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ORIGINAL ARTICLE

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Brain radiotherapy in patients treated for a newly diagnosed primary central nervous system lymphoma: professional practice evaluation in 19 French centers

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ABSTRACT

Introduction: The objective of this study was a multicentric evaluation of professional practices, analyzing the irradiation technique itself and its impact on survival and recurrence sites, in primary central nervous system lymphomas (PCNSLs).

Methods: We retrospectively analyzed the technical and clinical records of 79 PCNSL patients included in the database of the national expert network for oculocerebral lymphoma ('LOC') who were treated with brain radiotherapy as first-line treatment for newly diagnosed primary central nervous system lymphoma between 2011 and 2018.

Results: The number of patients treated with brain radiotherapy gradually decreased over time. The heterogeneity of radiotherapy prescriptions was significant, and 55% of them did not comply with published recommendations in terms of irradiation dose and/or volume. The proportion of complete responders to induction chemotherapy treated with reduced-dose radiotherapy increased over time. Partial brain radiotherapy was associated with significantly lower overall survival in univariate analysis. In partial responders to induction chemotherapy, increasing the total dose to the brain >30 Gy and adding a boost to the WBRT induced a trend toward improved progression-free and overall survival. Five recurrences (13%) occurred exclusively in the eyes, all in patients whose eyes had been excluded from the irradiation target volume and including 2 patients without ocular involvement at diagnosis.

Conclusion: The visibility of recommendations for prescribing brain radiotherapy for the treatment of newly diagnosed primary central nervous system lymphoma needs to be improved to harmonize practices and improve their quality. We propose an update of the recommendations.

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Introduction

Primary central nervous system lymphomas (PCNSLs) are high-grade non-Hodgkin's lymphomas located exclusively in the brain and/or spinal cord, eyes, and meninges in the absence of systemic lymphoma.

Historically, treatment of PCNSL was based on whole-brain radiotherapy (WBRT) alone at doses ≥40 Gy. The radiation doses were heterogeneous and radiation portals used ranged from local field to WB. Although it succeeded in most cases in achieving remission, relapses occurred rapidly and survival was poor: radiation doses of 20–55 Gy (median dose of 40 Gy) were reported to produce median OS of 24 months [1] and 42 months [2]. Treatment with high-dose methotrexate (HD-MTX) induction chemotherapy (CT) in combination with

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consolidation brain radiotherapy (RT) improved OS by a factor of 2–4 compared with brain RT alone [3–5]. However, this combined-modality therapy is associated with a significant risk of late neurotoxicity, which increases with age and total radiation dose [6–10].

Two recent randomized phase II trials concluded the efficacy of WBRT as well as myeloablative chemotherapy followed by autologous stem-cell transplantation (ASCT) for consolidation treatment of newly diagnosed PCNSL after HD-MTX-based induction CT [11,12]. ASCT was found to improve progression-free survival (PFS) and/or preservation of cognitive functions [11–13]. As a result, in many centers, ASCT is now preferred as a consolidation treatment for newly diagnosed PCNSL.

Currently, the indications for brain RT in the treatment of newly diagnosed PCNSL are (i) exclusive treatment of patients in whom CT is contraindicated and (ii) consolidation treatment in patients with a complete or partial response to HD-MTX-based induction CT who are ineligible for ASCT [14,15].

Reduced-dose WBRT (rdWBRT) (23.4 Gy in 1.8 Gy fractions) seems effective in patients with a complete response (CR) to HD-MTX-based induction CT [16], and the neurocognitive results obtained with this approach are encouraging [17–20].

The heterogeneity of radiotherapy regimens in recent prospective randomized trials containing a brain RT arm [11,12,18,19,21] as well as the heterogeneity of published recommendations [14,15,22,23] highlights the lack of consensus regarding the prescription of brain RT for the treatment of newly diagnosed PCNSL.

Because of the rare indications for brain RT in the treatment of newly diagnosed PCNSL and the heterogeneity of recommendations, difficulties in prescribing brain RT are observed in clinical practice.

