Primary intracerebral malignant lymphoma: a clinicopathological study of 89 patients


Departments of Neurological Surgery, Laboratory Medicine and Pathology, Health Sciences Research (Section of Biostatistics), Diagnostic Radiology, and Neurology, and the Cancer Statistics Unit–Mayo Comprehensive Cancer Center, Mayo Clinic and Foundation, Rochester, Minnesota

The authors report on a clinicopathological study of 89 surgical patients with histologically proven primary parenchymal brain lymphoma, all diagnosed between January 1975 and December 1990. The cohort included 60 men and 29 women whose median age at diagnosis was 60 years (range 14 to 84 years). The duration of symptoms was less than 8 weeks in 48% of the patients. Symptom groups included focal neurological deficit (73%), neuropsychiatric symptoms (28%), seizures (9%), and increased intracranial pressure (3%). A total of 132 tumors were seen in 89 patients; the most common sites were frontal (32 patients), temporoparietal (31 patients), and basal ganglia (17 patients); multiple lesions were reported in 23 patients. No patient had antecedent of human immunodeficiency virus positivity or acquired immunodeficiency syndrome. A family history of cancer was present in 33% of the patients, three-quarters of whom were first-degree relatives. Histological subtypes (National Cancer Institute Working Formulation) included 64 large cell (72%) and 13 immunoblastic (15%) tumors. Phenotype was determined in 66 patients; 63 were B-cell type and three were T-cell type. Surgical resection was performed in 47% of the cases, with the remainder undergoing biopsy only. All but six patients received radiation therapy. Thirty-one patients received chemotherapy, whereas 46 patients did not; data on the remaining 12 patients were unavailable. The end point of the study was death from any cause. At the time of last contact, 69 of the patients (78%) had died; the median survival time for this study group was 20.9 months. On univariate analysis, prognostic factors significantly associated with survival included age at diagnosis, family history of cancer, and focal neurological deficit. Multivariate analysis revealed four unfavorable prognostic factors: age greater than or equal to 60 years, history of cancer in first-degree relatives, focal deficit, and ependymal contact. After adjustment for these variables, clinical syndrome, size and number of lesions, extent of surgery, histological cell type, radiation dose, and use of chemotherapy were not significantly associated with survival.

**KEY WORDS** • primary central nervous system lymphoma • brain neoplasm • non-Hodgkin’s lymphoma

Intracerebral parenchymal lymphoma is the most frequent manifestation of primary central nervous system (CNS) malignant lymphoma. Other anatomical sites of involvement include infiltration of the posterior vitreous of the retina, which may either precede or accompany the development of a brain lesion, meningeal involvement with or without subependymal nodules, and intradural spinal lymphoma. Primary CNS malignant lymphoma arises in the CNS in the absence of apparent systemic lymphoma and typically fails there. It is a rare tumor, accounting for less than 2% of all primary brain tumors and having an estimated annual incidence of 1.83 per 1,000,000 people. Risk factors associated with the occurrence of primary CNS malignant lymphoma include acquired immunodeficiency syndrome (AIDS), immunosuppression for organ transplantation, putative autoimmune diseases, and congenital immunodeficiencies such as Wiskott–Aldrich syndrome. Over the past decade, the incidence of primary CNS malignant lymphoma has increased in both immunosuppressed and immunocompetent patient populations beyond that which can be accounted for by improved diagnostic capabilities. Furthermore, the increase in primary CNS malignant lymphoma exceeds the increasing frequency of systemic non-Hodgkin’s lymphoma (NHL).

Although primary CNS malignant lymphoma develops in the nervous system and in most cases does not spread elsewhere, its pathological findings are similar, if not identical, to those of systemic NHL. Treatment principles applicable to systemic NHL should also be relevant to primary CNS malignant lymphoma. However, the results of multiple radiation, chemotherapy, and combined treatment trials have shown that the fate of patients with primary CNS malignant lymphoma is very different from that of patients with lymphoma occurring at other extranodal sites. Thus, the treatment of this tumor continues.
to be a formidable challenge. With the incidence of primary CNS malignant lymphoma increasing, physicians and health-care workers in related fields will need to develop a clear understanding of this disease process as a prelude to developing more effective therapies. To that end, in this retrospective study we examined the clinical and neuroimaging findings and the histological and immunohistochemical features of 89 primary cerebral lymphomas treated at the Mayo Clinic between 1975 and 1990 with a particular emphasis on use of immunotyping to define the pathological characteristics of these tumors.

