Primary Central Nervous System Lymphoma

Diagnostic evaluation, neurocognitive functioning and health-related quality of life

Matthijs van der Meulen

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General introduction and scope of this thesis

CHAPTER 1 GENERAL INTRODUCTION AND SCOPE OF THIS THESIS

Primary central nervous system lymphoma (PCNSL) is a rare non-Hodgkin lymphoma (NHL) which is confined to the brain, leptomeningines, spinal cord and eyes without manifestations outside the central nervous system. This tumour was first described by Bailey as 'sarcoma of the brain, arising from the leptomeninges' at the beginning of the 20th century.[1] Later it was recognized as NHL.

The exact pathophysiology is unknown and although it is called a *primary* CNS lymphoma, there is evidence the tumour originates outside the central nervous system. Almost all PCNSL contained Bcl-6, an oncogenic protein that is only expressed on B-cells in the germinal centre. Since the central nervous system does not contain germ centre structures, it suggest an extraneural origin of the tumour that subsequently migrates to the central nervous system.[2] At histological examination, >90% of PCNSL are diffuse large B-cell lymphoma (DLBCL), the remaining 10% are Burkitt, T-cell or low-grade lymphoma.[3,4]

Epidemiology

Over the last decades the incidence of PCNSL has increased, mainly among elderly (>60-year old) to 0.44-0.47/ 100,000 per year.[5] The reason for this increase is unknown; the only known risk factors for this disease are older age and being immunocompromised. However, the incidence is increasing among immune competent patients and despite the ageing population, the incidence of systemic DLBCL and glioma did not increase with a similar rate.[6,7] Median age at diagnosis is around 65 years and the incidence in men is slightly higher than in women.[8]

Diagnosis

The most frequent presenting symptoms are focal neurological deficits (70%), signs of increased intracranial pressure, such as headache (51%) and cranial nerve palsies, neuropsychiatric/cognitive symptoms (26-43%) and seizures (14%).[9,10]

When a brain tumour, is considered, an MRI of the brain with and without gadolineum is the first designated test. On MRI a PCNSL is characterized by solitary (65%) or multiple (35%) space occupying lesions, surrounded by vasogenic oedema. Most (90%) lesions show homogeneous contrast enhancement, with diffusion restriction (Figure 1). Preferred locations are periventricular, the corpus callosum and basal ganglia.[11,12] However, more rarely non-enhancing space occupying lesions in addition to enhancing lesions may occur. These lesions diminished in size or even vanished after treatment, which suggests that these lesions should also be considered as tumor.[13]

Cytological or histological confirmation of the tumour is essential, as treatment is intensive and potentially toxic. In a minority of patients the diagnosis can be made by cytological analysis of cerebrospinal fluid (CSF) after a lumbar puncture, or of vitreous fluid in case

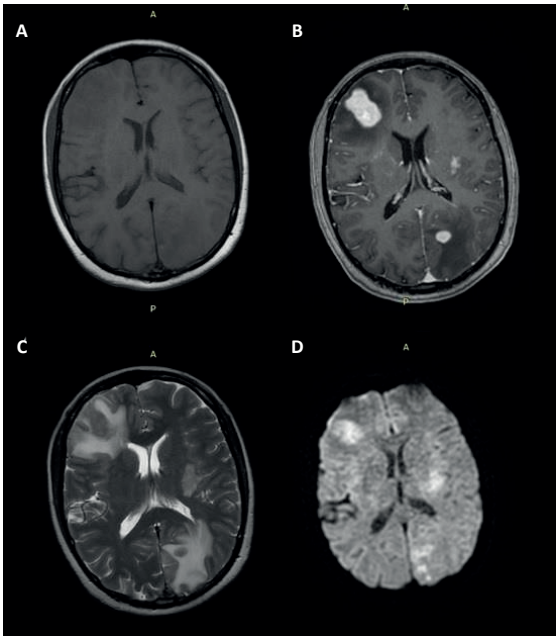

Figure 1. T1W (A) and T1W with gadolinium (B) images show multiple homogenous enhancing lesions. A T2W (C) shows vasogenic oedema around the lesions and the diffusion weighted image (D) shows diffusion restriction in all enhancing lesions.

of eye involvement. Although flow cytometry added tot cytology increases the sensitivity, compared to cytological analysis alone[14], diagnosis can be made on CSF-analysis alone in only 30% of the cases.[15] Eye involvement occurs in just circa 4% of the cases.[16] As a result, in most patients a brain biopsy is remains necessary to obtain a diagnosis. In addition to this cytological or histological confirmation a comprehensive screening is necessary to determine the extent of the disease and to determine whether the lymphoma is a primary CNS lymphoma or a secondary manifestation of a systemic lymphoma. Typically, the screening consists of a slit lamp eye examination, a lumbar puncture, a CT of the chest and abdomen, a bone marrow analysis and a complete blood analysis.

Treatment

The first described treatment for PCNSL was a gross total resection of the tumour, but this resulted in median overall survival (OS) of just 1-4 months.[17] After the failed effect of surgery, whole brain radiotherapy (WBRT) became the treatment of first choice, but despite rapid responses, survival remained more limited than that observed in other lymphoma limited to one organ.[18] Based on multiple large uncontrolled phase II studies, chemotherapy based on high-dose intravenous methotrexate (HD-MTX) became subsequently the cornerstone of first line treatment, with studies utilizing various HD-MTX-based regimens

reporting a median overall survival of about 60 months.[19-21] The addition of high-dose cytarabine (HD-Ara-C) to HD-MTX was then reported to further improve the progression free survival (PFS) and OS.[22]

The role of WBRT given after chemotherapy remains disputed. The addition of WBRT after chemotherapy, may improve the PFS compared to chemotherapy alone (12 versus 18 months); the overall survival remained similar, however.[23] On top, patients treated with combined chemotherapy and 45Gy WBRT, had significantly worse scores on neuropsychological tests, compared to patients treated with chemotherapy only.[24]

In particular because of these effects on neurocognitive functioning, alternatives for consolidation treatment with high-dose WBRT are necessary . An uncontrolled study showed a similar effect on survival but without these cognitive consequences with a reduced dose of WBRT (23.4Gy).[25] Two phase II randomized controlled trials compared autologous stem cell transplantation (ASCT) with WBRT as consolidation therapy. No significant differences in PFS were found but cognitive performance was reported to be significantly better in the ASCT group. Although the OS also seemed similar between both groups and comparable to historical treated patients, further follow-up is needed to explore outcome in the long run.[26,27]

Rituximab, a chimeric monoclonal antibody targeting the CD20 cell surface protein, is very effective if given in addition to standard chemotherapy in systemic CD20 positive B-cell lymphoma.[28,29] Since most PCNSL are CD20 positive diffuse large B-cell lymphoma, rituximab was assumed to be effective also in PCNSL. A phase II trial randomised 219 patients between HD-MTX/Ara-C, HD-MTX/Ara-C combined with rituximab of HD-MTX/ Ara-C combined with rituximab and thiotepa. The latter arm, now known as the MATRix-regime had significantly better PFS and OS.[30] Unfortunately there was no arm with thiotepa and without rituximab; in addition this study was not powered or designed for a comparison between three arms, this made the role of additional rituximab uncertain. In a large international phase III randomised controlled trial, the HOVON 105/ ALLG NHL 24 study, 199 patients were randomized between HD-MTX-based chemotherapy (MBVP: methotrexate, tenoposide, BCNU and prednisolone) with or without rituximab and followed by HD-cytarabine and, in patients up to 60 years-old with a lower dose of WBRT (30Gy). No differences were found between the arms regarding the 1-year event-free survival (R-MBVP versus MBVP: 52% (95% confidence interval [CI]: 42-61) versus 49% (95% CI: 39-58), p=0.99), PFS and OS.[31]

Cognitive functioning and health-related quality of life

Cognitive decline and other symptoms, caused by the tumour and/ or the treatment can compromise health-related quality of life (HRQoL).[32] Up to 43% of PCNSL patients have cognitive disturbances to a certain extent at diagnosis.[9] In PCNSL symptoms can greatly

improve following treatment but reports differ regarding the extent to which this is also the case for cognitive symptoms.

Since the prognosis of PCNSL patients has improved over the last decades, (late) effects on cognitive performance and HRQoL have become more important to measure.[5] Preventing cognitive decline and even better, improving cognitive functioning are major challenges in PCNSL patients. Assessment of this important part of patient functioning requires the evaluation of cognition at baseline and during follow-up.[33,34] In addition, assessing cognitive performance and HRQoL in research is necessary to determine the 'net clinical benefit' of a (new) treatment. Information on both, survival and neurocognitive functioning and HRQoL enables the physicians and patients to make a weighted decision regarding patients' treatment.

Prognosis

Although the prognosis for patients with PCNSL at group level improved over the last decades,[5] it remains difficult to predict the prognosis for the individual patient. Two prognostic models are currently widely used in PCNSL patients.

- The externally validated Memorial Sloan Kettering Cancer Center (MSKCC) model, consist of two factors: age and the Karnofsky performance score (KPS), in which a higher age (>50 years-old) and a lower KPS (<70) are unfavourable prognostic factors.[35]
- The International Extranodal Lymphoma Study Group (IELSG) developed a model of 5 unfavourable prognostic factors: higher age (>60 years old), higher ECOG/ WHO performance score (>1), a high serum LDH, a higher total protein in CSF (>45mg/dL in patients ≤60 years-old or >60mg/dL for elderly) and involvement of deep structures (i.e. brain stem, cerebellum, periventricular or basal ganglia).[36]

The latter model is unfortunately limited by missing data, and external validation is still needed.

Aims and scope of this thesis

The aims of this thesis are to describe incidence, primary treatment and survival among adult PCNSL patients in the Netherlands over the last three decades (**Chapter 2**) and to describe primary treatment and survival among elderly (>70 year-old) in the modern era: 2014-2017 (**chapter 3**). As described above, flow cytometry improves the sensitivity over immunohistochemistry alone in CSF. In **chapter 4** we aim to define the value of flow cytometry on brain biopsies from lesions suspected to be a brain lymphoma. Since PCNSL is a rare disease, and choices regarding treatment in clinical studies are generally based on local response assessment, we determined the value of a central radiology review and the influence of centrally determined response rate on survival (**chapter 5**). Secondary endpoints of the HOVON 105/ALLG NHL 24 study[31] were differences between treatment

arms regarding health-related quality of life and neurocognitive functioning. PART III starts with a comprehensive systematic literature review of neurocognitive functioning and HRQoL in PCNSL patients (**Chapter 6**). In **chapter 7 and 8** we describe neurocognitive functioning and HRQoL-scores over time and the effect of rituximab on these. **Chapter 7** also describes the association of brain atrophy and white matter abnormalities with neurocognitive functioning. Lastly, we aim to determine the prognostic value of the Mini-Mental State Examination score at baseline in **chapter 9**.

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PART I

Epidemiology

2

Improved survival in primary central nervous system lymphoma up to age 70 only: a population-based study on incidence, primary treatment and survival in the Netherlands, 1989-2015

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LETTER TO THE EDITOR

Primary central nervous system lymphoma (PCNSL) is a rare, aggressive form of extranodal non-Hodgkin lymphoma that exclusively affects the CNS. Although PCNSL has traditionally been associated with a sinister prognosis, recent findings from the few available prospective studies demonstrated improved outcome in PCNSL.[1-3] However, the results from such studies may not reflect the actual clinical practice due to patient selection. Population-based studies complement prospective intervention studies by addressing a non-selected group of patients within a well-defined geographic area. Currently, comprehensive population-based studies that assess long-term patterns of incidence, treatment and survival in PCNSL are virtually lacking.

Here we report the outcomes of a comprehensive nationwide population-based study on incidence, primary treatment and survival among adult PCNSL patients diagnosed in the Netherlands during a 27-year period.

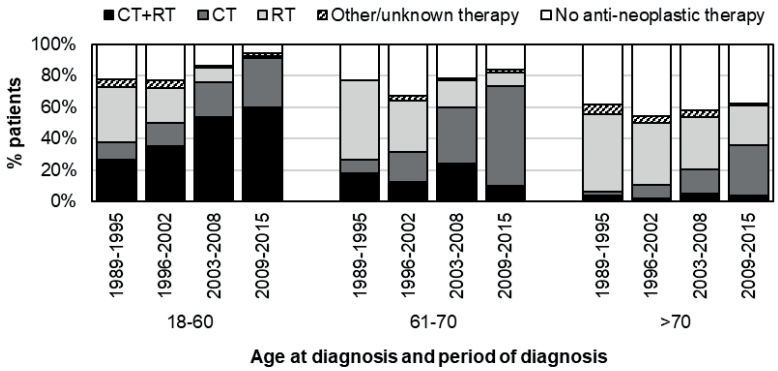
We identified all adult (≥18 years) PCNSL patients diagnosed between 1989-2015, with survival follow-up through February 2016, from the nationwide population-based Netherlands Cancer Registry (NCR). Established in 1989, the NCR, which is maintained and hosted by the Netherlands Comprehensive Cancer Organisation, has an overall coverage of >95% of all malignancies in the Netherlands.[4] The NCR is based on comprehensive case notifications through the Nationwide Network of Histopathology and Cytopathology and the National Registry of Hospital Discharges. PCNSL of the diffuse large B-cell type was defined using International Classification of Diseases for Oncology morphology and topography codes. The selected codes are described in the Supplementary Methods. Information on dates of birth and diagnosis, sex, disease topography and morphology, primary treatment (that is, no anti-neoplastic therapy, chemotherapy, radiotherapy, combined chemoradiotherapy (CT+RT), and other or unknown therapy), and vital statistics (that is, alive, emigration or death) is available for individual patients.

Age-standardized incidence rates (ASRs) were calculated per 100,000 person-years, using the annual mid-year population size as obtained from Statistics Netherlands. ASRs were standardized according to the European standard population. We calculated relative survival (RS) for four calendar periods (1989-1995, 1996-2002, 2003-2008 and 2009-2015) and three age groups (18-60, 61-70 and >70 years) using the cohort methodology.[5] RS is the observed patient survival (that is, overall survival, OS) corrected for the expected survival of an equivalent group in the general population with respect to age, sex and period. This to eliminate the effect of general changes in population survival over time. Expected survival was calculated using the Ederer-II methodology. RS was calculated from the time of diagnosis until death, emigration or end of follow-up, whichever occurred first. We applied a generalized linear model that assumed a Poisson distribution for the observed number of deaths to assess linear trends in RS over time and to estimate the relative excess risk

of mortality during the first 5 years after PCNSL diagnosis. For these analyses, a *P*-value <0.05 was considered statistically significant. Patients diagnosed without pathologic and/or cytologic confirmation (n=50) and patients diagnosed at autopsy were excluded (n=32). However, as is customary for incidence estimation, these cases were included to calculate the ASRs. This study was approved by the Privacy Review Board of the NCR.

A total of 1,673 adult PCNSL patients (median age 65 years; 53% males) were included in the study. The characteristics of these patients are presented in Supplemental Table S1. In the overall series, 35%, 34% and 31% of patients were aged 18-60, 61-70 and >70, respectively. The overall ASR of PCNSL increased from 0.30/100,000 persons in the period 1989-1995 to 0.44/100,000 persons in the period 2009-2015. The increase was a result of the increasing incidence in the age groups 61-70 and >70 years (Supplemental Figure S1).

Information on primary treatment according to age and calendar period of diagnosis is shown in Figure 1. There were some notable age-related treatment differences over time. The application of CT+RT increased exclusively among patients age 18-60; from 26% in the period 1989-1995 to 60% in the period 2009-2015. The use of radiotherapy alone among patients above age 60 decreased with each calendar period, following the wider use of chemotherapy alone over time. The use of chemotherapy alone increased most prominently for patients age 61-70 (64% in the most recent calendar period). Approximately 40% of patients above age 70 did not receive anti-neoplastic therapy throughout the entire study period.



Treatment	Column percentage											
CT+RT	26	35	54	60	18	13	24	10	4	2	5	4
CT	11	15	22	31	8	19	36	64	2	8	15	32
RT	35	22	9	2	51	33	17	8	49	40	33	26
Other/unknown therapy	5	5	1	2	-	3	2	2	6	4	5	1
No anti-neoplastic therapy	22	23	14	6	23	33	22	16	38	46	42	38

Figure 1. Primary treatment of adult patients with PCNSL in the Netherlands according to calendar period of diagnosis and age at diagnosis, 1989-2015. The table presents the proportion of patients receiving a particular treatment within a specific calendar period and age group. The absolute number of patients within a specific calendar period and age group is shown in Supplementary Table S1.

The overall 5-year age-standardized RS (95% confidence interval) among adult patients with PCNSL increased from 11% (8%-15%) in 1989-1995 to 30% (27%-34%) in 2009-2015 (Supplementary Figure S2).

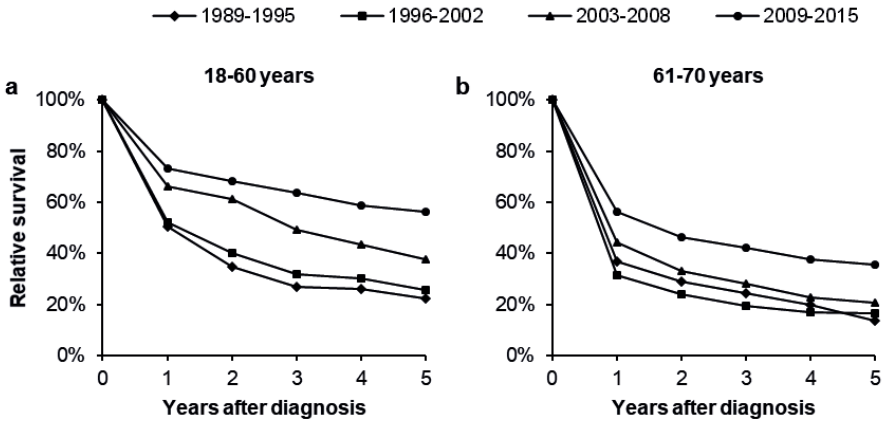
RS according to age and calendar period of diagnosis is shown in Figure 2. Significant improvement in 5-year RS was confined to patients age 70 or below. This improvement was most pronounced in the most recent calendar period. More specifically, 5-year RS (95% confidence interval) for patients age 18-60 improved from 22% (16%-30%) to 56% (47%-64%), and for patients age 61-70 from 13% (7%-22%) to 35% (28%-43%) between the calendar periods 1989-1995 and 2009-2015. Five-year RS for patients above age 70 remained poor throughout the calendar periods studied (6% in the calendar period 2009-2015).

We analyzed the influence of calendar period, age, sex and therapy on the relative excess risk of mortality in a multivariable model (Supplementary Table S2). The primary multivariable model (that is, without treatment) demonstrated an adverse effect of older age and an improvement of survival over time. However, when information on treatment was added to the model, the effect of period lost statistical significance. This fits with treatment contributing to the improved survival over time. Older age remained a predictor of poor prognosis.

In this comprehensive population-based study, we firstly observed an increasing incidence of PCNSL that was confined to patients above age 60. Similar trends were also observed in recent population-based studies from western and eastern countries.[6,7] This increase is most likely driven by immunocompetent patients, which may in part be explained by greater diagnostic diligence in elderly patients. This, however, does not completely explain the increase, as incidence rates of gliomas and non-CNS-related DLBCL in the Netherlands did not increase in a similar manner.[8,9]

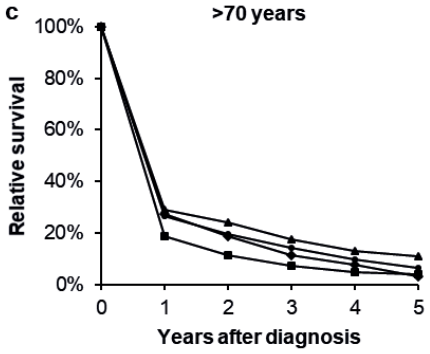
Second, we demonstrated a significant improvement in prognosis over the past 2 decades among PCNSL patients aged 18-70, with the major improvement taking place during the most recent calendar period (2009-2015). Similarly, Kasenda *et al.* found improved survival in elderly PCNSL patients in the last decades; however, age-related trends over time were not analyzed separately.[10] The improvements are most likely related to the increased application of chemotherapy (18-70 years) and combined chemoradiotherapy (18-60 years) over time. Most,[6,7,11] although not all,[12,13] population-based studies lack information on treatment and come from the US. The present comprehensive study thus extends on prior studies.

In the most recent study from the United States by Fallah *et al*.,[13] with survival follow-up through 2012, 3-year overall survival for the entire PCNSL cohort improved from 36% in the period 2004-2006 to 41% in the period 2010-2012. It was suggested that the improvement was related to the increased application of chemotherapy alone, and a concurrent decrease in the overall application of radiotherapy. Age-related trends in treatment and



RSR	Calender period				*P* for trend*
	1989-1995	1996-2002	2003-2008	2009-2015	
	RSR (in%) with 95% CI				
1-year	51 (42-59)	52 (42-61)	66 (58-73)	73 (66-79)	<0.001
3-year	27 (19-34)	32 (23-41)	49 (41-57)	64 (55-71)	<0.001
5-year	22 (16-30)	26 (18-34)	37 (30-45)	56 (47-64)	<0.001

RSR	Calender period				*P* for trend*
	1989-1995	1996-2002	2003-2008	2009-2015	
	RSR (in%) with 95% CI				
1-year	37 (26-47)	31 (23-40)	44 (36-53)	56 (49-62)	<0.001
3-year	24 (15-34)	20 (13-28)	28 (20-36)	42 (35-49)	<0.001
5-year	13 (7-22)	16 (10-24)	21 (14-28)	35 (28-43)	<0.001



RSR	Calender period				*P* for trend*
	1989-1995	1996-2002	2003-2008	2009-2015	
	RSR (in%) with 95% CI				
1-year	27 (18-37)	19 (11-27)	29 (21-37)	27 (21-37)	0.255
3-year	11 (5-20)	7 (3-14)	17 (11-25)	14 (9-21)	0.147
5-year	3 (1-10)	4 (1-10)	11 (6-18)	6 (2-13)	0.116

Figure 2. Relative survival rates (RSRs) of adult patients with PCNSL in the Netherlands according to calendar period of diagnosis and age at diagnosis, 1989-2015. RSRs are shown according to the following age categories: (a) 18-60 years, (b) 61-70 years and (c) >70 years. The table presents the projected 1-, 3- and 5-year RSRs with 95% CIs according to calendar period of diagnosis. **P*-value for linear trend from the calendar period 1989–1995 to the calendar period 2009–2015.

survival were, however, not assessed in that and most other studies. Similarly, we observed that the use of radiotherapy alone decreased substantially, with a concurrent increase in the use of chemotherapy alone, especially among patients age 61-70. This suggests that physicians and patients age 61-70 more often opt for curative treatment without whole-brain radiotherapy (WBRT) to prevent late radiotherapy-induced neurotoxicity, which constitutes a major concern among patients above age 60.[10] In contrast to the study by Fallah *et al.*,[13] we demonstrated an increased application of combined chemoradiotherapy among patients age 18-60. The disparity in treatment practices between the Netherlands and the US may be related to the ongoing debate about the risks and benefits of consolidation WBRT after high-dose methotrexate-based chemotherapy among younger (≤60 years) PCNSL patients.[14]

Although we demonstrated that the use of chemotherapy increased among patients above age 70, their survival was still disappointingly poor. Approximately 40% of these patients received no anti-neoplastic therapy throughout the entire study period. A population-based study among elderly (≥65 years) PCNSL patients in the United States showed that only ~20% of patients received no treatment over the study period (1994-2002).[12] Nevertheless, survival of these patients was poor and remained unchanged over time. At present, optimal treatment approaches for elderly PCNSL patients are yet to be defined.[10,14] Therefore, there is an urgent need to design more international trials in order to advance treatment approaches and improve outcomes without increasing (neuro) toxicity, especially, but not exclusively, for elderly PCNSL patients. Moreover, it has been recently shown that prospective studies in elderly patients are feasible, thereby providing good grounds for optimism to offer patients the newest therapeutic options.[15]

The strength of our study includes the use of a nationwide population-based cancer registry with comprehensive information available for individual patients. Therefore, unlike most population-based studies, we could directly link improvements in survival with changing treatment practices over time. Limitations of our study mainly pertain to the lack of detailed clinical information throughout most of the registry (1989-2013). Despite that limitation, cancer registries remain the gold standard for cancer surveillance.

In summary, the incidence of PCNSL continues to increase among patients aged over 60. Relative survival increased over the past decades for PCNSL patients aged 18-70. This is largely explained by the increased use of intensive therapy over time. Although the use of chemotherapy gradually increased among patients above age 70, their survival is still poor.

ACKNOWLEDGEMENTS

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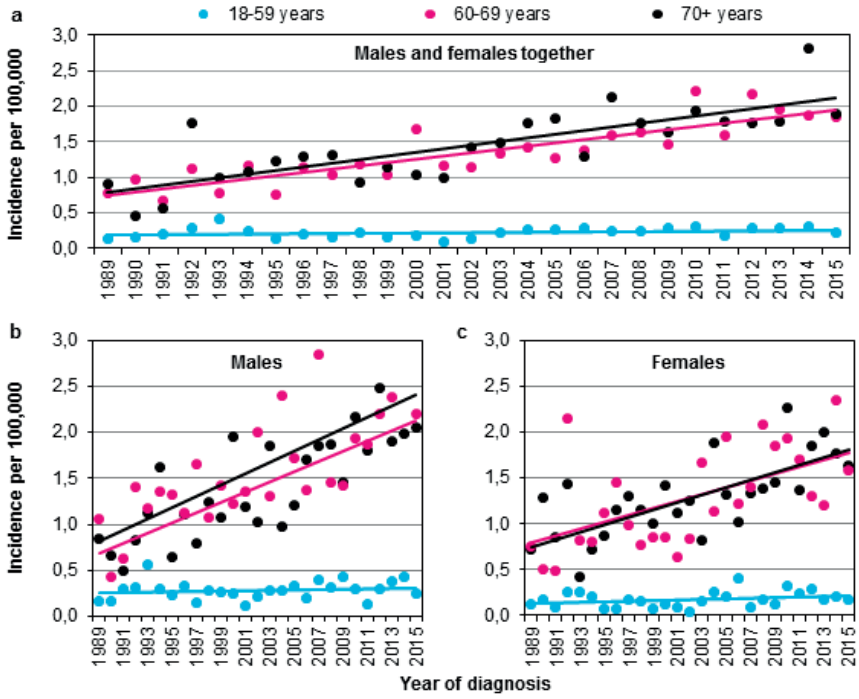
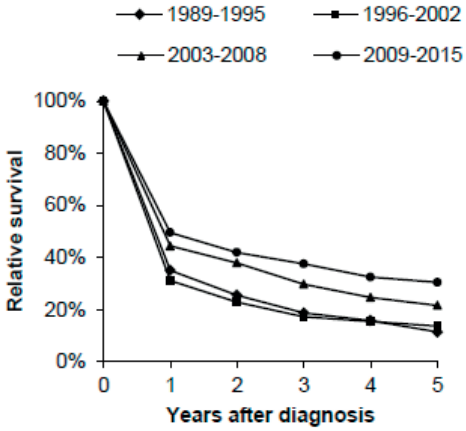
SUPPLEMENTARY INFORMATION

Supplementary Methods

Primary central nervous system lymphoma (PCNSL) of the diffuse large B-cell type was defined using International Classification of Diseases for Oncology morphology (i.e. 9590, 9591, 9593, 9595, 9675 and 9680-9684) and topography codes (i.e. C69.2, C69.4, C71.0-C71.9, C72.0 and C72.8). The selected topography codes are consistent with anatomical location in the brain (C71.0-C71.9; n=1,552), spinal cord (C72.0; n=54), eyes (C69.2 and C69.4; n=50), and leptomeninges or cerebrospinal fluid (C72.8; n=17). Although C72.8 is not specific for the latter two localizations, coding rules of the NCR designate C72.8 for localizations in the leptopmeninges or cerebrospinal fluid.



Supplementary Figure S1. Age-specific incidence rates of adult patients with PCNSL in the Netherlands, 1989-2015. Age-specific incidence rates are shown according to the following sexes: (a) males and females together, (b) only males and (c) only females.



	Calender period			
	1989-1995	1996-2002	2003-2008	2009-2015
	RSR (in%) with 95% CI			
1-year	35 (29-41)	31 (26-36)	44 (40-49)	50 (46-53)
3-year	19 (14-24)	17 (14-21)	30 (25-34)	38 (34-41)
5-year	11 (8-15)	14 (10-18)	22 (18-26)	30 (27-34)
	Numbers at risk			
1-year	119	107	195	283
3-year	62	60	129	133
5-year	37	36	83	81

Supplementary Figure S2. Age-standardized relative survival of adult patients with PCNSL in the Netherlands according to calendar period of diagnosis, 1989-2015. Relative survival was age-standardized according to the standard population as defined by the International Cancer Survival Standard (ICSS).

Supplementary Table S1. Patient characteristics

Characteristics	Calendar period												Total		
	1989-1995			1996-2002			2003-2008			2009-2015					
	No.	(%)	ASR[a]	No.	(%)	ASR[a]	No.	(%)	ASR[a]	No.	(%)	ASR[a]	No.	(%)	ASR[a]
Total No. of patients	300		0.30	316		0.29	416		0.39	641		0.44	1,673		0.35
Sex															
Male	155	(52)	0.33	177	(56)	0.33	217	(52)	0.42	336	(52)	0.48	885	(53)	0.39
Female	145	(48)	0.26	139	(44)	0.24	199	(48)	0.35	305	(48)	0.40	788	(47)	0.31
Age, years															
Median (range)		62 (20-87)			65 (19-87)			64 (25-87)			66 (21-87)			65 (19-87)	
18-60	136	(45)	0.23	108	(34)	0.17	153	(37)	0.25	188	(29)	0.27	585	(35)	0.23
61-70	83	(28)	0.90	112	(35)	1.20	130	(31)	1.44	242	(38)	1.87	567	(34)	1.35
>70	81	(27)	1.00	96	(30)	1.16	133	(32)	1.72	211	(33)	1.95	521	(31)	1.45

Abbreviation: ASR, age-standardized incidence rate.

[a]Age-standardized according to the European standard population and present per 100,000 person-years. Incidence rates were calculated using the annual mid-year population size as obtained from Statistics Netherlands.

Supplementary Table S2. Excess mortality ratio (EMR) during the first five years after PCNSL diagnosis

Covariate	Model without therapy			Model with therapy		
	EMR[a]	95% CI	*P*-value[b]	EMR[a]	95% CI	*P*-value[b]
Period of diagnosis						
1989-1995	1	Reference				
1996-2002	1.10	0.93-1.31	0.269	1.18	0.98-1.41	0.076
2003-2008	0.73	0.61-0.86	<0.001	1.04	0.87-1.25	0.650
2009-2015	0.59	0.50-0.70	<0.001	0.86	0.72-1.03	0.100
Sex						
Male	1	Reference		1	Reference	
Female	1.05	0.93-1.18	0.451	0.98	0.87-1.11	0.774
Age at diagnosis, years						
18-60	1	Reference		1	Reference	
61-70	1.67	1.44-1.93	<0.001	1.26	1.08-1.48	<0.001
>70	3.11	2.70-3.60	<0.001	1.50	1.28-1.76	<0.001
Primary therapy						
No anti-neoplastic therapy				1	Reference	
Chemotherapy and radiotherapy				0.08	0.06-0.09	<0.001
Chemotherapy				0.14	0.12-0.17	<0.001
Radiotherapy				0.22	0.19-0.26	<0.001
Other/unknown therapy				0.28	0.19-0.39	<0.001

Abbreviations: EMR, excess mortality ratio; PCNSL, primary central nervous system lymphoma.

[a]Each covariate is simultaneously adjusted for all other covariates in the table, along with five years of follow-up.

[b]*P*-values are compared with the reference category.

3

Primary therapy and survival in patients aged over 70-years-old with primary central nervous system lymphoma: a contemporary, nationwide, population-based study in the Netherlands

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LETTER TO THE EDITOR

Primary central nervous system lymphoma (PCNSL) is an uncommon, but aggressive non-Hodgkin lymphoma confined to the brain, leptomeninges, spinal cord, and eyes. Its incidence has increased substantially over the past decades among over 60-year-olds.[1] The median age at diagnosis is around 65 years, and approximately one-third of newly diagnosed patients are >70 years.[1] Nevertheless, elderly PCNSL patients–especially those above age 70–are frequently excluded from or underrepresented in clinical trials due to concomitant comorbidities, poor performance status, or concerns regarding treatment-related sequelae.[2,3] Prospective studies specifically designed for elderly PCNSL patients are scarce.[4-6] Furthermore, the few available, somewhat outdated series mostly included relatively small numbers of patients (range, 10-107). These studies congruently showed that the prognosis of elderly patients remained poor and unchanged over the past decades, with overall survival (OS) ranging between 14-37 months. Collectively, apart from omitting consolidation radiotherapy after chemotherapy, the optimal treatment for elderly PCNSL patients is ill-defined.[1,6,7]

Population-based studies can complement prospective trials, especially in settings where data from prospective trials are scarce. At present, contemporary population-based studies with detailed data regarding primary therapy specifically among over 70-year-old PCNSL patients to inform clinical practice are lacking. Therefore, in this contemporary, nationwide, population-based study, we assessed primary therapy and OS among over 70-year-old PCNSL patients diagnosed in the Netherlands.

Established in 1989, the nationwide Netherlands Cancer Registry (NCR) has an overall coverage of >95% of all malignancies in the Netherlands.[8] We identified all over 70-year-old PCNSL patients diagnosed–confirmed with cytology, histology, and/or flow cytometry–between January 1, 2014 and December 31, 2017 from the NCR. PCNSL of the diffuse large B-cell type was defined using the International Classification of Diseases for Oncology morphology and topography codes (Supplementary Methods). Two patients diagnosed at autopsy were excluded. We included patients diagnosed from 2014 because the NCR collected data on the therapeutic regimen from that year onwards. The NCR is based on comprehensive case notifications through the Nationwide Network of Histopathology and Cytopathology, and the National Registry of Hospital Discharges (i.e. outpatient and inpatient discharges). Information on dates of birth and diagnosis, sex, disease stage, topography, and morphology, performance score, and primary therapy was available for individual patients. This information is collected by trained registrars of the NCR through retrospective medical records review. Primary therapy was categorized into chemotherapy, radiotherapy only, and supportive care only. Corticosteroids are not standardly registered in the NCR and may have been given in all treatment groups. The category of

chemotherapy was broken down by the exact therapeutic regimen. The Privacy Review Board of the NCR approved the use of anonymous data for this study.

The primary survival endpoint was OS, defined as the time from diagnosis until death. Patients were censored at emigration or end of follow-up (February 1, 2019). OS was calculated for three age groups (71-74, 75-79, and ≥80 years) and according to primary treatment (chemotherapy, radiotherapy only, and supportive care only) using the Kaplan-Meier method. Survival distributions were compared with the log-rank test. Multivariable Cox regression was conducted to assess covariates (sex, age at diagnosis, a prior malignancy before PCNSL diagnosis, receipt of rituximab, and type of primary therapy) associated with OS. A $P<0.05$ was considered statistically significant. See Supplemental Data for further details about the statistical analyses.

A total of 145 over 70-year-old PCNSL patients (50% males) were included in the study. The median age was 75 years (range, 71-87), with 55 (38%), 58 (40%), and 32 (22%) of patients aged 71-74, 75-79, and ≥80 years at diagnosis, respectively (Table 1).

Table 1. Patient characteristics

Characteristic	N	(%)
Total no. of patients	**145**	
Sex		
Male	73	(50)
Female	72	(50)
Age at diagnosis, years		
Median (range)	75 (71-87)	
71-74	55	(38)
75-79	58	(40)
≥80	32	(22)
Performance score		
0-1	24	(17)
2-4	52	(36)
Unknown	69	(48)
Prior malignancy		
No	113	(78)
Yes	32	(22)
Vital status		
Alive	27	(19)
Death	118	(81)
Median follow-up, months (range)		
Overall	4.1 (0.0-60.0)	
Alive	31.7 (15.2-60.0)	
Death	2.6 (0.0-41.4)	

Overall, 43% of patients received chemotherapy, 20% radiotherapy only, and 37% supportive care only (Table 2). The receipt of chemotherapy decreased with older age (58%, 40%, and 22% across the three age groups), while radiotherapy only or supportive care only increased (*P*=0.002; Table 2 and Supplemental Table 1). All 62 (43%) chemotherapy-treated patients except one, were treated with either methotrexate (MTX)-monotherapy (n=25) or a variety of MTX-based regimens (n=36; Table 2). MTX with teniposide, carmustine, and prednisolone (MBVP) was the most commonly applied MTX-based regimen (25/36; 69%). Rituximab was added to chemotherapy in 17/62 (27%) patients (Table 2). Of note, six of seven chemotherapy-treated patients aged ≥80 years were treated with MTX-monotherapy.

Table 2. Detailed information on primary therapy in over 70-year-old patients with PCNSL

	Age at diagnosis, years						Total	
	71-74		75-79		≥80			
Primary therapy	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Total no. of patients	**55**		**58**		**32**		**145**	
Supportive care only	**17**	**(31)**	**22**	**(38)**	**15**	**(47)**	**54**	**(37)**
Radiotherapy alone	**6**	**(11)**	**13**	**(22)**	**10**	**(31)**	**29**	**(20)**
Chemotherapy	**32**	**(58)**	**23**	**(40)**	**7**	**(22)**	**62**	**(43)**
MTX-based	*20*	*(36)*	*15*	*(26)*	*1*	*(3)*	*36*	*(25)*
MBVP[a,e]	15	(27)	10	(17)	0	-	25	(17)
MP[b,f]	2	(4)	3	(5)	1	(3)	6	(4)
MCPM[c]	1	(2)	1	(2)	0	-	2	(1)
MCP[c]	1	(2)	0	-	0	-	1	(1)
R-CHOP + MTX	0	-	1	(2)	0	-	1	(1)
MA[c]	1	(2)	0	-	0	-	1	(1)
MTX only[d]	*12*	*(22)*	*7*	*(12)*	*6*	*(19)*	*25*	*(17)*
Other	*0*	*-*	*1*	*(2)*	*0*	*-*	*1*	*(1)*
PC	0	-	1	(2)	0	-	1	(1)

Abbreviations: MTX, methotrexate; MBVP, MTX, teniposide, carmustine, and prednisolone; MP, methotrexate and procarbazine; MCPM, methotrexate, lomustine, procarbazine, and cytarabine; MCP, methotrexate, lomustine, and procarbazine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; MA, MTX and cytarabine; and PC, procarbazine and lomustine.

[a]Cytarabine and rituximab were applied in 15 and 2 patients, respectively.

[b]Rituximab was applied in 5 patients.

[c]Rituximab was applied in 1 patient.

[d]Rituximab was applied in 6 patients.

[e]Whole brain radiotherapy was administered after chemotherapy in 3 patients.

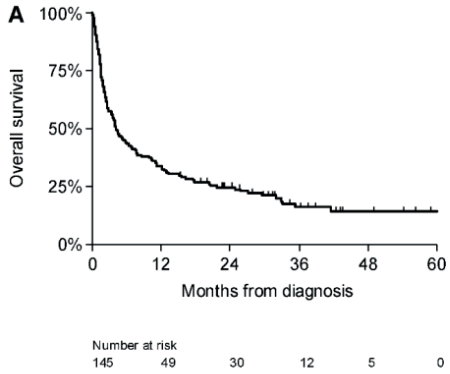
[f]Whole brain radiotherapy was administered after chemotherapy in 1 patient.

