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## Isolated intraocular relapses of primary cerebral lymphomas: an LOC network study

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#### **Data availability**

All the data are available in the national French database of the "Lymphome Oculo-Cérébral" (LOC) network.

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#### **Conflict of interest disclosure**

The authors report no disclosures relevant to the manuscript.

#### **Ethics approval statement**

The study was approved by the Institutional Ethical Committee of the coordinating center on the 24/04/2018 and by the French “Commission Nationale de l’Informatique et des Libertés” (CNIL) (n°913170). This study was conducted in accordance with the Declaration of Helsinki.

**Patient consent statement**

All patients gave informed consent for the submission of their data to the database and their use.

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## Abstract

Most relapses of primary central nervous system lymphoma (PCNSL) occur in the brain and are associated with a poor prognosis. Isolated intraocular relapses (IIRs) are rare and poorly described.

We retrospectively selected from the French LOC database PCNSL patients who initially presented with cerebral localization and who experienced IIR during the course of the disease.

Of the 1472 patients included in the database, 55 patients presented an IIR. Their median age was 68 years, and median Karnofsky Performance Status 80. IL-10 levels in the aqueous humor and/or in the vitreous were increased in 42/46 patients. 45/55 patients received systemic chemotherapy, and 11/55 received high-dose chemotherapy with autologous stem cell transplantation (HCT-ASCT) as consolidation treatment. After a median follow-up of 69 months, 42/55 patients had relapsed, including 90% of the patients who did not receive HCT-ASCT at IIR and 40% of the patients who received HCT-ASCT at IIR ( $p < 0.001$ ). The first relapse after the initial IIR was exclusively in the eye in 23/42 patients, and 29/42 patients had a subsequent brain relapse during the course of the disease. The median progression-free survival, brain-free survival and overall survival from IIR were 12.2, 48.6 and 57.1 months, respectively.

IIR is not exceptional in the course of PCNSL and deserves systematic ophthalmological follow-up. Its prognosis is much better than the prognosis of brain relapse, with an evolution close to that of primary vitreoretinal lymphoma. With the exception of patients who received HCT-ASCT at IIR, almost all patients subsequently relapsed, often with other IIRs.

## Introduction

Primary central nervous system lymphoma (PCNSL) is a rare extranodal lymphoma affecting mostly elderly immunocompetent patients. It is located in the brain in more than 90% of cases. Intraocular involvement is a classic feature of the disease. At initial diagnosis, it can be either isolated, in rare cases<sup>1</sup>, or associated with brain involvement in 10 to 20% of cases<sup>2-4</sup>. The association of an ocular location with a brain location does not seem to have an adverse prognostic impact<sup>3-5</sup>. However, it can be hard to eradicate and be a source of relapse.

The prognosis of PCNSL remains dismal, mainly due to a high risk of relapse during or after treatment. Due to unclear reasons, the disease remains confined to the central nervous system in most cases at relapse, with most of the relapses occurring in the brain<sup>6</sup>. Relapses in the brain can be associated with lymphomatous locations in the meninges, eye or spinal cord. Brain relapses have an adverse prognosis, with a median overall survival inferior to 12 months in most studies<sup>6-10</sup>, except for patients eligible for high-dose chemotherapy with autologous stem cell transplantation (HCT-ASCT)<sup>11</sup> or for late relapses when high-dose methotrexate (HD-MTX) can be rechallenged<sup>12-13</sup>.

Rarely, isolated intraocular relapses (IIRs) of primary cerebral lymphoma (PCL), without any brain involvement, can occur<sup>6</sup>. There are very limited data in the literature, and to our knowledge, no study specifically dedicated to this topic. The aim of the present study was to analyze, from a large cohort of PCNSL, patients with IIR at any time during their disease. The objectives were to search for risk factors for IIR and to describe cases of IIR, their management and their outcomes.

## Methods

This work is based on an analysis of the French LOC network database, a nationwide database registering all newly diagnosed PCNSL since 2011 from 32 different centers in France, representing the main centers involved in PCNSL management. The database was approved by the Institutional Ethical Committee of the coordinating center and by the French “Commission Nationale de l’Informatique et des Libertés” (CNIL). All patients gave their informed consent to participate in the database and for the use of their data. This study was conducted in accordance with the Declaration of Helsinki. No private funds were used.

