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CLINICAL STUDY

Diagnostic delay and outcome in immunocompetent patients with primary central nervous system lymphoma in Spain: a multicentric study

R. Velasco[1,2,29] · S. Mercadal[3] · N. Vidal[1,4] · M. Alañá[5] · M. I. Barceló[6] · M. J. Ibáñez-Juliá[7] · S. Bobillo[8] · R. Caldú Agud[9] · E. García Molina[10] · P. Martínez[11] · P. Cacabelos[12] · A. Muntañola[13] · G. García-Catalán[14] · J. M. Sancho[15] · I. Camro[16] · T. Lado[17] · M. E. Erro[18] · L. Gómez-Vicente[19] · A. Salar[20] · A. C. Caballero[21] · M. Solé-Rodríguez[22] · J. Gállego Pérez-Larraya[23] · N. Huertas[24] · J. Estela[25] · M. Barón[26] · N. Barbero-Bordallo[27] · M. Encuentra[3] · I. Dlouhy[28] · J. Bruna[1,2] · F. Graus[28] · GELTAMO and GENOSEN group

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Abstract

Introduction To assess the management of immunocompetent patients with primary central nervous system lymphomas (PCNSL) in Spain.

Methods Retrospective analysis of 327 immunocompetent patients with histologically confirmed PCNSL diagnosed between 2005 and 2014 in 27 Spanish hospitals.

Results Median age was 64 years (range: 19–84; 33% ≥ 70 years), 54% were men, and 59% had a performance status (PS) ≥ 2 at diagnosis. Median delay to diagnosis was 47 days (IQR 24–81). Diagnostic delay > 47 days was associated with PS ≥ 2 (OR 1.99; 95% CI 1.13–3.50; p = 0.016) and treatment with corticosteroids (OR 2.47; 95% CI 1.14–5.40; p = 0.023), and it did not improve over the years. Patients treated with corticosteroids (62%) had a higher risk of additional biopsies (11.7% vs 4.0%, p = 0.04) but corticosteroids withdrawal before surgery did not reduce this risk and increased the diagnostic delay (64 vs 40 days, p = 0.04). Median overall survival (OS) was 8.9 months [95% CI 5.9–11.7] for the whole series, including 52 (16%) patients that were not treated, and 14.1 months (95%CI 7.7–20.5) for the 240 (73.4%) patients that received high-dose methotrexate (HD-MTX)-based chemotherapy. Median OS was shorter in patients ≥ 70 years (4.1 vs. 13.4 months; p < 0.0001). Multivariate analysis identified age ≥ 65 years, PS ≥ 2, no treatment, and cognitive/psychiatric symptoms at diagnosis as independent predictors of short survival.

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R. Velasco and S. Mercadal contributed equally to the development of this article.

R. Velasco and F. Graus should be considered co-senior authors.

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Extended author information available on the last page of the article

Conclusions Corticosteroids withdrawal before surgery does not decrease the risk of a negative biopsy but delays diagnosis. In this community-based study, only 73.4% of patients could receive HD-MTX-based chemotherapy and OS remains poor, particularly in elderly patients ≥ 70 years.

Keywords Primary central nervous system lymphoma · Diagnostic delay · Steroids · Prognostic factors · Outcome

Introduction

Primary central nervous system lymphomas (PCNSL) account for less than 4% of primary brain tumours with an estimated incidence of 0.4 cases per 100.000 person-years [1, 2]. The great majority of PCNSL occur in immunocompetent patients. Despite PCNSL are rare, early diagnosis and treatment is important because survival and quality of live significantly improves with treatment and a few patients can be cured [3, 4]. Presently, there is no a universally accepted standard treatment although young patients are treated with high-dose methotrexate (HD-MTX)-based chemotherapy regimens and responders are consolidated with autologous stem cell transplantation (ASCT) or less frequently with whole brain radiotherapy (WBRT) [5]. In patients > 70 years, the optimal treatment is more controversial because consolidation with ASCT is not feasible and WBRT associates with an unacceptable risk of dementia [6, 7].

Community and population-based studies are important to confirm that management recommendations and the results of clinical trials have an impact in the routine clinical practice of brain tumors [8–10]. These goals are more difficult to accomplish in rare tumours, as PCNSL, in which management and therapy guidelines are not based on large randomized studies. For example, the use of corticosteroids is not advised because they may decrease the diagnostic yield of the biopsy [11] but retrospective studies have challenged this long-held practice [12, 13]. Despite its relevance, the impact on the use of corticosteroids before the histopathological diagnosis has not been systematically analysed in population-based series of PCNSL [10, 14–20].

