# Prognostic Scoring System for Primary CNS Lymphomas: The International Extranodal Lymphoma Study Group Experience

By Andrés J.M. Ferreri, Jean-Yves Blay, Michele Reni, Felice Pasini, Michele Spina, Achille Ambrosetti, Antonello Calderoni, Andrea Rossi, Vittorio Vavassori, Annarita Conconi, Liliana Devizzi, Françoise Berger, Maurilio Ponzoni, Bettina Borisch, Marianne Tinguely, Michele Cerati, Mario Milani, Enrico Orvieto, Juvenal Sanchez, Christine Chevreau, Stefania Dell'Oro, Emanuele Zucca, and Franco Cavalli

***Purpose:*** **To identify survival predictors and to design a prognostic score useful for distinguishing risk groups in immunocompetent patients with primary CNS lymphomas (PCNSL).**

***Patients and Methods:*** **The prognostic role of patient-, lymphoma-, and treatment-related variables was analyzed in a multicenter series of 378 PCNSL patients treated at 23 cancer centers from five different countries.**

***Results:*** **Age more than 60 years, performance status (PS) more than 1, elevated lactate dehydrogenase (LDH) serum level, high CSF protein concentration, and involvement of deep regions of the brain (periventricular regions, basal ganglia, brainstem, and/or cerebellum) were significantly and independently associated with a worse survival. These five variables were used to design a prognostic score. Each variable was assigned a value of either 0, if favorable, or 1, if unfavorable. The values were then added together to arrive at a final score, which was tested in 105 assessable patients for which complete data of all five variables were available. The 2-year overall survival (OS) ± SD was 80% ± 8%, 48% ± 7%, and 15% ± 7% ($P = .00001$) for patients with zero to one, two to three, and four to five unfavorable features, respectively. The prognostic role of this score was confirmed by limiting analysis to assessable patients treated with high-dose methotrexate-based chemotherapy (2-year OS ± SD: 85% ± 8%, 57% ± 8%, and 24% ± 11%; $P = .0004$).**

***Conclusion:*** **Age, PS, LDH serum level, CSF protein concentration, and involvement of deep structures of the brain were independent predictors of survival. A prognostic score including these five parameters seems advisable in distinguishing different risk groups in PCNSL patients. The proposed score and its relevance in therapeutic decision deserve to be validated in further studies.**

***J Clin Oncol 21:266-272.*** 

IN SERIES investigating the management of primary CNS lymphomas (PCNSL), the differences in outcome observed among various treatment options have been attributed to an inhomogeneous distribution of prognostic indicators rather than the real efficacy of therapeutic strategies.[1] Indeed, apart from age and performance status (PS), which are universally accepted prognostic factors,[1,2] no other parameters influencing outcome have been consistently identified.

Efforts to identify predictors of response and survival in PCNSL have produced isolated observations in small series, which have not been confirmed in successive studies. The characterization of predictors of response and survival using large series may allow us to identify different patient risk groups, facilitate the comparative analysis of prospective trials, and define stratification criteria for future trials. In this study, predictors of response and survival were analyzed in an international multicenter retrospective series of 378 immunocompetent patients with PCNSL. A prognostic score resulting from the combined analysis of the independent variables is proposed in light of its potential clinical relevance.

## PATIENTS AND METHODS

### *Study Group*

A questionnaire requesting information about patient characteristics, clinical presentation, diagnosis, staging, planned and actually performed treatment, objective response, site and date of relapse, second-line treatment, neurotoxicity, and survival was sent to 48 centers referring to the International Extranodal Lymphoma Study Group. Report forms were submitted to at least one clinician (hematologist or oncologist) and one pathologist per center. Only patient cases diagnosed and treated at the participating institutions that fulfilled the following criteria were selected: (1) histologic or cytologic diagnosis of lymphoma; (2) disease localized exclusively in the brain, cranial nerves, meninges, or eyes; and (3) no evidence of human immunodeficiency virus-1 infection (negative serologic tests and absence of

