Radiation Therapy In Management Of Primary Non-Hodgkin's Lymphoma Of Central Nervous System

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From 1982 to 1991, sixteen patients with primary non-Hodgkin's lymphoma of the central nervous system(CNS) were seen at Kyung Hee University Hospital. The most common subtypes were large, noncleaved cell lymphoma and immunoblastic lymphoma of B cells. Lesions most commonly involved were the parietal lobes and/or deep nuclei. Positive cerebrospinal fluid cytology was rare at initial presentation. Sixteen patients were treated with surgical biopsy or resection followed by whole brain radiotherapy at a median dose of 40 Gy(range=30-50 Gy) with variable boost doses. Of 16 patients who underwent surgery and postoperative radiotherapy, fourteen patients died between 2 and 49 months following treatment, and two are alive with no evidence of disease at 8 and 22 months. The 1-and 2-year survival rates were 55.6% and 34.7%, respectively with 12 months of median survival. Patterns of failure were analyzed in eleven patients of total 16 patients. Failure at the original site of involvement was uncommon after radiotherapy treatment. In contrast, failure in the brain at sites other than those originally invovled was common in spite of the use of whole brain irradiation. Failure occurred in the brain 11/16(68.7%), in spinal axis 4/16(25.0 %). The age, sex, location of involvement within CNS, numbers of lesion, or radiation dose did not influence on survival. The authors conclude that primary CNS lymphoma is a locally aggressive disease that is poorly controlled with conventional radiation therapy. The limitation of current therapy for this disease are discussed, and certain promising modality should be made in regarding the management of future patients with this disease.

Key Words : Central Nervous System, Non-Hodgkin's Lymphoma, Radiation Therapy

INTRODUCTION

Non-Hodgkin's lymphoma of the central nervous system(NHL-CNS)appears to be increasing in incidence during the past several decades. This, in past, reflects the association of primary CNS lymphomas with inherited and acquired immunodeficiency syndrome (AIDS). However, the incidence is also increasing within the immunologically normal population. Primary CNS lymphoma accounts for less than 1 % of all primary brain tumors, and for 1.5% of all cases of extranodal non-Hodgkin's lymphomas[1].

In early stage non-Hodgkin's lymphoma of the head and neck region, 30-65 Gy have produced local control rates of 91-100% and five year survival rates of 43-77%[2]. When treated CNS lymphoma with radiation therapy to 40-50 Gy, local control is approximately 90%, However, approxi-

mately 50% of the patients relapse outside of the treated volume and only approximately 10% of the relapse are local failures unlike Stage IA non-Hodgkin's lymphoma elswhere in the body.

Primary CNS lymphoma has been treated with doses of 40-50 Gy, approximately 90% of the patient who have died from their disease have died from loco-regional recurrence and only approximately 10% died of disseminated disease[3]. Only 4%(6/150) of the patients with primary CNS lymphoma had survived 5 years in Littman's literature review[4]. In the pre-CT scan era before 1975, the local failure was due to geographic or marginal miss because of inappropriate methods available to define tumor volume. With multifocal disease or gross disease frequently infiltrating the leptomeninges, the usual whole brain fields used to treat primary and metastatic brain tumors would not have encompassed all of the meninges. In 1982 when the RTOG undertook the task of trying to determine why the local failure rate was so high in primary CNS lymphoma, radiation dose of 20-55 Gy (median dose of 40 Gy) were reported to produce median survivals of 24 months[5].

Because of this, in 1983 the Radiation Therapy Oncology Group(RTOG) performed a Phase II clinical trial to determine whether 60 Gy to gross disease and 40 Gy to possible microscopic disease elsewhere in the brain/meninges could increase the cure rate. Despite of high dose of 60 Gy and large volume treating all areas at risk for microscopic disease to 40 Gy, the survival of patients with primary CNS lymphoma is no better than the survival of patients with malignant glioma[6]. Various treatment modalitis have failed to improve the long-term survival and it is difficult to determine the effectiveness of each treatment modality because of its rarity and lack of prospective study. We report the treatment results of this study, including an analysis of patterns of failure that allow us to suggest possible approaches for the more effective management of the disease.

