

## Results of Combined-modality Therapy for Primary and Secondary Malignant Lymphoma of the Central Nervous System (CNS)

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*Purpose:* We consider that whatever the vital prognosis of secondary CNS lymphoma (SCNSL), its local control is as serious as that of primary CNS lymphoma (PCNSL). In this study, both the treatment outcomes and local control of patients with SCNSL and PCNSL were compared, with the aim of improving the treatment of SCNSL.

*Materials and Methods:* This study included 11 patients with PCNSL and 14 with SCNSL treated from January 1984 to October 1997. PCNSL patients underwent partial tumor resection and received systemic chemotherapy. All SCNSL patients received systemic chemotherapy, and eight also received intrathecal anticancer drug infusion. Nine PCNSL patients and 11 SCNSL patients underwent whole-brain radiation therapy with 4-MV photons. Among the SCNSL patients, three patients underwent localized-brain irradiation and two patients also received whole-spine irradiation.

*Results:* Five-year survival rates were 34% for PCNSL and 33% for SCNSL. In SCNSL, survival times after CNS involvement were very short, irrespective of treatment. One-year local control rates after CNS irradiation were 38% for PCNSL and 14% for SCNSL. Recurrence was mainly found in the cranial region, in seven of 11 PCNSL patients and 10 of 14 SCNSL patients.

*Conclusions:* Patients with SCNSL had a poor prognosis, and local control in them was more problematic than in patients with PCNSL. It is necessary to develop new combined modality therapy for patients with SCNSL, including the participation of a radiation oncologist, before the disease becomes progressive.

*Key words:* local control of secondary CNS lymphoma, combined modality therapy, comparison with primary CNS lymphoma

### INTRODUCTION

**M**ALIGNANT LYMPHOMA of the central nervous system (CNS) was once considered a very rare condition and was reported by Woodman to account for only about 1% of all brain tumors.<sup>1,2</sup> However, with recent worldwide advances in diagnostic imaging techniques, this tumor is being found with increasing frequency.<sup>3-5</sup> Malignant lymphomas may spread to the CNS from

another primary site or may arise as primary tumors of the CNS. Although primary central nervous system lymphoma (PCNSL) is rare, secondary CNS lymphoma (SCNSL), in which lymphoma spreads to the CNS from other organs, is frequently encountered in clinical practice, and has been reported to have a poorer prognosis than PCNSL.<sup>6</sup> The present study was conducted in order to evaluate and compare the treatment outcomes of combined-modality therapy for SCNSL and PCNSL in order to improve the treatment of patients with SCNSL.

### MATERIALS AND METHODS

The study group included 25 patients, 11 with PCNSL and 14 with SCNSL, who underwent radiation therapy at the Division of Radiotherapy of the Department of

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**Table 1. Histopathological classification of patients (LSG classification)**

PCNSL	Diffuse large B cell lymphoma	4
	Diffuse lymphoblastic cell lymphoma	1
	Unknown	6
SCNSL	Diffuse large B cell lymphoma	10
	Diffuse medium B cell lymphoma	2
	Diffuse immunoblastic cell lymphoma	1
	Diffuse intermediate cell lymphoma	1

Radiology of Fujita Health University Hospital from January 1984 to October 1997. The patients ranged in age from 29 to 79 years (mean age, 61 years). The mean age of the patients in the PCNSL group was 66 years, and that of the patients in the SCNSL group was 57 years.

Table 1 shows the histopathological findings in these patients. Although the diagnosis was confirmed by histopathological examination after surgery in five patients in the PCNSL group, the diagnosis was based on diagnostic imaging findings and response to therapy in the other patients in this group. In the PCNSL group, five patients underwent partial resection of the tumor, three patients received systemic chemotherapy, and seven patients received corticosteroid therapy alone or in combination. One patient received intrathecal infusion of anticancer drugs. In the SCNSL group, all patients received systemic chemotherapy, and eight patients also received intrathecal infusion of anticancer drugs (Table 2).

