

## Primary Brain Lymphoma in Immunocompetent Patients-Prognostic Factors and Treatment Outcome

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### ABSTRACT

**Background:** Primary brain lymphoma (PBL) is an aggressive intracranial neoplasm of lymphocytic origin that involves the brain parenchyma and meninges. The increasing number of cases of PBL has resulted in a growing awareness of and interest in this disease and has promoted a large number of publications.

**Material and methods:** Twenty-nine immunocompetent patients with primary non-Hodgkin's Lymphoma of the brain (PBL) were seen at our institute between 1975 and 1998. Twenty-seven patients had received external radiation therapy (XRT). The treatment volume included the whole brain (WB) in 10 patients, WB plus boost in 12 patients and the craniospinal axis in 5 cases. The XRT dose ranged from 5.4 to 60 Gy with a median of 50 Gy. Two patients received pre-irradiation high dose methotrexate. One patient received intrathecal methotrexate and one had 3 cycles of adjuvant chemotherapy.

**Results:** The mean age at diagnosis was 53 years. Nine patients (31%) were found to have multifocal tumors. Eighteen patients were evaluable for assessment of treatment response. Complete response was achieved in 13/18 patients (72%), while 4 (22%) had partial response. Six of 13 patients (46%) who achieved complete response relapsed. Late neurotoxicity was reported in 9 of 15 patients who survived for more than 6 months after therapy. With a median follow up of 24 months, the 3 and 5-year overall survival (OS) rates were 40% and 16%, respectively. The median survival was 1.1 year. Age < 60 years, performance status < 4, solitary brain lesion, XRT dose > 40 Gy, WB XRT with boost and complete response to therapy were found to be associated with statistically significant higher OS rates. Cox regression analysis indicated that performance status, response to therapy and XRT dose > 40 Gy were the most significant prognostic variables.

**Conclusion:** The outlook with primary brain lymphoma in immunocompetent patients remains somewhat dismal. Randomized trials addressing the efficacy of chemotherapy (with and without radiation) over radiation alone are needed. New treatment approaches need to be considered in a multiinstitutional setting.

**Key Words:** Primary brain lymphoma - Immunocompetent patients - Treatment.

### INTRODUCTION

Primary brain lymphoma (PBL) is an aggressive intracranial neoplasm of lymphocytic origin that involves the brain parenchyma and meninges. It is often associated with acquired or congenital immunosuppression, but in the past 15 years, its incidence has risen threefold among apparently immunocompetent individuals [10]. This increase in incidence in immunocompetent hosts is not explained by improved diagnostic, or epidemiologic modalities [24]. The increasing number of cases of PBL lymphoma has resulted in a growing awareness and interest in this disease and has promoted a large number of publications.

Studies comparing the immunophenotypic patterns of PBL with those of systemic lymphomas have not shown any substantial differences [11].

Stereotactic biopsy provides a high rate of positive tissue diagnosis. No data suggest that extensive surgery benefits patients with primary brain lymphoma [4].

PBL is radiosensitive and external beam radiotherapy (XRT) was considered to be the conventional treatment. Although radiotherapy frequently produces radiologic complete remission, disease recurrence usually occurs intracranially, within or outside the treated volume. The median survival after radiotherapy is 12-18 months [18] and the 5-year survival is 14-26% [22].

Favourable results of combined chemotherapy and XRT for systemic non-Hodgkin's lymphomas suggest a potential benefit in PBL with the same approach. Some authors have reported a significant improvement in the therapeutic outcome with various chemotherapy schedules with a 5-year actuarial survival of 36% [5].

Most of the studies on this disease are retrospective with patients spanning a long period of time and treated with different modalities making intercomparison of data difficult. The poor prognosis of PBL in general is well known.

### PATIENTS AND METHODS

Over a 23-year period, from 1975 to 1998, 29 immunocompetent patients with the histologic diagnosis of non-Hodgkin's PBL were seen at King Faisal Specialist Hospital and Research Centre, which is a national tertiary centre for patients with cancers. None of the patients had a history of AIDS or any other immunosuppressive disorder. During the same period, 2094 non-Hodgkin's lymphomas were registered, giving a prevalence rate of 1.4% for PBL [3]. Clinical data were obtained directly from the patients' medical records. The World Health Organization (WHO) performance status (PS) was used to assess the PS at diagnosis [18]. All histologic materials were reviewed by pathologists at King Faisal Specialist Hospital and Research Centre at the time of initial referral. For the purpose of this review, all the charts and 20 pathological slides were reviewed by one lymphoma expert pathologist and the diagnosis was confirmed and they were re-classified according to the Revised European-American Lymphoma classification (REAL) [13]. The initial staging investigations performed in these patients at presentation were as follows: CT brain, chest X-ray and abdominal CT or ultrasonogram in all patients, brain MRI in 12, MRI of the spine in 3, bone marrow aspirate and biopsy in 15 and cerebrospinal fluid cytology in 10. The initial surgery was biopsy in 17 patients, partial excision in 10 cases and gross total excision in 2 cases. Twenty-three patients had received steroids peri-operatively and these were continued or tapered as the patient's condition required.

