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ABSTRACT

Purpose :

The purpose of our study was to assess the predictive and prognostic role of 2-18F-fluoro-2-deoxy-D-glucose (FDG) PET/MRI during high-dose methotrexate-based chemotherapy (HD-MBC) in de novo primary central nervous system lymphoma (PCNSL) patients aged 60 and above.

Methods:

This prospective multicentric ancillary study included 65 immunocompetents patients who received induction HD-MBC as part of the BLOCAGE01 phase III trial. FDG-PET/MRI were acquired at baseline, post two cycles (PET/MRI2), and post-treatment (PET/MRI3). FDG-PET response was dichotomized, with "positive" indicating persistent tumor uptake higher than the contralateral mirroring brain region. Performances of FDG-PET and International PCNSL Collaborative Group criteria in predicting induction response, progression-free survival (PFS), and overall survival (OS) were compared.

Results:

Of 48 PET2 scans performed, nine were positive and aligned with a partial response (PR) on MRI2. Among these, eight (89%) progressed by the end of the induction phase. In contrast, 35/39 (90%) of PET2-negative patients achieved complete response (CR). Among the 18 discordant responses at interim (PET_{CR}/MRI_{PR}), 83% ultimately achieved CR. 87% of the PET2-negative patients were disease-free at 6 months versus 11% of the PET2-positive patients ($p<0.001$). The MRI2 response did not significantly differentiate patients based on their PFS, regardless of whether they were in CR or PR. Both PET2 and MRI2 independently predicted OS in multivariate analysis, with PET2 showing stronger association.

Conclusion:

Our study highlights the potential of interim FDG-PET for early management of PCNSL patients. Response-driven treatment based on PET2 may guide future clinical trials.

Keywords : PET/MRI, FDG, Primary central nervous system lymphoma, Early assessment, prognosis

Trial : LOCALYZE, NCT03582254, ancillary of phase III clinical trial BLOCAGE01, NCT02313389

(Registered July 10, 2018 – retrospectively registered)

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

Keypoints :

1. FDG-PET provides early, reliable differentiation of PCNSL patient responses.
2. Interim FDG-PET robustly stratifies one-year PFS, outperforming MRI in cases of partial responses.
3. FDG-PET response's predictive power suggests a pivotal role in future clinical trials.

Importance of the Study

Management of primary central nervous system lymphomas (PCNSL) in the elderly is a critical challenge in neuro-oncology. Current tools for early risk stratification are insufficiently accurate, leading to suboptimal treatment strategies. This study highlights the potential of interim FDG-PET to differentiate between PCNSL patients with good and poor treatment responses. Interim FDG-PET may outperform interim morphological MRI in case of partial response, providing a more effective prediction of progression-free survival and response at the end of induction therapy.

In our study, the predictive ability of interim FDG-PET imaging was also confirmed by multivariate analysis. These results reinforce the role of FDG-PET in PCNSL management and may serve as a foundation for future FDG-PET-guided clinical trials. The integration of FDG-PET imaging into routine practice holds promise for refining risk-adapted treatment strategies and improving outcomes in PCNSL.

Introduction

Primary Central Nervous System Lymphoma (PCNSL) is a rare form of non-Hodgkin lymphoma that is confined to the brain, eyes, and cerebrospinal fluid, without any systemic spread (*1*). The treatment for PCNSL is based on high-dose methotrexate-based chemotherapy (HD-MBC) for elderly patients, and HD-MBC associated or not with stem cell auto-transplantation as consolidation for younger and fit patients (*2*–*7*). Prognosis of PCNSL is highly variable, in particular in the elderly and clinical markers such as age or performance status are insufficient to predict risks of chemoresistance or relapse after chemotherapy (*8*). The International Primary CNS Lymphoma Collaborative Group (IPCG) currently recommends the use of criteria based mainly on brain magnetic resonance imaging (MRI) for response assessment (*9*).

Tabouret *et al*. have described a correlation between objective response on T1 contrast-enhanced MRI at the end of treatment and overall survival (OS) (10). However, several studies have reported early detection of recurrence in patients who were in complete response (CR) on end of treatment MRI, thereby questioning its efficacy in assessing residual disease (11,12). Van der Meulen *et al*., in a randomized controlled trial involving 199 PCNSL patients, found no significant differences in progression-free survival (PFS) or OS between patients with CR or partial response (PR) on MRI at the end of first-line therapy (13). Hence, although MRI is a valuable tool in PCNSL assessment, there is a need for improved assessment methods, in particular for interim evaluation.

