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**[18F]FDG PET-MRI provides survival biomarkers in primary central nervous system lymphoma in the elderly: an ancillary study from the BLOCAGE trial of the LOC network**

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## ABSTRACT

**Purpose:** Primary central nervous system lymphoma (PCNSL) incidence is rising among elderly patients, presenting challenges due to poor prognosis and treatment-related toxicity risks. This study explores the potential of combining [18F]fluorodeoxyglucose ([18F]FDG) PET scans and multimodal MRI for improving management in elderly patients with de novo PCNSL.

**Methods:** Immunocompetent patients over 60 years with de novo PCNSL were prospectively enrolled in a multicentric study between January 2016 and April 2021. Patients underwent brain [18F]FDG PET-MRI before receiving high-dose methotrexate-based chemotherapy. Relationships between extracted PET (metabolic tumor volume - MTV, sum of MTV for up to five lesions - sumMTV, metabolic imaging lymphoma aggressiveness score - MILAS) and MRI parameters (tumor contrast-enhancement size, cerebral blood volume - CBV, cerebral blood flow - CBF, apparent diffusion coefficient - ADC) and treatment response and outcomes were analyzed.

**Results:** Of 54 newly diagnosed diffuse large B-cell PCNSL patients, 52 had positive PET and MRI with highly [18F]FDG-avid and contrast-enhanced disease (SUV<sub>max</sub>: 27.7 [22.8-36]). High [18F]FDG uptake and metabolic volume were significantly associated with low ADC<sub>mean</sub> values and high CBF at baseline. Among patients, 69% achieved an objective response at the end of induction therapy, while 17 were progressive. Higher cerebellar SUV<sub>mean</sub> and lower sumMTV at diagnosis were significant predictors of complete response: 6.4 [5.7-7.7] vs 5.4 [4.5-6.6] (p=0.04) and 5.5 [2.1-13.3] vs 15.9 [4.2-19.5] (p=0.01), respectively. Two-year overall survival (OS) was 71%, with a median progression-free survival (PFS) of 29.6 months and a median follow-up of 37 months. Larger tumour volumes on PET or enhanced T1-weighted MRI were significant predictors of poorer OS, while a high MILAS score at diagnosis was associated with early death (<1 year).

**Conclusion:** Baseline cerebellar metabolism and sumMTV may predict response to end of chemotherapy in PCNSL. Tumour volume and MILAS at baseline are strong prognostic factors.

**Keywords:** PET/MRI, [18F]FDG, primary central nervous system lymphoma, outcome analysis

Trial : LOCALYZE, NCT02313389, ancillary of phase III clinical trial BLOCAGE01

(Registered July 10, 2018 – retrospectively registered)

<https://clinicaltrials.gov/ct2/show/NCT03582254?term=LOCALYZE&draw=2&rank=1>

## Introduction

Primary central nervous system lymphoma (PCNSL) is a subtype of non-Hodgkin's lymphoma that affects the brain, eyes, and leptomeninges. It is the third-most common malignant primary brain tumor after glioblastoma and diffuse astrocytoma [1]. In recent years, the incidence of PCNSL has increased in immunocompetent patients and has received growing attention, resulting in numerous research efforts and publications [2]. The increase in incidence has been particularly marked in older patients, but despite improved survival rates in younger patients, the prognosis for the elderly remains poor [3,4]. To date, molecular biology and prognostic biomarkers of PCNSL are not well understood. Age and performance status, incorporated in the International Extranodal Lymphoma Study Group and Memorial Sloan-Kettering Cancer Center scores, are the only recognized survival biomarkers' [5,6].

Standard treatment for PCNSL is based on high-dose methotrexate (HD-MTX) induction chemotherapy for patients over 60 years and on a combination of HD-MTX based chemotherapy and high-dose chemotherapy with autologous stem cell transplantation for younger patients [7,8]. Response to first-line therapy is a key predictor of prognosis and survival, making it a reliable surrogate endpoint for assessing response before starting chemotherapy and tailoring treatment to the aggressiveness of the disease [9]. Currently, the size of contrast-enhanced tumor in magnetic resonance imaging (MRI) is the gold standard for assessing response to treatment for PCNSL [10]. Although studies have suggested the prognostic value of markers for tumor cellularity and perfusion, such as apparent diffusion coefficient (ADC) and relative regional cerebral blood volume (rCBV) measured prior to treatment, these results are based on series with a low number of subjects and need further validation [11–13].

