

# Primary Malignant Lymphomas of the Central Nervous System: Radiotherapy Results in 12 Cases

Chang Ok Suh<sup>1</sup>, John J.K. Loh,<sup>1</sup> Gwi Eon Kim,<sup>1</sup> Byung Soo Kim,<sup>3</sup>  
Joong Uhn Choi<sup>2</sup>, Sang Sup Chung,<sup>2</sup> and Kyu Chang Lee<sup>2</sup>

*Twelve patients with primary lymphomas of the central nervous system were treated in the Department of Radiation Oncology, Yonsei University College of Medicine, between 1976 and 1987. There were seven males and five females ranging from 19 to 63 years of age. They had single (6 cases) or multiple (6 cases) discrete intracerebral nodules. All patients were treated with radiation therapy. Surgical resection was performed in five cases and intrathecal chemotherapy with methotrexate was performed in seven cases after radiotherapy. All patients except one had received whole brain irradiation with a median dose of 4000 cGy. The radiation dose for a primary tumor was 4800-6000 cGy (median 5560 cGy). Initial response to radiation was excellent with a 91.7% complete response rate, but late recurrences were noted and the median survival was 42.3 months. Intracranial recurrences were observed in two patients who received less than 4000 cGy to the whole brain without intrathecal chemotherapy. Although intracranial recurrence was not seen in the patients receiving intrathecal chemotherapy after radiation, a high incidence of necrotizing leukoencephalopathy was noted. High dose irradiation with a minimum of 4000 cGy to the whole brain and more than 5000 cGy to the primary tumor is recommended for the treatment of primary CNS lymphomas. Combined use of chemotherapy should be carefully attempted because of the increased toxicity.*

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**Key Words:** Brain neoplasm, non-Hodgkin's lymphoma, lymphoma, radiation therapy

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CNS lymphoma can occur either solely in the CNS (primary CNS lymphoma) or along with systemic lymphoma (secondary CNS lymphoma). Primary CNS lymphoma is less common than secondary CNS lymphoma, representing only 0.85 to 1.5% of intracranial neoplasms, and shows a high incidence in patients receiving immunosuppression therapy for renal transplantation, systemic lupus erythematosus, etc, and in patients with acquired or inherited im-

munodeficiency disorders such as AIDS, Wiskott-Aldrich syndrome, and X-linked immunodeficiency disease.

Researchers have reported that CNS lymphoma is a rapidly progressing fatal disease without treatment. All the treatment modalities have failed to improve the long-term survival and it is hard to declare the effectiveness of each treatment modality because of the disease's rarity and lack of prospective study. Surgery alone has been abandoned because of the short average survival. Radiotherapy, with or without surgical resection also showed disappointing long-term results, nevertheless, CNS lymphomas respond well to radiation. Our retrospective study of twelve cases with primary CNS lymphoma was performed to evaluate the treatment outcome and to establish the appropriate treatment protocol.

## MATERIALS AND METHODS

Twelve patients with primary malignant lymphoma

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Departments of Radiation Oncology<sup>1</sup> and Neurosurgery<sup>2</sup>, Yonsei University College of Medicine.

Yonsei Cancer Center<sup>3</sup>, Yonsei University College of Medicine, Seoul, Korea

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Address reprint requests to Dr. C O Suh, Department of Radiation Oncology, Yonsei University College of Medicine, CPO Box 8044, Seoul, Korea.

phomas of the brain were referred to the Department of Radiation Oncology, Yonsei University Medical College, during the years 1976 to 1987.

### Patients characteristics

There were seven males and five females ranging from 19 to 63 years of age. A CT scan was done in all patients except case No. 1 who showed a single large mass in the left temporo-parietal area on cerebral angiography which was also confirmed by surgical findings. By CT scan finding, all patients revealed supratentorial tumors. Six patients revealed a single mass on corpus callosum (2 cases), basal ganglia (1 case), and deep white matter area (3 cases), but six patients showed multiple masses (Fig. 1,2). CSF seeding was noted in two patients, one at the initial presentation (No. 6), and the other at the late stage of disease (No. 8). Histological diagnosis was obtained in 9 patients, either by stereotaxic or open biopsy. Pathologists reported these diagnoses with a variety of terminology such as reticulum cell sarcoma, microglioma, large cell immunoblastic lymphoma, and B cell lymphoma. None had cell surface marker studies performed. In three patients, we didn't perform a tissue biopsy prior to radiotherapy because we had confidence in the clinical diagnosis by CT scan and hoped to avoid the morbidity accompanying surgical intervention. We observed good radioresponsiveness

