Outcome of Primary Central Nervous System Lymphoma

—A Study of 32 Patients—

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Abstract

The outcomes in 32 cases of histologically diagnosed primary central nervous system lymphoma were investigated. The 1-, 2-, and 5-year survival rates were 54, 36, and 8%, respectively. Good outcome was indicated by extensive surgical removal with 50-Gy irradiation and lower ages. 61% of patients receiving radiation therapy suffered recurrence within 1 year. The incidence of multiple lesions increased at recurrence. These lesions were almost all remote from the initial site in the brain, occurring more frequently in the central part of the supratentorial regions near the ventricle. Multiple lesions recurred more rapidly than single lesions. Longer survival times were indicated by a long tumor-free period after initial treatment. Extensive surgical removal results in long survival times for patients with a localized single tumor in the early stage. Radiochemotherapy should be given as part of the initial treatment.

Key words: brain neoplasms, malignant lymphoma, outcome, surgery

Introduction

Primary central nervous system (CNS) lymphoma is relatively rare, occurring in 0.85–1.5% of all brain tumors^{14,29)} and 1.6–2.0% of non-Hodgkin's lymphoma.^{6,12)} The characteristics of malignant lymphomas may differ with country and race.²⁸⁾ The mechanism of recurrence after initial treatment has not been investigated in detail. Long-term survival rate remains low, although whole-brain irradiation often results in complete remission.^{5,9,13,18)} Factors influencing the prognosis for this tumor are not well understood. In this study, we investigated the prognostic factors and recurrence mode in 32 patients with histologically diagnosed primary CNS lymphoma.

Materials and Methods

Thirty-two cases of primary CNS lymphoma histologically diagnosed by surgery or autopsy were

reviewed. The patients were treated at neurosurgical departments taking part in the Hiroshima Brain Tumor Study Group between 1979 and 1989. There were 22 males and 10 females. Ages ranged between 18 and 84 years with the mean and SE of 57.6 ± 13.0 years. Performance status on admission was Eastern Co-operative Oncology Group grades 0, 1, 2, 3, and 4 for one, five, 10, 12, and four patients, respectively. Histological examination using the Japanese Lymphoma Study Group classification revealed all patients to have diffuse type non-Hodgkin's lymphoma, divided into large cell, medium-sized cell, mixed, immunoblastic, pleomorphic, small cell, and lymphoblastic types in 14, six, four, three, three, one, and one patients, respectively.

Twenty-six patients (81%) were treated surgically. The tumor was extensively removed in nine cases, partially removed in eight, and a biopsy made in nine. Twenty-seven patients (84%) were given whole-brain irradiation at 20–65 Gy (mean $\pm$ SE, 48.7 ± 9.1 Gy), with complete response in 23 patients. Twenty-one patients (66%) received chemotherapy, mainly with nitrosourea (ACNU or MCNU)

or VEPA (cyclophosphamide, adriamycin, vincristine, and prednisone). Twenty-five patients (78%) have since died. The survival curve was estimated by the Kaplan-Meier method,¹⁶⁾ and analysis of age, sex, performance status, histology, extent of tumor removal, irradiation dosage, and efficacy of chemotherapy was by generalized Wilcoxon test.⁸⁾

Results

I. Analysis of prognostic factors

The 1-, 2-, and 5-year survival rates for 32 patients were 54, 36, and 8%, respectively (Fig. 1). Median survival time was 13 months. As radiation therapy had a marked influence on the outcome, the 23 patients who received radiation therapy, excluding four died due to complication, were selected to investigate the prognostic factors in similar cases. The 1-, 2-, and 5-year survival rates for these patients were 71, 49, and 9%, respectively. Median survival time was 20 months.

The use of age, sex, performance status, histology, extent of tumor removal, radiation dosage, and chemotherapy for factors to predict the prognosis was investigated in these 23 cases (Table 1). There was no significant difference between the factors. However, patients with extensive tumor removal survived much longer than those with biopsy or without surgery (Z , 1.797). Patients under 60 years of age also tended to live longer than older patients (Z , 1.402). Male, good performance status, and irradiation dosage of 50 Gy or more tended to achieve longer survival times, though not statistically significant. The histological grading was not related to outcome. Current chemotherapeutic regimens were not effective in prolonging survival.