The objective of present study was to evaluate the management and outcome of immunocompetent patients with PCNSL in Spain. In particular, we reviewed the patterns of care before and after the histopathological diagnosis, and we also specifically evaluated the management of elderly patients, that represents around 30% of the total population of PCNSL.

Methods

All immunocompetent patients with new PCNSL diagnosed between January 2005 and December 2014 in 27 Spanish hospitals were included in the study. All of the centres of the GELTAMO and GENOSEN groups could participate in the study. Patients were identified from the neuropathology, neuro-oncology, hematology, and/or radiotherapy databases from each center. The 27 participating hospitals cover approximately 20 million inhabitants (44.5% of the Spanish population). Demographic and clinical information was retrospectively collected using a specific data form. Each form was anonymized and sent to the coordinating study center (Hospital Universitari de Bellvitge-Institut Català d´Oncologia- L´Hospitalet de Llobregat). The study was approved by the Institutional Ethical Committee of the coordinating center and, subsequently, by each participating center. The WHO 2008 criteria were used for the diagnosis of the PCNSL [21].

During the duration of this study (2005–2014), two treatment protocols (2002 and 2008) issued by GELTAMO (Spanish group of lymphomas and bone marrow transplant) were recommended for PCNSL. The 2002 protocol included 6 cycles of MTX 2 g/m^2 and cytarabine 3 g/m^2 every 2 weeks plus 2 cycles of BCNU 100 mg/m^2, followed by WBRT, up to 45 Gy [22]. In 2008, the protocol was amended: MTX dose increased to 3 g/m^2 and ASCT was introduced as consolidation instead of WBRT in patients who achieved a partial or complete response to the induction treatment. None of these protocols included rituximab as part of first-line treatment. Elderly patients (> 70 years) were treated, if feasible, with HD-MTX-based chemotherapy without consolidation with ASCT or WBRT.

Statistical analysis

Descriptive statistics were used to summarize the clinical data. Categorical data were compared using Chi-Square test, whereas for continuous variables, non-parametric tests were used. Differences among the subgroups of patients were compared by using the Chi-square test (two-tailed), the Student's t-test or non-parametric tests when necessary. To identify variables associated with the need of more than one brain biopsy or longer time for achieving diagnosis, multivariate logistic binary regression analysis in a backward selection method introducing the significant ($p < 0.1$) variables identified in univariate analysis were performed. Diagnostic delay was defined as time (in days) from first symptom to pathological diagnosis. Cut-off for diagnostic delay was considered according the median of our series. The actuarial survival analysis was performed by the Kaplan

and Meier method and differences assessed by the log-rank test. Overall survival (OS) was calculated according to standard definitions. Prognostic factors significant in the univariate analysis were included in multivariate analyses. The multivariate analysis for survival was performed by using the proportional hazards model (Cox) in all patients. P values < 0.05 were considered statistically significant.

Results

Patient characteristics

The study identified 327 immunocompetent patients with new PCNSL. Demographic and clinical characteristics at diagnosis are summarized in Table 1. Median age was 64 [19–84] years with a slight predominance of men (54%). All histologies were included in the study. The great majority of patients (n = 314, 96%) were diffuse large B-cell lymphoma (DLBCL). Focal deficit (60%) and cognitive and/or behavioural changes (38%) were the most common presenting symptoms. Performance Status (PS), defined according to the Eastern Cooperative Oncology Group (ECOG), was ≥ 2 in 59% of patients. Brain neuroimaging demonstrated single (52%) or multiple (48%) lesions in the cerebral hemispheres in 259 (79%) patients. Lesions restricted to deep structures (corpus callosum, basal ganglia or infratentorial) were observed in 68 (21%) patients. PCNSL lesions showed gadolinium enhancement that was homogeneous or heterogeneous in 257 (87%) of patients and with a ring-pattern of enhancement in 29 (10%). Eight (3%) of patients presented diffuse, non-contrast enhancing lesions in FLAIR and T2 weighted sequences compatible with lymphomatosis cerebri.

Use of corticosteroids and need of additional biopsies for the histopathological diagnosis

Twenty-nine patients (9%) of the whole series required more than one biopsy to confirm the diagnosis of PCNSL. Among those 29 patients who required at least a second biopsy, final diagnosis was B and T-cell lymphoma in 28 and 1, respectively. Information on corticosteroids administration before the histopathological diagnosis was available in 280 (86%) patients. Corticosteroids were not used in 105 (37.5%) patients, 175 (62.5%) received corticosteroids that were withdrawn before surgery in 51 of them (29%) with a median of 15 days [IQR: 4–42]. Patients treated with corticosteroids more frequently required a second biopsy to stablish the diagnosis (20 (12%) vs. 4 (4%), p = 0.04). The tapering of corticosteroids before the biopsy did not decrease the risk of a negative result (5 (10%) vs. 15 (12%), p = 0.7).