We selected adult immunocompetent patients who had a histologically proven diffuse large B-cell PCNSL with at least one cerebral localization at diagnosis and at least one isolated intraocular relapse (IIOR) at any point in the history of the disease. At the time of IIOR, cerebral involvement had to be excluded by cerebral MRI. Patients with asymptomatic meningeal involvement were not excluded. The patients were selected in July 2018, and data were analyzed in June 2021. The main characteristics and outcomes of these patients were compared to those of the PCNSL patients in the LOC network database with cerebral or oculocerebral brain relapse<sup>4</sup>.

Response to therapy was assessed according to the IPCG criteria<sup>14</sup>. IL-10 at diagnosis of IIOR was considered elevated with a cutoff of 30 pg/ml in the aqueous humor (AH) and 65 pg/ml in the vitreous according to previous publications in primary vitreoretinal lymphoma (PVRL)<sup>15-17</sup>. IL-10 in the AH was also monitored at the end of the treatment and during the follow-up at the discretion of the physicians. IL-10 levels were classified as detectable ( $\geq 2.5$  pg/ml) or undetectable ( $< 2.5$  pg/ml) for the follow-up. The chi-square test was used to test the associations between variables. The main outcome endpoints were overall survival (OS), progression-free survival (PFS) and brain-free survival (BFS). All of the endpoints were

calculated from the date of diagnosis of IIOR. PFS was defined as the time without relapse (whatever its location) or without death (whatever its cause). BFS was defined as the time without brain relapse. Survival rates were calculated using the Kaplan–Meier method. The log-rank test was used to test for equality of the PFS, BFS and OS distributions. A multivariate analysis, including the variables with significant prognostic value in univariate analysis, was performed with the multivariate Cox proportional hazards regression model. Two-sided p values <0.05 were considered significant. The statistical analyses were carried out with SPSS 17.0 software.

## Results

### Patients' characteristics at initial diagnosis

Of the 1472 PCNSL patients included in the LOC database at the time of patient selection, 615 relapsed, including 55 patients with IIOR from 23 centers who met the inclusion criteria (4% of the patients, 9% of the relapses). Their main characteristics are summarized in Table 1. At the time of the initial diagnosis, 49% of the patients had an associated ocular location. Of note, a search for an ocular location was not conducted at the time of the initial diagnosis for 11/55 (20%) of the patients. None of these patients had visual complaints. In first-line treatment, all patients received HD-MTX-based induction chemotherapy. None of them was treated with HCT-ASCT consolidation. Eighty percent of patients were in complete response (CR) at the end of first-line treatment.

### Patients' characteristics at IIOR

The main characteristics at the time of diagnosis of IIOR are reported in Table 2. The median age at IIOR was 68 years (range 34-89), and the median KPS was 80 (range 50-100). IIOR occurred after a median duration of 16 months after the initial diagnosis. It was the first relapse in 48/55 patients and occurred during therapy in 5/48 patients. IIOR was asymptomatic in 5% of patients and revealed by visual acuity impairment in 86% (44/51). Ocular involvement was bilateral in 25/51 cases (49%). Hyalitis was observed in 44/48 (92%) of the cases. IL-10 levels in the AH and/or in the vitreous were increased in 42/46 patients (91%).

### Treatments of IIOR

The treatments of the IIOR are summarized in Table 3. A total of 45/55 (82%) patients received systemic chemotherapy, including ten patients who received a combination with local

treatment. The treatment was based on ifosfamide in 13/55 cases, HD-MTX in 10/55 cases and temozolomide in 10/55 cases. Subsequently, 11/55 (20%) patients received thiotepa-based HCT-ASCT as consolidation treatment.

At the end of the treatment of the IOR, 27/54 (50%) were in CR. IL-10 was undetectable in the AH in 100% of the patients who were in CR/unconfirmed complete response (uCR) and detectable in 100% of the patients in stable disease (SD) or progressive disease (PD). Among the patients who received HCT-ASCT, 9/11 achieved CR, 1/11 progressed, and 1/11 died from toxic complications.