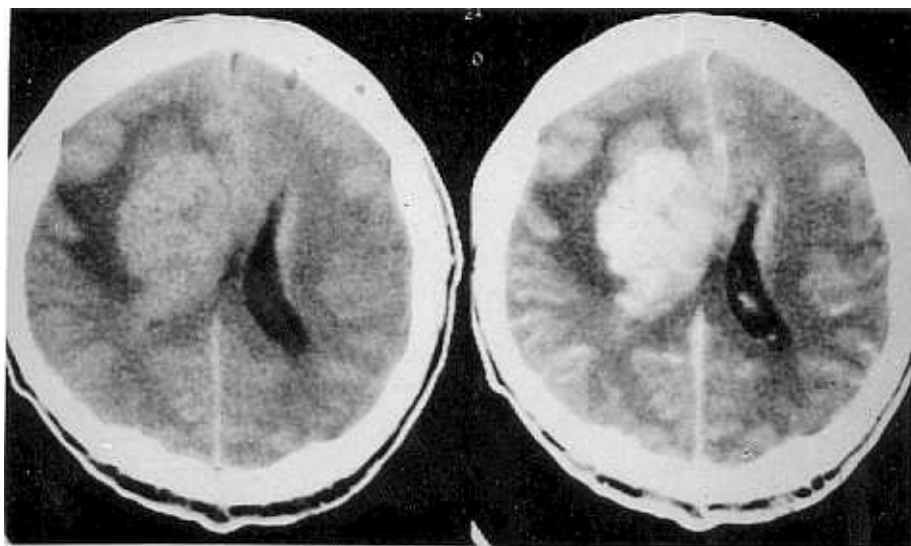
on follow-up CT scan done after a trial radiation of 2000 cGy in 2 weeks.

### Treatment

**Surgery:** In the earlier period, we performed a craniotomy in order to resect the lesions in five cases, but gross total removal was possible in only two cases because of the critical location of the tumor. In the later period, we preferred the stereotaxic biopsy to determine tissue pathology, which was followed by radiation without surgical resection. Recently, we tried radiation first without tissue pathology in patients who had characteristic CT scan findings suggesting lymphoma and who were anticipated to have a high risk of perioperative morbidity.

**Radiation therapy:** All patients except one received whole brain irradiation with Co-60 or 4MV linear Accelerator X-ray via a parallel opposed pair of lateral fields and boost radiation to the primary site was given in 9 patients. The total dose of whole brain irradiation was 3600-4800 cGy (median 4000 cGy) and the total dose for the primary site was 4800-6000 cGy (median 5560 cGy) with 180-200 cGy per fraction, five days a week. In two cases (No. 3 and No. 5), re-irradiation, 3000 cGy in 3 weeks, was given with local fields on recurrent tumor sites, 32 and 22 months after the first irradiation.

**Chemotherapy:** In seven of the twelve cases, in-



**Fig. 1. Case 6.** Plain CT scan (left) demonstrated slightly high density mass on right basal ganglia and linear increased density along lateral ventricular wall. On enhanced scan, they showed strong contrast enhancement. These findings suggested large solitary lymphoma mass with CSF seeding.

intrathecal chemotherapy was given after completion of radiotherapy. Most patients received intrathecal methotrexate, 12.5mg weekly for 5 times.

All patients were followed up until death or to the time of this writing.



Fig. 2. Case 7. Multiple masses with strong contrast enhancement on left thalamus and parietal area. Characteristic CT finding of primary NHL-CNS.

Table 1. Patient characteristics, treatment and results in primary CNS lymphoma

Patient No.	Age/Sex (years)	No. of Tumor	Surgery	Radiation dose(cGy)		CTX	Response	Recurrence	DFI (Months)	Survival (Months)	Status
				Primary	WB						
1.	19/M	S	TR	5000	0	No	CR	No	132	132	NED
2.	43/F	S	PR	4800	4800	IT MTX	CR	No	64	64	DID*
3.	57/M	S	SB	5000	3000	CVP	CR	intracranial intraperitoneal	32	40	DOD
4.	55/F	S	TR	5000	4000	IT MTX	CR	?	?	43	Dead
5.	49/F	M	SB	3600	3600	No	CR	intracranial	22	48	DOD
6.	41/M	S	PR	5000	4000	No	PD	intracranial	0	3	DOD
7.	43/F	M	PR	5560	3960	IT MTX	CR	No	15	15	NED
8.	47/M	M	SB	5560	3960	IT MTX	CR	No	7	7	DID*
9.	53/F	M	SB	5960	3960	No	CR	No	10	10	NED
10.	31/M	M	No biopsy	6000	4000	IT MTX	CR	No	8	8	NED*
11.	63/M	S	No biopsy	6000	4000	IT MTX	CR	No	12	12	DID*
12.	56/M	M	No biopsy	5400	4000	IT MTX	CR	No	12	12	NED