*From the Departments of Radiochemotherapy and Pathology, San Raffaele H Scientific Institute, and Divisione di Oncologia Medica, Istituto Nazionale dei Tumori, Milan; Divisione di Radioterapia, Ospedale di Circolo e Fondazione Macchi, and Anatomia e Istologia Patologica, Ospedale di Circolo Fondazione Macchi, Università dell'Insubria, Varese; Divisione Clinicizzata di Oncologia Medica, Ospedale Civile Maggiore, and Cattedra di Ematologia, Università di Verona, Ospedale Policlinico di Borgo Roma, Verona; Division of Medical Oncology "A," Centro di Riferimento Oncologico, National Cancer Institute, Aviano; Divisione di Ematologia, Ospedali Riuniti di Bergamo, Bergamo; Divisione di Anatomia Patologica, Azienda Ospedaliera di Lecco, Lecco; Istituto di Anatomia e Istologia Patologica, Ospedale Regionale di Treviso, Treviso, Italy; Unité Cytokines et Cancers, Hopital E. Herriot & Centre Léon Bérard, and Service de Pathologie, Centre Hospitalier Lyon-Sud, Lyon; Centre Claudius Regaud, Toulouse, France; Istituto Oncologico della Svizzera Italiana, Ospedale San Giovannia, Bellinzona; Institut für Medizinische Onkologie Inselspital, Bern; Division de Pathologie Clinique, Hôpitaux Universitaires de Genève, Hôpital Cantonal, Genève, Switzerland; and Departamento de Anatomia Patológica, Instituto de Enfermedades Neoplásicas, Lima, Perú.*

*Submitted September 27, 2001; accepted September 24, 2002.*

*Presented at the Forty-Second Annual Meeting of the American Society of Hematology, December 6-10, San Francisco, CA, 2000*

*Address reprint requests to Andrés J.M. Ferreri, MD, Department of Radiochemotherapy, San Raffaele H Scientific Institute, via Olgettina 60, 20132, Milan, Italy; email: andres.ferreri@hsr.it.*



*0732-183X/03/2102-266/$20.00*


DOI: 10.1200/JCO.2003.09.139

epidemiologic risk, opportunistic infections, or lymphopenia for patients diagnosed in the early 1980s) or other immunodeficiencies. The history of a prior cancer was not an exclusion criterion.

Thirty-four out of 48 centers responded (response rate, 71%); 11 centers did not register patients in the study. Therefore, data of 378 PCNSL patients diagnosed between 1980 and 1999 were collected by 23 cancer centers (48% of responding centers) from five different countries.

Questionnaire data were verified during a consensus meeting held at Ascona, Switzerland, on February 2000; equivocal submitted information was subsequently analyzed until consensus for every single patient case was reached. Each institution carried out a radiologic material review. Clinical staging work-up included at least total-body computed tomography scan and bone marrow biopsy. Staging procedures included slit-lamp examination of the eyes in 170 patients (45%) and CSF cytology examination in 241 patients (64%). The cutoff for normal CSF protein concentration was 45 mg/dL in patients ≤ 60 years old and 60 mg/dL in patients more than 60 years old.[3] PS was defined according to the Eastern Cooperative Oncology Group (ECOG) criteria. Histologic sample was obtained by stereotactic biopsy in 276 patients (72%), surgical resection in 86 patients (23%; total resection in 44 patients, subtotal in 42 patients), CSF cytology examination in 14 patients (4%), and vitrectomy and autopsy in one patient each (< 1%).

### *Therapeutic Management*

Therapeutic data were available from 370 patients. Planned treatment was radiotherapy (RT) alone in 98 patients (26%), RT followed by chemotherapy (CHT; RT → CHT) in 36 patients (10%), CHT alone in 32 patients (9%), and CHT followed by RT (CHT → RT) in 197 patients (53%). Seven patients (2%) did not receive any treatment. It is noteworthy that five patients who were planned to receive primary RT did not receive any treatment, whereas 61 patients who were planned to receive CHT → RT were not irradiated because of progressive disease (n = 25), early relapse (n = 11), toxic death (n = 15), refusal (n = 6), unrelated death (n = 1), or because they were lost to follow-up (n = 3).

Methotrexate (MTX) was the most commonly used drug (n = 169), followed by alkylating agents (n = 146, including procarbazine, thiotepa, cyclophosphamide, and nitrosoureas), high-dose (HD) cytarabine (n = 128), and anthracyclines (n = 117). MTX was administered at a dose ≥ 3 g/m$^2$ per course in 126 patients (75%). CHT regimen was alkylating agents alone in 25 patients, cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like regimens in 43 patients, HD cytarabine-based regimen in 11 patients, HD-MTX alone in 17 patients, HD-MTX plus alkylating agents in 23 patients, HD-MTX plus CHOP-like regimens in 24 patients, HD-MTX plus HD cytarabine in 34 patients, and HD-MTX plus HD cytarabine plus alkylating agent plus anthracycline in 67 patients. Other regimens were used in 16 patients. Intrathecal CHT was used in 109 patients and consisted of MTX in 61 patients, cytarabine in four patients, and both in 44 patients. RT was administered to the whole brain with a dose (± SD) of 42 ± 7 Gy in patients treated with primary RT and 34 ± 7 Gy in CHT → RT patients, followed or not by a tumor-bed boost; tumor-bed dose was 46 ± 9 and 45 ± 8 Gy, respectively. A more thorough description of variable distribution among therapeutic subgroups and therapeutic outcome has been recently published.[4]