One patient had biopsy only and refused any further treatment, while another patient with very poor performance status died 1 month after partial excision of the tumor.

Twenty-seven patients had received XRT. The treatment volume included the whole brain (WB) in 10 patients, WB plus boost in 12 patients and the craniospinal axis in 5 cases. Among the 5 patients who received craniospinal axis XRT, only one had positive CSF cytology and one had ventriculo-peritoneal shunt. The XRT dose ranged from 5.4 to 60 Gy with a median of 50 Gy. XRT doses were 50 Gy or higher in 14 patients, while 18 patients received doses higher than 40 Gy. The spinal axis received 20 Gy in 3 patients and 32 Gy in 2 cases. Five patients died shortly after commencing XRT; consequently, their total radiation doses were low. Radiation was delivered to all fields once daily. Patients were treated either on a cobalt unit or 6Mv linear accelerator.

Two patients received pre-irradiation high dose methotrexate 3 g/m<sup>2</sup>; one patient received 3 cycles and the second patient had 2 cycles only as he developed liver toxicity. One patient with positive CSF cytology received intrathecal methotrexate and one had 3 cycles of combined chemotherapy carmustine, procarbazine and vincristine after XRT. The patient's tumor response to treatment was assessed radiologically 2-3 months after XRT.

#### *Statistical methods:*

Overall survival (OS) was calculated from the date of diagnosis to the date of death or last follow-up. We used both univariate and multivariate analyses. The former was used primarily to individually screen the potential prognostic factors for those that were significantly related to survival. The log-rank test was used to assess their significance. The multivariate approach was used to examine the joint effect of those variables found to be significant in the univariate analysis. The likelihood ratio test was used to assess significance in the multivariate model.

### RESULTS

The mean age at diagnosis was 53 years (range 10-76 years). Fifteen patients were males. The common presenting symptoms were headache (84%), neurological deficit (69%) and vomiting (48%). Less frequently, confusion and seizure disorders in 24% and 14%, respectively, were reported. The median time between the onset of symptoms and the diagnosis of the tumor was 3 months. We did not have any instances of symptomatic, clinically detected in-

volvement of the eyes. None of these patients underwent a slit lamp examination at presentation with their brain lymphoma.

Nine of our patients (31%) were found to have multifocal tumor on their preoperative CT scan. The cerebrospinal fluid (CSF) was examined in 10 patients and only one patient had malignant cells present in the CSF.

The clinical characteristics of the 29 patients are listed in (Table 1).

Immunophenotyping was performed on the only available 20 patients' pathological slides; 16 were B-cell tumors, one T-cell and 3 could not be typed (Table 2).

Follow-up CT scans could not be obtained in 11 patients; 5 died during XRT treatment, 4 died without post treatment CT scan and 2 patients were lost during follow up. Eighteen patients only were evaluable for assessment for tumor response.

Complete response (CR) was achieved in 13/18 patients (72%), while 4 (22%) had partial response. One patient had disease progression after XRT. The overall response to XRT was 94%. The CR rate was 73% (8/11) in patients who received a dose of  $\geq 50$  Gy compared to 72% (5/7) with lower doses. Patients treated with WB and boost XRT fields, WB and whole CNS axis achieved CR rates of 58% (7/12), 100% (2/2) and 100% (4/4), respectively.

Six of 13 patients (46%) who achieved complete response relapsed 11 to 36 months after diagnosis. Tumor relapses were confined to the brain in 5 patients. One patient had multifocal relapse in the brain and in the mediastinal lymph nodes. Three of the patients with relapse had XRT to the whole CNS axis followed by a boost; in 2 of them local relapse occurred within the port of radiation boost. Two patients received XRT to the whole brain followed by a boost; both of them had relapse within the boost XRT field.