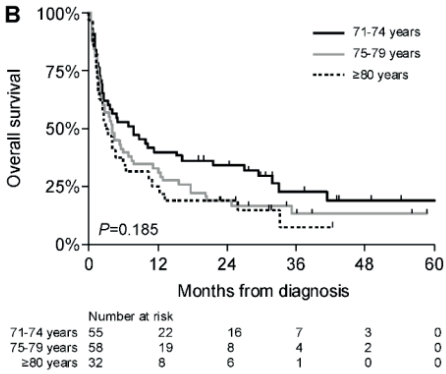
During follow-up, 118 (81%) patients died. The median follow-up of patients still alive was 31.7 months (range: 15.2-60.0). Overall, median OS was 4.1 months (95% confidence interval [CI], 2.8-6.8) and 2-year OS was 25% (95% CI, 18%-32%; Figure 1A). There were no significant differences in OS between the three age groups (*P*=0.185; Figure 1B). The difference in OS between 71-74 year-olds (7.7 months, 95% CI, 2.6-16.3) and those ≥75 years (3.9 months, 95% CI, 2.4-5.5) was also not statistically significant (*P*=0.08; Supplemental Figure 1). OS according to primary treatment did show significant differences, with chemotherapy-treated patients having a superior median OS (16.3 months 95% CI 7.8-35.2) compared with those who received radiotherapy only (7.7 months, 95% CI 4.6-13.2) or supportive care only (1.4 months, 95% CI 1.1-1.7; *P*<0.001; Figure 1C). Two-year OS was 45% (95% CI, 32%-57%) in recipients of chemotherapy, whereas it was exceedingly low in the other two treatment groups (Figure 1C). The multivariable Cox regression analysis revealed that primary treatment was the only factor associated with OS, whereas sex, age, a prior malignancy before PCNSL diagnosis, and the receipt of rituximab were not associated with OS (Supplementary Table 2). Excluding the four patients in the chemotherapy group who subsequently received whole-brain radiotherapy did not change survival estimates. Within the chemotherapy group, median OS for recipients of MTX-monotherapy was 5 months (95% CI, 2.6-41.4) and for MTX-based regimens 27 months (95% CI, 10.3-not reached; Figure 1D). That difference was not statistically significant (*P*=0.170). Also, and more importantly, the number of patients was small for a meaningful comparison. Therefore, a multivariable analysis of MTX only *versus* MTX-based regimens was not performed.

In this contemporary, nationwide, population-based study among newly diagnosed over 70-year-old patients with PCNSL, we observed that the prognosis of these patients remains poor. This finding is congruent with prior population-based studies spanning the past decades.[1]

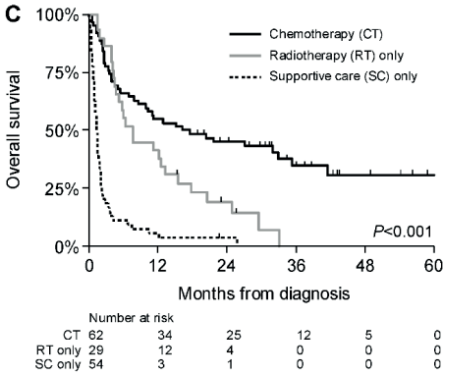
Age is a strong prognostic factor in adult PCNSL patients.[9,10] However, within our study population encompassing over 70-year-olds, there was no clear prognostic gradient with increasing age, although with greater patient numbers, the association of age on OS might show a statistically significant difference. Instead, despite the small patient numbers, treatment was a strong prognostic factor. Although only 22% of patients aged ≥80 years received chemotherapy—which possibly hints towards selection bias or confounding by indication—this finding suggests that treatment, more than age, influences survival in elderly patients judged fit enough to receive therapy. Selection bias might also hold for MTX-monotherapy versus MTX-based chemotherapy. Performance status and comorbidity–in particular renal insufficiency–might have influenced the choice of chemotherapeutic regimen.

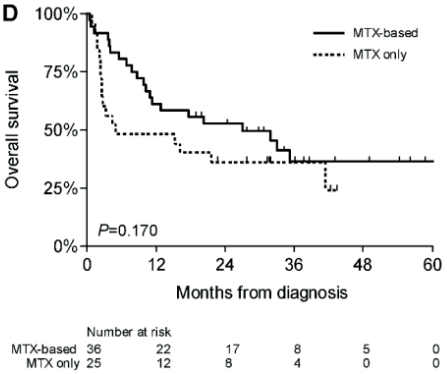
Prior prospective studies provided evidence that high-dose MTX–especially when combined with alkylating chemotherapy–is the most efficacious treatment for elderly PCNSL patients.[11] Although conflicting data exist on the therapeutic value of chemoradiation over





Covariate	Median, months			1-year			2-year		
	OS	95% CI		OS	95% CI		OS	95% CI	
71-74 years	7.7	2.6	16.3	40%	27%	53%	34%	22%	47%
75-79 years	4.0	2.2	7.5	33%	21%	45%	19%	10%	30%
≥80 years	2.9	1.5	6.5	25%	12%	41%	19%	8%	34%





Covariate	Median, months			1-year			2-year		
	OS	95% CI		OS	95% CI		OS	95% CI	
CT	16.3	7.8	35.2	55%	42%	66%	45%	32%	57%
RT only	7.7	4.6	13.2	41%	24%	58%	19%	7%	36%
No therapy	1.4	1.1	1.7	6%	1%	14%	4%	1%	11%

Covariate	Median, months			1-year			2-year		
	OS	95% CI		OS	95% CI		OS	95% CI	
MTX-based	27.0	10.3	NR	61%	43%	75%	52%	35%	67%
MTX only	5.0	2.6	41.4	48%	28%	66%	36%	18%	54%

Figure 1. Overall survival (OS) among over 70-year-old patients with primary central nervous system lymphoma in the Netherlands, 2014-2017. OS is shown for the total cohort **(A)**, and according to age at diagnosis **(B)**, treatment group **(C)**, and the type of therapy with methotrexate **(D)**. The tables below panels B through D show the median OS, and the projected 1- and 2-year OS with associated 95% confidence intervals. Abbreviations: OS, overall survival; CI, confidence interval; and MTX, methotrexate.

chemotherapy alone in elderly PCNSL patients,[11,12] it is unquestionable that consolidation with radiotherapy in this population carries a high risk of neurotoxicity and severe cognitive decline.[13]

Controversy exists regarding the therapeutic value of rituximab in PCNSL. Findings from the current study and a recent randomised phase III trial among PCNSL patients aged

18-70 years showed no added therapeutic value of rituximab on survival outcomes.[3] However, our results should be cautiously interpreted given the low number of rituximab-treated patients. Similarly, a meta-analysis encompassing 343 patients with PCNSL aged 50-67 years showed a possible effect of rituximab on PFS but not on OS.[14] In contrast, a recent population-based study among 164 adult PCNSL patients diagnosed between 2005-2010 in Austria–of whom 40% were >70 years–suggested that rituximab might augment survival, after a short follow-up: median 12 months.[15]

The strength of the current study is the use of a nationwide population-based cancer registry. As such, our study is not plagued by selection and/or referral biases to the extent encountered in clinical trials. Therefore, our study represents the general population of elderly PCNSL patients. Limitations of our study mainly pertain to the lack of data throughout most of the registry on comorbidities, the use of corticosteroids and the dose of steroids and chemotherapeutic agents, relapse rates, and salvage treatment. Also, the performance score is poorly documented in medical records, thereby hampering its inclusion in the regression analyses due to the high percentage of unknown values (48%; Table 1). The latter factor limits insight into the decision-making process of physicians based on performance status.

In summary, in this nationwide, population-based study, survival among over 70-year-old PCNSL patients remains poor in contemporary clinical practice. Nevertheless, our data demonstrate that MTX-based multi-agent chemotherapy–as compared with radiotherapy only and supportive care only–results in the best outcome in elderly patients judged eligible to receive such treatment, with a 2-year OS that approximates 50%. The challenge remains to balance the benefits and risks of intensive chemotherapy in this patient group. Therefore, future prospective intervention studies are needed to assess which elderly patients can benefit from intensive chemotherapy or less intensive approaches.

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SUPPLEMENTARY INFORMATION

Supplemental methods

Statistical analyses

The Fisher's exact test for categorical variables was applied to test for differences between groups. Univariable and multivariable logistic regression analyses were conducted to investigate the association of age at diagnosis (71-74, 75-79, and ≥80 years), sex, and a prior malignancy before primary central nervous system lymphoma (PCNSL) diagnosis with the receipt of chemotherapy. Linear trends in age with chemotherapy receipt were evaluated using Wald statistics. Also, univariable and multivariable Cox regression analyses were conducted to investigate the prognostic effect of age at diagnosis (71-74, 75-79, and ≥80 years), sex, a prior malignancy before PCNSL diagnosis, primary therapy (chemotherapy, radiotherapy only, and supportive care only), and the application of rituximab on overall survival (OS). For both the multivariable logistic and Cox regression analyses, we used a reduced model in which variables were included with a forward selection method, after adjusting for the influence of the variables already selected according to their level of significance. The reduced model was achieved when the *P*-value for entering an additional variable was below 0.05. Also, we developed a full model where all the variables mentioned earlier were simultaneously adjusted. The likelihood ratio test (LRT) was used to compare the fit of the reduced model to the full model. All statistical analyses were performed with STATA Statistical Software Release 14.2 (College Station, TX, United States).

Morphology and topography codes

Primary central nervous system lymphoma (PCNSL) of the diffuse large B-cell type was defined using International Classification of Diseases for Oncology morphology (i.e. 9590, 9591, 9593, 9595, 9675 and 9680-9684) and topography codes (i.e. C69.2, C69.4, C71.0-C71.9, C72.0, and C72.8). The selected topography codes are consistent with an anatomical location in the brain (C71.0-C71.9), spinal cord (C72.0), eyes (C69.2 and C69.4), and leptomeninges or cerebrospinal fluid (C72.8), according to the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.(1) Although C72.8 is not specific for the latter two localizations, coding rules of the NCR designate C72.8 for localizations in the leptomeninges or cerebrospinal fluid.

Supplemental results

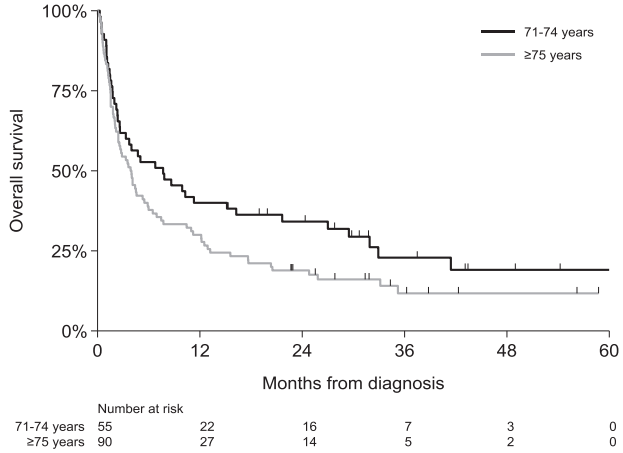
Chemotherapy receipt

Univariable and multivariable analyses revealed that only age ≥80 years at PCNSL diagnosis ($OR_{reduced\ model}$, 0.20; 95% CI, 0.07-0.54; *P*=0.002), as compared with age 71-74 years, was the sole variable associated with a lower odds to receive chemotherapy (Supplemental Table 1). However, though, there was a linear effect of a lower odds of chemotherapy

receipt with increasing age (*P* for trend = 0.002; Supplemental Table 1). The addition of the remaining covariates into the reduced model did not improve the fit of that model (*P* for LRT = 0.199). Also, the linear effect of a lower odds of chemotherapy receipt with increasing age remained significant in the full model (*P* for trend = 0.003; Supplemental Table 1)

Overall survival

As shown in Supplemental Table 2, the univariable analysis showed that patients who received radiotherapy only or supportive care only had a higher risk of mortality, as compared with recipients of chemotherapy. In addition, patients who received rituximab had a lower risk of mortality, as compared to patients who did not receive rituximab. However, multivariable analyses demonstrated that primary therapy (i.e. chemotherapy, radiotherapy only or supportive care only) was the sole variable that was associated with OS. The addition of the remaining covariates into the reduced model with primary therapy only did not improve the fit of the model (*P* for LRT = 0.930).



Supplemental Figure 1. Overall survival (OS) among over 70-year-old patients with primary central nervous system lymphoma in the Netherlands, 2014-2017. OS is shown according to age at diagnosis (that is, 71-74 *versus* ≥75 years). The median OS was 7.7 (95% CI, 2.6-16.3) and 3.9 (95% CI, 2.4-5.5) for patients aged 71-74 and ≥75 years (*P* for log-rank = 0.08), respectively. The corresponding estimates of 2-year OS were 34% (95% CI, 22%-47) and 19% (95% CI, 12%-28%), respectively.

Supplemental Table 1. Results of the logistic regression analyses on potential predictors associated with the receipt of chemotherapy

	Univariable			Multivariable					
				Reduced model			Full model		
Covariate	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Sex									
Male	1	(ref)					1	(ref)	
Female	1.28	0.66-2.48	0.458				1.09	0.54-2.21	0.815
Age at diagnosis, years			0.002*			0.002*			0.003*
71-74	1	(ref)		1	(ref)		1	(ref)	
75-79	0.47	0.22-1.00	0.050	0.47	0.22-1.00	0.050	0.47	0.22-1.01	0.053
≥80	0.20	0.07-0.54	0.002	0.20	0.07-0.54	0.002	0.21	0.08-0.59	0.003
Prior malignancy									
No	1	(ref)					1	(ref)	
Yes	0.44	0.19-1.04	0.062				0.45	0.19-1.10	0.081

Abbreviations: OR, odds ratio; and CI, confidence interval.
*, *P* for trend

Supplemental Table 2. Results of the Cox regression analyses on potential predictors associated with overall survival

	Univariable			Multivariable					
				Reduced model			Full model		
Covariate	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Sex									
Male	1	(ref)					1	(ref)	
Female	0.88	0.61-1.26	0.480				0.98	0.68-1.43	0.923
Age at diagnosis, years									
71-74	1	(ref)					1	(ref)	
75-79	1.34	0.89-2.04	0.166				0.99	0.63-1.55	0.958
≥80	1.52	0.94-2.47	0.089				0.91	0.53-1.56	0.723
Prior malignancy									
No	1	(ref)					1	(ref)	
Yes	0.92	0.60-1.42	0.709				0.91	0.57-1.45	0.696
Primary therapy									
Chemotherapy	1	(ref)			(ref)		1	(ref)	
Radiotherapy alone	1.92	1.15-3.20	0.013	1.92	1.15-3.20	0.013	1.85	1.02-3.36	0.042
Supportive care only	6.91	4.35-10.97	<0.001	6.91	4.35-10.97	<0.001	6.48	3.80-11.1	<0.001
Application of rituximab									
No	1	(ref)					1	(ref)	
Yes	0.37	0.19-0.74	0.005				0.71	0.33-1.51	0.373

Abbreviations: HR, hazard ratio; and CI, confidence interval.

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PART II

Diagnostic evaluation

4

Flow cytometry shows added value in diagnosing lymphoma in brain biopsies

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ABSTRACT

Background: To assess the sensitivity, specificity and turnaround time of flow cytometric analysis on brain biopsies compared to histology plus immunohistochemistry analysis in tumors with clinical suspicion of lymphoma.

Methods: All brain biopsies performed between 2010 and 2015 at our institution and analyzed by both immunohistochemistry and flow cytometry were included in this retrospective study. Immunohistochemistry was considered the gold standard.

Results: In a total of 77 biopsies from 71 patients, 49 lymphomas were diagnosed by immunohistochemistry, flow cytometry results were concordant in 71 biopsies (92.2%). We found a specificity and sensitivity of flow cytometry of 100% and 87.8%, respectively. The time between the biopsy and reporting the result (turnaround time) was significantly shorter for flow cytometry, compared to immunohistochemistry (median: 1 vs. 5 days).

Conclusions: Flow cytometry has a high specificity and can confirm the diagnosis of a lymphoma significantly faster than immunohistochemistry. This allows for rapid initiation of treatment in this highly aggressive tumor. However, since its sensitivity is less than 100%, we recommend to perform histology plus immunohistochemistry in parallel to flow cytometry.

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is a rare non-Hodgkin lymphoma confined to the brain, leptomeninges, eyes, or spinal cord.[1] Approximately 3% of all brain tumors are PCNSL. Secondary central nervous system lymphoma, or CNS localization of systemic lymphoma, occurs most frequently in Burkitt lymphoma (up to 43%) or in diffuse large B-cell lymphoma (DLBCL) patients (5-14%, depending on its stage or risk factors).[2,3] Common presenting symptoms of a CNS lymphoma are focal neurological deficits, neuropsychiatric symptoms, headache and, less typically, seizures.[4] MRI mostly shows single or multiple space occupying lesions, with homogeneous contrast enhancement. Before starting treatment, cytological, or histologic confirmation of the presence of a lymphoma is required. Since clinical deterioration is frequent in both primary and secondary CNS lymphoma, a rapid diagnosis is preferable. Sometimes a CNS lymphoma can be diagnosed by vitreous or cerebrospinal fluid (CSF) analysis.[5] However, a spinal tap may be contraindicated in space occupying lesions and even if safely possible, PCNSL is diagnosed on CSF in about 30% of patients only.[6] Consequently, a brain biopsy remains necessary in the majority of the patients. Similarly, systemic lymphoma may also present with intraparenchymatous lesions, and may present with diagnostic uncertainties requiring histological confirmation. Histology with immunohistochemistry (IHC) is considered the gold standard in the analysis of brain biopsies in diagnosing a lymphoma. Immunophenotyping by flow cytometry is an objective and quantitative method ideally suited to identify small populations of cells with aberrant phenotypes.[7] It is particularly helpful for the detection of small clonal populations of B-lymphocytes. The technique has proven its value in the analysis of bone marrow, fine needle aspiration of lymph nodes and in cerebrospinal fluid.[8-12] In cerebrospinal fluid the sensitivity increases 2 to 3 times.[13-17] However, few data defining the added value and diagnostic accuracy of flow cytometry in brain biopsies have been published. In our center immunophenotyping using eight-color flow cytometry has been utilized in addition to histology with IHC in brain biopsies since 2010 in brain tumor patients in whom a lymphoma was suspected, based on clinical and radiological features. The aim of this study was to determine the added clinical and diagnostic value of immunophenotyping by flow cytometry in brain biopsies. Furthermore, since analysis by flow cytometry is in general much faster than by immunohistochemistry, we also sought to investigate the difference in time needed to acquire a diagnosis by these two techniques.

METHODS

Patients

All brain biopsies performed at the Erasmus University Medical Center in Rotterdam, the Netherlands, between January 2010 and December 2015 were retrospectively extracted from patient and laboratory registries. See Figure S1 for the flowchart of selecting biopsies. Only biopsies which were analyzed by both IHC and flow cytometry were included for statistical analysis. Flow cytometric analysis was routinely performed when a lymphoma was suspected on radiological grounds. In addition, HIV-status, use of corticosteroids and immunomodulating medication, of all patients were collected. Turnaround time (time between biopsy and report of the analysis) was extracted from patient files or laboratory log. Preliminary results given to the clinician were not included in our statistical analysis. The size of the biopsies and the numbers of cells within the flow cytometric analysis were registered. As a check for lymphoma patients not included, all patients with CNS lymphoma diagnosed in the same period in our center were extracted from the national pathology database PALGRA. The study was approved of by the Independent Review Board of our institution.

Neurosurgical procedures

Brain tissue was collected by image-guided stereotactic biopsies; when a high grade glioma was suspected patients went for open surgery. The stereotactic biopsies were frameless performed using the Medtronic Stealth Treon™ Vertek® system until 2010 and the Brainlab® Varioguide neuronavigation system ever since.[18,19] In general, four biopsies were obtained at the preoperatively determined target, as well as two to four more biopsies at a site proximal to the target on the same biopsy trajectory. Open biopsies were performed using image-guided navigation and the operation microscope. After surgery the collected biopsies were divided for histopathology and flow cytometry by the neurosurgeon, or by the pathologist if all material had initially been sent to the pathology laboratory. Intraoperative freeze sections were not performed in most patients to maximize available tissue for definitive pathology and flow cytometry.

Histology and immunohistochemistry

All tumors were classified according to the World Health Organization (WHO) classification of Tumours of Haematopoietic and Lymphoid Tissues version 2008 by conventional histological assessment on 2 µm hematoxylin and eosin (H&E) stained sections and on 4 µm immunohistochemically stained sections. Sections were cut from formalin-fixed brain tumor tissues, embedded in paraffin blocks using standard pathology tissue processing procedures.[20] For immunohistochemistry, the following primary antibodies were used: CD3, CD5, CD10, CD19, CD20, CD79a, Bcl-2, Bcl-6, and Mib-1. When appropriate this panel

was extended with one or more of the following antibodies: BOB-1, MUM1, CD 15, cyclin D1, SmIgkappa, SmIglambda, CD21, CD23, CD68, CD138, CD4, GFAP, CD31, CD43, TIA-1, ALK-1, CD8 and PAX-5. All immunohistochemical procedures using primary and secondary antibodies and detection systems, were performed according to the manufacturer's recommendations on a Ventana Benchmark Ultra platform (Ventana Medical Systems Inc., Tucson, USA), tested and validated according to ISO 15189 standards. See Figure 1 for an example of a cerebral NHL, analyzed by histology with immunohistochemistry.

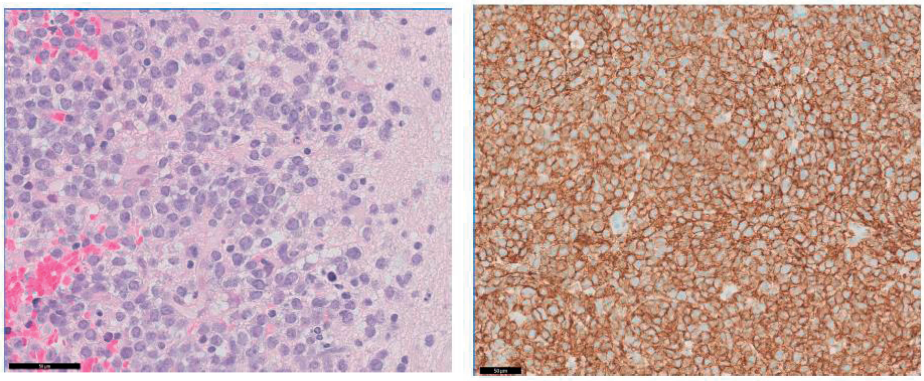

Figure 1. Histology and immunohistochemistry analysis
HE-staining with diffuse large B-cell lymphoma, activated blast type. Left: HE-staining with diffuse large B-cell lymphoma, activated blast type. Brain tissue with infiltration of blastic cells with large vesicular nuclei with nucleoli. Right: These tumour cells express CD20, CD79a, BCL-2, BCL-6 and MUM1 and very weak expression of CD10.

Flow cytometry

Cell suspensions were generated from a single, unfixed brain biopsy by gentle manual disaggregation on a 100 µm strainer using a 10 mL syringe plunger rod and wash buffer (PBS/BSA 0.5%; not using any enzymes). The released cells were collected by rinsing with a total volume of 10 mL wash buffer and washed twice in 10 mL wash buffer; centrifugation steps were for 5 minutes at 540*g*. After the last wash step, the supernatant was discarded and the pellet of cells was suspended in wash buffer. Fifty microliters of the cell suspension were stained using the EuroFlow Lymphocytosis Screening Tube (LST), according to the EuroFlow protocol.[21,22] The LST contains antibodies CD20-Pacific Blue (Clone: 2H7; Biolegend), CD4-Pacific Blue (RPA-T4; Biolegend), CD45-Pacific Orange (HI30; Invitrogen), CD8-FITC, SmIgλ-FITC, CD56-PE, SmIgκ-PE (SLPC mix; Cytognos), CD5-PerCP-Cy5.5 (L17F12, BD Biosciences, CD19-PC7 (J3-119; Beckman Coulter), SmCD3-APC (SK7, BD Biosciences), and CD38-APCH7 (HB7; BD Biosciences). Subsequently the suspension was acquired on a FACSCanto II flowcytometer (BD Biosciences, Erembodegem, BE) using EuroFlow settings.[23] We aimed to acquire at least 5000 B-cells (with a minimum of 50.000

leukocytes); if this could not be reached we acquired all available cells in the tube. Appropriate instrument set-up and staining protocols were monitored by the EuroFlow QA scheme.[24] After exclusion of debris, doublets and non-hematopoietic cells (CD45 negative, CD19 negative), which all together could add up to over 95% of acquired events in some samples, we defined the presence of a B-NHL population as a population with a marked shift in the SmIgKappa/SmIgLambda ratio (<0.7 or >2.8) and/or a clearly aberrant immunophenotype (e.g., abnormal expression of Ig, CD19, CD20 and/or CD38, abnormal (high) forward scatter). If a B-NHL was detected and sufficient cells were available, EuroFlow BCLPD tube 1 to 4 were stained as well. In all cases, the diagnosis of a B-NHL was based on the results of the LST tube only, the additional information resulting from the additional BCLPD tubes was used to further specify the immunophenotype and to hint to specific B-NHL subtypes. Even though pathologists and immunologists who evaluated the analyses were not blinded for each other's conclusion, the flow cytometry results were reported independently of histology plus IHC analysis. See Figure 2 for an example of a cerebral NHL, analyzed by flow cytometry.

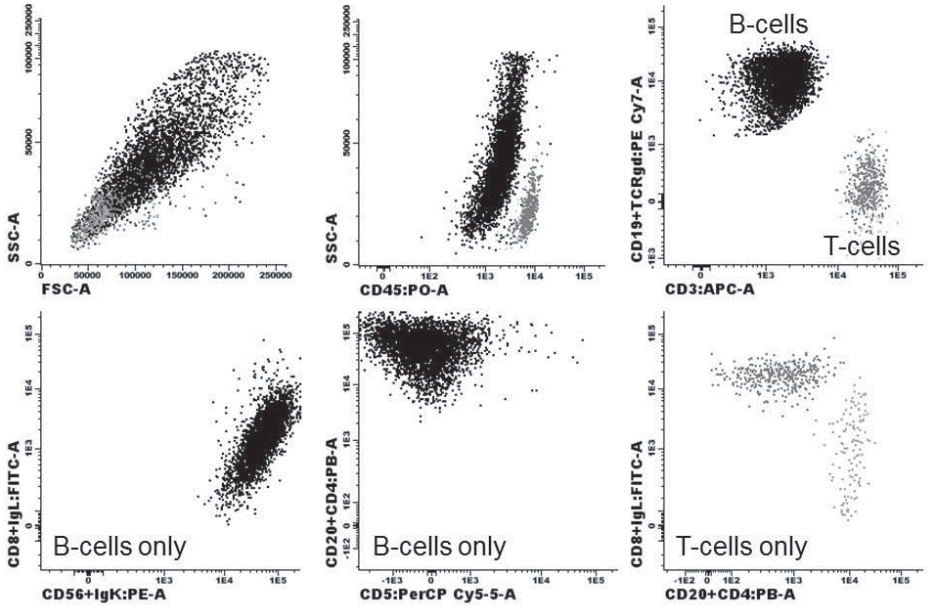

Figure 2. Flow cytometry analysis

Flowcytometric analysis on brain biopsy, showing a cerebral NHL with the presence of T-cells (11% of leukocytes) and B-cells (89% of leukocytes). Whereas the T-cells (grey) showed a normal CD4/CD8 ratio (lower row, third plot) and a normal immunophenotype (CD3+/CD45+; upper row, second and third), the B-cells (CD19+; black) were clearly abnormal, with monotypic Immunoglobulin kappa expression, low expression of CD45, and light scatter characteristics (FSC and SSC; upper row, first plot) compatible with large cells. The biopsy was stained with the EuroFlow Lymphocytosis Screening Tube according to EuroFlow procedures.

Statistical analysis

To determine the diagnostic value of flow cytometry, the reports of flow cytometry and immunohistochemistry were compared. Morphology plus IHC was considered the gold standard. In case the results were suspicious for a lymphoma but not conclusive, it was categorized as 'no lymphoma'. The turnaround time and whether the results were available within 24 hours, were compared between the two techniques using the Wilcoxon signed-ranks and a McNemar test, respectively. Differences with respect to use of dexamethasone and sample size, between concordant and discordant groups and between those who had multiple biopsies and who did not were analyzed by Mann-Whitney U or a Fisher's Exact test. All analyses were performed by SPSS Statistics 21.

RESULTS

Between January 2010 and December 2015 77 biopsies which have been analyzed by both histology and flow cytometry, were performed in 71 patients (59% male) with a median age of 63 (range 15-82). 10% of the patients were immunocompromised, which was defined as being HIV-infected (one patient) or using systemic immunomodulating treatment (e.g., methotrexate, azathioprine). Of all CNS lymphoma patients diagnosed in our hospital between 2010-2015 by histology and IHC, only four were not sent for flow cytometric analysis. In two cases all material was immediately preserved in formalin which made the tissue no longer suitable for flow cytometry, in two additional cases lymphoma was not considered in the pre-operative differential diagnosis.

Forty-nine biopsies were diagnosed as brain lymphoma by histology and immunohistochemistry; 43 of these were also diagnosed as lymphoma by flow cytometry (Table 1). By flow cytometry, all identified cases were CD19+/CD20+; Ig light chain restriction was observed in most cases (38; 83%) whereas no Ig expression was detected in nine cases (17%). None of the 28 tissue samples not diagnosed as lymphoma by histology plus IHC were identified as lymphoma by flow cytometry. We thus found a concordance, specificity and sensitivity of immunophenotyping by flow cytometry in brain biopsies of 92.2% (71/77), 100% (28/28) and 87.8% (43/49), respectively. The positive predictive value was

Table 1. Diagnostic value of flow cytometry on brain biopsies.

	Immunohistochemistry		
Flow cytometry	Lymphoma	No lymphoma	Total
Lymphoma	43	0	43
No lymphoma	6	28[a]	34
	49	28	77

[a] Including 8 cases in which both results were "inconclusive".

100% (43/43) and the negative predictive value was 82.4% (28/34). Numbers of leukocytes (after exclusion of debris, doublets and non-hematopietic cells) that could be analyzed by flow cytometric analysis ranged widely: 9425 (29-207,259), median (range). Although statistical analysis to compare biopsies with discordant and concordant results should be interpreted with caution due to small numbers, no significant differences were found with respect to sample size ($P = 0.06$), number of cells acquired by flow cytometry ($P = 0.62$), or corticosteroid use prior to biopsy ($P = 0.108$). All 6 discordant cases were DLBCL, without unusual evidence of necrosis. In 6/71 patients a second biopsy and in 2/71 patients even a third biopsy was necessary to make a diagnosis, because of an inconclusive diagnosis in previous biopsies. Only those biopsies which were investigated by both techniques (6/8) were included in the statistical analysis. In the biopsies, analyzed by IHC only, two additional lymphoma were found. Use of corticosteroids prior to first biopsy ($P = 0.06$), size of the biopsy ($P = 0.68$) and/ or number of cells for flow cytometric analysis ($P = 0.19$) were similar in patients with conclusive and inconclusive diagnoses. The 20 patients without a lymphoma were diagnosed with a myriad of diseases: 11 glioblastoma, 1 anaplastic astrocytoma, 1 germinoma, 1 stroke, 5 infections and one CLIPPERS syndrome (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids), a rare auto-immune disorder. We found a significantly shortened time to reporting of the results (turnaround time) for flow cytometry, compared to IHC (Table 2). Furthermore, in 54% of the biopsies the diagnosis was provided within 24 hours using flow cytometry, compared to 9% using histology plus IHC.

Table 2. Time to diagnosis

	Immunohistochemistry n=77	Flow cytometry n=76	
Turnaround time (days)	5 (0-18)	1 (0-7)	p <0.00[a]
Diagnosis <24 hours (biopsies)	7 (9%)	41 (54%)	p< 0.00[b]

Median time (range) in days between biopsy and diagnosis. Significance was calculated by [a]Wilcoxon signed-ranks test and [b]McNemar Test. In one biopsy the date of reporting was missing for flow cytometry analysis.

DISCUSSION

In this study, we compared flow cytometry with histology plus IHC on 77 brain biopsies, performed in patients clinically suspected of having a lymphoma. We found a high concordance between both techniques (92.2%) and a specificity and sensitivity of flow cytometry by immunophenotyping in brain biopsies of 100% and 88%, respectively. In 6 patients with histologically proven NHL, the presence of a lymphoma could not be identified by flow cytometry. No factors (e.g., sample size, use of corticosteroids prior to the biopsy) could be identified which could explain the missing diagnosis in flow cytometry. Unlike

in CSF or bone marrow analysis no additional cases of brain lymphoma were identified by flow cytometry that had not been identified by immunohistochemistry. We found a significant difference in turnaround time for the two techniques. After biopsy a diagnosis was given with a median time of 5 days (range 0-18) for immunohistochemistry, compared to median of 1 day (range 0-7) for flow cytometry. In 54% of the biopsies the presence or absence of a lymphoma could be confirmed within 24 hours by flow cytometry, compared to 9% for immunohistochemistry ($P < 0.00$), which means that correct treatment could be initiated within 24 hours. It should be noted that the preliminary results of the flow cytometric analysis were frequently reported to the clinician on the day of biopsy. Given the frequently rapid clinical deterioration in CNS lymphoma and the negative impact of a lower performance score on survival, according to the two largest validated prognostic models[25,26], early diagnosis may improve prognosis.[27] Similar findings were reported in a much smaller cohort of 18 stereotactic biopsies recently.[28] Cordone et al. found a significant agreement between flow cytometry and immunohistochemistry diagnosis ($P = 0.0034$). They described a sensitivity and specificity of flow cytometry by immunophenotyping of 89% and 100% respectively. In the 2/18 PCNSL biopsies not identified by flow cytometry more central necrosis was present, compared to biopsies with concordant results and both patients used corticosteroids prior to the biopsy.[28] We did not find more central necrosis in our discordant biopsies and corticosteroid use did not differ between concordant and discordant pairs. One other study analyzed flow cytometry on rinse fluid. Even though rinse fluid from the biopsy needle cannot be completely compared to brain tissue itself, this study showed similar results.[29] In a small sample, a high specificity (100%) and sensitivity (75% on rinse fluid and 100% on tissue sample) of flow cytometry in detecting a brain lymphoma were found. The added value was again the time in which the flow cytometry could confirm the diagnosis (±3-20 hours, compared to 2-10 days for histopathological diagnosis). Because the diagnosis could be confirmed within 24 hours in 75% of the cases, the authors recommend to use both techniques, allowing chemotherapy to commence within 24 hours. In contrast with the results of our study and two comparable, though much smaller studies on brain biopsies, flow cytometry on bone marrow and CSF allowed identification of additional lymphoma cases over cytology. The sensitivity of cytological analysis of CSF for lymphoma cells is low (2-32%).[30] Several authors found that additional flow cytometry on CSF improves the sensitivity, up to 2-3 fold.[13-15] In up to 80% the lymphoma cells are detected in the first CSF sample, analyzed by flow cytometry.[15] It is likely that this additional sensitivity of flow cytometry is a result of the low number of tumor cells available for diagnosis in CSF and bone marrow. Corticosteroids can induce apoptosis in lymphoma cells. This can mask the morphology and can even cause the tumor to vanish.[31-33] In lymph nodes and CSF samples, flow cytometry can confirm a diagnosis on samples with a low cell count. We hypothesized that flow cytometry, being a more sensitive technique, may be able to recognize lymphoma in patients in whom, after steroid use,

lympholysis had taken place and histology plus IHC was negative. Unfortunately, this was not the case in our series nor in the other two smaller studies available. Five patients who went for multiple biopsies and were diagnosed with brain lymphoma after their second or third biopsy, used corticosteroids prior to their first (and second) biopsy. In none of these patients flow cytometry analysis was able to make the diagnosis when histology plus IHC were non-diagnostic. Clearly, immunohistochemistry as well as flow cytometry analysis can be compromised in patients using corticosteroids prior to the biopsy.

The strengths of this study are the comprehensive clinical and laboratory data in a large, unselected sample, allowing calculation of the diagnostic and clinical value of flow cytometry on brain biopsies. To the best of our knowledge, this is the largest cohort ever described comparing flow cytometry to immunohistochemistry in brain biopsies. Furthermore, due to our large population, we were able to show that the negative effect of corticosteroids on the diagnostic value of flow cytometry was similar to that on IHC. Even our series, however, still concerns a relatively small number of cases. The main drawback of our study is its retrospective nature: we may have missed some biopsies, even though we did a thorough search through all available databases in our hospital (neurosurgery, flow cytometry, pathology and neuro-oncology) and the immunologist and pathologist were not blinded for each other's results. Nevertheless the flowcytometric result was always reported without knowledge of the pathological evaluation. In addition, we did not perform freeze sections, so comparison with intraoperative diagnosis could not be made.

CONCLUSION

Flow cytometry analysis in brain biopsy is a feasible technique with 100% specificity to confirm the diagnosis of brain lymphoma in patients suspected for lymphoma on clinical grounds. The added clinical value is the speed by which flow cytometry can establish or confirm the diagnosis, enabling a faster initiation of treatment, while false positive cases were not identified. Flow cytometry is complementary to, but not more sensitive than, histopathology with immunohistochemistry analysis. We recommend to perform flow cytometry and immunohistochemistry in parallel in brain biopsies, suspected for a lymphoma.

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SUPPLEMENTARY DATA

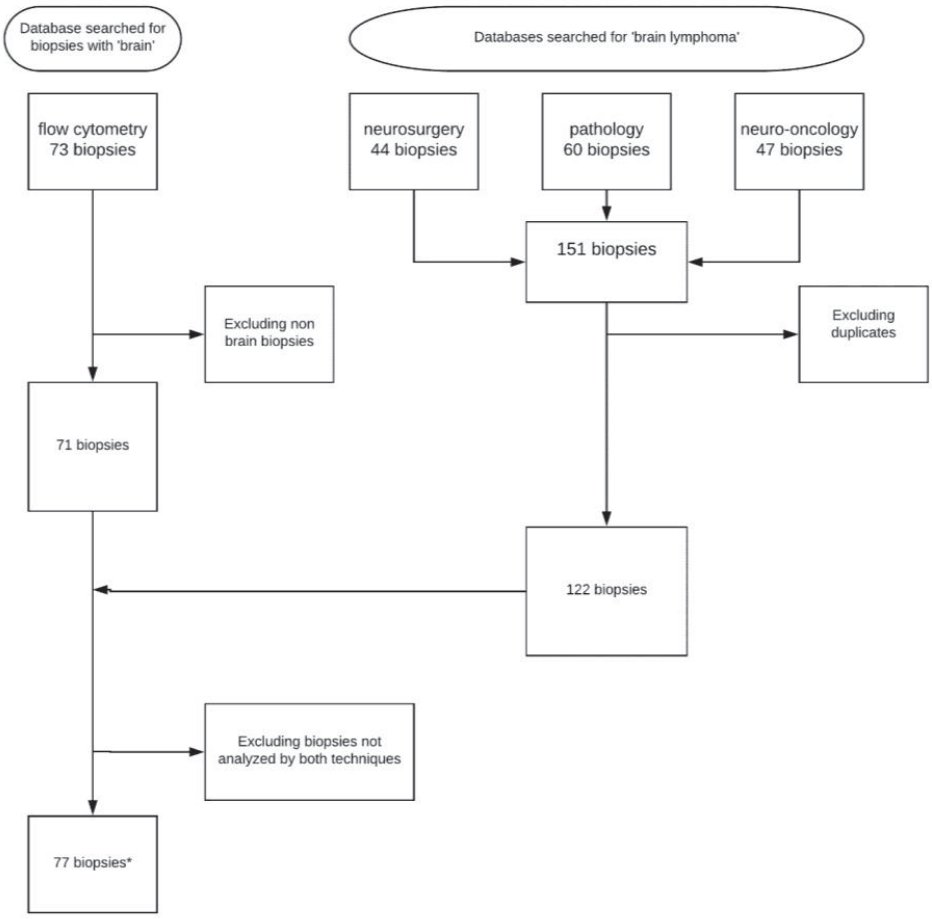

Figure S1 Flowchart
Selection of eligible biopsies. *Some biopsies turned out to be analyzed also by flow cytometry, in addition to immunohistochemistry

5

Extent of radiological response does not reflect survival in primary central nervous system lymphoma

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ABSTRACT

Background. In primary central nervous system lymphoma (PCNSL), small enhancing lesions can persist after treatment. It is unknown whether a difference in response category (complete response (CR), complete response unconfirmed (CRu) or partial response (PR)) reflects survival. We aimed to determine the value of a central radiology review on response assessment and whether the extent of response influenced progression-free and/or overall survival.