Table 1 Characteristics of 327 immunocompetent patients with PCNSL diagnosed between 2005 and 2014

Characteristic	N (%)
Median age [range]	64 [19–84]
Age > 70	109 (33)
Sex	
Male	176 (54)
Female	151 (46)
ECOG performance status	
PS < 2	113 (41)
PS ≥ 2	165 (59)
Year of diagnosis	
2005–2009	127 (39)
2010–2014	200 (61)
Histology	
DLBCL	314 (96)
T-cell lymphoma	8 (2.4)
MALT	2 (0.6)
Hodgkin	1 (0.3)
Anaplastic	1 (0.3)
Follicular	1 (0.3)
Main symptoms at presentation	
Focal deficit	171 (60)
Cognitive/behavioural	123 (38)
Headache	90 (27)
Gait disorder	68 (21)
Epilepsy	42 (13)
Number of lesions	
Single	162 (52)
Multiple	150 (48)
Location	
Cerebral hemispheres	259 (79.2)
Only in corpus callosum, basal ganglia, or infratentorial	68 (20.8)
Type of gadolinium enhancement	
Homogeneous	187 (63.6)
Heterogeneous	70 (23.8)
Ring-like	29 (9.8)
No enhancement	8 (2.7)
Study extension	
Whole body CT scan or PET/CT scan	327 (100)
Bone marrow aspirate or biopsy	199 (61)
Ophthalmologic evaluation	104 (32)
CSF examination	144 (44)

Diagnostic delay

The median time delay between the onset of first symptoms to the first neuroimaging was 15 days (IQR: 4–38 days), being longer in patients who had visual (27 days, p = 0.006) or vertigo/dizziness (19 days, p = 0.012) as predominant

complains, and shorter in patients that presented with seizures (4.5 days, p = 0.006). The median time delay from onset of symptoms to histopathological diagnosis in the whole series was 47 days (IQR: 24–81 days). Diagnostic delay was not improved over the years increasing from a median of 41 days (2005–2009) to 48 days in the subsequent years (p = 0.048). As expected, time delay was significantly longer in those patients requiring an additional biopsy (43 vs. 90 days, p < 0.001). Although more patients treated up front with corticosteroids needed a second biopsy for histopathological diagnosis, the diagnostic delay in the 124 patients that were biopsied on steroids was similar to that of the 105 patients who never received steroids. In contrast, the diagnostic delay was significantly longer in the 51 patients in whom steroids were stopped before the biopsy (Fig. 1). The multivariate analysis identified steroid withdrawal (OR 2.47, 95% CI 1.13–5.40; p = 0.023), and PS ≥ 2 (OR 1.99, 95% CI 1.13–3.50; p = 0.016) as independent variables for a longer diagnostic delay (> 47 days).

Treatment and outcome

Fifty-two patients of the whole series (16%) were not treated. Compared with treated patients, those that did not receive oncological treatment were older (70 vs. 62 years; p < 0.001) and with worse PS (PS ≥ 2, 88% vs. 54%; p < 0.0001). Of the remaining 275 patients, 240 (87%) received HD-MTX-based chemotherapy (73.4% of the whole series and 96% of patients of treated patients < 70 years), 7 (2.5%) received non-HD-MTX-based chemotherapy, and 23 (8.3%) only WBRT. WBRT was given to 36 of 65 (55.4%) patients treated according the 2002 protocol whereas 62/122 (51%) received an ASCT since the procedure was implemented in 2008. With a median follow-up of the whole series of 9 months, median OS was 8.9 months (95% CI 5.9–11.7) and that of the 240 patients treated with HD-MTX-based chemotherapy 14.1 months (CI 95% 11.1–16.3). The median OS of patients consolidated with WBRT was 48.5 months and that of those with ASCT 72.75 months (p = 0.309) (Fig. 2a).

