

Usefulness of ^{11}C -Methionine Positron Emission Tomography in Differential Diagnosis between Recurrent Tumours and Radiation Necrosis in Patients with Glioma: An Overview

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Abstract: Differential diagnosis between radiation necrosis and tumour recurrence is important in the clinical management of patients with glioma. We performed an overview of the literature in order to summarize the role of ^{11}C -methionine positron emission tomography (MET-PET) in this setting. This functional imaging method appears to have a high sensitivity, specificity, and accuracy in differentiating between glioma recurrence and radiation necrosis. Nevertheless, possible false negative and false positive results of MET-PET should be well kept in mind in the management of patients with glioma.

Keywords: ^{11}C -Methionine positron, Tomography, Differential diagnosis, Tumours and radiation, Necrosis, Glioma.

INTRODUCTION

Gliomas are the most common primary intra-axial brain tumours, astrocytomas being the most frequent among these. Currently, surgery followed by adjuvant radiation therapy and chemotherapy is the standard of care in high grade gliomas, while the optimal management of low grade gliomas is still controversial. However, early post-surgical radiation and/or chemotherapy have been advocated for high risk patients with low grade gliomas [1-4]. Unfortunately, even after this multidisciplinary approach, the majority of gliomas tends to recur within 2 cm from the primary tumour site and within the irradiated volume [1-4].

It is crucial to differentiate recurrent tumours from radiation necrosis since the two entities have different treatment approach and different prognosis.

Radiation necrosis is a delayed focal structural lesion at or close to the original tumour site that usually occurs within a 6-months to 2-years period after radiotherapy or stereotactic radiosurgery; nevertheless, there are reports of early onset radiation necrosis, which appears to be facilitated by the concomitant chemotherapy, as well as reports of late onset ones (up to 20 years after the treatment) [5-8]. Clinical presentation of radiation necrosis is unspecific, including seizures, focal neurological deficits, personality changes, memory loss, dementia, and/or recurrence of the initial tumour symptoms.

Differential diagnosis between recurrent glioma and radiation necrosis is challenging on conventional imaging, such as computed tomography (CT) and/or magnetic resonance (MR), since radiation necrosis usually presents as a lesion with surrounding oedema and nodular, linear, curvilinear enhancement due to blood-brain barrier breakdown, often resembling residual/recurrent tumour about resection cavity. Moreover, if a radiation-induced lesion is detected at a distant site from the primary tumour site it may be misinterpreted as multifocal glioma [9].

Different imaging techniques have been reported as possible tools to overcome these difficulties: perfusion MR, diffusion MR, MR spectroscopy and nuclear medicine techniques.

Nuclear medicine functional imaging is able to evaluate the metabolic activity of the lesion showed on conventional imaging so providing clues to differentiate tumour recurrence from radiation necrosis [10-12]. In the field of positron emission tomography (PET), fluorine-18 fluorodeoxyglucose (FDG) is the most studied radiopharmaceutical. This glucose analogue has some limitations in differentiating glioma recurrence from radiation necrosis such as the high background uptake of FDG in glucose-dependent brain tissue, the possible absence of high FDG uptake in recurrent low-grade glioma and the presence of non-specific increased FDG uptake (as it has also been observed in the inflammatory tissue). These limitations can explain the reported low sensitivity of FDG-PET in differentiating glioma recurrence from radiation necrosis [13-16].

Alternative PET radiopharmaceuticals have been studied to overcome these limitations. Since many brain tumours over-express a variety of amino acid (AA) transporters and the AA uptake in normal brain is low, AA labelled with ra-

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radioactive PET isotopes have been successfully applied for imaging of gliomas [17], such as methionine labelled with carbon-11.

Methionine, a sulfur-containing essential AA, has two main metabolic functions [16]:

- a) protein synthesis;
- b) conversion to S-adenosylmethionine, required in multiple metabolic pathways as transmethylation reactions, polyamine synthesis, transsulfuration pathway that leads to the synthesis of cysteine and other derivatives such as glutathione.