### **Outcome after IOR (Figure 1)**

The median follow-up after IOR was 69 months (95% CI: 63-74), and 42/55 (76%) patients had a subsequent relapse(s). Their characteristics are summarized in Table 3. The first relapse after the initial IOR was exclusively in the eye in 23/42 patients (55%). Twenty-nine/42 (69%) patients had a subsequent brain relapse during the course of the disease after IOR diagnosis. Only 4/42 (10%) patients who did not receive HCT-ASCT after IOR diagnosis had no subsequent relapse, while 6/10 (60%) patients who received HCT-ASCT after IOR diagnosis never relapsed subsequently ( $p < 0.001$ ). A total of 16/42, 17/42 and 10/42 patients received ibrutinib, lenalidomide or temozolomide, respectively, during subsequent relapse(s). The median PFS and BFS from the diagnosis of IOR were 12.2 months (95% CI: 8.7-15.7) and 48.6 months (27.3-63.9), respectively.

Twenty-six/55 (47%) patients died during the follow-up, due to cerebral progression of the PCNSL in 23 cases. The median OS from the diagnosis of IOR was 57.1 months (95% CI NR-NR), with 1-year, 2-year and 5-year OS rates of 87.3%, 78.1% and 49.9%, respectively.

## **Prognostic factors**

The main prognostic factors for OS are indicated in Table 4. Age >70 years at IOR, KPS ≤70 at IOR, male sex and delay between initial diagnosis and IOR <18 months were associated with a shorter OS in univariate analysis. Only age >70 years and male sex remained significantly associated with a shorter OS in multivariate analysis.

There was no correlation between the levels of IL-10 in the vitreous or aqueous humor at IOR or the type of treatment at IOR (local vs. systemic vs. local+systemic) and PFS, BFS or OS. The use of HCT-ASCT at IOR was significantly associated with prolonged PFS (p=0.005) but was not associated with prolonged BFS or OS. However, there was a 6-year OS rate of 63% in patients treated with HCT-ASCT compared to 42% without HCT-ASCT (Supplemental Figure 1).

The median OS after IOR was 24 months when the first relapse after IOR was cerebral (+/- ocular), while it was 57.1 months when the first relapse after IOR was only ocular (p=0.02).

## **Comparison of patients in the LOC network database with cerebral or oculocerebral relapse**

The cohort of IOR was compared to the patients with cerebral or oculocerebral relapse from the previously published cohort of the LOC network database<sup>4</sup>. The main results are indicated in Table 5. The median age was similar in both cohorts. The KPS was significantly higher at IOR than at first (oculo)cerebral relapse in the LOC database (p<0.001). The patients with IOR received significantly more active treatment (p=0.002) and more HCT-ASCT (p=0.05). The median PFS and median OS were significantly higher after IOR, in patients both older and younger than 70 years (p<0.001).

## Discussion

To our knowledge, this work represents the first series dedicated to IIOR of primary cerebral lymphomas. Although rare<sup>3</sup>, this situation was not exceptional in our series, as it concerned 9% of the patients who relapsed during the course of their disease.

Even if ophthalmological involvement at diagnosis was far more frequent in IIOR than in classical PCNSL relapses, it is interesting to note that more than 50% of the patients had no history of ocular involvement at the initial diagnosis, either because no ophthalmological work-up was performed at that time (22% of the patients) or because this work-up was normal (30% of the patients). This underlines the importance of a systematic ophthalmological examination at the time of the diagnosis of a primary cerebral lymphoma, as recommended by the IPCG<sup>14</sup>, especially given that, generally, ocular symptoms are mild or even absent<sup>3,5</sup>, whereas neurological symptoms are severe and are in the foreground. A systematic ophthalmological follow-up should also be recommended, at least in the first years after the end of the treatment. In the LOC network guidelines, an ocular assessment, including slit-lamp and fundus examination, is recommended once a year in PCNSL patients who had no ocular involvement at baseline. The site of disease in the brain at diagnosis was not recorded in this study but this analysis would be interesting to determine if some sites are associated with an increased risk of IIOR.