S: Single M: Multiple TR: Total resection PR: Partial resection SB: Stereotaxic biopsy WB: Whole brain

CTX: Chemotherapy DFI: Disease free interval NED: No evidence of disease DOD: Died of disease

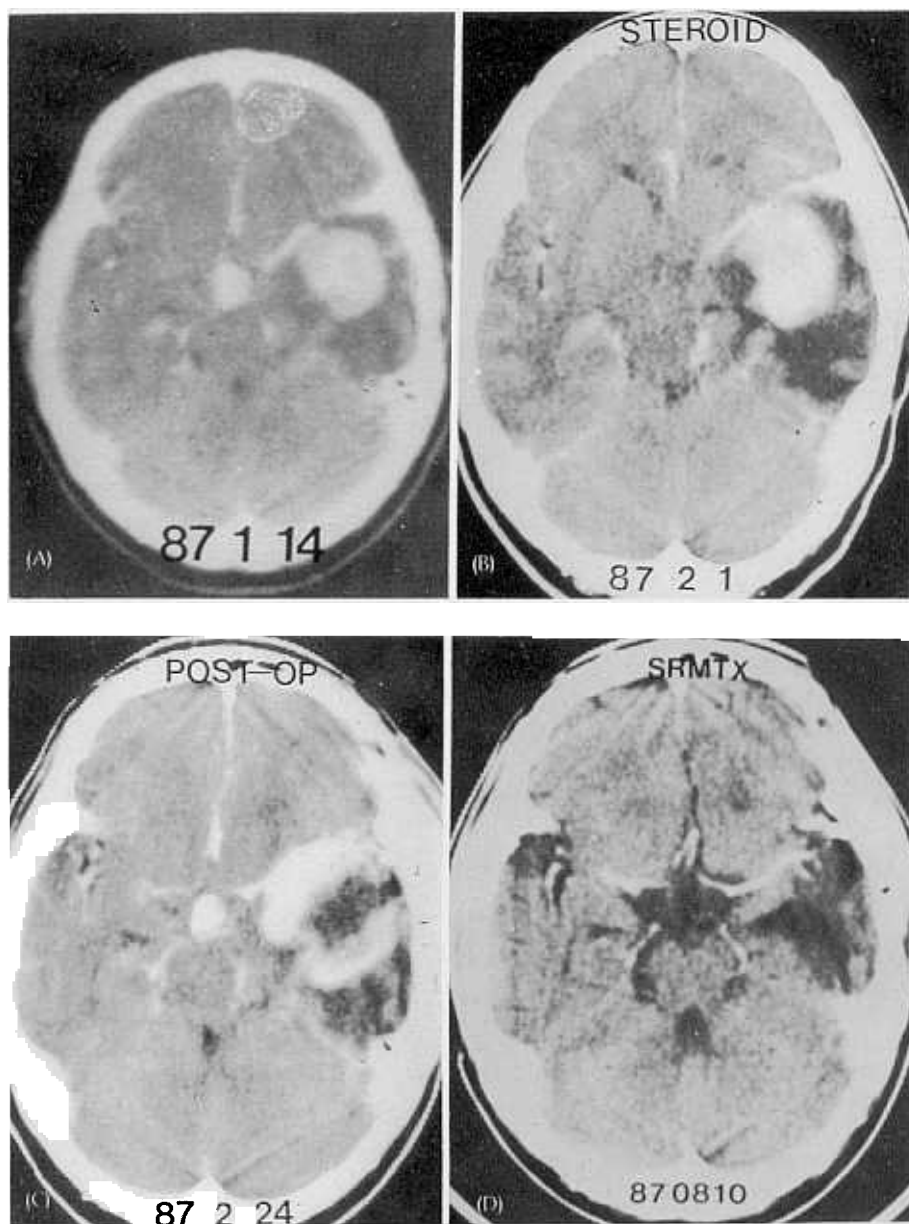
DID: Died of intercurrent disease IT MTX: Intrathecal methotrexate CR: Complete response PD: Progressive disease