Positron Emission Tomography (PET) has been validated as a reliable tool for the early evaluation of therapeutic responses, in 18F-Fluoro-deoxyglucose (FDG)-avid systemic lymphomas (*14*,*15*). Several methods have been developed for assessing therapeutic responses in FDG-avid systemic lymphomas, such

as the Deauville score (a visual score based on comparing glucose uptake to the liver and mediastinum) and the ΔSUVmax approach (percentage change in the SUVmax of the target lesion between baseline and interim FDG-PET staging) (*16*). Unfavorable results in systemic lymphoma are defined as uptake visually superior to the liver for the Deauville score and as a ≤66% relative SUVmax reduction for the ΔSUVmax approach (*17*).

As we have previously demonstrated, PCNSL tumor exhibit high FDG avidity at baseline with a ratio to unaffected cortex ranging from 3 to 5 (*18*,*19*). Few studies have explored FDG-PET for therapeutic assessment in newly-diagnosed PCNSL (*20–27*). These studies were mostly retrospective, with different time points and discordant conclusions. Birsen *et al.,* in a cohort of 25 patients, found that a negative interim FDG-PET, performed after two therapy cycles was associated with longer PFS. Conversely, Jo *et al*. found no effect with interim FDG-PET (performed after four therapy cycles) but identified prognostic value of the FDG-PET at the end of first-line therapy in a group of 66 patients (*22*,*24*). Considering potential toxicities and an unfavorable risk-benefit ratio with consolidation treatment, robust FDG-PET criteria for risk-tailored adapted treatment holds promise.

The LOCALYZE study (NCT03582254) is an ancillary investigation to the phase III randomized controlled trial BLOCAGE01 (NCT02313389). BLOCAGE01 aims to assess maintenance chemotherapy benefits versus observation in elderly newly diagnosed PCNSL patients, extending CR duration with acceptable toxicity after HD-MBC induction chemotherapy. LOCALYZE, conducted concurrently with BLOCAGE01 during induction chemotherapy, involves baseline, interim, and end of therapy brain FDG-PET/MRI. Our objectives were two-fold : i) to ascertain the predictive value of the interim FDG-PET/MRI (PET/MRI2) on the response to first-line treatment, and ii) to evaluate the prognostic implications of PET/MRI2 on PFS and OS.

Materials and Methods

1.1 Study design

Immunocompetent patients over 60 years old with newly diagnosed PCNSL included in the phase III clinical trial BLOCAGE01 and eligible to this ancillary prospectively multicentric study (LOCALYZE NCT02313389) were included between January 2016 and April 2021. Patients were recruited by five centers from the French "Lymphomes Oculo-Cerebraux" (LOC) network: 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. Main inclusion criteria consisted of: i) newly diagnosed PCNSL, ii) confirmed either by brain histology or cytology in the cerebrospinal fluid (CSF) or vitrectomy; iii) age of 60 years or older; iv) Karnofsky Performance Status (KPS) greater than 40; v) no evidence of systemic non-Hodgkin lymphoma as demonstrated by a contrast-enhanced CT and/or whole-body FDG-PET/CT scan. Main 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) CNS relapse of a systemic lymphoma, and vi) prior treatment for PCNSL. Patients included in LOCALYZE underwent a baseline FDG-PET/MRI within 21 days prior to the start of a HD-MBC, an interim FDG-PET/MRI after two cycles, and an end of therapy FDG-PET/MRI after completion of the chemotherapy. The chemotherapy regimen consisted of four 28 day-cycles of Rituximab

(375 mg/m^2, D1), Methotrexate (3.5 g/m^2, D1 and D15), Procarbazine (100 mg/m^2, D1 to D7), and Vincristine (1.4 mg/m^2, D1 and D15) followed by a cycle of Cytarabine (3 g/m^2, D1, D2) (R-MPVA).

Therapeutic efficacy was assessed at the end of the treatment regimen by board-certified experts in neuro-oncology and neuroradiology using the IPCG framework. This diagnostic scheme incorporates parameters such as gadolinium-enhanced MRI findings, corticosteroid use, CSF cytology and ocular assessment. Outcomes are categorized into Complete Response (CR), Unconfirmed Complete Response (CRu), Partial Response (PR), Stable Disease, and Progressive Disease (PD). CR necessitates the unequivocal absence of disease markers across all tests, while CRu pertains to cases meeting CR criteria yet continuing corticosteroid treatment or presenting with minor anomalies. PR entails a 50% reduction in the primary cerebral lesion, and PD is characterized by a 25% enlargement in lesion size or the appearance of novel disease sites.