Of note, very few of the 55 patients with IIOR had received a consolidation treatment in first line : none received HCT-ASCT and 20% received WBRT. This reflects the practices in France at the time of the study : in PCNSL patients from the LOC network database diagnosed between 2011 and 2016, 6% and 15% received HCT-ASCT and WBRT in 1st line treatment, respectively<sup>4</sup>. Since the publication in 2017 and 2019 of the two main randomized trials addressing the question of WBRT vs HCT-ASCT as consolidation in 1st line

treatment<sup>15,16</sup>, the use of HCT-ASCT in 1st line has increased a lot, so that there will surely be in the future some IIOR following HCT-ASCT. The eyes were not incorporated in the radiotherapy field of the patients who received WBRT in 1st line. We currently lack precise recommendations on the radiotherapy field in PCNSL, but these data support the incorporation of the eyes.

The IIOR clinical presentation was close to the PVRL clinical presentation, with mild visual acuity impairment and vitreous haze in most cases and frequent bilateral involvement<sup>1,3,5</sup>. As in PVRL<sup>17-19</sup>, the IL-10 level in the vitreous or aqueous humor was a useful tool in the diagnosis and follow-up of IIOR, with 84% of patients with elevated IL-10 at the time of IIOR diagnosis, 100% of patients in CR/uCR after IIOR treatment with undetectable IL-10 and 100% of patients in SD or PD after IIOR treatment with elevated IL-10. As the ophthalmological evaluation according to the IPCG criteria is difficult and somewhat subjective, we recommend measuring IL-10 in the aqueous humor at least at baseline and at the end of the treatment of IIOR. A persistently increased IL-10 level despite an improved ophthalmological examination must result in close monitoring given the high risk of an early relapse<sup>1</sup>. The search for a MYD88 mutation in the vitreous or in the aqueous humor, which is positive in 50 to 87% of cases<sup>20-22</sup>, has become an important diagnostic tool in PVRL in the past years. Unfortunately, it was not available in the present study. Given the limited data on CSF IL-10 and the absence of data on CSF MYD88 mutation in the present study, we were not able to evaluate the prognostic impact of IL-10 and MYD88 mutation in the CSF in the setting of an IIOR.

Approximately 3/4 of the patients had subsequent relapses after IIOR. Most of the first subsequent relapses (55%) were also IIOR, while 69% of the patients relapsed in the brain during the follow-up, with a prolonged median BFS of 48.6 months. As in PVRL, ocular

lymphomatous locations appeared difficult to eradicate, with the final risk of brain relapse frequently leading to death.

As treatments were very heterogeneous in this retrospective cohort, it is difficult to determine the best therapeutic option in this setting. Temozolomide, lenalidomide and ibrutinib are three drugs administered orally, with a good tolerance profile even in elderly patients, that have proven efficacy against vitreoretinal lymphomas<sup>7,8,23</sup>. They were offered in 20/55 (36%), 21/55 (38%), and 19/55 (34%) of the patients in this cohort, respectively, during the course of the disease. However, their exact place in relation to older and more toxic drugs such as MTX or ifosfamide is still unclear. The use of HCT-ASCT consolidation is standard in relapsed PCNSL who haven't received HCT-ASCT in first line treatment and who are young and fit enough for this treatment<sup>11</sup>. In this cohort, the use of HCT-ASCT was significantly associated with improved PFS but not with BFS or OS. However, the rate of long-term survivors was much higher when HCT-ASCT was used, and almost all of the patients who did not receive HCT-ASCT at IOR subsequently relapsed, while only 40% of the patients who received HCT-ASCT relapsed. HCT-ASCT appears to be the best chance to definitely cure the disease.

When compared to cerebral or oculocerebral relapses of PCNSL from the LOC database<sup>4</sup>, IOR not surprisingly led to a much less severe clinical impairment (median KPS 80 vs. 60). This probably explains why active treatments (rather than palliative care) and HCT-ASCT could be offered more frequently in IOR, despite the age being very similar in both cohorts. The prognosis of IOR also appeared to be much better than the prognosis of brain relapses, with a PFS of 12.2 months (vs. 3.7 months,  $p < 0.001$ ) and a median OS of 57.1 months (vs. 6.8 months,  $p < 0.001$ ). In both cohorts, the majority of the patients died from the consequences of cerebral relapse. Many features probably contribute to this better prognosis: later relapses, known to be associated with better prognosis<sup>6</sup>; better KPS; more vigorous treatments; and a majority of IOR at subsequent relapses after the first IOR. It is interesting

to note that this favorable prognosis was also found in elderly patients for whom the prognosis at relapse is usually disastrous.