Two patients were treated at relapse. They both received salvage chemotherapy. The first one relapsed locally after 18 months and received combination chemotherapy and intrathecal methotrexate, the salvage chemotherapy was successful and after 4 years the patient was still alive and free of disease. The second patient relapsed locally and in the mediastinal

lymph nodes 15 months after primary therapy; he had received combination chemotherapy with intrathecal methotrexate for 6 cycles. He achieved partial response and died 14 months after diagnosis of recurrence. The 4 patients who did not receive salvage therapy died within 2 months.

All patients who did not achieve complete response after XRT died within 8 months. The presence or absence of late neurotoxicity evaluated by clinical symptoms and CT scan or MRI was reported in 9 of 15 patients who survived for more than 6 months after therapy. This may represent a minimum estimate of incidence of late neurologic damage because the evaluation was not performed prospectively in this study. In the 6 patients treated with XRT alone, 3 had white matter changes, 2 atrophic changes, while one patient treated with WB XRT to 50 Gy developed severe disseminated necrotizing leukoencephalopathy and brain necrosis. Two patients received salvage chemotherapy after XRT failure and both had white matter changes. One patient (10 years old) who received 3 cycles induction high dose methotrexate with whole CNS axis XRT, had atrophic brain changes. The XRT dose in patients who developed late XRT toxicity ranged from 40.4 Gy to 60 Gy. The XRT fields were WB with boost in 5 patients, WB in 2 and whole CNS axis in 2 patients.

With a median follow up of 24 months (range 15 days-8.2 years), the 3 and 5-year OS rates for the whole group (29 patients) were 40 and 16%, respectively (Fig. 1). The median survival was 1.1 year. At the time of analysis, 19 patients had died and 8 patients were still alive, 7 of whom were free of disease. Two patients were lost during follow-up. Five patients died before completion of XRT, 4 of progressive disease and one of severe hypoglycemia. Two patients did not receive treatment after surgery and died within 2 months after diagnosis. The 2 patients who received induction high dose methotrexate died; one died during XRT due to severe hypoglycemia and the second died of disease relapse 37 months after therapy.

The final clinical evaluation is shown in Table (3).

The factors considered for univariate analysis were as follows: age, sex, performance status, location of tumor, multifocal disease, extent

of surgery, pathological subtype, XRT dose, XRT volume and response to therapy.

Age less than 60 years, performance status < 4, solitary brain lesion, XRT dose > 40 Gy, WB XRT with boost and complete response to therapy were found to be associated with statistically significant higher OS rates. Cox regression analysis indicated that performance status, response to therapy and XRT dose > 40 Gy were the most significant prognostic variables.

The statistically significant factors affecting the OS in univariate and multivariate analysis are shown in table (4).

Table (2): Pathology and immunophenotyping of studied cases.

Histology	Lineage	Number
Diffuse large cell	Not specified	11
Diffuse large-B-cell	B	13
Precursor (lymphoblastic)	B	2
Not otherwise specified	B	1
Peripheral-T-cell	T	1
Burkitt's	Not specified	1

Table (4): Prognostic factors.

	3-year survival	Median survival	p-value	CI 95 %
<i>Univariate analysis:</i>				
<i>Age:</i>				
≥ 60 y	16	0.5		
< 60 y	46	3.7	0.05	0.96-7.4
<i>Performance status:</i>				
0-3	39	3.7		
4	0.0	0.3	0.02	1.6-7.4
<i>Tumor location:</i>				
Single	42	3.7		
Multifocal	11	0.9	0.05	0.15-1
<i>Radiotherapy dose:</i>				
> 40 Gy	55	3.7		
≤ 40 Gy	0.0	0.32	0.03	0.13-0.92
<i>Radiotherapy field:</i>				
Whole brain (WB)	25	0.2		
WB plus boost	50	1.1		
WB plus spinal axis	33	3.7	0.03	0.33-0.94
<i>Response to therapy:</i>				
Complete	65	3.8		
Partial	0.0	0.5	0.0001	1.56-3.15
<i>Multivariate analysis:</i>				
Performance status			0.03	1.1-21.78
Radiotherapy dose			0.04	0.25-0.97
Response to therapy			0.002	1.3-4.2

Table (1): Patient's characteristics.

	Number	%
<i>Age:</i>		
≥ 60	14	48
< 60	15	52
<i>Gender:</i>		
Male	15	52
Female	14	48
<i>Tumor location:</i>		
Single	20	69
Multifocal	9	31
<i>Performance status:</i>		
0	2	7
1	4	14
2	3	10
3	11	38
4	9	31

Table (3): Final clinical evaluation.