Methods. All patients in the HOVON 105/ALLG NHL 24 study with at least a baseline MRI and one MRI made for response evaluation available for central review were included. Tumor measurements were done by two independent central reviewers, disagreements were adjudicated by a third reviewer. Crude agreement and interobserver agreement (Cohen's kappa) were calculated. Differences in progression-free and overall survival between different categories of response at the end-of-protocol-treatment were assessed by the log-rank test in a landmark survival-analysis.

Results. Agreement between the central reviewers was 61.7% and between local and central response assessment was 63.0%. Cohen's kappa's, which corrects for expected agreement, were 0.44 and 0.46 (moderate), respectively. Agreement on progression or not was 93.3% (kappa 0.87) between local and central response assessment. There were no significant differences in progression-free and overall survival between patients with CR, CRu or PR at the end-of-protocol-treatment, according to both local and central response assessment.

Conclusions. Reliability of response assessment (CR/CRu/PR) is moderate even by central radiology review and these response categories do not reliably predict survival. Therefore, primary outcome in PCNSL studies should be survival rather than CR or CR/CRu-rate.

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is a rare non-Hodgkin lymphoma confined to the brain, leptomeninges, spinal cord and eyes without manifestations outside the central nervous system. For response assessment in PCNSL the criteria from the International Primary CNS Lymphoma Collaborative Group (IPCG), are commonly used.[1] These response criteria are based on radiological, ophthalmologic and spinal fluid cytology examination, and the use of corticosteroids. The MRI response evaluation defines the following categories: complete response (CR): no signs of abnormal gadolinium-based contrast agent enhancement, complete response unconfirmed (CRu): a small but persistent contrast enhancement abnormality likely related to biopsy or focal hemorrhage, partial response (PR): a reduction of ≥50% of the contrast enhancing lesion, stable disease (SD): <50% reduction and ≤25% increase of the contrast enhancing lesion, progressive disease (PD): >25% increase in contrast enhancing lesion, relapse: a new contrast enhancing lesion after prior CR or CRu.[1] These response criteria do not take non-enhancing lesions into account. Recent findings and earlier reports suggest that these lesions might, however, be considered as tumor as well.[2,3]

The correlation of radiological response with survival endpoints (progression-free survival [PFS] and overall survival [OS]) is uncertain: one study showed that patients with a CR at the end of induction chemotherapy had a better OS than those who did not reach CR, but in this study PR, SD and progression were combined.[4] In another study highly variable outcomes were found in patients with PR at the end-of-treatment[2], and a third study did not show a survival difference between those who attained CR compared to those who did not reach CR at the end of induction treatment.[5] Thus, it is questionable whether in PCNSL the extent of radiological response is relevant for predicting OS, the golden endpoint in oncology studies. It is also unclear whether interobserver variation exists in assessing response in PCNSL, which if present, will affect the reliability of that endpoint.

In the HOVON 105/ ALLG NHL 24 trial, the primary endpoint was event-free survival (EFS). Events were defined as 'not reaching complete response' or 'complete response unconfirmed at the end-of-treatment', or 'progression or death after response'.[6] Because event-free survival includes a radiological evaluation as endpoint (i.e. achieving CR or CRu), based on local assessment, central MRI review is important for the trial analysis. The aim of the present study was to review the local assessment by central radiology review and to assess whether CR, CRu and PR reflect PFS and OS. In addition, we evaluated the relevance of non-enhancing lesions at baseline and after treatment.

METHODS

Patient selection

The HOVON 105/ALLG NHL 24 study is a phase III randomized controlled trial, in which between 2010 and 2016 199 patients were recruited from Dutch, Australian and New Zealand hospitals. The treatment protocol and primary outcome results have been published before.[6] In short, immunocompetent patients with a newly diagnosed, CD20 positive B-cell PCNSL aged 18-70 years with WHO/ECOG performance status 0-3 were included. Patients were randomized for two courses of high-dose methotrexate (HD-MTX)-based chemotherapy: methotrexate, teniposide, BCNU and prednisolone (MBVP) versus MBVP with rituximab (R-MBVP). This was followed by HD-cytarabine (Ara-C) chemotherapy. Patients ≤60 years-old subsequently received 30Gy whole brain radiotherapy (WBRT). A simultaneous focal boost of 10Gy was given to the original enhancing tumor in patients who only achieved partial response (PR).

Patients were included for the central MRI review if they gave informed consent for central radiology review, and if a baseline MRI as well as at least one follow-up MRI was available for central review. Additionally, a measurable brain lesion had to be present at baseline in order to be able to assess response. Patients were excluded if only a CT was available at baseline and/or if only CTs were used for evaluation at subsequent time points. The baseline MRI had to have been made within21 days before initiation of protocol treatment.

Radiological follow-up

According to protocol, MRI evaluations were performed before the initiation of chemotherapy (baseline), after the second (R-)MBVP course, after Ara-C and after WBRT, if applicable. Follow-up MRIs were made every 3 months in the first 2 years after treatment, followed by every 6 months up to 5 years after treatment and yearly thereafter.

At least the following MRI sequences were performed: an axial T1 weighted scan before and after gadolinium-based contrast agent administration, and an axial T2 weighted and/or fluid-attenuated inversion recovery (FLAIR) scan. If locally possible additional sagittal or coronal T1 weighted scans with gadolinium-based contrast agent administration were also performed or reconstructed. All MR images were acquired on a 1.5 or 3.0 Tesla scanner.

Central radiology review

Scans made at baseline and after each treatment component were centrally reviewed to evaluate response of the tumor to treatment. In case of relapse or progression, the MRI on which this was diagnosed according to the local physician, as well as the last MRI made before progression were also centrally reviewed, to verify progression and to make sure true progression had not occurred earlier than locally ascertained. Scans made in follow-

up were not reviewed if response was not changed according to the local evaluation. PD was defined as relapse or progression at any site (brain, spinal cord, cerebrospinal fluid or eyes). In case progression was located outside the brain parenchyma, the MRI was not included in this analysis.

At the end of the study, all MR images were submitted for review on DVD or CD, and stored on a secured central server. Except for the baseline scan, locally assessed response rates were collected for all MRIs performed for this study. Local physicians were not blinded for treatment arm and/or other clinical information.

Central evaluation of response was performed retrospectively, in parallel by two reviewers (M.M. and A.A.P.). In case of disagreement on the response between these reviewers, an adjudicator (M.S.) finalized the central response category. The central reviewers and the adjudicator were blinded for study-arm and clinical information.

Single evaluations were excluded if a) both central reviewers considered an MRI not assessable, b) no MRI with gadolinium-based contrast agent administration was made or c) the MRI was made outside +/- 3 weeks around the planned evaluation moment during the treatment period.

MRI Tumor measurement

For all enhancing lesions the largest diameters on the axial post gadolinium-based contrast agent T1 weighted images were measured as well as their perpendicular diameter on the same slice. The product of these measurements was used to define the size of the tumor. In case of multiple lesions, response assessment was based on the sum of all products, up to a maximum of four lesions.

Non-enhancing space occupying lesions were measured by one of the central reviewers (M.M.) on FLAIR images if possible, and otherwise on the T2 weighted images. In patients experiencing recurrent disease the localization of the recurrence was compared to the localization of the initial non-enhancing and enhancing lesions.

Landmark analysis

To estimate the survival probability for the different response categories (CR, CRu, or PR) in an unbiased way, a landmark analysis was performed.[7] Regardless of the type of last administered treatment on protocol, the response at the end-of-protocol-treatment was related to PFS and OS for those still at risk at that timepoint. PFS was defined as time from randomization to progression, relapse, or death from any cause, whichever came first. OS was defined as time from randomization to death from any cause. Patients still alive at the date of last contact were censored. Follow-up data were available up to October 1, 2019. In this landmark analysis, all patients alive at the landmark timepoint who had an MRI at end-of-protocol-treatment and were classified as CR, CRu or PR on that MRI were included. The reference time point (landmark) was set between 4 weeks after last treat-

ment, but before the first follow-up MRI (i.e. 3 months after end-of-protocol-treatment), in such a way that most patients could be included. The landmark analysis was performed for both local and central response assessment.

Statistical analysis

Since the HOVON 105/ ALLG NHL 24 study showed no differences in EFS, PFS or OS between the two treatment arms we analyzed both arms together.[6] For the interobserver agreement between the central reviewers, and between central and local response evaluations we calculated the crude agreement and Cohen's kappa[8], in which crude agreement is corrected for expected agreement (i.e. the agreement that would occur 'by chance'). First, interobserver agreement was assessed for all response categories separately; second, agreement was assessed for combined categories CR/CRu and PD/relapse, and third for three categories: response (CR/CRu/PR), SD, and progression (PD/relapse). Lastly, the crude agreement and kappa's interobserver agreement for progression versus no progression were calculated on the MRI on which progression was diagnosed and on the preceding MRI.

In the landmark analysis, the survival curves for PFS and OS were constructed using the Kaplan-Meier method for the different categories of response (i.e. CR, CRu and PR) according to central and to local response evaluation at the end-of-protocol-treatment. Differences by response were assessed with a log-rank test with a 5% significance level. All analyses were performed with Stata, version 15.0. The study was approved by the ethics committee of all participating centers. All participants signed informed consent for the randomized controlled trial and separately for the central radiology review.

RESULTS

Of the 199 trial patients, 115 were included in this study. Three patients were excluded because they did not give informed consent for the radiology review, 12 patients because no baseline MRI was present and 3 for whom only CT was available, 61 patients were excluded because baseline MRI was made outside the predefined time window, and 5 for other reasons (see CONSORT diagram, Figure 1). The median age of patients included in this study was 61 years (range: 38-70), 44% were female, and 73% had WHO performance score <2, see Table 1. On October 1, 2019 (last follow-up), in the central radiology review cohort 45 patients were alive without progression and 15 were alive with progression.

Of these 115 included patients, 396 scans were centrally reviewed: 115 baseline MRIs, 235 after treatment and 46 PD or last before PD scans. Scans were excluded if they were not received for central review (n=154), were made outside the predefined time window (n=7), or progression was not located in the brain parenchyma (n=14).

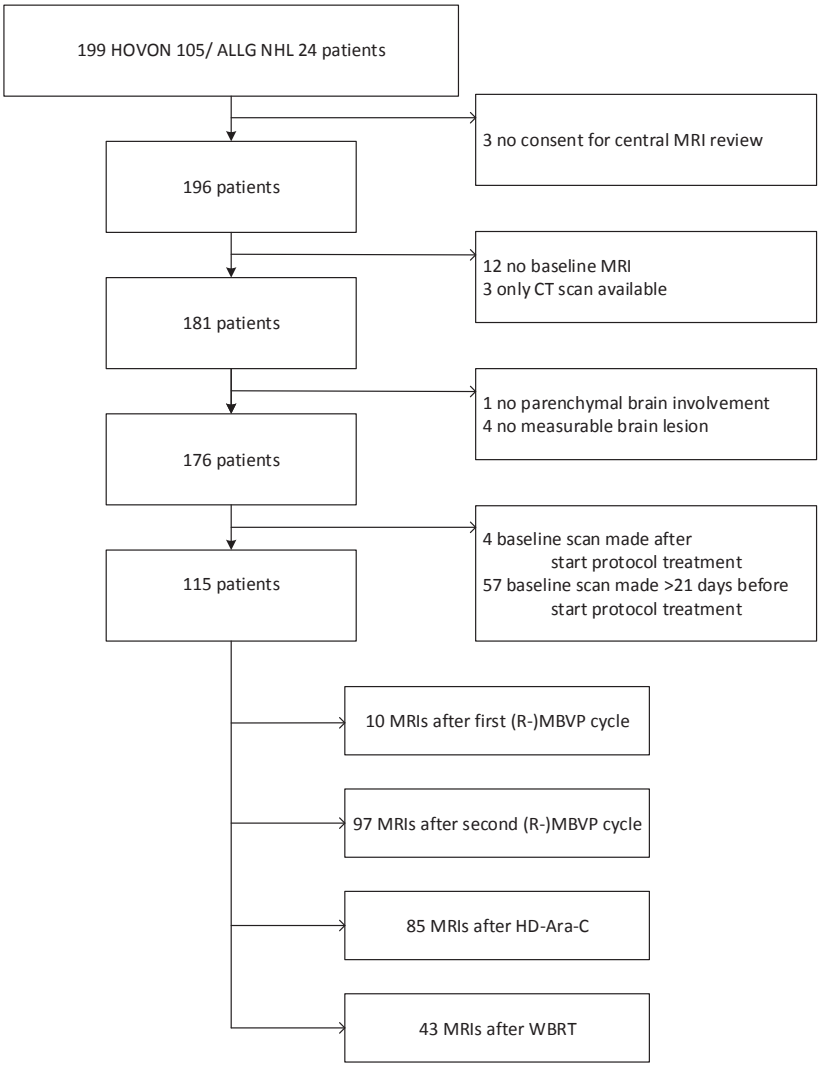

Figure 1. CONSORT diagram. 235 MRIs from 115 patients were assessed.
(R-)MBVP = (rituximab), methotrexate, teniposide, BCNU and prednisolone, HD-Ara-C = high-dose cytarabine, WBRT = whole-brain radiotherapy.

Central radiology review

For the MRIs made during treatment (n=235) the agreement between central reviewer 1 and 2 and between local and central response assessment was higher than the expected agreement by chance (p<0.001). Between the central reviewers the agreement for all response categories was 61.7%, with a kappa of 0.44, see Table 2. After adjudication, if necessary, the agreement between local and central response assessment was 63.0% with a kappa of 0.46, see Table 3.

Table 1. Baseline characteristics of the patients included in this study, those who were excluded and for the total study population.

	Included patients n=115	Excluded patients n=84	Total n=199
Sex (n, % males)	64 (56%)	45 (54%)	109 (55%)
Age (median, range)	61 (38-70)	61 (26-70)	61 (26-70)
WHO performance score (n, %)			
0	27 (23%)	16 (19%)	43 (22%)
1	57 (50%)	44 (53%)	101 (51%)
2	17 (15%)	17 (20%)	34 (17%)
3	14 (12%)	7 (8%)	21 (10%)
Comorbidities (n>2, %)	60 (52%)	44 (52%)	104 (52%)
Solitary lesions (n, %) Missing/ NA	66 (57%) 1 (1%)	37 (44%) 18 (21%)	103 (52%) 19 (10%)
Deep lesion (n, %)	83 (72%)	42 (50%)	125 (63%)
Periventricular (n, %)	61 (53%)	35 (42%)	96 (48%)
Basal ganglia (n, %)	8 (7%)	6 (7%)	14 (7%)
Cerebellar (n, %)	22 (19%)	8 (10%)	30 (15%)
Brain stem (n, %)	10 (9%)	2 (2%)	12 (6%)
Spinal (n, %)	2 (2%)	-	2 (1%)
Lobar (n, %)	58 (50%)	37 (44%)	95 (48%)
Study drug exposure			
High-dose cytarabine (n, %)	98 (85%)	63 (75%)	161 (81%)
WBRT (n, %)	48 (42%)	22 (26%)	70 (35%)
Radiation boost given (n, %)	24 (21%)	15 (18%)	39 (20%)
Intrathecal treatment given (n, %)	12 (10%)	4 (5%)	16 (8%)

NA = not applicable in case of no brain lesion; WBRT = whole brain radiotherapy.

Table 2. Level of agreement between central reviewer 1 and central reviewer 2 in all 235 scans made after each treatment module for all response categories.

		Reviewer 2						
		CR	CRu	PR	SD	PD	relapse	Total
Reviewer 1	CR	32	34	11	1	0	0	78
	CRu	0	38	15	0	0	1	54
	PR	0	17	74	4	0	0	95
	SD	0	0	2	1	1	0	4
	PD	0	0	0	1	0	1	2
	relapse	0	0	1	0	1	0	2
	Total	32	89	103	7	2	2	235

Agreement 62%, kappa 0.44. CR = complete response; CRu = complete response unconfirmed; PR = partial response; SD = stable disease; PD = progressive disease.

Table 3. Level of agreement between local and central assessment in all 235 scans made after each treatment module for all response categories.

		LOCAL						
		CR	**CRu**	**PR**	**SD**	**PD**	**relapse**	**Total**
CENTRAL	CR	42	12	8	0	0	1	63
	CRu	15	28	30	0	0	0	73
	PR	1	9	74	1	0	1	86
	SD	0	0	4	1	1	0	6
	PD	0	0	2	0	3	0	5
	relapse	0	0	2	0	0	0	2
	Total	58	49	120	2	4	2	235

Agreement 63%, kappa 0.46. CR = complete response; CRu = complete response unconfirmed; PR = partial response; SD = stable disease; PD = progressive disease.

When CR and CRu were combined into one category, and the categories PD and relapse were combined, the interobserver agreement and kappa values increased, but the latter remained in the moderate range. Between reviewer 1 and 2, agreement increased to 77.0% (kappa 0.57) and between local and central assessment agreement improved to 74.5% (kappa 0.54), see Supplemental Table 1 and Supplemental Table 2, respectively. When response categories were classified into response (CR, CRu or PR), stable disease, or progression (PD or relapse) the agreement increased to 95.3% (kappa 0.40) between the central reviewers and 94.9% (kappa 0.41) between local and central response assessment. The kappa remained relatively low, because of the increased expected agreement.

The response assessment for the MRIs on which progression or relapse was diagnosed, and the last MRI made before progression were analyzed separately. Agreement on whether there was progression or relapse versus 'no progression' was 96.7% between central reviewer 1 and 2 (kappa 0.93) and 93.3% between the local and central response assessment (kappa 0.87), both were significantly higher than expected agreement ($p<0.001$), Table 4A and 4B.

Table 4. Level of agreement A) between both central reviewers: agreement 96.7%, kappa 0.93 and B) between local and central assessment.

A		REVIEWER 2		
		No PD	PD	
REVIEWER 1	No PD	16	1	17
	PD	0	13	13
		16	14	30

B		LOCAL		
		No PD	PD	
CENTRAL	No PD	14	1	15
	PD	1	14	15
		15	15	30

Agreement 93.3%, kappa 0.87 in all scans which confirmed PD and made 'last before PD'**.** PD = progressive disease, including relapses.

Landmark analysis on CR, CRu and PR

In total 91 'end-of-protocol-treatment' MRIs were available and were locally and centrally assessed. The landmark, aiming to include as many patients as possible after the end-of-protocol-treatment MRI but before first follow-up MRI, was positioned at 6.9 months after randomization. Only those with a CR, CRu or PR at the end-of-protocol-treatment were included in this analysis. Two patients who had not had their end-of-protocol-treatment scan yet were excluded. For the PFS analysis we also excluded those who had less than PR (n=7 according to central response and 8 according to the local response assessment) at the end-of-protocol-treatment, had progression before the landmark (n=9 in central and n=6 in local response assessment) or died without progression (n=1). For the OS analysis we excluded those who had less than PR (see above) or died (n=2) Since we analyzed survival according to local as well as to central response assessment, the number of patients the analyses were based on differed: survival analysis was performed on 72 (central assessment) and 74 (local assessment) patients for PFS and 80 (central assessment) and 79 (local assessment) patients for OS.

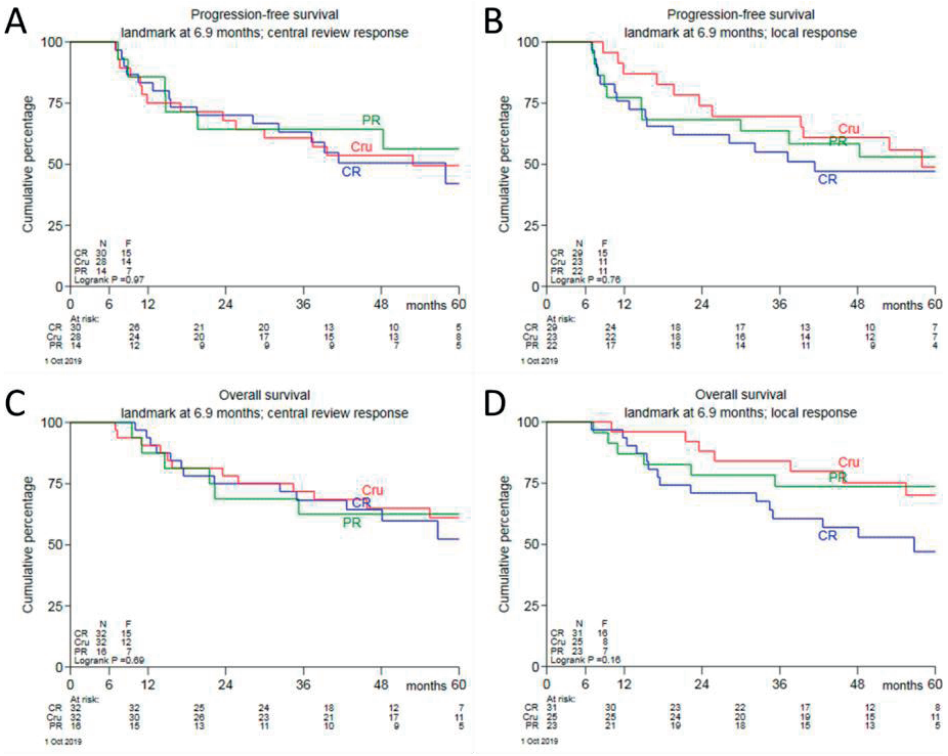

Figure 2. Progression free survival (A and B) and overall survival (C and D) for those patients who had a partial response (PR), complete response (CR) or complete response unconfirmed (CRu) at the end of treatment MRI, according to central (A and C) and local response (B and D) assessment.

Regarding PFS (Figure 2A and B) there was no statistically significant difference between those judged as CR, CRu or PR, both in central response assessment (p=0.97) and according to local judgement (p=0.76). Similar results were found for overall survival (Figure 2C and D), for central (p=0.69) and local (p=0.16) response assessment.

Non-enhancing lesions

At baseline seven patients were identified with non-enhancing space occupying lesions. Baseline characteristics in these patients were similar to the total trial population, Supplemental Table 3. After chemotherapy, in five of the seven patients, the lesions diminished with ≥50%.

Four of these patients relapsed, in two patients this was at the same location as the original enhancing lesion. None of the patients had a relapse at the location of the non-enhancing lesions.

DISCUSSION

We found an excellent crude agreement (96.7%) and kappa score (0.93) between the central reviewers and between local and central radiological evaluations (crude agreement 93.3%, kappa 0.86) in differentiating progression from no progression. However, for response assessment after treatment, interobserver agreement was moderate at best. Furthermore, the crude interobserver agreement and kappa statistics between the two central reviewers and between local and central radiology response assessment after each treatment component (n=235) were almost identical (local vs central kappa 0.46 and both central reviewers 0.44). This suggests that there is little added value of a central radiology review in PCNSL patients. Crude interobserver agreement increased when response categories were combined, but the kappa statistics remained in the range of moderate agreement. This is most likely due to increased expected agreement, since Cohen's kappa statistic is the agreement found, corrected for expected agreement to occur by chance. Thus, our data show that although the presence of response is well agreed upon, judgement regarding the extent of response is less reliable. This suggests, together with the excellent agreement regarding the moment of progression, that PFS and OS are more reliable endpoints than specific and more detailed response categories and which also better reflect patient benefit.

To the best of our knowledge, a central radiology review in PCNSL with assessment of the interobserver agreement has not been described before. Several studies assessed interobserver agreement in glioma patients.[9-13] Our excellent agreement on PD vs no PD contrasts with the interobserver agreement in standard radiology assessment for progression in glioma.[9,12] This might be explained by the rapid evolution of most PCNSL and its

easily recognizable appearance on the MR images: PCNSL, at relapse or progression as well as primary presentation, generally appears as a homogenously enhancing, circumscribed space-occupying lesion, rather than the ill-defined mass and irregular enhancement in high-grade glioma.

In our landmark analyses we found no difference in PFS or OS for the different types of response: CR, CRu and PR. The lack of difference in outcome between CR and CRu patients is in line with the current response criteria[1], which state regarding CRu lesions that if the type of abnormality does not change or slowly involutes over time without therapy or corticosteroids, it is reasonable to categorize these lesions as CR. However, we also found that partial response was associated with a similar PFS and even a similar OS, suggesting that these response categories do not translate into meaningful differences in outcome and are therefore not reliable surrogate endpoints in PCNSL. A few other studies compared survival for different response categories.[2,4,5,14] Only one of these studies[2] used a landmark analysis, resulting in selection bias in the other studies (i.e. immortal time bias), since response and survival are influenced by the passing time. If survival analysis is done after end-of-protocol-treatment, regardless of when the MRI was made, those who have had a later MRI would have had more chance to achieve CR. One large, prospective study (n=511) showed a significant difference between CR versus no CR (PR, SD and PD combined) for OS (39 versus 22 months; $p<0.0001$) and PFS (36 versus 6 months).[4] In that study, CR was defined as complete resolution of contrast enhancing lesions on MRI or on CT. The latter radiological examination might have missed small contrast enhancing foci. Furthermore, combining PR with non-responding and progressive patients does not allow conclusions regarding the partially responding (PR) patients. Similarly, in a retrospective analysis of a phase II study in 85 patients, differences in survival rates between patients with CR, PR, SD or progression after the end of chemotherapy were calculated using a single log-rank test. A significant difference was found for OS ($p<0.001$), and a nearly significant difference for PFS ($p=0.076$).[2] Again, due to the comparison of all groups including non-responding or progressive patients this analysis does not allow comparison between patients with different extents of response. Lastly, a small retrospective single center series, evaluated patients after chemotherapy. Those with CR after the completion of chemotherapy (n=10) had no better PFS or OS than those with no CR (n=30).[5] In that study, however, patients without CR subsequently received additional treatment: radiotherapy or autologous stem cell transplantation.

Two dimensional measurements are the golden standard in the current PCNSL response criteria[1], and were therefore also applied in this study. This might, underestimate volumetric changes. In glioma, volumetric measurements, either manual or computerized, improved agreement regarding radiological response compared to 2D measurements in some studies,[13,15] and fully automated segmentation was significantly better in predicting OS ($p<0.0001$) than the conventional 2D measurements.[13] In contrast, one other smaller

study showed no differences in predicting OS between manual 2D and 3D measurement or computerized segmentation of the tumor.[16] Response in PCNSL is generally easily recognizable with reductions > 50% being the rule, so small changes in the volume of the enhancing lesion are unlikely to influence response rates. However, small changes in residual abnormalities might result in a change in response category, between CRu and PR.

Our study has some limitations: first, the landmark analyses were performed for different categories of response based on the MRI made at the end-of-protocol-treatment. This might have led to bias, since patients >60 years-old with a PR at the end-of-protocol-treatment could have had additional treatment, depending on the discretion of the treating physician. Second, analyses were performed on a subgroup from a large clinical trial and inadvertent bias may have occurred in the selection of patients for this study, even though this selection was based on the availability of scans only. Our results should therefore be validated in a larger external cohort.

In conclusion, our results suggest that at the end-of-protocol-treatment, specific radiological response categories (CR, CRu, or PR) do not reliably predict survival in PCNSL patients, even after central radiology review, but that interobserver agreement in diagnosing relapse or progression is high. Therefore, the primary outcome measure in PCNSL studies should be PFS or OS; as secondary outcome measure combined response rate (CR, CRu and PR) is more reliable than CR or CR/CRu-rate.

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SUPPLEMENTARY INFORMATION

Supplemental Methods:

Kappa

kappa value	Agreement
0	absent
0.01-0.20	slight
0.21-0.40	fair
0.41-0.60	moderate
0.61-0.80	good
0.81-1.00	excellent

Supplemental Table 1. Level of agreement between central reviewer 1 and central reviewer 2 in all 235 scans made after each treatment module for clinically relevant response categories. Agreement 77.0%, kappa 0.40.

		Reviewer 2				
		CR/CRu	PR	SD	PD/relapse	Total
Reviewer 1	CR/CRu	104	26	1	1	132
	PR	17	74	4	0	95
	SD	0	2	1	1	4
	PD/relapse	0	1	1	2	4
	Total	121	103	7	4	235

CR = complete response; CRu = complete response unconfirmed; PR = partial response; SD = stable disease; PD = progressive disease.

Supplemental Table 2. Level of agreement between local and central assessment in all 235 scans made after each treatment module for clinically relevant response categories. Agreement 74.5%, kappa 0.54.

		LOCAL				
		CR/CRu	PR	SD	PD/relapse	Total
CENTRAL	CR/CRu	97	38	0	1	136
	PR	10	74	1	1	86
	SD	0	4	1	1	6
	PD/relapse	0	4	0	3	7
	Total	107	120	2	6	235

CR = complete response; CRu = complete response unconfirmed; PR = partial response; SD = stable disease; PD = progressive disease.

Supplemental Table 3. Baseline characteristics of the patients with and without non-enhancing lesions at baseline, and for the total study population.

	n=192	n=7	n=199
Sex (n, % males)	106 (55%)	3 (43%)	109 (55%)
Age (median, range)	61 (26-70)	61 (55-68)	61 (26-70)
WHO performance score (n, %)			
0	43 (22%)	-	43 (22%)
1	97 (51%)	4 (57%)	101 (51%)
2	32 (17%)	2 (29%)	34 (17%)
3	20 (10%)	1 (14%)	21 (11%)
Unilateral lesions (n, %)	103 (54%)	2 (29%)	105 (53%)
Missing/ NA	19 (10%)	1 (14%)	20 (7%)
Deep lesion (n, %)	120 (63%)	5 (71%)	125 (63%)
Treatment arm			
MBVP (n, %)	96 (50%)	4 (57%)	100 (50%)
R-MBVP (n, %)	96 (50%)	3 (43%)	99 (50%)

WHO = World Health Organisation; NA = not applicable, no brain lesion(s); MBVP = methotrexate, tenoposide, BCNU and prednisolone; R = rituximab

PART III

Neurocognitive functioning and health-related quality of life

6

Cognitive functioning and health-related quality of life in patients with newly diagnosed primary central nervous system lymphoma: a systematic literature review

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SUMMARY

Incidence of primary CNS lymphoma (PCNSL) is increasing, while prognosis is improving as treatment advance. However, declined cognitive functioning remains a major challenge in the treatment of PCNSL. This cognitive decline, in conjunction with other symptoms caused by the disease or its treatment, or both, can compromise health-related quality of life (HRQOL). The aim of this Review was to give a comprehensive overview on cognitive functioning and HRQOL for patients with PCNSL, including an evaluation of patient-related and treatment-related factors that can influence cognitive functioning and HRQOL. We reviewed the literature for studies on cognitive functioning and HRQOL in newly diagnosed adult patients with PCNSL using MEDLINE/Pubmed, Embase, Web of Science, Scopus, Cochrane, PsycINFO, CINAHL EBSCO, and Google scholar, up to Jan 4, 2018. Articles were selected using predetermined inclusion and exclusion criteria; 42 articles were eligible for inclusion. Findings show that the tumour itself has a great effect on cognitive functioning and HRQOL. Initially, induction chemotherapy results in improvement of cognition and HRQOL in most patients. In the long-term, additional whole brain radiotherapy (WBRT) has a negative impact on cognitive functioning, but the magnitude of this impact is not always clinically relevant. HRQOL scores were worse compared with controls, and worse after combined chemotherapy and radiotherapy when compared with chemotherapy only, particularly in the long term. Therefore, combined chemotherapy and radiotherapy seems to have a negative effect on HRQOL and cognition in PCNSL patients. Although prolonged progression-free survival is achieved with combined therapy, information on its effect on cognition and HRQOL should also be included in clinical decision-making.

INTRODUCTION

Primary CNS lymphoma (PCNSL) is a rare non-Hodgkin lymphoma confined to the brain, leptomeninges, spinal cord and eyes. In previous decades, the incidence rate has increased while prognosis has improved.[1-3] Improved survival is largely dependent on changes in treatment, particularly the addition of high-dose methotrexate-based chemotherapy to the previously standard treatment of whole-brain radiotherapy (WBRT). One phase 3 study has shown that the omission of WBRT decreased progression-free survival (PFS), but not overall survival (OS) in patients with PCNSL.[4] However, more patients who were given chemotherapy and radiotherapy, compared with chemotherapy alone, developed neurotoxicity (49% *vs* 26%), which was defined as progressive neurological or cognitive impairment as documented in serial clinical examinations in the absence of recurrent lymphoma.[4]

Although improved survival has been achieved in this population, declined cognitive functioning remains a major challenge in the treatment of PCNSL.[5] Subsequently, cognitive decline and other symptoms caused by the disease or its treatment, or both, can compromise health-related quality of life (HRQOL).[6,7] To establish the net clinical benefit of a treatment regimen, information on survival has to be combined with information from patient-centered outcomes, eg, HRQOL and cognition. Combining both sources of information allows informed decision making on the effect of a specific treatment, which is useful for all specialists involved in the treatment of patients with PCNSL.

In 2007, a systematic review based on a search in MEDLINE was done to identify studies reporting om the effect of different treatment modalities on cognition in PCNSL patients.[5] With the introduction of new treatment modalities, however, and the increased use of patient-reported outcomes, an update on the field is warranted. Therefore, the aim of this systematic Review was to give a comprehensive overview on the effect of PCNSL and different treatment types on cognitive functioning and HRQOL in adult patients with newly diagnosed PCNSL. Furthermore, we aimed to identify which patient-related and treatment-related factors were associated with cognitive functioning and HRQOL. Possible underlying pathophysiological mechanisms, which might explain a decline in cognition or HRQOL, or both, are beyond the scope of this Review, and thus will not be discussed.

DATA COLLECTION

Search strategy and selection criteria

We dis an extensive search for articles published up until Jan 4, 2018, using the electronic databases MEDLINE/PubMed, Embase, Web of Science, Scopus, Cochrane, PsycINFO, CINAHL EBSCO and Google scholar. Search terms related to “PCNSL” and “cognition” or

"HRQOL", or both, were used, and terms were formulated to exclude case reports and studies that only include animals (see appendix for the search strategy in MEDLINE). Original peer-reviewed articles published in English, and reported on cognitive functioning or HRQOL, or both, in newly diagnosed adult patients with PCNSL (whole population or reported separately as a subgroup) were eligible for inclusion. Cognitive functioning had to be assessed with a performance outcome instrument[8], including formal neurocognitive tests (eg, Neuropsychological Test Battery) or screening tools (Mini-Mental State Examination [MMSE][9] or Montreal Cognitive Assessment [MoCA][10]), and HRQOL had to be measured with a patient-reported outcome (PRO) measure. For both outcomes, the tests or scales used for assessment had to be reported, and results clearly described. There were no restrictions regarding the study design.

All identified abstracts were screened independently by two reviewers (MvdM and LD), and potentially relevant articles were reviewed. The reference lists of these articles were screened for additional eligible studies. Disagreements were discussed in a consensus meeting between MvdM and LD. The interpretation of the predefined were discussed when interpreted differently. If necessary, a third reviewer (JECB) was consulted in instances when there was a disagreement. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed to document the search strategy and selection process.[11]

Data extraction

In addition to information on study design, we extracted patient demographics (age, sex, and baseline performance status) from each study too. For cognition and HRQOL, the assessment schedule, tests or questionnaires used, and the results were extracted. To assess whether a change in score in cognitive tests and HRQOL assessments were clinically relevant, previously published cut-offs were used. These were MMSE scores less than 27,[12] or Z scores less than -1.5[13] in cross-sectional analyses, a change or difference of three or more points in MMSE score,[14] one or more points in Z score[15] for cognitive tests, or ten or more points for scales oritems of the EORTC QLQ-C30.[16]

FINDINGS

The search resulted in 1634 unique records, of which, 197 were assessed for further eligibility (figure). Of these, 42 articles were eligible according to our inclusion criteria. Most articles were excluded because of small sample sizes, because cognition was not formally tested or HRQOL was not assessed using a PRO. The study characteristics of the 42 eligible articles are described in the appendix. 25 articles (60%) described the effect of treatment on cognitive functioning only, two (5%) assessed the effect on HRQOL only, and 15 (36%)

mentioned the effect of treatment on both outcomes. Tables 1-3 show the rsults for formal cognitive tests, screening tools and HRQOL for patients with newly diagnosed PCNSL. Four studies were randomised controlled trials (RCTs), and the rest were cohort studies. Sample sizes from each study ranged from ten to 318 patients. Only four articles (10%) described the effect of treatment on cognition or HRQOL in elderly patients only.[17-20] We grouped the articles according to treatment modality: immunochemotherapy or chemotherapy alone (n=5), with blood-brain barrier disruption (n=5), chemotherapy followed by autologous stem cell transplantation (ASCT; n=4), intravenous and intrathecal chemotherapy (n=5), and chemotherapy combined with WBRT (n=21). For WBRT the results are separately reported for low (<35 Gy) and high dose radiotherapy (≥35 Gy), on the basis of the dose given to most patients. Lastly, two articles made a direct comparison between different treatment modalities.

COGNITIVE FUNCTIONING

Immunochemotherapy or chemotherapy

Four studies[17-19,21] reported on the effect of chemotherapy with or without rituximab, on cognitive functioning. Treatment with rituximab, methotrexate, procarbazine, and lomustine (R-MPL), a high-dose methotrexate-based chemotherapy with rituximab, in elderly patients (66-85 years, n=74)[18] resulted in a clinically relevant improvement in MMSE[18] directly after completion of chemotherapy, which remained stable during further treatment.[18] Another study observed an improvement immediately after initiation of rituximab, methotrexate, procarbazine, and vincristine (R-MPV) on all cognitive tests.[22] Nevertheless, on two tests, in the memory and motor speed domain, Z scores were worse compared to the general population (≤-1.5).[22] In an RCT in elderly people (≥60 years), most patients (48[80%] of 60) had serious cognitive impairments (Mattis Dementia Rating Scale[23] [MDRS], <135) at baseline, but improved to a statistically significant degree in several domains (attention and memory) after completion of treatment (high-dose methotrexate alone or in combination with temozolomide).[17] Similarly, MMSE scores remained stable[19,24] or improved[19,21] shortly after chemotherapy in most patients (92%), including the elderly population.[19] A direct comparison between chemotherapy and immunochemotherapy on the long term effects of therapy on cognitive functioning cannot be made, because treatment with different additional therapies were used (eg, reduced dose WBRT, full dose WBRT, or ASCT). In the short-term in changes in cognition between these treatment modalities (chemotherapy and immunochemotherapy) were observed. After an initial improvement, scores on the cognitive tests remained stable up to 22 months of follow-up in the general[21] and in the elderly[17,19] population, suggesting that chemotherapy does not have a detrimental effect on cognition.