\* Patients had necrotizing leukoencephalopathy CVP: Cytoxan, Vincristine & Prednisolone

## RESULTS

The clinical, therapeutic, and survival data of the

twelve patients are summarized in Table 1. Assessment of response and determination of the disease free state were made by CT scan and clinical evaluation. All patients except one showed complete disappearance of tumors on CT scan after completion of



**Fig. 3. Case 7.**(A) Two masses on left temporal and suprasellar area on initial presentation.  
 (B) Disappearance of suprasellar mass after steroid medication.  
 (C) Re-appearance of suprasellar mass after surgical resection of left temporal mass.  
 (D) Complete response after radiotherapy.

**Table 2. Treatment results by treatment methods in primary CNS lymphoma**

Status	Tx modality	Radiotherapy (5 cases)	RTX+IT MTX (7 cases)
Alive with NED		*2 (132, 7 mo)	2 (12, 15 mo)
Alive with necrotizing leukoencephalopathy			1 (8 mo)
Died of intracranial recurrence		3 (3, 40, 48 mo)	
Died of necrotizing leukoencephalopathy			3 (7, 10, 70 mo)
Died, cause known			1 (43 mo)

RTX; Radiotherapy, IT MTX: Intrathecal Methotrexate

\*No. of Cases (survival)

radiotherapy (complete response). One patient (No. 6) who initially presented with intraventricular seeding showed no clinical response to the radiotherapy and died of disseminated intra-CNS disease 3 months after beginning radiotherapy (Fig. 1).

Initial response to radiation was excellent, however, long-term disease-free survival was rarely achievable. Late intracranial recurrence and fatal treatment related complications were notable, and median survival was 42.3 months. Seven patients died 3 to 70 months after radiotherapy. Three patients died of intracranial recurrence, but three patients died of necrotizing leukoencephalopathy at 7, 12, and 64 months, respectively after commencing radiotherapy. Five patients are alive with a range of 10 to 132 months after beginning radiotherapy. Only three patients are living without any disability until the time of this writing at 132, 10, and 12 months, respectively. One patient is suffering from necrotizing leukoencephalopathy (patient 10) and patient 7 has persistent bilateral total blindness as a sequelae of disease.

The last patient was a 43 year old woman admitted due to severe headache. A CT scan showed multiple masses on the left temporal and suprasellar area. Differential diagnosis indicated a metastatic tumor or lymphoma. She was discharged with steroid medication only due to poor economic condition. When she returned to the emergency room 2 weeks later, the suprasellar mass had disappeared. We performed operation with partial removal of the tumor, but in the post-op period before beginning radiation, sudden bilateral blindness with re-growth of the suprasellar mass was noted. Now, she is alive without evidence of disease, but she has not recovered from total blindness (Fig. 3).

