Efficacy of Positron Emission Tomography in distinguishing brain tumours from inflammation
Nimra Hasnain,1 Rabia Maryam Mustafa,2 Saqib Kamran Bakhshi,3 Muhammad Shahzad Shamim4

Abstract
Positron Emission Tomography (PET) enables non-invasive evaluation of brain tumours, most commonly gliomas and metastases. However, the application of PET in distinguishing a tumour from an inflammatory lesion is still uncertain. The principle of this imaging test is based on fundamental differences in the central metabolic pathways in neoplastic and non-neoplastic tissues. 2-deoxy-2-fluoro-D-glucose (FDG) is the most widely used PET marker, whose uptake is closely related to the expression of the glucose transporter (GLUT) in malignant tumours. A limitation of FDG-PET studies is false-positive results, e.g., due to inflammation. This problem may be overcome by the use of different radiotracers targeted at different cellular sites; these include, fluoroethyl-l-tyrosine (FET), C-methionine (c-MET), 13-N ammonia, translocator receptor protein (TSPO) and ligand-11C-PK11195. All markers show variable diagnostic potential, however, more prospective trials are required to prove the efficacy.

Keywords: PET, Inflammation, Tumour, FDG.

Introduction
Distinguishing central nervous system (CNS) malignancies from infections has always been a clinical challenge. Although, surgical biopsy is the gold standard methodology for accurate diagnosis, it has associated morbidity and mortality, depending on the location of the lesion.1 Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) have long been the initial non-invasive diagnostic modalities, but their limited efficacy in differentiating between the two closely resembling conditions has prompted the need to discover better radiological imaging techniques. It has been suggested that Positron Emission Tomography (PET) may add significant diagnostic information to conventional techniques such as CT/ MRI. Literature suggests that PET seems useful at distinguishing recurrent lesions from radiotherapy-induced changes.2,3

The principle of PET imaging rests upon the fundamental differences in the central metabolic pathways of malignant tissue.4 It involves use of different metabolic markers. The role of various PET markers in differentiating inflammatory from neoplastic lesions has been recently explored. FDG (2-deoxy-2-fluoro-D-glucose), FET (fluoroethyl-l-tyrosine) and C-methionine (c-MET) are some of the widely used radiotracers, but their clinical application for identifying lesions in the brain is yet to be determined. We present a review of literature, discussing the effectiveness of currently utilized PET radiotracers in the diagnosis and differentiation of brain lesions.

Review of Evidence
FDG, a glucose analogue, is the principal radiotracer used for tumour grading and determination of prognosis in primary brain lesions.5 In tumour cells, there is a higher FDG uptake as most cancer cells exhibit elevated levels of glycolysis, a non-specific process essential for tumour growth, but also necessary for inflammatory response and tissue repair.6 Both neoplastic and inflammatory lesions demonstrate increased expression of glucose uptake transporters (GLUT-1 and GLUT-3); however, tumours have a considerably higher expression of GLUT-1.7 Therefore, both lesions show increased uptake, but relatively higher uptake is seen in malignancies. FDG-PET is a highly sensitive radiotracer (94%), but its low specificity (77%) has frequently been cited.8 It can effectively distinguish inflammation from low-grade glioma, but has low efficacy in distinguishing lesions from high-grade gliomas. Accumulation of glucose by macrophages (predominant in inflammation) and glial cells (tumour cells) makes it difficult to distinguish highly proliferative tumour lesions from inflammation, and hence, explains the incidence of false positivity.9 Both high grade and inflammatory lesions have higher expression of GLUT-1 and GLUT-3 receptors, due to which there is a greater uptake of glucose. Studies suggest that malignant cells have a lesser expression of glucose phosphatase, due to which they more easily trap FDG-PET and hence, result in increased activity on the scan, in comparison to the inflammation.10 Additionally, a study demonstrated that dual-time-point imaging (DTPI)
helps classify brain tumours with delayed images presenting a much better tumour-grading. The time interval between the two scans ranged from 30-120 minutes. Exploring the role of DTPI in differentiation of inflammatory and neoplastic lesions may offer some unique insights. Radiation necrosis, a type of inflammation, can be effectively distinguished from recurrent tumours utilizing FDG-PET owing it to be highly specific and sensitive (77%, 96%). Mascarenhas et al., described a case of ring-enhancing frontal lobe lesion which on MRI was found consistent with an abscess. On FDG-PET, increased uptake was noted which strongly correlated with metastatic activity, although the brain biopsy later revealed the presence of Nocardiosis. Similarly, in other instances of brain abscesses, increased uptake was noted for Corynebacterium and Staphylococcus Aureus.