Table 1A. Cognitive functioning (formal neuropsychological tests). Only clinically relevant and/or statistically significant results are shown

Article	n	Moment of measurement/ Cognitive tests	Median FU (range)	Results
(Immuno-)chemotherapy				
Omuro, 2015[17]	71	Baseline, every 6 months for the first 2 years, thereafter yearly/ MDRS	32 months IQR 26-36	No difference between groups (MTX + TMZ vs MTX + procarbazine, vincristine and cytarabine). Improvement after treatment, which remained stable during follow up, up to 16 months
Chemotherapy with blood brain barrier disruption (BBBD)				
Neuwelt, 1991[26]	12	Baseline, after completion of therapy, yearly thereafter/ WAIS-R, WMS(-R,) TMT-A,-B, RAVLT, CVLT, CFT, TAP, GRIP	Minimal 1 year (1-7)	Most patients remained stable or improved. Without radiation 2 patients improved (change in z-score ≥+1) and 5 remained stable. With radiation 4 patients remained stable, 1 declined (change in z-score ≥-1)
Dahlborg 1996[27]	23	Baseline, after completion of therapy, yearly afterwards/ WAIS-R, WMS-R, TMT-A, -B, CVLT, CFT, TAP, GRIP	Minimal 1 year (1-7)	Most patients remained stable or improved. Without radiation: 0/15 had a cognitive decline. With WBRT: 3/8 patients suffered cognitive decline, one declined clinically relevant (>1 point in z-score). Results partly described in Neuwelt, 1991
McAllister, 2000[25]	23	Pre-* and post-treatment/ FSIQ, GMI, DRI, ACI, CFT COPY, CFT RCL, CVLT INDX, TMT-B, TAPMN, GRP MN, Summary * Raw baseline scores are not reported	Mean 16,5 months (SD 11)	Change in mean Z-score(SD), showing that patients improved or remained stable in most domains; Number of patients improved/ stable/ declined. FSIQ: 0.55 (0.94); 7/15/1 GMI: 1.14 (1.13); 9/10/0 DRI: 1.17 (1.02); 9/8/0 ACI: 1.07 (1.09); 10/5/1 CFT COPY: 0.95 (1.19); 8/11/10 CFT RCL: 1.00 (1.14); 10/7/1CVLT INDX: 0.30 (1.30); 1/9/0 TMT-B: 0.69 (1.62); 6/14/2 TAPMN: 0.74 (1.27); 5/12/3 GRP MN: 0.53 (1.99); 6/12/2 Summary: 0.85 (0.94); 8/15/0
Neuwelt, 2005[28]	16	Baseline, 1 year after CT and yearly thereafter/ WAIS-R, WMS(-R), TMT-A,-B, RAVLT, CVLT, CFT, TAP, GRIP	55 months (Range NA)	Most patients improved clinically relevant after chemotherapy, compared to baseline: Mean total Z-score (SD) (n=16) changed from -1,1 (1.1) to -0.35 (0.52). At long-term follow up most remained stable (n=9), mean Z-score changed + 0.16 (range -0.37 to +0.71). Overlap with MCAllistar2000
Doolittle, 2013[29]	24	Baseline and minimal 2 years after achieving CR/ DF, DB, TMT A , -B, Verbal memory, HVLT R‡	12 years (2-26)	On individual level most patients improved or remained stable between baseline and 12 years of follow up. Number of patients improved/ stable/ declined in z-score are provided. DF: 0/14/3 DB: 2/11/4 TMT-A: 1/12/8 TMT-B: 3/9/8 Verbal memory: 2/8/4 HVLT R: 2/8/6
Chemotherapy combined with stem cell transplantation				

Table 1A. Cognitive functioning (formal neuropsychological tests). Only clinically relevant and/or statistically significant results are shown (continued)

Article	n	Moment of measurement/ Cognitive tests	Median FU (range)	Results
Abrey 2003[30]	14	Baseline, before CT, 6 months after ASCT, every 6 months thereafter/ DSB, DSF, TMT-A, -B, BTA, Stroop, Phonemic VF, HVLT, GPT, BNT, category fluency test, clock drawing‡	28 months (1-49)	Baseline (n=14) - After induction CT (n=7): improvement in all domains - Follow-up after ASCT (n=4): remained stable, no decline.
Omuro 2015[22]	16	Baseline, after R-MPV, 6, 12, 18 and 24 months after SCT/ TMT-A, -B, BTA, COWA, HVLT RTL, HVTL-RDEL, HVLT-RDI, GPT-D, GPT-ND‡	45 months (27-86)	Improvement after chemotherapy, remained stable after ASCT and at follow-up. Score on motor functioning remained lower than other domains. TMT-A: -1,5/-0,8/-0,6/-0,3/-0,1/-0,2 TMT-B: -1,6/-1,0/-0,7/-0,6/-0,3/-0,7 BTA: -1,1/-0,4/-0,1/-0,2/0,0/0,0 COWA: -1,0/-0,7/-0,4/-0,4/-0,2/0,1 HVLT-RTL: -1,9/-1,6/-1,4/-0,8/-0,8/-0,8 HVLT-RDEL: -2,2/-1,4/-1,6/-1,2/-0,8/-0,7 HVLT-RDI: -1,4/-0,9/-1,2/-0,8/-0,8/-0,4 GPD-D: -1,7/-1,6/-1,5/-1,0/-0,7/-1,2 GPT-ND: -2,2/-1,4/-1,6/-1,2/-1,2/-1,0
Intravenous and intrathecal chemotherapy (partially overlapping populations)				
Schlegel, 2001[34]	10	Baseline and at follow up (every 4 months)/ attention, verbal and non-verbal memory, verbal fluency, and visuoconstruction	32 months (2-59)	Raw baseline scores are not reported. The median score at last follow-up was 95 (range 89 to 107), with 100 = reference value for average cognitive function.
Pels, 2003[35]	22	First year every 4 months, and every 6 months thereafter/ attention, WF, verbal memory, visual retention, visuoconstruction	33 months (19-82)	Although no raw baseline score were reported, no cognitive decline in any of the patients was observed; patients over 60 years old tended to have lower scores.
Fliessbach, 2003[37]	10	Baseline, 4, 12 months after treatment, and at last follow-up/ BDT, BVRT, VLMT-L, VLMT-R, WF, ZVT	36 months (21-69)	Differences between 4 months and last FU. Number of patients Improved/ stable/ declined were: BDT: 1/8/0 BVRT: 2/5/1 VLMT-L: 3/6/1 VLMT-R: 1/8/1 WF: 1/8/1 ZVT: 1/8/0
Fliessbach, 2005[36]	12	Baseline, after treatment (3-4 months) and at last follow up/ Attention/ executive, memory, ST memory, WF, visuoconstruction, psychomotor speed‡	44 months (17-96)	Most patients improved or remained stable over time. Pre/ post/ follow-up scores were: Attention/ Exe: -1,7/-0,9/-0,5 Memory: -1,2/-0,3/-0,4 ST mem: -1,1/-0,8/-0,8 Word fluency: -2,0/-1,4/-1,2 Visuoconstruction: 0,5/0/0,5 Motor speed: -0,8/-0,6/-0,4

Table 1A. Cognitive functioning (formal neuropsychological tests). Only clinically relevant and/or statistically significant results are shown (continued)

Article	n	Moment of measurement/ Cognitive tests	Median FU (range)	Results
Juergens, 2010[33]	21	Baseline/ after treatment (median 4 months), follow-up / Attention/ executive, ST & working memory, verbal episodic memory, Nonverbal episodic memory, Visuoconstruction, WF, motor speed‡	100 months (77-149)	Improvement in all domains, except for non-verb episodic memory. Baseline / after/ at last follow-up scores were: Attention/Exe: 82,5/90,6/95,1* ST & W mem: 90,2/93,2/97,0* Verb E Mem: 91,0/102,1/103,2 Non-Verb E Mem: 99,3/102,3/**88,5** Visuoconstruction: 90,3/99,3/103,9 Word Fluency: 83,3/94,0/105,1 Motor speed: 81,9/92,4/100,4 *Of note, mean =100 (converted scores)*
Chemotherapy combined with whole brain radiotherapy				
Harder, 2004[55]	19	At least 6 months after treatment/ Digit Span, CVLT - Total learning, CVLT - IR, CVLT - Delayed free recall, Rey Complex t-recall, Digit Symbol, TMT- A, Stroop Test II, TMT-B, TAP dominant, TAP non-dominant, Single Motor time, Complex Motor time, Single Decision time‡	PCNSL Mean 23 months (SD: 14) Controls Mean: 16 months SD: 7)	Presented are mean (SD) score; percentage of impaired patients (based on the z-score, since no baseline scores were available). *PCNSL* / *Controls* DS: 11 (3) *0%* / 13 (3) *0%** / 58 (7)* TL: 41 (15) / 12 (2)* IR: 7 (4) DR: 8 (5) / 13 (2)* RCTR: 17 (7) *17%* / 24 (7) *11%** D Symbol: 39 (15) *11%* / 58 (9) *0%** TMT-A: 52 (33) *21%* / 25 (8) *0%** *PCNSL* / *Controls* Stroop II: 27 (7) *44%* / 22 (4) *11%** TMT-B: 122 (75) *26%* / 62 (24) *0%** TAP D: 286 (67) *47%* / 351 (46) *16%** TAP ND: 245 (59) *58%* / 310 (40) *5%** S mot time: 192 (55) *37%* / 130 (38) *11%** C mot time: 204 (75) *47%* / 136 (37) *11%** SDT: 358 (50) *27%* / 327 (52) *16%**
Correa, 2004[54]	28	After treatment (cross-sectional, baseline scores are lacking)/ Attention/ executive Memory, Psychomotor, Language, Visual-construction, VIQ	NA	*WBRT + Chemo(n=18) vs Chemo only (n=10)* Attention/ executive: -1,70 vs -0.46 Memory: -2.83 vs -0.84 Psychomotor: -4.89 vs -3.95 Language: -1.79 vs 1.19 Visuoconstruction: -0.15 vs -1.15 VIQ 109: (11) vs 112 (9.3)
Shah, 2007[39]	12	Baseline, post-R-MVP, 6 and 12 months/ DSF, DSB, TMTA, -B, BTA, VF, HVLT RTL, HVLT RD, HVLT DI, GPD, GPND, BNT, AF‡	37 months (18-55)	Scores for baseline/post R-MVP/6/12 months DSF: -0.03/-0.21/-0.33/-0.12 DSB: -0.72/-0.31/-0.13/-0.01 TMTA: -0.84/-0.35/-0.22/-0.34 TMTB: -1.80/-0.69/-0.05/-0.43 BTA: -1.92/-0.82/-0.77/-0.42 VF: -1.39/ -0.68/-0.75/-0.52 HVLTRTL: -1.90/-1.24/-1.23-0.58 HVLTRD: -1.94/-1.50/-1.19/-1.09 HVLT DI: -1.32/-0.89/-1.13/-0.68 GPD: -1.74/-1.67/-1.35/-1.17 GPND: -1.63/-1.59/-1.18/-0.86 BNT: -1.70/-0.40/-0.32/-0.14 AF: -1.82/-1.10/-0.59/-0.70

Table 1A. Cognitive functioning (formal neuropsychological tests). Only clinically relevant and/or statistically significant results are shown (continued)

Article	n	Moment of measurement/ Cognitive tests	Median FU (range)	Results	
Yamanaka, 2007[41]	13	Pretreatment and at last follow-up WAIS	59 months (40-108)	pre-/ post-treatment. Full –scale IQ Mean (range): 78 (58-96) / 83,5 (60-107)	All, but one improved (5) or scored similar (2) (improvement ranged +3 to +21)
Correa, 2009[40]	12	Baseline, post-R-MVP, 6,12, 18 and 24 months after treatment/ TMTA, -B, BTA, HVLTRTL, HVLTRD, GPD, GPND‡	9 patients completed 2y of FU	Scores for baseline/post R-MVP /6/12/18/24 months: TMT-A: -1.34/-0.35/-0.22/-0.34/-0.04/0.01 TMT-B: -1.80/-0.69/-0.05/-0.36/-0.15/-0.15 BTA: -1.92/-0.82/-0.77/-0.42/-0.62/-0.17	HVLT RTL: -1.90/-1.24/-1.23/-0.58/- 1.49/-1.22 HVLT RD: -1.94/-1.50/-1.19/-1.09/-1.39/-1.60 GPD: -1.74/-1.67/-1.35/-1.17/-1.17-0.78 GP ND: -1.63/-1.59/-1.18/-0.86/-1.20/-1.08
Correa, 2012[53]	50	After treatment (cross-sectional, baseline scores are lacking)/ DF, DB, TMT-A, -B, GP, BTA VF, HVLT Leaning, HVLT Delay, HVLT Discrimination‡	Follow-up after 16 versus 14 months	*Chemotherapy + WBRT vs Chemo only* DF: -0.5 vs 0.2 DB: -0.3 vs 0.1 TMT-A: -1.6 vs -0.8 TMT-B: -1.6 vs -1.0 GP: -2.3 vs 1-1.3	BTA: -1.7 vs -0.9 VF: -1.0 vs -0.7 HVLT Learning: -2.0 vs -1.2 HVLT Delay: -1.8 vs -1.1 HVLT Discrimination: -1.5 vs -0.4
Morris, 2013[38]	12	Baseline/ post R-MPV, 1, 2, 3 and 4 years after treatment/ TMT-A, -B, BTA, HVLT RTL, HVLT RD, HVLT DI, GPT-D, GPT-ND‡	6 year (range NA)	Mean z-scores (n=12) at baseline/ post R-MPV/ /2/3/4y : TMT-A: -1.2/-0.3/-0.3/0.2/-0.03/-0.1 TMT-B: -1.2/-0.7/-0.4/-0.3/-0.3/-0.4 BTA: -1.6/-0.6/-0.2/-0.2/-0.3/0.1 HVLT RTL: -2.0/-1.5/-1.2/-1.3/-0.8/-1.0	HVLT RD: -2.3/-1.5/-1.3/-1.5/-0.9/-1.3 HVLT DI: -1.3/-0.9/-0.6/-0.9/-0.4/-0.7 GPT D: -1.7/-1.6/-1.1/-0.9/-1.3/-1.5 GPT ND: -1.3/-1.5/-0.8/-1/-1.1/-1.7
Direct comparison of multiple treatment modalities					
Doolittle, 2013[62]	80	After achieving CR (cross-sectional, baseline scores are lacking)/ Attention, executive, verbal memory, motor skills, composite score‡	5.5 years (2-26)	*HD MTX alone vs HD MTX + BBBD vs HD MTX + ASCT* Attention/ executive: -0.56 vs -0.42 vs -0.32 Verbal memory: -0.57 vs -0.88 vs -1.17 Motor skills: -1.08 vs -1.06 vs -0.70 Composite score: -0.75 vs -0.80 vs -0.76	*HD MTX +WBRT* -1.10 -1.36 -2.18 -1.52

Table 1A. Cognitive functioning (formal neuropsychological tests). Only clinically relevant and/or statistically significant results are shown (continued)

Article	n	Moment of measurement/ Cognitive tests	Median FU (range)	Results	
Ferreri, 2017[63]	57	Baseline (scores are not reported), after consolidation therapy (CT), every 6 months thereafter/ DF, DB, TMT-A, -B, BTA, WCST number completed, WCST number of tot. errors, WCST preservation errors, RAVLT – delayed recall, RAVLT- total learning, CFT, CFT-R, Token Test, Phonemic Verbal Fluency, Semantic Verbal Fluency, GPT- left, GPT- right‡	40 months (IQR 32-49)	Improvement(+)/ decline(-)/ stable(0) between baseline and after consolidation treatment (*WBRT/ ASCT):* TMT-A: -/+* TMT-B: +/+* Phonemic Verbal Fluency: +/+*	Improvement(+)/ decline(-)/ stable(0) between after consolidation treatment (*WBRT/ASCT)* and 2 years of follow up: WCST numb. Completed: -/+* WCST numb. of tot. errors: -/+* WCST preservation errors: -/+* RAVLT – delayed recall: +/+*

Abbreviations: ACI Attention concentrate index; AF animal fluency; (A)SCT autologous stem cell transplantation; BBBD blood brain barrier disruption; BDT Block Design Test; BNT Boston Naming Test; BTA Brief Test of Attention; B(VR)T Benton Visual Retention Test; C mot time Complex Motor time; CFT/ RCFT Rey-Osterreith Complex Figure test; CTF copy, Rey-Osterreith complex figure copy; CFT (RCL)/ RCTR/ Rey-Osterreith complex figure recall; CLT-F Computer Learning Task-Figural; CLT-V Computer Learning Task-Verbal; COWA(T) Controlled Oral Word Association Task; CR complete response; CT chemotherapy; CVLT California verbal learning test; D Symbol Digit Symbol; DR Delayed free recall; DRI Delayed recall index; DS Digit Span; D(S)B Digit Span Backward; D(S)F Digit Span Forward; Exe executive; FSIQ Full Scale Intelligence quotient; FU follow-up; GMI general memory index; GP(T) Grooved Pegboard Test; GPTD Grooved Pegboard Test Dominant; GPTND Grooved Pegboard Test Non, Dominant; GRIP MN Grip mean score; Grip grip strength; Gy Gray; HD high dose; HVLT-D Hopkins Verbal Learning Test, Delayed Recall; HVLT-DI Hopkins Verbal Learning Test, Discrimination; HVLT-L Hopkins Verbal Learning Test, Total Learning; HVLT-R Hopkins Verbal Learning Test- revised; IQR interquartile range; IR Immediate free recall; MDRS Mattis dementia rating scale; Mem memory; MTX methotrexate; n number of patients; NA not available; PCNSL primary central nervous system lymphoma; R-MPV rituximab, methotrexate, procarbazine, and vincristine; RAVLT Rey Auditory Verbal Learning Tests; RT radiotherapy; S mot time Single Motor time; SD standard deviation; SDT Single Decision time; ST Mem: short term memory; TAP D TAP dominant; TAP MN TAP mean score; TAP ND TAP non-dominant; TL Total learning; TMT-A Trail Making Test A; TMT-B Trail Making Test B; TMZ Temozolomide; (Non) Verb E mem (non-) verbal episodic memory; VF verbal fluency; VIQ verbal Intelligence quotient; VLMT-L Verbal Learning and Memory Test–Learning; VLMT-R Verbal Learning and Memory; VLMT-R Verbal Learning and Memory Task – Recall; VR I Visual Reproduction I; VR II Visual Reproduction II; W Mem working memory; (rd)WBRT (reduced dose) whole brain radiotherapy; WF Word Fluency; WAIS(-R) Wechsler Adult Intelligence Scale–Revised; WCST Winconsin Cart Sorting Test; WMS (-R) Wechsler memory scale— revised; ZVT Letter Connection Test. *p<0.05; ‡ used minimal tests described and advise by by to Corea DD et al, Annals of Oncology, 2007

Table 1B. cognitive functioning (screening tools)

Article	n	Moment of measurement/ Cognitive tests	Median FU (range)	Results
(Immuno-)chemotherapy				
Batchelor, 2003[21]	19	Baseline and at least one follow-up/ MMSE	23 months (1-37)	Mean MMSE at baseline: stable disease (n=7) vs PR or CR (n=17) 25 vs 25 All but one patient improved.
Hoang-Xuan 2003[19]	38	Baseline, every 6 weeks during treatment and during follow up every 3 months/ MMSE	Up to 36 months (range NA)	Median baseline MMSE score: 22 (range7-30). Number (%) of patients that showed. Improve-ment/ stable/ decline MMSE after CT: 17 (45%)/ 18 (47%)/ 3 (8%). The majority remained stable or improved after completion of chemotherapy.
Fritsch, 2017[18]	93	Baseline, every 3 months (first year) every 6 months thereafter/ MMSE	34 months (range NA)	Mean MMSE score at baseline: 23 (0-30). Intra-individual mean differences in scores: after 1st cycle +3.15 (-7-+21), after 2nd cycle +3.07 (-4-+17), and after completing treatment +3.58 (-7-+16). Relevant improvement after 1st cycle, stable thereafter.
Chemotherapy combined with stem cell transplantation				
Illerhaus 2008[31]	10	At last follow up only (cross-sectional, baseline scores are lacking), no details/ MMSE	25 months (2-50)	Median (range) MMSE score: 29 (26-30). Moreover, 90% had a normal MMSE score (≥27) at last follow up
Illerhaus 2016[32]	73	Baseline, during and after completion of the study/ MMSE	57 months (54-61)	Slight improvement during treatment and stabilizing after treatment. Mean (SD); range at baseline was 25.4; (6.2) 1-30; during was 27.7; (3.0) 14-30; and after the study was28.2; (2.9) 16-30.
Chemotherapy combined with whole brain radiotherapy				
O'Neill, 1999[24]	46	Baseline, during treatment (weeks 3, 6, 16, 20, and 25), and at quarterly intervals thereafter/ MMSE	Up to 1 year after treatment	Median MMSE scores at baseline/ week 3/ week 6/ week 16/ week 20/ week 25/ 1 year were: 26/28/26/27/26/27/27. Patients over 60 years had higher MMSE scores than the younger (<60) patients.
DeAngelis, 2002[45]	40	Baseline and at 8 months follow-up/ MMSE	55.9 months (range NA)	Median MMSE score at baseline was 26.5. No significant difference in MMSE scores at 8 months, or in time to decrease of MMSE score below 24 between WBRT and hyper-fractionated RT.
Fisher, 2005[46]	40	Baseline and 8 months after treatment, twice a year after 3 years/ MMSE	Up to 4 years	Median baseline MMSE score was 26.5. Improvement at 8 months: 0.81 for RT and 1.1 for HFX arm. In the RT arm, 8/20 patients dropped below a score of 24 versus 2/9 in the HFX arm.

Table 1B. cognitive functioning (screening tools) (continued)

Article	n	Moment of measurement/ Cognitive tests	Median FU (range)	Results
Laack, 2006[20]	19	Baseline and during follow-up (nine patients had at least 1 follow-up MMSE)/ MMSE	No details	The majority of patients who received HD Methylprednisolone + WBRT had stable scores. Median (range) baseline MMSE score was 27 (12-30). During follow-up : 4 patients increased in score, 3 were stable, 2 decreased and 2 showed both increased and decreased scores.
Ferreri, 2009[49]	59	Baseline, after treatment and every 6 months thereafter/ MMSE	30 months (15-55)	*MTX + WBRT vs MTX + cytarabine + WBRT* Baseline median score: 25 (10-30) vs 27 (10-30) After 2 years median score: 28 (15-30) vs 29 (18-30)
Ferreri, 2011[51]	17	Baseline and at follow up (no details)/ MMSE	50 months (11-140)	Baseline median (range) score was 27 (22-29) and 28 (5-30) at last follow-up. Improved/ stable/declined: 11/1/5 patients A higher dose of WBRT (≥45Gy) is associated with a higher rate of cognitive decline.
Laack, 2011[43]	34	Baseline/ during follow-up (no details)/ MMSE	Minimal 1y (Details NA)	CHOD +BCNU+ BVAM + WBRT: 79% of patients had MMSE scores ≥27 at baseline. No significant changes in MMSE score over time.
Ichikawa, 2014[47]	23	Baseline, after M-CHOP, 6 months, 12 months/ MMSE(an extended NPE has been performed, but not reported	70 months (14-125)	*With WBRT (n=8) vs without WBRT (n=15)* Mean MMSE at baseline/ after M-CHOP/ 6/ 12 months: 24 vs 22/ 28 vs 25 / 25 vs 24 / 22 vs 24
Ferreri, 2014[52]	9	Before (baseline scores are not reported) and every 6 months after treatment / MMSE	144 months (47-153)	9/41 patients were long-term survivors. All but one had MMSE score ≥29 on the long-term. Cause of decline in one patient was unrelated herpetic encephalitis.
Glass, 2016[44]	50	Baseline, after RT, 6 months, 12 months, 3 year after / MMSE	43 months (range NA)	Median (range) IQR scores: Baseline: 28 (6-30) 23-29 Post RT: 29 (19-30) 26-30 6 months: 29 (15-30) 26.5-30 12 months: 29 (21-30) 27-30 3 years: 29 (26-30) 28-30
Herrlinger, 2017[48]	144	At randomization, every year onwards / MMSE	Up to 4y (range NA)	*Chemotherapy only vs CT + WBRT* Baseline score: mean 26 (range: 22-29) vs 27 (23-29) Score after 24 months: 29 (range: 27-29) vs 26 (24-29)*

Table 1B. cognitive functioning (screening tools) (continued)

Article	n	Moment of measurement/ Cognitive tests	Median FU (range)	Results	
Chanswangphuwana, 2017[50]	10	Two times after end of treatment (baseline scores are lacking)/ MoCA	1st 23 (9-19) 2nd 42 months (20-72)	*First MoCA* 1 dementia (score 9) 4 MCI (scores 21-23) 5 normal (scores 25-27)	*Second MoCa* 5 MCI (scores 18-21) 4 normal (scores 25-27) 2 declined, 1 improved, 1 lost
Kaburaki, 2017[42]	16	Before rdWBRT, 1 or 2, 3, 4, and 5 years thereafter / MMSE	49 months (15-95)	Median (range) MMSE scores: score before CT are not reported Pre rdWBRT: 27 (21-30) 1 or 2 years: 27 (19-30)	 3 years: 29 (21-30) 4 years: 28 (26-30) 5 years: 29 (25-30)

Abbreviations: BCNU Carmustine; BVAM, cytosine arabinoside and methotrexate; CHOD cyclophosphamide, doxorubicin, vincristine and dexamethasone; CR complete response; CT chemotherapy; Gy Gray; HD high dose; IQR interquartile range; M-CHOP Methotrexate-cyclophosphamide, hydrocydaunorubicin, vincristine and predinisolone; MCI: Mild Cognitive Impairment; MMSE mini mental state examination; MoCa: Montreal Cognitive Assessment; MTX methotrexate; NA not available; NPE neuropsychological evaluation; PR partial response; RT radiotherapy; SD standard deviation; (rd)WBRT (reduced dose) whole brain radiotherapy;

Table 2. Health-related Quality of Life - Only clinically relevant and/or statistically significant results are shown

Article	n	Moment of measurement/ Questionnaires	Median FU (range)	Results
(Immuno-)chemotherapy				
Guha-Thakurta1999[56]	11	Median 16 months after achieving CR (cross-sectional, baseline scores are lacking)/ FACT-Br	22 months (range NA)	Mean FACT-Br: 158,6 (moderate to good score)
Omuro 2015[17]	71	Baseline, every 6 months (first 2 years), yearly afterwards/ QLQ-C30 & QLQ BN-20	32 months (IQR 26-36)	Significantly impaired HRQoL at baseline. Improvement after treatment, compared to baseline. Remained stable up to 24 months
Fritsch, 2017[18]	74	Baseline, every 3 months (first year), every 6 months thereafter/ EORTC QLQ-C30	34 months (range NA)	Median (IQR) GH status score at baseline was impaired, 50 (33-58); slightly improved after R-MPL, 58.33 (50-79); and stable afterwards
Chemotherapy combined with stem cell transplantation				
Omuro 2015[22]	16	At baseline, after R-MPV, and 6, 12, 18, and 24 months after SCT/ FACT-Br	45 months (27-86)	FACT-Br mean scores improved over time. Scores at baseline/ after R-MPV/6/12/18/24months were*:* 120.0/134.0/144.0/149.0/152.0/158.0
Illerhaus2016[32]	77	No details/ EORTC QLQ-C30 & QLQ-BN 20	57 months (54-61)	Median GH status score (IQR): impaired at baseline, 50 (33-58); improvement after CT-ASCT, 59 (42-73); stable up to 3 months thereafter, 67 (42-83)
Intravenous and intrathecal chemotherapy (partially overlapping populations)				
Fliessbach, 2005[36]	23	Pre-treatment (scores are not reported), after treatment (3-4 months) and at last follow up (44 months)/ EORTC QLQ-C30	44 months (17-96)	Mean scores (SD) after 44 months which were clinically relevant worse than general population; number of patients normal/ abnormal scores. - GHS: 66.7 (22.6) - PF: 65.1 (32.8); 16/7 - RF: 56.1 (36.6); 16/7 - EF: 62.5 (29.7); 17/6 - CF: 62.9 (30.8); 15/8 - SF: 65.1 (35.6); 17/6
Juergens2010[33]	12	Baseline (scores are not reported)/ after treatment (4 months), longer-term follow-up (100 months)/ EORTC QLQ-C30	100 months (77-149)	Mean scores (SD) after 100 months; number of patients with normal/ abnormal scores: - PF: 68.2 (29.7); 10/8 - RF: 58.3 (37.2); 10/8 - EF: 64.8 (26.6); 13/5 - CF: 66.7 (24.3); 11/7 - SF: 56.5 (39.3); 10/8 (4/12 deteriorated* on the long-term)
Chemotherapy combined with whole brain radiotherapy				

Table 2. Health-related Quality of Life - Only clinically relevant and/or statistically significant results are shown (continued)

Article	n	Moment of measurement/ Questionnaires	Median FU (range)	Results	
Harder, 2004[55]	19	At least 6 months after treatment (cross-sectional, baseline scores are lacking)/ EORTC QLQ-C30 scales (mean (SD))	*Patients* Mean 23 months (SD: 14); *Controls* Mean 16 months (SD: 7)	*Patients* - GH: 68 ± 17 - FA: 35 ± 25 - PF: 82 ± 27 - PA: 16 ± 20 - RF: 63 ± 33 - DY: 2 ± 8 - EF: 62 ± 28 - SL: 3 ± 35 - CF: 64 ± 27 - AP: 9 ± 19 - SF 70 ± 32 - FI: 16 ± 30	*Controls* - GH: 78 ± 16 - FA: 22 ± 21 - PF: 92 ± 17 - PA: 6 ± 12 - RF: 80 ± 25 - DY: 16 ± 20* - EF: 81 ± 21* - SL: 19 ± 26 - CF: 82 ± 15 - AP: 0* - - SF: 88 ± 21* - FI: 11 ± 19
Correa, 2004[54]	28	Post-treatment (n=28) and 8 months after treatment (n = 14)/ FACT-Br	NA	No significant differences between chemo only (mean 142, SD: 18.4) and WBRT + chemo (mean: 131, SD: 25.9)	
Correa, 2009[40]	12	Baseline, post-R-MPV, and 6, 12, 18 and 24 months after treatment/ FACT-Br	n=9: 2y FU completed	Mean FACT-Br scores improved over time, up to 1y, after which it was stable. Scores at baseline/ post-R-MPV/ 6/ 12/ 18/ 24: 122.75/140.55/153.50/154.92/146.89/153.89	
Correa, 2012[53]	50	At follow-up (cross-sectional, baseline scores are lacking) / FACT-Br	At FU 16 vs 14 months	Scores were similar for chemo + WBRT (n=24), mean FACT-Br: 139,8, and chemo only (n=26), mean FACT-Br: 127,5.	
Morris, 2013[38]	12	Baseline, post R-MPV, 1 year, 2 year, 3 year and 4 years after treatment FACT-Br	6 years (range NA)	Mean FACT-Br scores improved over time. Scores at baseline/ post R-MPV/1y/2y/3y/4 year were: 129/142/157/154/157/156	
Glass, 2016[44]	52	Baseline, after WBRT, and 6, 12, and 36 months after treatment/ Spitzer QoL	43 months (range NA)	Small improvement in scores over time; median (range; IQR) scores - Baseline: 6 (0-10; 4-8) - 6 months: 8 (0-10; 5.5-10) - 3 years: 10 (3-10; 9-10) - Post RT: 7 (0-10; 5-10) - 12 months: 9 (0-10; 6-10)	
Okita, 2016[61]	27	After treatment (cross-sectional, baseline scores are lacking) / EORTC QLQ-C30 and BN20 *mean score (SD)*	3.3 years (1-14) after diagnosis	*year of diagnosis <5y* - RF: 64.8 (34.1) - EF: 82.4 (19.0) - CF: 64.8 (27.9) - SF: 68.5 (34.1)	*≥5 y* - RF: 76.7 (35.3) - EF: 84.2 (14.9) - CF: 83.3 (20.8) - SF: 81.7 (26.6) *year of diagnosis <5y* - FA: 35.0 (27.9) - FU: 25.3 (25.1) - WL: 40.7 (32.5) *≥5 y* - FA: 18.9 (20.3) - FU: 12.5 (14.3) - WL: 23.3 (22.5)

Table 2. Health-related Quality of Life - Only clinically relevant and/or statistically significant results are shown (continued)

Article	n	Moment of measurement/ Questionnaires	Median FU (range)	Results			
Herrlinger, 2017[48]	144	At randomization, every year thereafter/ EORTC QLQ-C30 and BN20 *mean change per year*	Up to 4 years after randomization	*No early WBRT* - GH: +1.74 - PF: +0.38 - RF: −0.29 - EF: +1.54 - CF: −1.06 - FA: −1.01 - PA: −0.37	*Early WBRT* - GH: -2.97* - PF: -6.11* - RF: −1.74* - EF: −4.48* - CF: −3.13* - FA: +2.5* - PA: +2.94*	*No early WBRT* - SL: -1.62 - AP: −1.48 - FU: +1.36 - VD: −1.58 - CD: −0.08 - DR: −0.06 - IS: +1.40 - WL: −0.40	*Early WBRT* - SL: +2.73* - AP: +2.31* - FU: +4.83* - VD: +3.21* - CD: +2.93* - DR: +4.28* - IS: +5.75* - WL: +4.86*
Direct comparing of multiple treatment modalities							
Doolittle 2013[62]	80	After achieving CR (cross-sectional, baseline scores are lacking) / EORTC QLQ-C30 and BN20 *mean scores*	5.5 years (2-26)	*MTX* - PF: 71.14 - RF: 63.69 - CF: 66.09 - SF: 55.75 - GH: 62.36 - FA: 29.31 - PA: 18.97 - SL: 30.86 - CO: 11.49 - FU: 31.61 - VD: 15.71 - MD: 24.90 - CD: 21.84 - HA: 17.24 - DR: 25.29 - WL: 19.54 - BC: 13.79	*MTX BBBD* - PF: 85.60 - RF: 84.00 - CF: 73.33 - SF: 79.33 - GH: 82.67 - FA: 23.56 - PA: 21.33 - SL: 29.33 - CO: 13.33 - FU: 18.00 - VD: 11.11 - MD: 12.00 - CD: 17.33 - HA: 16.00 - DR: 16.00 - WL: 9.72 - BC: 14.67	*MTX + ASCT* - PF: 83.33 - RF: 86.11 - CF: 72.22 - SF: 88.89 - GH: 72.22 - FA: 31.48 - PA: 16.67 - SL: 27.78 - CO: 5.56 - FU: 5.56 - VD: 1.85 - MD: 11.11 - CD: 22.22 - HA: 22.22 - DR: 27.78 - WL: 5.56 - BC: 16.67	*MTX + WBRT* - PF: 50.45* - RF: 48.48* - CF: 43.94* - SF: 39.39* - GH: 48.48* - FA: 61.62* - PA: 43.94* - SL: 60.61* - CO: 30.00* - FU: 50.51* - VD: 41.41* - MD: 48.48* - CD: 39.39* - HA: 27.27* - DR: 54.55* - WL: 54.55* - BC: 27.27*

Table 2. Health-related Quality of Life - Only clinically relevant and/or statistically significant results are shown (continued)

Article	n	Moment of measurement/ Questionnaires	Median FU (range)	Results
Ferreri, 2017[63]	57	Baseline (scores are not reported), after treatment, and every 6 months thereafter/ EORTC QLQ-C30 - GH	40 months (IQR 32-49)	After treatment both arms improved (no clinically relevant difference). After 2y of follow-up, WBRT treated patients declined, ASCT improved*.

Abbreviations: (A)SCT autologous stem cell transplantation; AP appetite loss; BBBD blood-brain barrier disruption; BC bladder control; BN20 brain module; CF cognitive function; CD communication deficit; CO constipation; CR complete responsive; DR drowsiness; CT chemotherapy; DY dyspnea; EF emotional function; (EORTC) QLQ-C30 European Organization Research and treatment of Cancer Quality of Life Questionnaire; FA fatigue; FACT-Br Functional Assessment of Cancer Therapy-Brain; FI financial difficulties; FU future uncertainty; FU follow-up; GH(S) global health status; HA headaches; HRQoL health related quality of life; IQR interquartile range; IS itchy skin; MD motor dysfunction; MTX methotrexate; n number of patients; NA not available; PA pain; PF physical function; R-MPL rituximab, methotrexate, probarbazine and lomustine; R-MPV rituximab, methotrexate, procarbazine, and vincristine; RF role function; RT radiotherapy; SD standard deviation; SF social function; SL insomnia; VD visual disorder; WBRT whole brain radiotherapy; WL weakness of legs; y year. *p<0.05

Chemotherapy with blood-brain barrier disruption

A small study (n=23) showed that all patients given chemotherapy with blood-brain barrier disruption had stable or a clinically relevant improvement in their summary cognition score at the end of treatment and in the short-term, after a mean follow-up of 16.5 months.[25] Three of 23 patients showed declined functioning in motor speed only.[25] Up to 7 years after treatment, most patients (75-83%) had stable or improved cognitive functioning. Of those patients who deteriorated cognitive functioning, 31% received WBRT before or after chemotherapy.[25-28] No details were available on radiotherapy dose. At a median of 12 years after chemotherapy, 24 patients showed improved mean scores on all cognitive test compared to baseline, of which the trail making tests A and B (measuring multiple cognitive domains) were statistically significant, but not clinically relevant.[29] These results suggest no detrimental effect of blood-brain barrier disruption chemotherapy on cognitive functioning, even in the long term.