In this study, we analyzed the clinical and technical records of patients treated with brain RT for newly diagnosed PCNSL in 19 French centers over the last 10 years to establish an overview of professional practices in France. Our secondary objective was to assess the correlation of irradiation patterns with survival outcomes and recurrence sites, with the aim of updating technical recommendations and improving the visibility of the recommendations among radiation oncologists.

Methods

Study design and participants

Patients were selected from the database of the national expert network for oculocerebral lymphoma ('LOC' network) according to the following inclusion criteria: (i) newly diagnosed PCNSL between 2011 and 2018 (ocular and/or cerebral, histologically proven or not), and (ii) treatment with cerebral RT as first-line therapy. There were no exclusion criteria, including age, Karnofsky performance status (KPS), or type of induction therapy before brain RT.

All patients or guardians provided written consent. The study was approved by the ethical committee of Ile de France, the federation of patient committees for clinical research in oncology, and the French agency for the safety of health products and was conducted according to the Declaration of Helsinki.

Records of patients meeting the inclusion criteria from all responding centers were included in the analysis.

Clinical characteristics

Demographic characteristics, tumor location, and presence of intraocular involvement were collected. Induction CT was considered HD-MTX based when MTX doses were $\geq$ 1 g/m^2. The therapeutic response to induction CT was established according to the International PCNSL Collaborative Group Response Criteria [24].

Irradiation characteristics

Data on irradiation technique (3D-RT/intensity-modulated radiotherapy (IMRT)), prescription volume, total dose, fractionation, and dates of radiation therapy sessions were collected from treatment records. Dosimetry data were retrieved in DICOM format and transferred to ARTIVIEW^{TM}Plan Check software (AQUILAB, Loos, France). The irradiated volume was defined as the volume receiving 95% of the prescribed dose.

Statistical analysis

PFS and OS times were calculated from the date of diagnosis and were estimated by the Kaplan–Meier method with a two-sided log-rank test.

Univariate and multivariate analyses were performed using Cox proportional hazard models to identify clinical and technical characteristics associated with survival.

All statistical analyses were performed using R software (version 4.1.0; http://cran.r-project.org).

Results

Demographic and tumor characteristics

One hundred seventy-two patients treated in 43 French centers met the inclusion criteria. For a significant number of these patients, the treatment record could not be retrieved due to the lack of response from the treatment center requested, or their difficulty in locating the patient's record. Of them, 79 patients treated in 19 responding centers were included in the study. Of note, 23 (29%) of these patients had been included in the PRECIS trial [12]. Twenty-four patients (30%) were older than 60 years, all treated in 2015 or earlier.

The number of patients treated with brain RT as first-line treatment for newly diagnosed PCNSL decreased over time and was even more pronounced after 2017 (Supplementary data 1).

The demographic and tumor characteristics at diagnosis are shown in Table 1. Four patients (5%) had not received HD-MTX-based induction CT (3 patients without induction CT

Table 1. Demographic and tumoral characteristics at diagnosis.

	Total ($n = 79$)
Age, years	
Median	56
Range	25–79
Sex, no. of patients	
Male (%)	44 (55%)
Female (%)	35 (45%)
Pre-RT KPS	
Median	80
Range	40–100
Histologically proven DLBCL, no. of patients	
Yes (%)	76 (95%)
No (%)	3 (5%)
Ophthalmologic evaluation, no. of patients	
Yes (%)	52 (65%)
No (%)	27 (35%)
HD-MTX based induction CT, no. of patients	
Yes (%)	75 (95%)
No (%)	4 (5%)
Response to HD-MTX based induction CT, no. of patients	$n = 75$
CR (%)	54 (72%)
PR (%)	17 (23%)
SD/PD (%)	4 (5%)
Tumoral localization, no. of patients	
Ocular (%)	1 (1.25%)
Cerebral (%)	70 (88.75%)
Ocular and cerebral (%)	8 (10%)
Intracerebral lesions, no. of patients	$n = 78$
Unique (%)	39 (50.6%)
Multiple (%)	39 (49.4%)
Lateralized (%)	57 (73.4%)
Median (%)	7 (8.9%)
Lateralized and median (%)	14 (17.7%)
Supratentorial (%)	57 (73.6%)
Infratentorial (%)	5 (6.4%)
Supra and infratentorial (%)	16 (20%)