To counter this, other PET tracers have been developed, targeting areas of tumour biology such as cellular proliferation, protein and membrane biosynthesis, and tumour receptor and/or gene product expression. Amino acid markers seem to contain a higher diagnostic value in distinguishing inflammation from low-grade gliomas, and amongst those, c-MET appears to be the most effective radiotracer. With a sensitivity and specificity of 92% and 100% respectively, c-MET exhibited elevated uptake in gliomas, with normal to decreased uptake in benign inflammatory pathologies. However, metastasis, oligodendroglioma, cystic hygroma and chordoma came out to be falsely hypointense on the scan. It was concluded that c-MET might be a superior marker in terms of its ability to differentiate the lesions having similar or lower uptake on FDG-PET. The higher sensitivity of this marker is attributed to the increased protein synthesis in rapidly proliferating tumour cells, but raised uptake of the c-MET has also been reported in one-third of the demyelinating lesions. Inflammation results in disruption of the blood-brain barrier (BBB), which results in elevated uptake of the tracer and hence may explain the occurrence of the few false-positive cases. FET, an amino acid tracer, depicted similar efficacy as that of c-MET; FET showed a parallel uptake to that of neoplastic lesions in inflammatory pathologies such as brain abscesses and demyelinating lesions. Therefore, an amino acid tracer may, at times, provide inconclusive results.

Tarkkonen et al., used 11 c-MET, and 11C-PK11195, a ligand to translocator receptor protein (TSPO), to diagnose an MR ring-enhancing frontal lesion in a patient with the clinical history of Multiple Sclerosis (MS) and Charcot Marie Tooth (CMT) disease. Thus, for demyelinating diseases such as MS, TSPO site is assumed
to be crucial in differentiating low-grade gliomas from active MS lesions. However, both markers (c-MET and 11C-PK11195) were unreliable, and a brain biopsy later suggested grade II glioma. Another tracer, 11-C choline demonstrates increased uptake in highly proliferative tumour cells and is considered to have higher efficacy than FDG in differentiating tumours from non-neoplastic lesions.\(^\text{17}\) The animal models suggest that inflamed liver tissues showed increased uptake but in clinical use, choline PET yields lower specificity, as it also accumulates in non-cancerous lesions such as meningioma, craniopharyngioma, tuberculosis, and abscess.

Recently, the diagnostic potential of another tracer, 13-N ammonia, has been evaluated in the differentiation of gliomas from lesions of inflammatory etiology. Ammonia is easily diffusible across the BBB and utilized for glutamine synthesis.\(^\text{18}\) Tumour cells having higher rates of cell division are associated with increased uptake as compared to inflammatory lesions. Furthermore, inflammatory mediators are believed to block the uptake of ammonia, hence, linked with a lower uptake. Glutamate is considered to play a significant role in trapping ammonia and various inflammatory markers are believed to block glutamate uptake. This, in combination with the direct inactivation of the synthesis of glutamine, could ultimately result in decreased ammonia uptake.\(^\text{19}\) Owing to its unique mechanism, it can emerge as a more specific marker for brain lesions.

The clinical use of PET scan is limited due to certain factors. Many neoplastic and inflammatory lesions often operate through a similar pathological mechanism; therefore, identification of highly specific markers is extremely difficult. Additionally, as different tumour pathologies constitute diverse cell origins, with each cell line having a different propensity for tracer uptake, a low-grade lesion of one tumour type may show a similar uptake to a high-grade of another. Moreover, the inherent limitations of standardized uptake value (SUV) remain a significant factor influencing the diagnostic accuracy.

**Conclusion**

Since the literature on the subject is scarce, standardized clinical trial protocols and multicenter studies utilizing diverse cohorts are required to examine the clinical implications of PET. Though, the use of PET in the diagnosis of brain and spinal cord lesions is still in preliminary stages, it has the potential to be advantageous in the early detection of tumours. It is likely that the answer does not lie with one non-invasive investigation such as MRI or PET, but a combination of two. Until then, histopathology remains the mainstay for absolute diagnosis.

**References**