[18F]Fluoro-deoxyglucose Positron Emission Tomography ([18F]FDG PET) has been widely used in oncology imaging and its utility has been firmly established in the management of systemic lymphoma [14]. The use of whole-body [18F]FDG PET to rule out systemic disease in PCNSL has been established and plays a crucial role in patient treatment decisions [15]. However, the role of brain PET scans in PCNSL remains less clear. Several brain [18F]FDG PET survival markers have shown potential, but results are inconsistent across studies. For instance, some studies have shown that higher [18F]FDG uptake of brain lesions, whether measured through the sum of the maximum standardized uptake value (SUVmax) or visually represented by a 10-step color scale, has an inverse relationship with progression-free survival (PFS). Other studies have reported shorter survival in patients with larger metabolic tumor volume (MTV) or total lesion glycolysis (TLG) [16–18]. With the advent of new clinical trials on new treatments such as CAR T cell therapies, monoclonal antibody therapy, or Bruton tyrosine kinase inhibitors, timely identification of patients with aggressive disease through PET or MRI would allow clinicians to more promptly direct these patients toward novel treatments instead of traditional chemotherapy regimens.

This study (LOCALYZE, NCT03582254) is part of a phase III randomized controlled trial (BLOCAGE01 NCT02313389) that aimed to evaluate the benefits of maintenance chemotherapy (Rituximab, Methotrexate,

Temozolomide) versus observation, to prolong complete remission (CR) with acceptable toxicity in elderly patients with PCNSL after standard induction chemotherapy. This ancillary study was conducted i) concurrently with the BLOCAGE01 study, ii) during the induction chemotherapy regimen – identical for all patients –, and iii) included a brain [18F]FDG PET-MRI at baseline. Our objectives were: i) to compare the PET and MRI findings at diagnosis in elderly immunocompetent patients with *newly diagnosed* PCNSL; ii) evaluate the predictive value of baseline [18F]FDG PET-MRI on the response at the end of induction therapy in a homogeneously-treated group of patients; iii) evaluate the prognostic value of baseline [18F]FDG PET-MRI on patients' survival.

## Materials and Methods

### 1.1 Clinical Study

Patients included in the BLOCAGE01 study were eligible to this prospective ancillary study (LOCALYZE) and recruited by five centers from the french “Lymphomes Oculo-Cerebraux” Group (LOC) (Neuro-Oncology department in Saint-Louis Hospital, APHP, Paris; Haematology department in Institut Curie, Saint Cloud, Neuro-Oncology and Haematology departments in Pitié-Salpêtrière Hospital; APHP, Paris and Haematology department in Cochin Hospital; AP-HP, Paris) between January 2016 and April 2021. The inclusion criteria included i) newly diagnosed PCNSL, confirmed either by brain histology or cytology in the cerebrospinal fluid (CSF) or vitrectomy ii) age of 60 years or older, iii) Karnofsky Performance Status (KPS) greater than 40; iv) no evidence of systemic non-Hodgkin lymphoma as demonstrated by a contrast-enhanced CT and/or whole-body [18F]FDG PET/CT scan. Exclusion criteria included i) any other active malignancy (with the exception of basal cell carcinoma of the skin and cervical carcinoma in situ), ii) pre-existing immunodeficiency (from HIV or organ transplant treatment), iii) low-grade histology, iv) isolated primary vitreoretinal lymphoma, v) Central Nervous system (CNS) relapse of a systemic lymphoma, and vi) prior treatment for PCNSL. At the start of chemotherapy and registration into LOCALYZE, patients underwent a pretherapeutic evaluation including ophthalmologic examination, lumbar puncture with Interleukine-10 bio-assay, bone marrow analysis, brain MRI, and [18F]FDG PET-CT to rule out systemic involvement.