	Number	%
<i>Response:</i>		
Complete	13	45
Partial	4	14
Progression	1	3
Non evaluable	11	38
Alive	8	28
Dead	18	62
Lost during follow up	3	10

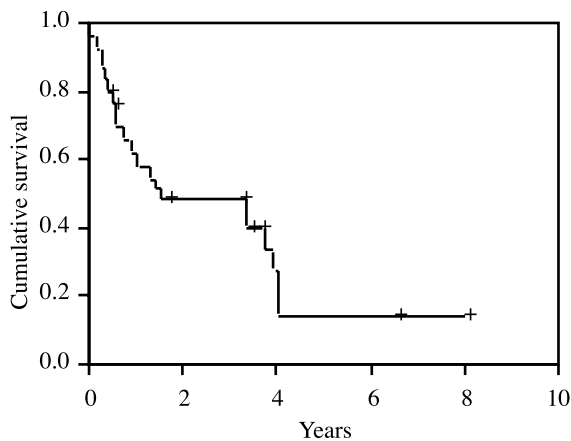


Fig. (1): Overall survival.

## DISCUSSION

The incidence of PBL has been increasing at a 2% per year rate in the last decades and may represent the first brain tumor in the next 5 years [2,11]. Our objectives were to study the OS and prognostic variables of these patients and to evaluate their long-term outcome.

This series is similar to other series in the literature in term of age and sex distribution [14,16].

In our series, a median interval of 3 months elapsed between the development of first symptoms and pathological diagnosis, as compared to Laperriere et al., who reported a median of 2 months [16].

Thirty-one percent of our patients presented with multifocal intracranial tumors. This figure for multifocality is similar to the 33% reported by Mendenhall et al. [19], but higher than the data reported by Letendre et al., 12% [17].

Conflicting results about malignant cells within the CSF have been reported, with an incidence of 10-30% [11]. In our series, one of 10 patients with CSF studies (10%) exhibited such CSF involvement. Few patients in other series could have such an exploration because of increased intracranial pressure at presentation.

Many series of PBL cases have been subdivided according to varied pathological classification schemes, often with the support of immunohistochemical typing. In our study, the diffuse large cell lymphoma was the most common, accounting for 83% of our cases. Similar

distribution was reported [11]. In contrast, in another study immunoblastic tumors were the most common [15].

When immunophenotyping was done, almost all cases in the present study were of B-cell phenotype (16/17-94%). Fine and Mayer reported similar results [11].

The median survival in our series was 1.1 year, which is comparable to most series in the literature where radiation therapy was the predominant form of therapy [16,21]. The median survival of 50 patients treated primarily by XRT at Massachusetts General Hospital was 13.5 months [15]. The 3-year OS in the present study was 40%. The Medical Research Council randomized trial showed 29% 3-year OS rate with XRT [18].

Our results did not show that extensive surgery benefits patients with PBL. The extent of surgical resection showed no impact on survival. Mead et al. [18], in a study that included 53 patients, did not find any evidence that resection of tumor masses improved prognosis. While surgery is an essential procedure, it seems to have no therapeutic role in PBL [23]. Stereotactic biopsy is a safe method for obtaining pathology samples, while craniotomy is associated with an elevated risk of irreversible sequelae [11].

In the present study, patient age was of prognostic significance for survival on univariate analysis. Most authors reported a statistically significant better survival in younger patients [18,23,24]. Reni et al. [23] analyzed 50 studies between 1980 and 1995 that included 1180 patients with PBL and concluded that age is a powerful independent prognostic factor.

Eight out of nine patients with PS grade 4 died within 5 months after diagnosis. The PS grade 4 was of unfavorable prognostic significance for survival on univariate analysis and remained of independent prognostic importance on multivariate analysis. Similarly, Nelson et al., reported a median survival of 21 months for patients with good PS compared to only 5.7 months for those with poor PS [21].

In the current study, patients presenting with a solitary tumor mass had a significant survival advantage as compared with those with multifocal disease, a finding seen in several series [12,16]. However, other series looking at this

factor found no association with outcome [18,21].

Although, exclusive XRT was considered the standard treatment for PBL for some time, none of the irradiation parameters were clearly defined in either prospective trial or retrospective experience. These trials principally consisted of small series of patients treated with heterogeneous XRT volume, doses and fractionation schedule [22].