RT: radiotherapy; KPS: Karnofsky performance status; DLBCL: diffuse large B-cell lymphoma; HD-MTX: high-dose methotrexate; CT: chemotherapy; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

and 1 patient treated with an induction CT not containing HD-MTX: rituximab and cytarabine). Patients who had not been treated with HD-MTX were significantly older (median age = 74.5 years) and had significantly lower KPS (median KPS = 40%) than those treated with HD-MTX ($p < .001$ and $p = .03$, respectively).

Patients treated with HD-MTX induction CT ($n = 75$) achieved CR in 72% ($n = 54$), partial response (PR) in 23% ($n = 17$), and stable (SD) or progressive disease (PD) in 5% ($n = 4$) of cases.

RT dose and volume

Three RT volumes were reported: whole brain (WB) in 71% ($n = 56$), WB with an additional boost in 20% ($n = 16$), and partial brain (PB) in 9% ($n = 7$) of cases. In patients who had not been treated with HD-MTX, 2 were treated with WBRT at a dose of 30 Gy in 15 fractions, one of whom received an additional boost of 20 Gy in 10 fractions, and 2 patients were treated with PBRT at a dose of 20 Gy in 5 fractions. The distribution of RT volumes according to the presence and, if applicable, the response to HD-MTX-based induction CT is shown in Supplementary data 2(A). After 2015, the proportion of patients in CR to induction CT treated with WBRT alone increased from 64% to 93% (Figure 1(A)).

The total doses prescribed to the WB ranged between 23.4 and 45 Gy (13-25 fractions). In the case of an additional boost, boost doses ranged between 40 and 56 Gy (20-28 fractions). In the case of PBRT, the prescribed dose ranged between 20 and 50 Gy (5-25 fractions).

The proportion of patients receiving a dose to the WB $\leq$30 Gy versus >30 Gy (in 15 fractions), according to the response to induction CT, is shown in Supplementary data 2(B). After 2015, the proportion of patients in CR to induction CT receiving $\leq$30 Gy to the WB increased from 36% to 100% (Figure 1(B)).

RT doses and volumes were very heterogeneous, and the RT dose and/or volume prescriptions did not comply with published recommendations in 55% of cases. After the 2015 recommendation publications, the proportion of patients in whom the prescribed RT dose and volume met the recommendations [15,22] increased from 21% to 78%.