Clinical Material and Methods

Patient Characteristics

The clinical records of 89 patients with histologically proven primary intracerebral lymphoma who underwent primary treatment at Mayo Medical Center between 1975 and 1990 were reviewed retrospectively. Patients whose tumor was diagnosed at autopsy, inferentially by the association of a mass lesion with intraocular lymphoma, on the basis of the detection of malignant cells in the cerebrospinal fluid (CSF), or by a positive meningeal biopsy alone were excluded from the study. Testing to exclude systemic lymphoma was performed for all cases identified as primary intracerebral lymphoma. Although these tests varied somewhat according to when the diagnosis was made and according to the practice of the responsible physician, most patients had a consultation with a hematologist and underwent bilateral iliac crest bone marrow aspirate and biopsy as well as abdominal computerized tomography (CT). Patients seen fairly recently also had CT scans of the chest as well as an ophthalmological evaluation. Male patients also had an ultrasound examination of the testes.

For each patient, information was obtained concerning 1) personal and family history of autoimmune disorders such as collagen vascular disorders, thyroiditis, or myasthenia gravis, and of cancer; 2) personal history of blood transfusions, organ transplantation, malignancy, or use of immunosuppressive drugs; 3) signs and symptoms at primary diagnosis; 4) preoperative assessment; 5) initial surgery; 6) adjuvant radiation and/or chemotherapy; 7) examination of removed tissue; and 8) postoperative care. Death certificates and autopsy reports were examined when available. Follow-up information was obtained from the medical records of patients who returned for further evaluation and treatment or by correspondence with patients or their local physicians.

Histological and Immunoperoxidase Staining

Hematoxylin and eosin–stained slides from all specimens were reviewed by two pathologists, a neuropathologist (B.W.S.) and a hematopathologist (P.J.K.) to verify the diagnosis of lymphoma and to classify the lymphomas according to the criteria of the Working Formulation.29 Phenotypic studies were performed using the labeled streptavidin biotin–peroxidase immunoperoxidase staining technique on paraffin sections (74 specimens) or on frozen sections (15 specimens) of the neoplasms. The methods for these techniques have been published previ-

### TABLE 1

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* L-26 and UCCHL-1 antibodies supplied by Dako Corporation, Carpentry, California; Leu-22, Leu-1, Leu-4, Leu-3ab, and Leu-2a supplied by Becton-Dickinson Corporation, Santa Barbara, California; and B1 antibody supplied by Coulter Corporation, Hialeah, Florida.

Statistical Evaluation

Duration of patient survival, from definitive surgery to death from any cause, was estimated using the Kaplan–Meier method.16 Expected survival was estimated using a cohort of age- and sex-matched individuals from the northwestern–central region of the United States. The log-rank test33 was used to assess the strength of the association between survival time and single variables corre-
sponding to factors thought to be prognostic for survival. To assess the association of survival with multiple patient, tumor, and treatment characteristics, both backward and forward stepwise procedures for generating proportional hazards general linear models, as proposed by Cox, were used. Due to the retrospective nature of the study, data points for some potential prognostic variables were lacking. When the forward stepwise procedure was performed, values that were not available were set to “no” or “negative;” thus, some finding may be underrepresented. When the backward stepwise procedure was performed, potential prognostic variables were redefined to indicate that there was no value available for a patient.

Results

Patient Characteristics at Diagnosis

The study involved 60 male and 29 female patients. The median age was 59 years (range 14 to 84 years; mean 57.4 years). Symptoms at presentation included focal neurological deficit in 65 (73%), neuropsychiatric disturbance in 25 (28.1%), seizures in eight (9%), and signs of increased intracranial pressure in three (3%). The median duration of symptoms was 8 weeks (range 1 week to 24 months). No patient had a prior diagnosis of human immunodeficiency virus positivity or of AIDS. A family history of cancer was present in 29 (33%) of the patients, three-quarters of whom were first-degree relatives. Five of the 89 patients had a prior personal history of malignancy, including two patients with chronic lymphocytic leukemia and three with adenocarcinoma (breast, prostate, or colon). Six patients had a history of an immunodeficiency disorder, six an autoimmune disorder, two an organ transplant, and five blood transfusion.