Despite the initial response to radiation, long-term survival is rare with XRT alone. Almost all authors advocate WB XRT over involved field based on the multicentric and infiltrative nature of PBL, the receding risk from non-irradiated areas and the relapse in sites located at a distance from the primary tumor. However, this has not been confirmed by retrospective or prospective studies [23].

In the present study, the survival of patients receiving > 40 Gy to the whole brain was significantly longer than that obtained with  $\leq$  40 Gy. There was no statistical survival advantage with doses  $\geq$  50 Gy. Several studies have shown that there is a plateau in local tumor control with 45-50 Gy [2,23]. In fact, this is in agreement with most of the studies that concluded those patients should receive at least 40 Gy to the whole brain [21,23].

In our study, there was a significant survival improvement in univariate analysis with addition of a boost XRT field. Similar results were reported by Mendenhall et al. [19], who recommended a tumor dose of 60-64 Gy and Murry et al. [20], who observed a significant survival improvement with  $\geq$  50 Gy.

On the other hand, The Radiation Therapy Oncology Group (RTOG) evaluated a high-dose radiation protocol in 41 patients with PBL using 40 Gy to WB followed by 20 Gy boost to the involved areas. The median survival of patients was only 12.2 months, no better than that of historical control [21].

In the current study, 6 patients had recurrences. In 4 patients the recurrences were in the boosted field. This pattern of local failure has been observed in the RTOG study as 22/25 of the relapses were in the sites of previous involvement [21]. These are comparable with the experience at Memorial Sloan-Kettering Cancer Centre, where relapses occurred with equal fre-

quency in a boosted region receiving a total 54.4 Gy and in other areas of brain treated with only 40 Gy. Because the added XRT did not improve local control and could contribute to late neurologic sequelae, they eliminated the boost dose and used 45 Gy WB in their modified protocol [10].

The addition of spinal axis irradiation in this study did not benefit survival as it did not prevent cerebral relapse. Moreover, whole CNS XRT will destroy substantial amount of bone reserve, making subsequent administration of chemotherapy difficult. XRT alone, even when employed with optimal fields and doses, yields poor results and as in other intermediate and high grade extranodal lymphoma, is insufficient to eradicate PBL. Several limited experiences adding various chemotherapy regimens to XRT alone showed an improved outcome in comparison with XRT alone, but only a few prospective trials have been reported [23].

Although, chemotherapy did not influence outcome in our series, it was administered to too few patients and it is difficult to comment on its possible contribution to the outcome.

Mead et al., randomized 53 patients to XRT alone and post-XRT adjuvant chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) for 6 cycles. There was no evidence of a benefit from XRT-CHOP with respect to OS [18].

Most studies have focused on the use of pre-XRT chemotherapy for two reasons: it permits assessment of response to treatment and the administration of chemotherapy before XRT may reduce the synergistic toxicity of chemotherapy with cranial XRT [8].

High dose methotrexate has emerged as the most important drug for the treatment of PBL. Two large retrospective studies have convincingly demonstrated that it is the single most active agent [6,23].

Preliminary results of the intergroup trial with RTOG and Southwest Oncology Group, using a 10-week pre-XRT regimen of high dose methotrexate, procarbazine and vincristine, showed a median survival of 30 months [9].

The prolonged survival seen with combined regimen has led to greater appreciation of treatment-induced late neurologic toxicity. This is-

sue led to an exploration of systemic chemotherapy alone as an effective treatment for PBL, especially in older patients. Dahlborg et al. [7] in 1996 was the first author to report a durable response and better OS (41 months) using blood brain barrier disruption followed by intra-arterial methotrexate, combined with systemic cyclophosphamide, procarbazine and dexamethazone without XRT. At Memorial Sloan Kettering it became the standard policy to treat patients over 60 years of age with chemotherapy alone reserving XRT for recurrent or progressive disease [1]. However, the reduction in complication rate with deferred XRT has yet to be adequately assessed and should be compared with the toxicity induced by modern XRT techniques, using conformal 3-dimensional XRT, smaller fields and lower doses [22].

In conclusion, the outlook with primary brain lymphoma in immunocompetent patients remains somewhat dismal. In this study, multivariate analysis demonstrated that good performance status, doses of XRT > 40 Gy and complete response to therapy were associated with a relatively better prognosis. Randomized trials addressing the efficacy of chemotherapy (with and without radiation) over radiation alone are needed. The assessment of the impact of treatment on neuropsychological functions and quality of life should be considered as a mandatory endpoint in future trials. New treatment approaches need to be considered in a multi-institutional setting.

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