

# The Accuracy of Fluorodeoxyglucose Positron Emission Tomography with Computer Tomography (FDG-PET CT) and Magnetic Resonance Spectroscopy (MRS) in Differentiating between Primary Central Nervous System Lymphoma (PCNSL) and Non-malignant CNS lesions in HIV infected patients.

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## ABSTRACT

### Background

In the investigation of ring enhancing cerebral lesions in HIV infected patients, standard current scanning modalities are unable to differentiate between Primary CNS lymphoma (PCNSL) and Non-malignant CNS lesions. Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) and Magnetic Resonance spectroscopy (MRS) may provide a non-invasive means to more accurate differentiation, enabling rapid initiation of therapy and avoidance of morbidity associated with current practice. In this study we have prospectively investigated the utility of FDG PET and MRS in distinguishing between primary cerebral lymphoma and non-malignant CNS lesions in HIV infected patients.

### Method

HIV patients presenting with neurological symptoms and with either solitary or multiple contrast-enhancing brain lesion on CT or MR were prospectively recruited from two centres in the North of England. All patients were commenced on anti-toxoplasmosis therapy as per standard practice and underwent a FDG-PET & MRS. All images were reviewed by two independent assessors. Brain biopsies were sought in those with FDG PET suggestive of lymphoma and those with a negative FDG-PET CT who failed to respond to standard therapy at two weeks. Final Diagnosis was based on clinical and radiological response to treatment or histology where available. A total of 10 patients were recruited (8 male, mean CD4 61cells/uL, mean age 38 years). Ten underwent PET and Eight MRS. Two patients had Lymphoma, one confirmed by brain biopsy and one by CSF cytospin. FDG PET was suggestive of lymphoma in both cases. Six patients had cerebral toxoplasmosis, five confirmed by clinical & radiological response to therapy and one by autopsy. One patient had Progressive Multifocal Leucoencephalopathy (PML) based on clinical & radiological response to therapy. One patient had metastatic non-small cell lung cancer (NSCLC) confirmed by brain biopsy.

### RESULTS

FDG-PET CT accurately identified both cases of lymphoma and all cases of cerebral toxoplasmosis were identified as non-malignant disease. It was equivocal in the case of PML. FDG-PET wrongly identified metastatic NSCLC as non-malignant disease. The presence of haemorrhage within the lesion was suggested as a reason for the inaccurate result. MRS was performed in eight subjects. Three scans were suggested of lymphoma; one true positive & two false positives (toxoplasmosis & PML). Four scans were suggestive of non-malignant lesions; one false negative and three true negative. One scan was equivocal (toxoplasmosis)

### CONCLUSIONS

All cases of PCNSL and cerebral toxoplasmosis were correctly identified by FDG-PET CT confirming this to be a useful technique in this setting. MRS was unhelpful in this cohort.

## Background

Despite the advent of highly active antiretroviral therapy (HAART) neurological disease is still the presenting feature of HIV in 2-3% (compared to 15% pre-HAART) of cases<sup>1</sup>. Around two-thirds result from opportunistic infections and HIV-related malignancies. Despite available treatment options mortality remains high and the morbidity significant, with long hospital stays, reduced quality of life and marked disability. Current scanning modalities such as CT and MR are unable to differentiate between PCNSL and cerebral toxoplasmosis, the most common and serious differentials.

Current practice recommends empiric anti-toxoplasmosis therapy for two weeks. Patients that fail to respond to treatment require a brain biopsy for diagnosis. The impact of this trial of treatment approach can lead to significant delays in the management of PCNSL along with morbidity associated with a brain biopsy

Fluorodeoxyglucose positron emission tomography (FDG-PET) and Magnetic resonance spectroscopy (MRS) may provide a non-invasive means to a more accurate differentiation. Enabling rapid initiation of therapy and avoidance of morbidity associated with current practice.

There have been several small studies which have shown FDG-PET CT to be a promising technique in reliably differentiating between PCNSL and non-malignant cerebral lesions in HIV-infected patients<sup>2,3</sup> The largest study of 23 patient found FDG-PET CT to be 100% sensitive and specific for identifying lymphoma<sup>4</sup>. The use of MRS in this setting has been evaluated in a small number of studies, the results however have been inconsistent<sup>5,6,7</sup>.

