


# Utility of flouro-deoxy-glucose positron emission tomography/computed tomography in the diagnostic and staging evaluation of patients with primary CNS lymphoma

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## Practice points

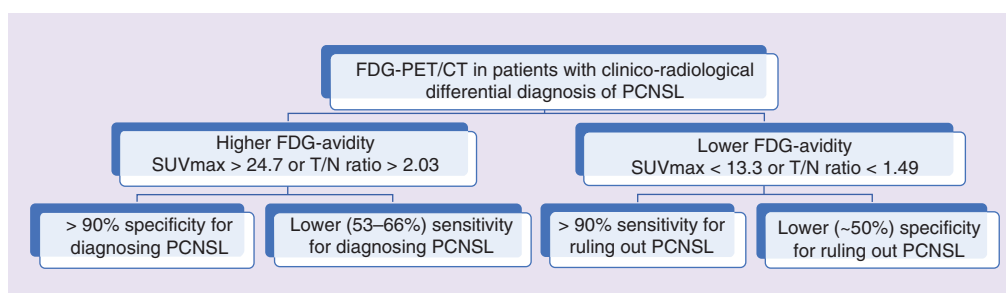
- MRI may not be able to reliably differentiate primary central nervous system (CNS) lymphoma (PCNSL) from morphologically similar lesions (glioblastoma, brain metastases and infection/inflammation).
- Flouro-deoxy-glucose positron emission tomography/computed tomography (18F-FDG-PET/CT) is a functional imaging modality that assesses glucose metabolism and has an established role in systemic lymphoma.
- Clinical utility of whole-body FDG-PET/CT in the diagnostic and staging evaluation of PCNSL has not been studied systematically.
- PCNSL has significantly higher FDG-uptake compared with other morphologically similar lesions in the brain.
- Whole-body FDG-PET/CT identifies occult systemic foci of lymphoma in a small proportion of patients presenting with disease apparently confined to the CNS.

**Aim:** Toprospectively assess the clinical utility of pretreatment flouro-deoxy-glucose positron emission tomography/computed tomography (18F-FDG-PET/CT) in patients with primary central nervous system (CNS) lymphoma (PCNSL). **Materials & methods:** Patients with suspected/proven PCNSL underwent baseline whole-body 18F-FDG-PET/CT. Maximum standardized uptake value and tumor/normal tissue ratios were compared between CNS lymphoma and other histological diagnoses. **Results:** The mean maximum standardized uptake value (27.5 vs 18.2;  $p = 0.001$ ) and mean tumor/normal tissue ratio (2.34 vs 1.53;  $p < 0.001$ ) of CNS lymphoma was significantly higher than other histologic diagnoses. Five of 50 (10%) patients with biopsy-proven CNS lymphomas had pathologically increased FDG-uptake at extraneuraxial sites uncovering systemic lymphoma. **Conclusion:** Pretreatment whole-body 18F-FDG-PET/CT provides valuable complementary information in the diagnostic and staging evaluation of patients with PCNSL to guide therapeutic decision-making.

**Lay abstract:** There is considerable overlap in conventional imaging features of primary central nervous system (CNS) lymphoma with other lesions such as glioblastoma and metastases. Flouro-deoxy-

glucose positron emission tomography/computed tomography can reliably differentiate primary CNS lymphoma from brain lesions with similar morphology on conventional MRI. Based on significantly high flouro-deoxy-glucose-avidity of CNS lymphoma, semiquantitative flouro-deoxy-glucose positron emission tomography/computed tomography parameters were able to differentiate between brain lymphoma and nonlymphomatous lesions with acceptable diagnostic accuracy. A small proportion (10%) of patients also had pathological flouro-deoxy-glucose-uptake in other body parts resulting in the diagnosis of systemic lymphoma with spread to the brain.

#### Graphical abstract:



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**Keywords:** brain • FDG-PET/CT • lymphoma • MRI • systemic staging

Primary central nervous system (CNS) lymphoma (PCNSL) comprises <2% of all primary brain tumors and 2–3% of all non-Hodgkin lymphoma [1,2]. Contrast-enhanced MRI is the recommended imaging modality for all suspected CNS tumors including PCNSL. In immunocompetent adults with primary CNS diffuse large B-cell lymphoma (DLBCL), MRI generally shows a solitary intracranial mass lesion (in nearly two-thirds of patients), mostly located in the cerebral hemispheres, basal ganglia, corpus callosum and deep periventricular regions with multiple lesions reported in approximately a third of patients [3]. Lesions of PCNSL are typically iso-intense on T1-weighted images, hypo-intense on T2-weighted images, that show homogenous and intense contrast enhancement, diffusion restriction and variable perifocal edema [3,4]. Since there is considerable overlap in the imaging characteristics of PCNSL with other common brain lesions such as glioblastoma, brain metastases and inflammatory or infectious pathologies, conventional morphologic MRI is generally insufficient to reliably and unequivocally differentiate between them. By definition, PCNSL is restricted to the brain, leptomeninges, spinal cord or eyes, without any evidence of involvement outside the neuraxis [1]. Any extraneuraxial involvement at initial diagnosis is considered as systemic lymphoma with secondary CNS involvement. Following the diagnosis of a CNS lymphoma, the extent of staging required to evaluate for a systemic lymphoma remains controversial [5,6]. Between 4–13% of patients presenting with disease apparently confined to the CNS have extraneuraxial involvement on systemic imaging [7]. The current recommendation of the International Primary CNS Lymphoma Collaborative Group is to perform a baseline CT scan of the chest, abdomen and pelvis along with testicular ultrasonography (in males) to detect any site(s) of systemic involvement in PCNSL [8]. The identification of systemic involvement in suspected PCNSL alters patient management significantly and adversely affects prognosis [9,10].