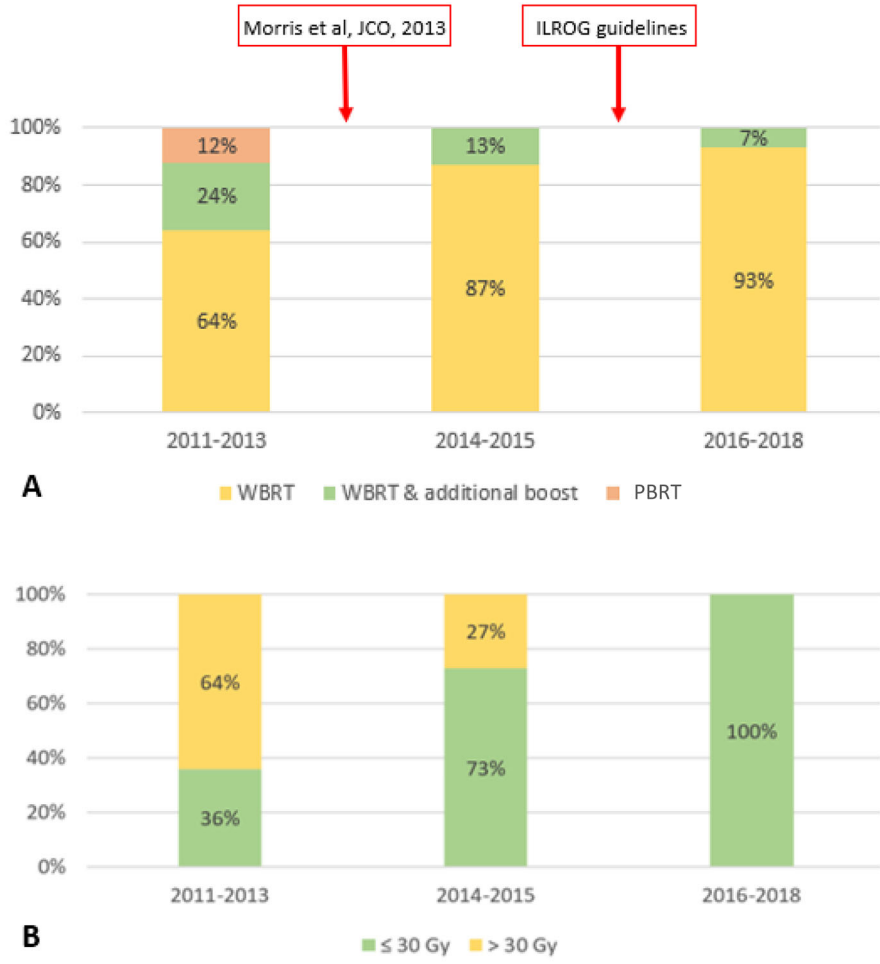
In our series, 16 patients received an additional boost to WBRT. Of these, dose delivery was performed in IMRT or 3D-RT in 8 patients each. The median safety margin between GTV and PTV-boost was 1 cm (0.3–2 cm). Among the 6 patients in PR to induction CT, the irradiated volume was the initial tumor site in 4 patients and the residual lesion after induction CT in 2 patients.

Clinical outcomes

The 2- and 5-year OS rates were 75% (95% CI [66%; 85%]) and 58% (95% CI [48%; 70%]), respectively. The 2- and 5-year PFS rates were 63% (95% CI [53%; 74%]) and 56% (95% CI [46%; 69%]), respectively. Patients treated with HD-MTX-based induction CT had a significantly prolonged OS compared with patients who had not received HD-MTX-based induction CT (median OS of 61 vs. 12.5 months, respectively, $p < .001$).

In patients who received HD-MTX induction CT ($n = 75$): age and pre-RT KPS were the only factors significantly associated with OS in univariate and multivariate analyses (age >60 years: respectively HR 4.66, 95% CI [2.28; 9.49], $p < .001$ and HR 2.98, 95% CI [1.18; 7.51], $p = .02$; pre-RT KPS <80%: HR 3.59, 95% CI [1.57; 8.23], $p = .002$ and HR 3.87, 95% CI [1.61; 9.34], $p = .002$) (Table 2). PR to induction CT was associated with poorer OS in univariate analysis (HR 2.72, 95% CI [1.29; 5.71], $p = .008$) (Table 2).

Subgroup analyses identified prognostic factors based on the response to induction CT: in patients with PR to induction CT, there was a trend toward improvement in PFS by increasing the dose delivered to the WB >30 Gy ($p = .14$) (Supplementary data 3) and by adding a boost to the WBRT (median PFS of 60 and 17 months with and without a boost, respectively ($p = .071$)). These benefits observed in the PR population were not found in the population with CR to induction CT (Supplementary data 3).



Abbreviations: ILROG = international lymphoma radiation oncology group; WBRT = whole brain radiotherapy; PBRT = partial brain radiotherapy

Figure 1. Evolution of irradiation volumes over time (A) and of the prescribed dose to WBRT (B) in patients who reached CR after HD MTX-based induction CT, according to the date and publications [15,19].

Table 2. Univariate and multivariate analysis of factors affecting overall and progression-free survival in patients treated with HD-MTX-based induction CT.