Radiotherapy was performed using a 4-MV photon beam. In the PCNSL group, nine patients underwent whole-brain irradiation: six of them were irradiated at the planning dose (40 Gy) and the other three received 39 Gy, 38 Gy and 20 Gy, respectively (mean dose, 37.4 Gy). Six patients underwent localized brain irradiation, four were irradiated at the planning dose (40 Gy), and each of the other two patients received 20 Gy (mean dose, 33.3 Gy). In the SCNSL group, 11 patients underwent whole-brain irradiation: six of them were irradiated at the planning dose (40 Gy), three of them received 30 Gy, and the remaining two patients received 24 Gy and 12 Gy, respectively (mean dose, 33.3 Gy). In addition, two of these 11 patients also received whole-spine irradiation at doses of 20 Gy and 30 Gy, respectively. The other three patients underwent localized brain irradiation: one received 10 Gy and the others 40 Gy and 30 Gy (mean dose, 26.6 Gy) (Table 3).

For statistical analysis, survival curves were obtained using the Kaplan-Meier method, and differences

between survival rates were evaluated using log-rank tests.

## RESULTS

Five-year actuarial survival rates from the time of diagnosis of malignant lymphoma were 34% for PCNSL patients and 33% for SCNSL patients. There was no statistically significant difference between the PCNSL and SCNSL groups (Fig. 1). One-year survival rates after CNS involvement were 80% for PCNSL patients and 45% for SCNSL patients, and no patients with SCNSL survived for more than two years (Fig. 2). Median survival periods were 29 months for PCNSL and 10 months for SCNSL. Survival rates for the entire period from the time of diagnosis of malignant lymphoma were then compared against survival rates after CNS involvement in SCNSL patients in order to evaluate the effects of CNS involvement on prognosis. Survival rates were found to fall rapidly after CNS involvement, indicative of a significantly poorer prognosis (Fig. 3).

One-year local-control rates after brain irradiation were 14% for SCNSL patients as compared with 38% for PCNSL patients. Median local-control periods were 11 months for PCNSL patients and four months for SCNSL patients. There was no statistically significant difference between the PCNSL and SCNSL groups (Fig. 4). Recurrence was mainly observed in the intracranial region, in seven of 11 patients in the PCNSL group (5 of 7 within the radiation field) and in 10 of 14 patients in the SCNSL groups (7 of 10 within the radiation field) (Table 4). Recurrence of SCNSL was frequently observed as intrathecal involvement. The intrathecal infusion of anticancer drugs in SCNSL patients failed to prolong survival.

## DISCUSSION

It is said that the incidence of CNS involvement of lymphomas arising in other areas is about 5 to 9 percent.<sup>7,8</sup> The actuarial 5-year survival rates for SCNSL patients were clearly poorer than those for lymphoma patients without CNS involvement at our hospital, and the outcome of SCNSL was as poor as the results for PCNSL that have frequently been reported in the literature.<sup>9-12</sup>

In particular, survival rates fell markedly after the occurrence of CNS involvement. As the numbers of PCNSL patients and SCNSL patients in the present study were small, no statistically significant differences were observed in the survival rates in the PCNSL and SCNSL groups after CNS involvement. Nevertheless, the 2-year survival rate for SCNSL patients after CNS involvement

**Table 2. Treatment methods**

	Surgery	Chemotherapy	Intrathecal infusion
PCNSL	Partial tumor resection	4	Therapy with multiple anticancer agents* 3
	Tumor biopsy	1	Continuous corticosteroid administration 7
SCNSL		Therapy with multiple anticancer agents**	MTX (15 mg) Ara C (40 mg) 7 PSL (10 mg)

MTX: Methotrexate, Ara C: Cytarabine, PSL: Prednisolone, Cisplatin (20 mg/m<sup>2</sup>), Etoposide (60 mg/m<sup>2</sup>), Cyclophosphamide (500 mg/m<sup>2</sup>)

\*,\*\*CHOP (Cyclophosphamide, 5-FU, Oncovine, Prednisolone)

\*\*DeVIC (Dexamethasone, Etoposide, Ifosfamide, Carboplatin)

\*\*EPOCH (Cyclophosphamide, Prednisolone, Vincristin, Carboplatin, 5-FU)