We analyzed treatment results according to the

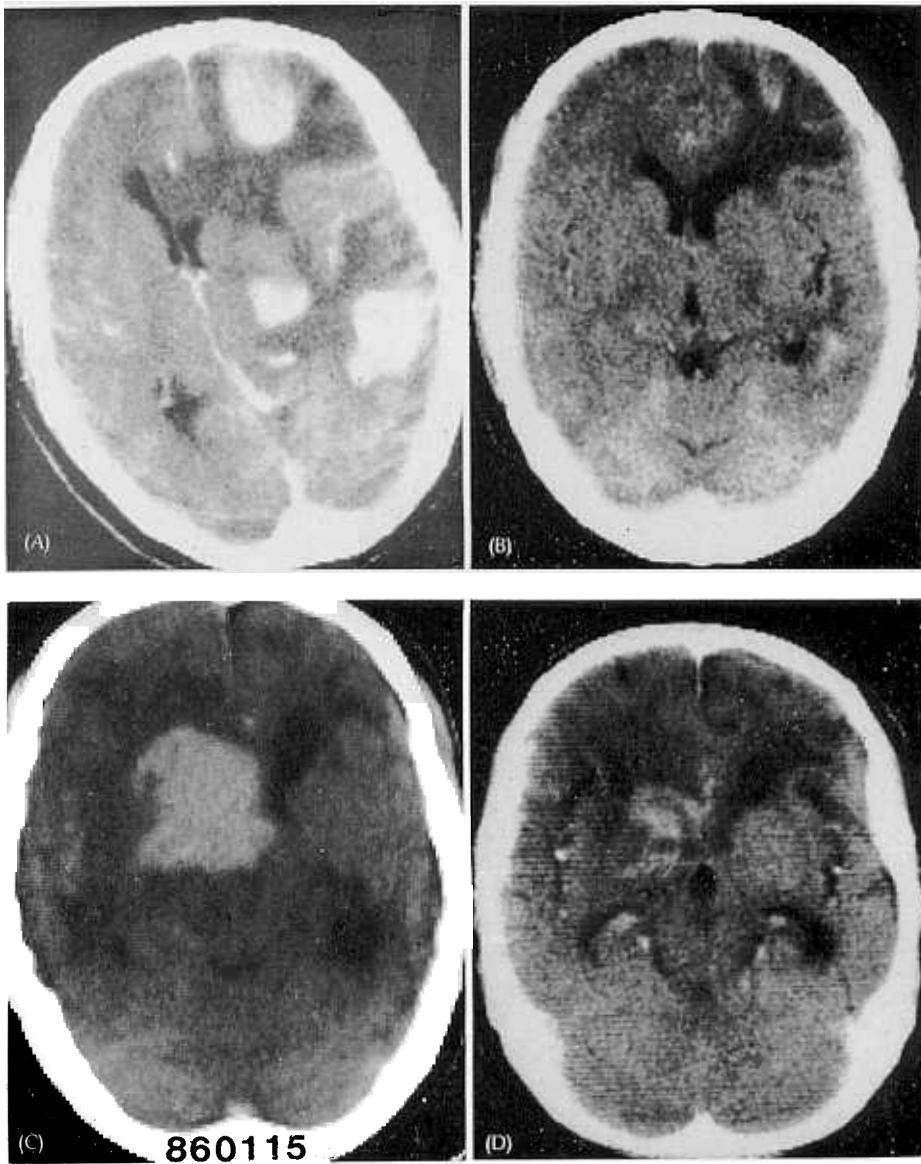
treatment methods (Table 2). Of five patients who received radiotherapy alone after operation, three failures were observed, one in the brain, one in the brain and systemic, and one with persistent leptomeningeal seeding. The times to intracranial recurrences were 22 and 32 months after beginning radiotherapy. Patient 5, who showed multiple masses with strong contrast enhancement on initial CT scan, was treated with whole brain irradiation of 3600 cGy for two and a half weeks under the impression of a metastatic brain tumor without tissue confirmation. At the completion of radiation, excellent response was shown on the follow-up CT scan and she was discharged without any other treatment. About two years later, she returned to us with intracranial recurrence. CT scan findings suggested lymphoma and stereotaxic biopsy proved this tumor to be a large cell lymphoma. Re-irradiation with a local field, 3000 cGy in 3 weeks, resulted in partial response and death ensued 26 months afterward or 4 years after diagnosis (Fig. 4).

On the other hand, patients treated with radiotherapy and intrathecal methotrexate showed no intracranial recurrence but necrotizing leukoencephalopathy occurred in 4 cases, of whom three died (Fig. 5).

Only one patient (No. 3) demonstrated extraneural lymphoma. He revealed supraclavicular and retroperitoneal lymph node enlargement 6 months after radiation, but this was controlled by subsequent systemic chemotherapy. When he died of intracranial recurrent disease 40 months after diagnosis, he was free of systemic disease.

## DISCUSSION

Primary lymphoma of the brain has been



**Fig. 4. Case 5.** (A) Multiple masses with strong contrast enhancement at first admission.  
 (B) Complete disappearance of tumors after radiotherapy, 3600 cGy in 2 1/2 weeks, under the impression of metastatic brain tumor.  
 (C) Two years later, newly developed mass on right basal ganglia, proved to be large cell lymphoma by stereotaxic biopsy.  
 (D) Partial response after re-irradiation.

designated by a variety of terms including "perithelial sarcoma", "microglioma", "reticulum cell sarcoma", and "histiocytic lymphoma", but has been recently clarified as there are no histologic differences between

primary CNS lymphoma and non-Hodgkin's lymphoma arising in extraneural sites, and the majority are of B cell origin or diffuse histiocytic type by Rapaport classification (Allegranza *et al.* 1984; Helle *et al.*



**Fig. 5. Case 2.** (Left) A large lobulating mass on the corpus callosum which completely disappeared after subtotal resection plus radiotherapy. (Right) Follow-up CT scan at 5 years after radiotherapy plus intrathecal methotrexate demonstrated hypodense white matter with hydrocephalus, suggesting necrotizing leukoencephalopathy. There was no evidence of disease. She died at 64 months after treatment.