### *Statistical Considerations*

Response rates and clinical characteristics of the different groups of patients were compared using the $\chi^2$ test or the Fisher's exact test for categorical variables, according to the sample size. Objective response was defined according to the World Health Organization criteria; overall response rate included complete remission, continued complete remission (ie, patients with no measurable disease after surgical resection), and partial response. Survival curves were generated by the Kaplan-Meier method. Overall survival (OS) was calculated from the date of histologic diagnosis to death or last date of follow-up, whereas failure-free survival (FFS) was calculated from the first day of treatment to relapse, progression, or death, or to last date of follow-up. Impact on survival of clinical and therapeutic variables was evaluated by comparing the survival curves using the log-rank test. Comparison of the therapeutic variables was performed on an intent-to-treat basis; each patient was assigned to a therapeutic group according to the planned first-line treatment.

**Table 1. Patient Characteristics and Extension of Disease**

| Characteristic | No. of Patients (N = 378) | % |
|---|---|---|
| Age, years | | |
| Median | 61 | |
| Range | 14-85 | |
| Age > 70 years | 52 | 14 |
| Male sex | 220 | 58 |
| ECOG PS | | |
| 0-1 | 117 | 31 |
| 2-3 | 175 | 46 |
| 4 | 47 | 12 |
| Not specified | 39 | 10 |
| Prior cancer | 16 | 4 |
| Histotype* | | |
| A-C | 11 | 3 |
| D-G | 220 | 58 |
| H-K | 77 | 20 |
| Unclassified | 70 | 19 |
| T cell | 8 | 2 |
| Systemic symptoms | 7 | 2 |
| LDH ratio > 1† | 69/195 | 35 |
| Ocular disease† | 22/170 | 13 |
| Positive CSF cytology examination† | 38/241 | 16 |
| High CSF protein level† | 82/134 | 61 |
| Multiple lesions | 130 | 34 |
| Involvement of deep structures‡ | 136 | 36 |
| Site of disease | | |
| Frontal lobe | 166 | 44 |
| Parietal lobe | 50 | 13 |
| Temporal lobe | 52 | 14 |
| Occipital lobe | 24 | 6 |
| Basal ganglia | 104 | 28 |
| Brain stem | 21 | 6 |
| Cerebellum | 23 | 6 |
| Meninges | 39 | 10 |
| Cranial nerves | 3 | < 1 |

*Histotype was defined according to the Working Formulation Classification.

†Relationship between the number of positive cases and the total number of assessed patients.

‡Involvement of deep structures of the brain, ie, basal ganglia and/or corpus callosum and/or brain stem and/or cerebellum.

The independent prognostic value of variables was analyzed using the Cox proportional hazard model. The year of diagnosis was included as a continuous variable in the multivariate analysis to rule out the possibility that modern medical management could have influenced outcome more than the treatment itself. All of the probability values were two-sided.

## RESULTS

### *Patient Characteristics*

The main patient characteristics are listed in Table 1. The median age of the 378 patients was 61 years (range, 14 to 85 years), and 222 patients (58%) had an ECOG PS more than 1. An elevated lactate dehydrogenase (LDH) serum level was detected in 69 (35%) of the 195 patients assessed. Deep structures of the brain, that is periventricular regions, basal ganglia, corpus callosum, brainstem, and/or cerebellum, were involved in 136 patients (36%). Lymphomatous cells were found in 38 (16%) of the 241 patients assessed by CSF cytology examination. A higher proportion of patients (82 of 134, 61%) had an elevated concentration of CSF protein.

*Predictors of Response*

Of the 370 assessable patients, 226 (61%) achieved an objective response, including complete remission, continued complete response in patients with no measurable disease after resection, and partial response. Lymphoma remained unchanged in 22 cases, 102 patients had progressive disease during treatment, and 20 patients experienced toxic death. According to the planned therapeutic modality, 55 patients (56%) achieved an objective response after RT, 25 patients (69%) achieved an objective response after RT → CHT, 19 patients (59%) achieved an objective response after CHT alone, and 127 patients (64%) achieved an objective response after CHT → RT ($P = .42$). Among the 160 patients treated with primary CHT containing HD-MTX (CHT alone in 25 patients and CHT → RT in 135 patients), 111 (69%) achieved an objective response. Age, PS, LDH serum level, use of HD-MTX, and use of HD cytarabine were significantly correlated with overall response rate (Table 2).