Within the scope of the BLOCAGE01 trial, those attaining CR or CRu statuses were subsequently randomized into two distinct arms. One arm underwent a seven-month maintenance treatment involving Rituximab, Methotrexate, and Temozolomide, while the other was subjected to observational management. Clinical prognostic indices such as gender, age, and KPS were recorded.

The PFS was defined as the time from the end of the second cycle of chemotherapy to progression, relapse, or death from any cause. The OS was defined as the time from the end of the second cycle

of chemotherapy to death from any cause. The cut-off date for PFS and OS event was the 26th of October 2022.

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

1.2 FDG-PET/MRI protocol

The imaging studies for this study were conducted at the nuclear medicine department of the Pitié-Salpêtrière Hospital using a hybrid 3T PET/MRI system (Signa PET/MR General Electric Healthcare). Static FDG-PET images were acquired 90 minutes post-injection of 2 MBq/kg (125-250 MBq) of FDG over 20 minutes. Patients fasted for at least 4 hours and blood glucose was measured before the exam could be performed. 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®) (Supplemental Figure 1).

1.3 FDG-PET/MRI analysis

MRI assessments were conducted independently from FDG-PET findings and interpreted by a board-certified neuroradiologist (DG) in accordance with IPCG criteria. Using the General Electric Healthcare Advantage Workstation (ADW) software, we generated maps for Apparent Diffusion Coefficient (ADC), Cerebral Blood Volume (CBV), and Cerebral Blood Flow (CBF) (*28*,*29*). The pre-processing of perfusion data included automatic arterial input function generation, deconvolution, and leakage correction. We also

performed quantitative measurements on multiparametric MRI images through a region-of-interest (ROI) analysis. For both diffusion and perfusion metrics, a 50 mm^2 ROI was manually outlined on the most conspicuous tumor area, intentionally excluding any cystic, necrotic, or hemorrhagic components, as previously reported in the literature (*28–30*). A contralateral ROI within normal-appearing white matter served as a standardization reference for calculating relatives ADC (rADC), CBV (rCBV) and CBF (rCBF). Percentage changes between baseline and interim examinations were computed for ADC, and CBF based on the ASL sequence, denoted as $\Delta ADC_{1\text{-}2}$, and $\Delta CBF_{1\text{-}2}$, respectively.

FDG-PET scans underwent both visual and semi-quantitative analyses using the ADW software. For the former, independent evaluations were carried out by two board-certified nuclear medicine specialists (L.R., A.K.) using a dichotomous rating scale. A FDG-PET scan was classified as positive if it exhibited pathologic tracer uptake in the brain that exceeded the intensity observed in the corresponding mirroring unaffected contralateral cortex, whether white or grey matter based on the specific location. Conversely, a FDG-PET scan was categorized as negative if it showed no evidence of pathologic uptake.

In the semi-quantitative analysis, the target lesion was identified as the one displaying the highest maximum standard uptake value (SUVmax). We recorded the percentage changes (Δ)

in SUVmax, SUVmean, and SUVpeak for this lesion between the baseline and subsequent interim examinations, denoted as $\Delta SUVmax_{1\text{-}2}$, $\Delta SUVmean_{1\text{-}2}$, $\Delta SUVpeak_{1\text{-}2}$.

Concurrently, assessments were made in the contralateral brain hemisphere that was uninvolved, using a mirror ROI to calculate the tumor-to-background ratio. Specifically, the SUVmax in the tumor was compared to both the SUVmax and the SUVmean in the contralateral cortex, generating TBRmax and TBRmean, respectively.

Measurements in an unaffected region of the cerebellar hemisphere were also taken to compute the tumor-to-cerebellum ratio: specifically, the SUVmax of the lesion was compared divided by to the SUVmean of the cerebellum. The metabolic volume for the target lesion was determined using a threshold of 41% of the SUVmax, both at baseline and in subsequent FDG-PET scans, in accordance with the EANM procedure guidelines for tumor imaging for 18F-FDG avid and homogeneous tumors, independently of the MRI evaluation (*31*). Percentage volume change was documented as (ΔMTV1-2).

We used the same target lesion on the enhanced MRI sequence to assess changes in the volume of the enhancing target lesion, denoted as ΔVol.1-2.