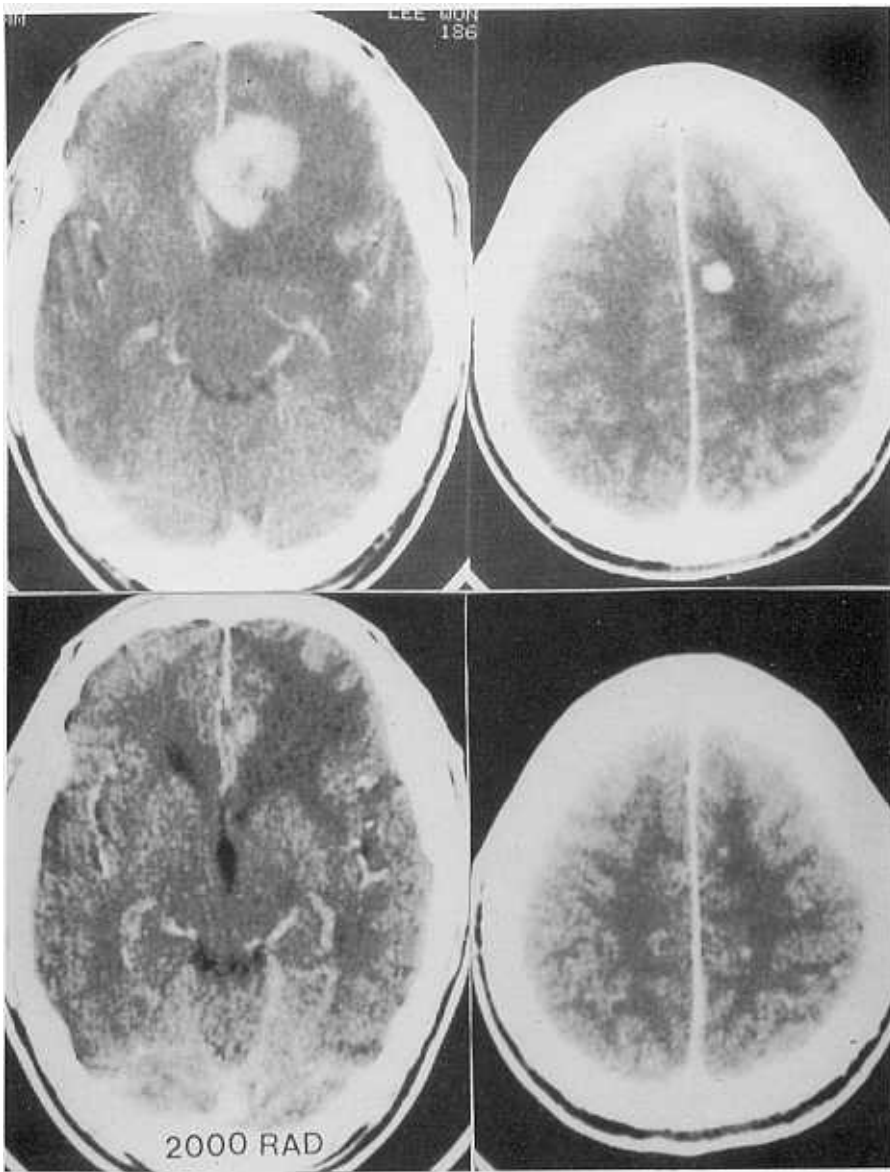
1984; Henry *et al.* 1974; Letendre *et al.* 1982). Before the mid-1970's, we seldom experienced primary CNS lymphoma cases because of its rarity and difficulty in diagnosis and surgical approach to confirm the diagnosis.

Recently, with the advent of the CT scan, improvement of neurosurgical techniques, and actual increase in frequency, we have gained more experience in the clinical presentation of CNS lymphoma and have confirmed more cases pathologically. Consequently, we are able to perform prompt diagnosis and timely treatment in the management of CNS lymphoma.