MATERIALS AND METHODS

Between 1982 and 1991, sixteen patients with primary CNS lymphoma were seen at Department of Therapeutic Radiology of Kyung Hee University Hospital. We evaluated the treatment results of whole brain and meningeal irradiation to 40 Gy, plus a 15-20 Gy boost to gross disease. Patients were excluded if they had lymphomatous meningitis without a parenchymal lesion, prior radiotherapy and/or chemotherapy, inadequate radiation dose less than 30 Gy, or histologically unproven non-Hodgkin's lymphoma. According to the Working Formulation system, the predominant histologic subtypes were large non-cleaved cell, diffuse mixed small and large cell, and large cell imunoblastic cell types, seen in 31.3%, 25.0%, 25.0% of cases, respectively. Distribution of total 16 patients by age, sex, symptoms, pathologic cell types, radiation dose, and multiplicity of lesions is given in Table 1.

The first 40 Gy in 1.8 Gy fractions was delivered by a helmet field that extended down to the bottom of C2 to encompass the brain and meninges by parallel opposed portals using cobalt-60 unit. A boost dose of 15-20 Gy was then delivered to the contrast enhancing lesion. The daily dose of dexamethasone ranged between 0-44 mg/d (median dose=16 mg/d) was used concomitantly with radiation. CT or MR scans were performed pre-operatively, post-operatively prior to radiotherapy, three months after the completion of radiotherapy, and at least at the time of neurologic deterioration.

Survival rates were calculated from the date radiation therapy started. Progression was recorded when disease recurred either locally or distantly as determined clinically and/or by CT or MRI scan. The survival curves were estimated by Kaplan-Meier method and were compared using the log-rank test.

Table 1. Clinical Characteristics of 16 Patients with Primary Cental Nervous System Lymphoma

Variable	Number of Patients (percent)
Age	
median	52 years(26-71 years)
<50 yr	9(56.3)
≥50 yr	7(43.7)
Sex	
Male	11(68.7)
Female	5(31.3)
Symptoms	
Headache	10(62.5)
Focal deficits, hemiparesis	9(56.3)
Confusion, memory loss	4(25.9)
Seizures	3(18.8)
Pathology	
Large non-cleaved	5(31.3)
Large immunoblastic	4(25.0)
Diffuse mixed	4(25.0)
Small non-cleaved	2(12.5)
Diffuse lymphocytic	1(6.2)
Lesion	
Single	10(62.5)
Multiple	6(37.5)
Surgery	
Biopsy	11(68.7)
Resection	5(31.3)
Radiation dose	
Over 50 Gy	8(50.0)
Less 50 Gy	8(50.0)

RESULTS

Analysis of this study after completion of treatment reveals that total of 12 out of 16 patients(75%) died of their lymphoma. Two out of 16 patients(12.5%) survived without evidence of disease at last follow-up visit with survival of 8 and 22 months from start of radiation therapy. The overall survival of the 16 patients from first day of radiation therapy is given in Fig.1 Analysis of the 16 eligible patients
revealed the median survival to be 12 months from the start of treatment, with 55.6% 1-year survival rate and 34.7% of 2-years.

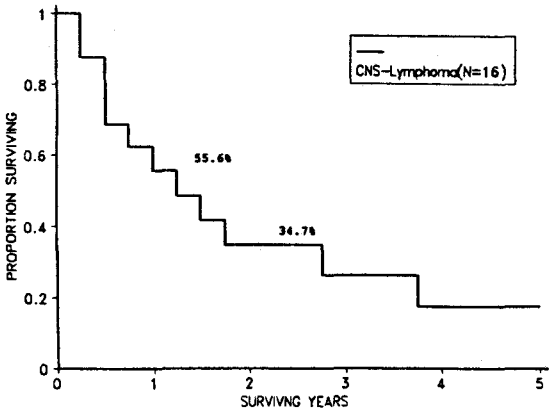

Fig. 1. Overall survival rates of 16 patients with primary CNS lymphoma treated with radiothreapy(median survival=12 months).