In follow-up assessments, patients were grouped into two categories: "Good responders" and "Poor responders". For MRI, the Good responders group included CR and CRu while the Poor responders group included the patients with SD, PR or progression. For PET, Good responders group had negative scans, indicating complete normalization of any prior pathological uptake. Poor responders had positive FDG-PET scans, indicating either partial response, stable disease, or progression. A partial response was marked by reduced lesion metabolism, yet with residual activity exceeding that of the contralateral mirror cortex. Stable disease showed no change in the target lesion, while progression was defined by new foci, extension, or increased lesion metabolism. It should be emphasized that treatment decisions were exclusively guided by the IPCG criteria upon completion of the induction therapy, and were not affected by interim or final FDG-PET assessment findings.

1.4 Statistical analysis

Continuous variables are expressed as medians [Q1-Q3] and categorical variables as percentages. PFS and OS functions were estimated using Kaplan-Meier method and median PFS with 95% confidence interval (95% CI) were provided. Associations between clinical factors and FDG-PET parameters with PFS or OS was assessed through univariate and multivariate Cox proportional hazard models. Hazard ratios (HR) are presented with 95% CI. Log-linearity was explored for continuous variables. Schoenfeld residuals plots were used to check assumption of proportional hazards. 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. For age and KPS, cut-offs were defined based on clinical knowledge. For all other continuous predictors, log-linearity was explored, and in the case of non-respect of this assumption, variables were dichotomized at the median value (observed on the dataset). Sensitivity, specificity, PPV and NPV of interim FDG-PET and MRI were calculated considering response group at the end of treatment as gold standard of response (where CR or CRu were defined as negative). Corresponding 95 CI% were estimated using bootstrap on 5000 iterations. A Mc Nemar paired test was used to compare specificities of interim PET and MRI on patients who were evaluated for both exams. All tests were two-tailed and used a significance level of 0.05. In order to take into account the large number of comparisons explored across the analysis, Benjamin-Hochberg method was used to correct p values testing the prognostic effect of parameter variation between examinations 1 and 2. Analyses were computed using R software version 4.1.1 (https://cran.r-project.org/).

Results

1. *Patients characteristics*

A total of 65 patients were included in the LOCALYZE study, of which 59 underwent baseline FDG-PET/MRI (PET/MRI1). Clinical assessments based on IPCG criteria were unavailable for five patients: one declined further evaluation, and four died due to causes unrelated to tumor progression within a month following diagnosis. Therefore, the analysis was conducted on a total of 54 patients. The median age was 71.5 years (range 60-85) and the median KPS 70% (range 50-100%). All observed lesions were identified as diffuse large B-cell lymphoma (Table 1). FDG-PET was positive for 52 out of 54 patients at baseline (FDG-PET1) with a median SUVmax of 27.7 [22.8-36] and a median TBRmax of 5.3 [3.8-7.9]. Two patients exhibited a negative FDG-PET1, which was attributed to prior surgical biopsies that left sub-centimetric partial residues, smaller than the resolution capacity of the PET camera. T1-weighted sequence after contrast showed high contrast enhancement for all lesions. Baseline characteristics of FDG-PET/MRI and demographic data comparing response groups have been described and can be found in our previous work (*18*).

Out of 54 patients, 48 (89%) had a FDG-PET/MRI2 after the second chemotherapy cycle (median 28 days, IQR [23-29]). Two patients withdrew, and four discontinued treatment before the second R-MPVA cycle (three due to toxicities, one to progressive disease). Of the total cohort, 43 patients (80%) had the final FDG-PET/MRI (PET/MRI3) after the last chemotherapy cycle (median 28 days, IQR [23-34]). Five patients were excluded due to disease progression before completing the final R-MPVA cycle. See Figure 1 and Supplemental Figure 2 for the study flow chart and visual FDG-PET/MRI assessment results.

Following completion of induction chemotherapy, 33/54 (61%) of the patients were randomized in the phase III BLOCAGE01 trial. Among them, 18 patients (55%) were assigned to the observation arm, while 15 patients (45%) were assigned to the maintenance arm.

Among the 48 patients with a FDG-PET/MRI interim evaluation, 34 were in CR/CRu, one in PR, and 12 had progressive disease at the end of induction therapy (Time 3) according to IPCG criteria. None of the patients had stable disease. Of the 48 patients, one was excluded from the interim MRI evaluation due to the lack of contrast-enhanced imaging, resulting in 47 patients being analyzed at this stage.

2. *Results of the interim FDG-PET/MRI based on visual assessment*

Concordant Poor responder patients

Nine out of 47 patients (19%) were in PR on FDG-PET2 with concordant PR on MRI2. Eight of these patients (89%) experienced disease progression between T2 and T3, and one achieved a complete response.