As with other brain tumors, most primary CNS lymphomas are suspected by neuroradiologic study including CT scan or MRI imaging. Characteristic CT scan findings of CNS lymphoma are fairly diagnostic, they reveal single or multiple isodensity or high density masses usually on the periventricular region, basal ganglia, thalami and corpus callosum with well defined homogeneous contrast enhancement. It is interesting that transient spontaneous regression of the tumors can be observed. Weingarten *et al.* (1983) suggested that when initial neuroradiologic study suggests a diagnosis of lymphoma, the subsequent spontaneous resolution of lesions should not be regarded as a

benign, self-limiting disease but should be aggressively pursued early in the patient's clinical course when therapy would be most beneficial. We experienced one case of spontaneous regression, as described above (patient 7). In that case, delayed diagnosis and treatment resulted in bilateral total blindness despite complete disappearance of the tumor after radiotherapy. Besides solitary or multiple discrete intracranial nodules as described above, less frequently, patients with primary CNS lymphoma can present with diffuse meningeal or periventricular lesions, uveal or vitreous deposits, and localized intradural spinal mass. In these patients, brain CT scans often reveal negative findings and CSF study including cytology or myelography is more diagnostic.

When CNS lymphoma is suspected in the CT scan, the next step in the management of CNS lymphoma is surgical intervention for pathologic diagnosis as well as surgical resection of the tumor. However, the role of surgery is very limited because CNS lymphoma is often multiple and extensive surgical resection of these deep seated tumors results in high morbidity and mortality rates. Many authors reported less than 6 months median survival after surgery alone (Henry *et al.* 1974; Bogdahn *et al.* 1986). So Surgery alone



*Fig. 6. Case 12. (Upper) Two well enhanced masses on corpus callosum and parietal area were suspected as NHL-CNS. (Lower) Follow-up CT scan after trial radiation, 2000 cGy in 2 weeks revealed near complete response.*

has been an abandoned treatment method and, furthermore, the stereotaxic needle biopsy to establish the diagnosis followed by radiotherapy has recently received increased interest because lymphoma is very sensitive to radiation and there is an apparent lack of benefit from subtotal or gross total excision. Trial radiation without biopsy, which is a popular method

in pineal tumors, has not been widely accepted in CNS lymphoma. However, we think that it is a reasonable approach in this deep seated, radiosensitive tumor when the patient refuses an operation or in biopsy failed cases. Delayed diagnosis and treatment after pathology confirmation often lose the time when radiation is most beneficial. In this series, we perform-



ed trial radiation without biopsy with 20 Gy in 2 weeks in 3 patients who had multiple tumors or had declined surgery. They showed almost complete response after only 20 Gy which could not be achieved in other pathologies (Fig. 6).

Radiation therapy with or without surgical resection is standard treatment in the management of primary CNS lymphoma. Although the initial response to radiation is very good, long-term results are disappointing. Median survival after radiation was reported as 15.2 months by Henry *et al.* (1974), 15.3 months by Kawakami *et al.* (1985), and 18 months by Sagerman *et al.* (1984). Murray *et al.* (1986) reported in their extensive literature review including 693 cases that 8% of 3 year survivals and 3% of 5 year survivals, even then half of the 5 year survivors relapsed after 5 years.

Because of unsatisfactory results by operation and radiotherapy, adjuvant systemic and/or intrathecal chemotherapy has been tried by many investigators. Loeffler *et al.* (1985) observed that the median survival of patients receiving chemotherapy was 44 months compared to 14 months for those patients not receiving chemotherapy and all four long-term survivors received chemotherapy. Kawakami *et al.* (1985) also suggested that systemic chemotherapy is a meaningful addition in the treatment of primary CNS lymphoma. When he used combined chemotherapy including CHOP (cytoxan, adriamycin, vincristine and prednisolone), VENP or VEMP (vincristine, cytoxan, procarbazine or 6-mercaptopurine, and prednisolone), or ACNU (1-(4-amino-2-methylpyrimidine-5-yl-methyl)-(2-chloroethyl)-3-nitrosourea), survival time was prolonged in comparison with that of patients not receiving chemotherapy. Neuwelt *et al.* (1986) have shown, in three patients with CNS lymphoma, rapid tumor regression after receiving combination chemotherapy (cytoxan, intra-arterial methotrexate, leucovorin rescue, procarbazine, dexamethazone) administered in association with osmotic blood-brain barrier disruption (mannitol). Some authors (Loeffler *et al.* 1985; Mackintosh *et al.* 1982) had used intrathecal chemotherapy with methotrexate or Ara-C, and intravenous administration of high dose methotrexate was also tried after the report by Ervin and Canellos (1980). They reported a recurrent CNS lymphoma case who revealed complete response after intravenous high dose methotrexate.