	Univariate analysis						Multivariate analysis		
	OS			PFS			OS		
	HR	CI 95%	*p*-val	HR	CI 95%	*p*-val	HR	CI 95%	*p*-val
Irradiation volume			**.004**			.6			.24
WB/WB plus boost/PB	2.07	1.25; 3.42		1.16	0.65; 2.07		1.48	0.76; 2.89	
Total dose to the WB (Gy)			.82			.9			
≤30									
>30	0.91	0.42; 1.96		1.02	0.49; 2.13				
Response to induction CT			**.008**			.07			.17
CR/PR	2.72	1.29; 5.71		1.96	0.92; 4.18		1.88	0.75; 4.71	
Age (years)			**<.001**			.26			**.02**
≤60									
>60	4.66	2.28; 9.49		1.55	0.72; 3.34		2.98	1.18; 7.51	
Pre-RT KPS			**.002**			.13			**.002**
>80									
≤80	3.59	1.57; 8.23		0.56	0.26; 1.19		3.87	**1.61; 9.34**	
Sex			.052			.6			.57
M (1)									
F (2)	0.45	0.21; 1.007		1.2	0.6; 2.38		0.77	0.3; 1.92	
Presence of intraocular lymphomatous involvement at diagnosis			.23						
No									
Yes	0.29	0.03; 2.21		2.26	0.87; 5.84	.09			

OS: overall survival; PFS: progression-free survival; HR: hazard ratio; CI: confidence interval; p-val: p value; WB: whole brain; PB: partial brain; RT: radiotherapy; CT: chemotherapy; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; KPS: Karnofsky performance status.

Pattern of relapse

In our study, intracerebral relapses ($n = 28$) occurred in the initial tumor site, distant locations, or both in 30%, 51%, and 19% of cases, respectively. In patients treated with PBRT, the proportion of relapses distant from the initial tumor site tended to be higher than that in patients who received WBRT (83.4% vs. 56%, respectively; $p = .24$). Moreover, irradiation volume was a significant factor affecting OS in univariate analysis (HR 2.07, 95% CI [1.25; 3.42], $p = .004$) (Table 2). Survival analyses showed a significantly poorer OS in patients treated with PBRT than in patients treated with WBRT ± boost ($p = .009$) (Supplementary data 4).

Ocular field limits

Of the patients who received WBRT ($n = 72$), the eyes were totally included ($n = 5$), included in their posterior thirds ($n = 6$), or totally excluded ($n = 61$) from the irradiation target volume. Among the patients with confirmed ocular involvement at diagnosis ($n = 9$), the eyes were totally excluded from the irradiation target volume in 55% of cases ($n = 5$). The distribution of ocular irradiation of patients according to their ophthalmologic assessment at diagnosis is presented in Supplementary data 5. Five relapses (13.8%) occurred exclusively in the eyes, in patients whose eyes had been totally excluded from the irradiation target volume. Of these patients, 2 (40%) had no ophthalmologic involvement at diagnosis. Several recommendations have been published regarding eye irradiation, but without consensus, particularly in the absence of ocular involvement at diagnosis (Table 3).

Discussion

Demographic and tumor characteristics

Our results showed a decrease over time in the number of patients treated with brain RT as first-line treatment for newly diagnosed PCNSL, even more pronounced after 2017, consistently with the publication date of a randomized phase II trial recommending ASCT over WBRT for consolidation treatment of newly diagnosed PCNSL [11]. In our study, 5 patients were treated with radiotherapy in 2017 or 2018. These 5 patients were less than 60 years old, had a complete response to induction chemotherapy, and received WBRT at a dose of 23.4 Gy in 13 fractions.

Currently, experts agree that WBRT $\geq$40 Gy in patients older than 60 years is not appropriate, and this treatment is very rarely performed in this population in clinical practice [24,25]. Indeed, the risk of neurotoxicity induced by the combination of HD-MTX and brain RT is higher in patients older than 60 years [10] and increases with the dose of radiation. A meta-analysis found no benefit on quality-of-life-adjusted life expectancy of WBRT (at doses ranging from 24 to 45 Gy) in patients >60 years of age newly diagnosed with PCNSL [26]. The feasibility of lower-dose WBRT in patients older than 60 years is controversial: some experts rule out any option for brain RT in patients older than 60 years [22], while others do not specify an age limit [14,15,23].