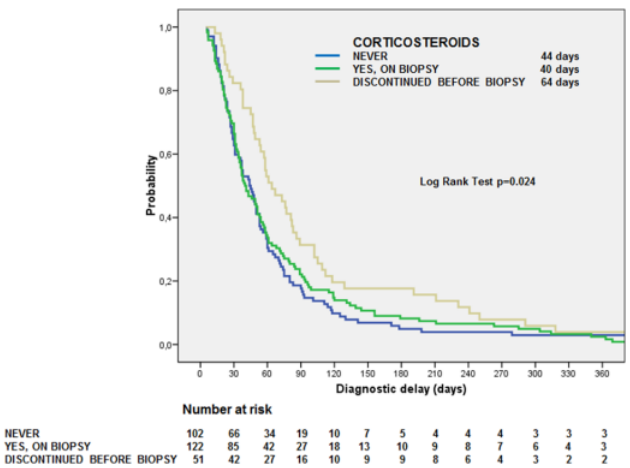

Fig. 1 Diagnostic delay according to previous steroids administration. Five patients with missing data regarding diagnostic delay were excluded

At the time of this analysis, January of 2018, 226 patients were dead, 63 were alive (8 of them with active PCNSL) and 38 were lost of follow-up. A sub-analysis regarding the two different periods (2005–2009 and 2010–2014) is summarized in a Supplementary Table. One hundred patients were early deaths, considered less than 3 months from the diagnosis; fifteen percent of these were toxic/sepsis and 85% due to progression of the lymphoma. The multivariate analysis showed age ≥ 65 years (OR 1.348 95% CI (1.003–1.813); p = 0.048), PS ≥ 2 (OR 1.615 95% CI (1.195–2.184); p = 0.002), presence of cognitive/psychiatric impairment at diagnosis (OR:1.483 95% CI (1.113–1.977); p = 0.007) and no oncological treatment (OR 5.715 95% CI (3.726–8.765; p < 0.0001) as independent factors associated with worse outcome. Neither diagnostic delay, nor periods of treatment (2005–09 vs 2010–14), nor histology were associated with survival.

The analysis comparing older (≥ 70 years) and younger (< 70) patients, identified that elderly patients were more likely to present PS ≥ 2 and cognitive/psychiatric symptoms at diagnosis (Table 2). There were no differences in diagnostic delay. Elderly patients were less frequently treated (27.5% vs. 10.1%; p < 0.001) and HD-MTX-base chemotherapy could be given to only 54 of 76 (71%) treated patients. Median OS of the elderly patients was 4.1 months (95% CI 2.2–6.0 months) (Fig. 2b). In those who received HD-MTX-base chemotherapy median OS (10.5 months; 95% CI 0.5–20.4 months) was shorter than that of younger patients (15.9 months; 95% CI 5.6–26.2, p = 0.007) (Table 2).

Discussion

Our study provides relevant information on the management and outcome of immunocompetent patients with PCNSL in a community setting. First, corticosteroids were given to 62% of patients before surgery despite the advice of PCNSL guidelines to withhold this treatment in patients with suspected PCNSL [11]. Second, the decision to stop corticosteroids several days before the biopsy did not decrease the risk of a false negative result but delayed the diagnosis. Third, despite medical advances, 16% of patients could not be treated and no improvement in OS with time was observed that remains poor with a median of 9 months. Lastly, the considered standard treatment of HD-MTX-based chemotherapy was given to the great majority (87%) of treated