To date, while these reports are encouraging and chemotherapy may theoretically augment irradiation effects and/or eradicate micrometastases within the neuroaxis or beyond the CNS, the use of chemotherapy is still investigational. Furthermore, if combined radiotherapy and chemotherapy is to be

considered, the possibility of complications such as leukoencephalopathy must be taken into account. In this regard, the sequence of radiation therapy and chemotherapy may be very important. Bleyer (1981) suggested that intrathecal MTX or high-dose intravenous MTX followed by CNS RT would be the least neurotoxic approach and methotrexate given during or after CNS RT would be much more likely to produce severe neurologic sequelae. Although Loeffler *et al.* (1985) reported no necrotizing leukoencephalopathy in their 4 patients who received intrathecal methotrexate, the addition of methotrexate to high dose radiotherapy would result in a high rate of necrotizing leukoencephalopathy (Mackintosh *et al.* 1982; Meadows and Evans 1976). In this series, we tried intrathecal chemotherapy with methotrexate after radiotherapy in 7 cases. In these cases, primary site recurrence was not documented but four patients had suffered from necrotizing leukoencephalopathy, of whom three patients succumbed to that complication. We didn't perform a surgical biopsy or autopsy in these cases to verify this complication, but the diagnosis of necrotizing leukoencephalopathy was possible by CT scan finding and the downhill clinical course. Intrathecal administration of methotrexate after high dose radiotherapy may be the possible cause of the unfortunate high complication rate in our cases. Nowadays we eliminate intrathecal chemotherapy in the management of primary CNS lymphoma. We think that systemic chemotherapy for the control of systemic disease would not be warranted because of the relatively low rate of extra-CNS involvement.

There is no disagreement about the importance of irradiation in increasing the median survival time of CNS lymphoma patients. However, current questions about the dose required for local control as well as the volume of the CNS that should be included within the irradiation fields have not been answered yet. A dose-response relationship has not been established because of the small number of patients, but, many authors agreed that improved survival time could be anticipated with doses greater than 50 Gy to the primary tumor (Berry and Simpson 1981; Littman and Wang 1975; Murray *et al.* 1986; Sagerman *et al.* 1983). Littman and Wang (1975) and Sagerman *et al.* (1983) recommended at least 45 Gy to the whole brain plus a boost dose of 5 to 15 Gy to the primary site. We observed intracranial recurrence in two patients whose recurrent masses occurred in the area receiving irradiation of 30 Gy in 3 weeks and 36 Gy in 2 1/2 weeks. Thus, we also agree with higher dose irradiation of more than 50 Gy with the hope that this

more vigorous regimen will lead to greater longterm survival.

It is difficult to define the volume to be treated, whole brain or local field or craniospinal irradiation by literature review. Although Gonzalez and Schuster-Litterhoeve (1983) reported slightly improved survival time in patients with local field irradiation (less than whole brain), the nature of multifocal involvement and diffuse infiltration justifies whole brain irradiation rather than local field irradiation. In Yasunaga's review (1986), all 5 patients initially receiving only local irradiation to the primary site relapsed outside the primary field. The role of spinal irradiation or intrathecal chemotherapy for the eradication of the undetected CSF or spinal cord involvement is still investigational. In the literature review by Murray *et al.* (1986), nine (9.3%) of 92 patients were reported to have a positive CSF finding at diagnosis and 15 (5.6%) of 267 cases showed positive CSF cytology or overt spinal cord disease at disease recurrence. Although some authors recommended craniospinal irradiation because of this risk, and Loeffler *et al.* (1985) reported that control of CNS lymphoma was seen only in patients receiving craniospinal radiation or CNS-penetrating chemotherapy, many authors doubt the necessity of spinal irradiation because of the rarity of spinal metastasis and sequelae of spinal irradiation such as bone marrow suppression. Although an increase in local control and survival time may result in an increased recurrence rate within the neuraxis outside the primary tumor, the main problem in the control of CNS lymphoma is currently primary site recurrence. So, we advise spinal irradiation only for patients with positive CSF cytology or overt spinal cord metastasis.

In conclusion, high dose irradiation with a minimum 4000 cGy to the whole brain and more than 5000 cGy to the primary site is a safe and recommendable approach for the treatment of primary CNS lymphoma. To increase tumor control with an acceptable complication rate, the careful and precise combination of irradiation and chemotherapy needs to be studied in a future trial.

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