Neuro-Oncology

*Neuro-Oncology* 18(9), 1297–1303, 2016
doi:10.1093/neuonc/now033
Advance Access date 6 March 2016

# Primary CNS lymphoma at first relapse/progression: characteristics, management, and outcome of 256 patients from the French LOC network

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***Background.*** Treatment of relapsed/refractory (R/R) primary CNS lymphoma (PCNSL) is poorly defined, because randomized trials and large studies are lacking. The aim of this study was to analyze the characteristics, management, and outcome of R/R PCNSL patients after first-line therapy in a nationwide cohort.

***Methods.*** We analyzed R/R PCNSL patients following first-line treatment who had been prospectively registered in the database of the French network for oculocerebral lymphoma (LOC) between 2011 and 2014.

***Results.*** Among 563 PCNSL patients treated with first-line therapy, we identified 256 with relapsed ($n = 93$, 16.5%) or refractory ($n = 163$, 29.0%) disease. Patients who were asymptomatic at relapse/progression (25.5%), mostly diagnosed on routine follow-up neuroimaging, tended to have a better outcome. Patients who received salvage therapy followed by consolidation (mostly intensive chemotherapy plus autologous hematopoietic stem cell transplantation [ICT + AHSCT]) experienced prolonged survival compared with those who did not receive salvage or consolidation therapy. Independent prognostic factors at first relapse/progression were:

*Received 2 December 2015; accepted 5 February 2016*

KPS ≥ 70 vs KPS < 70), sensitivity to first-line therapy (relapsed vs refractory disease), duration of first remission (progression-free survival [PFS] ≥1 y vs <1 y), and management at relapse/progression (palliative care vs salvage therapy). Patients who relapsed early after first-line therapy (ie, PFS < 1 y) had a poor outcome, comparable to that of refractory patients. Conversely, patients experiencing late relapses (PFS ≥ 1 y) and/or undergoing consolidation with ICT + AHSCT experienced prolonged survival.

***Conclusions.*** About a third of PCNSL patients are primary refractory to first line treatment. We identified several independent prognostic factors that can guide the management of R/R PCNSL patients.

**Keywords:** primary CNS lymphoma, progression, relapse.



Primary CNS lymphoma (PCNSL) is an aggressive malignancy that is confined to the CNS at the time of diagnosis. It represents 3% of primary CNS tumors and 4%–6% of all extranodal lymphomas.[1,2]

Despite significant improvements in the management of PCNSL, about a third of patients are refractory to first-line treatment, and up to 60% of the patients will eventually relapse.[3–5] The current standard initial treatment relies on high-dose methotrexate-based polychemotherapy with or without consolidation.

Several studies evaluated second-line salvage therapies, including high-dose methotrexate rechallenge,[6] temozolomide,[7] platine/cytarabine,[8] topotecan,[9] whole brain radiotherapy (WBRT),[10] lenalidomide,[11] ifosfamide/carboplatin/etoposide,[12] rituximab,[13] or intensive chemotherapy (ICT) with thiotepa/busulphan/cyclophosphamide followed by autologous hematopoietic stem cell transplantation (AHSCT).[14] They show heterogeneous response rates (range, 14%–85%) and survivals (range, 4–59 mo). However, due to the limited number of patients in these studies, the optimal management of refractory and relapsed (R/R) PCNSL patients remains poorly defined.

In this study, we aimed to analyze the characteristics, management, and outcome of R/R PCNSL patients after first-line therapy in a large cohort of patients registered in the database of the French oculocerebral lymphoma (LOC) network for PCNSL.

## Patients and Methods

### *Inclusion Criteria*

Patients with diagnoses of PCNSL after January 2011 have been prospectively entered into the French LOC registry, a nationwide database centralizing information from 28 different centers in France, representing the main centers involved in PCNSL management.

PCNSL patients were included in the study if they fulfilled the following criteria: (i) age over 18 years, (ii) pathologically proven PCNSL at initial diagnosis, (iii) refractory or relapsed disease after first-line therapy, and (iv) clinical data on patient characteristics, treatment, and outcome available for analysis.

This study was approved by the local human investigational committee. Informed consent was obtained for all participating patients.