In cancer cells, there is an increase in protein synthesis, transmethylation and transsulfuration, leading to an increased uptake of methionine. *In vitro* methionine dependence has been demonstrated in human glioma cell lines [18, 19]. Moreover, it has been shown that in a human glioblastoma cell line the uptake of radiolabeled methionine is higher in proliferating cells than in resting plateau-phase cells [20].

Currently, carbon-11 methionine (MET) PET is the most common AA-imaging modality for brain tumours, although its use is restricted to PET centres with cyclotron facility because of the short half-life of the isotope. Several studies evaluated the role of MET-PET in the detection of cerebral gliomas, showing high sensitivity and specificity in detecting both low and high grade tumours, the former being sometimes more difficult to diagnose on conventional imaging and with FDG-PET [16,17, 21-30].

Several studies also evaluated the role of MET-PET in differentiating tumour recurrence from radiation necrosis (Table 1).

An early article by Ogawa *et al.* presented a series of 15 patients with suspected recurrent brain tumour after radiotherapy: 10/15 patients underwent a MET-PET that matched in 100% of cases with histopathological results (3 radiation necrosis and 7 tumour recurrences) [31].

Sonoda *et al.* also reported that 5/5 patients with recurrent tumour showed increased MET uptake, while only 1/7 patients with radiation necrosis showed MET uptake [32].

In 2004, Tsuyuguchi *et al.* reported a series of 11 patients with recurrent malignant glioma or radiation injury after

stereotactic radiosurgery; MET-PET correctly identified 6/6 patients with recurrent tumours and 3/5 cases of radiation necrosis. From this result, the MET-PET sensitivity, specificity, and accuracy in detecting tumour recurrence were determined to be 100%, 60%, and 82% respectively [33].

Van Laere *et al.* have performed a comparison between FDG-PET and MET-PET in suspected recurrence of gliomas; they found an abnormal MET uptake in 28/30 cases, whereas only 17/30 cases showed FDG uptake. The main limit of this study is the empirical classification of patients in radionecrosis group and recurrence group, since the histological results was present only in 3 cases. In fact all cases of death was considered recurrent, and all cases of alive patients at the end of follow-up period was considered as radiation necrosis [17].

More recently, Terakawa *et al.* reported an interesting case series of 26 gliomas who underwent conventional radiotherapy. Overall, 32 MET-PET scans were performed at a mean interval of 36 months from irradiation. Recurrence was confirmed by tumour resection or biopsy, while radiation necrosis diagnosis was based on pathologic examination or on clinical course. Mean standardised uptake value (SUV_{mean}) and maximum standardised uptake value (SUV_{max}) were generated over the region of interest (ROI) and the lesion-to-normal tissue (L/N) count ratios were generated by dividing the SUV_{mean} of the lesion and the SUV_{mean} of the contralateral frontal lobe gray matter (L/N_{mean}) and by dividing the SUV_{max} of the lesion and the SUV_{max} of the contralateral frontal lobe gray matter (L/N_{max}). The Authors found a significant difference in all of the indices except for the L/N_{max} between tumour recurrence and radiation necrosis. Receiver-operating-characteristic (ROC) curves analysis of each index indicated that L/N_{mean} is the most informative index between tumour recurrence and radiation necrosis and an L/N_{mean} of 1.58 provided the best sensitivity and specificity for gliomas, 75% and 75%, respectively. However in this study some necrotic tissue also had some high level of MET uptake, which can be a factor that reduces the specificity of MET-PET. This is most likely due to the blood-brain barrier disruption that may occur in radiation-induced lesion [34]. Therefore, some Authors suggested to repeat the MET-PET scanning after corticosteroid administration in cases with borderline

Table 1. Studies Evaluating the Role of MET-PET in Differentiating Recurrent Gliomas from Radiation Necrosis