Rapid advancements in imaging technology have now made it feasible to study various aspects of the tumor micro-environment such as hypoxia, angiogenesis, cellularity, proliferation and metabolism. Flouro-deoxy-glucose positron emission tomography/computed tomography (18F-FDG-PET/CT) that assesses glucose metabolism in the tumor remains by far the most widely used functional imaging modality in the diagnosis, staging, prognosis and monitoring of response in contemporary oncologic practice [11]. Over the years, the role of FDG-PET/CT in systemic lymphoma for staging at initial diagnosis, early interim response assessment after 1–2 cycles of chemotherapy and post-treatment surveillance following completion of therapy [12] has been firmly established. However, the clinical utility of baseline FDG-PET/CT in the diagnosis and staging of PCNSL has not been evaluated systematically. The primary aim of the study was to assess the diagnostic utility of baseline (pretreatment) brain FDG-PET/CT in patients with suspected PCNSL by reliably differentiating it from other lesions with similar morphology (i.e., glioblastoma, brain

metastases, infectious/inflammatory lesions) on conventional neuroimaging. A secondary aim was to assess the utility of whole-body FDG-PET/CT for detection of systemic involvement in patients who present with disease apparently confined to the CNS.

## Materials & methods

### Study design & participants

The imaging study consisted of two parts; in Part A, adult patients with a strong clinicoradiological suspicion of PCNSL on conventional neuroimaging such as MRI (with or without spectroscopy and diffusion-weighted imaging) were included in the study and underwent baseline (pretreatment) whole-body FDG-PET/CT imaging after discussion in a multidisciplinary joint clinic. A planned neurosurgical intervention either limited to biopsy (stereotactic or open) or resection as deemed appropriate and safe by the operating neurosurgeon provided confirmatory histopathological diagnosis. Patients with deep seated lesions wherein biopsy was deemed hazardous, and in patients with obvious leptomeningeal enhancement, cerebrospinal fluid (CSF) was tested for malignant cell cytology and supplemented with flow-cytometry to arrive at a cytological diagnosis. Patients presenting with histopathologically proven CNS lymphoma (following brain or vitreous biopsy) were accrued directly in Part B and underwent whole-body FDG-PET/CT scan for baseline (pretreatment) staging before the initiation of definitive chemo(radio)therapy. The diagnostic utility of baseline FDG-PET/CT was measured using pathological diagnosis (biopsy/cytology) as reference standard. Any nonphysiologically increased FDG uptake outside the neuraxis suspicious of lymphomatous involvement was confirmed by either fine needle aspiration cytology or biopsy to establish the presence of systemic disease. Baseline (pretreatment) FDG-PET/CT was used for determining the incidence and patterns of systemic involvement in patients with histopathologically proven CNS lymphoma presenting with disease apparently confined to the neuraxis. Known cases of systemic lymphoma with secondary CNS involvement and patients with prior history of known malignancy with newly diagnosed brain lesion(s) were excluded from the study. The study was approved by the Institutional Ethics Committee and all patients provided written informed consent prior to study participation. All FDG-PET/CT scans were funded through a competitive study-specific intramural research grant, with the sponsor having no role in study design, conduct, analysis and reporting.