Patients included in LOCALYZE underwent a baseline [18F]FDG PET-MRI in a median of 3.5 [1-5] days prior to the start of a high-dose Methotrexate-based chemotherapy (HD-MTX-based CT). The chemotherapy regimen consisted of four 28 day-cycles of Rituximab (375 mg/m<sup>2</sup>, D1), Methotrexate (3.5 g/m<sup>2</sup>, D1 and D15), Procarbazine (100 mg/m<sup>2</sup>, D1 to D7), and Vincristine (1.4 mg/m<sup>2</sup>, D1 and D15) (R-MPV) followed by a cycle of Cytarabine (3 g/m<sup>2</sup>, D1, D2).

Therapeutic response was assessed at end of therapy by board-certified neurooncologists and neuroradiologist (CH, KH, DG) using International PCNSL Collaborative Group criteria (IPCG), based on MR imaging, corticosteroid use, and CSF cytology and slit lamp examination in case of CSF or ocular involvement at baseline [19,20]. The ICPG criteria classify treatment response into five categories: complete response (CR), unconfirmed complete response (CRu), partial response (PR), stable disease, and progressive disease (PD). CR requires complete disappearance of all signs of the disease on gadolinium-enhanced MRI as well as on CSF cytology and ocular examination. CRu includes patients who meet CR criteria but continue to require

corticosteroids or show minor abnormalities. PR involves a 50% decrease in the primary brain lesion, while PD involves a 25% increase in the lesion or new disease sites [20]. Only patients who obtained a CR or uCR were subsequently randomized into two groups in the BLOCAGE01 study: maintenance arm with Rituximab, Methotrexate, and Temozolomide or observation arm.

Progression-free survival (PFS) was defined as the time between the diagnosis and the progression of the disease or the death of the patient. Overall survival (OS) was calculated as the time between the diagnosis and the death of the patient whatever the cause. The cut-off date for PFS and OS event was the 26<sup>th</sup> of October 2022.

All participants provided informed consent for their participation in the study. The study was approved by the protection of persons committee (2014-002597-37) and the French National Agency for the Safety of Medicines and Health Products (ANSM), and abided by the principles of the Declaration of Helsinki.

### *1.2 [18F]FDG PET-MRI imaging protocol*

All PET/MR studies were performed with hybrid PET/MRI system (Signa PET/MR 3T General Electric Healthcare) at the Pitié-Salpêtrière Hospital's nuclear medicine department. Brain PET images were acquired 90 minutes after the injection of 2 MBq/kg of [18F]FDG [and lasted for 20 minutes. Patients fasted for at least 4 h and blood glucose was measured before the exam could be performed. PET reconstruction with OSEM-3D included time-of-flight and spatial resolution modeling (6 iterations, 28 subsets, 6.4 mm transaxial post-reconstruction Gaussian filter). Reconstructed voxel size was 1.2x1.2x2.8mm. MRI included 3D susceptibility-weighted imaging (SWAN), 3D Fluid attenuated inversion recovery (FLAIR), T2\* weighted perfusion, diffusion, monovoxel spectroscopy, 3D arterial spin labelling (ASL) sequences and 3D T1 weighted spin-echo sequence before and after injection of 0.2 ml/kg of Gadoterate Dimeglumine (Dotarem®). Four-tissue-class (soft tissue, fat, lung, and air) attenuation correction maps were calculated from the 2-point Dixon sequences, supplemented by a single atlas to capture bone information. Each patient underwent an interim PET-MRI (after 2 cycles of induction therapy) and a final PET-MRI (at end of therapy), in addition to the baseline PET-MRI performed at diagnosis. The results presented in this article focus on the significance of the baseline PET-MRI.