*Predictors of Survival*

Treatment failure was experienced by 267 patients; toxic death occurred in 20 patients, progressive disease during treatment occurred in 102 patients, and relapse after response to first-line therapy occurred in 145 patients (relapse rate, 64%; 145 of 226 responders). The median FFS time was 9 months, with a 2-year FFS rate ± SD of 32% ± 2%. One hundred sixteen patients are alive (105 with no evidence of disease [NED]), with a median follow-up of 24 months (range, 2 to 174 months) and a 2-year OS rate ± SD of 37% ± 2%. The causes of death (n = 254) were lymphoma in 221 patients, toxic death in 20 patients, neurologic deterioration in three patients, unrelated causes while NED in seven patients, and unknown causes while NED in three patients. In the group treated with HD-MTX–based CHT ± RT, 90 patients experienced a treatment failure, with a median FFS time of 12 months and a 2-year FFS rate ± SD of 46% ± 4%. Seventy-six patients treated with HD-MTX are alive (71 NED), with a median follow-up of 26 months (range, 2 to 174 months) and a 2-year OS rate ± SD of 52% ± 4%.

Among the variables tested, age ≤ 60 years (2-year OS rate ± SD, 46% ± 3% *v* 29% ± 3%; $P = .00006$), ECOG PS less than 2 (50% ± 5% *v* 31% ± 3%; $P = .00001$), normal LDH level (49% ± 4% *v* 29% ± 5%; $P = .008$), normal CSF protein concentration (61% ± 7% *v* 39% ± 5%; $P = .003$), and absence of involvement of deep regions of the brain (42% ± 3% *v* 28% ± 4%; $P = .0006$) were significantly associated with a better survival. Multivariate analysis adjusted by the main prognostic factors (Table 3) showed an independent association between OS and age, PS, LDH serum level, CSF protein concentration, involvement of the deep structures of the brain, planned treatment, and the use of HD-MTX.

*Prognostic Score*

The variables independently associated with survival in the entire series were used to design a scoring system. These variables were age (≤ 60 *v* > 60 years), ECOG PS (0 to 1 *v* 2 to 4), LDH serum level (normal *v* elevated), protein CSF concentration (normal *v* elevated), and involvement of the deep structures of the brain (no *v* yes). Each variable was assigned a value of either 0, if favorable, or 1, if unfavorable. The values of these five variables were then added together to arrive at a final score. The score was analyzed in the 105 assessable cases in which complete data from all five variables were available. The number of adverse features was significantly correlated to survival, with a 2-year OS of 80% ± 8%, 48% ± 7%, and 15% ± 7% ($P = .00001$) for patients with zero to one, two to three, or four to five unfavorable features, respectively (Fig 1). In addition, this score was analyzed in the 75 assessable patients treated with HD-MTX–containing CHT. Once again, it revealed a 2-year OS of 85% ± 8%, 57% ± 8%, and 24% ± 11% ($P = .0004$) for patients with zero to one, two to three, or four to five unfavorable features, respectively (Fig 2).

## DISCUSSION

This study is an effort to identify patient- and disease-related predictors of response and survival in an international retrospective series of 378 immunocompetent patients with PCNSL. This is the second largest published PCNSL series and includes the largest group of patients treated with primary CHT containing HD-MTX. Age, ECOG PS, LDH serum level, CSF protein concentration, and involvement of deep structures of the brain were independent survival predictors in PCNSL patients. The combined analysis of these five variables resulted in a prognostic score that allows three different risk groups to be distinguished.

The identification of reliable and validated prognostic factors is an important issue in PCNSL; their impact on survival has been regarded as more important than the effect of treatment itself.[1,5] The statistical analysis conducted on small retrospective series has not allowed the identification of parameters with an independent predictive value, and some methodologic pitfalls have probably affected the definition of prognostic factors in prospective trials as well.[6] In some trials, the inclusion of patients with relapsed disease, systemic lymphoma, or histologically unproven diagnosis introduced important interpretation biases, and the initial extension and location of brain disease, CSF cytology status, and ocular disease were not consistently analyzed.

Age and PS are the only two universally accepted prognostic factors[1,2,7-14]; several other potential prognostic parameters such as histotype,[15] duration of symptoms, subtentorial localization,[11,15] and bilateral brain involvement[11,12] were proposed but failed to be confirmed in subsequent studies. In the past, some investigators suggested that age is a factor influencing therapeutic choice rather than an independent survival indicator,[13] whereas a critical review of 50 published PCNSL series confirmed age as a powerful independent prognostic variable in 676 assessable immunocompetent patients.[7] In our series, the planned therapeutic strategy played a prognostic role independent of age and PS (Table 3). Nevertheless, it is plausible that within each treatment subgroup, age and PS have influenced patient selection to receive more or less aggressive therapy, mainly in relation to CHT combinations and doses.