### *Treatment*

The choice of the treatments (initial and salvage therapy) was left to the discretion of the treating physicians.

### *Response Assessment*

Response to therapy was evaluated according to criteria of the International CNS Lymphoma Collaborative Group.[15] By convention, relapsed patients were defined as those experiencing appearance of a new disease (assessed by CNS MRI, ophtalmic examination, or CSF analysis) after a complete response or an unconfirmed complete response, or progression of a residual mass after a partial response following initial therapy. Patients were considered refractory when they had stable or progressive disease during or at the end of first-line treatment.

### *Statistical Analyses*

Progression-free survival from date of initial diagnosis (PFS1) and from date of first relapse/progression (PFS2) were calculated until the next relapse or death. Overall survival from date of first relapse/progression (OS2) was calculated until death. Qualitative parameters were expressed in numbers and were compared between groups using the chi-square test or Fisher's test. Quantitative parameters were represented in medians (min-max) and compared using the Wilcoxon rank sum test. Survival curves were plotted with the Kaplan–Meier method. To determine prognostic factors for OS2, we used the log-rank test for univariate analysis. The Cox model was performed for multivariate analysis, which was applied to all variables with a *P*-value <.25 in the univariate analysis. This method allows for an adjustment on the different prognostic factors. Since the choice of treatment may have been influenced by patient selection, we ran a sensitivity analysis based upon propensity scores to confirm robustness of the standard analysis. Two propensity scores were developed using a multivariate logistic regression (1 = salvage treatment without consolidation vs no treatment and 2 = salvage treatment without consolidation vs salvage treatment with consolidation). These scores were used as explanatory variables in a model comparing the 3 treatment modalities.

Results were considered statistically significant at $P < .05$. All statistical analyses were performed with R software.

## Results

### *Patient Characteristics*

At the time of analysis, 563 patients with diagnosed PCNSL between 2011 and 2014 had been registered in the LOC database and given first-line treatment. With a median follow-up of 9 months (range, 0.3–43.0) from diagnosis, we identified 256 (45.5%) patients with refractory ($n = 163$, 29.0%) or relapsed ($n = 93$, 16.5%) PCNSL during/after first-line therapy

(Table 1). Most R/R patients had received first-line high-dose methotrexate-based chemotherapy (92.6%), and 10.1% (25/248) had received a consolidation therapy (Supplementary Table S1).

**Table 1.** Patient characteristics at first relapse/progression

| Characteristic | $N = 256$ |
|---|---|
| Demographic and clinical data | |
| Age, y | 68 (26–93) |
| Age ≥ 60 y | 199 (77.7%) |
| Male gender | 133 (52.0%) |
| KPS | 60 (10–100) |
| KPS < 70 | 94/167 (56.3%) |
| Relapse | 93 (16.5%)[a] |
| Progression | 163 (29.0%)[a] |
| Symptoms at relapse or progression | |
| Symptomatic | 137/184 (74.5%) |
| Gait disorder | 100/168 (59.5%) |
| Cognitive impairment | 96/173 (55.5%) |
| Sensorimotor impairment | 80/170 (47.1%) |
| Balance disorder | 68/148 (45.9%) |
| Aphasia | 27/167 (16.2%) |
| Increased intracranial pressure symptoms | 27/172 (15.7%) |
| Epilepsy | 8/177 (4.5%) |
| Asymptomatic | 47/184 (25.5%) |
| Diagnosed on CNS imaging | 41/184 (22.3%) |
| Diagnosed after ophthalmic examination | 5/184 (2.7%) |
| Diagnosed in CSF | 1/184 (0.5%) |
| Site of relapse/progression | 185 |
| CNS | 180 (97.3%) |
| Extra-CNS | 2 (1.1%) |
| CNS + extra-CNS | 3 (1.6%) |
| Site of relapse/progression in CNS[b] | 180 |
| Brain only | 158 (87.8%) |
| Brain + eye[c] | 17 (9.4%) |
| Eye only | 5 (2.8%) |
| Site of relapse/progression in brain | |
| Initial site[d] | 100/151 (66.2%) |
| Initial + distant site[d] | 20/151 (13.2%) |
| Distant CNS site[d] | 31/151 (20.5%) |
| Unifocal | 63/144 (43.8%) |
| Diffuse or multifocal | 81/144 (56.3%) |
| Median PFS1, mo | 5.1 (0.3–35.8) |
| PFS1 ≥ 1 y | 42 (16.4%) |