Concordant Good Responders patients

38 of 47 patients (81%) were FDG-PET2 negative, including 20 patients with a concordant CR on MRI2. Among them, 18 (90%) maintained a CR on the final FDG-PET/MRI assessment (PET/MRI3), while 2 (10%) experienced treatment failure between T2 and T3.

Discordant Responders patients on PET and MRI

Among the 38 FDG-PET2 negative patients, 18 showed a discordant PR on MRI2. Of these, the majority (15/18, 83%) achieved a CR at the end of induction MRI (MRI3). Two patients (11%) had a progressive disease at T3, and one patient (6%) remained in a discordant $PET3_{CR}/MRI3_{PR}$ state but achieved a complete response after a 47-month follow-up.

It's worth noting that the patient with an available FDG-PET but an unanalyzable MRI achieved CR on his FDG-PET2 scan and maintained this CR status through a 29-month follow-up.

The sensitivity of a positive interim exam for predicting end-of-therapy response was higher for FDG-PET2 compared to MRI2: 97% (95% CI [90-100]) versus 55% (95% CI [37-72]) ($p < 0.001$). The positive predictive values were close for both exams (85% (95% CI [72-95]) for MRI2 and 90% (95% CI [75-100]) for FDG-PET2), but the negative predictive value was higher for FDG-PET2 over MRI2: 89% (95% CI [61-100]) versus 44% (95% CI [26-63]) ($p < 0.001$) (Supplemental Table 1). There was only one false-positive patient reported on FDG-PET2 (Poor responder), but the FDG uptake for this patient was minimal, with a TBRmax of 1.06. This value is significantly below the median of positive FDG-PET2, which stands at 3.0 [2.4-6.7] (Supplemental Table 2).

3. *Prognostic value of interim FDG-PET/MRI based on visual assessment*

The median follow-up from T2 was 34 months (CI95% [26.7;44.4]), the median PFS was 31.6 months (95% CI [15; NA]). Twelve progressions were observed between T2 and T3 and ten additional progressions were noted in the concordant $PET3_{CR}/MRI_{CR}$ group after the completion of induction therapy, with a median time to progression of 11 months. Throughout the follow-up period, a total of 20 patients died, with lymphoma progression accounting for 14 cases, toxicity for 1 case, and other comorbidities for the remaining cases.

87% (CI: 77-98%) of the PET2-negative patients were disease-free at 6 months versus 11% (CI: 2-70%) of the PET2-positive patients (Logrank $p<0.001$). The PFS of patients with CR on MRI2 did not significantly

differ from patients with PR on MRI2. Notably, the PFS of patients with discordant responses at T2 (PET2CR/MRI2PR) was similar to that of patients with concordant CR (Supplemental Figure 3). The predictive value of FDG-PET2 remained significant independently of patient demographics, including sex, age, and KPS. Multivariate analysis further confirmed that CR on FDG-PET2 served as an independent predictor of improved PFS, with a HR of 10.36 (95% CI [3.82, 28.07], p<0.001) (Table 2). Of note, steroid therapy was not included in the multivariate model, as we previously demonstrated that this therapy had no statistically significant impact on 18F-FDG avidity at baseline (18).

Regarding OS prediction, both FDG-PET2 and MRI2 responses were significantly associated with patient outcomes, in univariate and multivariate analyses. However, associations with OS was higher with FDG-PET compared to MRI : HR was 87.76 [10.37,742.56], p<0.001 for FDG-PET2 and 11.40 [1.46,88.81], p=0.003 for MRI2 (Supplemental Table 3 and Supplemental Figure 4).

4. Quantitative analysis of FDG-PET/MRI

The change in SUVmax value between the first and second assessments ($\Delta SUVmax_{1\text{-}2}$) was significantly higher in the Good responders group compared to the Poor responders group: -76.1% ([IQR] -61.6% to -82%) versus -36.4% (IQR -7.2% to -74%), p=0.021. The change in contrast-enhanced volume ($\Delta Vol._{1\text{-}2}$) was also significantly higher in the Good responders group compared to the Poor responders group (p=0.0001), although both groups demonstrated a high level of decrease in enhanced lesion: -96.18% (IQR -82.62% to -100%) in the Poor responders group versus -100% in the Good responders group. No significant difference was observed in the decrease of contrast-enhanced volume between the concordant FDG-$PET2_{PR}$/$MRI2_{PR}$ and the discordant FDG-$PET2_{CR}$/$MRI2_{PR}$ groups: -77% (IQR -60% to -96%) versus -84% (IQR -79% to -95%), respectively (p=0.54). The analyses of visual and semi-quantitative parameters from PET-positive examinations across the three time points are presented in Supplemental table 2.