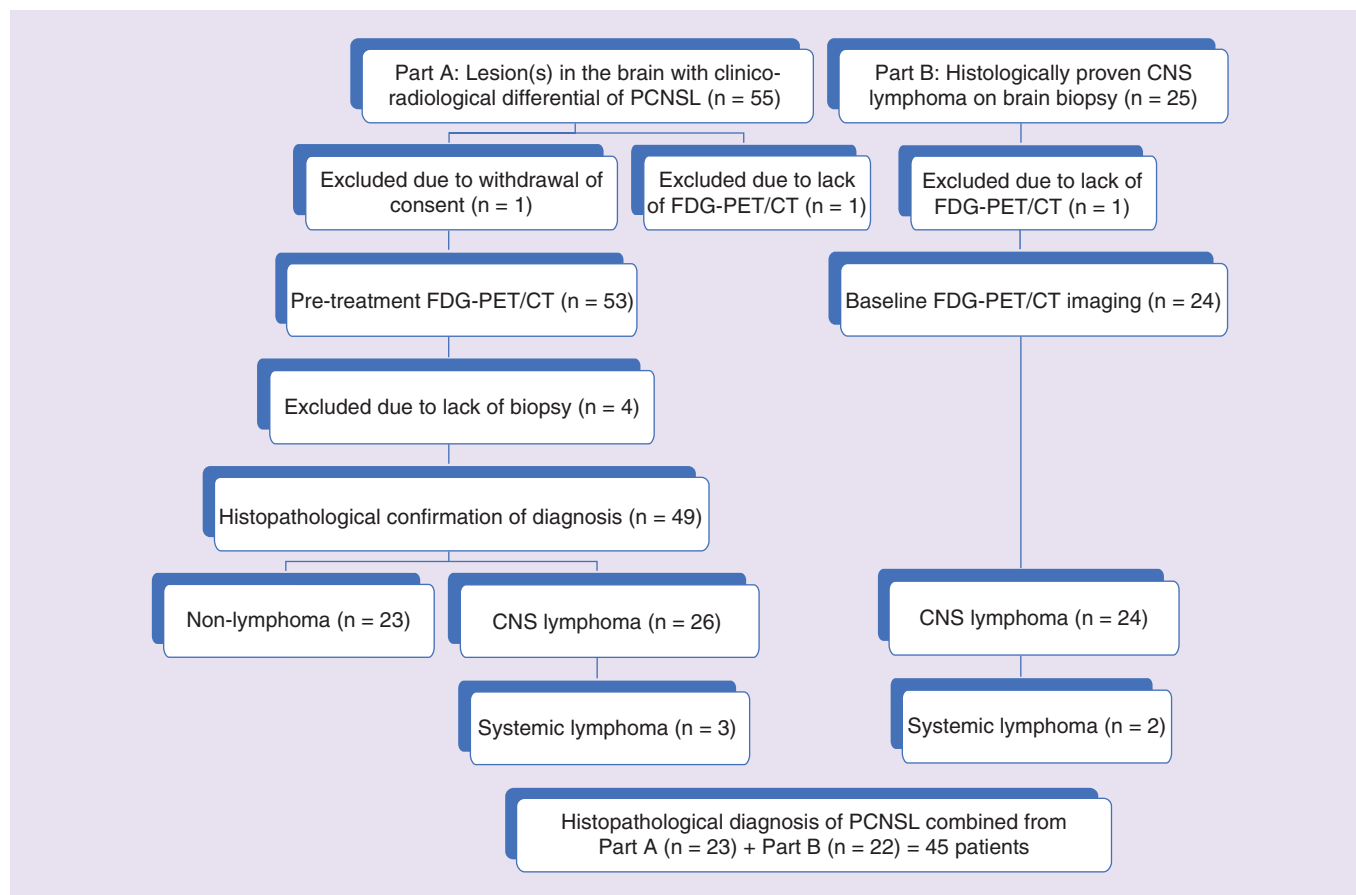
### Study procedures

#### *FDG-PET/CT imaging*

After 6 h of fasting and confirming normal plasma glucose levels (<150 mg/dl), 5 MBq/kg bodyweight of the radiotracer (18F-FDG) was injected intravenously. Static whole-body images (scan volume extending from skull vertex till mid-thigh) were obtained 45–60 min postinjection of the radioisotope on dedicated PET/CT scanners (Discovery ST, GE Healthcare, IL, USA and Astonish TF, Philips Healthcare, Guildford, UK). PET images were acquired on a time-of-flight system using approximately eight bed positions (60–90 s per bed position) and 50% overlap for the emission study. PET images were reconstructed iteratively using the row action maximal likelihood algorithm. The corresponding CT with nonionic intravenous contrast was acquired at 120 kV and set to auto mA as tube current for the CT. Attenuation correction of time-of-flight acquired data was done using postacquisition correction algorithms. Dead time correction and decay correction was also applied as appropriate. Two commonly used relative measures of FDG-PET/CT imaging, in other words, maximum standardized uptake value (SUV<sub>max</sub>) and tumor/normal tissue (T/N) ratio were calculated using standardized and validated methodology. Region of interest (ROI) was placed on the tumor using image slices corresponding to maximum tracer uptake. SUV<sub>max</sub> was expressed as a ratio of the maximum tissue radioactivity concentration 'c' of FDG in the selected ROI at time point 't' (MBq/kg) and decay corrected amount of injected FDG (MBq) divided by bodyweight (kg). T/N ratio also referred to as the uptake ratio was computed by dividing the SUV<sub>max</sub> in an ROI by the SUV<sub>max</sub> in a mirror image ROI placed manually in the contralateral hemisphere within normal uninvolved brain tissue. High-dose methotrexate-based chemotherapy with or without radiotherapy was offered to all fit patients with PCNSL as per the standard institutional protocol. Patients deemed unfit or ineligible for methotrexate were treated with alternative chemotherapy regimens or palliative radiotherapy based on physician discretion.

### Statistical considerations

SUV<sub>max</sub> and T/N ratios were calculated for all patients as described. Mean and median SUV<sub>max</sub> and T/N ratio of patients with histopathologically proven CNS lymphoma was compared with the mean and median SUV<sub>max</sub> and mean T/N ratio of other histologic diagnoses (nonlymphomas) using the Mann–Whitney U test. Any p-value



**Figure 1. Schematic workflow of patients through the study.**

CNS: Central nervous system; FDG-PET/CT: Fluoro-deoxy-glucose positron emission tomography/computed tomography; PCNSL: Primary central nervous system lymphoma.

less than or equal to 0.05 was considered as statistically significant. Receiver operating characteristics (ROC) curves were generated to identify the optimal cut-offs of SUVmax and T/N ratios for reliably discriminating PCNSL from other histological diagnoses. Metrics of diagnostic accuracy such as sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) with corresponding 95% confidence intervals (CI) were also calculated for the ROC defined cut-offs. Overall diagnostic accuracy was defined as the area under the curve of the ROC curves and was presented as a point estimate with corresponding 95% CI. The incidence of systemic lymphoma (with 95% CI) was calculated based on cytological or histological confirmation of extraneuraxial disease.

## Results

### Patient flow & characteristics

Patient flow on the FDG-PET/CT imaging study conducted between 2014 and 2017 is described in Figure 1. A total of 55 patients consented and were accrued in Part A of the study as suspected PCNSL based on MRI after discussion in the multidisciplinary neuro-oncology joint clinic. Of them, 53 (96%) patients underwent whole body FDG-PET/CT; however, diagnosis was confirmed histologically and/or cytologically in 49 (93%) of 53 patients. Four of 53 (7%) patients could not undergo histological/cytological confirmation of disease, one died waiting for biopsy while the other three were treated a clinico-radiological presumptive diagnosis of PCNSL. However, given the lack of histopathological diagnosis, they were excluded from the final analysis of diagnostic utility. All pretreatment FDG-PET/CT scans were reviewed independently and interpreted qualitatively by a senior imaging specialist, who reported the 'likely' diagnosis on FDG-PET/CT blinded to the final pathological diagnosis. Performance of baseline FDG-PET/CT using standardized metrics of diagnostic test accuracy with histology/cytology as reference standard has been reported in detail previously [13]. Twenty six of 49 (53%) patients were proven to have DLBCL type of

