Matthijs van der Meulen,¹,² Jacoline E.C. Bromberg,¹ Marcel Nijland,³ Otto Visser,⁴ Jeanette K. Doorudijn⁵ and Avinash G. Dinmohamed⁶,⁷

¹Department of Neuro-Oncology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam; ²Department of Neurology, Medical Spectrum Twente, Enschede; ³Department of Hematology, University Medical Center Groningen, Groningen; ⁴Department of Registration, Netherlands Comprehensive Cancer Organisation (iKNL), Utrecht; ⁵Department of Hematology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam; ⁶Department of Research and Development, Netherlands Comprehensive Cancer Organisation (iKNL), Utrecht and ⁷Department of Public Health, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands

Correspondence: M. VAN DER MEULEN - m.vandermeulen.2@erasmusmc.nl
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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

Authors and affiliations
Matthijs van der Meulen¹, Jacoline E.C. Bromberg¹, Marcel Nijland², Otto Visser³, Jeanette K. Doorduijn⁴, Avinash G. Dinmohamed⁴⁶

¹Erasmus MC Cancer Institute, University Medical Center Rotterdam, Department of Neuro-Oncology; ²Department of Hematology, University Medical Center Groningen, Groningen, The Netherlands; ³Department of Registration, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, The Netherlands; ⁴Erasmus MC Cancer Institute, University Medical Center Rotterdam, Department of Hematology; ⁵Department of Research and Development, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, The Netherlands; ⁶Erasmus MC, University Medical Center Rotterdam, Department of Public Health
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

| Age Group | 0 | 12 | 24 | 36 | 48 | 60 |
|-----------|---|----|----|----|----|----|
| 71-74 years | 55 | 22 | 16 | 7  | 3  | 0  |
| ≥75 years   | 90 | 27 | 14 | 5  | 2  | 0  |

Overall survival vs. Months from diagnosis
Supplemental Table 1

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

| Covariate                  | Univariable | Multivariable |              |              |              |              |
|----------------------------|-------------|---------------|--------------|--------------|--------------|--------------|
|                            | OR         | 95% CI        | P            | OR          | 95% CI       | P            | OR          | 95% CI       | P            |
| **Sex**                    |            |               |              | Reduced model|              |              | Full model   |              |              |              |
| 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**|            |               |              | Reduced model|              |              | Full model   |              |              |              |
| 71-74                      |            |               |              | 0.002*      |              | 0.002*       | 0.003*       |              |              |
| 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

| Covariate                        | Univariable | Multivariable |
|----------------------------------|-------------|---------------|
|                                  |             | Reduced model | Full model    |
|                                  | HR  | 95% CI       | P  | HR  | 95% CI       | P  | HR  | 95% CI       | P  |
| **Sex**                          |     |              |    |     |              |    |     |              |    |
| Male                             | 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)        |     |     |              |    |     |              |    |
| 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)        |     |     |              |    |     |              |    |
| Yes                              | 0.92| 0.60-1.42    | 0.709| 0.91| 0.57-1.45    | 0.696|
| **Primary therapy**              |     |              |    |     |              |    |     |              |    |
| Chemotherapy                     | 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)        |     |     |              |    |     |              |    |
| 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.