## Study Aims

To prospectively investigate the utility of FDG-PETCT and MR spectroscopy in differentiating between primary CNS lymphoma and non-malignant CNS lesions in HIV-infected patients.

## Study Design

- Full ethics approval.
- Prospective recruitment over a period of 40 Months from North Manchester General Hospital and the Royal Liverpool Hospital in the North of England.
- All patients were commenced on anti-toxoplasmosis therapy as per standard practice.
- MRS and FDG-PET CT performed within 3 days of entry into study.
- Brain biopsy was sought when imaging suggested a diagnosis of PCNSL or when there was failure of response to two weeks of anti-toxoplasmosis therapy.
- All images reviewed by two independent consultant radiologists.
- Confirmation of final diagnosis was based on clinical and radiological response to treatment or histology where available

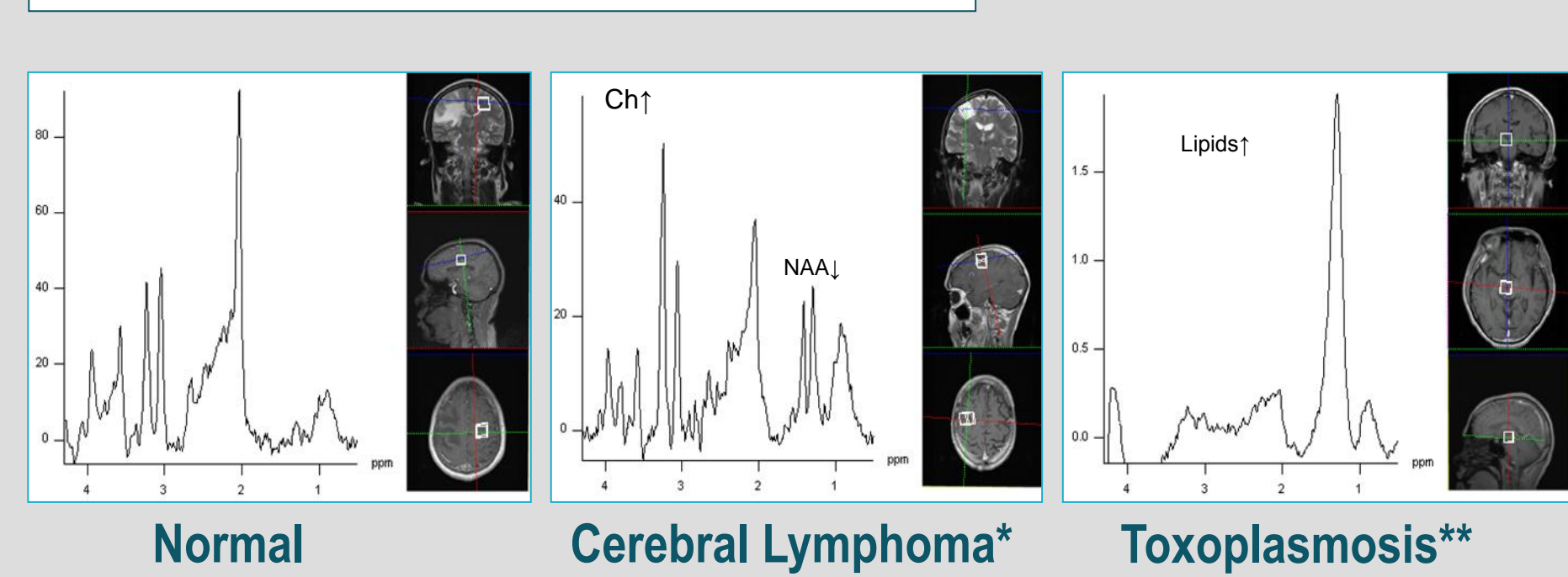
Table 1. Inclusion and Exclusion Criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
<ul style="list-style-type: none"> <li>• HIV infection</li> <li>• Aged 18 years and over</li> <li>• Presentation with neurological dysfunction.</li> <li>• Solitary or multiple contrast enhancing lesions on brain CT or conventional MRI</li> </ul>	<ul style="list-style-type: none"> <li>• Contraindication to MRI.</li> <li>• Lack of capacity to consent.</li> <li>• Not medically fit to undergo ambulance transfer</li> <li>• Pregnant</li> </ul>