Neuroimaging Studies

Multiple lesions were reported in 26% of the patients. Information on steroid use was available for 67 patients, 28 of whom were taking some form of corticosteroid at the time of neuroimaging. Among the 64 patients for whom tumor size was known, the maximum dimension ranged from 9 to 80 mm (median 29 mm). The location of the 120 lesions encountered included frontal lobe (38), parietal lobe (26), basal ganglia (18), cerebellum (12), temporal lobe (nine), corpus callosum (seven), hypothalamus/septum (six), brainstem (three), and occipital lobe (one). Ependymal contact was present in 35 patients, absent in 33 patients, and unknown in 21. Eight of the patients’ scans showed hydrocephalus. Four tumors occurred at the site of a prior surgical procedure, either a biopsy or craniotomy. No patient’s scan displayed hemorrhage or cystic change. We were unable to estimate the frequency and the degree of steroid effect on these lesions.

Histology and Phenotype

There were 63 B-cell lymphomas and only three T-cell lymphomas. In the remaining cases T- or B-cell lineage could not be determined, usually because the tissue proved to be insufficient to run a panel of antibodies that would unambiguously establish the phenotype. In 64 cases (72%) the tumors were diffuse large cell lymphomas (Fig. 1 left) and in 13 cases (15%) they were of the immunoblastic type (Fig. 1 right). Of the 47 large cell and the 10 immunoblastic lymphomas that were successfully phenotyped, all were of B-cell lineage (Fig. 2). All B-cell lymphomas lacked staining for T cell–associated antigens, including CD3, CD4, CD5, CD8, and/or CD45RO. A small subset of the B-cell lymphomas aberrantly expressed CD43 (four cases). In addition there were four cases of diffuse small noncleaved cell lymphoma (all pleomorphic variant and of B-cell phenotype), two cases

Fig. 1. Photomicrographs showing two malignant lymphomas. Left: Large noncleaved cell type, B-cell phenotype. The neoplastic cells are large with round nuclei, dispersed chromatin, multiple nucleoli apposed to nuclear membranes, and a modest amount of cytoplasm. Right: Immunoblastic type, B-cell phenotype. The neoplastic cells are large with round to irregular nuclear outlines, marginated heterochromatin, and single central prominent nucleoli. H & E, original magnification x 300.

Fig. 2. Photomicrographs showing a malignant lymphoma, large noncleaved cell type, B-cell phenotype. The neoplastic cells are strongly immunoreactive for CD20 (left) and aberrantly coexpress CD43 (right). Immunoperoxidase stains on paraffin sections, aminoethyl carbazole chromogen and hematoxylin counterstain, original magnification x 350.
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of diffuse mixed cell lymphoma (one of B-cell and one of T-cell phenotype), two cases of diffuse small lymphocytic lymphoma with plasmacytic differentiation (one B-cell and one indeterminate phenotype), two T-cell lymphomas that were difficult to classify by the Working Formulation\textsuperscript{29} (Fig. 3), and one case of an unclassifiable lymphoma that could not be phenotyped due to lack of sufficient tissue. Regardless of the classification of the lymphomas, three histological patterns of brain involvement were noted. Most often, the neoplastic cells produced destructive parenchymal masses with variable angiocentricity and expansion of Virchow-Robins spaces (Fig. 4). In some cases, tumor was present only in a perivascular distribution (Fig. 5), and in one case there was patchy infiltration of the brain parenchyma associated with vascular proliferation and gliosis (Fig. 6). Tumor necrosis was present in only two cases.