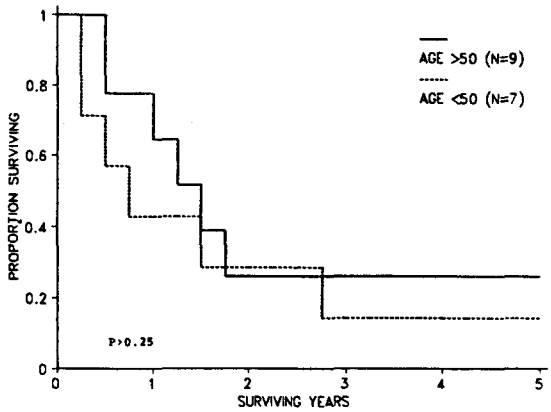

Fig. 2. Survival rates by age($z^2=0.88$;$p>0.25$).

The patients younger than 50 years had a median survival of 7 months compared with 12 for those aged 50 years or older. The respective 1-year survival rates were 42.9% versus 64.8%, and the 2-year survival rates were 25.9% versus 28.6%. The influence of age is statistically not significant($p>0.25$) as the effects of treatments result on survival(Fig.2). Survival for females was slightly better than for males, but there was no significant difference in survival($p>0.5$)(Fig.3). The presence of multiple discrete lesions did not adversely affect survival. The 1-year survival rates of 50% in patients with multiple lesions was no survival difference compared to 58.3% of single lesion($p>0.5$) as shown

Table 2. Survival of Total 16 Patients by Prognostic Variables

Variables	No.of patients	Median(Mo.)	1Yr.(%)	2 Yr(%)	P
Sex:					
Male	11	12	53.0	21.2	
Female	5	18	60.0	40.0	>0.5
Age:					
Age≥50	9	14	64.8	25.9	
Age<50	7	7	42.9	28.6	>0.25
Multiplicity:					
Single	10	12	58.3	46.7	
Multiple	6	14	50.0	0.0	>0.5
Radiation dose:					
Over 50 Gy	8	16	75.0	60.0	
Less 50 Gy	8	12	37.5	0.0	>0.1

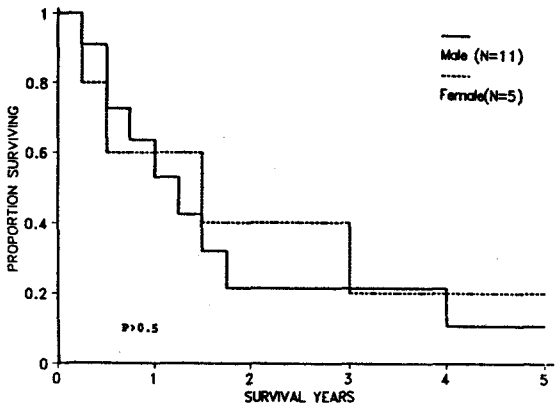

Fig. 3. Survival rates by sex(z^2=0.26;p>0.5).

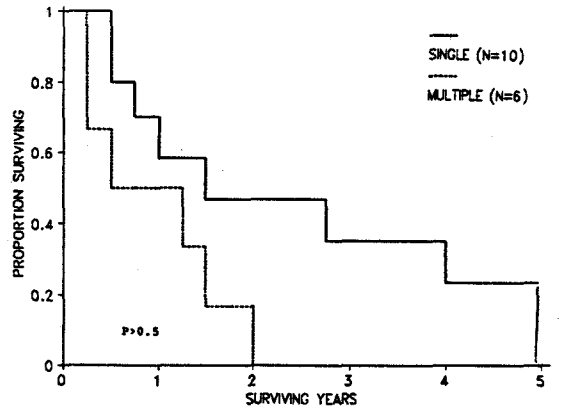

Fig. 4. Survival rates by multiplicity of lesion(z^2= 0.28;p>0.5).