In a nationwide survey conducted on 466 patients treated at 62 Japanese institutions,[5] age, PS, B status, number of lesions, meningeal disease, and LDH serum level were related to survival. In that study, the influence of various prognostic factors was even greater than the effect of CHT; the small proportion of

**Table 2. Variables Tested for Objective Response Either in the Entire Series (n = 370) or in the Group of Patients Treated With Primary CHT Containing HD-MTX (n = 160)**

| Variables | Entire Series | | | | HD-MTX Group | | | |
|---|---|---|---|---|---|---|---|---|
| | No. of Patients | ORR | | P | No. of Patients | ORR | | P |
| | | No. | % | | | No. | % | |
| Age | | | | .001 | | | | .01 |
| ≤ 60 years | 187 | 123 | 66 | | 96 | 72 | 75 | |
| > 60 years | 191 | 103 | 54 | | 64 | 39 | 61 | |
| Sex | | | | .28 | | | | .09 |
| Female | 158 | 86 | 57 | | 61 | 47 | 77 | |
| Male | 220 | 140 | 63 | | 99 | 64 | 65 | |
| ECOG PS | | | | .00003 | | | | .005 |
| 0-1 | 117 | 83 | 71 | | 62 | 47 | 76 | |
| > 1 | 222 | 120 | 54 | | 93 | 62 | 66 | |
| Histotype | | | | .13 | | | | .74 |
| A-C | 11 | 8 | 73 | | 4 | 3 | 75 | |
| D-K | 297 | 168 | 57 | | 119 | 82 | 67 | |
| LDH serum level | | | | .009 | | | | .01 |
| Normal | 126 | 86 | 68 | | 80 | 63 | 79 | |
| Elevated | 69 | 36 | 52 | | 42 | 25 | 59 | |
| Systemic symptoms | | | | .99 | | | | .48 |
| A | 371 | 222 | 60 | | 155 | 108 | 70 | |
| B | 7 | 4 | 57 | | 5 | 3 | 60 | |
| Ocular disease | | | | .64 | | | | .77 |
| No | 148 | 95 | 64 | | 101 | 76 | 75 | |
| Yes | 22 | 15 | 68 | | 11 | 8 | 73 | |
| CSF cytology | | | | .32 | | | | .36 |
| Negative | 203 | 135 | 66 | | 126 | 93 | 71 | |
| Positive | 38 | 21 | 55 | | 12 | 7 | 58 | |
| CSF protein level | | | | .16 | | | | .08 |
| Normal | 52 | 36 | 69 | | 31 | 26 | 84 | |
| Elevated | 82 | 47 | 57 | | 54 | 36 | 67 | |
| No. of lesions | | | | .21 | | | | .34 |
| Single | 248 | 136 | 55 | | 82 | 61 | 74 | |
| Multiple | 130 | 80 | 62 | | 57 | 38 | 67 | |
| Deep lesions | | | | .52 | | | | .19 |
| No | 236 | 147 | 62 | | 88 | 59 | 67 | |
| Yes | 134 | 79 | 59 | | 49 | 38 | 78 | |
| Planned treatment | | | | .42 | | | | .53 |
| RT | 98 | 55 | 56 | | — | | — | |
| RT → CHT | 36 | 25 | 69 | | — | | — | |
| CHT | 32 | 19 | 59 | | 25 | 15 | 60 | |
| CHT → RT | 197 | 127 | 64 | | 135 | 96 | 71 | |
| HD-MTX | | | | .008 | | | | |
| No | 91 | 51 | 56 | | — | | — | |
| Yes | 169 | 117 | 69 | | — | | — | |
| HD cytarabine | | | | .004 | | | | .05 |
| No | 142 | 82 | 57 | | 61 | 37 | 61 | |
| Yes | 118 | 86 | 73 | | 99 | 74 | 75 | |
| Alkylating agents | | | | .48 | | | | .33 |
| No | 70 | 43 | 61 | | 46 | 30 | 65 | |
| Yes | 194 | 128 | 66 | | 114 | 81 | 71 | |
| Anthracycline | | | | .32 | | | | .71 |
| No | 118 | 74 | 62 | | 72 | 52 | 72 | |
| Yes | 142 | 94 | 66 | | 88 | 59 | 67 | |
| Intrathecal CHT | | | | .27 | | | | .52 |
| No | 156 | 97 | 62 | | 79 | 57 | 72 | |
| Yes | 109 | 74 | 68 | | 81 | 54 | 67 | |

Abbreviation: ORR, overall response rate (complete remission, continued complete response in patients with no measurable disease after resection, and partial response).

patients treated with HD-MTX–based CHT (6.5%) could, however, explain these results. In other large comprehensive retrospective series, age[16,17] and CSF protein level[17] were independently associated with survival. The analysis of large multicenter retrospective series of unselected immunocompetent PCNSL patients could be helpful in better defining predictors of survival. However, the retrospective nature of these studies and the prolonged observation period, during which standard of care and diagnosis notably evolved, could introduce some interpretation bias. In an attempt to overcome these difficulties, a consensus