Values are given in median (min-max) or *n* (%).
[a]563 treated patients in the database.
[b]For patients with diffuse or multifocal disease diagnosis, relapse/progression was considered to be at the initial site if one or more sites were identical between initial diagnosis and relapse/progression.
[c]Only 48 out of 180 patients (27%) underwent ophtalmic examination at first relapse/progression.
[d]In the relapsed group (excluding refractory patients), relapse was at initial site for 35/61 patients (57.4%), at a distant site for 20/61 patients (32.8%), and at a local + distant site for 6/61 patients (9.8%). Site of relapse was missing for 32 relapsed patients.

Patient characteristics at first relapse/progression are summarized in Table 1. At relapse/progression, 77.7% of the patients were over 60 years. Median KPS was 60 (10–100), with 56.3% of the patients presenting a KPS score <70. Only 2% of the patients were immunodeficient (Supplementary Table S1).

Relapse/progression was asymptomatic in 25.5% of the cases, diagnosed on routine follow-up neuroimaging (22.3%), ophthalmic evaluation (2.7%), or CSF analysis (0.5%). Performance status was significantly better in asymptomatic patients compared with symptomatic patients (median KPS = 80 vs 60, respectively, $P = .03$). Rarely, relapse/progression affected extracerebral sites (2.7%). At relapse/progression, 12.2% of the 48 patients who underwent an ophtalmic assessment presented with eye involvement, either isolated (2.8%) or associated with brain involvement (9.4%). Relapse/progression in the brain occurred primarily at initial site (79.4%) and was frequently diffuse or multifocal (56.3%). Of note, the site of relapse was missing in the database for 71 of the 256 patients (27.7%).

### *Management at First Relapse/Progression*

At first relapse/progression, patients were managed in groups according to 3 modalities (Fig. 1): group 1, palliative care (28.1% of patients); group 2, salvage treatment without consolidation (57.1%); and group 3, salvage chemotherapy followed by consolidation (14.7%). In group 2, salvage treatment was mainly ifosfamide-based (28.0%), methotrexate-based (18.2%), or cytarabine-based (25.0%) chemotherapy, WBRT (13.6%), or other regimens (15.2%). In group 3, consolidation consisted mostly of ICT + AHSCT (85.3%), and more rarely WBRT (14.7%). Of note, the type of salvage therapy was missing in the database for 25 of the 191 treated patients (13.1%). Characteristics of the 3 groups are summarized in Supplementary Table S2.

Patients in group 1 (palliative care) tended to be older (92.3% were ≥60 y), with a poor performance status (94.7% had KPS < 70) and refractory disease (83.1%). In group 3 (salvage chemotherapy with consolidation), patients were younger (median age = 63 y [range, 26–78]) and tended to have a better performance status (75% had KPS ≥ 70) and more chemosensitive disease (objective response rate = 67.6% and 73.5% after first- and second-line therapy, respectively) compared with patients in group 2 (salvage chemotherapy without consolidation).

### *Survival*

Median progression-free survival (PFS2) and overall survival (OS2) for the 256 R/R patients at first relapse/progression were 2.2 months (range, 0–29.6) and 3.5 months (0–29.6), respectively. In relapsed patients, OS2 was not statistically different between those who achieved a complete response and those who achieved a partial response following first-line therapy (median OS2 = 16 mo vs not reached, respectively, $P = .60$, data not shown).

The survival of patients in group 1 was very poor, with a median PFS2 and OS2 of 0.6 months (range, 0–5 mo) (Supplementary Fig. S1). Survival was significantly better in patients who received salvage therapy (median OS2 = 8.4 mo [range, 0–29.6], $P < .01$). Among R/R patients who received a second-line

therapy, 33 (19.9%) remained alive at 1 year, including 10 refractory patients.