RT dose and volume

No prospective randomized phase III trial has been conducted to determine the optimal dose after HD-MTX-based induction CT [27]. In 2013, a trial demonstrated the feasibility

Table 3. Review of the different published guidelines for the implementation of brain radiotherapy as consolidation treatment of newly diagnosed PCNSL.

	Irradiation dose and volume		Ocular irradiation (associated with brain radiotherapy)	
	CR to HD-MTX based CT	PR to HD-MTX based CT	Intraocular lymphomatous involvement at diagnosis: no	Intraocular lymphomatous involvement at diagnosis: yes
French recommendations, LOC network, 2014–2015	WBRT [23–30] Gy [1.8–2] Gy/fr	WBRT 40 Gy [1.8–2] Gy/fr	Respect of the dose constraints: Dmax eyes <40 Gy Dmax lens <10 Gy	
ILROG guidelines, 2015 (Yahalom et al.)[15]	WBRT 24 Gy 2 Gy/fr	WBRT [36–45] Gy 1.8 Gy/fr	Inclusion of the posterior third of the eyes in the irradiation target volume	Inclusion of full eyes in the irradiation target volume
Guidelines for the diagnosis and management of PCNSL, 2019 (Fox et al.)[14]	WBRT 36 Gy 1.8 Gy/fr Option: WBRT 23.4 Gy 1.8 Gy/fr	WBRT 36 Gy 1.8 Gy/fr + Boost to 45 Gy 1.8 Gy/fr	Irradiation of full eyes, 30 Gy	Irradiation of full eyes, 36 Gy
NCCN guidelines CNS Cancers, v3.2020	WBRT 23.4 Gy 1.8 Gy/fr	WBRT [30–36] Gy + Boost to 45 Gy 1.8 Gy/fr Option: PBRT 45 Gy 1.8 Gy/fr	Unspecified	Inclusion of full eyes in the irradiation target volume

CR: complete response; PR: partial response; HD-MTX: high-dose methotrexate; CT: chemotherapy; WBRT: whole-brain radiotherapy; PBRT: partial brain radiotherapy; LOC: lymphomes oculo-cérébraux; ILROG: international lymphoma radiation oncology group; PCNSL: primary central nervous system lymphoma; NCCN: national comprehensive cancer network.

and efficiency of rdWBRT (23.4 Gy in 1.8 Gy fractions) consolidation therapy in patients with CR to HD-MTX-based induction CT [16]. Between 2015 and 2020, several recommendations regarding RT dose and volume for the treatment of newly diagnosed PCNSL were published [14,15,22,23]. All of them propose an approach adjusted to the response to induction CT but are not consensual (Table 3). The results of our study reflect this lack of consensus. The significant increase in the proportion of patients in whom the prescribed RT dose and volume met the recommendations after 2015 recommendation publications [15,22] illustrates the effectiveness of publishing recommendations on standardizing prescriptions. We believe that the language of the international commission on radiation units and measurements (ICRU) should be adopted to describe the recommendations of radiotherapy, in order to harmonize them.

Boost field design

If an additional boost to the WBRT is prescribed, the guidelines for performing it lack precision regarding (i) the target volume (initial tumor site or residual lesion after induction CT), (ii) margins to be applied to determine the CTV-boost from the volume visible on imaging, and (iii) the technique to be used for dose delivery (3D-RT or IMRT). In the different studies and guidelines published with patients treated for newly diagnosed PCNSL with an additional boost to WBRT, the recommendations are heterogeneous and often unspecified (Supplementary data 6). The only guidelines that specify how to perform an additional boost to WBRT are the guidelines for the diagnosis and management of PCNSL published by Fox et al. in 2019 [14], which recommend irradiation of the residual contrast-enhancing lesion(s) after induction CT with safety margins of 1–2 cm.