### *1.3 [18F]FDG PET-MRI images analysis*

Images were analyzed by two board-certified nuclear medicine specialists, who were blinded to patients' follow-up, using the General Electric Healthcare Advantage Workstation (L.R., A.K.). For patients with multiple lesions on baseline PET-MRI, the target lesion was defined as the lesion with the highest SUV<sub>max</sub>. Quantified parameters extracted from PET included [18F]FDG-uptake (SUV<sub>mean</sub>, SUV<sub>peak</sub> and SUV<sub>max</sub>) in the lesions as well as in normal contralateral brain (using a mirror region-of interest [ROI]) to calculate tumor-to-background ratio (TBR), and normal cerebellum (using a spherical volume-of-interest [VOI] of 1.5 cm<sup>3</sup> positioned on cerebellar hemisphere unaffected by diaschisis or tumor infiltration) to calculate metabolic imaging lymphoma aggressiveness score (MILAS), respectively [18]. The MILAS score, as described by Kasenda et al., is a custom-made 10-step scale that reflects the uptake of [18F]FDG in comparison to the cerebellum, which is designated as grade 1. Any [18F]FDG uptake below that of the cerebellum is coded as grade 0 (black), while uptakes exceeding cerebellar levels are represented in eight distinct gradations based on intensity, which range from grades 2 to 9. In this study, we employed this numerical grading scale from 0 to 9 as a replacement for the original color representation.

Metabolic volume of the target lesion was established using a 41% SUVmax threshold and TLG calculated by multiplying the MTV and SUVmean of the lesion. The sum of SUVmax (sumSUVmax) and the sum of MTV (sumMTV) using up to five target lesions were calculated as a measure of patient tumor burden [17].

For MRI analysis, the 3D tumor was delineated using a semi-automated volume on the T1-weighted enhanced sequence. Apparent diffusion coefficient (ADC), relative cerebral blood volume (rCBV), and cerebral blood flow (CBF) maps were generated with Syngo® Software (Siemens Healthineers) for diffusion and perfusion sequence analysis<sup>14,15</sup>. A 50 mm<sup>2</sup> ROI was manually drawn on the most significant area of the tumor, avoiding the cystic, necrotic, and hemorrhagic components. A contralateral ROI within the normal-appearing white matter was used for standardization (relative ADC –rADC- and relative –rCBF-). The size of the FLAIR hypersignal was calculated using the sum of the cranio-caudal, antero-posterior, and transversal axes.

#### *1.4 Statistical analysis*

Continuous variables are expressed as medians [Q1-Q3] and categorical variables as percentages. Comparisons of patients were undertaken according to their response status group at the end of therapy. “Responders” include patients with complete IPCG response (CR), unconfirmed complete response (CRu), and partial response (PR) in opposition to “Non-responders” (i.e. patients in progression at end of therapy). Patients with missing primary endpoint were excluded from analysis, reasons of missing primary endpoint were described. Continuous variables were compared between groups using non-parametric Wilcoxon rank sum test. Categorical variables were compared with the Fisher’s exact test. For the exploration of correlations between PET and MRI parameters non parametric Spearman correlation coefficients were reported. OS function was estimated using Kaplan-Meier method and median OS with 95% confidence interval were provided. Associations between clinical factors and PET parameters with OS was assessed through univariate and multivariate Cox proportional hazard models. Hazard ratios (HR) are presented with 95% confidence intervals (95% CI). Log-linearity was explored for continuous variables. Schoenfeld residuals plots were used to check assumption of proportional hazards. In case of non-respect, a time-varying effect variable was introduced; thus it was reported on distinct time intervals in order to fulfill the hypothesis overall. Final multivariate model was established using a backward selection based on likelihood ratio test, where clinical pertinent covariates (sex, age, KPS) were imposed in the model. All tests were two-sided and used a significance level of 0.05. Analyses were computed using R software version 4.1.1 (<https://cran.r-project.org/>).

## **Results**

### *2.1 Clinical study*

In our study, out of the total 65 participants, 59 patients underwent a baseline PET-MRI, carried out 90 ± 4 minutes post-injection of 140 (125-250) MBq of [18F]FDG. The blood glucose level was uniformly recorded at 1.1±0.3 g/L for all these patients. IPCG or clinical response were missing for 5 patients (1 refusal and 4 premature death unrelated to tumor progression within one month of diagnosis), thus 54 patients were analyzed. The flowchart of the study is presented in Figure 1, and the baseline characteristics of the patient cohort are summarized in Table 1. The median age of the patients was 71.5 years (66-77y), and the median KPS was 70 (range: 50-100). Of the 43 patients who underwent ophthalmological examination, 3 (7%) were diagnosed with