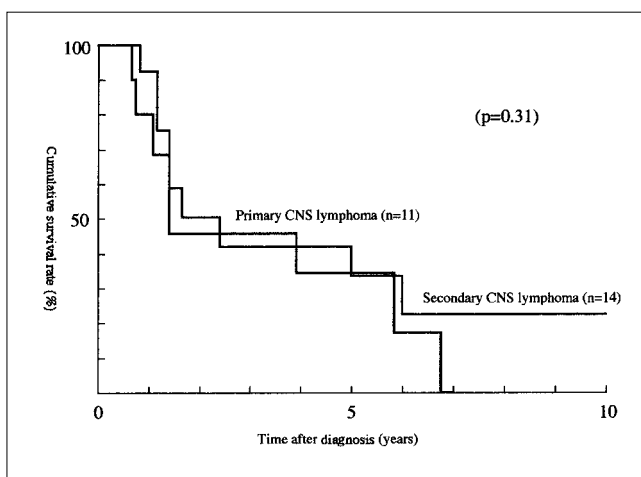
\*\*CAMBO-VIP (Cyclophosphamide, Adriamycin, Methotrexate, Bleomycin, Vincristin, Etoposide, Ifosfamide, Prednisolone)

Multiple chemotherapy regimens were employed according to each patient's clinical condition.

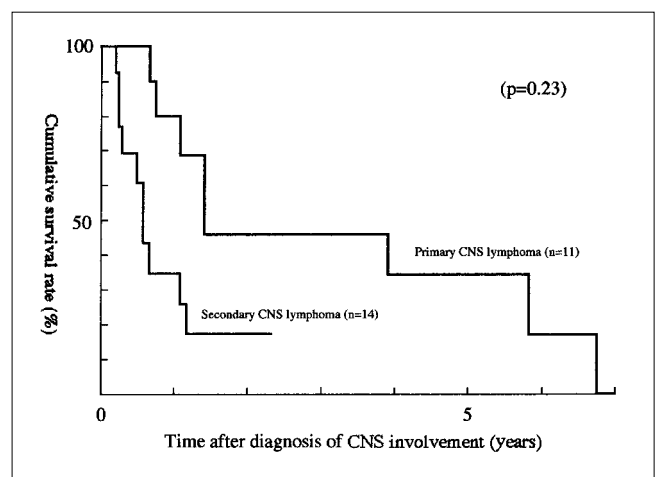
**Table 3. Radiation therapy**

	Whole-brain irradiation	Wide localized brain irradiation	Whole-spine irradiation
PCNSL	9 patients (37.4 Gy)	6 patients <4 patients> (33.3 Gy)	No patients
SCNSL	11 patients { 2 patients } (33.3 Gy)	3 patients (26.6 Gy)	2 patients (25 Gy)

( ): Mean dose, < >: patients also undergoing whole-brain irradiation, { }: patients also undergoing whole-spine irradiation.



**Fig. 1. Cumulative survival curves for PCNSL and SCNSL after diagnosis of lymphoma.**



**Fig. 2. Comparison of cumulative survival rates for SCNSL after CNS involvement and PCNSL.**

was 17%, an extremely poor outcome. One-year survival rates of 12% have been reported,<sup>7,8</sup> which are as poor as the results obtained in the present study. CNS

involvement is associated with significantly shorter survival in SCNSL patients and may represent the terminal stage of the illness.

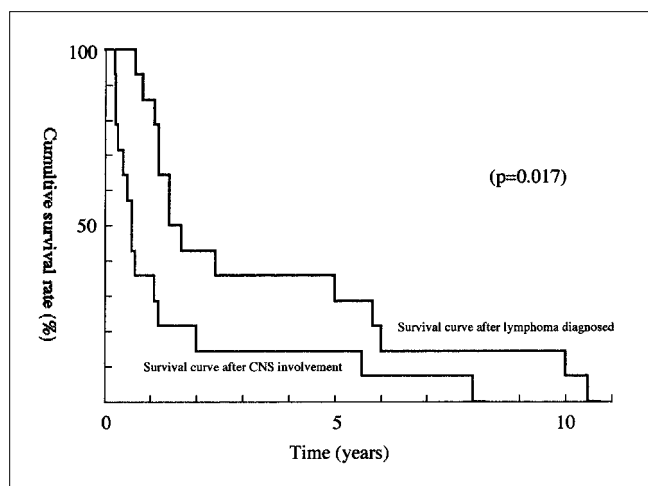


Fig. 3. Changes in survival after CNS involvement relative to overall survival after the diagnosis of lymphoma.