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## **Conclusion**

IIOR of PCNSL with initial cerebral involvement is rare but not exceptional. It mainly occurs in patients with ocular involvement at initial diagnosis, but can also occur in patients without any ocular history, supporting the need for systematic ophthalmological follow-up of patients with PCNSL. The course of the disease is often similar to the course of PVRL, with many subsequent relapses still confined to the eyes and a high risk of final cerebral relapse. The prognosis of IIOR appears much better than the prognosis of cerebral relapses, even in elderly patients. The optimal treatment remains unclear, but the better functional status at IIOR allows for different treatment options ranging from classical drugs such as HD-MTX to newer drugs such as ibrutinib or lenalidomide and HCT-ASCT consolidation, which appears to be the best option to prevent subsequent relapses.

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Table 1: Patient characteristics at initial diagnosis, details of first-line treatment

Table 2: Patient characteristics at IIOR

Table 3: Treatments of IIOR and outcomes

Table 4: Prognostic factors in terms of OS (uni- and multivariate analysis)

Table 5: Comparison between characteristics of IIOR and characteristics of first (oculo)cerebral relapses in the whole LOC network database cohort

Figure 1: Progression-free survival, brain-free survival and overall survival after IIOR

Supplemental Figure 1: Progression-free survival, brain-free survival and overall survival after IIOR according to the use of HCT-ASCT at IIOR or not

Table 1: Patient characteristics at initial diagnosis, details of first-line treatment

|   |              |
|---|--------------|
| N   | 55           |
| Age : median (range)                            | 67 (33-88)   |
| Sex ratio (M/W)                                 | 25/30        |
| KPS: median (range)                             | 70 (40-100)  |
| Associated ocular disease                       |              |
| Yes (%)   | 27/55 (49%)  |
| No (%)  | 17/55 (31%)  |
| Unknown (%)                                     | 11/55 (20%)  |
| Cerebral lesions                                |              |
| Unique (%)                                      | 23/48 (48%)  |
| Multiple (%)                                    | 25/48 (52%)  |
| Meningeal involvement (%)                       | 5/30 (17%)   |
| 1 <sup>st</sup> line treatment                  |              |
| HD MTX-based CT                                 | 55/55 (100%) |
| Rituximab                                       | 28/53 (53%)  |
| Consolidation treatment                         |              |
| HCT-ASCT  | 0/55 (0%)    |
| WBRT  | 11/55 (20%)  |
| With eyes incorporated in the RT field          | 0            |
| With eyes not incorporated in the RT field      | 10           |
| Unknown   | 1            |
| Response to 1st line treatment (including WBRT) |              |
| CR/uCR  | 44/55 (80%)  |
| PR  | 4/55 (7%)    |
| SD  | 0/55 (0%)    |
| PD  | 7/55 (13%)   |
| PD in the brain                                 | 2/55 (4%)    |
| IIOR  | 5/55 (9%)    |