Survival was significantly better in group 3 than in group 2, in terms of both PFS2 (median = 13.5 vs 2.6 mo, $P < .01$) and OS2 (median = not reached vs 6.7 mo, $P < .01$) (Table 2, Supplementary Table S2, Supplementary Fig. S1). Survival of patients consolidated specifically with ICT + AHSCT (excluding patients consolidated with radiotherapy) was the same as group 3. Among patients who received a consolidation with ICT + AHSCT, 44.8% (13/29) experienced a PFS2 (13.5 mo [range, 0–29.6]) longer than their PFS1 (9.0 mo [2.6–23.6]).

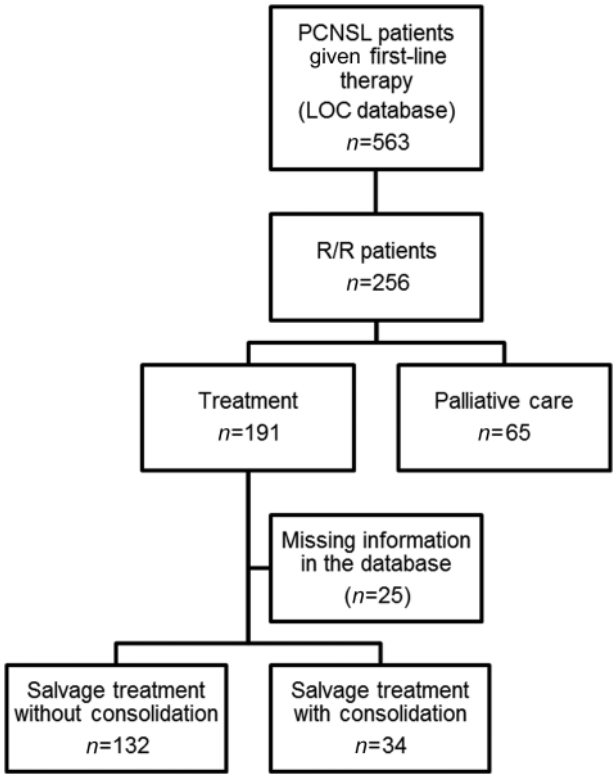


**Fig. 1.** Consort diagram.

### *Prognostic Factors at First Relapse/Progression*

We next searched for prognostic factors that could predict survival at first relapse/progression. In univariate analysis (Table 2), we found that prognostic factors for OS2 were: age at relapse/progression (≥ vs <60 y), KPS ≥ vs <70, sensitivity to first-line therapy (refractory vs responding patients), duration of first remission (PFS1< vs ≥1 y), administration of a salvage therapy, and use of rituximab as second-line associated therapy (yes vs no). Refractory patients had a very poor prognosis, with a median OS2 of 2.1 months (Fig. 2D). Out of 163 refractory patients, only 10 (6.1%) remained alive at 1 year. These patients had received the following treatments: radiotherapy ($n = 4$) and methotrexate-based ($n = 2$), ifosfamide-based ($n = 3$), and cytarabine-based ($n = 1$) chemotherapy. Relapsed patients ($n = 93$) with PFS1 < 1 year ($n = 52$) had a significantly worse prognosis than relapsed patients with PFS1 ≥ 1 year ($n = 41$, median OS2 = 3.7 mo vs not reached, $P < .01$) (Fig. 3). Patients who were asymptomatic at first relapse/progression tended to have a better survival (median OS2 = 8.4 vs 4.6 mo, $P = .048$). Other factors, such as gender, site of relapse/progression, use of rituximab at first line or consolidation at first line did not impact survival after relapse/progression. No direct comparison could be done between the different salvage regimens due to the heterogeneity and small number of patients in each group (Supplementary Table S3, Supplementary Fig. S2). In