## Imaging Modalities

- MRS is a non-invasive technique for measuring biochemicals in tissue, which uses the same general principle as MRI.
- Whilst MRI builds from signals from hydrogen ions, MRS measures signals from magnetic nuclei of numerous tissue metabolites such as choline, creatine and lactate.
- MRI provides morphological information whereas MRS provides biochemical information.

### CHARACTERISTIC SPECTRA EXPECTED



\* Lymphoma typically shows an elevation in Choline  
 \*\* Toxoplasmosis typically shows increased levels of lipids and lactate, depletion of all other metabolites

- FDG-PET is a scintigraphic technique that provides three-dimensional information about the rate of glucose metabolism in the body and is a sensitive method for detecting, staging, and monitoring the effects of therapy for many malignancies.
- CT images provide information about the size and shape of abnormalities within the body. Combined PET/CT devices provide both the metabolic information from FDG-PET and the anatomic information from CT in a single examination.
- The information obtained by PET/CT has been shown to be more accurate in evaluating patients with known or suspected malignancy than either PET or CT alone or PET and CT obtained separately but interpreted together<sup>8</sup>

## Baseline Characteristics

Table 2. Baseline Characteristics

Male	8 (80%)
Mean Age	38 years
Mean CD4 at presentation	61 cells/uL
MSM	4 (40%)
Ethnicity	UK 4 (40%) African 5(50%) South East Asia 1 (10%)
HIV Viral load detectable	10 (100%) mean 150,000 copies/ml

## Results

Table 3. Diagnosis and 12 month outcome

Patient	Final Diagnosis	Confirmed by	Outcome at 12 months
1	Toxoplasmosis	Post Mortem	Dead
2	Toxoplasmosis	Clinical Diagnosis	Full Recovery
3	Toxoplasmosis	Clinical Diagnosis	Full Recovery
4	Toxoplasmosis	Clinical Diagnosis	Disability
5	Toxoplasmosis	Clinical Diagnosis	Unknown
6	Toxoplasmosis	Clinical Diagnosis	Unknown
7	Lymphoma	CSF Cytospin	Full Recovery
8	Lymphoma	Brain Biopsy	Died
9	Metastatic NSCLC	Brain Biopsy	Died – Post Brain Biopsy
10	PML	Clinical Diagnosis	Disability

## RESULTS

Table 4. Scan Results

Patient	Final Diagnosis	PET CT Result	MRS Result
1	Toxoplasmosis	Non-malignant	Non-malignant
2	Toxoplasmosis	Non-malignant	Non-malignant
3	Toxoplasmosis	Non-malignant	Lymphoma
4	Toxoplasmosis	Non-malignant	Equivocal
5	Toxoplasmosis	Non-malignant	Not performed
6	Toxoplasmosis	Non-malignant	Not performed
7	Lymphoma	Lymphoma	Lymphoma
8	Lymphoma	Lymphoma	Non-malignant
9	Metastatic NSCLC	Non-malignant	Non-malignant
10	PML	Equivocal	Lymphoma