**Table 1. Clinical characteristics of the study cohort (n = 80).**

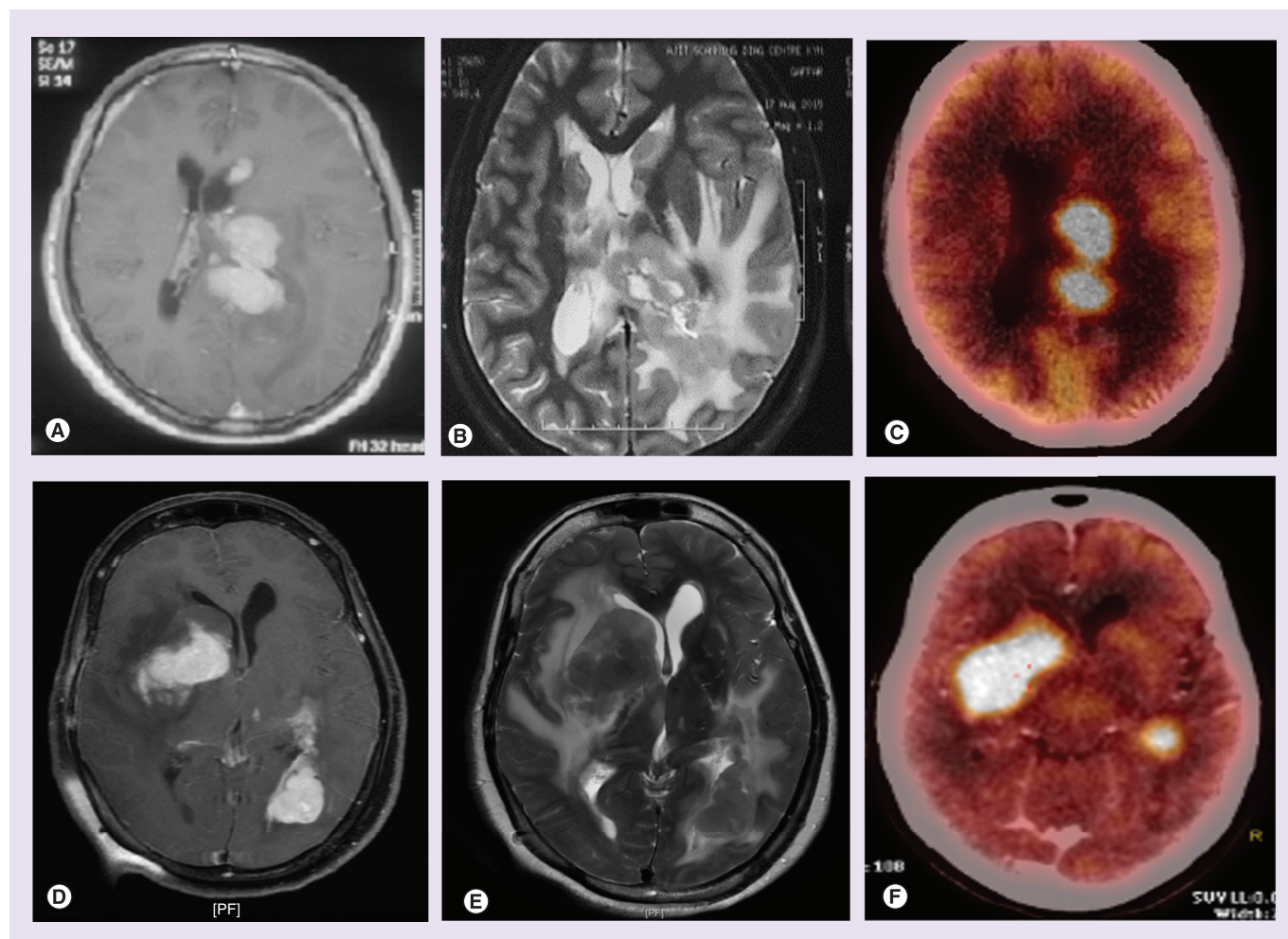
Characteristics	n (%)
<b>Age distribution (in years)</b>	
– Median	54 y
– Range	18–77 y
<b>Sex distribution</b>	
– Males	46 (57.5%)
– Females	34 (42.5%)
<b>Eastern Co-operative Group performance status</b>	
– Performance status: 0–1	60 (75%)
– Performance status: 2–3	20 (25%)
<b>Focality of disease</b>	
– Unifocal disease	40 (50%)
– Multifocal disease	40 (50%)
<b>Histologically/cytologically confirmed diagnosis (n = 70<sup>†</sup>)</b>	
– Lymphoma (includes five systemic lymphoma)	50 (68.5%)
– Glioblastoma	12 (16.5%)
– Astrocytoma	05 (06.9%)
– Brain metastases	02 (02.7%)
– Granulomatous inflammation	02 (02.7%)
– Nonspecific inflammation	02 (02.7%)

<sup>†</sup> Seven patients were excluded from analyses due to various reasons (see study workflow).

CNS lymphoma, including three patients with systemic involvement outside the neuraxis, which was subsequently confirmed pathologically. The remaining 23 (47%) patients had histologic diagnoses other than lymphoma such as high-grade glioma (n = 17), infectious/inflammatory pathology (n = 4) and brain metastases (n = 2). All 26 patients with histological/cytological diagnosis DLBCL from Part A were also consented and included in Part B of the study. In addition, 25 patients referred after a histopathological diagnosis of DLBCL type of CNS lymphoma on brain/vitreous biopsy were consented directly on Part B of the study for undergoing pretreatment FDG-PET/CT. One (4%) of these 25 patients worsened and died within 2 weeks of surgery prior to the baseline FDG-PET/CT and was excluded from analysis. Of the total of 50 patients (26 from Part A and 24 patients directly in Part B) with proven CNS lymphoma, 45 (90%) patients were diagnosed on brain biopsy, four (8%) on CSF cytology/flow-cytometry and one (2%) on vitreous biopsy. Two (8%) of 24 patients in Part B had undergone complete resection of their solitary brain lesion that was confirmed as lymphoma on histopathology. Consequently, no FDG-avid lesion could be demonstrated on the postresection baseline FDG-PET/CT scan. In three (12%) of 24 patients from Part B (biopsy-proven lymphoma), either the primary lesion in the brain could not be localized on the FDG-PET/CT (n = 2) or did not show any FDG-uptake (n = 1) precluding the calculation of semiquantitative FDG-PET/CT parameters. Two of them did not have identifiable brain lesion(s) on FDG-PET/CT; they were diagnosed as PCNSL on CSF flow-cytometry and vitreous aspirate respectively. The third patient had multiple, nonenhancing, signal changes in bilateral periventricular region which were iso-to-hyperintense on T2 and fluid attenuation inversion recovery images; however, differentially higher FDG-uptake compared with normal brain parenchyma was not demonstrated. Consequently, these five (10%) patients had to be excluded from the total 50 patients, leaving 45 patients of CNS lymphoma for inclusion in the final analysis of diagnostic utility. However, these five were included in the analysis for systemic staging. Patient characteristics of the study cohort are briefly described in Table 1.