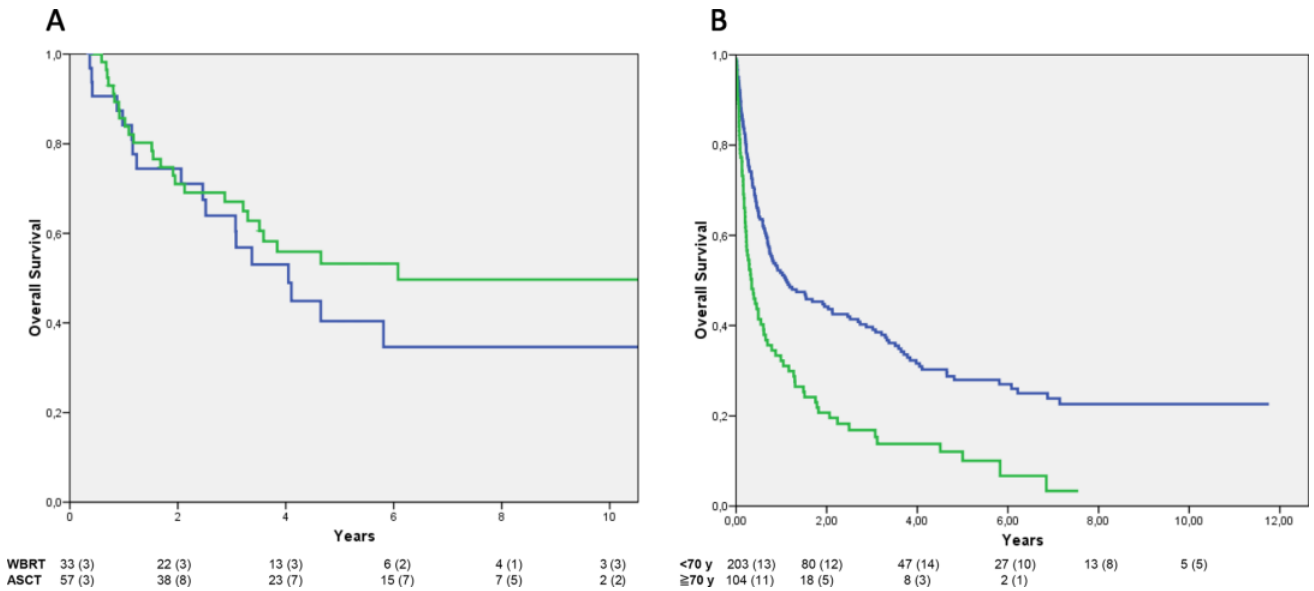

Fig. 2 **a** Overall survival of PCNSL patients treated with high-dose MTX-based chemotherapy and consolidated with whole brain radiotherapy (blue line) or autologous stem-cell transplantation (green line) p = 0.309. **b** Overall survival of elderly (≥ 70 years (green line) compared to younger (< 70 years (blue line) PCNSL patients (p < 0.001). Eight patients with missing survival data were excluded

Table 2 Characteristics of PCNSL patients according to age

	≥ 70 years n = 109 (%)	< 70 years n = 218 (%)	p
Median age (range)	74 (70–84)	58 (19–69)	*< 0.0001*
Male/female	61/48	115/103	0.58
PS ≥ 2	61(67.8)	103 (54.8)	*0.039*
Presenting symptoms (%)			
Epilepsy	7 (6.4)	35 (16.1)	*0.014*
Focal deficit	64 (58.7)	107 (49.1)	0.1
Cognitive/psychiatric	48 (44.0)	74 (33.9)	0.075
Imaging			
Single lesion	60 (58.8)	102 (48.6)	0.089
Only deep lesions	21 (19.3)	47 (21.6)	0.630
Ring enhancement	10 (9.9)	19 (10.3)	0.921
Treatment with corticosteroids	62 (56.9)	113 (51.8)	0.679
Diagnostic delay (days)	77	85	0.095
Oncological treatment			*< 0.0001*
None	30 (27.5)	22 (10.1)	
WBRT alone	17 (15.6)	6 (2.8)	
HD-MTX	54 (49.5)	186 (85.3)	
Non-HD-MTX	5 (4.6)	2 (0.9)	
Unknown	3 (2.8)	2 (0.9)	
Median overall survival (months)	4.1	13.4	*< 0.0001*
2-year survival rate (%)	18	39	*< 0.0001*

HD-MTX high-dose methotrexate-based chemotherapy, *PS* performance status, *WBRT* whole brain radiotherapy

patients reflecting a good compliance with the recommended guidelines [11].

The demographic, clinical, and imaging features of the present series is not different from other contemporary series of PCNSL (Table 3) [10, 14–20]. Up to 13% of the patients did not show the typical MRI features of PCNSL in immunocompetent patients [23, 24]. Ring-like enhancement, more frequent in immunocompromised patients, was observed in 10% of patients, as previously reported [23, 25], and diffuse non-contrast enhancing lesions compatible with lymphomatosis cerebri in 3% [26].

Contemporary population or community-based series of PCNSL have not routinely addressed the frequency and impact of the use of corticosteroids on diagnostic yield of biopsy in PCNSL an issue that remains controversial [10, 14–20]. Although the practice to avoid treatment with corticosteroids, if clinically feasible, has been recommended for at least two decades [27] and included in the 2015 guidelines from the European Association of Neuro-Oncology (EANO) [11], the majority of our patients received corticosteroids before biopsy with a frequency (62.5%) similar to that observed in other series [12, 28]. The frequency of false-negative biopsies may increase to 50% in those patients with MRI tumor response after corticosteroids [4, 29]. However two retrospective studies indicated that the corticosteroid treatment did not increase the risk of second biopsies or delay the histological diagnosis of PCNSL [12, 13]. In contrast, we observed that corticosteroids use carried 3 times more risk of requiring an additional brain biopsy to achieve a histological diagnosis. The discrepancy with previous

Table 3 Community and population-based contemporary large series of immunocompetent patients with PCNSL