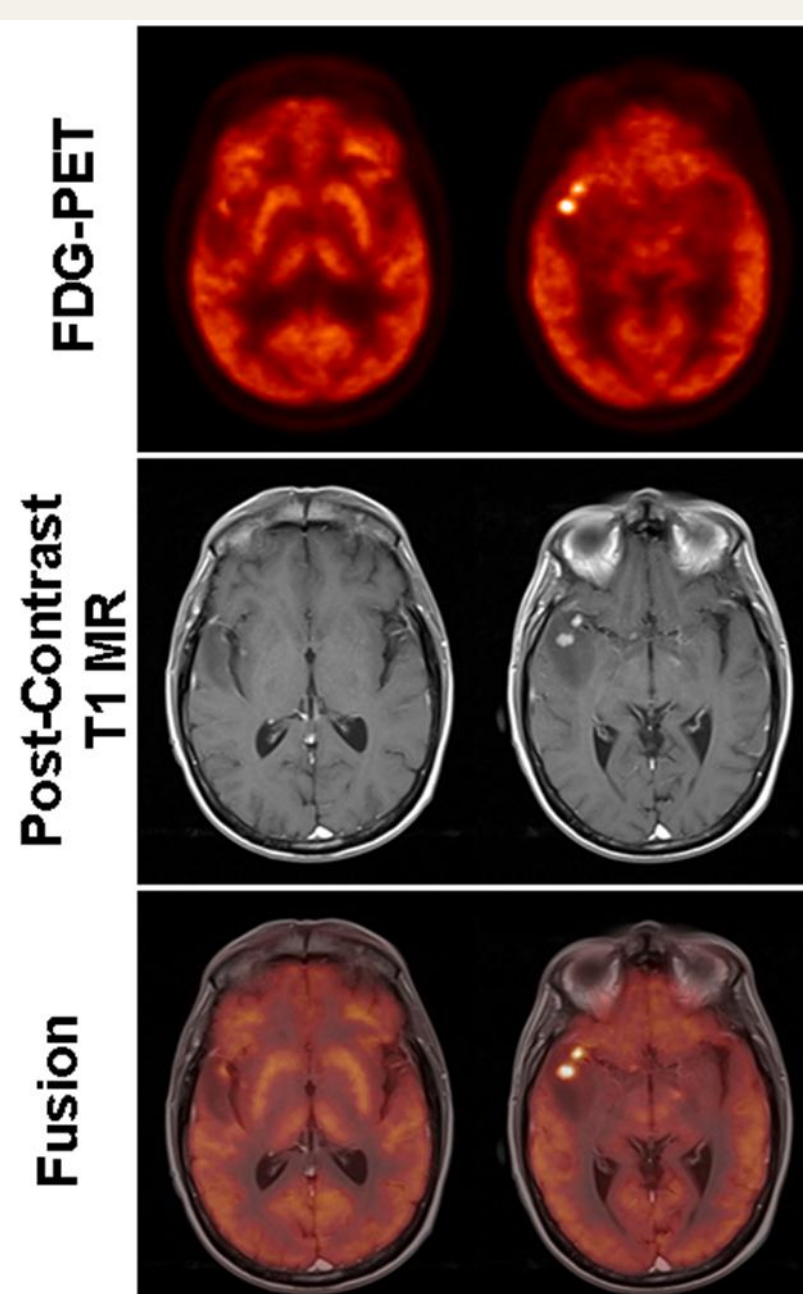
Green: Correct diagnosis. Red: Wrong Diagnosis. Yellow: Equivocal