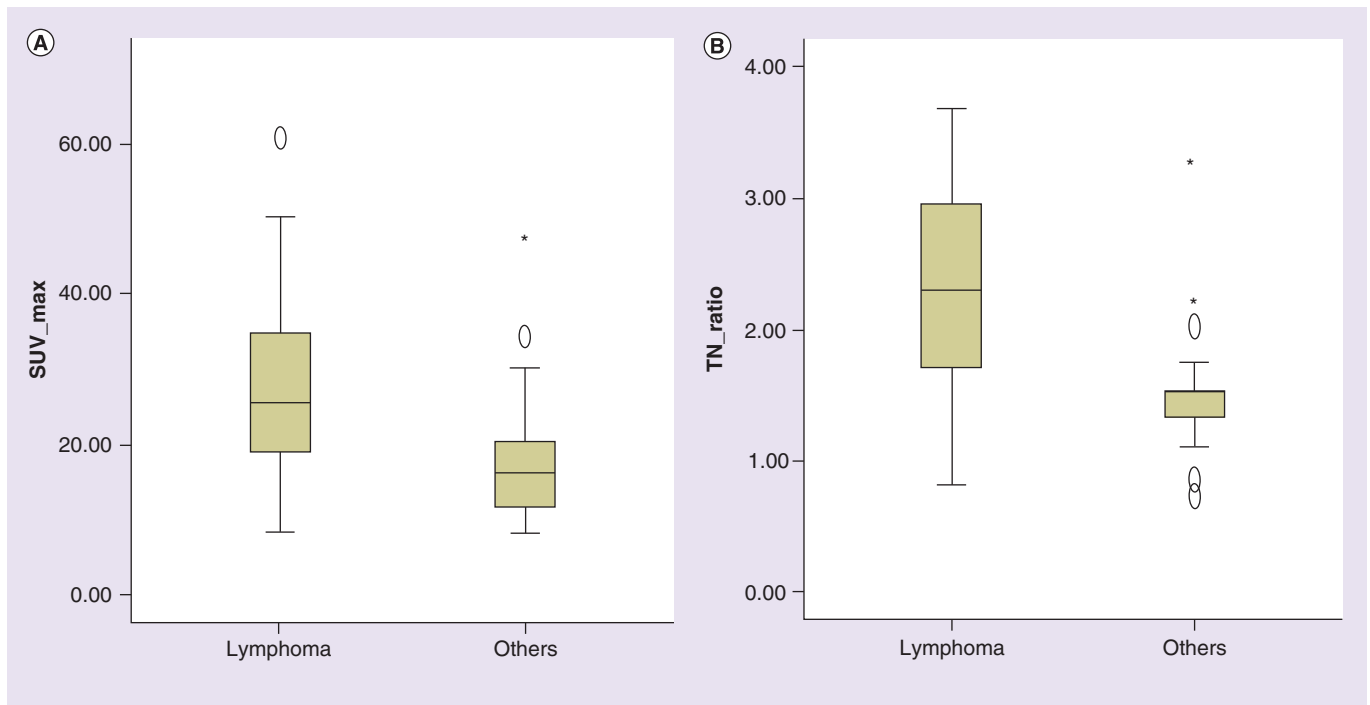
### Diagnostic accuracy

There was significantly higher FDG-uptake in CNS lymphomas (n = 45) compared with other histologic diagnoses (n = 23) as illustrated in two representative cases from the study cohort (Figure 2). Box plots comparing SUVmax and T/N ratio of CNS lymphomas versus nonlymphomas are depicted in Figure 3. The mean ( $\pm$  standard deviation) SUVmax of CNS lymphomas was significantly higher at 27.5 ( $\pm$  12.53) compared with 18.2 ( $\pm$  9.75) for nonlymphomas (p = 0.001). Similarly, the mean T/N ratio of CNS lymphomas was significantly higher than other histologic diagnoses (2.34  $\pm$  0.72 vs 1.53  $\pm$  0.55; p < 0.001). ROC curves for defining optimal cut-offs of SUVmax and T/N ratio for reliably differentiating CNS lymphomas from nonlymphomas are presented in Figure 4. The optimal cut-off of SUVmax for diagnosing CNS lymphoma was 18.8 with a sensitivity, specificity, PPV and NPV of 75% (95% CI: 53–81%), 76% (95% CI: 52–90%), 85% (95% CI: 74–92%) and 52% (95%



**Figure 2. Representative case examples from the study cohort.** Cranial MRI in the upper panel shows multiple, solid, periventricular lesions enhancing intensely on axial T1-weighted postcontrast image (A) and hypo-intense on axial T2-weighted image (B) with perifocal edema. Axial fused FDG-PET/CT image (C) shows significantly increased FDG-uptake with a maximum standardized uptake value (SUVmax) of 27 favoring lymphoma. Biopsy confirmed the diagnosis of PCNSL. MRI in the lower panel shows similar morphologic features on conventional neuroimaging in the form of multiple ill-defined lesions in the parietal lobe enhancing inhomogeneously on axial T1-weighted postcontrast image (D) and iso-intense on axial T2-weighted image (E) with perifocal edema. In contrast to PCNSL, axial fused FDG-PET/CT image (F) shows only moderately increased FDG-uptake in the lesions with SUVmax of 12 suggestive of nonlymphomatous pathology. Diagnosis was confirmed as glioblastoma on surgical decompression. FDG: Flouro-deoxy-glucose; FDG-PET/CT: Flouro-deoxy-glucose positron emission tomography/computed tomography; MRI: Magnetic resonance imaging; PCNSL: Primary CNS lymphoma.