lymphomatous ocular involvement, and 12 out of 41 (28%) with a lumbar puncture had CSF involvement. Diagnostic confirmation was obtained from brain biopsy / surgery in 50 patients and from CSF analysis in 4 patients, with a diagnosis of diffuse large B-cell lymphoma in all cases. Baseline CSF IL-10 assay results were available for 42 out of 54 patients, with a median value of 17.5 pg/mL (range: 0-1731 pg/mL; lower limit of sensitivity: 2.5 pg/mL). Of the 54 patients, 38 received corticosteroids (median dose of hydrocortisone: 240mg daily) at the time of PET-MR imaging.

Twenty-six percent of the patients (14/54) did not complete induction chemotherapy due to methotrexate-related renal toxicity (n=5) or progression (n=9). Response to treatment was assessed by MRI at the end of induction therapy using the IPCG criteria : 69% of patients (n=37) were found to have an MRI objective response, including 35 CR, one CRu, and one PR. These patients were considered the responder group, while the non-responder group consisted of 17 (31%) patients with disease progression on MRI or as established by clinical assessment.

At end of therapy, 61% of patients (n=33/54) were randomized in the BLOCAGE trial, with 15 in the maintenance arm and 18 in the follow-up arm.

## *2.2 PET-MRI PCNSL Features at diagnosis*

PCNSL displayed contrast enhancement in 96% of cases on MRI with 26 (48%) having unifocal lesions and 28 (52%) patients having multifocal disease, with up to 13 solid non-confluent lesions. 44 patients (85%) had a homogeneously enhancing lesion, two (4%) had a ring-shaped lesion and six (11%) had heterogeneous enhancement. The majority of the lesions were located in supra-tentorial areas (69%), but eleven patients (20%) had tumors infiltrating both supra- and infra-tentorial regions. Most of the lesions were found in deep brain structures, including the thalamus (n=7), striatum (n=13), corpus callosum (n=15), and brainstem (n=10). Lesions showed high diffusion restriction, with median ADC<sub>mean</sub> and rADC<sub>mean</sub> values of 679 mm<sup>2</sup>/sec [594-775] and 0.89 [0.76-1], respectively. Spectroscopy analysis revealed a high Choline/Creatine ratio of 1.7 [1.4-2.2] (Figure 2). Perfusion was low on dynamic susceptibility contrast (DSC) sequence with median rCBV<sub>max</sub> values of 1.57 [1-2.37]. Hyperperfusion was detectable in 41 patients on the CBF parametric map of the ASL sequence.

Fifty-two of the 54 analyzed patients had PET-positive lesions at the time of diagnosis, with the remaining two having a residual sub-centimetric lesion not detected following surgical biopsy. At baseline, MRI scans detected more lesions than [18F]FDG PET in 44% of cases, primarily due to the confluent aspect of multiple lesions on the PET scans. However, no lesions were missed in a patient-based analysis, apart from the two patients with partial exeresis. PCNSL were found to be highly avid for [18F]FDG, with median values for SUV<sub>max</sub> and TBR<sub>max</sub> (ratio of SUV<sub>max</sub> of the lesion on SUV<sub>mean</sub> of the contralateral healthy parenchyma) 27.7 [22.8-36] and 5.3 [3.8-7.9], respectively. Of the three patients with ocular involvement, none was detectable on PET. Baseline PET and MRI parameters are detailed in Table 2.

Tumor cellularity, indicated by low ADC<sub>mean</sub> values, was inversely correlated with [18F]FDG uptake ( $\rho = -0.59$  for the ratio of tumor SUV<sub>peak</sub> to contralateral normal brain SUV<sub>max</sub>) and volume ( $\rho = -0.54$  for MTV and  $-0.53$  for sumMTV). In contrast, perfusion as assessed by CBF on ASL was positively correlated with [18F]FDG



uptake ( $\rho = 0.61$  for the ratio of tumor SUV<sub>peak</sub> to contralateral normal brain SUV<sub>max</sub>). The correlations between these parameters are presented in Figure 3. Interestingly, our results show that the dose of corticosteroid therapy at the time of the baseline [18F]FDG PET did not exhibit a linear correlation with [18F]FDG avidity or MRI parameters in our study cohort. The coefficients for the relationships between corticoid therapy dose and these parameters were  $\rho = 0.26$  for SUV<sub>max</sub>,  $\rho = 0.01$  for MTV,  $\rho = -0.02$  for ADC<sub>mean</sub>, and  $\rho = 0.15$  for contrast-enhancement volume of the target lesion.