over 50 Gy had 1-year, 2-year survival rates of

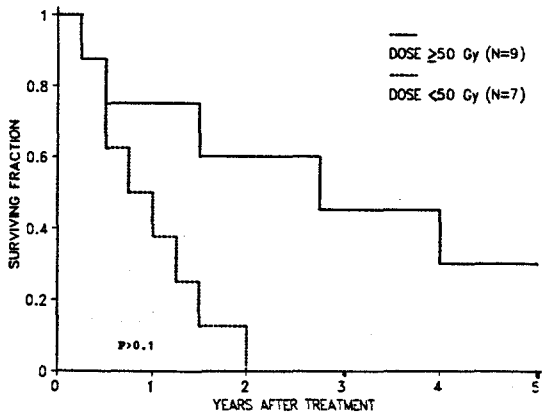

Fig. 5. Survival rates by radiation dose(z^2= 1.75;p>0.1).

in Fig.4. Patients who received radiation doses 75% and 60%, respectively, compared to 37.% and 0%, for patients who received smaller doses less than 50 Gy. Survival was marginally better for 8 patients who received 50 Gy or more compared with a lesser dose, but it was not statistically significant(p>0.1) as shown in Fig.5. Median survival from start of radiation therapy and percent survival 1-and 2-years are summarized according to variable factors as shown in Table 2.

Among total sixteen patients, eleven patients (68.7%) recurred in the brain and four patients (25.0%) recurred in the spinal axis. One patient developed disease outside the CNS. Distant failure, with or without local recurrence, occurred in

Table 3. Relapse Patterns in 12 Patients with CNS-lymphoma Who Completed Radiotherapy and Died of Recurrent Disease.

Site of recurrence	No. of patients
Brain	11
brain only	7
with CSF	3
with Systemic disease	1
Spinal cord alone	1

five patients(31.4%), with four in the spinal cord and one outside the CNS as shown in Table 3.

DISCUSSION

Primary CNS lymphomas derived from reticuloendothelial system are relatively rare and have historically been designated under a variety of synonyms(reticulum cell sarcoma, microgliomatosis, periadventitial sarcoma, perithelial sarcoma, perivascular sarcoma, reticuloendothelial sarcoma, malignant reticuloendotheliosis, and malignant lymphoma)[7]. This reflects the controversy regarding their histogenesis. It is now recognized that these tumors are of lymphoid origin and that the neoplastic cells are similar to those in non-Hodgkin's lymphoma arising outside the CNS[8].

CNS lymphoma is found in 1.9-2.6% of patients with AIDS and represents 50% of all lymphomas affecting both AIDS patients and renal transplant recipients[9]. According to Eby et al[10], the incidence of CNS lymphoma increased from 2.7 cases per 10 million in 1973 through 1975, to 7.5 per 10 million population during the years between 1982 and 1984, As a result of the AIDS epidemic, primary CNS lymphoma has been more prevalent and, it will become the most commonest primary CNS tumor during the 1990s[11]. It is estimated that, with the increasing numbers of patients with AIDS, more than 1,800 new cases of CNS lymphoma may be diagnosed in 1991[12].

The etiology of CNS lymphoma is not well understood at present and might be multifactorial. An etiologic association between CNS lymphoma and the Epstein-Barr virus has been suggested both in immuocompromised patients and organ-transplant recipients[13]. Bashir et al[14] documented EBV sequences in four patients with immunodeficiency by studying CNS lymphoma tissue with in situ hybridization techniques. In a similar review from UCSF all cases of AIDS-related CNS lymphoma studied were positive for EBV sequences [15]. If the association of Epstein-Barr virus with CNS lymphoma is proven, potential interventions with antiviral agents might be helpful in this treatment.