**Table 3. Multivariate Analysis: Clinical and Therapeutic Variables Associated With Survival**

| Variable | Subgroup | Entire Series (N = 370) Odds Ratio | 95% CI | P |
|---|---|---|---|---|
| Age | Continuous variable | 1.02 | 1.01-1.03 | .0001 |
| Sex | Female/male | 1.24 | 0.95-1.62 | .11 |
| ECOG PS | 0-1/2-4 | 1.64 | 1.21-2.23 | .001 |
| Histotype | A-C/D-K | 0.97 | 0.73-1.31 | .87 |
| Systemic symptoms | A/B | 2.31 | 0.51-9.12 | .27 |
| LDH serum level | Normal/elevated | 1.41 | 1.01-2.08 | .05 |
| CSF protein level | Normal/elevated | 1.71 | 1.03-2.79 | .03 |
| No. of lesions | Single/multiple | 0.98 | 0.73-1.31 | .91 |
| Meningeal disease | No/yes | 1.28 | 0.81-2.01 | .28 |
| Ocular disease | No/yes | 0.81 | 0.45-1.49 | .51 |
| Deep lesions | No/yes | 1.45 | 1.11-1.91 | .007 |
| Planned treatment | RT/RT-CHT/CHT/CHT-RT | 0.91 | 0.83-0.99 | .05 |
| HD-MTX | Yes/no | 1.32 | 1.01-1.89 | .05 |
| HD cytarabine | Yes/no | 1.15 | 0.78-1.69 | .45 |
| Anthracycline | Yes/no | 1.01 | 0.68-1.48 | .97 |
| Alkylating agents | Yes/no | 1.27 | 0.81-2.01 | .28 |
| Intrathecal CHT | Yes/no | 1.21 | 0.85-1.72 | .28 |
| Year of diagnosis | Continuous variable | 0.99 | 0.96-1.02 | .81 |

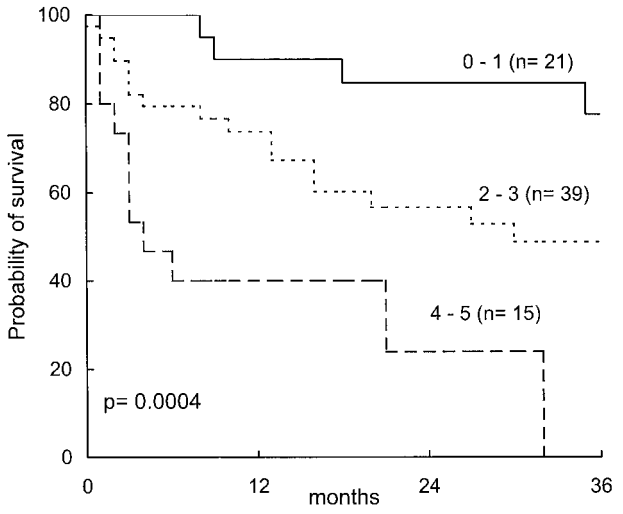


**Fig 2. Survival curves for patients grouped according to the proposed prognostic score: patients with 0 to 1 (solid line), 2 to 3 (dotted line), or 4 to 5 (dashed line) unfavorable features. Analysis was performed on the subgroup of 75 assessable patients treated with high-dose methotrexate-based chemotherapy ± radiotherapy.**

meeting to verify the questionnaire data was performed in this study, and the year of diagnosis was included in multivariate analysis to rule out the possibility that progressive changes in medical management could have introduced a bias in evaluation of outcome. Therapeutic results were poor in the present series (2-year OS rate ± SD, 37% ± 2%), which could be a result of the use of ineffective and outdated therapeutic strategies. This could have affected the identification of survival predictors. However, the value of the proposed prognostic variables and score was confirmed when analysis was limited to a group of patients treated according to modern criteria; that is, HD-MTX–based primary CHT with or without RT.

This study confirms the prognostic role of age and PS and establishes the value of LDH serum level, CSF protein concentration, and involvement of deep structures of the brain as predictors of survival. LDH serum level was previously analyzed as a part of the International Prognostic Index, without a significant association with survival in PCNSL patients.[18] In fact, that Index did not clearly distinguish low-risk patients from low-intermediate– and high-intermediate–risk groups.[17] This could be because two of the five parameters contained in the International Prognostic Index (ie, stage of disease and number of extranodal sites) have no variability in PCNSL. In this series, a high LDH serum level was significantly associated with a lower objective response rate and was independently related to a worse prognosis.

