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

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ONLINE APPENDIX

Title

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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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).

Supplemental methods

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)

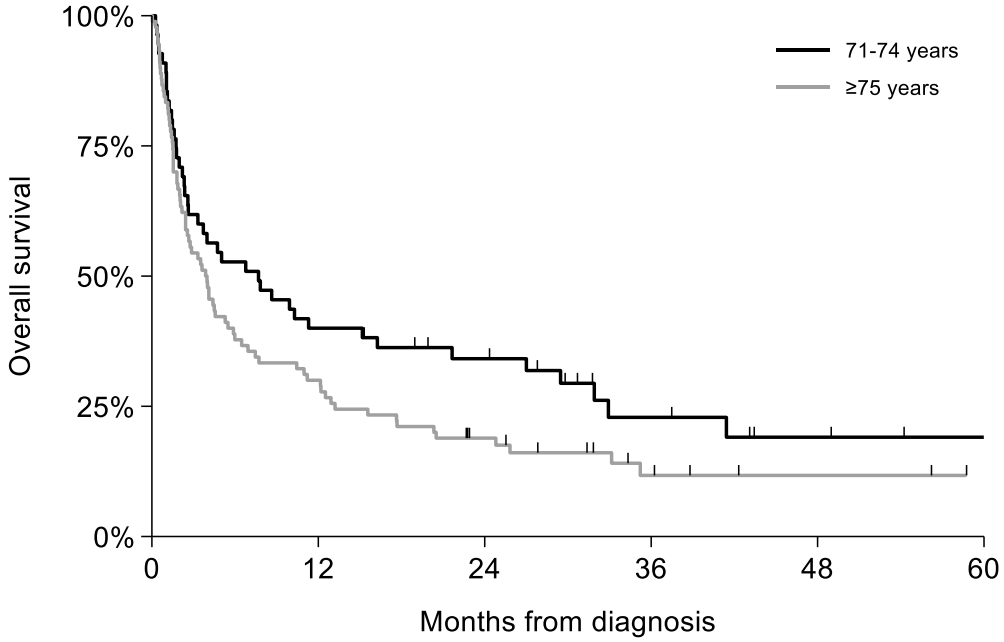
Overall survival

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 legend

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 Figure 1



Number at risk						
71-74 years	55	22	16	7	3	0
≥75 years	90	27	14	5	2	0

Supplemental Table 1

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

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.

Supplemental references

1. Swerdlow SH. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 2008.