Table 2: Patient characteristics at IIOR

|   |               |
|---|---------------|
| N   | 55            |
| Median age (range)  | 68 (34-89)    |
| Median KPS (range)  | 80 (50-100)   |
| Median delay from initial diagnosis (months) (range)                              | 16 (3-101)    |
| In patients with ophthalmological involvement at baseline                         | 13 (3-51)     |
| In patients without ophthalmological involvement at baseline                      | 18 (8-101)    |
| Time of IIOR  |               |
| First relapse   | 48/55 (87%)   |
| - refractory  | 5/48 (10%)    |
| - relapsed  | 43/48 (90%)   |
| Second relapse  | 7/55 (13%)    |
| -refractory   | 2/7 (29%)     |
| -relapsed   | 5/7 (71%)     |
| Symptoms  |               |
| Visual acuity impairment (%)  | 44/51 (86%)   |
| No symptom (%)  | 3/55 (5%)     |
| Vitreous haze   | 44/48         |
| Unilateral ocular involvement   | 26/51 (51%)   |
| Bilateral ocular involvement  | 25/51 (49%)   |
| Median best corrected visual acuity of affected eyes at diagnosis, logMAR (range) | +0.3 (0-1.3)  |
| IL10 and IL6 dosage in AH and/or vitreous   |               |
| Number of data available  | 46/55 (84%)   |
| Median IL10 in AH (pg/ml) (range)   | 214 (4-5000)  |
| Median IL10 in vitreous (pg/ml) (range)   | 720 (0-10453) |
| Increased IL10 in AH and/or vitreous (%)  | 42/46 (91%)   |
| IL10/IL6 >1 in AH and/or vitreous   | 33/36 (92%)   |
| CSF analysis  |               |
| Lumbar puncture performed   | 35/52 (67%)   |
| Lymphomatous cells (cytology or flow cytometry)                                   | 2/35 (6%)     |
| No lymphomatous cells   | 33/35 (94%)   |
| CSF IL-10   |               |
| Detectable  | 4/10 (40%)    |
| Undetectable  | 6/10 (60%)    |

Table 3: Treatments of IIOR and outcomes

| N  | 55           |
|--|--------------|
| Type of treatment                                |              |
| Only systemic CT                                 | 35/55 (64%)  |
| Only local treatment                             | 8/55 (15%)   |
| IVT MTX  | 6            |
| Ocular RT  | 2            |
| Both systemic and local treatment                | 10/55 (18%)  |
| Only steroids                                    | 1/55 (2%)    |
| No treatment                                     | 1/55 (2%)    |
| Systemic treatment                               | 45/55 (82%)  |
| ifosfamide-based                                 | 13/55 (24%)  |
| methotrexate-based                               | 10/55 (20%)  |
| temozolomide alone                               | 10/55 (20%)  |
| lenalidomide                                     | 4/55 (7%)    |
| AraC-based                                       | 3/55 (5%)    |
| ibrutinib  | 3/55 (5%)    |
| other  | 2/55 (4%)    |
| rituximab  | 19/55 (35%)  |
| Local treatment                                  | 18/55 (33%)  |
| IVT MTX  | 13/55 (24%)  |
| Ocular RT  | 5/55 (9%)    |
| Thiotepa-based HCT-ASCT                          | 11/55 (20%)  |
| Median age at IIOR (range)                       | 60 (50-73)   |
| Median KPS at IIOR (range)                       | 80 (70-90)   |
| Response to treatment                            |              |
| CR/uCR   | 27/54 (50%)  |
| PR   | 0            |
| SD   | 1/54 (2%)    |
| PD   | 24/54 (44%)  |
| PD only in the eye                               | 15/54 (28%)  |
| PD in the brain +/- in the eye                   | 9/54 (17%)   |
| Not evaluable                                    | 2/54 (4%)    |
| IL-10 in the AH at the end of the treatment      | N=33         |
| In patients with CR/uCR in the eye               |              |
| Detectable                                       | 0            |
| Undetectable                                     | 18/18 (100%) |
| In patients with SD/PD in the eye                |              |
| Detectable                                       | 15/15 (100%) |
| Undetectable                                     | 0            |
| Number of patients who relapsed after the IIOR   | 42/55 (76%)  |
| In patients with HCT-ASCT at IIOR                | 4            |
| In patients with no HCT-ASCT at IIOR             | 38           |
| Number of patients who never relapsed after IIOR | 13/55 (24%)  |
| Early death after IIOR                           | 3            |
| In patients with HCT-ASCT at IIOR                | 6            |

|   |             |
|---|-------------|
| In patients with no HCT-ASCT at IIOR                      | 4           |
| Localization of the first relapse post-IIOR               |             |
| - Only brain  | 14/42 (33%) |
| - Only eye  | 23/42 (55%) |
| - Both brain and eye                                      | 5/42 (12%)  |
| Localization of relapses throughout the disease post IIOR |             |
| - Only Brain  | 12/42 (29%) |
| - Only eye  | 13/42 (31%) |
| - Both brain and eye                                      | 17/42 (40%) |
| HCT-ASCT at subsequent relapses after IIOR                | 4/42 (10%)  |
| Death N (%)   | 26/55 (47%) |
| Cause of death  |             |
| Cerebral progression of the lymphoma                      | 23          |
| Treatment-related toxicity                                | 2           |
| Other   | 1           |