Clinical outcomes

In our study, the 2- and 5-year OS rates were 75% and 58%, respectively. These results seem close to those obtained after WBRT in the literature (median 2-year OS of 82% [4,11,12] and 5-year OS of 62% [13]) and of those obtained after ASCT in the literature (median 2-year OS of 75.5% [11,12] and 5-year OS of 59% [13]). With regard to the PFS results, the randomized phase II PRECIS trial suggested a benefit of ASCT over WBRT on PFS, particularly on long-term PFS): 2-year [12] and 8-year [13] PFS results were significantly higher after ASCT than WBRT (8-year PFS rates of 67% in the ASCT arm vs. 39% in the WBRT arm, $p = .03$). However, the randomized phase II IELSG 32 trial did not find a significant difference in 2-year PFS after WBRT or after ASCT [11].

Prognostic factors

In the literature, age, and KPS are identified as the most robust therapy-independent prognostic factors [28–32] and the results of our study found these factors as strongly associated with OS.

Consistent with the results of our study, PR to induction CT has been described in the literature to be associated with poorer OS [33,34].

Consistent with the results of our study, the administration of an HD-MTX induction CT prior to brain RT has been robustly shown to be a prognostic factor affecting OS in the literature: patients treated with HD-MTX induction CT had median OS ranging from 30 to 72 months [3,5,35], while those treated without HD-MTX-based induction CT had median OS results ranging from 11.5 to 42 months (median: 17 months) [2,36–38]. For patients considered unsuitable for HD-MTX induction CT, brain RT, corticosteroid therapy and/or oral temozolomide chemotherapy are palliative treatment options [39] in combination with the best supportive care [14]. Radiation-induced delayed neurotoxicity generally begins to appear approximately 6 months after WBRT and therefore is less of a limiting factor in the case of palliative brain RT in patients with short life expectancy. Therefore, recommendations suggest accelerated treatment regimens (20–30 Gy in 1.8–4 Gy fractions) [14] and/or doses $\geq$30 Gy [15] for these patients.

Subgroup analyses

In our subgroup analyses, the number of patients was very small and the results were not statistically significant. These results must therefore be taken with great caution. However, and consistent with the published recommendations [14,15,22,23], our results carefully suggest the prescription of a dose to the WB $>$30 Gy and the addition of a boost to the WBRT in the case of PR but not in the case of CR to induction CT. In the literature, the benefit of a boost is controversial [36,40]: the prospective phase III RTOG 8315 trial found most relapses occured in the area of the boost and an absence of benefit of the boost on OS [36]. On the other hand, a review of the literature concluded a benefit on OS of an additional boost to the WBRT [40].

Pattern of relapse

Autopsy and pattern of relapse reports concluded that PCNSL tumor cells widely infiltrate the brain parenchyma, even distant from the initial tumor site [41,42]. Consistent with our results in terms of sites of relapse, PBRT does not appear to be suitable for the treatment of PCNSL.

The rarity of the disease and the low visibility of the recommendations due to the presence of several recommendations that sometimes lack precision and contradictory result in management that does not always comply with the published recommendations. Sometimes the physician's therapeutic choices are adapted more to the individual patient than to the official recommendations, and this may not ultimately benefit the patient.

Based on the results of our study and consistent with the published recommendations, we present in Table 4 a proposal for the implementation of brain radiotherapy as a consolidation treatment of newly diagnosed PCNSL.

Table 4. Proposal from our study for the implementation of brain radiotherapy as consolidation treatment of newly diagnosed PCNSL.

		Irradiation dose and volume		Ocular irradiation (associated with brain radiotherapy)	
		CR to HD-MTX based CT	PR to HD-MTX based CT	Intraocular lymphomatous involvement at diagnosis: no	Intraocular lymphomatous involvement at diagnosis: yes
Proposal from our study	Volume	WBRT	WBRT + Boost	Inclusion of the posterior third of the eyes in the irradiation target volume	Inclusion of full eyes in the irradiation target volume
	Dose	23.4 Gy 1.8 Gy/fr	36 Gy 1.8 Gy/fr Boost to 45 Gy 1.8 Gy/fr	23. Gy or 36 Gy (according to the response to HD-MTX based induction CT) 1.8 Gy/fr	

CR: complete response; PR: partial response; WBRT: whole brain radiotherapy; RT: radiotherapy; HD-MTX-based induction CT: high-dose methotrexate-based chemotherapy.