Author [References]	Study period	n	Country	Median age (range)	Time to diagnosis (days)	PS ≥2 (%)	Median survival (months)	No treatment (%)	Comments
Haldorsen et al. [12]	1989–2003	98	Norway	68 (11–83)	91	55	7	20	18 patients diagnosed at autopsy Diagnostic delay and survival did not improve with time
Enblad et al. [13]	2000–2012	*96*	Sweden	66 (17–95)	–	50	4	25	Eight patients were receiving immunosuppressive therapy
Eloranta et al. [14]	2000–2013	*359*	Sweden	66 (18–95)	–	52	7.6	–	Survival did not improve with time
Fallah et al. [16]	2004–2013	*9165*	USA	67 [58–75]	–	–	16*	17	Survival improved with time
Shan et al. [17]	1973–2014	*5138*	China	61	–	–	–	17	Survival increased in chemotherapy-treated patients from 18 months (1973–84) to 34 months (2007–14)
van der Meulen et al. [18]	1989–2015	*1673*	Netherlands	65 (19–87)	–	–	–	19	OS increased over time except in patients > 70 years
Houillier et al. [10]	2011–2016	*1002*	France	68 (18–91)	35	**60	25.3	3	HD-MTX in 92% of patients OS 38% of the patients at 5 years
Present study	2005–2014	*327*	Spain	64 (19–84)	47	59	8.9	16	

*Patients who where not treated were excluded

**Median KPS

studies could be explained by the number of patients that underwent a biopsy of masses that were responding to corticosteroids in follow-up MRI [12, 13]. Unfortunately, our study could not review if negative biopsies occurred more frequently in patients with documented tumor shrinkage because information if an MRI had been done immediately before the biopsy was not collected.

An issue not addressed in previous studies is the need to stop corticosteroids and to delay the biopsy one or two weeks. In our series we did not observed that withholding corticosteroids decreased the risk of an additional biopsy but contributed to a significantly longer diagnostic delay. Therefore, corticosteroids discontinuation should not be indicated unless a new brain MRI confirmed a partial or complete remission of the lesion. In this setting, biopsy probably should be delayed until further evidence of tumor relapse or progression [11].

In the present study, the median time delay from onset of symptoms to histopathological diagnosis was 47 days that is similar to that of other contemporary series [10, 17, 30, 31]. Despite recent advances, diagnostic delay was not shortened in our study in agreement with the observation in the population-based study of Norway over a 15-year period [14]. The diagnostic delay is still suboptimal and probably reflects the access to imaging studies when symptoms are less severe, as visual symptoms or vertigo [28], and the impact of corticosteroid treatment, particularly when corticosteroids have to be stopped before the biopsy. Alternatively, the no reduction of diagnostic delay may reflect the increasing diagnosis of PCNSL in patients with comorbidities or poor PS that in the past were not considered for biopsy. In fact, in our study there was an increase of 20% in the number of cases of PCNSL diagnosed in the last 5 years.

Our study confirms previous data on the uniformly positive influence of younger age and good performance status at diagnosis as the main favourable prognostic factor in immunocompetent PCNSL patients [32, 33]. The impact of diagnostic delay in the outcome of PCNSL is unclear as

this variable was not included in the two most recognized prognostic models [32, 33]. However, one of these studies included in the analysis duration of symptoms (without to specify if duration was to first neuroimaging or to histological diagnosis) that was not identified as an independent prognostic variable for survival [32]. In line with the findings of the present study, other series did not find a correlation between diagnostic delay and survival, or delay from first symptom to treatment [10, 34, 35], whereas in a small series of 28 patients with PCNSL, survival was negatively correlated with delay time to fist brain MRI scan [30].

Similar to other community-based series of PCNSL, the outcome in our study was poor (Table 3). In addition, 16% of the patients could not receive oncological treatment mainly due to a poor PS and advance age [14–16]. These figures are also very similar to that observed in series of patients with glioblastoma [9, 36] suggesting that the increased tumor chemosensitivity of the PCNSL does necessarily provides a better chance of survival and probably it is counterbalanced by the higher frequency of poor PS (59% of patients with a PS ≥ 2 in this study) due to the rapid growing of the tumor and the involvement of multiple brain areas in more than 30% of the patients [3]. Another reason for the poor OS in community-based series of PCNSL is the inclusion of elderly patients > 70 years in whom no appropriate consolidation treatments can be given [6]. In our study, this elderly population is not negligible and represented a third of the whole series. And we can confirm that elderly patients > 70 years were less likely to be treated, or to receive HD-MTX-based chemotherapy and had a poorer PS than younger patients with a median OS of only 4.1 months [37]. The inclusion of this elderly population in this "real life" PCNSL study could contribute to the poor outcome of the global series.