### *2.3 Association of baseline [18F]FDG PET-MRI parameters with treatment outcome*

Results showed that both high SUV<sub>mean</sub> of the normal cerebellum and low sumMTV were associated with being in the good-responder group (6.4 [5.7-7.5] vs 5.4 [4.6-6.5],  $p=0.04$  and 5 [1.8-10.8] vs 17.1[5.3-19.9],  $p=0.01$ , respectively). The study also found a trend of a lower rADC<sub>mean</sub> being related to the non-responder group, but statistical significance was not reached. Details can be found in Table 2 and Figure 4.

### *2.4 Association of baseline [18F]FDG PET-MRI parameters with survival*

Median PFS was 29.6 months (95%CI [9.9;NA]) with a median follow-up of 37 months (95%CI [33.3;47.4]). 19 parameters extracted from MRI and PET tested were tested in univariate analyses. Tumor burden measured by sumMTV on PET and volume of the contrast-enhancement of the target lesion on MRI were significantly associated with poorer PFS (Table 3). A lower rADC<sub>mean</sub> was also significantly associated with poorer PFS. Once adjusted on clinical factors (gender, age and KPS), sumMTV on PET, volume contrast enhancement of the target lesion on PET and low rADC<sub>mean</sub> on MRI remain independent significant prognostic factors of poorer PFS (Table 4). In contrast, our study did not demonstrate a significant association between perfusion parameters (DSC or ASL) and disease prognosis. SUV<sub>mean</sub> cerebellum seemed to be a time-varying effect covariate with lower SUV<sub>mean</sub> cerebellum associated with poorer PFS in late progressions in multivariate analysis.

The OS at six months was 76% [67;89.6], 73% [62;86.3] at one year, and 71% [59.1;84.5] at 2 years. In univariate analyses, biomarkers of poorer OS were high sumMTV (HR=1.66, 95%CI 1.27-2.17 ( $p<0.001$ )) and high volume of the enhanced target lesion (HR=1.52, 95%CI 1.24-1.87 ( $p<0.001$ )) (Supplemental Table 1). MILAS score was found to be a time-varying effect covariate with higher score associated to poorer immediate survival (< 1 year): 2.16 [1.11;4.19],  $p=0.02$ . The sumMTV and MILAS remained independent PET prognostic factors for OS in multivariate analysis including the clinical variables (gender, age, KPS), with a C-index of 0.84 [0.76-0.92]. Enhanced target lesion volume was found to be an independent MRI prognostic factor for OS in multivariate analysis including the clinical variables (gender, age, KPS), with a C-index of 0.77 [0.65-0.90] (Supplemental Table 2).

In this study, clinical variables such as age, gender, and KPS were not found to have a significant impact on OS in univariate analysis, but age (and gender in PET model) became significant predictors of OS in final multivariate models.

## **Discussion**

This prospective study assessed the value of simultaneous [18F]FDG PET-MRI to provide prognostic biomarkers for PCNSL in immunocompetent elderly patients homogeneously treated with an HD-MTX-based CT regimen at first-line. Currently, age and KPS are the only well-established clinical markers, but they are not

sufficient in guiding the management of PCNSL in elderly patients, which has a poor prognosis [23]. The use of hybrid PET-MR system in this study provided the opportunity to compare multimodality data with optimal temporal synchronization and spatial co-registration between both modalities [24]. We found that larger tumor volume on PET-MRI and lower [18F]FDG uptake in the normal cerebellum were associated with nonresponse to HD-MTX-based CT. Additionally, the study confirmed the impact of MILAS on OS once adjusted on clinical factor. Association between high sum MTV and poorer prognostic (both PFS and OS) was also confirmed in our study, the largest cohort published so far.