Chemotherapy followed by stem cell transplantation

Three small[22,30,31] (n=13-32 patients) and one larger cohort study (n=79)[32] described the effect of combined treatment with chemotherapy and ASCT on cognitive functioning. At 3-6 months after ASCT, additional ASCT resulted in improved cognition in most domains (attention, executive function and verbal memory) compared with baseline, but these changes were not clinically relevant.[22,30,32] Over time, with a median follow-up of 45 months, cognition remained largely stable after initial improvement, with slightly improved scores on motor speed, although these were still lower than normative values.[22] Similarly, an improvement in MMSE score was seen at 57 months; from 25 at baseline to 27 during combined treatment, and up to 28 after a median follow-up of 57 months.[32] Lastly, a cross-sectional analysis in ten patients, after a median follow-up of 25 months, showed that 90% had a normal MMSE score (≥27) in the long-term, even though four out of ten had received WBRT (36-50 Gy).[31]

Intravenous chemotherapy combined with intrathecal chemotherapy

Five articles[33-37] were published describing partially overlapping small populations (n=20-65), in which patients were given combined intravenous and intrathecal methotrexate-based chemotherapy. After a median of 4 months, this treatment resulted in clinically relevant improvements in verbal episodic memory, word fluency and psychomotor speed domains, whereas other domains remained stable.[33] After a median follow-up of 32-44 months, most patients (70%) improved or remained stable.[34-37] In a subgroup op 12 patients, mean standard values slightly improved at 100 months in all domains except for non-verbal episodic memory, in which scores diminished (102.3 to 88.5).[33]

Chemotherapy combined with WBRT

Three articles[38-40] described the effect of R-MPV followed by reduced-dose WBRT (23.4 Gy) in overlapping populations (n=52 in total). In the short-term, improved cognition was seen in all domains, but it was only clinically relevant for executive function. Scores in motor domain improved the least (n=12).[38-40] Up to 4 years after treatment, cognition scores remained stable after treatment in these 12 patients, implying that reduced-dose radiation did not have a clinically relevant negative effect on cognitive functioning.[38,40] Additionally, the majority (six of eight) of a small subset had stable or improved intelligence approximately 5 years after treatment (20 Gy),[41] and MMSE scores improved or remained stable directly after treatment and remained stable up to five years after combined chemotherapy and radiotherapy (23.4 Gy).[42] Studies of high-dose radiotherapy reporting MMSE and MoCA[10] scores showed improved or stable results[43] in 24 of 33 patients (73%)[44] directly after combined chemotherapy and radiotherapy (high-dose methotrexate-based; 36-45Gy),[45,46] lasting up to 1 year.[24,42] Even in the elderly a stable MMSE score of 27 (normal-good) was reported over time.[20] One study (n=24) showed an initial improvement in cognition after treatment with chemotherapy (high-dose methotrexate, cyclophosphamide, doxorubicin, vincristine, and prednisolone) alone or combined with WBRT (36-60 Gy), at 6 months post-treatment, patients treated without WBRT had stable MMSE scores (from baseline to 6 months after treatment, 25 to 24) whereas patients given WBRT declined from baseline to 6 months after treatment (28 to 22), representing a clinically relevant detoriation.[47] For long-term data, results are conflicting. One study reported that patients given WBRT (45 Gy) had worse MMSE scores to a clinically relevant degree 2 years after randomisation compared with those treated without WBRT (26 *vs* 29).[48] By contrast, other studies showed that MMSE scores improved (from 25 to 28 for high-dose methotrexate and WBRT treated patients, and from 27 to 29 in high-dose methotrexate, Ara-C, and WBRT treated patients, radiation dose 36-40 Gy)[49] or remained stable for up to 3 years,[44,46,50] irrespective of radiation dose.[46] By contrast, a small retrospective study reported that a higher dose (>40Gy) was related to poorer cognitive functioning (three of four patients [75%] *vs* two of 13 patients [15%] with a lower dose of <40 Gy).[51] After a median of 12 years after combined chemotherapy and radiotherapy, eight of nine patients still had an MMSE score of 29 or more.[52]

Cognition formally measured with a neuropsychological test battery showed slightly different results. Two articles, describing partially overlapping populations (total n=50), showed that, when measured cross-sectionally, scores in patients given WBRT (36-59 Gy) were statistically significantly worse than in patients treated without WBRT immediately after treatment. Clinically relevant differences were found for attention and verbal memory.[53,54] Moreover, patients with PCNSL treated with chemotherapy and radiotherapy were significantly more impaired, compared with normative data 2 years after treatment, in all domains except verbal and visuoconstructive ability.[55]

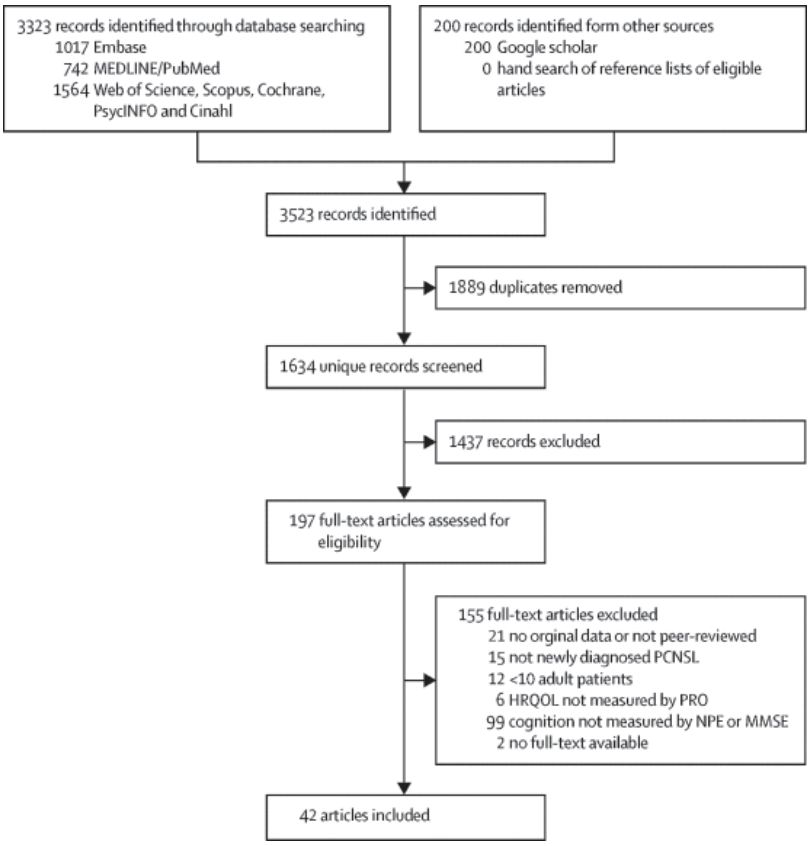

Figure 1. PRISMA flowchart
PCNSL=primary CNS lymphoma. QOL=quality of life. PRO=patient-reported outcome. NPE=neuropsychological evaluation. MMSE-Mini-Mental State Examination.

HEALTH-RELATED QUALITY OF LIFE

Immunochemotherapy or chemotherapy

Three studies[17,18,56] reported HRQOL results in patients given immunochemotherapy or chemotherapy only. Immediately after completion of chemotherapy, patients showed statistically significant and clinically relevant improvements in HRQOL scores, as measured with the FACT-Br (improvement from 120 to 134) and the EORTC QLQ-C30[57] global health status scale (50 to approximately 66).[17,22] The global health scores at 24 months did not further improve nor decline.[17] In 11 patients given high-dose methotrexate, HRQOL was measured cross-sectionnally with the FACT-Br (mean 158) after a median follow-up of 22 months[56]; similar to FACT-Br scores measured in another study at 24 months follow-up.[22] In elderly patients with PCNSL, global health status improved, though not to a clinically relevant degree, straight after treatment with R-MPL (50 *vs* 58), and remained stable up

to 18 months thereafter.[18] Similar results are found, both in the short and long term, for chemotherapy[17,56] and immunochemotherapy.[18,22] Although 83% of patients reported an average to good global health status score, and 72% a good to very good score, following intravenous and intrathecal chemotherapy after a median follow-up of 44[36] and 100[33] months, respectively, patients' functioning levels (functional scales of the EORTC QLQ-C30) were worse to a clinically relevant degree compared with that of the general population.[33,36] Longitudinal measurements up to 100 months in 12 patients showed a significant deterioration in social functioning over time.[33] Since raw HRQoL scores are absent, it is not clear whether this was also a clinically relevant deterioration.

Chemotherapy combined with ASCT

Two studies[22,32] showed that 4-6 months after treatment with chemotherapy and ASCT the FACT-Br[58] score improved significantly (120 to 144)[22] and that the global health status improved to a clinically relevant degree (50 to approximately 66).[32] After 1 year of follow-up, global health status remained relatively stable (66 to 60).[32] The FACT-Br score, however, showed a further improvement over time, to 149 points at 12 months and 158 points at 24 months after treatment.[22]

Chemotherapy combined with whole brain radiotherapy

Two studies of reduced dose WBRT (23.4 Gy) showed that FACT-Br scores improved from baseline (122 to 129) at 1 year after reduced dose WBRT (154 to157) and remained stable up to 2 years thereafter (154 to 156).[38,40] Two articles,[53,54] describing partially overlapping populations, showed that immediately after treatment, HRQoL scores (FACT-Br) were worse in patients given combined chemotherapy and radiotherapy (36-54 Gy) compared with those given chemotherapy only (131 *vs* 142; n=28 in total). However, after 14-16 months of follow-up (n=50), these scores were 139 versus 127, in favour of patients given chemotherapy and radiotherapy.[53,54] Also the Spitzer QOL score[59] improved from a median score of six at baseline to ten (maximum) 3 years after treatment with combined chemotherapy and radiotherapy (36 Gy) compared to the chemotherapy alone group.[44] Several significant differences in HRQOL, among physical, role, emotional and cognitive functioning, weakness of the legs, and future uncertainty, were found in favour of no early WBRT (45 Gy), compared with upfront WBRT. However, whether these differences were clinically relevant or not, remains unknown because crude data were not reported.[48] Compared with controls (patients treated for systemic haematologic malignancies), HRQOL was worse in almost all domains, about 2 years after treatment with combined chemotherapy and radiotherapy (39-40 Gy) to a statistically significantly and clinically relevantly degree.[55]

In one remaining article, the radiation dose was unknown; after a median follow-up of 3.3 years, younger patients less than 65 years had better scores to a statistically significantly and clinically relevant degree on several scales and items of the EORTC QLQ-C30 and

QLQ-BN20 questionnaires[60] than older patients, indicating that age influences the effects of treatment on HRQOL. HRQOL scores in the first 5 years after high-dose methotrexate and WBRT (dose unknown) were similar to the scores thereafter (maximum of 14 years), underscoring the fact that HRQOL remains stable on extended follow-up.[61]

Direct comparison of multiple treatment modalities

In two studies[62,63], the effect of different treatment modalities on cognition and HRQOL were directly compared. One RCT compared ASCT with WBRT (36 Gy), and showed improvement in cognition and HRQOL in most patients after consolidation therapy in both arms of the study.[63] 2 years after treatment, a significant impairment in attention and executive functions[63] was observed in patients given WBRT, although no clinically relevant differences[62] could be discerned from the results.[63] Concerning HRQOL, in all scales or items except for emotional functioning[62] or global health status[63], patients given WBRT (45-60 Gy[62]) had a significantly[62,63] and clinically relevant[62] lower score compared with those who were treated without WBRT.

DISCUSSION

Most studies included in this systematic Review showed that, compared with baseline, cognition and HRQOL were improved to a clinically relevantly degree after induction chemotherapy in patients with PCNSL, implicating that the tumour itself had negative effects on both outcome measures. However, this rapid improvement after initial treatment has not been reported in patients with glioma.[64-66] As corticosteroids are a part of induction chemotherapy, they might have contributed to the improvement observed for both outcome measures. Although it might be expected that treatment with chemotherapy that disrupts the blood-brain barrier results in a deterioration in cognitive functioning, two studies[26,29] have shown that patients; cognitive functioning improves directly after treatment, and that this improvement is maintained over time, even long term. The effect of treatment on cognition is therefore similar to that of convention chemotherapy (ie, immunochemotherapy or chemotherapy and intravenous chemotherapy combined with intrathecal administrated chemotherapy).[17,19,21,33] Likewise, combined chemotherapy with ASCT[22,30] also resulted in an initial improvement, with stable cognition and HRQOL during follow-up. The effect of WBRT on cognitive functioning, however, is ambiguous. Few studies have shown clinically relevant differences in scores on several neuropsychological tests[53] and in MMSE scores[47,48], both in favour of patients treated without WBRT. By contrast, other studies have shown that cognition remained stable up to 4 years after reduced-dose WBRT, implying no adverse effects of low-dose radiation on long-term cognitive functioning.[38,40] As cognitive screening tools, like MMSE and MoCA, lacks sensitivity to detect

cognitive impairment[67] and results should be interpreted with caution, we combined the results of these tests with those from formal neuropsychological evaluation (ie, the gold standard) in case they showed a similar trend. It remains important, however, to note that MMSE scores - either measured cross-sectionally or longitudinally - are likely to provide an underestimation of the incidence of cognitive impairment and changes that may have occurred over time in patients with PCNSL. Thus, results from screening instruments, such as MMSE or MoCA, are most likely represent an underestimation of the patients' actual level of impairment, limiting the interpretation of the magnitude of the cognitive adverse effects of the various treatment regimens used in PCNSL. Moreover, it is important to emphasise that future clinical studies use appropriate standard measures in this population, as proposed by the International Primary CNS Lymphoma Collaborative Group, to better evaluate cognition.[5]

For HRQOL, most studies showed stable HRQoL directly after WBRT, with a further improvement over time in one study[44]. Only one study showed did a direct comparison bewteen patienst given WBRT and those treatedwith other modalities, which showed a worse score for a small group (n=11) of patients given WBRT compared with those given other modalities (n=60 in total).[62] As an example, the global health score was 48 for those treated with chemotherapy followed by radiotherapy, and 62-82 for those treated with other modalities without radiotherapy.[62] Although not always clinically relevant, these results do suggest that treatment with radiotherapy results in worse cognitive functioning and HRQOL compared with treatment with chemotherapy only, or in combination with other therapies. This information should be included in clinical decision making, together with information about survival. Although the interpretation of the study is difficult due to a large amount of cross-over between study arms, a prolonged progression-free survival (18 *vs* 12 months) was achieved in patients given combined chemotherapy and radiotherapy, compared with chemotherapy only;[4] however, overall survival did not differ between groups.[4,63] Benefits of extended progression-free survival with WBRT and the associated delayed negative effects of recurrent disease on cognition and HRQOL should be weighed against the negative effects of full-dose radiotherapy on cognition and HRQOL. It could also be argued to preclude the addition of full-dose WBRT from first-line therapy, because of its negative impact on cognition and HRQoL without proof of prolonged overall survival. As such, reduced-dose WBRT could be an appropriate alternative. Treatment with ASCT may also be an alternative to WBRT, as progression-free survival outcomes are similar bewteen modalities,[63,68] and the effects on cognition are likely to be less detrimental than WBRT. The Effect of ASCT on overall survival, however, remains to be seen.

With respect to patient-related factors that are associated with cognition or HRQOL, age was only described in a few studies. Most elderly patients (80%) had serious cognitive impairment (MDRS, <135) at baseline,[17] which improved immediately after treatment and at short-term follow-up (up to 1 year),[18,19] and remained stable afterwards.[17,21] HRQOL

was also shown to improve after treatment in the elderly population, although this was not clinically relevant.[18] Nevertheless, younger patients (<65 years) had statistically significantly better scores to a clinically relevant degree on several scales and items of the EORTC QLQ-C30 and QLQ-BN20 questionnaires when compared with older patients, indicating that age influences the effects of treatment on HRQOL long-term.[61]

It has been recognized that both cognitive functioning and HRQOL are important outcome measures in patients with PCNSL.[69] However, both outcomes are measured, evaluated and described in many different ways, which make it difficult to perform a meta-analysis and draw conclusions on the effect of different treatment modalities in this patient population. Moreover, it is difficult to determine the long-term impact of treatments, because of the large drop-out rate of participants on cognitive tests or HRQOL questionnaires over time. In addition, results from the available cross-sectional studies are often hampered by selection bias; those who had neurotoxicity may not have returned for their MMSE or neuropsychological testing appointments during follow-up.[21] Another limitation is the level of reporting of the results described in the included studies. Unfortunately, many articles only reported cross-sectional post-treatment results. Without baseline scores it is not possible to determine the net change in cognitive functioning that has occurred over time. Additionally, sometimes statistically significant differences were described, without presenting the actual scores, which meant it was not possible to identify if these differences were also clinically relevant. If raw scores were present, significant differences should not be automatically interpreted to be clinically relevant too.

CONCLUSION

The results of the studies included in this Review showed that both the tumour and additional full-dose WBRT can effect cognition and HRQOL in a clinically relevant, and negative, way. It is important that this information is included in clinical decision making, when discussing the benefits and risks of certain treatments. We advise that research in patients with PCNSL address cognition and HRQOL, as recommended by the guideline[5] to help clinicians to make a reasoned decision, regarding treatment.

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SUPPLEMENTARY DATA

Content:

Search strategy in Medline ovid (Pubmed)

Table: study characteristics of all included articles

References

SEARCH STRATEGY IN MEDLINE OVID (PUBMED)

((Lymphoma/ AND (exp "Central Nervous System"/)) OR "Intraocular Lymphoma"/ OR ((primar* ADJ6 ("central nervous system" OR CNS OR intraocular OR intra-ocular OR brain* OR cerebral* OR spine OR spinal) ADJ3 lymphoma*) OR PCNSL OR (Primar* ADJ6 CNSL)).ab,ti.) AND ("quality of life"/ OR "Health Status"/ OR "health status indicators"/ OR exp "fatigue"/ OR "depression"/ OR exp "Depressive Disorder"/ OR exp "emotions"/ OR "Social Environment"/ OR "Social Isolation"/ OR "Social Alienation"/ OR "Social Perception"/ OR "Social Participation"/ OR "Social Learning"/ OR "Emotional Adjustment"/ OR psychology.xs. OR exp "Psychological Tests"/ OR "Adaptation, Psychological"/ OR "self report"/ OR "Symptom Assessment"/ OR "Sexual Dysfunctions, Psychological"/ OR sexuality/ OR "Sexual Behavior"/ OR exp "cognition"/ OR "learning"/ OR exp Memory/ OR "Language Tests"/ OR "Cognition Disorders"/ OR "Neuropsychiatry"/ OR "Outcome Assessment (Health Care)"/ OR Neuropsychology/ OR "Mental Health"/ OR ((quality ADJ3 life) OR hrql OR hrqol OR qol OR ((health OR function* OR patient* OR mental* OR perform*) ADJ3 (status* OR outcome* OR assess*)) OR "mental health" OR (outcome* ADJ3 assess*) OR fatigue OR depress* OR emotion* OR anxi* OR fear OR social* OR psychosocial* OR stress OR distress* OR psycholog* OR neuropsycholog* OR well-being OR wellbeing OR coping OR ((self OR patient*) ADJ report*) OR burden OR (symptom* ADJ3 assess*) OR sexual* OR functioning* OR cognit* OR learning OR neurocogniti* OR memory OR neuropsych* OR language* OR reading* OR pro OR pros OR attention* OR Neurobehav* OR (Executive* ADJ3 function*) OR Aggressi*).ab,ti.) AND english.la. NOT ((exp child/ OR exp infant/) NOT exp adult/) NOT ("case reports"/ OR ("case report*").ti.)

TABLE: STUDY CHARACTERISTICS OF ALL INCLUDED ARTICLES

Article	n tested/ n PCNSL	Median age; Percentage older patients (if available)	Performance Score (range)	Design	Cognition/ HRQoL/ Both	Primary, secondary aim
Immunochemotherapy or chemotherapy						
Guha-Thakurta, 1999[57]	11/31	63 (35-87) Tested: 56 (46-79)	KPS 40 (10-80)	Single center prospective Cohort	HRQoL	Primary: Radiological response, PFS, overall survival and HRQoL in patients with PCNSL who received high-dose MTX.
Batchelor, 2003[39]	19/25	Mean age 60 (SD 12)	KPS 80 Mean 78	Multicenter, single-agent, prospective cohort, phase II	Cognition	Primary: radiographic response. Secondary: survival and toxicity and cognition
Hoang-Xuan, 2003[40]	38/50	72 (60-81);	KPS 50 (40-100)	Prospective cohort, phase II	Cognition	Primary: efficacy (response to therapy, OS) and toxicity, including cognition, in older patients
Omuro, 2015[17]	71/95	72 (60-85)	KPS 70 (40-100)	Prospective randomized controlled trial, phase II	Both	Primary: 1 year PFS after two different MTX based chemotherapy regimens. Secondary: cognition and HRQoL
Fritsch, 2017[41]	74-93/ 112; HRQoL 74	73 (66-85)	KPS 70 (30-100)	Prospective cohort	Both	Primary: CR and PFS with R-MPL in elderly with PCNSL Secondary: cognition and HRQoL
Chemotherapy with blood brain barrier disruption (BBBD)						
Neuwelt, 1991[18]	12/30	Mean age WBRT + BBBD 42.5 years versus BBBD (± WBRT) 53.7 years	Mean KPS WBRT+BBBD: 73.1 Versus BBBD (± WBRT): 77.4	Prospective, non-randomized comparing cohort study	Cognition	Primary: Response and survival of BBBD alone, before or after radiation Secondary: cognition
Dahlborg, 1996[19]	23/58	56 (5-71); 34% >60 years	KPS 80 (40-100)	Prospective, non-randomized comparing cohort	Cognition	Primary: radiographic tumor response and survival in BBBD chemotherapy with or without WBRT. Secondary: cognition

Article	n tested/ n PCNSL	Median age; Percentage older patients (if available)	Performance Score (range)	Design	Cognition/ HRQoL/ Both	Primary, secondary aim
McAllister, 2000[20]	23/74	51% ≥60 years	62% KPS>70	Prospective cohort	Cognition	Primary: 5-year overall survival and cognitive outcome
Neuwelt, 2005[21]	16/16	47 (10-68)	NA	Prospective Cohort	Cognition	Primary: relation between imaging changes and cognition after achieving CR
Doolittle, 2013[22]	24/26	50 (range NA); 8 (33%) ≥60 years	29% KPS <70	Prospective cohort	Cognition	Primary: Cognitive functioning in long term follow up cohort treated with chemotherapy only.
Chemotherapy combined with stem cell transplantation						
Abrey, 2003[23]	14/28	53 (25-71)	KPS 70 (30-100)	Prospective cohort	Cognition	Primary: Feasibility of MTX, cytarabine (induction) and HD-CT (BEAM). Secondary: EFS and OS, cognition
Illerhaus, 2008[42]	10/13	54 (38-67)	KPS 90 (30-100)	Prospective cohort , pilot	Cognition	Primary: DFS and OS of chemotherapy and ASCT, with limited WBRT, secondary: cognition
Omuro, 2015[24]	16/ 32	57 (23-67); 36 (34%) >60 years	KPS 80 (40-100)	Prospective cohort, phase II	Both	Primary: 1 year PFS after R-MPV and ASCT. Secondary: cognition, HRQoL Population is partially overlapping with Correa, 2009
Illerhaus, 2016[43]	73-77/ 79; HRQoL 77	56 (51-62); 25 (32%) >60 years	KPS 90 (70-90)	Prospective cohort, phase II	Both	Primary: proportion achieving a CR 30 days after completing CT-ASCT. Secondary: cognition and HRQoL
Intravenous and intrathecal chemotherapy (partially overlapping populations)						
Schlegel, 2001[25]	10/20	64 (27-71); 10 (50%) ≥65 years	KPS 70 (30-80)	Prospective cohort, pilot	Cognition	Primary: response rate, response duration, and toxicity after systemic and intraventricular chemotherapy
Pels, 2003[26]	22/65; >60 years 35 (54%)	62 (27-75) Tested: 61 (range NA)	KPS 70 (20-90)	Prospective cohort, phase II	Cognition	Primary: Response rate, response duration, OS, and toxicity after systemic and intraventricular chemotherapy with deferred radiotherapy

Article	n tested/ n PCNSL	Median age; Percentage older patients (if available)	Performance Score (range)	Design	Cognition/ HRQoL/ Both	Primary, secondary aim
Fliessbach, 2003[27]	10/20	60 (27-67); 50% > 60 years	NA	Prospective cohort, pilot	Cognition	Primary: longitudinal cognitive performance with extended follow up) and related to MRI findings
Fliessbach, 2005[28]	23/47	54 (28-68)	KPS 70 (50-90)	Multicenter prospective cohort, phase II.	Both	Primary: the impact of the tumor itself and its treatment on with HD-MTX chemotherapy plus it CT on long term cognition and HRQoL
Juergens, 2010[29]	12-21/65 HRQoL 12	62 (27-75); 35 (54%) >60 years	KPS 70 (20-90)	Prospective cohort: Pilot/ phase II (combined)	Both	Primary: long-term OS, PFS, HRQoL and cognitive functioning after systemic and intraventricular chemotherapy without WBRT.
Chemotherapy combined with whole brain radiotherapy						
O'Neill, 1999[44]	46/53	60 (Range NA)	Median ECOG 2	Prospective cohort, phase II	Cognition	Primary: cognition (MMSE) and performance status (ECOG) during treatment
DeAngelis, 2002[45]	40/102	57 (range NA); 42% > 60 years	KPS 80 (range NA)	Prospective cohort	Cognition	Primary: 2-year overall survival. Secondary: response to therapy prior to radiotherapy and cognitive functioning
Harder, 2004[30]	19/25	44 (24-63); 2 (5%) >60 years	Mean KPS 87 (SD 8)	Prospective cohort, phase II	Both	Primary: cognitive status and HRQoL in patients with PCNSL in complete remission compared to patients with other hematological malignancies.
Correa, 2004[31]	28/62	60 (36-85)	NA	Retrospective cohort	Both	Primary: cognitive functioning and HRQol in survivors of PCNSL
Fisher, 2005[46]	40/102	NA	NA	Prospective, non-randomized comparing cohort, phase II	Cognition	Primary: survival between WBRT and fractionized radiation. Long term follow up from population described by DeAngelis, 2002. Secondary: cognition
Laack, 2006[47]	19/19	76 (70-83)	Median ECOG 1.5 (0-3)	Prospective cohort	Cognition	Primary: efficacy, toxicity, and survival of WBRT treated and high-dose methylprednisolone treated in elderly patients

Article	n tested/ n PCNSL	Median age; Percentage older patients (if available)	Performance Score (range)	Design	Cognition/ HRQoL/ Both	Primary, secondary aim
Shah, 2007[32]	12/30	57 (30-76)	KPS 70 (50-90)	Prospective cohort	Cognition	Primary: safety of adding rituximab to MTX chemotherapy and efficacy of reduce dosed WBRT after CR. Secondary: cognition Partially overlapping population with Morris, 2013; Correa, 2009
Yamanaka, 2007[33]	13/32	61 (34-73) tested: mean age 64 (34-73); 8 (62%) >60 years	KPS 70 (range NA) Tested KPS 90 (40-100)	Prospective cohort	Cognition	Primary: 2-year and 5-year OS and tumor response, with and without salvage therapy. Cognition before and after treatment described separately for patients without a relapse.
Correa, 2009[34]	12/19	58 (47-76)	NA	Prospective cohort	Both	Primary: side-study of a phase II clinical trial: effect of additional rituximab to standard treatment. Secondary: cognition and HRQoL Partially overlapping population with Shah, 2007; Morris, 2013
Ferreri, 2009[48]	59/79	MTX: 58 (27-72) versus MTX+Ara-C: 59 (25-74)	ECOG >1 MTX: 50% versus MTX+Ara-c: 26%	Multicenter prospective, randomized controlled trial, phase II	Cognition	Primary: complete remission rate after chemotherapy MTX +WBRT or MTX-cytarabine + WBRT. Secondary: cognition Partially overlapping population with Ferreri, 2011 and 2014
Ferreri, 2011[49]	17/33	55 (26-73); 13 (39%) >70 years old	ECOG 0-1: 91%	Retrospective cohort	Cognition	Primary: the impact on outcome and neurological performance of different radiation fields. Secondary: cognition Partially overlapping population with Ferreri, 2009 and 2014
Laack, 2011[50]	34/36	61 (34-69)	ECOG 0-1: 83%	Prospective cohort, phase II	Cognition	Primary: effect of treatment in radiological response, toxicity and survival

Article	n tested/ n PCNSL	Median age; Percentage older patients (if available)	Performance Score (range)	Design	Cognition/ HRQoL/ Both	Primary, secondary aim
Correa, 2012[35]	50/95	Chemo + WBRT 52 (36-72) versus Only chemo 73 (56-85)	NA	Retrospective cohort	Both	Primary: Cognitive functioning and HRQol in survivors of PCNSL Population partly described in Correa, 2004
Morris, 2013[36]	12/52	60 (30-79) Tested 58 3 (25%) >60 years	KPS 70 (50-100)	Prospective cohort	Both	Primary: safety of adding rituximab to MTX chemotherapy and efficacy of reduce dosed WBRT after CR. Secondary: cognition and HRQoL Partially overlapping population with Shah, 2007; Correa, 2009
Ichikawa, 2014[51]	23/24	64 (50-67); >65years (54%) With RT 58 (50-67) versus Without RT 68 (53-78)	KPS 70 (40-100) With RT KPS 60 (40-80) versus Without RT KPS 70 (40-100)	Prospective, non-randomized cohort	Cognition	Primary: the effect (RFS, OS) of M-CHOP +/-WBRT. Secondary: cognition
Ferreri, 2014[52]	9/41	57 (19-70)	ECOG 0-1: 63%	Prospective cohort, phase II	Cognition	Primary: Long-term follow-up (overall response rate) cross sectional. Secondary: cognition Partially overlapping population with Ferreri, 2009 and 2011
Glass, 2016[53]	50-52/53 HRQoL 52	57 (24-73)	NA	Prospective cohort, phase II	Both	Primary: 2-year OS rate Secondary: cognition and HRQoL
Okita, 2016[58]	37/ 37	63 (33-77)	22 (60%) KPS ≥80	Retrospective cohort	HRQoL	Primary: determining the factors can contribute to a decline in HRQoL in outpatient PCNSL patients.

Article	n tested/ n PCNSL	Median age; Percentage older patients (if available)	Performance Score (range)	Design	Cognition/ HRQoL/ Both	Primary, secondary aim
Herrlinger, 2017[54]	144/318	61 (53-68)	KPS 80 (60-90)	Prospective randomized controlled trial, phase III	Both	Primary: differences in cognition and HRQoL between chemotherapy and chemotherapy combined with WBRT upfront
Chanswangphuwana 2017[55]	10/37	56 (16-78)	NA	Retrospective cohort	Cognition	Primary: the role of low-dose WBRT and treatment outcomes of MTX based chemotherapy. Secondary: cognitive impairment
Kaburaki, 2017[56]	16/17	63 (43-72)	NA	Prospective cohort	Cognition	Primary: the efficacy of treatment protocol for PIOL to prevent new CNS relapse and prolong OS by early initiation of CNS prophylaxis with a combination of MTX and rdWBRT. Secondary: cognition
Direct comparing of multiple treatment modalities						
Doolittle, 2013[37]	80/80	59 (10-78); 35 (44%) ≥60 years	KPS 80 (20-100)	Prospective cohort	Both	Primary: describe cognition and HRQoL and correlate to radiology in long-term survivors who were treated with high-dose methotrexate–based regimens with or without WBRT
Ferreri, 2017[38]	57/113	57 (IQR 51-63) 17 (14%) ≥65 years	ECOG >1 31 (27%)	Randomized controlled trial	Both	Primary: 2-year PFS after second randomization (WBRT or ASCT as consolidation) Secondary: cognition and HRQoL

Abbreviations: Ara-C Cytarabine; ASCT autologous stem cell transplantation; BBBD blood brain barrier disruption; BEAM carmustine, etoposide, cytarabine and melphalan; CR complete response; CT chemotherapy; DFS disease free survival; ECOG Eastern Cooperative Oncology Group performance score; EFS event free survival; HD high dose; HRQoL health related quality of life; it intrathecal; KPS Karnofsky performance score; M-CHOP Methotrexate-cyclophosphamide, hydrocydaunorubicin, vincristine and predinisolone; MMSE mini-mental state examination; MTX methotrexate; n number of patients; NA not available; OS overall survival; PIOL primary intra-ocular lymphoma; PCNSL primary central nervous system lymphoma; PFS progression free survival; RFS relapse free survival; R-MPL rituximab – methotrexate, probarbazine and lomustine; R-MPV rituximab – methotrexate, probarbazine and vincristine; RT radiotherapy; SD standard deviation; (rd)WBRT (reduced dose) whole brain radiotherapy.

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7

Neurocognitive functioning and radiological changes in primary CNS lymphoma: results from a RCT

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ABSTRACT

Objective: To analyze the effect of treatment on neurocognitive functioning and the association of neurocognition with radiological abnormalities in primary central nervous system lymphoma (PCNSL).

Methods: 199 patients from a phase III trial (HOVON 105/ALLG NHL 24), randomized to standard chemotherapy with or without rituximab, followed in patients ≤60 years-old by 30Gy WBRT, were asked to participate in a neuropsychological evaluation before and during treatment, and up to 2 years post-treatment. Scores were transformed into a standardized z-score; clinically relevant changes were defined as a change in z-score of ≥1 standard deviation. The effect of WBRT was analyzed in irradiated patients. All MRIs were centrally assessed for white matter abnormalities and cerebral atrophy, and their relation with neurocognitive scores over time in each domain was calculated.

Results: 125/199 patients consented to neurocognitive evaluation. Statistically significant improvements in neurocognition were seen in all domains. A clinically relevant improvement was seen only in the motor speed domain, without differences between the arms. In the follow-up of irradiated patients (n=43), no change was observed in any domain score, compared to after WBRT. Small but significant inverse correlations were found between neurocognitive scores over time and changes in white matter abnormalities (regression coefficients: -0.048 to -0.347) and cerebral atrophy (-0.212 to -1.774).

Conclusions: Addition of rituximab to standard treatment in PCNSL patients did not impact neurocognitive functioning up to two years post-treatment, nor did treatment with 30Gy WBRT in patients ≤60 years-old. Increased white matter abnormalities and brain atrophy showed weak associations with neurocognition.

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is a rare non-Hodgkin lymphoma confined to the brain, leptomeninges, spinal cord and eyes. Over the last three decades the prognosis for patients with PCNSL improved significantly due to improvement of treatment, though mainly among patients below the age of 70 years.[1,2] Preservation of neurocognitive functioning remains a major challenge in the treatment of PCNSL.[3] Neurocognitive decline, along with other symptoms caused by the tumor and/ or treatment, may subsequently compromise health-related quality of life (HRQoL).[4,5]

In systemic diffuse large B-cell lymphoma (DLBCL) patients, rituximab, a chimeric anti-CD20 monoclonal antibody that targets the CD20 cell surface protein, improves survival when added to standard chemotherapy.[6,7] It has been hypothesized that rituximab added to standard high-dose methotrexate (HD-MTX) based chemotherapy could also improve survival in PCNSL patients. The HOVON 105/ ALLG NHL 24, a large international multicenter phase III randomized controlled trial (RCT), investigated the addition of rituximab to MBVP (methotrexate, tenoposide, BCNU and prednisolone) chemotherapy, followed in patients ≤60 years-old, by whole brain radiotherapy (WBRT). This study showed that rituximab did not improve event-free, progression free and overall survival (OS), although OS data were still immature.[8]

For any new treatment regimen, information on the impact of this treatment on both the quantity and quality of life should be evaluated to determine the 'net clinical benefit'. Neurocognitive impairment is an important factor that may negatively influence HRQoL in brain tumor patients and should therefore be considered in this evaluation. Although a direct effect of rituximab on neurocognition was not necessarily expected, improved efficacy of treatment resulting in fewer patients needing radiotherapy (boost) could influence the neurocognitive effect of the treatment. Combined survival and quality of survival will allow clinicians and patients to make informed decisions about the best treatment for each individual patient.

Radiological features, in particular brain volume and white matter lesions, have been found to correlate with worse neurocognitive functioning in patients treated for PCNSL in some, but not all, studies.[9-13] Most of these studies were limited by a cross sectional design and/or small cohorts (n=16-28).[11,12]

Rituximab was found not to affect HRQoL in patients from the HOVON 105/ ALLG NHL24 trial.[14] The primary aim of this study was to determine the effect of rituximab, when added to standard treatment for PCNSL, on neurocognitive functioning, which was a predefined secondary endpoint of the HOVON 105/ALLG NHL 24 trial. In addition, we aimed to evaluate the effect of low-dose WBRT on neurocognitive functioning in irradiated patients. Lastly, we aimed to identify whether there is a relation between brain volume and/ or white matter lesions and neurocognitive functioning over time in PCNSL patients.

METHODS

Study design and patient population

In the HOVON 105/ ALLG NHL 24 trial 199 immunocompetent patients, aged 18-70 years, with newly diagnosed CD20 positive B-cell PCNSL were included from Dutch, Australian and New Zealand hospitals between 2010 and 2016. Only patients who were fluent in English or Dutch and were treated in a center that was equipped for neuropsychological evaluation (NPE) were eligible for participation in this neurocognitive study. The trial design and treatment details were published elsewhere.[8] In short, patients were randomized for two cycles of MBVP without or with rituximab (R-MBVP). Irrespective of treatment arm, this induction treatment was followed by consolidative HD-cytarabine chemotherapy. Patients ≤60 years-old subsequently received 30Gy (20x1.5Gy) WBRT. An integrated boost of 10Gy to the tumor-bed was given simultaneously with WBRT to patients who achieved only a partial response.[15] All participants signed informed consent for the RCT and separately for undergoing neurocognitive assessments. The study and the neurocognitive testing part were approved by the ethics committees of all participating centers. The HOVON 105/ ALLG NHL 24 trial was registered: EUdraCT number 2009-014722-42 and in the Netherlands Trial Register: Trial NL2321.

Neuropsychological evaluation

All patients were tested by a trained research nurse or neuropsychologist using a standard test battery, as described in the assessment guidelines in PCNSL.[3] For testing attention/ executive functioning, the WAIS III digit span (DS) forward and backward[16] and the Trail Making Test parts A and B[17] were used. The written version of the Letter Digit Substitution Test (LDST)[18] was used to determine information processing speed. Memory was tested with the Rey Auditory Verbal Learning Test (RAVLT)[19], and motor speed with the Grooved Pegboard Test[20] in the dominant and non-dominant hand. To prevent practice effects, different versions were used at different visits for the RAVLT, LDST and DS. At baseline, premorbid intelligence (IQ) was determined with the national adult reading test (NART) or Dutch adult reading test in English and Dutch speaking patients, respectively.[21,22]

According to protocol, patients underwent NPE before chemotherapy (baseline), after completion of chemotherapy, after radiotherapy (if given), and at 3, 6, 12, and 24 months post-treatment. NPEs were discontinued if a patient received <2 cycles of (R-)MBVP, when a relapse or progression occurred, or when a patient chose to withdraw from the either the RCT or NPE side-study.

Radiological assessments

At baseline, after each treatment part (i.e. (R-)MBVP, HD-cytarabine, WBRT (if applicable)), and thereafter every three months in the first two years of follow-up, all patients under-

went cranial MRI. The degree of white matter abnormality (WMA) and brain atrophy were assessed centrally. For this evaluation the 'end of treatment' MRI, irrespective of the final treatment modality, was considered the reference scan. MRI scans at 6, 12 and 24 months of follow-up were used to determine changes.

WMA were scored in five brain areas on both sides (frontal, temporal, parieto-occipital, basal ganglia and infratentorial) according to Fazekas (range 0-3), with 0 denoting no lesions or symmetrical caps or bands, 1 indicating small focal lesions and 2 and 3 indicating beginning or diffuse confluent lesions, respectively.[23] The lobe or lobes in which the tumor lesion or lesions and its surrounding edema were located were not scored to prevent overestimation of WMA. The sum score (0-30) of WMA in all scored brain areas at each time point was used to calculated individual changes over time. The WMA ratio, defined as the sum score divided by the maximum possible sum score for each patient (excluding brain areas with tumor), was used to assess the correlation between WMA and neurocognitive functioning at each time point, for each domain. Grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) volume were calculated by automatic segmentation to determine brain volume, using a validated method.[24] Total brain volume was defined as GM+WM volumes, while total intracranial volume was defined as GM+WM+CSF.

STATISTICAL ANALYSIS

Calculation of neurocognitive scores

For the adult reading test individual test scores were converted to a standardized score, corrected for age and sex, and transformed into an IQ-score.[25] For all other tests individual test scores were transformed into a z-score, corrected for age, sex and/or level of education[26], using scores from the general population.[27]

Descriptive analysis

Clinical and sociodemographic characteristics were compared between treatment arms, and between patients who did and did not participate in the NPEs to address selection bias. Differences were tested using a Chi-Square test for categorical data, and a Mann-Whitney U or an independent t-test for continuous data, depending on the distribution of the tested variable. Compliance with NPE at each time point was calculated, and defined as the number of completed NPEs (i.e. all tests in at least one domain should have been completed) at a specific time point divided by the number of evaluations expected at that time point. A specified time window was defined for each evaluation point (Supplemental Methods). Only tests performed within the specified time windows were considered compliant with the assessment protocol and were analyzed. A domain score was calculated as the mean of the z-scores of the different tests within that domain. A change in z-score

over time or a difference between groups of ≥1 point (1 standard deviation [SD]) was considered clinically relevant.

