standard uptake value maximum of 7.32) that was suspicious of recurrence [Figure 4 arrow]. The patient underwent a repeat surgery with the postoperative HP diagnosis of GBM.

At presentation, patient had complaints of mild headache, left hemiparesis, and severe bowel and bladder urgency, which had increased after surgery. Patient was subsequently subjected to RT with concurrent TMZ and she tolerated the treatment well. She was also given adjuvant TMZ for six cycles as per standard treatment protocol. Presently, she is faring well and is neurologically well preserved.

PP and radiation necrosis (RN) are a well-known occurrence in previously treated HGG patients. Contrast-enhanced (CE) MRI represents the best available method for measuring treatment response and predicting survival after standard first-line therapy and is used to define progression-free survival.[8]

Currently, treatment decisions are guided by criteria (Macdonald, RANO) that equate increasing

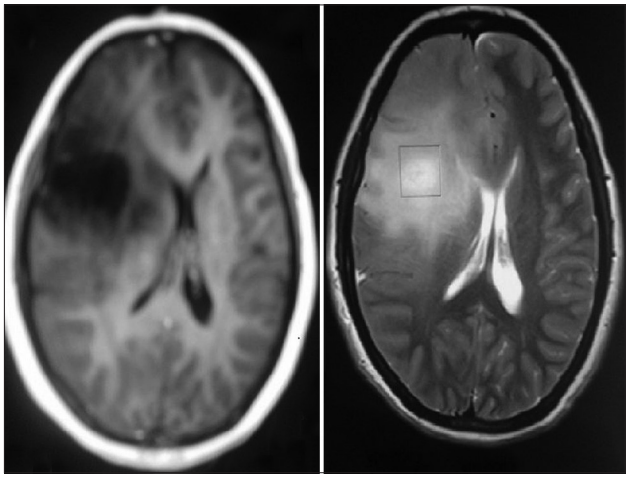

Figure 1: First scan, June 2010

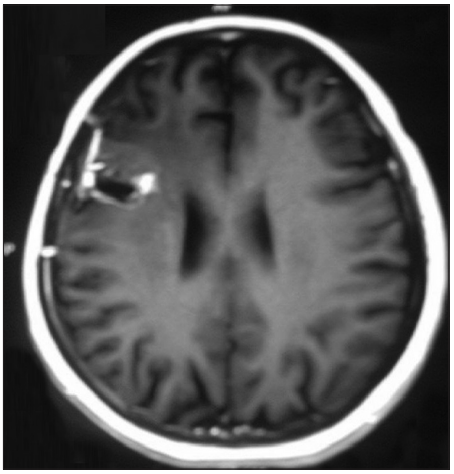

Figure 2: Postsurgery radiotherapy scan, November 2010

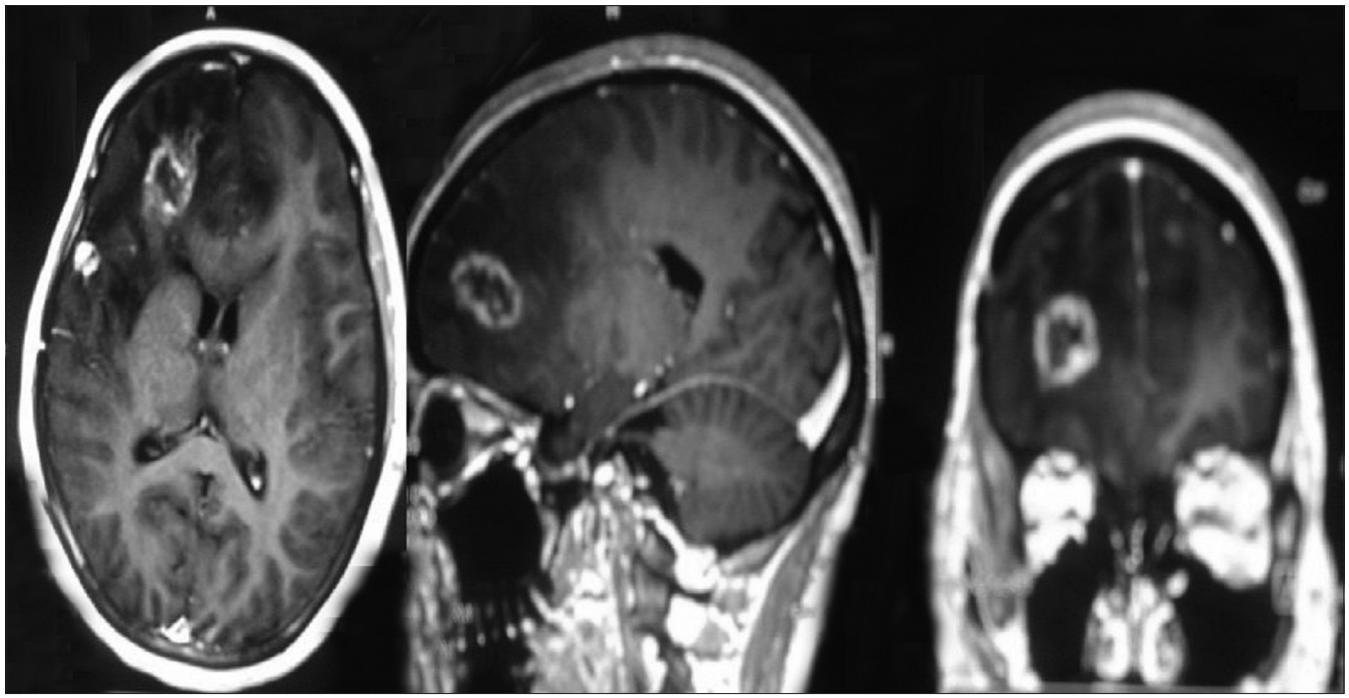

Figure 3: Positron emission tomography-magnetic resonance images

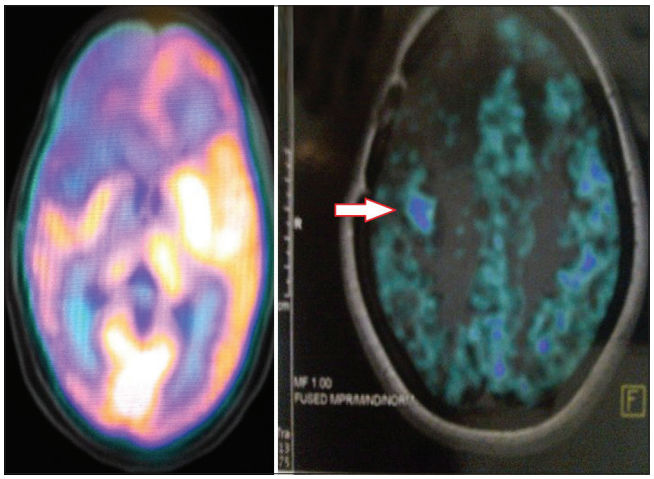

Figure 4: 18-Fluoro deoxy glucose PET-MRI brain images (see arrow)

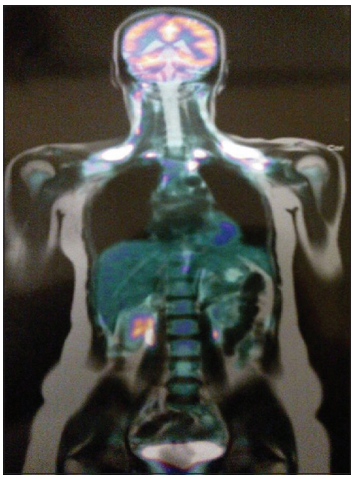

Figure 5: Whole body 18-FDG PET-MRI

size of CE-MRI enhancement with progressive tumor burden, treatment failure, and poor prognosis.[9,10] Despite widespread use, this approach has distinct limitations owing to which invasive procedures in the form of surgical biopsy and histologic evaluation remain the current benchmark.[3]

Imaging modalities like diffusion tensor images, perfusion MRI, and MR spectroscopy (MRS) can be useful in differentiating between TP and RN with restricted diffusion and an elevated relative cerebral blood volume being seen much more frequently in TP than in RN.[11] In addition, dynamic susceptibility-weighted contrast-enhanced (DSC), dynamic contrast-enhanced (DCE), and proton spectroscopic imaging are the latest tools in this regard. Although having provided additional information for distinguishing treatment effects from TP, yet no single technique can be regarded as a gold standard.[12-14]

DCE MRI, for example, provides a marker of enhancement, but enhancement depends on the permeability of the capillary bed and the surface area of the capillary bed. Finding out which of these is changing after a given treatment can be challenging. Furthermore, CE in the brain is dependent on the integrity and/or disruption of the blood–brain barrier. PET tracers for studying amino acid transport,

cellular proliferation, and tissue hypoxia have been demonstrated to have the potential to circumvent several of these limitations.[7]