**Table 2.** Prognostic factors for OS2 at first relapse or progression

| | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| Factors | HR (95% CI) | *P* | Adj HR (95% CI) | *P* |
| Age at relapse/progression <60 vs ≥60 y | **0.50 (0.33–0.77)** | **<.01[a]** | 0.76 (0.37–1.58) | .47 |
| Gender (ref = male) | 1.04 (0.76–1.43) | .79 | – | – |
| KPS ≥70 vs <70 at relapse/progression | **0.24 (0.14–0.39)** | **<.01[a]** | **0.36 (0.18–0.70)** | **<.01[a]** |
| PFS1 ≥1 y vs <1 y | **0.20 (0.10–0.41)** | **<.01[a]** | **0.29 (0.09–0.99)** | **.049[a]** |
| Relapsed vs refractory[b] | **0.37 (0.25–0.54)** | **<.01[a]** | **0.40 (0.19–0.86)** | **.02[a]** |
| Asymptomatic vs symptomatic relapse/progression | **0.62 (0.38–1.02)** | **.048[a]** | 1.04 (0.53–2.04) | .91 |
| Local progression vs not local | 1.57 (0.89–2.75) | .12 | 1.51 (0.79–2.86) | .21 |
| Salvage treatment without consolidation | | | | |
| vs palliative treatment | **9.86 (6.53–14.89)** | **<.01[a]** | **4.38 (1.94–7.21)** | **<.01[a]** |
| vs salvage treatment with consolidation[c] | **0.29 (0.14–0.60)** | **<.01[a]** | 0.56 (0.25–1.26)) | .16 |
| Rituximab in first line vs no rituximab | 0.78 (0.56–1.07) | .12 | 1.14 (0.62–2.09) | .67 |
| Rituximab in second line vs no rituximab | **0.39 (0.25–0.58)** | **<.01[a]** | 0.85 (0.46–1.57) | .61 |
| Consolidation in first line vs no consolidation | 0.65 (0.36–1.17) | .15 | 0.96 (0.38–2.44) | .94 |

Abbreviation: HR, hazard ratio.
[a]Statistically significant if $P < .05$.
[b]In separate multivariate analysis because of the correlation between these parameters: refractory vs relapsed and duration of PFS1.
[c]Results remain the same if consolidation includes only ICT + AHSCT without the 5 cases of radiation.