Neurooncological Data

Of those patients who had lumbar punctures, 16 of 28 (57.1\%) had abnormal nucleated cell counts and 25 of 32

![Fig. 3](image1.png)

*Fig. 3. Photomicrographs showing a malignant lymphoma, pleomorphic small lymphocytic type, T-cell phenotype. Left: There is massive infiltration of the brain and expansion of the Virchow-Robins spaces by a monomorphous population of small lymphocytes with markedly irregular hyperchromatic nuclei and sparse cytoplasm. H & E, original magnification $\times$ 150. Right: The neoplastic cells are uniformly immunoreactive for CD45RO. Immunoperoxidase stain on paraffin sections, aminoethyl carbazole chromogen and hematoxylin counterstain, original magnification $\times$ 150.*

![Fig. 4](image2.png)

*Fig. 4. Photomicrograph showing a case of large cell lymphoma that has a marked involvement of the brain parenchyma with expansion of the Virchow-Robins spaces. H & E, original magnification $\times$ 150.*

![Fig. 5](image3.png)

*Fig. 5. Photomicrograph showing a case of large cell lymphoma in which the lymphomatous involvement was distinctly perivascular and infiltration of the cerebral cortical parenchyma was minimal. H & E, original magnification $\times$ 150.*

![Fig. 6](image4.png)

*Fig. 6. Photomicrograph illustrating a diffuse mixed-cell lymphoma that involves the brain in a patchy fashion. Aggregates of neoplastic lymphocytes are associated with vascular proliferation, gliosis, and collections of foamy macrophages. H & E, original magnification $\times$ 150.*
had abnormal total protein values. Four of 31 patients (12.9%) had diminished glucose values (below 50 mg/dl). Lymphoma cells were not present in any CSF specimen.

Surgical resection was undertaken in 42 patients (47.2%); the remaining patients underwent biopsy only. Eight-three patients (93.3%) received radiation therapy. In the radiation group the total dose received ranged from 1600 to 6120 cGy with a median value of 5000 cGy. Thirty patients received less than 48 Gy, 35 received between 48 and 51 Gy, and 16 received more than 53 Gy. Four patients died prior to completing their planned course of radiation therapy. Six patients received no radiation therapy; reasons for this included death (one patient), treatment with chemotherapy only (three patients), and clinical deterioration (two patients). Of the 31 patients who received chemotherapy, 23 received it prior to radiation, five after irradiation, and three as the sole treatment modality. Forty-six patients were not treated with chemotherapy, and data were unavailable for the remaining 12.

**Patterns of Failure**

Data regarding response to therapy and pattern of failure were available in only 54 patients, and failure was confirmed in 35. Seven patients, none of whom achieved a complete remission with initial therapy, had disease progression/recurrence at the primary tumor site. Of these seven patients, one had failure at the primary site only and one experienced progression/recurrence at another brain site as well. Of the remaining 28 patients, 22 patients had tumor recurrence at one or more CNS sites, including one patient who had meningeal relapse alone and two patients who also relapsed outside the CNS. Six patients had no evidence of CNS disease at the time of systemic relapse; instead one patient had disease in the soft tissues, three in the testis, and two at other sites. Of note is one patient who had testicular relapse without CNS disease only to develop brain recurrence 18 months later. A total of 22 patients had some form of additional therapy at the time of progression/recurrence; these included chemotherapy only (17), radiation therapy (two), resection and chemotherapy (one), and radiation with chemotherapy (two).

**Survival Data**

Survival data were available for all patients. At the time of last contact 69 patients (78%) had died; 43 were dead of disease, eight died of unrelated causes, and 18 died of unknown causes. The median survival time was estimated to be 20.9 months. Among the 20 patients alive at last contact the median length of follow up was 2.8 years (range 170 days to 8.9 years).

To identify independent prognostic factors, we defined several variables to quantify patient characteristics (age, sex, residence, year of diagnosis, symptoms at diagnosis, family history of cancer), tumor factors (histological number of lesions, size and location of lesions, and ependymal contact), and treatment variables (surgery, radiation, adjuvant chemotherapy). For each of the potential prognostic factors, Kaplan–Meier survival curves were constructed and the log-rank test was used to assess whether survival differed with respect to that variable. Table 2 shows the median survival in months as well as log-rank p values given for patient characteristics, tumor characteristics, and treatment variables. Of these variables, age greater than or equal to 60 years, presence of a focal neurological deficit, and having a family history of cancer were found to be univariately associated with decreased survival.