MR-based motion correction has the potential to improve PET as a quantitative method. First, the nominal spatial resolution of the current state-of-the-art scanners can be achieved. Second, the mismatch between the attenuation and emission volumes can be eliminated and a better estimate of the radiotracer arterial input function could be obtained using image-based approaches from the motion corrected data.[7]

PET and MRI provide complementary information in the study of the human brain. Simultaneous PET/MRI data acquisition allows the spatial and temporal correlation of the measured signals, creating opportunities impossible to realize using stand-alone instruments.[5] In addition, in comparison to PET/CT, the effective dose (related to CT) is reduced that may be of particular relevance in the pediatric population.[15]

Combined PET/MRI systems are now commercially available in our country and are facilitating in the accurate diagnosis in conditions like the case mentioned. It may also aid in further research, experimentation and formulation of advanced treatment protocols in the management of brain tumors.

PET-MRI of the brain has the potential to provide new insights in the field of neuroscience by simultaneous study of brain function, metabolism, oxygen consumption, perfusion, and allowing exact spatial and temporal coregistration of data. In addition, an accurate spatial match between PET and MRI data is mandatory for both radiation therapy planning and biopsy guidance. PET may detect especially small lesions with higher sensitivity than MRI.[4]

Even in cases of HGG, simultaneous MR measurements of microvascular proliferation, permeability, and PET tracer uptake could help quantify precisely how tumor proliferation, tumor vascular properties, and antitumor effects occur and interact enabling a more precise understanding of tumor biology on an individual basis.[7]

India, along with the rest of world has taken its step forward toward a more comprehensive and molecular brain imaging in the form of PET-MRI. This letter highlights that in conjunct with the already available and relatively time tested imaging modalities, the addition of PET-MRI may well be the beginning of a major change in the management of HGG of the brain in the Indian scenario.

The limited availability of the modality and cost factor are the two drawbacks at present but we hope of these fading away as the modality finds more indications in the management of other neurological ailments as well. The technology of PET-MRI, although in its incipient stages in India, has made its presence felt. We advocate further studies starting as case series up to a large cohort of patients that may provide us with the needful data and evidence to support this hypothesis.

Vivek Tiwari, S. C. Pande, Sandeep Goel, Kamal Verma

Department of Radiation Oncology, Artemis Health Institute, Sector 51, Gurgaon, Haryana, India

Address for correspondence:
Dr. Vivek Tiwari,
B-79, Rajved Colony, Nayapura, Kolar Road, Bhopal - 462 042, Madhya Pradesh, India.
E-mail: dr_vivektiwari@rediffmail.com

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