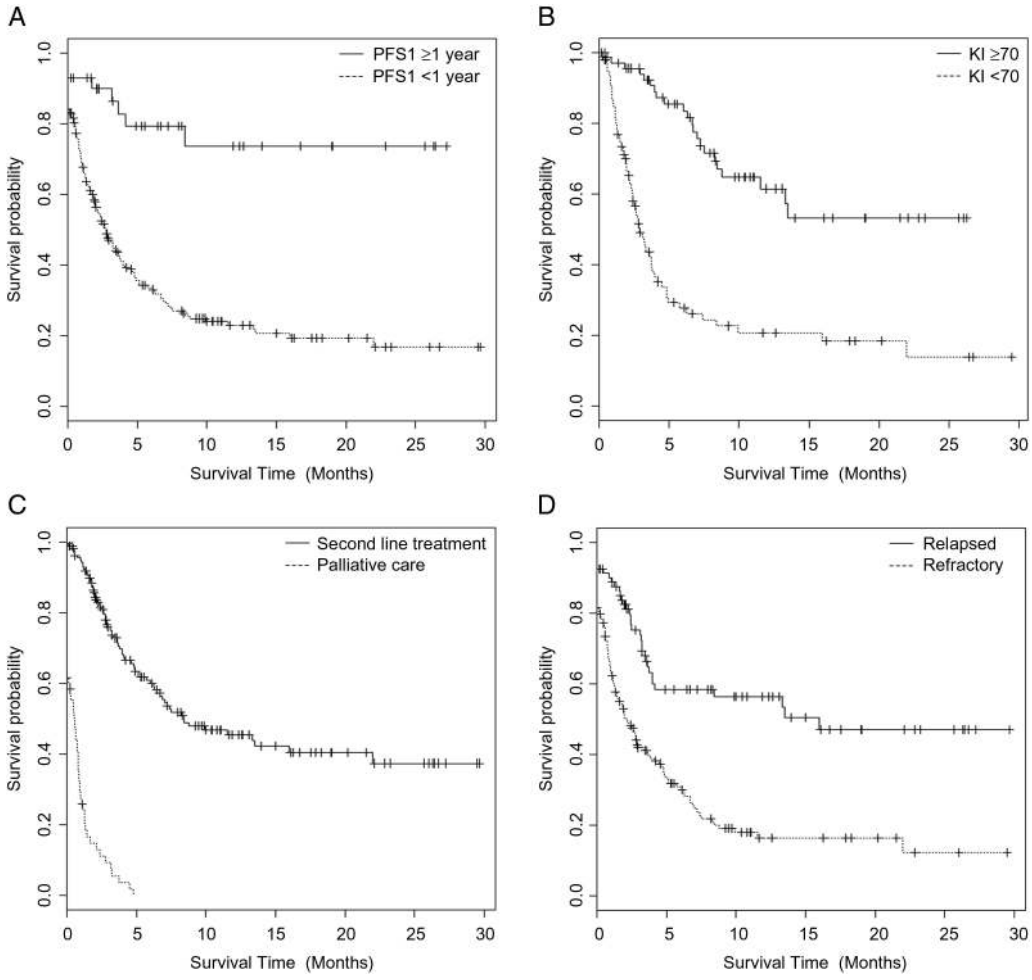


**Fig. 2.** OS2 according to independent prognostic factors. (A) Duration of PFS1. (B) Karnofsky performance status. (C) Salvage vs palliative care. (D) Relapsed vs refractory patients.

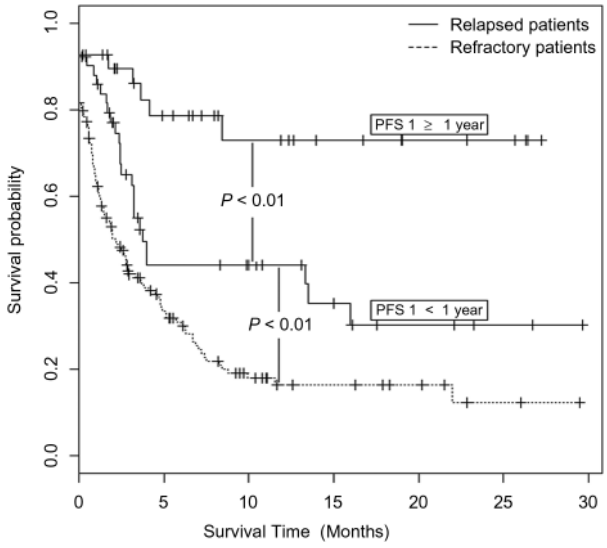


**Fig. 3.** OS2 according to the duration of first remission.

multivariate analysis (Table 2), only 4 prognostic factors remained statistically independent for survival (OS2): sensitivity to first-line therapy, duration of first remission (PFS1), administration of a salvage therapy, and KPS (Fig. 2).

Since these results may have been influenced by patient selection, we ran a sensitivity analysis based upon propensity scores (Supplementary Tables S4 and S5). The propensity-score analysis further supported the previous results.

## Discussion

The aim of this study was to analyze the characteristics, management, and outcome of R/R PCNSL patients after first-line therapy. Two hundred and fifty-six patients were analyzed, which represents to our knowledge the largest published study on R/R PCNSL.

Out of 563 patients treated with first-line therapy (mostly methotrexate-based regimens), we found that 29% ($n = 163$) were primary refractory. This is in line with prior reports.[16,17] Nevertheless, in our study, only 43.8% of the patients had

received rituximab at first line. This proportion will probably increase in the future and may result in a diminished number of refractory patients. Due to a short follow-up (median = 9 mo), the percentage of relapsed patients (16.5% of the entire cohort) appears lower than what has been previously described.[3] Our study confirms the very poor prognosis of primary refractory patients, with a median OS2 of about 2 months and very few long-term survivors. The frequency and the poor outcome of refractory patients emphasize the urgent need for new therapeutic agents in this disease.