The majority of CNS lymphoma are classified as diffuse histiocytic and diffuse undifferentiated lymphomas in the Rappaport System. The tumors are most commonly large-cell immunoblastic lymphomas, as classified according to the international Working Formulation. Small cleaved cell lymphoma and large noncleaved cell lymphoma are the next most common cell types. These types comprised 77% of the lesions included in the review by Helle et all[16]. In our cases, the predominant histologic types were diffuse large cell, diffuse mixed small and large cell, and large cell imunoblastic types in 43.8%, 25.0%, 25.0%, respectively. There may be some correlation between the tumors histology and the prognosis for survival, however, it depends on many factors, including the patients age and the type of therapy, and performance status of the patients.

CNS lymphomas most frequently arise in the paraventricular supratentorial region, but they may also occur in the cerebellum and the brain stem, Rarely, they present only in the leptomeninges or spinal cord. It was founded that 52% of cases were supratentorial, 34% were multiple, 12% were cerebellar, 2% were in the brain stem, and fewer than 0.5% were spinal in a recent literature[17]. CNS lymphomas tend to infiltrate extensively along the corpus callosum or other deep white matter tracts. Rarely, they involve only in the leptomeninges or spinal cord. The tumor is often multicentric in location;single or multiple homogenous enhancing lesions in paraventricular region, basal ganglia, thalami and

corpus callosum are sometimes distinctive findings on CT or MRI studies. The appearance on MR images is that of an isointense central area on T1W images, with hyperintense regions in T2W images[18].

The biologic behavior of CNS lymphoma is clinically aggressive and comparable to that of disseminated high-grade systemic lymphomas. Corticosteroid administration has been used as a diagnostic test in patients who are not candidates for biopsy. A biopsy performed after corticosteroid treatment may reveal nondiagnostic tissue. Corticosteroids may cause transient shrinkage or complete disappearance of tumor masses on neuroimaging studies in a significant proportion of patients[19]. When initial neuroradiologic study suggests a diagnosis of lymphoma, the subsequent spontaneous resolution of lesions should not regard as a benign, self-limiting disease but should be aggressively pursued early in the patient's clinical course.

The role of surgery is to make a tissue diagnosis, usually by means of stereotactic biopsy or craniotomy with sampling of the tumor. No survival advantage has been observed from attempts to subtotally or totally resect the lesions[20]. Because of the multifocal and infiltrative nature of this tumor, the extent of resection does not influence survival, also results in high morbidity and mortality rates. Survival after surgical resection ranges from 0.9 to 4.6 months without adjunctive therapy[7]. This observation has lead to the use of stereotactic needle biopsy combined with immunochemical analysis as the initial diagnostic procedure when CNS lymphoma is suspected[16].

Radiation therapy with or without surgical resection generally results in prompt clinical and radiographic improvement, but the duration of response is short, lasting for an average of 12 to 24 months, and local recurrence usually ensues. The median survival time after treatment with radiation therapy range from 10 to 24 months with a 5-year disease-free survival rate of only about 3%(Table 4). Because of the multifocal nature of CNS lymphomas, their predilection for leptomeningeal infiltration, and their tendency to be more widespread than indicated by neuroimaging studies, the entire intracranial contents are included within the treatment fields. Survival data from the CNS lymphoma series treated at UCSF reveals a median survival of 134 days if radiation was used, but only 42 days in patients treated solely with surgery[15]. Formenti et al[21] treated CNS lymphoma patients with various doses of radiation, obtaining a median

Table 4. Literature Review of Ages and Survival Rates*

Author	Year	No.of patients	Age in years range(median)	Survival in mos. range(median)
Rampen	1980	12	31-71(55)	3-41 (14)
Letendre	1982	21	29-78(57)	2-91 (24)
Gonzalez	1983	15	46-74(55)	3-54 (21)
Sagerman	1983	12	15-81(55)	0-188(18)
Loeffler	1985	10	10-71(50)	2-97 (15)
Freeman	1986	19	38-87(62)	3-56 (12)
Ashby	1988	22	47-72(63)	3-55 (10)
Pollack	1989	27	16-77(59)	3-108(25)
Suh CO	1989	12	19-63(54)	3-132(42.3)
Shibamoto	1990	30	11-79(57)	2-188(14)
Nelson	1992	41	20-79(66)	1-67 (11.6)
This data	1993	16	17-71(52)	2-49 (12)