Authors	PET Scans Performed	Sensitivity (%)	Specificity (%)
Ogawa <i>et al</i> [31]	15	100	100
Sonoda <i>et al</i> [32]	12	100	86
Tsuyuguchi <i>et al</i> [33]	11	100	60
Van Laere <i>et al</i> [17]	30	75	70
Terakawa <i>et al</i> [34]	32	75	75
Kim <i>et al</i> [36]	10	75	100
Nakajima <i>et al</i> [37]	18	86	100
Yamane <i>et al</i> [38]	80	88	80
Okamoto <i>et al</i> [39]	29	86	91

MET uptake; the repeat scans may serve to distinguish between radiation necrosis and tumour lesions reducing the MET uptake due to blood-brain barrier breakdown in radiation injury while leaving the MET uptake due to intact active transport in gliomas [16].

Other hypotheses which could explain the uptake of MET in radiation necrosis can be an increased methionine metabolism induced by reactive gliosis mediated by astrocytes and microglial cells [35] or a methionine accumulation as a result of proliferative changes in glial cells in the area of radiation necrosis [33]. On the other hand, false negative results with MET-PET are possible, mainly due to the lack of detection of small lesions.

Kim *et al.* compared perfusion MR, FDG-PET and MET-PET in making the distinction between radiation necrosis and tumour recurrence in 10 patients with high grade glioma who underwent surgical resection followed by radiotherapy with or without chemotherapy and showed newly enhanced lesions on follow-up conventional MRI. After co-registering the PET images with the MR, the maximum uptake values of the lesion and of the contralateral cerebral white matter as reference area were measured to calculate the lesion/reference uptake ratio. There was no difference between radiation necrosis and tumour recurrence groups in terms of lesion/reference uptake ratio as derived from the FDG and MET-PET. The Authors also stated that a perfusion MR might be superior to FDG and MET-PET in order to distinguish a recurrence of high-grade glioma from radiation necrosis [36].

In 2009, Nakajima *et al.* evaluated the usefulness of MET-PET in differential diagnosis between radiation necrosis and tumour recurrence in 18 patients with glioma. The uptake of MET was determined as the ratio of the lesion to the contralateral reference region (L/R). The final diagnoses were determined by histological examination and/or follow-up MR imaging and clinical course. MET-PET demonstrated significant difference in the L/R ratio between patients with tumour recurrence and radiation necrosis (2.18 vs. 1.49, $p < 0.01$). According to a 2 x 2 factorial table analysis, the borderline values of L/R to differentiate recurrence from necrosis was 2.00 [37].

In their retrospective study, Yamane *et al.* examined the clinical efficacy of MET-PET in patients with brain neoplasm, especially whether the MET-PET changed the clinical management. The Authors demonstrated that MET-PET was useful in differentiating tumour recurrence from radiation necrosis, changing the clinical management in half of the scans [38].

Recently, Okamoto *et al.* evaluated with PET-MET 29 patients (33 lesions) suspected of recurrent brain tumors by MR after radiation therapy. Semi-quantitative analysis was performed using SUV_{max} and L/N ratio. ROC analysis was also assessed about the diagnostic value of MET-PET. Histological analysis or clinical follow-up confirmed the diagnosis of tumour recurrence in 22 lesions, and radiation necrosis in 11 lesions. L/N ratios of recurrence and necrosis for overall lesions were 1.98 and 1.27, respectively ($p < 0.01$). The areas under the ROC curve were 0.886 for L/N ratio and 0.738 for SUV_{max} . The Authors demonstrated that

semi-quantitative analysis of MET-PET provided high diagnostic value enabling early diagnosis of recurrence of brain tumour in the follow-up after the radiation therapy [39].

In summary, long from being a gold standard for diagnosis in differentiating glioma recurrence from radiation necrosis, MET-PET appears to have a high sensitivity, specificity, and accuracy in this setting.

CONFLICT OF INTEREST

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