Neurocognitive scores over time

To estimate the impact of the treatment on neurocognitive functioning over time, linear mixed models were used, which allow the inclusion of all patients who underwent a NPE at least once, with fixed effects for treatment arm, time (as factor), and their interaction. Estimated marginal mean scores and their 95% CI were calculated for each domain.

In patients who completed at least two NPEs, one of which was before treatment, we assessed the change from baseline in each domain for each individual patient. Next, patients were classified as improved, stable or deteriorated, depending on a change in z-score of ≥1 SD in each time period.

Impact of WBRT

Using the same methods, we studied neurocognitive functioning after WBRT in irradiated patients. For these analyses the scores after WBRT measurement were considered as baseline.

Relation of neurocognition with brain volume and white matter abnormalities

Pearson correlation coefficients were calculated between the z-score of each neurocognitive domain and the WMA ratio of the Fazekas score, and the total brain volume at the 6, 12 and 24 months follow-up visits, cross-sectionally. Next, linear mixed model analyses were performed to assess the association between changes in WMA or atrophy up to two years post-treatment, and changes in neurocognitive functioning over time. These analyses were corrected for time (i.e. visits), multiple lesions, sex, age, and education, and brain volume was also corrected for total intracranial volume. All analyses were conducted with Stata, version 15, and a two-tailed p-value <0.05 was considered statistically significant.

DATA AVAILABILITY STATEMENT

Individual de-identified participant data, collected for this study, including the statistical analysis plan will be made available for other research to others upon request, after approval by the HOVON executive board. The data will be available until a maximum of 15 years after the study has ended.

Please find the trial protocol, a Data Request Form and the criteria for data sharing on www.hovon.nl.

RESULTS

Patients

in the HOVON 105/ ALLG NHL 24 trial 199 patients were included, of whom 125 (63%) signed informed consent for this side-study. Compliance with NPE was ≥50% at all evaluation points, Figure 1.

In the patients evaluated for neurocognitive functioning, there were no differences between treatment arms with respect to baseline clinical and sociodemographic characteristics and drug exposure, including baseline IQ. However, more patients in the R-MBVP-arm had cognitive impairments (<-1 SD) in at least 1 domain compared to the MBVP-arm (68% versus 55%; Table 1). No differences in sociodemographic or clinical characteristics were observed between patients who participated in NPEs (n=125) and those who did not (n=74). Patients included in this analysis had a median age of 61 years (interquartile range 55-66), 72% had a median WHO performance of <2 and 38% received WBRT, which is comparable to the total trial population[8] (Supplemental Table 1). Mean baseline z-scores for each neurocognitive domain are shown in Table 1, and for each test in Supplemental Table 2.

Neurocognitive functioning over time

The results of the linear mixed models showed a statistically significant difference over time in all neurocognitive domains (all p<0.01), without any significant or clinically relevant difference between treatment arms (Figure 2). The main change in most domains was improvement between baseline and after treatment, with a stabilization thereafter. Although these difference in all domains were statistically significant, only in the domain of motor speed this improvement was also clinically relevant. Nevertheless, the estimated marginal mean scores in the motor speed domain still remained below those of the norm population (i.e. >-1 SD). For memory, scores did not quite improve to a clinically relevant extent, but over time the mean score improved from a clinically relevant impaired level to within the range of the norm population (i.e. above -1 SD). Scores in attention/executive functioning and information processing speed remained within the range of the norm population up to two years post-treatment.

At the individual level, we combined both treatments arms since groups became too small and no differences were found between treatment arms. Compared to baseline, after 12 months the majority (52-61%) remained stable in all neurocognitive domains, except for the domain of motor speed in which the majority improved (58%). After 24 months, 53% had improved scores in the memory and 68% in motor speed domain. For attention/executive functioning and information processing speed most patients remained stable: 59% and 48%, respectively. Only a minority of patients had worse neurocognitive functioning at 12 and 24 months (0-7%), Figure 3 and Supplemental Table 3.

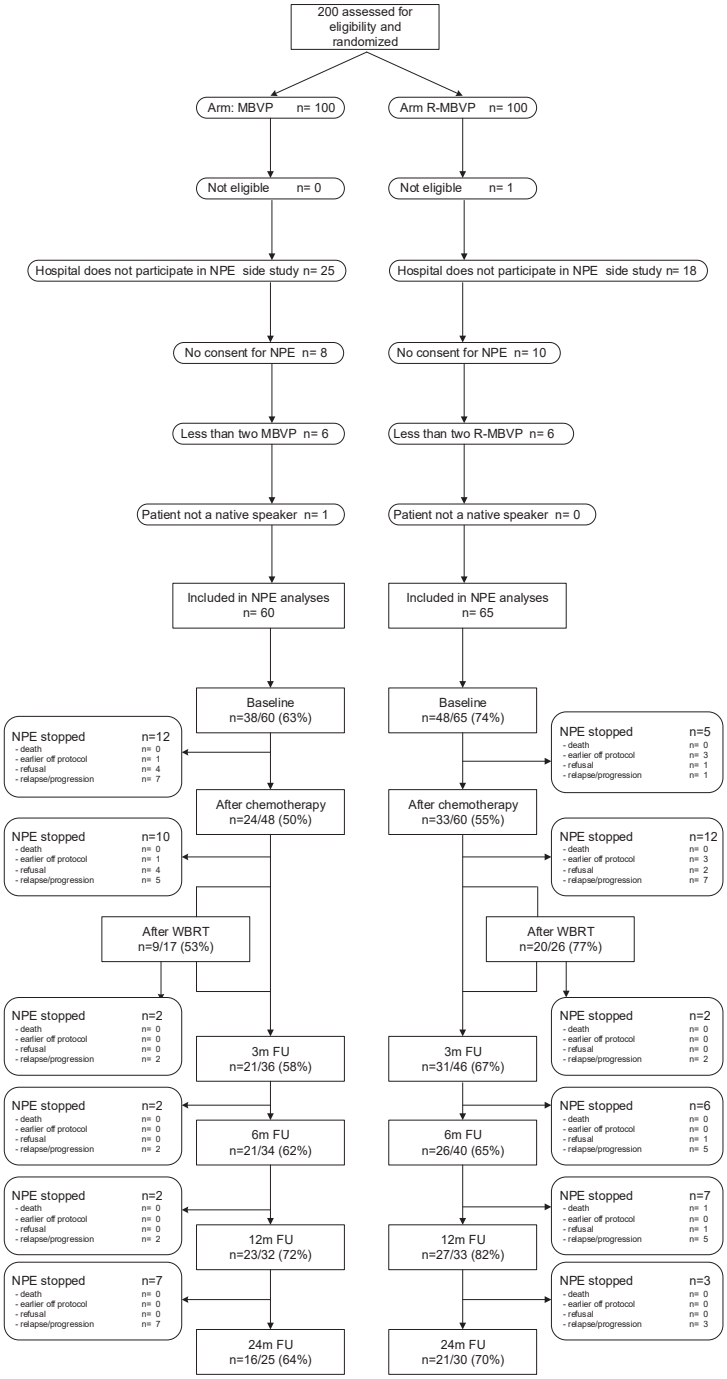


Figure 1. CONSORT diagram showing reasons for not-participating in the neuropsychological evaluations as well as the compliance rates at each time point, separately for the treatment arms.
'After WBRT' was assessed only in those who had WBRT. FU=follow-up; NPE=Neuropsychological evaluation

Table 1. Baseline clinical and sociodemographic characteristics of the patients included in the neuropsychological evaluations, per treatment arm and for the total study population.

	MBVP n=60	R-MBVP n=65	Total n=125
Sex (n, % male)	35 (58%)	29 (45%)	64 (51%)
Age (median, IQR)	60 (55-66)	61 (55-67)	61 (55-66)
WHO performance score (n, %)			
WHO 0	16 (27%)	16 (25%)	32 (26%)
WHO 1	28 (47%)	33 (51%)	61 (49%)
WHO 2	11 (18%)	9 (14%)	20 (16%)
WHO 3	5 (8%)	7 (11%)	12 (10%)
Comorbidities active at baseline (n, % ≥2)	29 (48%)	33 (51%)	62 (50%)
Baseline IQ (median, IQR)	93 (76-106)	92 (77-106)	93 (77-106)
Level of education (years of education; n,%)			
Low (≤6)	10 (17%)	11 (17%)	21 (17%)
Average (7-9)	30 (50%)	36 (55%)	66 (53%)
High (10-18+)	12 (20%)	11 (17%)	23 (18%)
Missing	8 (13%)	7(11%)	15 (12%)
Solitary lesion (n, %)	35 (58%)	32 (49%)	67 (54%)
Missing/ NA	3 (5%)	3 (5%)	6 (5%)
Bilateral involvement (n, %)	22 (37%)	27 (42%)	49 (39%)
Missing/ NA	3 (5%)	3 (5%)	6 (5%)
Deep structures involved (n, %)	39 (65%)	43 (66%)	82 (66%)
Study drug exposure			
HD Cytarabine (n, %)	55 (92%)	59 (91%)	114 (91%)
WBRT (n, %)	22 (37%)	26 (40%)	48 (38%)
Radiation boost given (n, %)	10 (17%)	16 (25%)	26 (21%)
Intrathecal treatment given (n, %)	6 (10%)	6 (9%)	12 (10%)
Baseline score for each neurocognitive domain			
Neurocognitive domain	**MBVP**	**R-MBVP**	**Total**
Attention/ executive functioning (mean, SD)	-0.52 (0.95)	-0.85 (1.03)	-0.70 (1.00)
Information processing speed (mean, SD)	-0.99 (1.74)	-1.29 (1.72)	-1.16 (1.72)
Memory (mean, SD)	-1.52 (1.20)	-1.70 (1.19)	-1.62 (1.19)
Motor speed (mean, SD)	-2.78 (3.11)	-4.43 (5.57)	-3.62 (4.57)
Impaired cognitive functioning (<1 SD) in at least one domain	33 (55%)	44 (68%)	77 (62%)

NA = not applicable in case of no brain lesion(s)

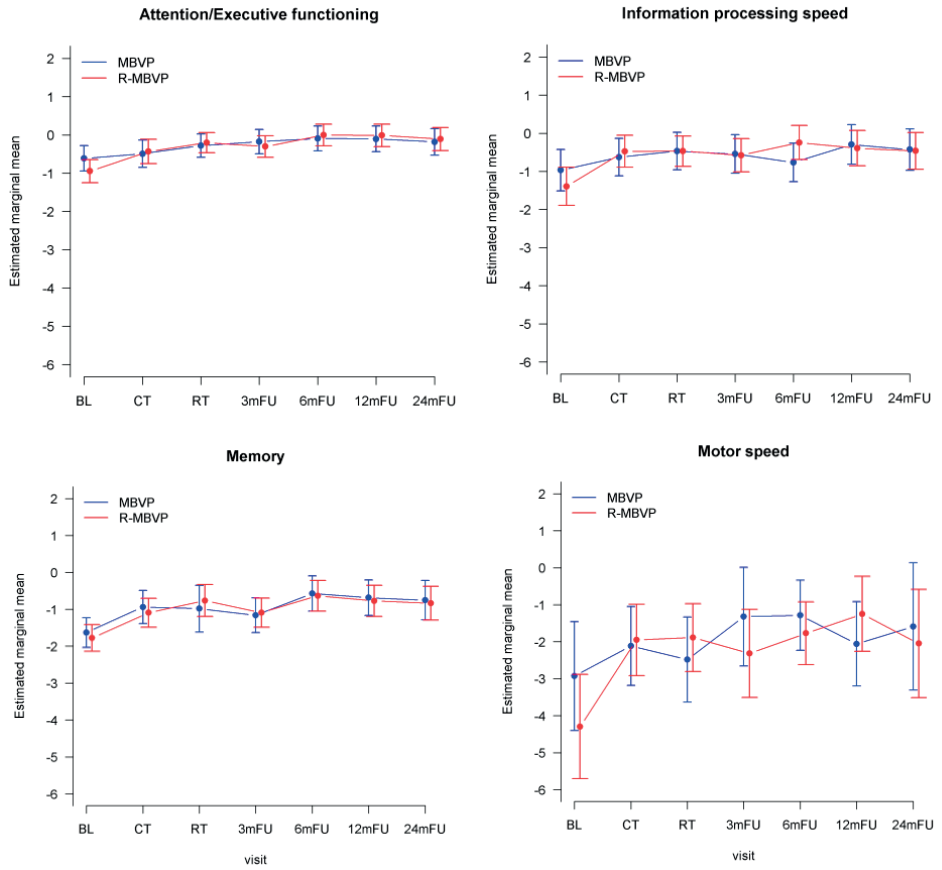


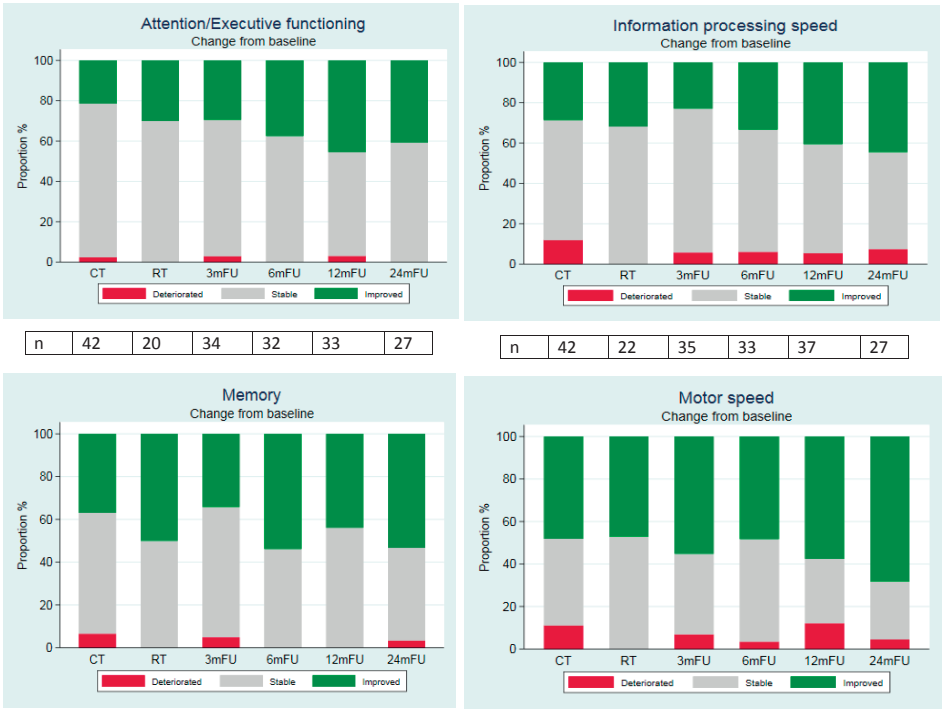
Figure 2. Mean z-scores for the different neurocognitive domains over time (A: attention/ executive functioning; B: information processing speed; C: memory; D: motor speed), separately for the treatment arms. Estimated marginal means for each evaluation point separately for each treatment arm, with the vertical bars representing the 95% confidence interval of the group mean.

Neurocognitive functioning in irradiated patients

In the irradiated patients (n=43) we assessed the effect of WBRT on neurocognitive functioning over time, up to 2 years post-radiotherapy. The results of the linear mixed model analyses showed no significant and clinically relevant changes over time, neither improvement or deterioration, except for a clinically relevant improvement in motor speed in the control-arm at 3 and 6 months post-treatment. There were no other differences between treatment arms (Figure 4).

Neurocognitive functioning in relation to radiological features

For brain volumes and Fazekas score at group level at each time point, see Supplemental Table 4. In the cross-sectional analyses at 6, 12 and 24 months, without adjustment for



n	42	20	34	32	33	27

n	42	22	35	33	37	27

n	46	24	41	39	41	30

n	27	17	29	29	33	22

Figure 3. Percentage of patients at each evaluation point with a clinically relevant change in neurocognitive domain scores compared to baseline combining both treatment arms.

the amount of WMA or brain volume at baseline on MRI, we observed weak correlations between neurocognitive scores and the degree of WMA (between +0.01 and -0.66) or brain atrophy (between +0.06 and -0.50; Supplemental Table 5).

In the longitudinal analysis we observed inverse associations between changes in the degree of WMA or brain atrophy, and changes in neurocognitive scores, with increasing WMA and atrophy correlating with a deterioration in neurocognitive functioning up to two years post-treatment (Table 2). Although significant in all domains except for memory, the changes in neurocognitive scores were rather small (regression coefficients ranged between -0.048 and -0.347), indicating that 1 point increase in the Fazekas sum score resulted in only a small, not clinically relevant, deterioration in neurocognitive functioning. For brain atrophy, a 10% decrease of brain volume was significantly associated with a deterioration in memory of -0.921 points (Table 2). Other associations were not significant or clinically relevant.

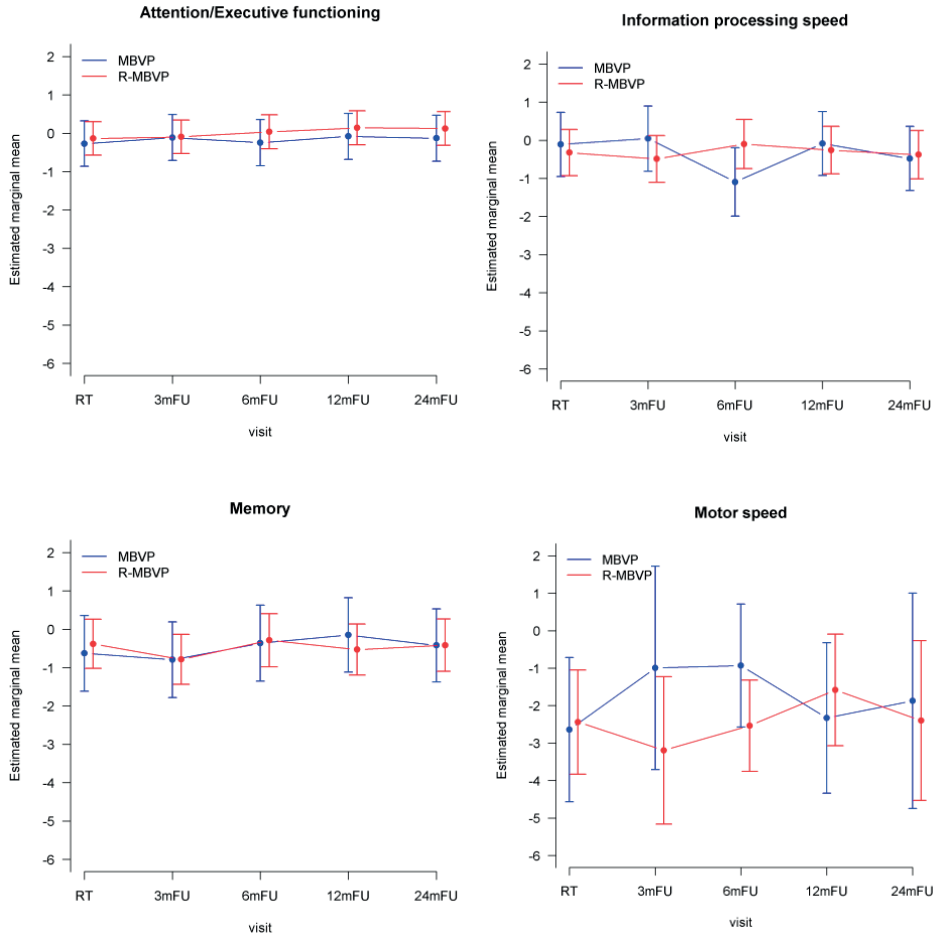


Figure 4. Mean z-scores for each neurocognitive domain over time (A: attention/ executive functioning; B: information processing speed; C: memory; D: motor speed), separately for the two treatment arms in the irradiated patients only.
Estimated marginal means are shown for each evaluation point separately for each treatment arm, with the vertical bars representing the 95% confidence interval of the group mean.

DISCUSSION

The addition of rituximab to standard MBVP-chemotherapy did not improve the event-free survival and did not impact HRQoL.[8,14] The current analysis shows that this treatment regimen resulted in a significant improvement in all neurocognitive domains, compared to baseline, although these differences were not clinically relevant except for motor speed. There were no significant or clinically relevant differences in neurocognitive functioning between those treated with and without rituximab.

Impairments in neurocognitive functioning or behavioral problems are reported to be presenting symptoms in 32-48% of patients with PCNSL.[28] In this study, 62% of the patients had impairments in at least one neurocognitive domain before treatment. The slightly better scores in all domains at the 'end of treatment' compared to baseline, with a stabilization thereafter, is a pattern that has been described in multiple PCNSL cohorts.[12,29-31] These findings suggest that neurocognitive functioning is mostly hampered by the tumor itself, and that treating the tumor results in improved neurocognitive functioning. Additionally, we found that the extent of improvement between baseline and 'end of treatment' was not clinically relevant, except for motor speed.

The results at the individual patient level support the finding that neurocognitive scores improved over time, although most patients remained stable, and only a minority (0-7%) deteriorated. Only in the motor speed domain the majority of the patients improved at 12 and 24 months, compared to baseline. This supports the results of the longitudinal analyses (linear mixed models) suggesting that motor speed improved over time to a clinically relevant extent. This finding is, however, in contrast with other studies showing less pronounced improvements or even deterioration in this domain, particularly when compared to other domains.[32,33] An explanation for this may be that patients in our cohort had very low scores at baseline, allowing patients to improve. It should be noted though, that despite the improvement, the estimated marginal means continued to be lower than the norm population (i.e. <-1SD).

In irradiated patients, scores on all neurocognitive domains rather unexpectedly remained stable for up to two years after treatment with 30Gy (20x1.5Gy) WBRT in both arms, compared to the scores shortly after WBRT. We used 'after WBRT' as baseline because we expected maximal reduction of tumor and tumor-related symptoms at that timepoint. Stable neurocognitive functioning was also found in a previously reported small cohort of PCNSL patients treated with HD-MTX based chemotherapy combined with rituximab and followed by reduced dose (rd)WBRT (23.4Gy).[12] In that same cohort, a small but significant decline in the neurocognitive domains attention and memory was observed between three and five years post-treatment.[34] This late, non-clinically relevant deterioration, however, was also observed in patients who received autologous stem cell transplantation (ASCT) instead of WBRT.[34] Two randomized trials in adult PCNSL patients compared WBRT with ASCT as consolidation therapy.[29,31] In the IELSG-32 study, 118 patients who achieved at least stable disease after induction chemotherapy were randomized for ASCT or 36Gy WBRT as consolidation.[29] After two years of follow-up, those who received WBRT had significantly worse scores in attention/executive functioning and memory domains.[29] In the PRECIS study 104 patients aged 18-60 years were randomized between ASCT and 40Gy WBRT as consolidation therapy.[31] Similarly, significant deterioration was seen in attention/executive functioning in irradiated patients compared to 'end of induction chemotherapy', while those treated with ASCT remained stable for up to three years of follow-up.[31] Several

factors could explain the discrepancy between the above two contemporary studies and our study regarding neurocognitive functioning after WBRT. First, the lower total dose and fraction dose used in our study could reduce the negative impact of WBRT, as suggested by the findings of Morris et al.[12] Second, it is possible that in our study longer follow-up will show deterioration of neurocognitive function. Such late deterioration has also been found to occur in patients with other brain tumors, such as low-grade glioma, in whom neurocognitive deterioration after (focal) radiotherapy was found after 12 years but not after 6 years.[35,36] Lastly, the absence of published individual scores and/or z-scores of the neurocognitive tests in the IELSG-32[29] and PRECIS[31] studies do not allow estimation of the magnitude of changes in neurocognition, and consequently the clinical relevance of these changes, which may affect the interpretation of results.

Up to two years post-treatment, we observed that the increase in the degree of WMA was significantly associated with worsening in all neurocognitive domains except memory, while an increase of brain atrophy was associated with worsening in the memory domain only. The associations, however, were weak to moderate, indicating that in the first two years post-treatment the impact of WMA and brain atrophy on neurocognitive functioning seems modest, possibly partially because the extent of decrease in brain volume was limited. In a large (n=80) long-term PCNSL survivors cohort (median follow-up of 5·5 years, range 2-26 years), the amount of WMA was significantly correlated with worse neurocognitive functioning on the long-term. Moreover, those treated with WBRT (n=15; 45-60Gy) in this survivors cohort had twice as much WMA as those treated without WBRT (n=65; $p<0.001$), though this resulted in a clinically relevant difference in the motor speed domain only.[10] In contrast, although more WMA were observed after rdWBRT (23.4Gy) than after ASCT (70% versus 40%, p=0·03), there was no difference in neurocognitive functioning between these groups, up to five years post-treatment.[34] While assessed in small groups and with different durations of follow-up, these results suggest that radiation dose could be crucial for neurocognitive functioning in PCNSL patients and this is supported by our findings. Longer follow-up is nevertheless needed to determine the effect of 30Gy WBRT and of white matter changes and cerebral atrophy on neurocognitive functioning in our cohort on the longer term. We were unable to investigate a direct effect of rituximab on WMA or cerebral atrophy because the number of patients in these subgroups became too small for a meaningful analysis. A recent, small (n=47) retrospective study, however, found after a mean follow-up of five years that more patients treated with rituximab plus HD-MTX developed white matter lesions (68%), compared to rituximab naïve patients (46%).[37] Although this finding does not necessarily support causation, further analysis might help to determine the etiology of these lesions.

The strengths of this study are the large, uniformly treated group of patients in which radiological assessments were done over time and neurocognitive functioning in multiple domains was assessed prospectively, allowing extensive analyses. Limitations of our study

are the limited time of follow-up, i.e. two years after end-of-treatment, and our relatively crude, visual measurement of the WMA with the Fazekas score as opposed to automatic exact measurements of white matter abnormalities, which may have masked an existing effect of WMA on neurocognition. Automatic segmentation of WMA was not possible due to different scan protocols in different including centers. Although we had some missing neurocognitive data over time, our longitudinal analyses were not hampered by this since we used linear mixed models, which deal with missing data in a sophisticated way. Lastly, we could not compare irradiated with non-irradiated patients with respect to neurocognitive functioning and radiological changes, because these patients differed in age due to the study design (i.e. irradiation in younger patients only). For this same reason we could not compare younger and older patients.

In conclusion, this analysis showed no effect of the addition of rituximab on neurocognitive functioning, neither positive nor negative. The lack of effect on event-free survival[8], the primary endpoint, as well as HRQoL[14] and this neurocognitive study, as secondary endpoints, do not, however, support the use of rituximab in patients with newly-diagnosed PCNSL. Whether specific subgroups of patients benefit from this treatment regimen remains to be investigated. Moreover, in the first two years post-treatment, a lower dose of WBRT was not harmful for neurocognitive functioning, compared to just after WBRT. The association between white matter abnormalities and brain atrophy and neurocognitive functioning was modest and longer follow-up is needed to draw definitive conclusions.

For supplemental Tables and Figures: Neurocognitive functioning and radiologic changes in primary CNS lymphoma patients: results from the HOVON 105/ ALLG NHL 24 randomised controlled trial | Neuro-Oncology | Oxford Academic (oup.com)
https://academic.oup.com/neuro-oncology/advance-article/doi/10.1093/neuonc/noab021/6131741?login=true

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8

Health-related quality of life after chemotherapy with or without rituximab in primary central nervous system lymphoma patients: results from a randomized phase III study

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ABSTRACT

Background: The impact of rituximab on health-related quality of life (HRQoL) in primary central nervous system lymphoma patients is not well-known. We determined the impact of rituximab added to standard high-dose methotrexate-based treatment on HRQoL from patients in a large randomized trial.

Patients and methods: Patients from a large phase III trial (HOVON 105/ALLG NHL 24), randomized to standard chemotherapy with or without rituximab and followed by 30Gy whole brain radiotherapy (WBRT) in patients ≤60 years, completed the EORTC QLQ-C30 and QLQ-BN20 questionnaires before and during treatment, and up to 24 months of follow-up or progression. Differences between treatment arms over time in global health status, role functioning, social functioning, fatigue, and motor dysfunction were assessed. Differences ≥10 points were deemed clinically relevant. The effect of WBRT on HRQoL was analyzed in irradiated patients.

Results: 160/175 patients eligible for the HRQoL study completed at least one questionnaire and were included. Over time, scores improved statistically significant and clinically relevant in both arms. Between arms, there were no differences on any scale (range: -3.8 to +4.0). Scores on all scales were improved to a clinically relevant extent at 12 and 24 months compared to baseline in both arms, except for fatigue and motor dysfunction at 12 months (-7.4 and -8.8, respectively). In irradiated patients (*N*=59), scores in all preselected scales except motor dysfunction, remained stable up to 24 months compared to shortly after WBRT, overall mean difference ranging between 0.02 and 4.570.

Conclusion: Compared to baseline, treatment resulted in improved HRQoL scores. The addition of rituximab to standard chemotherapy did not impact HRQoL over time. WBRT did not result in deterioration of HRQoL in the first two years.

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is a rare non-Hodgkin lymphoma confined to the brain, leptomeninges, spinal cord and eyes. Over the last three decades the incidence rate has increased, mainly amongst patients >60 years-old, and prognosis has improved significantly.[1,2] This prolonged survival has largely been determined by improvements in treatment.[1,3]

In systemic diffuse large B-cell lymphoma (DLBCL) patients, the addition of rituximab, a chimeric monoclonal antibody targeting the CD20 cell surface protein, to standard treatment has been shown to improve progression-free (PFS) and overall survival (OS).[4,5] Since most PCNSL are DLBCL, it has been hypothesized that the addition of rituximab to standard treatment with HD-MTX-based chemotherapy could also improve survival in PCNSL patients. The HOVON 105/ALLG NHL 24, a large international multicentre phase III randomized controlled trial (RCT), investigated the addition of rituximab to standard high-dose methotrexate (HD-MTX)-based chemotherapy, followed by 30Gy whole-brain radiotherapy (WBRT) in patients aged ≤60 years. The primary endpoint, the 1-year event-free survival (EFS), was not improved by rituximab D-MTX, tenoposide,BCNU (carmustine), and prednisolone without (MBVP)versus with rituximab (R-MBVP): 49% versus 52%, *P*=0.99].[6]

When introducing a new treatment, information on both survival and the patients' functioning and well-being should be taken into account. Combined, these outcomes determine the 'net clinical benefit' of a treatment strategy. By combining both sources of information, clinicians and patients are better able to make well-informed decisions concerning which treatment is most suitable for an individual patient.

In this study we describe the HRQoL trajectories in one of the largest RCT's in PCNSL patients and determined whether the addition of rituximab to standard therapy had an impact on HRQoL. Second, we aimed to determine the effect of a lower dose WBRT on HRQoL in this patient population.

METHODS

Study design and patient population

In the HOVON 105/ALLG NHL 24 study, 199 immunocompetent patients aged 18-70 years with a newly diagnosed, CD20 positive B-cell PCNSL were included from Dutch, Australian and New Zealand hospitals between 2010 and 2016.[6] Patients were randomized between two courses of HD-MTX, tenoposide, BCNU and prednisolone without (MBVP) or with rituximab (R-MBVP). Irrespective of treatment arm, this induction regimen was followed by consolidative HD-cytarabine chemotherapy in responding patients, and in patients ≤60 years-old 30Gy WBRT was subsequently added. An integrated boost to the tumour-bed of

10Gy was given to patients who only achieved partial response.[7] (Immuno-)chemotherapy treatment duration was 2.5-3.5 months and WBRT was administered in one month. Further details on the study design and treatment have been published previously.[6] The study was approved by the ethics committees of all participating centres. All participants who signed informed consent for the RCT and for participating in the HRQoL study were eligible for inclusion in this analysis.

Health-Related Quality of Life

HRQoL was one of the prespecified secondary outcomes. HRQoL was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30)[8], and the brain cancer module (QLQ-BN20).[9,10] The QLQ-C30 comprises five functional scales (physical, role, emotional, social and cognitive functioning), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status/quality of life scale, and six single items assessing additional symptoms (dyspnoea, sleep disturbance, appetite loss, constipation and diarrhoea) and perceived financial difficulties. The QLQ-BN20 module includes 20 items, comprising four scales (visual disorders, motor dysfunction, communication deficit and future uncertainty), and seven disease- or toxicity-related symptoms (headache, seizures, drowsiness, hair loss, itchy skin, weakness of the legs, and bladder control).

According to protocol, patients had to complete the questionnaires before starting chemotherapy, after completion of all chemotherapy, after completion of radiotherapy (if given), and 3, 6, 12, and 24 months after completion of protocol treatment. The assessment of HRQoL was stopped when a relapse or progression occurred, or when a patient wanted to withdraw from participation in either the RCT or HRQoL sub-study. Only questionnaires that were completed within a prespecified time window (see Supplemental methods) for each evaluation point were included in the statistical analysis.

STATISTICAL ANALYSIS

Calculation of HRQoL Scores

Following the EORTC procedures, raw item scores were converted to a linear scale ranging from 0 to 100.[11] A difference of ≥10 points on each HRQoL scale/item was defined as clinically relevant.[12] Based on clinical relevance for PCNSL patients, these five scales were selected for primary analysis: three functional scales (global health status (GH), role functioning (RF) and social functioning (SF), with higher scores representing better functioning), and two symptom scales (fatigue and motor dysfunction (MD), with high scores representing worse functioning). Results of the primary analysis (i.e. scores over time assessed with linear mixed models in the 5 predetermined scales, were corrected for

multiple testing. The remaining scales and items were analysed on an exploratory basis. All analyses were conducted with Stata, version 15, and a *P*-value <0·05 was considered to be statistically significant.

Descriptive statistics

Patients eligible for the HOVON 105/ ALLG NHL 24 study who received less than two courses of (R-)MBVP, or did not give consent for the HRQoL sub-study, were excluded from the analysis. We performed a non-response analysis to assess possible imbalances between those who gave consent for the HRQoL sub-study and those who did not with respect to sociodemographic and clinical characteristics.

Differences were tested using a Chi-Square test for categorical data and Mann-Whitney U or independent t-test for continuous data, depending on the distribution of the data. Normality was determined with the Kolmogorov-Smirnov test. In addition, for each time point the compliance was evaluated, defined as the number of completed questionnaires divided by the number of questionnaires expected at that time point. We defined a completed questionnaire as a returned form from which at least a score of one of the predetermined primary scales could be derived.

HRQoL scores over time

At group level, mean changes from baseline were calculated and plotted for those patients who filled in the questionnaire at baseline and at least at one follow-up point. Differences between arms at 12 and 24 months of follow-up were assessed with an independent t-test. A linear mixed model, which allows inclusion of all patients, with fixed effects for treatment arm, time (i.e. evaluation moments) as a categorical covariate, and their interaction, was used to assess whether there is a difference in the HRQoL scores over time between the treatment arms. For each scale, the most suitable covariance structure was chosen to estimate the impact of the treatment on HRQoL over time.

At the individual patient level, changes in HRQoL between baseline and both 12 and 24 months of follow-up were calculated for those patients the questionnaires at these time points were available. Patients were categorized as deteriorated, stable or improved, based on a change of ≥10-points. Differences between treatment arms were assessed with the Chi-square statistic.

Deterioration-free survival and time to deterioration

Deterioration-free survival was defined as a deterioration of ≥10 points on a scale/item compared to baseline without an improvement of ≥10 points at the subsequent HRQoL assessment, or progressive disease (PD), or death in the absence of definite deterioration before the next assessment. Time to deterioration was defined similarly as deterioration-free survival, only excluding PD as an event.[13] PD was defined according to the international

PCNSL response criteria.[7] MRI's were centrally reviewed; the centrally scored progression data were used for these analyses. Questionnaires filled in at the time of or after centrally scored PD were excluded. Kaplan-Meier curves were generated for both deterioration-free survival and time to deterioration and 95% confidence intervals were calculated using the Greenwood formula.

Impact of WBRT

In a subgroup, those who received WBRT (*N*=59), we evaluated the impact of radiation on HRQoL. The mean changes from the 'after WBRT' time point onwards were calculated and linear mixed model analyses were performed to analyse HRQoL scores over the post-WBRT period.

RESULTS

Patients

Of the 199 patients included in the HOVON 105/ALLG NHL 24 trial, 193 (97%) gave informed consent for HRQoL assessment. Eighteen patients were excluded because they did not complete two courses of (R-)MBVP, resulting in 175/199 (88%) eligible patients for the HRQoL analysis. Of these 175 patients included in the HRQoL analysis, 160 completed at least one questionnaire. Compliance of HRQoL evaluation was ≥60% at each time point, except 'after WBRT' in the MBVP-arm (46%), Figure 1.

In the population participating in the HRQoL analysis, patients in the treatment arms were well-balanced with respect to clinical and sociodemographic features and study drug exposure. Those included in this HRQoL analysis had a median age of 61 years (interquartile range 55-66 years), and 74% had a WHO performance score <2, which is similar to the total trial population[6] (Table 1). The non-response analysis showed that there were no significant differences with respect to baseline characteristics between those who gave consent for the HRQoL sub-study and those who did not (Supplemental Table 1). Baseline HRQoL scores for all scales and items for both treatment arms are summarised in Supplemental Table 2.

HRQoL scores over time

In all selected primary scales, the mean change from baseline, assessed in those who filled in the questionnaires at baseline and at least once thereafter, showed a statistically significant (all $P<0.002$) and clinically relevant improvement in both arms after the end of treatment (i.e. 'after chemotherapy' or 'after WBRT'), when compared to baseline, except for fatigue. Fatigue improved more slowly: clinically relevant improvement was not reached before 3 months post-treatment. The differences in scores between the arms at

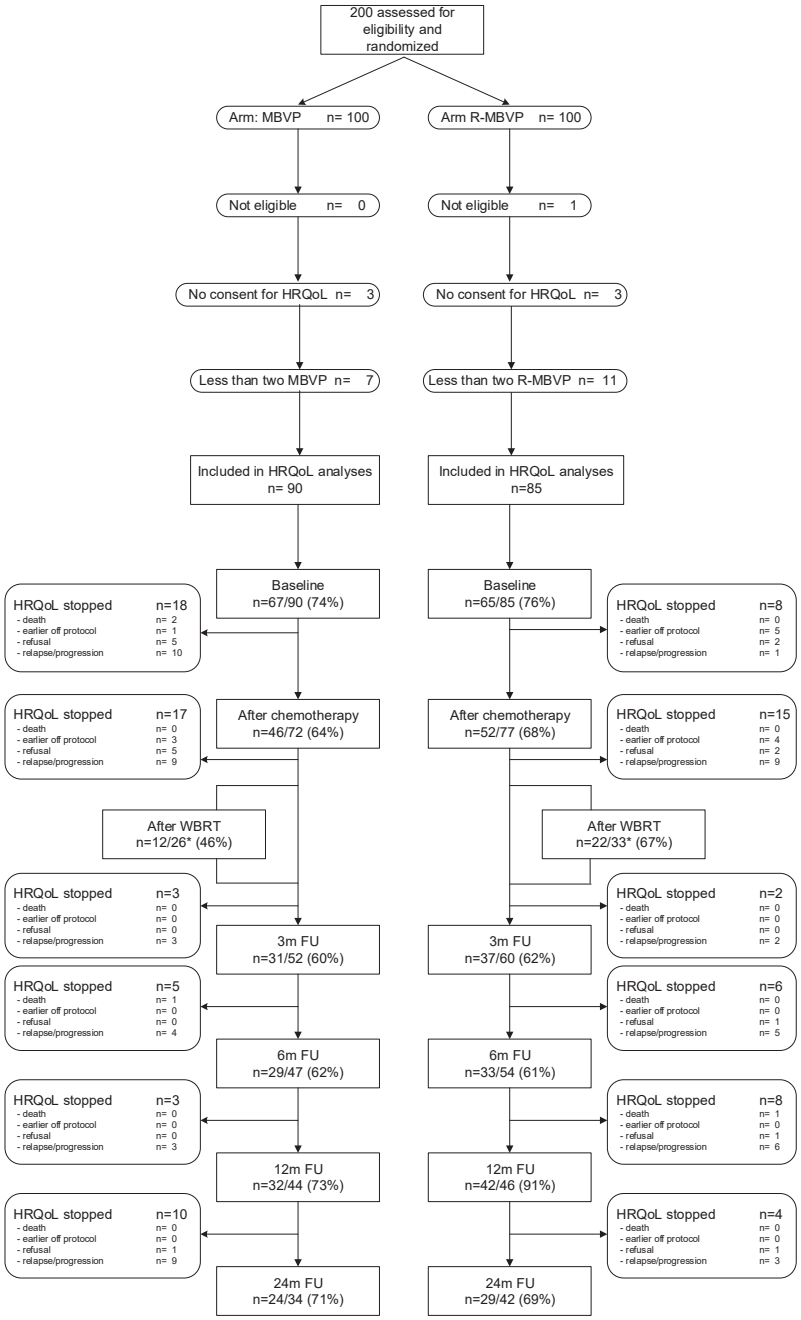

Figure 1. CONSORT Diagram representing the compliance with HRQoL assessments during follow-up, separately for the two treatment arms. FU, months of follow-up after end of treatment; HRQoL, health-related quality of life; MBVP, methotrexate, tenoposide, BCNU (carmustine), and prednisolone; R-MBVP, rituximab with methotrexate, tenoposide, BCNU (carmustine), and prednisolone; WBRT, whole brain radiotherapy. *In those who had WBRT only.