A series of Cox models was generated using a forward selection process. A new variable was added to the previous model if it had the smallest p value of all the variables not yet in the model, measuring the strength of its association with survival after adjustment for the effects of the variables already in the model. The “best” multivariate Cox model was defined to be the largest model such that all variables in the model had p values less than 0.05 measuring the strength of their association with survival after adjustment for the effects of the other variables in the model. The best forward model had four variables, all unfavorable: age greater than or equal to 60 years (yes/no; p = 0.0046), ependymal contact (yes/no or unknown; p = 0.0463), focal neurological deficit (yes/no; p = 0.0312), and family history of cancer (yes/no; p = 0.0367). Based on the results of the log-rank tests, several variables were omitted (those with < 0.20) from the backward selection process. Backward stepwise Cox models were generated whereby the first model contains all the candidate variables and then, at each step, the variable with the weakest association with survival is eliminated. Four variables were contained in the best backward model: age greater than or equal to 60 years (yes/no; p = 0.0023), family history of cancer (yes/no; p = 0.0533), focal deficit (yes/no; p = 0.0396), and ependymal contact (yes/no/unknown) (p = 0.251).

**Discussion**

Although this study represents the largest reported series of patients seen at one institution, it must be cautiously interpreted in light of its retrospective nature. All patients reported were diagnosed during the “modern” neuroimaging era. The neuroimaging studies employed accurately displayed the tumors’ site(s), number, associated phenomena (mass effect, meningeal contrast enhancement, hydrocephalus, and so forth), response to therapy, patterns of failure, and side effects of therapy. Clinical diagnostic criteria differed over the time course of the study. Furthermore, patients recently diagnosed were subjected to more extensive clinical staging than those entered earlier in the series. However, inclusion of the earlier patients in the study is valid because 1) the clinical criteria used were based upon diagnostic criteria accepted at that time; 2) the subsequent clinical course following diagnosis was no different than that of the patients entered later; and 3) all histological diagnoses were reconfirmed, there being no variations in tumor subtype over the period of the study. In addition, the main prognostic features of interest were related to patient age and family history of cancer, factors that did not vary over the duration of the study. The degree and frequency with which lesions exhibited ependymal contact could have varied over the course of the study, because MR imaging scans, which more accurately display small lesions and men-
ingeval involvement, only became widely available toward the end of the study and were used in only two cases. None of these patients had, or was suspected of having, AIDS. The conclusions, therefore, should be taken to represent a non-AIDS group. However, according to clinical, neuroimaging, and survival data, primary CNS malignant lymphoma in the context of AIDS is different and is well summarized elsewhere.11,15,30,35

Radiation therapy was received by 83 of the patients (93.3%). The total dose ranged from 1600 cGy to 6120 cGy (median 50 Gy). To assess whether radiation therapy was associated with survival (death from any cause), the total dose was split at the group’s median, 50 Gy. Available radiotherapy data suggest that a dose–response relationship exists for primary CNS malignant lymphoma with an improved survival time associated with doses greater than 50 Gy to the primary tumor.1,19,24 For these reasons 50 Gy was selected as a treatment variable. However, we observed no significant association with survival (p = 0.1603) and at 1 year, the 95% confidence interval for the Kaplan–Meier estimates of survival began to overlap for the two groups. Because whole-body radiation therapy was not administered within the context of a prospectively randomized trial, it is possible that the group of patients who did not receive whole-body radiation therapy included those who died early or otherwise deteriorated rapidly following craniotomy; in effect, removing the patients with the worst prognosis from the radiotherapy group and placing them in the nonradiotherapy group. Unfortunately, there was some evidence that such a bias might exist: the patients who survived less than 8 weeks received either no radiation or less than 48 Gy and terminated radiation therapy within 10 days prior to their death. This same bias flaws many reported series. Typically, only patients who complete therapy are counted in determining treatment response, data regarding the interval between tumor diagnosis and the start of therapy rarely being available.