In our cohort, PCNSL presented as homogeneously enhanced lesions, with the majority involving the supratentorial brain parenchyma, a pattern in line with previous reports of immunocompetent patients [25–27]. We also reported low diffusivity, a hallmark of PCNSL due to its hypercellularity [28,29]. This study also conformed the high avidity of PCNSL for [18F]FDG in immunocompetent patients, with lesions metabolism five times higher than that of the healthy tissue. This is slightly higher than that reported in previous literature [10]. The high sensitivity of the PET-MRI system equipped new generation silicon photomultiplier detectors, the quantification of delayed PET images acquired between 90 and 110 min post-injection (to increase tumor contrast) and different methods for quantifying the ratios between studies (using either SUVmean or SUVmax as for uptake reference) may explained these differences with previous published data and limit direct comparison with prior studies [30]. Rapid regression of primary brain lymphomas under corticosteroid therapy has been reported in a number of cases on MRI [31]. For [18F]FDG PET, studies on corticosteroid's impact have been conducted on small sample sizes with contradictory results and interestingly, our study showed no impact of corticosteroids on PET measurements.

We found an inverse correlation between tumor [18F]FDG uptake and volume on baseline PET and the ADC value on MRI. Previous studies have described the high cellularity of PCNSL on diffusion-weighted imaging but only Zhou et al. previously reported an inverse correlation between ADC and uptake intensity in a cohort of 28 patients [31–33]. In our study, we also observed a positive correlation between cerebral blood flow measured using ASL perfusion and [18F]FDG PET uptake, which to our knowledge, has not been reported in the literature. PCNSL typically lacks neoangiogenesis, as reflected by moderately increased relative cerebral blood volume (rCBV) values in T2\* dynamic susceptibility contrast perfusion studies [34]. Our study found a low rCBVmax ratio ( $2.6 \pm 3.9$ ), in the range of values previously reported in the literature [31]. However, ASL is a perfusion technique that allows absolute quantification of CBF without the use of contrast media and which may provide additional diagnostic value in brain tumors [35].

Our results showed that a lower cerebellar metabolism, as measured by SUVmean, was associated with nonresponse to induction HD-MTX-based CT, poorer PFS and poorer OS. Hanaoka et al. previously demonstrated that [18F]FDG is diverted from the brain to the tumor tissue in systemic lymphoma and showed that SUVmax of the cerebral cortex and the cerebellum were significantly different between the lymphoma and control subjects and correlated with tumor volume [36]. To evaluate the possible competition between the tumor and normal brain FDG uptake, we analyzed the correlation of cerebellum SUVmean with PET volume, intensity, and tumor location, but no significant relationships was found despite a lack of power may not be excluded. Furthermore, the SUVmax of the normal contralateral brain region was found to not significantly differentiate

between non responders and responders. In systemic lymphoma, the mean SUV of the cerebellum has been shown to correlate with tumor burden, making it a useful indicator for tumor burden measurement. To further explore the relationship between healthy tissue metabolism and survival, univariate models incorporating healthy areas such as cerebellar SUV<sub>mean</sub> or normal liver SUV<sub>mean</sub> have been studied, with findings indicating that these parameters correlate with survival [37,38].

In our study of patients with CNS lymphoma, we also found that higher volume on PET or enhanced T1-weighted MRI sequence was a second independent biomarker of poor response to induction therapy and poor survival. Although tumor burden is well established as a prognostic factor in systemic lymphomas, data in the CNS setting is limited [39–42]. Our findings align with previous research by Albano et al., who reported in a study of 52 patients that patients with larger MTV had shorter PFS and OS [16].