CI: 42–63%), respectively. Similarly, the optimal cut-off of T/N ratio was 1.66 with a sensitivity, specificity, PPV and NPV of 84% (95% CI: 68–92%), 81% (95% CI: 60–95%), 90% (95% CI: 79–96%) and 69% (95% CI: 54–81%), respectively. The sensitivity of FDG-PET/CT in diagnosing a CNS lymphoma increased to >90% at an SUVmax cut-off of 13.3 and T/N ratio cut-off of 1.49; however, this was at the cost of reduced specificity (just above 50% for both). Conversely, a SUVmax cut-off value of 24.7 and a T/N ratio cut-off value of 2.03 substantially increased the specificity of FDG-PET/CT (>90%) for the diagnosis of CNS lymphoma, albeit at the cost of lower sensitivity (53 and 66% for SUVmax and T/N ratio, respectively). Area under the curve of ROC-defined cut-off values of SUVmax (18.8) and T/N ratio (1.66) provided an overall accuracy of 75% (95% CI: 65–90%) and 83% (95% CI: 72–94%), respectively.



**Figure 3. Box-plots of quantitative flouro-deoxy-glucose positron emission tomography/computed tomography parameters.** Boxplots comparing SUVmax (A) and T/N ratio (B) between central nervous system lymphoma and nonlymphomatous histology. Note significantly higher SUVmax and T/N ratio in lymphoma.

SUVmax: Maximum standardized uptake value; T/N: Tumor/normal tissue.

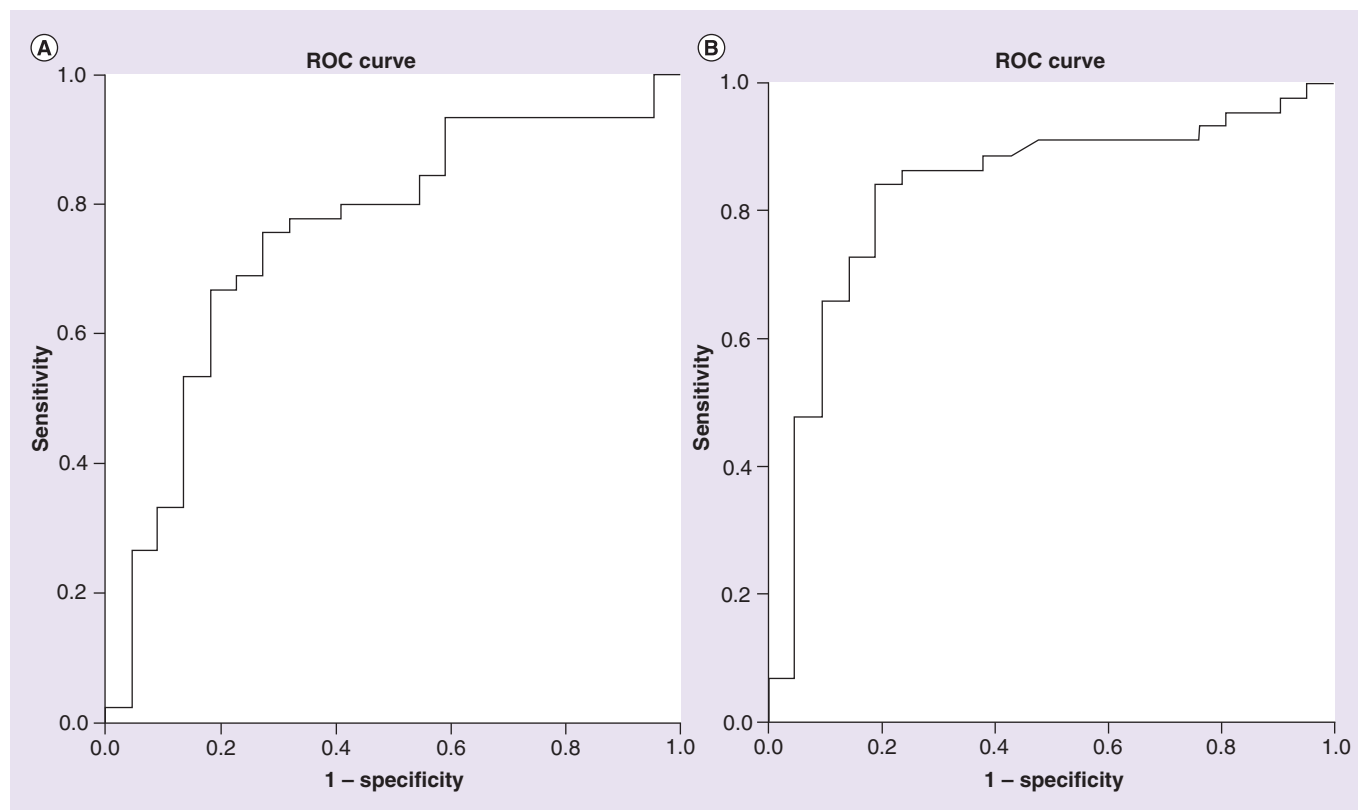
### Systemic staging

Five of the 50 patients with proven DLBCL type of CNS lymphomas had nonphysiologically increased FDG-avidity at extraneuraxial sites, which were subsequently confirmed as sites of involvement by lymphoma on fine needle aspiration cytology/biopsy. The sites of extraneuraxial uptake in these five patients included bone, abdominal nodes, paratesticular mass, adrenal glands and soft tissue deposits in muscles and subcutaneous tissues. The overall incidence of detecting systemic lymphoma in patients who presented with disease apparently confined to the CNS was 10% (95% CI: 3.3–21.8%).