* Modified from Nelson et al (1992)

survival of 5.5 months overall. Murray et al[17] found that patients who received 50 Gy or more to the primary tumor site had a better result than those given less than 50 Gy. Hochberg and Miller [22], treating 44 patients with 50-60 Gy to the whole brain, achieved a 79% complete-plus-partial response rate and a median survival of 21.5 months in the patients who would be evaluated. Suh et al[23] observed intracranial recurrences in two patients who were treated less than 40 Gy to the whole brain without intrathecal chemotherapy. In present cases, analysis of the 16 eligible patients revealed that the median survival was 12 months from start of treatment, with 55.6% 1-year surviving rate and 34.7% of 2-years. This was similar with that reported in the literatures.

It is generally recommended that patients with solitary lesions receive 40 Gy to 50 Gy to the whole brain supplemented by an additional 10 Gy to 15 Gy to the primary tumor site using conventional fractionation schedules. The RTOG recently completed a prospective phase II study in which patients were given 40 Gy to the whole brain followed by an additional 20 Gy to the primary lesion to examine the efficacy of high-dose radiation therapy. The median survival of 41 evaluable patients was 11.6 months;the 1-year, and 2-year survival rates were 48% and 28%, respectively. Age and Karnofsky performance status(KPS) were the most important predictors of outcome; patients who were 60 years or older or who had a KPS of less than 70 had an especially poor prognosis(median survival time 5.6-7.6 months) compared with younger and more functionally intact patients(median survival time 21-23 months). These results suggest that even 60 Gy is inadequate and provide convincing evidence that more aggressive therapeutic regimens are needed[6]. However, we could not find any significant prognostic factors such as age, sex, multiplicity of lesions, or radiation dose lesions, or radiation dose in presented cases.

The role of spinal irradiation for eradication of the undetected CSF or spinal cord involvement is still investigational. Although craniospinal irradiation may be of value in patients with primary leptomeningeal lymphoma, its efficacy is unproved[24]. Because most patients, including those who develop spinal seeding, fail at the primary site, it is unlikely that prophylactic craniospinal axis irradiation will improve survival. In most situations, spinal irradiation has been replaced by intrathecal chemotherapy. There was relatively higher recurrence rate of spinal axis in our cases (25%) compared to 5.6%(15/267) of Murray's literature review[17]. We gave treatment to the spinal axis in patients who have spinal relapse confirmed by CSF cytology or radiological examination.

Systemic chemotherapy was used at the time of recurrence or progression in early studies. But recently, chemotherapy has been used either adjuvant or primarily in patients with NHL-CNS who do not have AIDS in an attempt to improve local control and survival rates because of unsatisfactory results by operation and radiotherapy. The reported data suggest that the combination of chemotherapy and irradiation is more effective than radiation therapy alone. Loeffler et al[25], reported a median survival of 44 months for 5 patients treated with combined therapy, whereas the median survival of 5 patients treated with radiation therapy alone was 14 months. Although different chemotherapeutic regimens were used, four of 5 patients who were alive at the time of reporting received intrathecal methorexate as part of their treatment program. Shibamoto et al[26] added 4-6 courses of VEPA chemotherapy(Vincristine, Cyclophosphamide, Doxorubicin, and Prednisolone) after 30-40 Gy to the whole brain and 50-60 Gy to the primary tumor site. Eight out of 10 patients completed the planned therapy and survived 16-100 months after diagnosis and three patients were alive without disease more than 5 years. The one-year, two-year, and 5-year survival rates were 64%, 44%, 37%, respectively. Brada et al[27] gave MACOPB (Adriamycin and Cyclophosphamide alternating between either Methotrexate