Most primary CNS malignant lymphoma series describe young and healthy patients, individuals different from those in our study and primary CNS malignant lymphoma patients as a whole. These characteristics confer a
survival advantage, not only in primary CNS malignant lymphoma but in other forms of brain tumor as well. An analysis of nine papers reporting the results of treatment in at least 10 patients each showed that median survival ranged from 9 to 44.5 months and that the median age of the total 130 patients in these reports was 53.7 years.\(^{2,3,7,12,17,27,28,38,40}\) In our study a significantly improved survival was seen in patients under 60 years of age, a finding also noted in other studies of primary CNS malignant lymphoma.\(^{3,26}\) and of systemic NHL wherein age was found to be a significant prognostic factor.\(^{8,41}\)

The reason why older age is associated with a poorer prognosis is not readily apparent. It may be related to differing metabolism of chemotherapeutic agents in older patients, reduced organ tolerance to these agents (toxicity), a reluctance on the part of clinicians to administer to older patients therapy as intensive as that given to younger patients, alterations in delivery of drugs to the nervous system with age, reduced tolerance to radiation therapy in older patients, and even a biological difference in the malignant lymphocytes themselves. A parallel exists in other high-grade primary cerebral neoplasms such as glioblastomas.\(^{57}\) In these tumors, age is also an important prognostic factor with survival of patients younger than 50 years being twice that of patients older than 50 years.\(^{36}\) This observation suggests that the immunological mechanisms of the brain in later decades are less efficient in both recognizing tumor cells and handling an accumulation of toxic byproducts following radiation therapy.

Although a family history of cancer has been reported to occur more frequently in patients with glioblastoma, neuroblastoma, and malignant lymphoma of the brain,\(^{20}\) an unexpected finding in our study was the substantial percentage of patients who had a family history of cancer and the recognition of this factor as an indicator of poor prognosis. The occurrence of cancer in families has long been recognized.\(^{21}\) For instance, the Li-Fraumeni syndrome, which is characterized by tumors in both the CNS and at systemic sites, has been shown to be due to an inherited germline p53 mutation.\(^{44}\) It is also notable that a population-based case-control study of Swedish patients with multiple myeloma reported an increased risk for the disease for persons with first-degree relatives who had hematological malignancies, as well as an increased risk if the close relative(s) had a tumor of another type.\(^{10}\) The reason why a family history of cancer in first-degree relatives should be associated with a poor prognosis is not apparent from our study. This finding, however, suggests the possible role of an inherited altered genome product capable of influencing the clinical course of the tumor. If the mechanism has to do with immune-mediated destruction and clearance of cancer cells, the CNS sanctuary site could be more critically affected by such an inherited defect in immunocompetence.

Diffuse large cell lymphoma was the predominant cell type noted in this study, accounting for 72% of cases. The percentage is higher than that reported by Jellinger and Paulus\(^{55}\) in their recent review but is in keeping with other reports.\(^{13,14,26,30}\) Our criteria for the classification of a lymphoma as immunoblastic type were rigidly defined, thus some tumors diagnosed in other series as immunoblastic type would have been classified as large cell type in our study. The incidence of diffuse large cell lymphoma in our series is also double that seen in HIV-associated primary CNS malignant lymphoma, in which the predominant subtypes are the higher grade immunoblastic and small noncleaved cell types. This observation suggests the possibility of a pathogenesis of CNS lymphomas in immunocompromised patients that differs from that found in immunocompetent patients. Our study also confirms other reports that low-grade lymphomas and T-cell lymphomas are rare in the CNS.\(^{3,13,23,30}\)

Prognostic variables reported to be significant in primary CNS malignant lymphomas have included lesion number, relationship of tumor to the ependyma or meninges, and the anatomical location of the tumor.\(^{24}\) In our series, patients with multiple lesions did not have a poorer prognosis compared to patients with single lesions. A similar conclusion was reached by Namasiyavam and Teasdale\(^{25}\) but not by Hochberg and Miller.\(^{14}\) We cannot exclude the possibility that some tumors lacked contrast enhancement.\(^{5}\)