Table 4: Prognostic factors in terms of OS (uni- and multivariate analysis)

|  | N  | Univariate analysis |      | Multivariate analysis |      |
|--|----|---------------------|------|-----------------------|------|
|  |    | Median OS           | p    | HR                    | P    |
| Age at IIOR <70 years                  | 32 | NR                  | 0.01 | 2.9                   | 0.02 |
| Age at IIOR >70 years                  | 23 | 37.1                |      |                       |      |
| KPS at IIOR ≤70                        | 8  | 24                  | 0.05 | 0.4                   | 0.07 |
| KPS at IIOR >70                        | 43 | NR                  |      |                       |      |
| Female sex                             | 30 | NR                  | 0.03 | 2.5                   | 0.04 |
| Male sex                               | 25 | 45.9                |      |                       |      |
| Delay diag-IIOR <18 months             | 35 | 40.1                | 0.01 | 0.4                   | 0.14 |
| Delay diag-IIOR > 18 months            | 20 | NR                  |      |                       |      |
| IIOR at 1 <sup>st</sup> relapse        | 48 | 57.1                | 0.3  |                       |      |
| IIOR at 2d relapse                     | 7  | NR                  |      |                       |      |
| Unilateral IIOR                        | 26 | NR                  | 0.2  |                       |      |
| Bilateral IIOR                         | 25 | 55.6                |      |                       |      |
| IL-10 in AH or vitreous < median value | 23 | 57.1                | 0.9  |                       |      |
| IL-10 in AH or vitreous ≥ median value | 22 | 51.1                |      |                       |      |
| Type of treatment                      |    |                     | 0.3  |                       |      |
| Systemic                               | 35 | NR                  |      |                       |      |
| Local                                  | 8  | 40.4                |      |                       |      |
| Local + systemic                       | 10 | 34.1                |      |                       |      |
| Type of systemic treatment             |    |                     | 0.1  |                       |      |
| ifosfamide-based                       | 13 | 37.5                |      |                       |      |
| methotrexate-based                     | 10 | NR                  |      |                       |      |
| temozolomide alone                     | 10 | 37.1                |      |                       |      |
| Rituximab at IIOR                      | 19 | NR                  | 0.3  |                       |      |
| No rituximab at IIOR                   | 36 | 51.1                |      |                       |      |
| HCT-ASCT at IIOR                       | 11 | NR                  | 0.4  |                       |      |
| No HCT-ASCT at IIOR                    | 44 | 55.6                |      |                       |      |
| Localization of 1st relapse post IIOR  |    |                     | 0.02 |                       |      |
| Brain+/- eye                           | 19 | 24                  |      |                       |      |
| Only eye                               | 23 | 57.1                |      |                       |      |

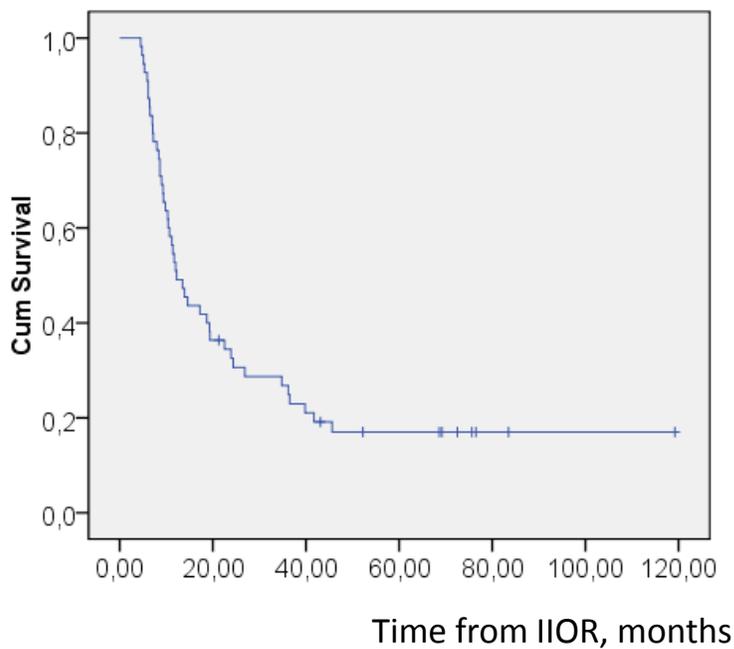
NR : not reached

Table 5: Comparison between characteristics of IIOR and characteristics of first (oculo)cerebral relapses in the whole LOC network database cohort