The MTV variation of the target lesion between T1 and T2 ($\Delta MTV_{1\text{-}2}$) was the only FDG-PET/MRI parameter significantly correlated with treatment failure and OS (Supplemental table 4). No significant changes were observed in diffusion or perfusion MRI parameters that could serve as prognostic indicators of outcome (Table 3).

Discussion

Despite advances in managing older patients, the prognosis for elderly PCNSL patients remains poor. The standard of care includes HD-MBC with or without consolidation treatment like maintenance chemotherapy or autologous stem cell transplantation for fit patients (4,5). However, this approach is debated due to its high risk of toxicities. Established prognostic factors like age or functional status are insufficient to guide physicians in predetermining which patients would benefit from consolidation treatment.

The clinical efficacy of MRI, as per IPCG criteria, has shown limitations, particularly in its predictive capacity. It often fails to identify patients at risk of relapse despite showing a CR or PR on T1 contrast-enhanced sequences at interim assessment. It also struggles to predict disease-free status post-induction therapy (*13*). Indeed, the use of T1 contrast-enhanced weighted MRI as a response marker is challenging due to variations in sequence parameters, timing, and contrast dosage (*32–34*). Multimodal parametric MRI, incorporating diffusion and perfusion sequences, has been investigated as a prognostic tool in PCNSL at baseline, but not yet for therapeutic assessment (*35*). In our study, we found no significant correlation between variations in diffusion or perfusion markers and patient outcomes.

This indicates the need for more robust tools in the management of PCNSL patients. Our study emphasizes the potential role of early FDG-PET, conducted after two chemotherapy cycles, in predicting patient's

responses. In newly diagnosed elderly patients with PCNSL, we demonstrated that interim FDG-PET scans were more effective than interim MRI scans in cases of partial response or complete response unconfirmed, and clinical parameters at distinguishing between Good responders and Poor responders. Moreover, interim FDG-PET's prognostic impact on PFS and OS was independent of baseline clinical factors like age, gender, and KPS.

Few studies have examined the role of FDG-PET in PCNSL assessment, often limited by small sample sizes and retrospective designs (*22–27*). Our findings emphasize that interim FDG-PET offers a more timely and reliable assessment compared to MRI in the evaluation of PCNSL patients. Many patients show partial PR on interim MRI even when their early FDG-PET is negative, with the majority ultimately achieving CR by the end of treatment (*25*). For example, Birsen *et al.,* in a 25-patient's cohort, found interim PET scans, following two Rituximab, Methotrexate, and Temozolomide therapy cycles, strongly correlated with end-of-therapy MRI responses (PPV of 66.67% -CI 95%: 33.34–88.89%- and an NPV of 94.74% -CI 95%: 75.61–99.05%-). Jo *et al*., in a 66-patients cohort, determined that end-of-therapy FDG-PET could stratify patients by PFS, but interim results had no significant impact (*22*). The interim FDG-PET in their study was conducted later than in ours and in Birsen's work (after the fourth methotrexate cycle instead of the second). This timing suggests that an early interim FDG-PET might facilitate the detection of distinct "on/off" responses, as observed in studies of Hodgkin's lymphoma (*36*). On the other hand, it could be hypothesized that changes observed through MRI may lag behind the actual tumor response. In our patient cohort, we observed that the persistence of residual disease on interim FDG-PET, as indicated by higher uptake than in the contralateral healthy brain, was correlated with a suboptimal response at the end of therapy and with the overall prognosis. This finding implies that our dichotomous scale might be employed as conveniently as the Deauville score for systemic lymphoma in future clinical trials involving PCNSL.

It is significant to note that in our study, 8/9 patients (89%) exhibited a pattern of local progression. In these cases, the tumor, which had previously been classified as PR or CR at the interim assessment, reemerged at the same location during the end-of-treatment evaluation. While previous studies have mainly described patterns of relapse occurring at distinct sites, they did not specifically look at patients who showed early progression but rather focused on the recurrence following initial line therapy (*10*,*37*,*38*).