In this series, the survival of patients with tumors involving deep gray matter was not found to differ from that of patients with tumors at other locations. One might think that lymphoma with proximity to the ventricular system would have a greater risk of cerebrospinal dissemination.\(^{6,39}\) In fact, Namasiyavam and Teasdale\(^{25}\) noted that those tumors close to the meninges had a better prognosis. Studies have not confirmed the notion that a failure pattern can be predicted based on the location of the primary tumor. Furthermore, therapeutic programs specifically directed toward treatment of the CSF have not as yet demonstrated a survival advantage compared to irradiation alone or irradiation plus systemic chemotherapy.\(^{3,7,26,28,31}\)

In our series, the frontal lobe was involved in 32 (36%) of the 89 cases, a frequency similar to that reported by other authors.\(^{24}\) This large percentage has been attributed to the fact that the frontal lobes volumetrically represent a substantial part of the brain. Because they also constitute the part of the CNS which has the greatest amount of ependymal surface area, the frontal lobes would be expected to be the part most affected if the CSF were found to be important to failure pattern. However, in our series, there was no evidence to suggest that a poorer survival rate was associated with tumor location.

Our series found that male patients were affected twice as often as female patients and that the median patient age was 59 years. Furthermore, in half of the cases symptoms were less than 8 weeks in duration. For the purposes of our study we arbitrarily divided clinical presentation into groups of patients with focal neurological deficit, seizures, signs of increased intracranial pressure, and neuropsychiatric symptoms. Nearly three-quarters of patients had a presentation consistent with focal deficit, confirming that the typical primary CNS malignant lymphoma patient is a late–middle aged man who presents with a syndrome of a subacute mass lesion.\(^{6,14,30}\) The low frequency of seizures in this group of patients probably relates to the subcortical location of most of these tumors. The high concentration of neuropsychiatric symptoms in our primary CNS malignant lymphoma patients may relate to the large numbers of frontal lobe tumors and also to the involvement of other
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areas of the brain important in affective behavior such as the septal region and hypothalamus. Given that the latter regions are much less commonly affected by glial tumors, they are associated with a lower frequency of neuropsychiatric symptoms.

Primary CNS malignant lymphoma is unique among primary brain tumors in that it may recur at the primary site, at other brain sites, elsewhere in the neuraxis, in the eyes, systemically, or at any combination of these sites. As a general rule, those tumors exhibiting a complete therapeutic response at the primary site do not recur there, whereas those with less than a complete response will recur, with or without involvement at other sites.14,19,22,30

The frequency of systemic failure has been variously estimated at between 2% and 10%,14,22,30 but is rarely clinically significant because it is typically a postmortem finding alone.22 No clear association has been made between systemic spread and identifiable risk factors. Indeed, in our series, six of nine patients with systemic relapses had no evidence of neurological progression or failure at the time of relapse. Staging procedures may have failed to detect occult systemic disease in two patients in this study, both of whom developed systemic lymphoma before brain radiation was complete. However, the interval between diagnosis of the primary tumor and the systemic disease was sufficiently long in the remaining seven patients (6 to 44 months) that an alternate explanation must be considered. In patients with Stage IE systemic NHL in whom relapse may occur more than 5 years after successful treatment, speculation has centered on recurrent or ongoing immunodeficiency that permits another clone of neoplastic lymphocytes to develop.43 Whether that is the case with primary CNS malignant lymphoma remains to be proven.

Because the mechanism of CNS lymphomagenesis is not known and treatment decisions have been largely empirical, based primarily on conclusions derived from systemic NHL trials, one must take into consideration unique features of the CNS that may be important such as the blood-brain barrier. Extrapolating from the systemic NHL literature, Stage IE CNS lymphoma should be curable. However, the results of this study and other studies in the literature confirm the fact that the survival in patients with this tumor is dismal, resembling that of patients with glioblastoma multiforme. Hopefully, data from this study will aid in the design of more effective treatment schemes for primary CNS malignant lymphoma.

References


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Address reprint requests to: Brian P. O’Neill, M.D., Department of Neurology, Mayo Clinic, 200 First Street, S.W., Rochester, Minnesota 55905.