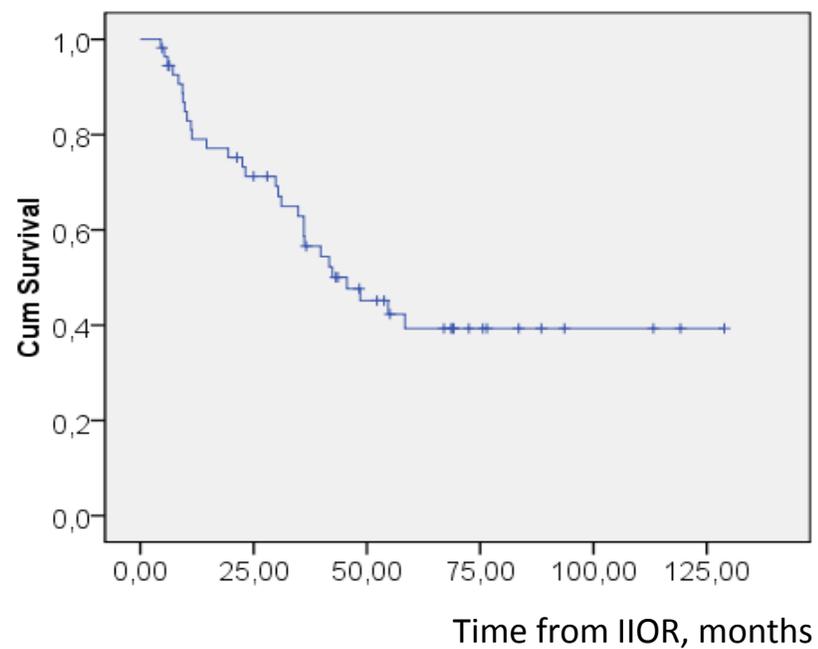
|  | IIOR      | First relapses in the whole LOC network database cohort | p      |
|--|-----------|---|--------|
| N  | 55        | 471   |        |
| Median age (years)   | 68        | 69  | NS     |
| Sex ratio M/W  | 0.8       | 1.2   | NS     |
| OPH involvement at baseline                                |           |   |        |
| Yes  | 27 (49%)  | 56 (13%)  | <0.001 |
| No   | 17 (31%)  | 233 (52%)   |        |
| No work-up   | 11 (20%)  | 157 (35%)   |        |
| 1 <sup>st</sup> line of treatment                          |           |   |        |
| HD-MTX based CT  | 56 (100%) | 451 (96%)   | NS     |
| Median time between initial diagnosis and relapse (months) | 16        | 8   |        |
| Refractory to previous treatment                           | 7         | 232   | <0.001 |
| Not refractory to previous treatment                       | 48        | 239   |        |
| Median KPS at relapse                                      | 80        | 60  | <0.001 |
| KPS $\geq$ 70  | 50        | 105   |        |
| KPS <70  | 1         | 346   |        |
| Treatment at relapse                                       |           |   |        |
| Active treatment   | 54 (98%)  | 378 (82%)   | 0.002  |
| Palliative care  | 1 (2%)    | 82 (18%)  |        |
| HCT-ASCT (at any time of the follow-up after relapse)      | 15 (27%)  | 76 (17%)  | 0.05   |
| No HCT-ASCT  | 40 (73%)  | 384 (83%)   |        |
| Median PFS after relapse (months)                          | 12.2      | 3.7   | <0.001 |
| Median OS after relapse (months)                           | 57.1      | 6.8   | <0.001 |
| In patients > 70 years                                     | 37.1      | 4.6   | <0.001 |
| In patients < 70 years                                     | NR        | 8.4   | <0.001 |

NS : not significant

Progression-free survival



Brain-free survival



Overall survival