Various studies have investigated the association between tumor [18F]FDG avidity and response to treatment or survival in lymphoma, with some studies reporting a positive association and others reporting that only TLG provides prognostic information [17,18,43–45]. In our cohort of 54 patients, the SUV<sub>max</sub> failed to predict response to end of therapy. However, the MILAS score emerged as a prognostic biomarker of OS. This score is a simple visual assessment system that uses the cerebellar [18F]FDG uptake as a reference to semi-quantitatively evaluate the relative metabolism of the tumor compared to the reference region [18]. However, it should be noted that the MILAS score is based on a cerebellar uptake ratio and therefore may reflect the dominant role of normal cerebellar uptake on survival prognosis

With regards to the utilization of multimodal MRI, our study revealed that ADC<sub>mean</sub> was the only parameter which correlated with overall survival, with a lower ADC<sub>mean</sub> being linked to a higher risk of death. This result aligns with previous studies on primary central nervous system lymphoma (PCNSL) [9,12,13,46]. Barajas found an inverse relationship between ADC values and tumor cell density, which was determined to be a significant factor in determining the outcome [13]. In contrast, our study showed that perfusion parameters derived from DSC or ASL did not emerge as prognostic biomarkers, unlike previous findings, using dynamic-contrast-enhanced perfusion, that indicated a lower baseline volume transfer constant ( $K^{trans}$ ) was associated with a poorer prognosis [9,11,12]. Valles et al. hypothesized that a low tumor rCBV in PCNSL may reflect a lack of tumor angiogenesis and a reduction in the number of vessels capable of delivering intravenous methotrexate to the tumor, which could account for the worse prognosis in these patients [12]. Further research is required to confirm the prognostic role of perfusion and its kinetic evolution under treatment.

Our study is limited by its relatively small sample size of patients. Nevertheless, this is the largest prospective study investigating the role of PET imaging in PCNSL so far. It benefited from a prospective design and the utilization of a new hybrid PET-MRI system, which facilitated precise registration of both modalities. Of note, we have included two patients who had undergone partial excisions at baseline, which could have potentially influenced the outcome analysis. However, it's important to note that surgery is typically not recommended for patients with PCNSL and its impact on the prognosis remains uncertain. Our analysis yielded no significant conclusions when these two patients were excluded. Another potential limitation of the study is that patients

received different treatment regimens after induction chemotherapy, but the first 5 months of therapy was consistent for all participants and our primary endpoint was the response at the end of therapy. Furthermore, identification of prognostic factors will always be contaminated by subsequent lines of treatments. The data analysis for the BLOCAGE 01 clinical trial is scheduled to be conducted in 2024, providing further insights into the study's findings. Interestingly, the KPS did not emerge as a prognostic factor in our cohort. This outcome might be attributed to our study's inclusion criteria, which incorporated only patients with a KPS greater than 40%. Comparable findings have been previously documented in cohorts comprising patients with relatively good performance status [17]. Several other non-invasive baseline biomarkers have shown potential impact on outcome prediction, such as IL-10 or circulating tumor DNA, and future studies should further investigate potential combined biomarkers (biological and imaging) to enhance the accuracy of patient stratification [47,48].

### **Conclusion**

Our study is one of the largest to investigate imaging biomarkers in patients with PCNSL and the first to benefit from a PET-MRI scan at baseline. Our findings highlight the significance of tumor volume and cerebellum uptake as key indicators of treatment response. Furthermore, our results show that baseline tumor volume and MILAS score have an impact on overall survival. Further studies are needed to evaluate the potential role of [18F]FDG PET-MRI in therapeutic assessment.

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### **Competing Interests**

The authors have no relevant financial or non-financial interests to disclose.

### **Author Contributions**

Professors Kas and Galanaud, as well as Drs. Houilier, Rozenblum, V. Causse Lemercier, and M. Soret, contributed to the study's conception and design. Dr. Rozenblum and Prof. Galanaud performed the MRI images data collection, while P. Naggara, Dr. Rozenblum, and Prof. Kas performed the PET images data collection. Drs. Soussain, Ursu, Willems and Houillier, as well as Prof. Choquet and Hoang-Xuan, recruited the patients. A. Baptiste and L. Belin, in collaboration with Dr. Rozenblum, performed the statistical analysis. All authors reviewed and approved the final version of the manuscript.

### **Ethics approval**

The study was approved by the protection of persons committee (2014-002597-37) and the French National Agency for the Safety of Medicines and Health Products (ANSM), and abided by the principles of the Declaration of Helsinki.

## Consent to participate

Informed consent was obtained from all individual participants included in the study.

## Consent to publish

The authors affirm that human research participants provided informed consent for publication of the images in Figure 2.

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