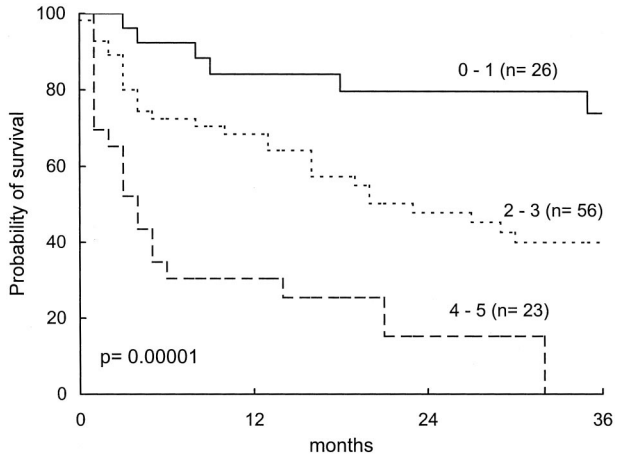


**Fig 1. Survival curves for patients grouped according to the proposed prognostic score: patients with 0 to 1 (solid line), 2 to 3 (dotted line), or 4 to 5 (dashed line) unfavorable features. Analysis was performed on the 105 assessable cases in which complete data from all 5 variables were available.**

As previously reported,[17,19] an increased CSF protein level was significantly associated with a lower response rate and independently related to shorter survival. The use of CSF protein level as well as any other CSF parameter as survival predictor is problematic because diagnostic lumbar puncture is not feasible in all PCNSL patients. This procedure has been considered contraindicated in a widely variable percentage of cases, ranging from 0%[1] to 42%.[20] The use of CSF variables could introduce a bias because they can be assessed in only a selected and, probably, favorable subgroup of patients. This selection bias has, however, been excluded by previous studies,[17,19] in which both patients with available CSF protein levels and patients in whom lumbar puncture was not performed at diagnosis showed a similar survival. These results were confirmed in our series, where lumbar puncture at diagnosis was tested as a dichotomic variable (performed *v* not performed) in a multivariate analysis adjusted for the other prognostic factors (data not shown). Another difficulty is related to the cutoff level chosen to define the unfavorable feature. In this series, the cutoff for normal CSF protein concentration was 45 mg/dL in patients ≤ 60 years old and 60 mg/dL in patients more than 60 years old,[3] whereas a cutoff of 150% of maximum normal level was previously used.[17] Because the CSF protein level may be an indicator of a more aggressive disease, the use of a more restrictive cutoff could result in the misjudging of some high-risk patients.[19] CSF protein level may be a measure of tumor burden, involvement of

deep structures of the brain, and/or meningeal dissemination. In this series, no correlation between CSF protein level and involvement of deep structures of the brain was observed. This feature was reported in 41% of cases with normal CSF protein levels and 33% of cases with elevated CSF protein levels ($P = .36$). Moreover, the distribution of cases with deep tumor locations was similar in patients with (36%) or without (41%) lumbar puncture at diagnosis ($P = .33$). In sum, these data seem to suggest that CSF protein level may be a measure of tumor burden and not of the involvement of deep structures of the brain. On the other hand, the role of CSF protein level as indicator of meningeal dissemination is unclear. In effect, elevated CSF protein concentrations are seen in a wide variety of brain tumors that do not have meningeal involvement. In this series, no correlation between CSF cytology status and CSF protein level was observed. In fact, although 90% of cases with normal CSF protein concentrations were associated with a negative CSF cytology examination, and 80% of cases with a positive CSF cytology examination also had an increased CSF protein concentration, only 22% of cases with increased CSF protein level had a concomitant positive CSF cytology examination ($\chi^2$, $P < .0000$). The well-known high percentage of false-negatives observed in CSF cytology examination in PCNSL[21] may explain this situation. In fact, the rate of leptomeningeal seeding is largely underestimated[21] because the detection of lymphomatous cells is sometimes impossible, even in the presence of extensive meningeal infiltration.[22-24]

This is the first study reporting an independent prognostic role of the involvement of deep structures of the brain in PCNSL patients. In fact, the involvement of periventricular regions, basal ganglia, brainstem, and/or cerebellum was associated with a poor prognosis. This feature was previously related to a worse survival only in univariate analyses,[17,19] although a potential association between involvement of the deep structures of the brain and a subclinical meningeal dissemination was hypothesized.[17] In our experience, the association between the involvement of deep structures of the brain and worse outcome was independent of the CSF parameters studied.

The combination of the five independent patient- and lymphoma-related predictors (ie, age, PS, LDH serum level, CSF protein concentration, and involvement of deep structures of the brain) resulted in a prognostic score significantly associated with survival. Three different risk groups were identified according to the presence of zero to one, two to three, or four to five unfavorable predictors, with a 2-year OS rate ± SD of 80% ± 8%, 48% ± 7%, and 15% ± 7% ($P < .0000$), respectively. These results were also confirmed when tested exclusively in the subgroup of patients treated with HD-MTX–based CHT ± RT. The independent role of these five variables and the clinical relevance of the proposed prognostic score deserve to be assessed in further studies. A wider use of well-defined prognostic factors will facilitate the critical comparison of reported therapeutic results, and an established prognostic score may allow the identification of different risk groups of patients who perhaps require distinct therapeutic strategies.