Table 1. Baseline sociodemographic and clinical characteristics of the patients included in the HRQoL analysis.

	MBVP *N*=90	R-MBVP *N*=85
Sex (*N*, % male)	56 (62%)	41 (48%)
Age (median, IQR)	61 (55-66)	61 (55-67)
WHO performance score (*N*, %)		
WHO 0	19 (21%)	23 (27%)
WHO 1	46 (51%)	42 (49%)
WHO 2	15 (17%)	12 (14%)
WHO 3	10 (11%)	8 (9%)
Comorbidities active at baseline (*N*, % ≥2)	54 (60%)	51 (60%)
Solitary lesion (*N*, %)	46 (51%)	44 (52%)
Missing/ NA	10 (11%)	4 (5%)
Bilateral involvement (*N*, %)	33 (37%)	33 (39%)
Missing/ NA	10 (11%)	4 (5%)
Deep structures involved (*N*, %)	55 (61%)	57 (67%)
Study drug exposure		
HD cytarabine (Ara-C) (*N*, %)	82 (91%)	76 (89%)
WBRT (*N*, %)	33 (37%)	34 (40%)
Radiation boost given (*N*, %)	15 (17%)	23 (27%)
Intrathecal treatment given (*N*, %)	8 (9%)	8 (9%)

MBVP, methotrexate, tenoposide, BCNU (carmustine), and prednisolone; R-MBVP, rituximab with methotrexate, tenoposide, BCNU (carmustine), and prednisolone; NA = not applicable in case of no brain lesion(s); IQR = interquartile range; HD = high-dose; WBRT = whole brain radiotherapy; WHO = World Health Organisation

12 and 24 months of follow-up were not statistically significant or clinically relevant for any of the scales. Only fatigue at 12 months post-treatment was clinically relevant worse in the R-MBVP arm, but this was not statistically significant; R-MBVP versus MBVP: -18.1 vs -7.4 (P=0·677). For most exploratory scales and items, similar patterns were observed. See Supplemental Figure 1 and Supplemental Table 3 for the graphs presenting the mean change from baseline over time for all scales/items and the actual mean difference at each time point, respectively.

In a next step, HRQoL scores over time were assessed with linear mixed models, allowing inclusion of all patients as these models impute data at all time points (Figure 2). These analyses showed that the mean HRQoL score improved significantly in all primary selected scales over time in both arms (P<0.001), confirming the previous analyses. We did not find any statistically significant nor clinically relevant differences over time between the treatment arms for any of the preselected scales: overall mean difference over time in MBVP vs R-MBVP: GH=-0.074 (P=0.981), RF=2.160 (P=0.635), SF=0.531 (P=0.902), FA=-3.350 (P=0.378), and MD=2.139 points (P=0.511). The results of the linear mixed models show

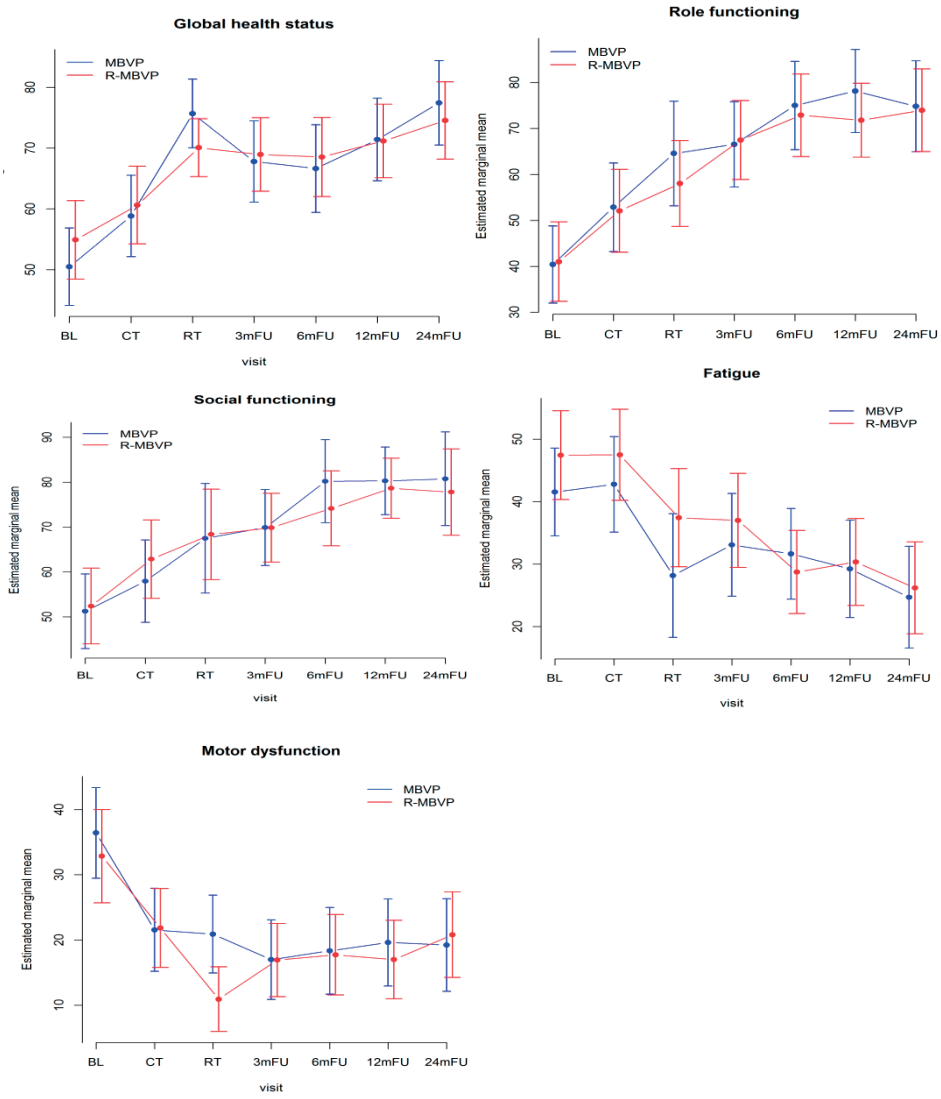

Figure 2. HRQoL scores over time for the five primary scales (A: global health status; B: role functioning; C: social functioning; D: fatigue; E: motor dysfunction), separately for both treatment arms in the total study population, based on results of the linear mixed model analyses. BL, baseline; CT, chemotherapy; FU, follow-up; MBVP, methotrexate, tenoposide, BCNU (carmustine), and prednisolone; R-MBVP, rituximab with methotrexate, tenoposide, BCNU (carmustine), and prednisolone; RT, radiotherapy.

that the largest improvement in scores were between baseline and 'end of treatment', thereafter the scores gradually improved further, but to a lesser extent. GH remained stable from end of treatment until 24 months post-treatment. Exploratory scales and items are shown in Supplemental Figure 2.

Assessing the change from baseline scores at the individual level, in all patients who filled in the questionnaires at baseline and at least at one point thereafter, we observed in a large proportion of patients in both arms an improvement to a clinically relevant extent in HRQoL scores on all primary scales. At 12 months of follow-up, 46-78% of the patients had improved scores compared to baseline and these percentages were between 53-82% at 24 months of follow-up (Figure 3). There were no significant differences between the arms. See Supplemental Table 4 for the exact number of patients who improved, remained stable or deteriorated in both the preselected and exploratory HRQoL scales and items.

Figure 3. **Individual changes in HRQoL from baseline to 12 months and 24 months of follow-up.** FA, fatigue; GH, global health status/quality of life; MBVP, methotrexate, tenoposide, BCNU (carmustine), and prednisolone; MD, motor dysfunction; R-MBVP, rituximab with methotrexate, tenoposide, BCNU (carmustine), and prednisolone; RF, role functioning; SF, social functioning

Deterioration-free survival and time to deterioration

The addition of rituximab to MBVP-chemotherapy did not result in a statistically significant longer deterioration-free survival or time to deterioration in any of the preselected scales. The median deterioration-free survival in RF was not reached. The median deterioration-free survival in MBVP versus R-MBVP were for GH: 19.6 vs not reached, SF: 19.6 vs 22.7, FA: 6.7 vs 6.7, and MD: 4.2 vs 3.8 months. For time to deterioration, the median was not

reached in GH, RF, and SF. Median time to deterioration in MBVP versus R-MBVP in FA was 10.2 vs 7.5 and MD: 4.7 vs 3.8 months. See Figure 4 for the deterioration-free survival and time to deterioration for GH and Supplemental Figure 3 and Supplemental Table 5 for the remaining primary scales/items.

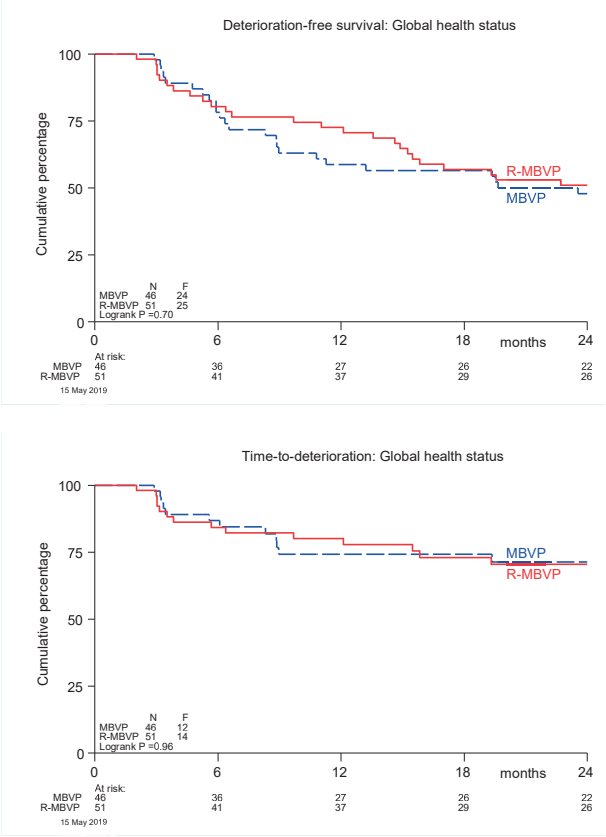

Figure 4. Deterioration-free survival and time-to deterioration for Global health status (GH), separately for the treatment arms. MBVP, methotrexate, tenoposide, BCNU (carmustine), and prednisolone; R-MBVP, rituximab with methotrexate, tenoposide, BCNU (carmustine), and prednisolone.

Impact of WBRT

Seventy patients received WBRT, of whom 59 participated in the HRQoL evaluation. The linear mixed model analysis (which allows inclusion of all 59 patients) showed no statistically significant change over time after WBRT up to 24 months, except for a deterioration in MD (*P*=0.048). There were no significant differences between treatment arms: overall mean difference MBVP vs R-MBVP GH=1.951 (*P*=0.694), RF=4.570 (*P*=0.542), SF=3.007 (*P*=0.677), FA=-1.887 (*P*=0.776), and MD=0.020 (*P*=0.997), see Figure 5.

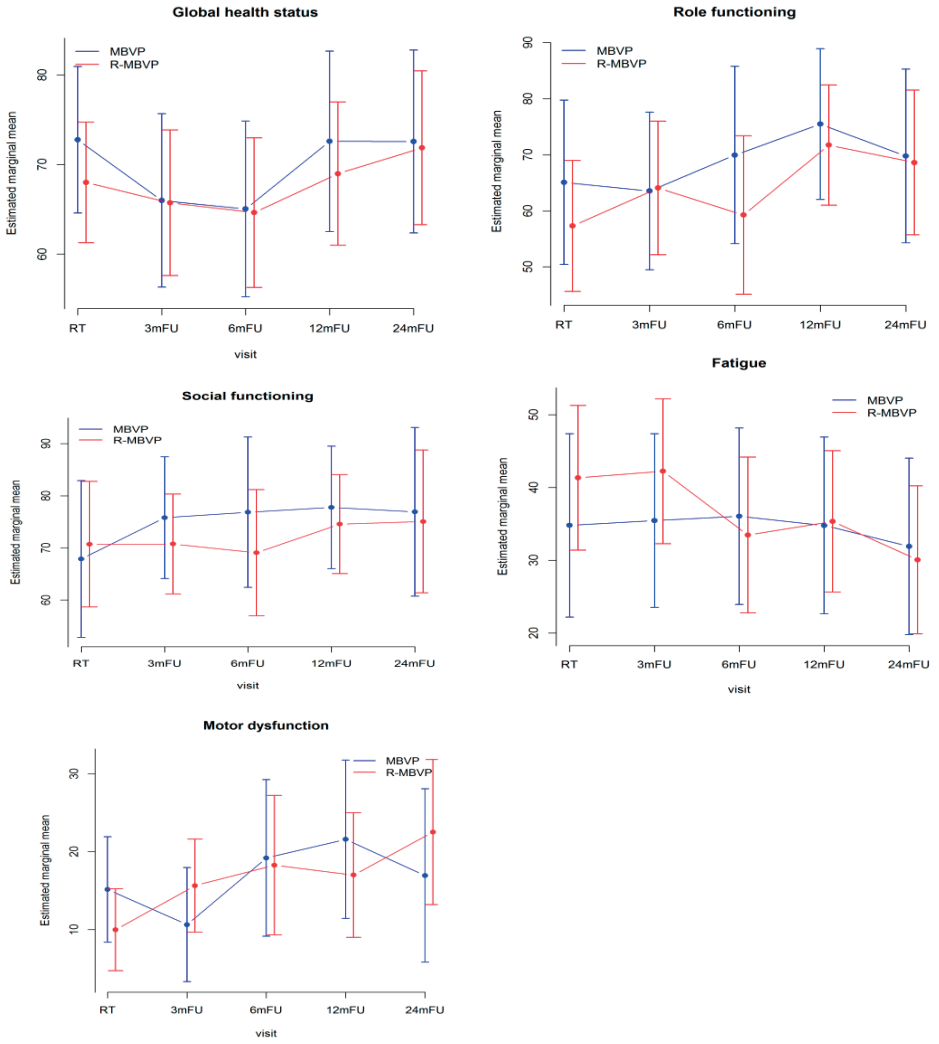

Figure 5. HRQoL scores from post-WBRT up to 24 months follow-up for the preselected scales (A: global health status; B: role functioning; C: social functioning; D: fatigue; E: motor dysfunction), separately for the treatment arms, in the irradiated patients only (n=59). Estimated marginal means for each evaluation point by treatment arm, where the vertical bars represent 95% confidence interval of the group mean. FU, follow-up; MBVP, methotrexate, tenoposide, BCNU (carmustine), and prednisolone; R-MBVP, rituximab with methotrexate, tenoposide, BCNU (carmustine), andprednisolone; RT, radiotherapy

The change in HRQoL from WBRT onwards was only determined in those patients who were irradiated and who filled in the questionnaires at the evaluation 'after WBRT' and at least at one of the follow-up evaluations (*N*=34). This subpopulation was comparable to the total irradiated population (data not shown). We observed an improvement (>10 points) in RF in both arms (*P*=0.002), from 62.1 after WBRT to 78.8 at 24 months follow-up

in the R-MBVP arm, and from 65.3 to 77.5 in the MBVP arm. Scores in the other preselected scales remained stable in both treatment arms (see Supplemental Figure 4 for the preselected scales).

DISCUSSION

In the HOVON 105/ALLG NHL 24 trial, the addition of rituximab to standard chemotherapy in adult PCNSL patients did not prolong EFS or PFS; in this HRQoL analysis in 160 patients (80% of total study population), we showed that the addition of rituximab did not improve or deteriorate the patients' functioning and well-being either. We did, however, observe that anti-tumour treatment resulted in improvements in HRQoL, which were statistically significant and clinically relevant, but did not differ between patients treated with or without rituximab.

The largest improvements in HRQoL were observed directly after treatment (i.e. after induction chemotherapy with or without rituximab and after consolidation with WBRT if given). Thereafter, HRQoL scores remained relatively stable or improved more slowly, but gradually over time. Other non-randomized studies investigating the effect of chemotherapy and/or chemotherapy with rituximab on HRQoL have described a similar pattern: an initial improvement after treatment, followed by stabilization of HRQoL scores up to three years of follow-up.[14-16] Two small studies (in which 12/52 and 16/33 of the patients participated in the HRQoL sub-study) even showed an ongoing improvement in HRQoL scores (as measured with the FACT-Br) up to 12[17] and 24 months of follow-up.[18] Clinical relevance of this change was, however, not defined. Nevertheless, this pattern suggests that HRQoL in PSCNL patients is mainly compromised by the lymphoma itself rather than by the treatment, and that treating the tumour improves patient-reported HRQoL.

Mean baseline HRQoL scores in our cohort are much lower (≥20 points) than in the general population,[19] and also lower (≥10 points) than in patients with brain metastases, low-grade glioma and glioblastoma.[20-22] HRQoL scores in our population improved significantly over time, to levels of the general population for some scales, whereas scores in low and high-grade glioma patients typically remain stable up to 24 months of follow-up.[21,22] The non-significant differences between treatment arms in deterioration-free survival and time to deterioration for any of the HRQoL scales suggest that treatment itself did not cause a major deterioration in HRQoL.

WBRT as consolidation treatment is under debate because of its presumed negative effect on neurocognitive functioning and subsequently on HRQoL.[23] Surprisingly, we found that the HRQoL scores of those patients receiving radiation remained stable for up to two years of follow-up after WBRT, suggesting that the WBRT dose (30Gy) used in this study does not compromise HRQoL in patients up to 60 years in the period covered by this analy-

sis, despite the fact that 17% of the patients in the MBVP-arm and 27% in the R-MBVP arm also received an integrated boost of 10Gy to the tumor-bed. A possible explanation for the stable HRQoL in our cohort after WBRT may be that the 24 month period in our study is too short to develop radiation-induced damage detectable with HRQoL instruments, or that the lower radiation dose is less detrimental. Our findings are supported by a study by Correa et al. in which patients treated with R-MPV followed by low-dose WBRT (23.4Gy) also remained stable in their HRQoL scores, even up to five years of follow-up.[24] Only a small number of patients could be analysed in our sub analysis and results should therefore be interpreted with caution. In addition, patients who received WBRT could not be compared directly to those who did not receive WBRT because of the age difference between the irradiated and non-irradiated patients. Thus, although our results cannot be generalized and follow-up is still short, our results do challenge the negative role of a relatively low-dose WBRT in this younger subpopulation.

The strengths of our study are the size and standardized treatment of the population studied, the use of validated measures for brain cancer patients, the fact that the majority of this trial population participated in the HRQoL sub-study and that the compliance at every time point was relatively high (>60%). Nevertheless, the actual number of patients who filled in the questionnaires was relatively low at 12 and 24 months of follow-up (*N*=74 and *N*=53, respectively) due to progression or death, and patients filling out the questionnaires might have a higher level of functioning and well-being than those not filling-out the questionnaires. Also, HRQoL was not systematically assessed at the moment of and beyond progression, hampering information on the impact of progression on HRQoL in this patient population. Another limitation is possible selection bias, because we analysed (subgroups of) a trial population and results may therefore not be generalizable to all patients. However, most patients in the trial also participated in the HRQoL sub-study and only those who did not tolerate two complete courses of (R-)MBVP were excluded. Lastly, the impact of treatment on neurocognition is important in this patient population, and will be described in a separate publication.

In conclusion, HRQoL scores improved after treatment but were not impacted by the addition of rituximab to standard chemotherapy in adult PCNSL patients. Secondly, treatment with 30Gy WBRT did not reduce HRQOL in the first two years after treatment in patients up to 60 years old.

For supplemental Tables and Figures: Health-related quality of life after chemotherapy with or without rituximab in primary central nervous system lymphoma patients: results from a randomised phase III study - ScienceDirect
https://www.sciencedirect.com/science/article/pii/S0923753420393133

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PART IV

Prognosis

9

MMSE is an independent prognostic factor in primary central nervous system lymphoma patients

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ABSTRACT

Objective: To assess the value of the Mini-Mental State Examination (MMSE)-score at baseline in predicting survival in adult primary central nervous system lymphoma (PCNSL) patients.

Methods: In the HOVON 105/ ALLG NHL 24 phase III study patients with newly-diagnosed PCNSL were randomized between high-dose methotrexate-based chemotherapy with or without rituximab. Data on potential (MMSE-score), and known baseline prognostic factors (age, performance status, serum LDH, cerebrospinal fluid (CSF) total protein, involvement of deep brain structures, and multiple cerebral lesions) were collected prospectively. Multivariate stepwise Cox regression analyses were used to assess the prognostic value of all factors on progression free survival (PFS) and overall survival (OS) among patients with available MMSE score at baseline. Age was analysed as continuous variable, the MMSE-score both as a continuous and as a categorical variable.

Results: In univariate analysis, age, MMSE-score and whether the patient received rituximab were statistically significantly prognostic factors for PFS. Age and MMSE-score were statistically significantly associated with OS. In a multivariate analysis of the univariately significant factors only MMSE-score was independently associated with the survival endpoints, as a continuous variable (HR for PFS 1.04, 95% CI 1.01-1.08; OS 1.06 (95% CI 1.02-1.10) and as categorical variable HR (<27 versus ≥27 for PFS 1.55 (1.02-2.35); OS 1.68 (1.05-2.70). In our population, performance status, serum LDH, and CSF protein level were not of prognostic value.

Conclusion: Neurocognitive disturbances, measured with the MMSE at baseline, are an unfavourable prognostic factor for both PFS and OS in adult PCNSL patients up to 70 years-old.

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is a rare non-Hodgkin lymphoma confined to the brain, leptomeninges, spinal cord and eyes. Over the last decades prognosis has improved significantly.[1] Although several prognostic factors have been identified and prognostic models have been developed, it remains difficult to predict the prognosis of individual patients.

Two prognostic models are currently widely used in PCNSL patients: the externally validated Memorial Sloan Kettering Cancer Center (MSKCC) prognostic score:[2]age (>50 years-old) and Karnofsky Performance score (KPS; <70), and the International Extranodal Lymphoma Study Group (IELSG) score: age (>60 years-old), WHO/ECOG Performance Status (PS; >1), Lactate dehydrogenase (LDH) serum level, cerebrospinal fluid (CSF) protein level and involvement of deep brain structures.[3]

The Mini-Mental State Examination (MMSE)[4] is a crude screening tool for neurocognitive impairment. In high-grade glioma, the MMSE-score was an independent prognostic factor for both progression free survival (PFS) and overall survival (OS).[5]

In PCNSL patients, data regarding the prognostic value of the MMSE are scarce, despite the fact that cognitive symptoms occur frequently (up to 43%) in this disease.[6] One study describes 95 elderly (>60 years-old) PCNSL patients, and found that MMSE-score ≤24 was the only independent prognostic factor for OS, while age and PS were not.[7] In the present study we aimed to assess whether the MMSE-score at baseline was independently prognostic for both PFS and OS, in a large trial population with adult PCNSL patients up to 70 years-old.

METHODS

Patients in the HOVON 105/ALLG NHL 24 study, a large multicentre phase III randomized controlled trial (RCT) for immunocompetent adult patients with newly diagnosed CD20 positive B-cell PCNSL with WHO/ECOG PS 0-3, were included.[8] The treatment regimen consisted of two cycles of high-dose methotrexate-based chemotherapy, with or without rituximab, followed by high-dose-cytarabine. Patients <61 years-old subsequently received 30Gy whole brain radiotherapy. The study was approved by the ethics committee at all participating centres and all participants gave informed consent. Patients underwent an MMSE if possible and baseline scores were obtained before chemotherapy was started.

All patients for whom an MMSE-score at baseline was available were included in this study. In addition, the following information was collected: sex, age, WHO/ECOG PS, CSF protein and serum LDH levels at baseline and whether the patient had multiple cerebral lesions, involvement of deep brain structures (periventricular regions, basal ganglia, brainstem and/ or cerebellum), and whether they received rituximab.

First, possible imbalances were assessed with respect to baseline characteristics, treatment details and survival between those who participated in this side-study and those who could not due to missing MMSE-scores at baseline.

Subsequently, all the above mentioned prognostic factors were assessed separately for association with PFS and OS using univariate Cox regression analysis. PFS was defined as time from randomization to progression, relapse or death from any cause, whichever came first. OS was defined as time from randomization to death from any cause.[8] Patients still alive at the date of last contact were censored. MMSE was included both as a continuous variable and as categorical variable (<27 or ≥27). Age was included as a continuous variable. ECOG status (≤1 versus >1), serum LDH (above versus below local upper limit of normal), and CSF protein (above versus below cut-off values according to the IELSG score[3]) were included as categorical variables. Factors that were statistically significant in univariate analysis were included in the stepwise multivariate Cox proportional hazards models. A p-value <0.05 was considered statistically significant. All analyses were performed with Stata version 15.

Data availability statement

Individual de-identified participant data, collected for this study, including the statistical analysis plan will be made available for other research to others upon request, after approval by the HOVON executive board. The data will be available until a maximum of 15 years after the study has ended.

Please find the trial protocol, a Data Request Form and the criteria for data sharing on www.hovon.nl.

RESULTS

MMSE-score at baseline was available for 153 of the 199 (77%) trial patients. Baseline characteristics and survival were comparable between those who were included and were not, Supplemental Table 1 and Supplemental Figure 1A and B.

In the univariate regression analyses age, receipt of rituximab and baseline MMSE-score were associated with PFS. Only age and MMSE were statistically significant predictors of OS (Table 1). In multivariate analysis, only MMSE-score at baseline was independently associated with both PFS and OS. We found that each unit decrease in MMSE-score was associated with a poorer prognosis: for PFS (Hazard Ratio [HR], 95% confidence interval [CI] 1.04, 1.01-1.08) and OS (HR, 95% CI: 1.06, 1.02-1.10), Table 2. When including the MMSE-score as categorical variable in multivariate analyses, corrected for age and rituximab, a baseline-score <27 (as compared to a score ≥27) was the only factor associated with PFS (HR 1.55, 95% CI: 1.02-2.35) and overall survival (HR 1.68, 95% CI: 1.05-2.70), Table 2 and Figure 1.

Table 1. Univariate and multivariate Cox regression analysis for all risk factors with MMSE as a continuous variable for the progression-free survival and overall survival.

Progression-free survival					
		Univariate		Multivariate	
	n	HR (95% CI)	p	HR (95% CI)	p
Female	153	0.85 (0.57-1.28)	0.44		
Age (increase; unit = 10 years)	153	1.33 (1.04-1.71)	0.025	1.28 (0.99-1.65)	0.061
WHO/ECOG >1	153	0.92 (0.57-1.50)	0.74		
Multiple lesions	138	0.89 (0.58-1.37)	0.59		
Deep structures involved	153	1.39 (0.92-2.09)	0.12		
Elevated CSF total protein	93	0.78 (0.45-1.37)	0.40		
LDH >ULN	153	1.19 (0.77-1.82)	0.44		
Rituximab	153	0.66 (0.44-1.00)	0.049	0.69 (0.45-1.04)	0.075
MMSE (decrease unit = 1 point)	153	1.05 (1.01-1.08)	0.0042	1.04 (1.01-1.08)	0.008
Overall survival					
		Univariate		Multivariate	
	n	HR (95% CI)	p	HR (95% CI)	p
Female	153	1.12 (0.71-1.76)	0.64		
Age (increase; unit = 10 years)	153	1.36 (1.02-1.82)	0.036	1.32 (0.97-1.77)	0.069
WHO/ECOG >1	153	1.29 (0.77-2.16)	0.32		
Multiple lesions	138	1.01 (0.62-1.63)	0.97		
Deep structures involved	153	1.25 (0.79-1.99)	0.34		
Elevated CSF total protein	93	0.64 (0.33-1.26)	0.20		
LDH >ULN	153	1.15 (0.71-1.88)	0.57		
Rituximab	153	0.86 (0.55-1.35)	0.51		
MMSE decrease unit = 1 point)	153	1.06 (1.02-1.10)	0.001	1.06 (1.02-1.10)	0.002

Hazard ratio's (HR) and 95% confidence intervals (CI) are shown with their p-value. WHO = World Health Organization, ECOG = Eastern Cooperative Oncology Group, CSF = cerebrospinal fluid, LDH = lactate dehydrogenase, ULN = upper limit of normal, MMSE = mini-mental state examination.

Table 2. Multivariate Cox regression analysis for univariately significant risk factors with MMSE as a categorical variable for the progression-free survival and overall survival.

Progression-free survival		
	Multivariate	
	HR (95% CI)	p
Age (increase; unit = 10 years)	1.24 (0.95-1.60)	0.109
Rituximab	0.70 (0.47-1.05)	0.087
MMSE <27	1.55 (1.02-2.35)	0.040
Overall survival		
	Multivariate	
	HR (95% CI)	p
Age (increase; unit = 10 years)	1.26 (0.94-1.71)	0.127
MMSE <27	1.68 (1.05-2.70)	0.031

Hazard ratio's (HR) and 95% confidence intervals (CI) are shown with their p-value. MMSE = mini-mental state examination.

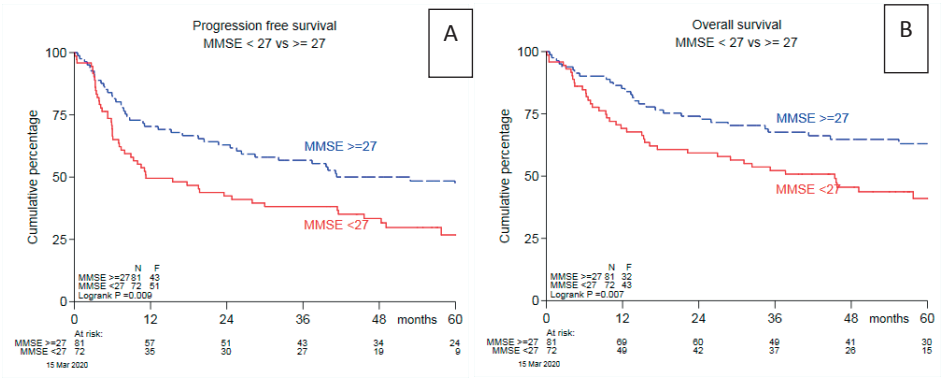

Figure 1. A. Progression free survival and B. Overall survival for those with an MMSE-score of <27 and ≥27 at baseline.

DISCUSSION

In this large, prospectively examined study-population of PCNSL patients, we showed that the MMSE-score at baseline, both as a continuous variable and as a categorical variable (<27), is an independent prognostic factor for both PFS and OS.. Interestingly, MMSE was not evaluated in either of the two most-used prognostic scores in PCNSL but our data suggest this factor is the most valuable for predicting outcome.[2,3]

Our results are consistent with a previously published analysis performed in elderly PCNSL patients: those with an MMSE-score ≤24 had a worse OS than those with a score >24.[7] Moreover, in a recent RCT among over 60 year-olds the Mattis Dementia Rating Scale, another screening tool for neurocognitive impairment, was significantly associated with OS, though in univariate analysis only. In multivariate analysis, only WHO/ECOG PS was associated with both PFS and OS.[9]

Age and PS are common prognostic factors in oncology patients. In our study, both factors were not independently prognostic for survival in multivariate analysis, although age showed a trend towards significance both for PFS (p=0.061) and OS (p=0.069). For age, this might be explained by the small number of patients ≤50 years-old and the exclusion of patients >70-years-old in this study. Some other studies also did not find a prognostic effect of age, even as categorical variable, although these studies included only younger or only elderly patients.[7,9,10] Categorizing age has been very useful for stratifying patients in clinical trials, but ageing is a continuous process. So, from a biological perspective, it is more logical to include age as a continuous variable. In addition, continuous variables yields more statistical power. Similarly, in contrast to most other studies[2,3,9] we did not find an effect of the WHO/ECOG PS on survival. Of note, patients with a WHO/ECOG PS of 4 were ineligible. Although some other studies[7,10] also did not identify a prognostic effect of performance status, it remains unexpected.

The major strength of our study is the prospective data collection within a large clinical trial resulting in MMSE-scores for the majority of patients and a uniform treatment and evaluation protocol. A limitation is the relatively small number of patients for prognostication; our sample size is smaller than that in the MSKCC (n=238) and IELSG models (n=378). A down-side of all studies based on trial patients is that findings may not be generalizable to the whole PCNSL population.

To conclude, the MMSE is an easily assessable and relevant clinical factor which has not been included in prior prognostic studies in patients with PCNSL. In this dataset the MMSE-score at baseline is an independent clinical prognostic factor in adult PCNSL patients up to 70-years-old. If validated in another large population, patients should be counselled with this effect in mind, and other prognostic scores should be re-evaluated.

For supplemental Tables and Figures: MMSE is an independent prognostic factor for survival in primary central nervous system lymphoma | SpringerLink
https://link.springer.com/article/10.1007/s11060-021-03708-8

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10

General discussion

Epidemiology

Primary central nervous system lymphoma is a rare disease and due to stringent inclusion criteria in clinical trials, large population-based studies can complement data from prospective intervention studies by addressing an unbiased group of patients within a well-defined geographic area. In **chapter 2** we described the incidence, primary treatment and survival among 1,673 PCNSL patients diagnosed in the Netherlands between 1989 and 2015 using the comprehensive data of the Netherlands Cancer Registry (NCR). We showed that the incidence of primary central nervous system lymphoma increased, but only among those over the age of 60. Two major factors have been identified as risk factors for PCNSL: being immunocompromised and higher age. However, the incidence increased mainly among immunocompetent patients and although the population in the Netherlands is ageing, the incidence of systemic lymphoma and of glioma did not increase as much as the incidence of PCNSL.[1,2] Other population-based studies in Western and Eastern countries described similar trends in incidence and survival, also without an explanation for the increased incidence.[3-5] So it remains undermined which factors contributed to this increase.

Survival in PCNSL has improved over the last decades. In this study on 1,673 patients we showed that the 5-year relative survival rate, correcting for survival in the general population increased from 11% (95% confidence interval [CI] 8-15%) to 30% (95% CI 27-34%) over the past 30 years. However, this increased survival was observed only among those below the age of 70. In a multivariate regression analysis we demonstrated that age and treatment were significantly associated with survival; more chemotherapy was associated with better survival. Survival in patients over 70 remained poor, with a 5-year relative survival rate of 6% (95% confidence interval [CI] 2-13%) in 2009-2015. This poor survival among elderly PCNSL patients is also described in a population-based study on nearly 26,000 elderly in the United States, based on the Central Brain Tumor Registry of the United States (CBTRUS) and Surveillance, Epidemiology, and End Results (SEER) database, entitled 'The elderly left behind'.[6]

In **chapter 3** we described the primary treatment and survival of 145 elderly (>70 year-old) patients with PCNSL diagnosed in the Netherlands between 2014 and 2017. Overall, median overall survival was only 4.1 months (95% CI, 2.8-6.8) After dividing the elderly into three groups (71-74, 75-80, >80 years-old) we found no difference in survival between these three groups. This might be explained by small numbers (n=58-32) in each group, the poor survival even in the youngest of these age groups, or other factors, such as performance status or comorbidity. Details on the latter two factors are, unfortunately, incomplete. We found that over the last 27 years, the increased use of chemotherapy did not result in an improved survival among over 70 year-olds. In the contemporary era (2014-2017), however, those elderly patients (>70 years-old) judged fit enough to receive chemotherapy had a better overall survival (median: 16.3 months, 95% CI 7.8-35.2) than

those who received radiotherapy only (median 7.7 months, 95% CI 4.6-13.2) or supportive care only (median 1.4 months, 95% CI 1.1-1.7). Siegal and Bairey, who summarized trials done in elderly PCNSL patients, described the treatment challenges in elderly.[7] First, elderly are defined differently in the performed trials, which complicates clear treatment recommendations for elderly PCNSL patients. Second, although methotrexate causes more treatment-related toxicities in elderly patients, a considerable number of elderly patients are nevertheless eligible for this important antineoplastic treatment in PCNSL. The key here is to identify those who are too much at risk for treatment-related toxicity and those who are not. In line with these authors we concluded that new prospective studies are needed to define the best treatment for different groups of elderly diagnosed with PCNSL.

Diagnostic evaluation

Before a long, intensive and potentially toxic treatment for PCNSL can be initiated, a definitive diagnosis is essential. This diagnosis can be obtained by the examination of vitreous fluid in case of eye involvement, of cerebrospinal fluid (CSF) or by a brain biopsy. Flow cytometry on CSF, in addition to cytological analysis, is more sensitive than cytology alone.[8-10] In **chapter 4** we showed that flow cytometry analysis on brain biopsies has a 100%-specificity for the diagnosis of lymphoma, but sensitivity was only 88%. A major added value of flow cytometry on brain biopsies was the speed in which a diagnosis could be given: median time in days (range) was 1 (0-7) for flow cytometry and 5 (0-18) for histology and immunohistochemistry. Because of the highly aggressive nature of PCNSL, patients can quickly deteriorate, and a faster diagnostic process is therefore beneficial. Our analysis was limited by a retrospective single centre design, but two smaller series, one on brain biopsies and one on brain biopsy rinse fluid, gave the same results.[11,12] We recommend to perform both, histology and immunohistochemistry and flow cytometry, if the latter is positive for a lymphoma, treatment steps can be initiated.

After treatment is initiated it is important to measure treatment response, in order to be able to adapt treatment in patients not responding sufficiently. According to current guidelines, an MRI is made at baseline, after each treatment component, and during follow-up.[13,14] After treatment and during follow-up response criteria are used to determine whether there is a response, what the extent of response is, or whether there is stable or progressive disease (progression or relapse).[14] Since PCNSL is a rare disease, most hospitals have limited experience in assessing radiological response in PCNSL. Most treatment decisions, however, are based on these response criteria. In **chapter 5** we assessed the value of a central radiology review based on patients treated in the HOVON 105/ ALLG NHL 24 study, an international multicentre phase III study on the effect of rituximab in newly diagnosed patients with PCNSL.[15] In 235 MRIs made after each treatment component, the interobserver agreement was rather modest and similar between the two central radiology reviewers and between local and central response assessment: kappa 0.45.

Even between the experienced central reviewers we observed great discrepancies (e.g. complete response versus partial response). However, interobserver agreement regarding progression or no progression was excellent between the central reviewers (kappa 0.93) as well as between local and central radiology assessment (kappa 0.86). Together, these data suggest that there is little added value of a central radiology review in PCNSL trial for assessing progression and that response categorisation is not straightforward.