### Discussion

This study assessed the clinical utility of baseline whole-body FDG-PET/CT in the diagnosis and staging of patients with suspected and/or proven PCNSL. It clearly demonstrates significantly higher FDG-uptake in CNS lymphomas compared with its common mimics on conventional neuroimaging (glioblastoma, metastases and inflammatory/infectious lesions). The specificity of FDG-PET/CT increases significantly (>90%) with increasing SUVmax and T/N ratio, although at the cost of decreased sensitivity. Thus, any lesion in the brain with a SUVmax of >25 and T/N ratio >2 is highly likely to be a CNS lymphoma. Conversely, the sensitivity of SUVmax and T/N ratio of 13.3 and 1.49 respectively is >90%, suggesting that any lesion with lesser values is highly unlikely to be lymphomatous in origin. Although histopathology remains the gold-standard for the diagnosis of PCNSL, whole-body FDG-PET/CT provides valuable complementary information that can influence decision-making, particularly in the setting of deep-seated lesions not amenable to a safe biopsy. Yamaguchi *et al.* [14] proposed the use of very high FDG-uptake combined with substantial regression in tumor size after one week of corticosteroid administration for diagnosing PCNSL in deep-seated brain lesions without histologic confirmation.

The results of this study are generally in accordance with previously published literature on FDG-avidity in PCNSL. Researchers from Duke University (NC, USA) [15] were the first to report increased FDG-uptake in a series of ten patients with PCNSL, which was significantly higher than lower grade gliomas, but not different from anaplastic astrocytoma. Unfortunately, this was largely based on visual and qualitative interpretation without any quantification. Selected studies that include greater than five patients reporting semiquantitative FDG-PET/CT



**Figure 4.** Receiver operating characteristics curves of quantitative fluoro-deoxy-glucose positron emission tomography/computed tomography parameters. ROC curves of SUVmax (A) and T/N ratio (B) in the diagnosis of central nervous system lymphoma. Note that the upper left corner of the respective curves provides the most optimal cut-off of SUVmax and T/N ratio for diagnosing lymphoma. ROC: Receiver operating characteristic; SUVmax: Maximum standardized uptake value; T/N: Tumor/normal tissue.

parameters in PCNSL are summarized chronologically in Table 2 [16–31]. The reported mean/median values, however, have been variable, possibly due to differences in technical performance (image acquisition and quantitation), small number of patients in individual studies and interobserver variability. Most studies reported good utility of FDG-PET/CT in differentiating PCNSL from high-grade gliomas and brain metastases with some even providing ROC-defined cut-offs for the semiquantitative PET parameters with clinically acceptable diagnostic accuracy. However, other studies reported substantial overlap of SUVmax and T/N ratios between PCNSL and other non-lymphomatous CNS lesions, thereby questioning the incremental value of added FDG-PET/CT in the diagnostic evaluation of suspected PCNSL. In a systematic review and meta-analysis of eight retrospective studies involving a total of 129 patients, Zou *et al.* [32] reported good diagnostic performance of FDG-PET and FDG-PET/CT for diagnosing PCNSL with an overall pooled sensitivity of 0.88 (95% CI: 0.80–0.94), specificity of 0.86 (95% CI: 0.73–0.94), positive likelihood ratio of 3.99 (95% CI: 2.31–6.90), negative likelihood ratio of 0.11 (95% CI: 0.04–0.32) and diagnostic odds ratio of 33.40 (95% CI: 10.40–107.3). Area under the summary ROC curve and Q-index (point on summary ROC curve where sensitivity equals specificity), measures of comprehensive diagnostic effect were acceptably high at 0.9192 and 0.8525, respectively. Apart from the anatomic and functional imaging, modern technological advances including proteochemical, immunophenotypic and molecular genetic analyses of CSF can also provide high diagnostic accuracy in PCNSL [33].

The need for systemic staging in patients with biopsy-proven brain lymphoma has always been debated [5–7]. The current International Primary CNS Lymphoma Collaborative Group guidelines [8] recommend baseline CT scan of the thorax, abdomen and pelvis along with testicular ultrasonography (in males) for systemic staging keeping whole-body FDG-PET/CT as an optional investigation. However, it is being increasingly appreciated and acknowledged that, apart from its diagnostic utility, whole-body FDG-PET/CT can easily identify site(s) of extraneuraxial uptake indicating presence of systemic lymphoma with CNS involvement rather than PCNSL. In a large retrospective study [34] involving 262 patients with newly diagnosed lymphomatous brain lesions, 24 (11.8%)



**Table 2. Selected studies reporting maximum standardized uptake value and tumor/normal tissue ratio of flouro-deoxy-glucose positron emission tomography in primary central nervous system lymphoma.**

Author [Ref.]	Number of PCNSL patients	Mean ( $\pm$ SD) of SUVmax	Mean ( $\pm$ SD) of T/N ratio	[Ref.]
Karantanis <i>et al.</i>	13	13.0 (range 5.3–28.4)	2.45 (range 1.22–3.91)	[16]
Kosaka <i>et al.</i>	07	22.1 ( $\pm$ 5.0)	2.31 ( $\pm$ 0.7)	[17]
Kawai <i>et al.</i>	17	13.5 ( $\pm$ 5.4)	2.54 (SD not reported)	[18]
Kawase <i>et al.</i>	13	13.9 ( $\pm$ 5.7)	2.74 ( $\pm$ 1.25)	[19]
Makino <i>et al.</i>	14	16.8 ( $\pm$ 7.2)	Not reported	[20]
Das <i>et al.</i>	20	15.7 ( $\pm$ 0)	Not reported	[21]
Ghesquieres <i>et al.</i>	24	13.9 ( $\pm$ 9.3)	Not reported	[22]
Okada <i>et al.</i>	07	20.4 ( $\pm$ 8.9)	Not reported	[23]
Yamaguchi <i>et al.</i>	19	22.6 ( $\pm$ 12.6)	2.79 ( $\pm$ 0.91)	[24]
Mercadal <i>et al.</i>	14	17.0 (range 6–39)	Not reported	[25]
Wang <i>et al.</i>	15	26.2 ( $\pm$ 10.5)	8.3 ( $\pm$ 4.0)	[26]
Purandare <i>et al.</i>	25	†20.3 (range 8.1–46.3)	†3.5 (range 2.6–4.9)	[27]
de-Bonilla-Damia <i>et al.</i>	18	17.6 (range 9–31)	3.55 (range 2.1–7.5)	[28]
Okuyucu <i>et al.</i>	14	15.3 ( $\pm$ 7.2)	Not reported	[29]
Albano <i>et al.</i>	38	15.6 ( $\pm$ 9.2)	3.1 ( $\pm$ 1.7)	[30]
Zhou <i>et al.</i>	40	17.7 ( $\pm$ 7.4)	2.46 ( $\pm$ 1.04)	[31]
Present study	45	27.5 ( $\pm$ 12.53)	2.34 ( $\pm$ 0.72)	