Ocular field limits

The results of our study regarding the ophthalmologic relapses suggest an indication to irradiate the eyes at therapeutic dose in all patients. In the literature, 11.5%–15% of PCNSL relapses occur in the eyes [42,43].

Retinas are known to be histologically considered part of the CNS [42,43]. The usual ocular dose constraints are Dmean to retina $\leq$45 Gy, Dmean to lacrymal gland $<$25–32 Gy, maximal dose (Dmax) to lens $<$5–10 Gy, and Dmax to cornea $<$30–50 Gy [44]. Regardless of whether the prescribed dose is 23.4 or 36 Gy, ocular irradiation should not induce retinal toxicity. Irradiation of full eyes may, however, increase the risk of corneal abrasions/ulcerations, dry eye syndrome and cataracts compared to irradiation of the posterior third of the eyes only. This is why, in patients without ocular damage at diagnosis and in line with the 'ALARA' ('as low as reasonably achievable') concept [45], limiting ocular irradiation to the posterior third of the eyes seems to be a well-balanced compromise between the risk of radiation-induced cataract, dry eye syndrome and antitumor efficacy. In cases of ocular lymphomatous involvement at diagnosis, the inclusion of full eyes in the irradiation target volume is recommended [14,15,23]. Regarding the dose prescription in the ocular target volume, the same dose as that prescribed for WBRT (i.e., 23.4 Gy or 36 Gy depending on the response to induction CT) should be prescribed (Table 4).

This work has several limitations, mainly due to the inherent biases of a retrospective study. There were no missing data regarding irradiation doses, target volume, or RT beam anterior borders (ocular area). However, there were missing data in other items but never exceeding 10%. The number of patients was limited due to difficulties in retrieving patient records from treatment centers because of a large number of nonresponding centers. This led to a certain lack of power in the statistical analyses, especially in the subgroup analyses. In addition, this could constitute a patient selection bias, since it can be assumed that the responding centers are those with the greatest interest in the management of patients with PCNSL. As a result, Table 4 (presenting a proposal from the results of our study for the implementation of brain radiotherapy as consolidation treatment of newly diagnosed PCNSL) must be taken with extreme caution and cannot claim to be official recommendations because the results of our study are based on a small number of patients and on retrospective, non-randomized data.

Of the 79 patients included in the analysis, 27 had not had an ophthalmologic evaluation at diagnosis, and 7 were lost to follow-up. Importantly, especially in elderly patients, data on neurotoxicity (the evaluation of which requires neuropsychological assessments) and on ophthalmologic toxicity are lacking.

Conclusion

Professional practices change after the publication of guidelines, demonstrating their usefulness in the daily management of patients.

To our knowledge, this study is the only real-life study of technical prescriptions for brain RT in the treatment of newly diagnosed PCNSL. The multicentricity allows an accurate representation of professional practices in France.

The analysis of the prescriptions for patients treated after 2018 would allow an evaluation of the evolution after this date: (i) of the number of patients treated by brain RT for a newly diagnosed PCNSL, (ii) of the RT protocols prescribed after the publication of the recommendations written by Fox et al. in 2019 and by the 'national comprehensive cancer network' (NCCN) in 2020.

Based on the results of our study and on the literature review of the published recommendations [14,15,22,23], we present (summarized in Table 4) a proposal for the implementation of brain RT as consolidation treatment of newly diagnosed PCNSL. Even if this proposal must be taken with the required precautions due to the lack of statistical robustness of our results, it may help to guide the radiation oncologists in the prescription of brain RT in rare cases where a patient would be referred for this indication. The results of our study are consistent with those of previously published recommendations concerning RT dose and volume. They underline the importance of including the eyes in the RT volume, limited to their posterior thirds in cases of absence of ocular involvement at diagnosis.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Data availability statement

The data that support the findings of this study are available from Dr Loïc Feuvret, LF, loic.feuvret@yahoo.fr, upon reasonable request.

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