## APPENDIX

The appendix is available online at www.jco.org.

## REFERENCES

1. Corry J, Smith JG, Wirth A, et al: Primary central nervous system lymphoma: Age and performance status are more important than treatment modality. Int J Radiat Oncol Biol Phys 41:615-620, 1998

2. Abrey LE, Yahalom J, Deangelis LM: Treatment for primary CNS lymphoma: The next step. J Clin Oncol 18:3144-3150, 2000

3. Levinson SA, MacFate RP: Clinical Laboratory Diagnosis. Philadelphia, PA, Lea & Febiger, 1961, pp 916-917

4. Ferreri AJ, Reni M, Pasini F, et al: A multicentre study of treatment of primary CNS lymphoma. Neurology 58:1513-1520, 2002

5. Hayabuchi N, Shibamoto Y, Onizuka Y: Primary central nervous system lymphoma in Japan: A nationwide survey. Int J Radiat Oncol Biol Phys 44:265-272, 1999

6. Ferreri AJ, Reni M, Villa E: Therapeutic management of primary central nervous system lymphoma: Lessons from prospective trials. Ann Oncol 11:927-937, 2000

7. Reni M, Ferreri AJ, Garancini MP, et al: Therapeutic management of primary central nervous system lymphoma in immunocompetent patients: Results of a critical review of the literature. Ann Oncol 8:227-234, 1997

8. Nelson DF, Martz KL, Bonner H, et al: Non-Hodgkin's lymphoma of the brain: Can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315. Int J Radiat Oncol Biol Phys 23:9-17, 1992

9. Fine HA, Mayer RJ: Primary central nervous system lymphoma. Ann Intern Med 119:1093-1104, 1993

10. Maher EA, Fine HA: Primary CNS lymphoma. Semin Oncol 26:346-356, 1999

11. Michalski JM, Garcia DM, Kase E, et al: Primary central nervous system lymphoma: Analysis of prognostic variables and patterns of treatment failure. Radiology 176:855-860, 1990

12. Pollack IF, Lunsford LD, Flickinger JC, et al: Prognostic factors in the diagnosis and treatment of primary central nervous system lymphoma. Cancer 63:939-947, 1989

13. Jellinger KA, Paulus W: Primary central nervous system lymphomas: An update. J Cancer Res Clin Oncol 119:7-27, 1992

14. Shibamoto Y, Sasai K, Oya N, et al: Systemic chemotherapy with vincristine, cyclophosphamide, doxorubicin and prednisolone following radiotherapy for primary central nervous system lymphoma: A phase II study. J Neurooncol 42:161-167, 1999

15. Helle TL, Britt RH, Colby TV: Primary lymphoma of the central nervous system: Clinicopathological study of experience at Stanford. J Neurosurg 60:94-103, 1984

16. Bataille B, Delwail V, Menet E, et al: Primary intracerebral malignant lymphoma: Report of 248 cases. J Neurosurg 92:261-266, 2000

17. Blay JY, Conroy T, Chevreau C, et al: High-dose methotrexate for the treatment of primary cerebral lymphomas: Analysis of survival and late neurologic toxicity in a retrospective series. J Clin Oncol 16:864-871, 1998

18. Anonymous: A predictive model for aggressive non-Hodgkin's lymphoma: The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 329:987-994, 1993

19. Blay JY, Lasset C, Carrie C, et al: Multivariate analysis of prognostic factors in patients with non HIV-related primary cerebral lymphoma: A proposal for a prognostic scoring. Br J Cancer 67:1136-1141, 1993

20. Bessell EM, Lopez-Guillermo A, Villa S, et al: Importance of radiotherapy in the outcome of patients with primary CNS lymphoma: An analysis of the CHOD/BVAM regimen followed by two different radiotherapy treatments. J Clin Oncol 20:231-236, 2002

21. Ferreri AJ, Reni M, Villa E: Primary central nervous system lymphoma in immunocompetent patients. Cancer Treat Rev 21:415-446, 1995

22. Hochberg FH, Miller DC: Primary central nervous system lymphoma. J Neurosurg 68:835-853, 1988

23. Deangelis LM, Yahalom J, Heinemann MH, et al: Primary CNS lymphoma: Combined treatment with chemotherapy and radiotherapy. Neurology 40:80-86, 1990

24. Loeffler JS, Ervin TJ, Mauch P, et al: Primary lymphomas of the central nervous system: Patterns of failure and factors that influence survival. J Clin Oncol 3:490-494, 1985