† Median (not mean) value with range in parentheses.

PCNSL: Primary CNS lymphoma; SD: Standard deviation; SUVmax: Maximum standardized uptake value; T/N ratio: Tumor/normal tissue ratio.

patients were detected to have non-CNS malignancies (19 with systemic lymphoma and five with other secondary malignancies) on systemic staging, highlighting the importance of such evaluation. On the contrary, Suh *et al.* [35] recently reported very low diagnostic yield (2%, six of 304 patients, 95% CI: 0.7–4.3%) of whole-body FDG-PET/CT for initial systemic staging in PCNSL. Somewhat more disturbing was double the number of false-positive findings (4%, 13 of 304 patients, 95% CI: 2.3–7.2%) leading to further unnecessary procedures, re-igniting the debate on the extent of systemic staging. The 10% incidence of systemic lymphoma observed in this study in patients who present with disease apparently confined to the CNS is in accordance with previously published data [7,34]. Though seemingly uncommon, this has major diagnostic, prognostic and therapeutic implications [9,10] that supports the current recommendation of pretreatment systemic staging in patients with PCNSL. Based on the results of this prospective study as well as previously published literature, baseline whole-body FDG-PET/CT should now be strongly considered as a useful imaging modality (adjunctive to cranial MRI) in the diagnostic and staging evaluation patients with PCNSL.

### Strengths & limitations

The strength of the study lies in its prospective design that included consecutive patients with clinicoradiological suspicion of PCNSL on conventional imaging such as MRI (with or without spectroscopy and diffusion-weighted imaging) who underwent pretreatment FDG-PET/CT imaging prior to definitive diagnosis. Such a design considerably reduces the bias inherent to any retrospective analysis. Quantification and calculation of FDG-PET/CT parameters was done using standardized validated methodology by a single observer eliminating potential interobserver bias. Though some patients were treated on a presumptive diagnosis of PCNSL, only patients with histologically/cytologically confirmed disease were included in the final analysis. All CNS lymphoma patients with increased FDG-uptake at extraneuraxial sites also underwent cytological/pathological confirmation to establish the diagnosis of systemic lymphoma. This is the largest study to date that compares quantitative FDG-PET/CT parameters between CNS lymphoma and other brain lesions with similar radiographic appearance. Despite these strengths, some caveats and limitations remain. A significant proportion of patients had undergone baseline MRI scans at outside centers with possibly different acquisition protocols for various sequences and variable magnet strengths that could potentially interfere with interpretation. Perfusion imaging and diffusion-weighted imaging including apparent diffusion coefficient maps were not routinely available on the baseline MRI scans in all patients. It has recently been demonstrated that perfusion and/or diffusion-weighted MRI can differentiate glioblastoma

from PCNSL with high diagnostic accuracy [36–38]. In addition, this study did not use modern radiomic approaches such as support vector machine classifiers [39] based on textural features of postcontrast T1-weighted images that can more reliably differentiate glioblastoma from lymphoma compared with semantic MRI features. It is common knowledge that SUVs can be affected by several factors, including technical performance of the scan [40]. Nearly 10% of patients underwent FDG-PET/CT at outside centers with possible differences in quantitation of imaging parameters compared with the institutional protocol. At last, patients with no significant increase in FDG-avidity in the brain lesions were excluded from the quantitative analysis, potentially introducing bias.

## Conclusion

MRI remains the recommended standard first-line imaging modality in the diagnostic evaluation of patients with intracranial lesions including PCNSL. Although histology remains the gold-standard for diagnosis, whole-body FDG-PET/CT provides valuable complementary information in the evaluation of patients with suspected PCNSL that can be used for presumptive diagnosis to guide therapeutic decision-making, particularly in deep-seated lesions not amenable to safe biopsy coupled with negative CSF cytology and flow-cytometry. In addition, it also identifies clinically occult foci of systemic lymphoma in a small proportion of patients with resultant implications for diagnosis, prognosis and therapy.

## Author contributions

M Gupta and T Gupta are co-first authors contributing equally to the work. T Gupta is the guarantor of integrity of the entire study. The study concepts and design were given by T Gupta. M Gupta, A Janu, A Mahajan and T Gupta contributed in literature research. The clinical studies were done by N Purandare, V Rangarajan, A Puranik, B Bagal and H Menon. The experimental studies/data analysis was done by P Shetty, A Moiyadi, A Sahay and S Epari. Statistical analysis was done by M Gupta, S Kannan and T Gupta. M Gupta and T Gupta were involved in manuscript preparation. Manuscript editing was done by R Krishnatry, GJ Sastri and R Jalali.

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No writing assistance was utilized in the production of this manuscript.

## Ethical conduct of research

All procedures performed in the study (Project No. 145) were in accordance with the ethical standards of the Institutional Ethics Committee (IEC) of Tata Memorial Centre, India that functions in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All the patients provided written informed consent before participation in the study.

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