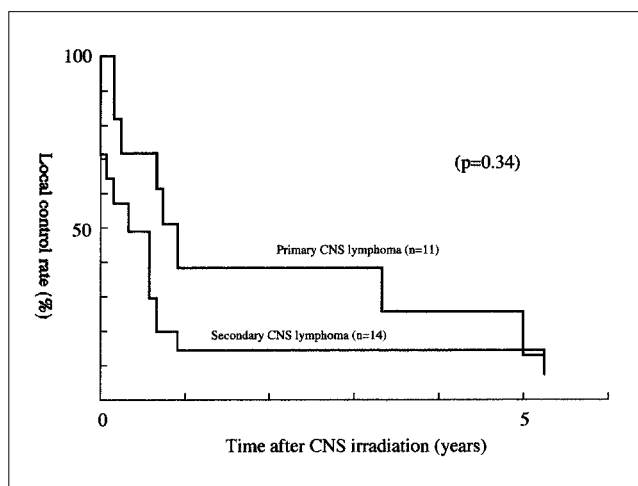


Fig. 4. Comparison of probability of local control after CNS irradiation in PCNSL and SCNSL.

Table 4. Sites of recurrence after radiation therapy

	PCNSL	SCNSL
No tumor recurrence	1	4
Tumor recurrence		
Within the radiation field	5	7
Outside the radiation field	2	3
Unknown	3	none
Patient summary	11	14
Patients with tumor infiltration in spinal fluid	1/11	5/14
Patients with systemic progression of disease	1/11	8/14

As to the local control of CNS lymphoma, one-year disease-free survival rates following CNS irradiation in both the PCNSL and SCNSL groups were clearly worse than the disease-free survival rates for patients with malignant lymphoma in regions other than the CNS. This finding further demonstrates the difficulty of achieving local control in CNS lymphoma. In particular, the local control rate in the SCNSL group was even shorter, an outcome that suggests that radiation therapy was of little value. Our results were similar to those reported by Magrath *et al.*<sup>13</sup> in this regard, but as their report failed to clearly describe each patient's general condition and the drug response of each patient's tumor at the time of radiation therapy, we feel that their conclusions regarding radiation therapy may not be valid. There were also some patients in the present study in whom the disease was resistant to medications and who therefore received intensive chemotherapy with multiple anticancer drugs, and some of these patients showed a

marked deterioration in general condition before radiation therapy.

It is useful to consider why the local control of SCNSL has been worse than that of PCNSL. First, in PCNSL, the tumor itself has been demonstrated to have a blood-brain barrier.<sup>14</sup> This may explain the finding that lymphoma cells of PCNSL infiltrated into normal brain tissues not only from sites where the blood-brain barrier had broken down but also from sites where the blood-brain barrier was intact.<sup>15</sup> Even if the blood-brain barrier is disrupted, brain tissue permeability returns to normal within five weeks after the start of treatment.<sup>16</sup> O'Neill *et al.*<sup>17</sup> have reported that only certain drugs that penetrate the blood-brain barrier have an effect on infiltrating malignant tumor cells. O'Neill *et al.*<sup>18</sup> have also reported that the neoplastic lymphocytes of PCNSL are indistinguishable from those of extracranial NHL on the basis of morphologic, ultrastructural, and immunologic studies.

Therefore, if extracranial lymphoma has the above-mentioned characteristics, the poor local control of SCNSL may be attributable to the following factors. (1) The tumor is protected by both its own blood-brain barrier and similar structures of the tumor that has infiltrated through the damaged normal blood-brain barrier, preventing sufficient doses of anticancer drugs from reaching the tumor. (2) Radiation therapy is ineffective owing to both the lack of an immunological system and the presence of the skull. (3) Many patients already have intrathecal involvement and are in poor general condition. (4) Even if local control is achieved in the CNS, malignant lymphocytes from other sites can enter the brain again through the damaged blood-brain barrier.

In addition, it has been reported that SCNSL is systemically more advanced at the time of recurrence.<sup>6-8,13</sup> We consider that a reason for the difficulty in achieving local control may be that radiation therapy is not able to deliver an adequate radiation dose because of the worsened systemic condition.

On the basis of the above considerations, it can be concluded that SCNSL, which is encountered more frequently than PCNSL, has worse local control.<sup>7,8,19</sup> In addition, it is difficult to achieve a cure using current treatment methods. Furthermore, because of the short period from the diagnosis of CNS involvement until death, which is the period during which curative treatment is possible, intensive therapy to prevent CNS involvement is advisable. We consider that SCNSL patients should not give up a chance for radiation therapy on account of long-term chemotherapy. Instead, it is necessary to develop new combined modality therapy, including the participation of a radiation oncologist, before the disease becomes progressive.

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