Our study's limitations include a relatively small patient sample size, due to the disease's rarity. However, our cohort, with predefined evaluation time-points and uniform induction chemotherapy, is among the largest PET study reported. The study's strengths encompass its prospective design and the use of an innovative hybrid PET/MRI system. This advanced technology facilitates concurrent analysis of underlying pathophysiological mechanisms by allowing for simultaneous study of metabolic uptake, as well as diffusion and perfusion patterns (*39*). A further limitation is the variation in post-induction PET-MRI management strategies, with some patients receiving maintenance therapy and others only monitored. Subgroup analyses are pending until the BLOCAGE-01 trial concludes (primary analysis planned for 2024). Despite these limitations, our study's key finding is that interim FDG-PET imaging could serve as an easy, early, and independent biomarker of PCNSL progression. These findings, however, require further validation in a larger patient cohort.

Other imaging modalities, such as 11C-Methionine and 18F-Fludarabine, are being investigated for their usefulness in managing PCNSL. However, data on their utility remains limited and further studies are required to ascertain their role in this disease (*40–42*). Circulating tumor DNA have also been found to be independent predictors of aggressive lymphomas and may play a role in therapeutic assessment in the future (*43*).

To the best of our knowledge, our study is the first to provide prospective evidence supporting the role of early FDG-PET evaluation in predicting chemotherapy response and outcomes in elderly PCNSL patients. This approach, which can be readily incorporated into clinical practice, holds promise as a key tool in the management of PCNSL. Our findings suggest that close MRI follow-up should be promptly considered for patients with positive interim FDG-PET results. While our study underscores the potential of PET in personalized medicine strategies for PCNSL, further research is needed to fully substantiate its prediction role.

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Conflict of Interest

None declared

Authorship

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.

Data availability

Original data will be made available upon reasonable request by e-mail.

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Figures captions

Figure 1. Flow chart.

Figure 2. Kaplan-Meier survival curves depicting the progression-free survival of PCNSL patients according to FDG-PET and MRI results after 2 cycles of chemotherapy (interim evaluation).

Figure 3. Representative cases

Negative interim PET patient: 79-year-old woman with PCNSL. Contrast-enhanced T1-weighted MRI showed a partial response on interim assessment (ΔVol.1-2 = -81%) but interim FDG-PET showed a complete metabolic response. The end of therapy assessment was normal for both FDG-PET and MRI and the patient was still alive at the end of the follow-up period.

Positive interim PET patient: first column; 70-year-old woman with PCNSL. Contrast-enhanced T1-weighted MRI showed a partial response on interim assessment ($\Delta Vol._{1\text{-}2}$ = -77%) concordant with a partial response on FDG-PET ($\Delta SUVmax_{1\text{-}2}$ = -12%). End of therapy evaluation showed a concordant progression and the patient died of lymphoma three months later. The second column displays the image of a 64-year-old man with a significant reduction in tumor volume on interim MRI (ΔVol.1-2 = -91%), indicating a good partial response. However, his interim PET scan shows positive findings, and the patient experienced disease progression three months after the interim assessment.

Table 1. Patients characteristics

	All patients (n=54)
Sex, n (%)	
Male	21 (38.9%)
Female	33 (61.1%)
Age (years)	
Median [Q1-Q3]	71.5 [66-77]
Karnofsky Performans Status	
Median (range)	70 [60-80]
Diagnostic	
Lumbar puncture	5 (9.3%)
Biopsy	47 (87.0%)
Surgery	2 (3.7%)
Randomization, n (%)	
No	21 (39%)
Yes – observation arm	18 (33.3%)
Yes– maintenance arm	15 (27.7%)
Treatment completion, *n (%)*	
4 to 5 RMPV and cytarabine	40 (74.1%)
< 4 RMPV	14 (25.9%)

Table 2. Multivariate analysis of clinical and FDG-PET/MRI scans based on visual analysis on PFS

	Multivariate analysis (PET) n=48		**Multivariate analysis (MRI) n=47**	
PFS	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Male (ref F)	1.67 [0.60,4.64]	0.33	1.69 [0.65,4.36]	0.29
Age ≥70 (ref < 70 years)	1.38 [0.50,3.80]	0.53	1.37 [0.52,3.56]	0.52
KPS ≥70 (ref < 70)	0.76 [0.32,1.79]	0.54	0.88 [0.37, 2.08]	0.77
INTERIM PET response PR (ref CR)	**10.36 [3.82, 28.07]**	**<0.001**		
INTERIM MRI response PR (ref CR)			1.33 [0.54,3,23]	0.53