Fig. 1 Survival curves for all 32 patients with primary CNS lymphoma (dotted line) and for 23 patients receiving radiation therapy (solid line).

Table 1 Analysis of prognostic factors

Factor	No. of patients	Survival time* (months)	Generalized Wilcoxon test	
			Z	
Age				
< 60 years	11	37.3 ± 30.0	1.402	NS
≥ 60 years	12	21.0 ± 14.4		
Sex				
male	15	30.5 ± 23.7	0.466	NS
female	8	25.7 ± 18.6		
PS				
grades 0-2	16	30.9 ± 24.1	0.704	NS
grades 3-4	7	21.7 ± 14.7		
Histology				
IG	17	25.2 ± 4.74	0.509	NS
HG	6	30.5 ± 10.6		
Surgery				
extensive	9	35.1 ± 24.7	1.797	p < 0.10**
partial	7	25.9 ± 15.6		
none/biopsy	7	19.9 ± 13.2		
Radiation				
< 50 Gy	6	24.5 ± 12.9	0.039	NS
≥ 50 Gy	17	32.1 ± 25.4		
Chemotherapy				
+	15	24.2 ± 17.6	0.789	NS
-	8	38.7 ± 30.7		

*Values are means ± SE. **Comparison between extensive removal and none/biopsy. HG: high grade including immunoblastic, pleomorphic, and lymphoblastic types, IG: intermediate grade including small cell, medium-sized cell, mixed, and large cell types, NS: not significant, PS: performance status.

II. Prevention of recurrence by initial treatment

The relationship between survival time and time to tumor progression (TTP) was investigated in these 23 patients (Fig. 2). There were 14 patients (61%) with TTP within 1 year. The TTP tended to be much longer in long survivors than in short survivors. The three longest survivors had no recurrence after surgery and radiation therapy.

The effect of tumor removal and irradiation on TTP was evaluated to determine the optimum combination therapy for initial treatment (Fig. 3). Even with extensive removal, the TTP did not increase when the irradiation dosage was under 50 Gy. Limited removal did not increase TTP, even with a high irradiation dosage. Radical removal prolonged TTP considerably in some patients with 50-Gy irradiation.

III. Pathology of recurrence

Multiplication of lesions between onset and recurrence was investigated by computed tomography (CT) in 32 patients (Table 2). Twenty-four patients (75%) had a single lesion and the others had multiple lesions initially. However, only seven patients (39%) had a single recurrent lesion, multiple lesions were

Fig. 2 Relationship between survival time and TTP. ●: patients who died, ○: patients surviving.

Fig. 3 Relationships between extent of surgical removal, irradiation dosage, and TTP. A small circle indicates no operation or biopsy; an intermediate circle, partial removal of the tumor; and a large circle, extensive or total removal of the tumor. ●: patients who died, ○: patients surviving.

found in nine (50%). The other two patients had spinal metastases. Mean TTP for multiple lesions was somewhat shorter than that for single lesions.

Change in tumor location was also examined by CT (Table 3). Thirty-six (86%) of the 42 initial lesions were in the supratentorial regions, mainly the frontal lobe. Eight lesions (19%) were in the central part of the telencephalon such as periventricle, corpus callosum, and basal ganglia. Six lesions (14%) were infratentorial. In contrast, 23 (79%) of the 29 recurrent lesions were in the supratentorial regions. Ten lesions (34%) were in the central part of the supratentorial regions. Except for two lesions (7%), all recurred at a different site despite remission of the initial lesions.

Discussion

Primary CNS lymphoma demonstrates rapid growth. The median survival time for cases with this tumor after conservative therapy, surgery only, and radiation therapy with or without surgery are reported to be 1.5–3.3,^{12,14)} 3.6–5.5,^{2,17)} and 13.5–30.3

Table 2 Number of tumors in initial and recurrent patients

Lesion	No. of patients		TTP (months)
	Initial	Recurrent	
Intracranial			
single	24 (75%)	7 (39%)	11.8 ± 5.6*
multiple	8 (25%)	9 (50%)	8.0 ± 8.7*
Spinal	0	2 (11%)	4, 19

*Values are means ± SE.