Based on the treatment response at the end-of-treatment MRIs we did a landmark analysis based on the central response assessment: there were no differences in progression free survival or overall survival between those categorized as complete response (CR), complete response unconfirmed (CRu) or partial response (PR) at 6.9 months after randomization (the landmark). Since progression can be clearly recognized and no differences in survival was found between different types of response, this suggests that survival endpoints are more reliable in clinical trials than the complete response rate. Other articles did find a difference between those categorized as CR versus no CR.[16,17] However, in these studies a landmark analysis was not performed and patients who did not respond (SD) or even already had progression were included in the 'no CR' group. One article describes a landmark analysis and found a significant difference between response categories, however, all response category: CR, CRu and PR, but also stable disease and progression were compared with each other in a single log-rank test.[18] Our study concerns a modest number of patients and results would need to be validated in a larger cohort. However if validated, the response criteria could be simplified into: response, defined as a decrease of enhancement of >50%, stable disease or progression.

Cognition and health-related quality of life

In the HOVON 105/ ALLG NHL 24 study, 199 immunocompetent patients with a newly diagnosed CD20+ B-cell PCNSL and aged between 18-70 years-old were randomized 1:1 between high-dose methotrexate based chemotherapy (MBVP) with or without rituximab: R-MBVP versus MBVP.[15] This induction treatment was followed by consolidative high-dose cytarabine (Ara-C), and for patients ≤60 years-old also by reduced dose (30Gy) whole-brain radiotherapy (WBRT). The primary endpoint of this study, the 1-year event-free survival, did not differ between the treatment arms: R-MBVP versus MBVP: 52% (95% CI 42-61) versus 49% (95% CI 39-58), p=0.99. Moreover, the progression-free survival and overall survival, after a median follow-up of 32.9 months, also did not differ. Secondary endpoints of this randomized controlled trial were differences in neurocognitive function and health-related quality of life (HRQoL). In the search for the best treatment the aim is to prolong both the length of survival and the quality of survival. The latter can be influenced by neurocognitive functioning and HRQoL. Information about both, survival and quality of survival – the net clinical benefit - can help physicians and patients to make a well-informed decision regarding individual treatment options.

In **chapter 6** we systematically reviewed the current literature on neurocognitive functioning and HRQoL in PCNSL patients. The main conclusions were that the tumor itself had a large impact on both cognitive functioning and HRQoL, and that WBRT in addition to chemotherapy had a negative impact on cognitive functioning. However, the magnitude of this effectt was mostly not considered clinically relevant (with clinical relevance defined as a change in z-score of >1 or >1.5 standard deviation).

In the HOVON 105/ ALLG NHL 24, neurocognitive functioning and HRQoL was assessed before, during and up to 2-years after treatment. At group level, we found a significant improvement over time in all cognitive domains (**chapter 7**) and all primary scales of the HRQoL analysis (**chapter 8**), without differences between the treatment arms. In addition to a statistically significant improvement, at 12 and 24 months of follow-up, HRQoL-scores also improved to a clinically relevant extent (≥10 points), compared to baseline. The largest improvement was seen between baseline and end-of-treatment, thereafter scores remained stable, which is a pattern that has been described in other studies.[19-24] Again, this suggests that neurocognitive functioning and HRQoL is mostly compromised by the tumor itself.

At the individual level, we observed that scores at 12 months after treatment in all cognitive domains, compared to baseline, improved in 33-58% of the patients. After 24 months, 53% had improved scores in the memory and 68% in motor speed domain. For attention/executive functioning and information processing speed most patients remained stable: 59% and 48%, respectively. Only a minority of patients had worse neurocognitive functioning at 12 and 24 months (0-7%).In the HRQoL analysis, at individual level, the majority improved at 12 (46-78%) and 24 (53-82%) months post-treatment, compared to baseline.

In irradiated patients we observed, surprisingly, that up to 2 years post-treatment, scores in all cognitive domains and HRQoL scales remained stable, compared to shortly after WBRT. The role of WBRT in the treatment of PCNSL continues to be under debate, mainly because of its negative effect on neurocognitive functioning. Since only younger patients (≤60 years-old) received WBRT, our results cannot be generalized to the PCNSL patients of all ages. The effect of WBRT, both on survival and cognitive functioning has been assessed in multiples studies, but in different ways.[16,19-21] WBRT prolonged progression free survival when WBRT was added to high-dose methotrexate (HD-MTX) chemotherapy, compared to chemotherapy only in a large randomised study: 18 versus 12 months, although overall survival was similar between both groups.[16] However, more neurotoxicity, unfortunately only measured with clinical and radiological examinations, was found in those treated with 45Gy WBRT compared radiation naïve patients. Formal cognitive testing was not performed. A meta-analysis showed that those who received WBRT (45-60Gy; n=65) had more white matter lesions and significantly worse scores on multiple cognitive domains, compared to those treated without WBRT (n=15, $p<0.001$). These differences were,

however, small and not clinically relevant.[25] This comparison was made after a median follow-up of 5.5 years, range 2-26 years.

Two recent trials randomized PCNSL patients responding to induction chemotherapy, to WBRT or to autologous stem cell transplantation (ASCT).[20,21] Both showed significantly better neurocognitive functioning in the ASCT-arm, up to two[20] and three[21] years of follow-up. Both studies used a higher dose of radiotherapy (36-40 Gy), neither presented individual scores or standardised scores of neurocognitive functioning and HRQoL was not performed[21] or reported on.[20] This hampers conclusions about the clinical relevance of the changes in neurocognitive functioning and the comparison with our data.

Lastly, a single arm phase II study showed that HD-MTX-based chemotherapy followed by 23.4Gy WBRT gave similar survival compared to earlier trials with higher doses of radiation, and with neurocognitive functioning remaining stable even up to 5-years post-treatment.[26] These results are in line with our study: patients ≤60 years-old, were treated with 30Gy WBRT (20x1.5Gy) and remained stable during the follow-up of 2 years. These findings suggest that radiation dose is crucial in the effect of cognitive functioning in PCNSL patients. However, longer follow-up is necessary to draw definitive conclusions on neurocognitive function after 30Gy WBRT in our population.

In patients for whom a neuropsychological evaluation and MRI images were available at end-of-treatment, at 6, 12 and/or 24 months of follow-up we determined the correlation between white matter abnormalities (WMA) and brain atrophy on changes (i.e. deterioration) in each cognitive domain. There was a significant association between an increase in WMA and a decrease in z-score in the domains of attention/executive functioning, information processing speed and motor speed and between brain atrophy and the domain of memory. The associations were modest, the regression coefficients ranged between -0.048 and -0.921, which is the decrease in z-score after an increase of 1 point in the Fazekas[27] sumscore for white matter lesions (the Fazekas score in 5 brain areas on both sides (0-30)) or after a decrease in brain volume with 10%. One study, which combined data on neurocognitive functioning and WMA from multiple studies, also showed a significant effect between increased WMA and decreased neurocognitive functioning.[25]

Prognosis

As discussed in chapter 2, the prognosis of PCNSL patients has improved significantly over the past decades. Despite the fact that multiple prognostic models[28-30] and prognostic factors[31-35] have been described, it remains difficult to predict survival for individual patients. The two most used prognostic models today are the externally validated Memorial Sloan Kettering Cancer Center (MSKCC) prognostic model, including only age (>50) and Karnofsky Performance Score (PS; >70) and the International Extranodal Lymphoma Study Group (IELSG) score, including age (>60), WHO/ECOG PS (>1), the involvement of deep

brain structures, increased serum LDH and/ or increased cerebrospinal fluid (CSF) total protein.[36,37]

The Mini-Mental State Examination (MMSE[38]) score, a simple bedside test originally developed for patients with dementia, is a prognostic factor in both low and high-grade glioma.[39,40] In **chapter 9** we showed that, based on HOVON 105/ALLG NHL 24 trial patients, the MMSE-score at baseline, i.e. before the start of chemotherapy, is an independent prognostic factor associated with progression free and overall survival in PCNSL patients up to the age of 70.

Interestingly age and performance status were not independent prognostic factors in our multivariate analysis. Several factors could explain the discrepancy between our results in this prognostic study, the population-based studies[3,41] and the MSKCC and IELSG scores.[36,37] The small number of patients included below the age of 50 and the exclusion of those over 70 years-old in the trial, as well as the relatively small number of patients might play a role. The other four studies were larger (n=238-3,100) than ours (n=153), and thus had more power to detect correlations. Furthermore, there may be an interaction between age, performance status and cognition – all significant in univariate analysis, resulting in only one of them remaining significant in multivariate analysis. Lastly, prospective clinical trials use stringent inclusion criteria regarding age, performance status and comorbidity.

Future directions

Given the data from recent randomized phase II trials,[20,21] which showed a comparable efficacy but less cognitive deterioration in patients treated with autologous stem cell transplantation (ASCT), probably fewer PCNSL patients, will receive WBRT as consolidative therapy in the near future. However, reduced dose WBRT could be a reasonable option for some patients, given the above described results, if cognition remains stable even with longer-term follow-up. For elderly or frail patients, in whom neither WBRT nor ASCT are therapeutic options, maintenance therapy is under investigation.[45,46] All considered options have advantages and disadvantages, which are influenced by age, comorbidity and immune status. Taking all these factors into account, treatment will likely become more personalized.

It is becoming more and more clear that not only the length but also the quality of survival counts. Combining these can help determine the so called 'net clinical benefit' of treatments. The challenge here is to measure, calculate and report on neurocognitive functioning and HRQoL in a standardized manner so that information from different studies can be compared. Due to difference in these aspects, as shown above, we could not compare results between trials. A consensus paper was published previously about when to measure neurocognitive functioning and HRQoL and which tests can be used best.[47] a universal protocol how to measure and to report on these data would facilitate comparison across trials, as was developed for research in patients with brain metastases.[48]

Because survival has increased and neurocognitive functioning remains below the level of the norm population (<-1 in z-scores), a more personalized approached, based on toxicity, white matter lesions and cognitive functioning would be a helpful in order to counsel patients through their follow-up.

Lastly, many PCNSL researchers are currently already collaborating, but in order to answer important research questions that a stronger international collaboration is needed. Questions such as: what are the reasons for the increased incidence?, which factors maintain prognostic value in large, unbiased populations? can perhaps be answered if national databases, such as the American SEER and CBTRUS databases, our NCR database, and the French Oculo-Cerebral Lymphoma (LOC)-network were combined. This will, however be quite a challenge since these databases are organized differently and do not include the same parameters. Wider collaboration is however clearly needed in this rare disease.

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11

Summary en samenvatting in het Nederlands

SUMMARY

In this thesis we describe aspects of the epidemiology, diagnostic evaluation, neurocognitive function, health-related quality of life and prognosis in primary central nervous system lymphoma (PCNSL) patients. A PCNSL is a rare non-Hodgkin lymphoma limited to the brain, leptomeninges, spinal cord and the eyes without systemic localizations.

Epidemiology

In **chapter 2** we described the incidence, primary treatment and survival of PCNSL in the Netherlands between 1989 and 2015. Using the comprehensive data of the Netherlands Cancer Registry (NCR) we identified 1,673 patients diagnosed with PCNSL in this era. After dividing patients into three categories: 18-60, 61-70, and >70 years-olds we found that the incidence over time increased, but only among those over the age of 60. Although our finding is supported by other population-based studies, a clear explanation for this increase could not be found.

The primary treatment changed over the last three decades: the use of combined chemo- and radiotherapy and the use of chemotherapy only increased among 18-60 year-olds and a decreasing number of patients were treated with radiotherapy only. Among 61-70 year-olds and to a lesser extent in those over the age of 70 we found an increase of the use of chemotherapy in lieu of radiotherapy only. Lastly we found a clear improvement in survival in PCNSL patients, but only in those up to 70-years-old. By multivariate analysis we found that the change in treatment contributed significantly to the improved survival.

Despite the increased use of chemotherapy only instead of radiotherapy only, the survival of elderly (>70 years-old) did not increase since 1989. In **chapter 3** we described the primary treatment and survival of all patients (n=145) over the age of 70, diagnosed with PCNSL between 2014 and 2017 in the Netherlands. Again, patients were divided into three categories: 71-74, 75-80, and >80 years-old. In general, age is a strong prognostic factor in PCNSL patients, however, above the age of 70, we found no difference in survival between these three groups. Primary treatment was the only significant factor associated with overall survival: those judged fit enough to receive chemotherapy had a significantly longer median overall survival (OS; 16.3 months 95% CI 7.8-35.2), than those who received radiotherapy only (7.7 months, 95% CI 4.6-13.2) or best supportive care only (1.4 months, 95% CI 1.1-1.7; p<0.001) with a 2-year overall survival of nearly 50%.

Diagnostic evaluation

A quick, but reliable diagnosis is essential before starting anti-tumour therapy targeting lymphoma. In most cases a brain biopsy is necessary to obtain a diagnosis. In **chapter 4** we examined the value of flow cytometry on brain biopsies, in addition to classical histology and immunohistochemistry. We found a high specificity of flow cytometry (100%), but

lower sensitivity (88%). In other words, if a brain lymphoma was found by flow cytometry analysis, the diagnosis was confirmed, but some cases were missed by flow cytometry. The additional value of flow cytometry on brain biopsies in lesions suspected for a brain lymphoma was the speed in which the diagnosis was obtained. In our retrospective series, the median time to diagnosis obtained by flow cytometry was 1 day, compared with 5 days by histology plus immunohistochemistry.

After initiation of treatment, treatment response is assessed with MR imaging. In **chapter 5** we assessed the value of a central radiology review in MRIs made in a large, international, phase III study in patients with newly diagnosed PCNSL, the the HOVON 105/ ALLG NHL 24 study. Each MRI was assessed for response by a local physician in the hospital in which the patient was treated. Central radiology review was based on two experienced reviewers, and in case of disagreement a third reviewer was asked to adjudicate. In 235 MRIs, made after each treatment component, we found a rather modest interobserver agreement between local and central radiology review: kappa 0.46. Surprisingly, the interobserver agreement between both central reviewers was similar, suggesting that there is no added value of a central radiology review in PCNSL in clinical studies. In defining progression versus no progression, the interobserver agreement was excellent, both between the central reviewers (kappa 0.93) and between local and central radiology review (kappa 0.87).

In addition, we calculated differences in progression free survival (PFS) and overall survival for three different levels of response: complete response (CR), complete response unconfirmed (CRu), and partial response (PR) at the end-of-treatment MRI, which had to have been made before a predetermined timespan after randomization (the landmark). In this landmark analysis, in which all 'end-of-treatment' MRIs made before 6.9 months after randomization were included, we found no differences in PFS or OS for those categorized as complete response, complete response unconfirmed or as partial response, both according to central and local radiology review. The latter finding suggests that survival endpoints (PFS and OS) or combined response rate are more useful endpoints in clinical studies, than the complete response rate.

Neurocognitive function and health-related quality of life

In **chapter 6** we describe the results of a systematic review of the literature on neurocognitive functioning and health-related quality of life (HRQoL) in PCNSL patients, published before January 2018. The main conclusions were that the tumour itself had a large impact on both neurocognitive functioning and HRQoL, and that whole-brain radiotherapy (WBRT) in addition to chemotherapy had a negative impact on neurocognitive functioning. However, the magnitude of this impact was not always clinically relevant, with clinical relevance defined as a change in z-score of >1 or >1.5 standard deviation.

In the HOVON 105/ ALLG NHL 24 study, 199 immunocompetent patients with a newly diagnosed CD20+ B-cell PCNSL were randomized 1:1 between high-dose methotrexate based chemotherapy (MBVP) with or without rituximab. This was followed by consolidative high-dose cytarabine (Ara-C) and, for patients ≤60 years-old, also by 30Gy WBRT. There were no differences between event-free, progression-free and overall survival between the treatment arms. In **chapter 7** and **chapter 8** we described two secondary endpoints of this trial: neurocognitive functioning and HRQoL, respectively. Both neurocognitive functioning and HRQoL improved significantly over time, between baseline and up to two years post-treatment. The largest improvement was seen between baseline and end-of-treatment, implicating that the tumour itself has a large impact on neurocognitive functioning and HRQoL. The primary scales we assessed in het HRQoL analysis improved to a clinically relevant extent (≥10 points). Scores in all cognitive domains, improved but not to a clinically relevant extent, defined as a change in z-score of ≥1 standard deviation. Only motor speed showed a clinically relevant improvement. In those patients who received both chemotherapy and WBRT we found that neurocognitive functioning and HRQoL-scores maintained stable, up to 2-years of follow-up, compared to scores after WBRT. This contrasts with most other studies, which might be explained by the lower dose of radiation we used (30Gy), compared to most other trials (36-45Gy). Furthermore, our follow-up of two years might be too short to detect deterioration in neurocognitive functioning, although this has previously been described to occur as early as 6-12 months following treatment.

In **chapter 7** we described not only cognitive changes but also the investigation of an association between cognitive changes and radiological changes over time in white matter abnormalities (WMA) and brain atrophy. We found a significant, but rather modest relation between increased WMA and brain atrophy and a decrease in neurocognitive functioning over time.

Prognosis

Many patients with PCNSL present with cognitive symptoms and in glioma, cognitive impairment at diagnosis is associated with a worse prognosis. The Mini-Mental State Examination (MMSE) is a screening tool to detect cognitive impairment. In **chapter 9** we showed in the HOVON 105/ALLG NHL 24 study that the MMSE-score at baseline is an independent prognostic factor in predicting progression free survival (PFS) and overall survival (OS). We found that each unit decrease in MMSE-score was associated with a decreased prognosis for PFS (Hazard Ratio [HR], 95% confidence interval [CI] 1.04, 1.01-1.08) and OS (HR, 95% CI: 1.06, 1.02-1.10). When including the MMSE-score as categorical variable, a baseline-score <27 (as compared to a score ≥27) was again the only factor associated with PFS (HR 1.55, 95% CI: 1.02-2.35) and overall survival (HR 1.68, 95% CI: 1.05-2.70). Age and performance status, common prognostic factors in oncology and both included in the

most used prognostic models in PCNSL, were not significantly associated with progression free survival (PFS) and overall survival (OS) in multivariate analysis of our PCNSL cohort of 153 patients aged up to 70 years. Of note, age did show a trend towards significance for both PFS (p=0.061) and OS (p=0.069).

In **chapter 10** we discussed the most relevant results of chapters 2 to 9 described in this thesis in the light of recent literature.

SAMENVATTING IN HET NEDERLANDS

Het primair centraal zenuwstelsel lymfoom (PCZSL) is een zeldzame vorm van een non-Hodgkin lymfoom dat zich beperkt tot de hersenen, de hersenvliezen (ofwel leptomeningen), het ruggenmerg en de ogen, zonder aanwijzingen voor ziekteactiviteit in de rest van het lichaam. De tumor presenteert zich meestal met klachten die binnen enkele weken ontstaan, zoals uitval (verlamming of niet kunnen spreken) of cognitieve veranderingen. In dit proefschrift beschrijven we aspecten van de epidemiologie, diagnostiek, neurocognitief functioneren, kwaliteit van leven en prognose van het primair centraal zenuwstelsel lymfoom.

Epidemiologie

In **hoofdstuk 2** beschrijven we onderzoek naar het voorkomen, de primaire behandeling en de overleving van patiënten met het PCZSL in Nederland tussen 1989 en 2015 gebruik makend van de data van de Nederlandse Kanker Registratie (NKR). In deze periode werden 1.673 patiënten met PCZSL gediagnosticeerd. De patiënten werden verdeeld in drie groepen: 18-60 jaar, 61-70 jaar en >70 jaar. We zagen dat het voorkomen (de incidentie) van de ziekte sterk was toegenomen, maar alleen onder patiënten >60 jaar. Deze bevinding komt overeen met bevolkingsonderzoeken in andere landen, maar de oorzaak hiervan is niet bekend.

De primaire behandeling van het PCZSL is sterk veranderd in de afgelopen dertig jaar: zowel behandeling met chemotherapie in combinatie met radiotherapie als behandeling met alleen chemotherapie nam toe in de leeftijdscategorie 18-60, en behandeling met alleen radiotherapie nam juist af. In de categorieën 61-70 jaar en in mindere mate in patiënten >70 jaar nam behandeling met alleen chemotherapie toe en nam behandeling met alleen radiotherapie af. Tenslotte zagen we dat de overleving sterk was toegenomen de afgelopen dertig jaar, maar alleen in patiënten tot 70 jaar. Doordat de Nederlandse Kanker Registratie ook behandelgegevens bevat konden we vaststellen dat deze verbeterde overleving werd verklaard door veranderingen in de behandeling.

Ondanks het toegenomen gebruik van chemotherapie bij patiënten ouder dan onder 70 blijft de overleving in deze groep slecht. In **hoofdstuk 3** beschrijven we de primaire behandeling en overleving van 145 ouderen (>70 jaar) met een PCZSL in Nederland, gediagnosticeerd tussen 2014 en 2016. Deze groep werd verdeeld in leeftijdsgroepen: 71-74, 75-80 en >80 jaar. In zijn algemeenheid is leeftijd een sterke prognostische factor in PCZSL patiënten, echter wij zagen geen verschil meer in overleving tussen de drie groepen die allen ouder waren dan 70 jaar. De primaire behandeling was de enige factor die significant geassocieerd was met totale overleving: diegene die kennelijk geschikt waren bevonden om chemotherapie te krijgen hadden een significant betere overleving (mediane totale overleving [mOS] 16,3 maanden, 95% betrouwbaarheidsinterval [BI]: 7,8-35,2) dan die-

gene die alleen radiotherapie (mOS 7,7 maanden, 95% BI 4,6-13,2) of alleen 'supportive care' kregen (mOS 1,4 maanden, 95% BI 1,1-1,7; p<0,001).

Diagnostiek

Het vaststellen van een zekere diagnose van een PCZSL is noodzakelijk voordat chemotherapie kan worden gestart en doordat deze patiënten vaak snel achteruit gaan is hierbij haast geboden. In veel gevallen is er een hersenbiopt nodig om de diagnose te stellen. In **hoofdstuk 4** onderzochten we de waarde van flowcytometrie op hersenbiopten in aanvulling op de gebruikelijke histologie en immuunhistochemie. Flowcytometrie had een specificiteit van 100% en een sensitiviteit van 88%. Met andere woorden, indien er een lymfoom werd gevonden met flowcytometrie, dan was de diagnose bevestigd. Er werden wel enkele gevallen gemist. De toegevoegde waarde van flowcytometrie was de snelheid waarmee een diagnose kon worden bevestigd. In onze retrospectieve serie kon de diagnose <24uur worden gegeven in 54% van de biopten met behulp van flowcytometrie, ten opzichte van 9% met histologie en immuunhistochemie.

Na het starten van de behandeling wordt het effect van die behandeling gemonitord middels MRI beelden van de hersenen. In **hoofdstuk 5** onderzoeken we de waarde van een centrale radiologische beoordeling van MRI's die gemaakt werden in het kader van de behandeling van patiënten in de HOVON105/ ALLG NHL24 trial. Elke MRI werd beoordeeld op de mate van respons van de tumor in het ziekenhuis waar de patiënt werd behandeld door een lokale arts. De centrale radiologiebeoordeling was gebaseerd op twee ervaren beoordelaars en in geval zij van mening verschilde, besliste een derde beoordelaar. In 235 MRI's, gemaakt gedurende de behandeling, vonden we een matige overeenstemming tussen de beoordelaars (interobserver agreement) tussen de lokale en centrale beoordeling: kappa 0.46. Verrassend genoeg was de interobserver agreement tussen beide centrale beoordelaars niet beter. Dit suggereert dat de beoordeling voor de mate van respons beperkt is en dat er geen toegevoegde waarde is van een centrale radiologische beoordeling van de respons bij PCZSL in klinische studies. Bij het onderscheid tussen progressie of recidief en geen progressie of recidief was de interobserver agreement uitstekend, zowel tussen de centrale beoordelaars (kappa 0.93) als tussen de lokale en centrale beoordeling (kappa 0.87).

Daarnaast berekenden we verschillen in progressie vrije overleving en totale overleving voor erkende categorieën van de mate van respons: complete respons (CR), onbevestigde complete respons (CRu) en partiële respons (PR) op de MRI gemaakt aan het einde van de behandeling. Deze MRI moest zijn gemaakt binnen een vooraf gedefinieerde periode (zogenoemde landmark analyse) vanaf de randomisatie. In deze landmark analyse, werden alle 'end-of-treatment'-MRI's meegenomen die vóór 6,9 maanden na randomisatie waren gemaakt. Hierin vonden we geen verschillen in progressie vrije overleving en totale overleving tussen patiënten met een complete respons (CR), onbevestigde complete res-

pons (CRu) en partiële respons (PR), zowel volgens de centrale als de lokale radiologische beoordeling. De laatste bevinding suggereert dat de verschillende response maten geen goed surrogaat eindpunt zijn, noch voor progressie vrije noch voor totale overleving.

Neurocognitief functioneren en kwaliteit van leven

In **hoofdstuk 6** geven we een uitgebreid, systematisch overzicht van de literatuur over neurocognitief functioneren en kwaliteit van leven in PCZSL patiënten, gepubliceerd vóór januari 2018. De belangrijkste conclusies waren dat de tumor zelf een grote impact heeft op zowel neurocognitief functioneren als kwaliteit van leven, en dat totale schedelbestraling in aanvulling op chemotherapie een negatief effect heeft op neurocognitief functioneren. De mate van deze impact was echter niet altijd klinisch relevant, waarbij relevantie gedefinieerd was als een verandering in z-score van >1 of >1,5 standaarddeviatie.

In de HOVON 105/ ALLG NHL 24 trial werden 199 immuun competente patiënten met een nieuw gediagnosticeerde CD20+ B-cel PCZSL 1:1 gerandomiseerd tussen chemotherapie, gebaseerd op hoge dosis methotrexaat (MBVP), met of zonder rituximab. Dit werd gevolgd door consolidatie behandeling met hoge dosis cytarabine (Ara-C) en voor patiënten ≤60 jaar gevolgd door 30Gy bestraling van de gehele schedelinhoud. Er waren geen verschillen tussen de event vrije, progressie vrije en totale overleving tussen de twee behandelarmen. In **hoofdstuk 7** en **hoofdstuk 8** beschrijven we de secundaire eindpunten van deze trial: respectievelijk neurocognitief functioneren en kwaliteit van leven. Zowel het neurocognitief functioneren als de kwaliteit van leven verbeterden significant in de tijd, vanaf baseline tot twee jaar na behandeling. De grootste verbetering trad op tussen de start en het einde van de behandeling. Doordat het PCZSL heel goed kan reageren op de behandeling impliceert dit dat de tumor zelf een grote invloed heeft op het neurocognitief functioneren en kwaliteit van leven. De verbetering in de primaire schalen die we gebruikten in de kwaliteit van leven analyse was ook klinisch relevant (≥10 punten). De scores in alle cognitieve domeinen, behalve motorsnelheid, verbeterden niet dusdanig dat dit klinisch relevant genoemd mag worden, waarbij dit gedefinieerd was als een verandering in z-score van ≥1 standaarddeviatie. Bij die patiënten die chemotherapie en totale schedelbestraling kregen, zagen we dat neurocognitief functioneren en kwaliteit van leven-scores stabiel bleven tot 2 jaar follow-up, ten opzicht van scores na WBRT. Dit is in tegenstelling tot de meeste andere studies, hetgeen mogelijk verklaard kan worden door de lagere dosis bestraling die wij hebben gebruikt (30Gy), vergeleken met de meeste andere onderzoeken (36-45Gy) en onze follow-up is mogelijk nog te kort om achteruitgang in neurocognitief functioneren te detecteren. Echter, het is eerder beschreven dat cognitieve achteruitgang al na 6-12 maanden na de bestraling kan optreden.

In **hoofdstuk 7** beschrijven we niet alleen de cognitieve veranderingen, maar ook of er een relatie is tussen cognitieve veranderingen en radiologische veranderingen: witte

stof afwijkingen en breinatrofie. Er was een significante, maar zwakke relatie tussen een toename in WSA en hersenatrofie en een afname van neurocognitief functioneren.

Prognose

Veel patiënten met PCZSL hebben cognitieve stoornissen bij het debuut van de ziekte. De Mini-Mental State Examination (MMSE) is een grove screeningstool om neurocognitieve stoornissen te detecteren. In **hoofdstuk 9** is de prognostische waarde van de MMSE onderzocht in patiënten uit de HOVON105/ ALLG NHL24 studie. De MMSE-score, als continue variabele bij de start van de behandeling , voor start van de chemotherapie, bleek een onafhankelijke prognostische factor is bij het voorspellen van de progressievrije overleving en totale overleving. We zagen dat elk punt daling van de MMSE-score geassocieerd was met een slechtere prognose: voor progressievrije overleving (Hazard Ratio [HR], 95% betrouwbaarheidsinterval [BI] 1,04, 1,01-1,08) en voor totale overleving (HR, 95% BI: 1,06, 1,02-1,10). Wanneer de MMSE-score als categoriale variabele (afwijkend versus normaal) werd gebruikt voor de analyse was een baseline-score <27 (vergeleken met een score ≥ 27) opnieuw de enige factor die geassocieerd was met progressievrije (HR 1,55, 95% BI: 1,02-2,35) en totale overleving (HR 1,68 95% BI: 1,05-2,70). Leeftijd en 'performance status' zijn belangrijke prognostische factoren bij veel oncologische aandoeningen en beide worden gebruikt in de belangrijke prognostische modellen voor PCZSL patiënten. In ons cohort van 153 PCZSL patiënten, waarin alleen patiënten tot de leeftijd van 70 werden geïncludeerd, waren deze in multivariate analyse niet geassocieerd met progressievrije overleving en totale overleving. Echter, leeftijd vertoonde wel een trend naar significantie voor progressievrije overleving (p=0,061) en totale overleving (p=0,069).

In **hoofdstuk 10** bespreken we de meest relevante resultaten van de hoofdstukken 2 tot en met 9 die in dit proefschrift werden beschreven in het licht van recente literatuur.

A

LIST OF PUBLICATIONS

Van der Meulen M*, Dinmohamed AG*, Visser O, Doorduijn JK, Bromberg JEC. (2017) **Improved survival in primary central nervous system lymphoma up to age 70 only: a population-based study on incidence, primary treatment and survival in the Netherlands, 1989-2015**. *Leukemia,* 31(8): 1822-1825.

Van der Meulen M, Dirven L, Habets EJJ, van den Bent MJ, Taphoorn MJB, Bromberg JEC. (2018). **Cognitive functioning and health-related quality of life in patients with newly diagnosed primary CNS lymphoma: a systematic review**. *Lancet Oncology,* 19(8): e407-e418.

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Accepted in Neuro-Oncology

Van der Meulen M, Postma AA, Smits M, Bakunina K, Minnema MC, Seute T, Cull G, Enting RH, van der Poel M, Stevens WBC, Brandsma D, Beeker A, Doorduijn JK, Issa S, van den Bent MJ, Bromberg JEC. (2021) **Extent of radiological response does not reflect survival in primary central nervous system lymphoma.**
Neuro-Oncology Advances, 3(1)

Van der Meulen M, Dirven L, Bakunina K, van den Bent MJ, Issa S, Doorduijn JK, Bromberg JEC. (2021) **MMSE is an independent prognostic factor for survival in primary central nervous system lymphoma.**
Accepted in Journal of Neuro-Oncology

Bromberg JEC, **van der Meulen M**, Doorduijn JK. (2020) **The Role of Rituximab in Primary Central Nervous system Lymphoma.**
Current Oncology Reports, 22(8): 78.

Van der Meulen M, van den Bent MJ, Doorduijn, JK, Bromberg JEC. (2020). **Primair centraal zenuwstelsel lymfoom: een behandelbare hersentumor -** Een praktisch overzicht van de diagnostiek en behandeling. *Tijdschrift voor Neurologie en Neurochirurgie*, 121(2):79-84

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**Shared first author position*

ABOUT THE AUTHOR

Matthijs van der Meulen was born on February 6, 1986 in Wezep (Oldebroek), the Netherlands. He graduated from pre-university education (gymnasium) at the Thomas a Kempis College in Zwolle in 2004 and started subsequently medical school at the University of Utrecht. He obtained his medical degree in 2011 and started to work as a resident (ANIOS) in the Slotervaart hospital in Amsterdam, and in April 2012 he started his residency training at the Erasmus Medical Center in Rotterdam (head: prof. dr. P.A.E. Sillevis Smitt). In March 2016 he started with his PhD project about diagnostic evaluation, neurocognitive functioning and health-related quality of life in primary central nervous system lymphoma patients under supervision of dr. J.E.C. Bromberg and prof. dr. M.J. van den Bent. The research in this project led to this thesis. He obtained his neurology degree at October 1, 2020 and started to work in Medisch Spectrum Twente as a neurologist/ neuro-oncologist and from July 1, 2021 he will do a one-year neuro-oncology fellowship in the Princess Margaret Cancer Center in Toronto, Canada (head: dr. W.P. Mason).

PHD PORTFOLIO

General courses	Year	Workload (ECTS)
Basiscursus Regelgeving Klinisch Onderzoek (BROK)	2016	0.9
Integriteit in medisch onderzoek	2017	0.3
Biostatistical methods I: Basic principles	2017	5.7
Biostatistical Methods II: Classical Regression Models	2017	4.3
Biomedical English Writing and Communication	2019	3.0
		14.2
Presentations		
Wetenschapsdagen Nederlandse Vereniging voor Neurologie, Nunspeet, the Netherlands (oral presentations)	2016	1.0 1.0
European Association of Neurology Congress Amsterdam, the Netherlands (oral presentation) Lisbon, Portugal (e-poster presentation) Oslo, Norway (oral presentation)	 2017 2018 2019	 1.0 0.5 1.0
Wetenschappelijke vergadering Landelijke Werkgroep Neuro-oncologie, Utrecht, the Netherlands (oral presentations)	2017 2019	1.0 1.0
European Association of Neuro-Oncology Congress Stockholm, Sweden Lyon, France (oral presentations)	 2018 2019	 2.0
Society of Neuro-Oncology Phoenix, Arizona, United States (poster presentation)	 2019	 0.5
Journal Club neuro-oncology/radiology	2016-2019	1.0
		10
Teaching		
Lecture about PCNSL, Rotterdam, the Netherlands	2020	1.0
Lecture 'neurological complications of hematological malignancies'	2018 2020	1.0 1.0
Teaching nurses 'neuro-oncology'	2018	1.0
Supervising Master Thesis M.A.J. Snoek	2018	1.5
Supervising Master Thesis S. Ahmed	2019	1.5
		7.0
Total		**31.2**

DANKWOORD

Er zijn veel mensen die mij geholpen hebben het proefschrift dat voor u ligt te voltooien. Voordat ik diegene hieronder bedank, wil ik allereerst graag alle patiënten die hebben meegedaan aan de HOVON 105/ ALLG NHL 24 studie enorm bedanken. In het bijzonder voor het ondergaan van meerdere neuropsychologische onderzoeken en het invullen van de kwaliteit van leven vragenlijsten. Zonder jullie had ik niet kunnen promoveren.

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Dr. J.E.C. Bromberg, beste Jacoline, toen ik begon aan deze promotie, begon jij aan 3 nieuwe projecten tegelijkertijd: opleider worden van ca. 40 A(N)IOS, supervisor binnen de algemene neurologie (na 12 jaar Daniël den Hoed) en co-promotor van je eerste promovendus. Hoe je de afgelopen jaren tussen al deze taken tijd wist te maken voor mij, mijn stukken en de overleggen met Linda, Katerina, Marion, Esther en Martin zijn mij een raadsel. Naast de kans en het vertrouwen dat ik kreeg om met de data van 'jouw' HOVON 105/ ALLG NHL 24 studie aan de slag te gaan, heb je mij ook betrokken in de samenwerking met het IKNL en mocht ik ook kijken naar allerhande radiologische aspecten van primair centraal zenuwstelsel lymfomen. Je geeft veel vertrouwen, stimuleert en benadrukt wat er goed gaat, wat er al wél af is of wat er al wél gedaan is, in plaats van wat nog moet. Dit werkt enorm stimulerend en ik hoop, ondanks je volle agenda, dat er na mij nog vele promovendi mogen volgen die door jou begeleid gaan worden.

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dr. J.K. Doorduijn and **dr. Issa**, beste Jeanette and dear Samar, thank you for your confidence and support I received as PhD candidate, but also as resident of neurology doing analyses and writing manuscripts about your 'hematological' HOVON 105/ ALLG NHL 24 trial. I am grateful I had the possibility to write many manuscripts with both of you. Jeanette, dank dat je het manuscript kritisch hebt willen beoordelen en hebt willen plaatsnemen in mijn promotiecommissie.

Het HOVON data center heeft de afgelopen jaren veel data bijgehouden voor de HOVON 105/ ALLG NHL 24 studie. Ook data die niet dagelijks in hematologie studies wordt geregistreerd: kwaliteit van leven en in het bijzonder cognitief functioneren. Met veel dank aan **Martine Abrahamse**, voor het achterhalen en bijhouden van al deze gegevens.

prof. dr. M.J.B. Taphoorn, beste Martin, ik mocht de afgelopen jaren een beetje deel uitmaken van jouw onderzoeksgroep waarin kliniek en onderzoek naar neurocognitief functioneren en kwaliteit van leven gecombineerd worden. Mede dankzij jouw vertrouwen hebben we onze systematic review aangeboden aan *The Lancet Oncology*, die het artikel gelukkig wilde publiceren. Hopelijk kunnen we de komende jaren nog veel samenwerken in het onderzoek.

prof. dr. M. Smits, beste Marion, mede dankzij jou hebben we het eerste artikel over de waarde van een centrale radiologie review in primair centraal zenuwstelsel lymfoom patiënten kunnen schrijven. Voor de verschillende radiologische projecten binnen mijn promotie wist je mensen uit jouw onderzoeksgroep te vinden om mee samen te werken en de beelden snel door te laten analyseren. Hopelijk gaat het nog een keer lukken om de prognostische waarde van diffusie en perfusie samen op te schrijven.

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betrokken bij 'jouw' population-based studies. Ik heb in korte tijd veel geleerd van de epidemiologische analyses op populatieniveau. Hopelijk kunnen we over een paar jaar een update schrijven. **Dr. E.J.J. Habets**, beste Esther, als dokter wilde ik meteen een soort sumscore maken van de cognitieve scores, "dat werkt veel makkelijker", maar jij hebt me uitgelegd dat dat niks zegt en dat de cognitieve tests afzonderlijk gewogen en bekeken moeten worden. Dank voor je hulp en uitleg over alle tests en domeinen, tussen jouw drukke spreekuren en eigen promotie door. **Dr. A.A. Jacobi-Postma**, beste Linda, ondanks een niet erg behulpzaam programma heb je meer dan 600 MRI's beoordeeld in het kader van onze centrale radiologie review en hebben we het eerste artikel hierover in primair centraal zenuwstelsel lymfoom patiënten kunnen schrijven. **Dr. Sebastian van der Voort** en **dr. Hakim Achterberg**, dank voor jullie hulp en snelheid waarmee de verzamelde MRI's konden worden geanalyseerd. **Dr. V.H.J. van der Velden**, beste Vincent, dankzij jullie analyses konden we het eerste artikel schrijven over de waarde van flowcytometrie op hersenbiopten wanneer gedacht wordt aan een centraal zenuwstelsel lymfoom. Dank voor de hulp bij het schrijven van dit artikel en het was erg leuk om een ochtend mee te lopen op jullie laboratorium.

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Enschede, voorjaar 2021