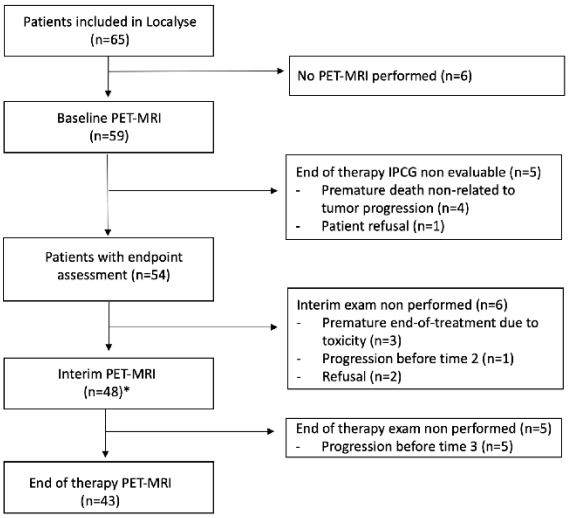
Table 3. Prognostic Interim FDG-PET/MRI biomarkers of PFS on univariate analysis

	Univariate (n=54)	
	HR (95% CI)	**p**
PFS		
Male (ref F)	1.41 [0.62,3.21]	0.41
Age ≥70 (ref < 70 years)	0.95 [0.42,2.14]	0.90
KPS ≥70 (ref < 70)	0.87 [0.38,2]	0.75
$\Delta SUVmax_{1-2}$ (increase unit =10)	0.89 [0.81,0.98]	0.26 *
ΔMTV_{1-2} (ref< 100)	0.13 [0.05,0.37]	**<0.001 ***
$\Delta Vol._{1-2}$ enhanced lesion (ref< 98.3%)	0.86 [0.36;2.07]	1 *
$\Delta rADCmean_{1-2}$ (increase unit =10)	1 [0.91,1.09]	1 *
ΔADCmin1-2 (increase unit =10)	0.95 [0.87,1.03]	1 *
$\Delta rCBFmax_{1-2}$ (increase unit =10)	0.99 [0.87,1.11]	1 *
$\Delta rCBVmax_{1-2}$ (increase unit =10)	0.98 [0.94,1.01]	1 *

KPS : Karnofsky performans status, Vol. : volume

* p-values reported were corrected using Benjamini-Hochberg to take into account multiple comparisons computed in the analysis.

Figure 1



* One incomplete MRI due to lack of gadolinium injection

Figure 2

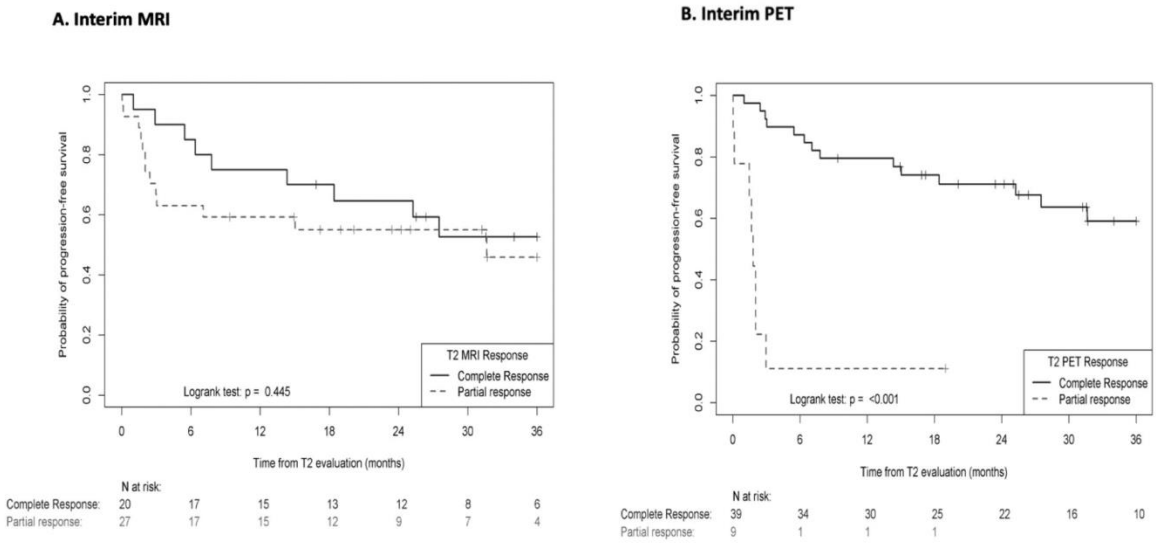


Figure 3