## FDG-PET CT Results

### CEREBRAL LYMPHOMA

FDG-PET CT suggested lymphoma in both confirmed cases

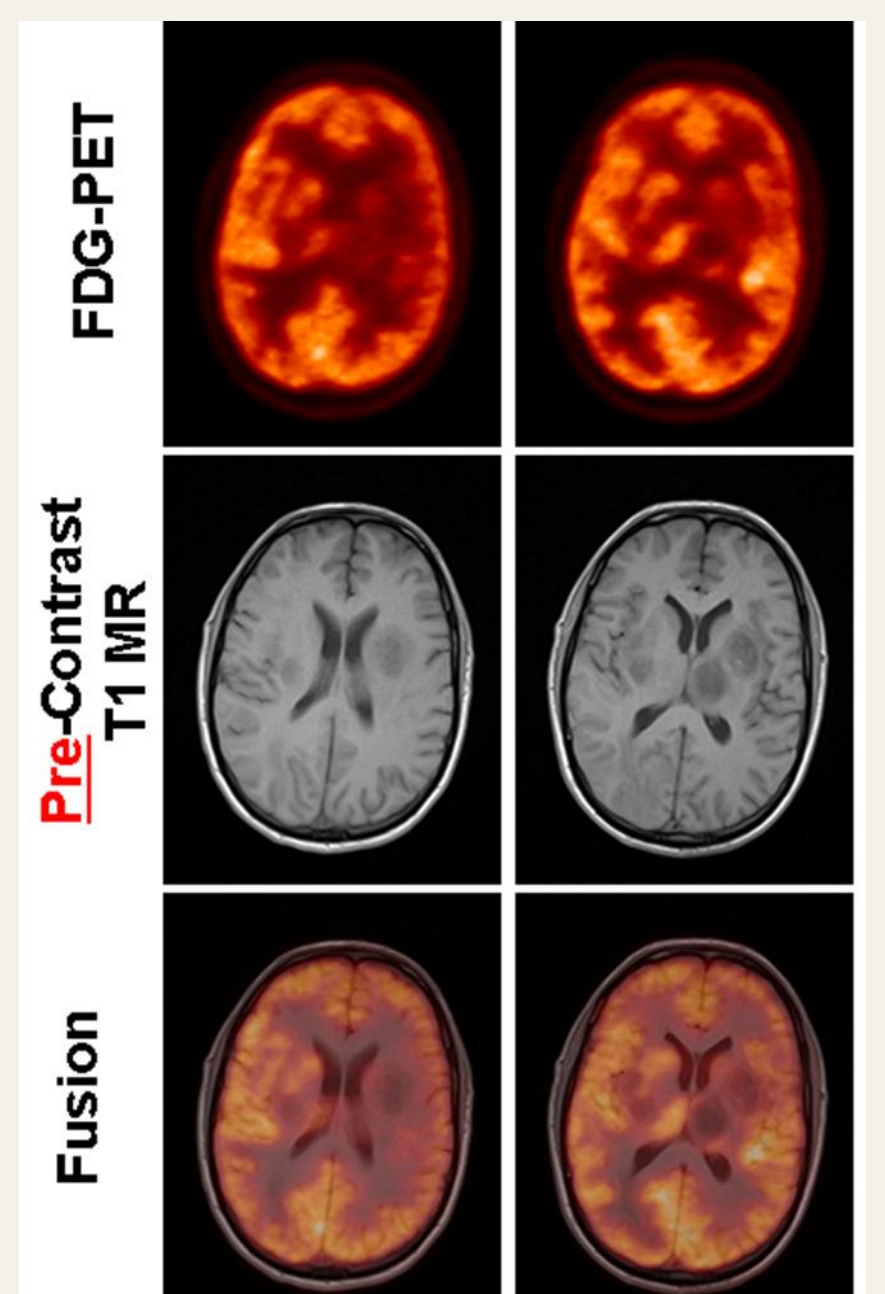
Figure 1. LYMPHOMA IMAGE. Note the metabolically active lesion typically seen in lymphoma.



### TOXOPLASMOSIS

FDG-PET CT was suggestive of non-malignant disease in all six confirmed cases of toxoplasmosis

Figure 2. TOXOPLASMOSIS IMAGE. Note the metabolically inactive lesions



- FDG-PET CT was equivocal in the case of PML
- In the case of metastatic non-small cell lung cancer FDG-PET CT wrongly identified non-malignant disease. The presence of haemorrhage within the mass was suggested for the inaccurate result.

## MR Spectroscopy Results

- MRS successfully performed in eight patients.
- The two failures were due to small lesion size leading to spectral contamination by adjacent structures.

Three studies were suggestive of lymphoma; **one true positive** and **two false positive** (toxoplasmosis & PML).

Four scans suggestive of a non-malignant aetiology; **one false negative** and **three true negatives**.

One scan was equivocal (toxoplasmosis).

## Discussion

All cases of cerebral lymphoma and cerebral toxoplasmosis were correctly identified by FDG-PET CT confirming this to be a useful technique in this setting. Within this study two patients underwent a brain biopsy. One patient had a cerebral bleed at the time of biopsy and died shortly after. The early use of FDG-PET CT may preclude the need for brain biopsy and thus eliminating the associated morbidity and mortality. The small sample size reflected the reduction in cases with the advent of HAART and toxoplasmosis prophylaxis

MR spectroscopy did not aid diagnosis within this cohort.

## References

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