In the 10 years of the study we did not observe an improvement of OS despite the progressive introduction of ASCT as the preferred consolidation therapy. However, ASCT was almost double comparing WBRT as consolidation in median OS in our series although not statistically significant. Two similar studies in the same period conducted in Sweden also confirmed this observation that suggest that the poor survival of untreated patients neutralizes the improved OS observed in those that receive oncological treatment [15, 16]. Other studies that analysed the survival evolution across several decades confirmed an improvement on median OS only in patients ≤ 70 years whereas in older patients OS has not changed in the last decades [1, 20].

HD-MTX-based chemotherapy was given to 87% of patients that receive oncological treatment (96% in < 70 years) of the present series reflecting a similar compliance with PCNSL guidelines than in other contemporary series that reported the use of this therapy [10, 15–17]. However, when considered all 327 patients, only 240 (73.4%) received HD-MTX-based chemotherapy, what probably justifies, in part, the short OS of the whole series. A relevant data of the study is that 51% (62/122) of patients received an ASCT after at least partial response or stable disease after HD-MTX-based chemotherapy. Compared to clinical trials that evaluate the efficacy of ASCT as first-line treatment, the frequency of patients that received ASCT in our series is similar to the 53.9% reported in International Extranodal Lymphoma Study Group-32 trial and inferior to the 66.7% in the PRECIS study in which patients were eligible for ASCT regardless of response to induction chemotherapy [5, 38].

Our study has some limitations that must be considered. Despite its multicentre population-based design, it is not a comprehensive nationwide study and no information regarding the prevalence and incidence of the PCNSL in Spain can be done. All patients included in the study had confirmed pathology of PCNSL and no suspected cases were included. However, in this study, a central pathology review could not be performed. In a contemporary series, 18% of the 98 PCNSL patients were only diagnosed at autopsy indicating that despite neurosurgical and medical advances a fraction of patients cannot be diagnosed in life what worsens the already poor OS of PCNSL [14]. The retrospective character of this study was based on medical records and brain MRI imaging central review was not performed. Furthermore, the lack of data of immunophenotype and some cytogenetic features of PCNSL prevented their analysis. However, the data obtained indicate that the clinical and radiological features were very similar to those of other contemporary series of PCNSL [10, 14–20]. Formal neuropsychological evaluations were seldom included in the baseline assessment of patients or during the follow-up and no reliable data could be provided on the impact of different therapies on the development of cognitive impairment [39, 40].

This study demonstrates that patients with a rare tumour, as PCNSL, can receive an appropriate and reasonable uniform treatment in Spain. The study also clearly identified areas that require more research and a different approach as for example to decrease the number of patients, particularly those ≥ 70 years, that cannot receive HD-MTX-based chemotherapy, or to take actions to better implement accepted recommendations as the restrictive use of corticosteroids before biopsy.

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Vall d'Hebron. Barcelona (Pau Abrisqueta), Department of Hematology. Hospital Universitario de Salamanca, Salamanca, Spain (Alejandro Martin García-Sancho; Míriam Lopez Parra), Department of Hematology. ICO-Hospital Universitari de Tarragona Joan XXIII. Universitat Rovira I Virgili, Tarragona, Spain. (Lourdes Escoda), Department of Hematology. ICO-Hospital Germans Trias i Pujol. Badalona (Marc Sorigué). **GENOSEN (Grupo de Estudio de Neurooncología de la Sociedad Española de Neurología):** Department of Neurology, Hospital Universitario La Fe, Valencia (Luis Bataller), Department of Neurology, Fundación Jimenez Diaz, Madrid (Raúl Córdoba), Department of Neurology, Hospital Universitario Miguel Servet, Zaragoza (Miguel González Sánchez), Department of Neurosurgery, Hospital Universitario Marqués de Valdecilla, Santander (Juan Martino), Department of Neurology, Hospital Rey Juan Carlos, Madrid (Javier Pardo-Moreno)

Author contributions RV, SM, NV, JB conceived and designed the analysis. RV,SM, NV, FG, MA, AM, IB, MJIJ, LB, SB, PA, RC, EG, PM, PC, AM, JM, JMS, IC, TLL, EE, LG, AS, AC, MS, JG, NH, JE, MB, NB, JP, RC, LE, ED, EGB, ID collected the data. RV, SM, JB, and ME performed the analysis. RV, SM, and FG wrote the paper.

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Compliance with ethical standards

Conflict of interest R.V. discloses membership on speaker bureau for Gilead and Novartis. A.S. discloses research funding and membership on advisory committees or speakers bureau for Roche, Celgene, Gilead or Janssen. F.G. holds a patent licensed to Euroimmun for the use of IgLON5 in an autoantibody test, for which he receives royalties, and receives honoraria from MedLink Neurology. The other authors declare no conflict of interest.