Table 3 Location of tumors in initial and recurrent patients

Lesion	No. of tumors	
	Initial	Recurrent
Supratentorial regions	36 (86%)	23 (79%)
frontal lobe	14	7*
parietal lobe	7	1
occipital lobe	4	2
temporal lobe	3	3
periventricle	4	3
corpus callosum	3	3
basal ganglia	1	3
thalamus	0	1
Infratentorial regions	6 (14%)	4 (14%)
brainstem	0	2
cerebellum	4	1
periventricle	2	1
Spinal regions	0	2 (7%)

*Includes two lesions at the same site as the initial lesion.

months,^{2,12,17)} respectively. The survival rates at 1, 2, and 5 years are 44–70, 16–54, and 4–45%,^{1,13,18,24,26)} respectively. Although radiation therapy is quite effective, the prognosis for CNS lymphoma is not good.^{13,18,19)} Our results show that the survival time for patients receiving radiation therapy was prolonged by 1 or 2 years compared to that for patients not receiving radiation therapy (median survival, 5 months).

The prognostic factors for primary CNS lymphoma are not well-known. These factors were investigated using patients given radiation therapy because of its strong influence on the prognosis. Although no factor was shown to be significant, the degree of tumor removal tended to influence the outcome. Surgical intervention does not generally prolong survival because of early recurrence even with total removal.^{10,15,21,24)} However, the combined effects of extent of surgery and total dose of irradiation have not been previously examined.^{10,18,24)} Our results indicate that long-term survivors had received extensive removal and 50-Gy irradiation. There were no long-term survivors with only biopsy or irradiation under 50 Gy. Edwards and Balch³⁾ suggested that patients with extranodal non-Hodgkin's lymphoma in the early stage might be treated effectively by surgical removal. Extensive tumor removal before irradiation appears to prolong survival in patients with a single localized lesion.

Some reports^{13,20,24)} state that younger patients have a significantly better prognosis. Our results also showed that patients under 60 years old lived longer. Among 44 patients, including suspected cases diagnosed by neuroradiological examination, the mean age of 14 patients who died within 2 years from tumor progression was 58.5 ± 8.7 years. However, the mean age of nine patients who survived more than 3 years was 45.1 ± 16.4 years. Younger patients have a significantly better outcome than older patients ($p < 0.05$).

Some authors have reported that the Karnofsky score,²⁴⁾ tumor location,^{11,13,25)} histological malignancy,^{2,11,13,14)} irradiation dosage,^{13,18)} and chemotherapy^{4,13,17,20,22)} influence survival, but we did not find these factors significant. Outcome in patients with chemotherapy was worse than in those without chemotherapy, presumably because the drugs were administered for early recurrence.

The mode of recurrence after whole-brain irradiation was analyzed, because it tends to occur early in spite of a good response. Multiple lesions occurred remote from the initial site. The incidence of tumor in periventricle, basal ganglia, and corpus callosum is greater for recurrent than for original lesions.

However, overall initial and recurrent tumors were most frequent in the frontal lobe. Multiple lesions recurred more rapidly than single lesions. These observations imply that the tumors recur quickly at multiple remote sites by dissemination through Virchow-Robin spaces. Patients with complete remission at the initial site are reported to have had recurrence at another CNS site,^{7,23)} presumably resulting from an inadequate radiation dosage and field.^{17,24)} We found some patients with a recurrent lesion at the frontal base and middle fossa, which suggests that irradiation of the skull base was inadequate. As multiple, diverse lesions reappeared within 1 year in many patients, however, conventional radiation therapy may not eradicate concealed tumor cells around the vessels. Some authors^{11,13,25)} have suggested that multiple lesions, brainstem lesions, spinal metastases, paraventricular and meningeal dissemination, and recurrent lesions imply a poor prognosis. Presumably, these imply the advanced stage of primary CNS lymphoma.

Long-term survivors generally have a long tumor-free period after initial therapy. We suggest that a reinforced initial and maintenance therapy with high penetration of drugs into the fenestrated vessels of the tumor²⁷⁾ and Virchow-Robin spaces should be given at the early stage. In patients with early localized single tumors, extensive surgical removal before radiochemotherapy may also prolong survival if achieved as early as possible, because tumors tend to extend into deeper structures in the cerebral hemisphere.

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