We found that a fourth of the patients were asymptomatic at first relapse/progression. In most cases, relapse/progression was diagnosed on routine follow-up neuroimaging (87.2%). These patients had a better performance status (median KPS = 80 vs 60, $P = .03$). Since performance status at relapse/progression is a major, independent prognostic factor (Table 2), it may explain why asymptomatic patients tended to have a better survival in univariate analysis ($P = .048$). Also, early detection of relapse/progression may precede the development of neurological defects and alteration of performance status, which may compromise optimal salvage therapy. This observation supports the need for systematic neuroimaging in the surveillance of PCNSL as recommended by international guidelines.[15] This is in contrast to systemic diffuse large B-cell lymphoma, where routine imaging during follow-up did not show any benefit.[18,19] However, given the retrospective nature of our study and potential confounding factors, the benefit of routine follow-up neuroimaging should be evaluated prospectively in a randomized trial in order to confirm these results.

In our cohort, we also found that the longest survivals (PFS2 and OS2) were obtained with salvage therapy followed by consolidation (mostly ICT + AHSCT), although the benefit of consolidation was not statistically significant in multivariate analysis. This may result from the selection of patients with more favorable characteristics, since these patients undergoing ICT + AHSCT tended to be younger, with a better performance status and more chemosensitive disease. However, we found that up to 44.8% of the patients consolidated with ICT + AHSCT had a PFS2 longer than their PFS1. These results highlight the fact that ICT can induce prolonged remissions in a subset of patients, as previously reported by our group.[14]

Although we could not directly compare the salvage chemotherapy regimens due to the heterogeneity and small size of the groups, we found that the ifosfamide-based regimen induced a response rate of 42.4% (Supplementary Table S2), similar to what was previously reported by Mappa et al and Arellano-Rodrigo et al.[20,21] In a limited number of patients ($n = 18$), radiotherapy was able to induce significant response rates (objective response rate = 55.6%; Supplementary Table S3) and prolonged survival (Supplementary Fig. S2) as shown previously,[22,23] despite the fact that most of these patients had a poor performance status (68.8% with KPS < 70) and refractory disease (83.3%). However, the antitumor efficacy of radiotherapy may be counterbalanced by its neurological toxicity (not evaluated in this study), especially in this elderly population of patients.

Finally, our study identified several prognostic factors at first relapse/progression. Notably, we found that the duration of first remission (PFS1) was a major, independent prognostic factor. Specifically, patients who relapse within a year from initial diagnosis (PFS1 < 1 y) appear to have a very poor prognosis (median OS2 = 3.7 mo) that is comparable to that of refractory patients (median OS2 = 2.1 mo; Fig. 3). These patients should be considered for clinical trials testing new therapeutic strategies. Conversely, patients who relapse beyond a year from diagnosis (PFS1 ≥ 1 y) have a favorable prognosis, with the median OS2 not reached. Interestingly, the one-year cutoff in PFS1 has been previously reported as being a major prognostic factor in systemic diffuse large B-cell lymphoma at first relapse/progression.[24] This observation indicates that PFS1 (with a cutoff at 1 y) may be used to guide the management of R/R patients rather than the usual dichotomy between refractory and relapse patients, as previously suggested by Reni et al.[25]

Our study has several limitations. First, the follow-up is short (median = 9 mo). This artificially enriches the proportion of refractory patients, who represent the majority of the patients in our cohort (72%). Also, it does not allow the capture of late relapses. Second, the retrospective nature of the study may generate some biases due to confounding factors. For these reasons, no definitive conclusion can be drawn regarding the optimal management of R/R patients.

In conclusion, our study shows that almost a third of PCNSL patients are primary refractory and have a very poor outcome. This highlights the need for new therapeutic agents in this disease. Our study also supports routine follow-up neuroimaging, as recommended by international guidelines, since early detection of relapse/progression while patients are still asymptomatic tends to be associated with a better survival. Management of R/R PCNSL patients may be guided individually using prognostic factors identified in this study. Notably, we found that the duration of first remission (PFS1) is an independent prognostic factor at relapse. Finally, consolidation with ICT + AHSCT following salvage chemotherapy is associated with prolonged remission in a subset of patients and may thus be considered in eligible patients. These results can serve as a landmark for the design of future clinical trials.

## Supplementary Material

Supplementary material is available at *Neuro-Oncology Journal* online (http://neuro-oncology.oxfordjournals.org/).

## Funding

The French LOC network is supported by Institut National du Cancer (INCa).

*Conflict of interest statement*. None declared.

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