Ethical approval The study was approved by the Institutional Ethical Committee of the coordinating center and, subsequently, by each participating center.

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Affiliations

R. Velasco[1,2,29] · S. Mercadal[3] · N. Vidal[1,4] · M. Alañá[5] · M. I. Barceló[6] · M. J. Ibáñez-Juliá[7] · S. Bobillo[8] · R. Caldú Agud[9] · E. García Molina[10] · P. Martínez[11] · P. Cacabelos[12] · A. Muntañola[13] · G. García-Catalán[14] · J. M. Sancho[15] · I. Camro[16] · T. Lado[17] · M. E. Erro[18] · L. Gómez-Vicente[19] · A. Salar[20] · A. C. Caballero[21] · M. Solé-Rodríguez[22] · J. Gállego Pérez-Larraya[23] · N. Huertas[24] · J. Estela[25] · M. Barón[26] · N. Barbero-Bordallo[27] · M. Encuentra[3] · I. Dlouhy[28] · J. Bruna[1,2] · F. Graus[28] · GELTAMO and GENOSEN group

✉ R. Velasco
rvelascof@bellvitgehospital.cat

[1] Neuro-Oncology Unit, Hospital Universitari de Bellvitge-ICO Duran i Reynals, IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain

[2] Department of Cell Biology, Physiology and Immunology, Institute of Neurosciences, Universitat Autònoma de Barcelona, and Centro de Investigación Biomédica en Red Sobre Enfermedades Neurodegenerativas (CIBERNED), Bellaterra, Spain

[3] Department of Hematology, Catalan Institute of Oncology-Hospital Duran i Reynals, IDIBELL, Universitat de Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain

[4] Department of Pathology, Unit of Neuro-Oncology. Hospital Universitari de Bellvitge-ICO Duran i Reynals, IDIBELL, L'Hospitalet del Llobregat, Barcelona, Spain

[5] Department of Neurology, Complejo Asistencial Universitario, Salamanca, Spain

[6] Department of Neurology, Hospital Universitario Son Espases, Palma de Mallorca, Spain

[7] Department of Neurology, Hospital Universitario y Politécnico La Fe, Valencia, Spain

[8] Department of Hematology, Vall d'Hebron Institute of Oncology (VHIO), University Hospital Vall d'Hebron, Barcelona, Spain

[9] Department of Neurology, Hospital Universitario Miguel Servet, Zaragoza, Spain

[10] Department of Neurology, Virgen de la Arrixaca University Hospital, Murcia, Spain

[11] Department of Hematology, Hospital Universitario 12 de Octubre, Madrid, Spain

[12] Department of Neurology, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, La Coruña, Spain

[13] Department of Hematology, Hospital Universitario Mutua de Terrassa, Terrassa, Spain

[14] Department of Neurosurgery, Hospital Universitario Marqués de Valdecilla, Santander, Spain

[15] Department of Hematology, ICO-IJC-Hospital Germans Trias i Pujol, Badalona, Spain

[16] Department of Neurology, Hospital Universitario Cruces, Barakaldo, Vizcaya, Spain

[17] Department of Hematology, Hospital Clínico Universitario de Valladolid, Valladolid, Spain

[18] Neurology Department, Complejo Hospitalario de Navarra, Navarra Institute for Health Research (IdiSNA), Pamplona, Spain

[19] Department of Neurology, Hospital Universitario Quirónsalud Madrid, Pozuelo de Alarcón, Madrid, Spain

[20] Department of Hematology, Hospital del Mar, Barcelona, Spain

[21] Department of Hematology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

[22] Department of Hematology, Hospital Universitario Virgen del Rocío, Sevilla, Spain

[23] Departament of Neurology, Clínica Universidad de Navarra, IdiSNA, Instituto de Investigación Sanitaria de Navarra, Pamplona, Spain

[24] Department of Neurology, Hospital Universitario Severo Ochoa, Leganés, Madrid, Spain

[25] Department of Neurology, Hospital Parc Taulí, Sabadell, Spain

[26] Unit of Neurology, Hospital Universitario Fundación Alcorcón, Madrid, Spain

[27] Department of Neurology, Hospital Universitario Rey Juan Carlos, HURJC-HUIE-HCV, Madrid, Spain

[28] Department of Hematology and Neurology, Hospital Clínic de Barcelona, Barcelona, Spain

[29] Department of Neurology, Neuro-Oncology Unit, Hospital Universitari de Bellvitge and ICO L'Hospitalet, C/Feixa Llarga S/N, L'Hospitalet de Llobregat, 08907 Barcelona, Spain