(with Follinic Acid rescue) and Vincristine, or Bleomycin and Vincristine all with Prednisolone). This was followed by 30-40 Gy to the brain and a 15-20 Gy boost to the primary site to a total dose of 55 Gy. Overall median survival was 16 months for 25 patients treated with radiotherapy alone. The preliminary results(median survival= 14 months) of combined modality therapy are so far not significantly different when compared to historical series. DeAngelis et al[12] obtained the best results treated 32 patients on a protocol of high-dose intravenous Methorexate followed by whole brain irradiation to 40 Gy plus a 14.4 Gy boost to the primary site and subsequently 2 cycles of high dose Cytosine Arabinoside(Ara-C). The median survival of 32 patients treated was 42.5 months compared to 21.7 months for 16 patients treated with radiation therapy alone. Chamberlain and Levin[28] reported 10 patients treated with radiation therapy and concomitant hydroxyurea followed by PCV. Median and 25% survival times were 30 and 50 months. Neuwelt et al[29] treated 12 patients with Cytoxan and Methotrexate in conjunction with osmotic blood-brain barrier(BBB) modification. Leucovorin rescue was used with Procarbazine, and Dexamethasone. For the 12 patients treated at initial presentation, the median survival was 21 months, with a 1 year survival of 75% and a 2 year survival of 33%.

In the RTOG study, it has completed a Phase I/II trial using 2-3 cycles of CHOD(Cytoxan, Adriamycin, Vincristine, Dexamethasone) followed by 41.4 Gy whole brain irradiation and 18 Gy boost to the primary tumor. If disease progresses after the second cycle, radiation therapy was begun without further chemotherapy. Patients with tumor cells in the CSF at the time of diagnosis also receive intrathecal Methotrexate. Unfortunately, there have been no randomized trials to compare the results of chemotherapy and irradiation with those obtained using radiation therapy alone. Because of the rarity of CNS lymphoma and the different schedules and treatment regimens being evaluated, it is impossible to establish which may be the most effective strategy against the tumor. Furthermore, if combined radiotherapy and chemotherapy is to be considered, the possibility of complications such as necrotizing leukoencephalopathy must be taken into account. We think that systemic chemotherapy for the control of systemic disease should be carefully considered because of the relatively low rate of extra-CNS involvement.

For many years, surgery and postoperative radiotherapy has been the accepted treatment for this disease. However, current questions about the radiation dose required for local control as well as the treatment volume that should be included within the irradiation fields have not been answered. Many authors recommanded at least 45 Gy to the whole brain with boost dose of 5 to 15 Gy to the primary site. Although radiation therapy prolongs survival, its curative potential is limited. Yet neither the optimal extent of the surgical procedure, nor the required radiotherapy treatment fields and doses are clearly defined, and the role for chemotherapy is entirely unknown. The careful and precise combination of radiation and chemotherapy should be investigated to increase tumor control with an acceptable complication rate by prospective randomized trial.

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=국문초록=

원발성 중추신경계 림프종에 대한 방사선치료

경희대학교 의과대학 치료방사선과학교실

홍 성 언

1982년부터 1991년까지 경희대학병원 치료방사선과에서 원발성 중추신경계 림프종으로 확진되어 방사선치료를 받은 16명의 환자를 대상으로 치료결과를 후향적으로 분석하였다.

가장 흔한 세포아형은 large, noncleaved cell과 B cell의 immunoblastic 림프종이었으며 측두엽과 심핵부위에 호발하였다.

치료는 환자를 생검 또는 절제술후 전뇌에 40 Gy(range=30-50 Gy)를 방사선 조사하였으며 원발병소에 15-20 Gy를 추가조사하였다. 16명의 환자중 14명은 방사선치료후 2개월에서 49개월 사이에 사망하였으며, 2명은 재발없이 각각 8개월과 22개월째 생존하고 있다. 1년 및 2년생존율은 각각 55.6%와 34.7%이었고, 중간 생존기간은 12개월이었다. 16명의 환자중 재발된 11명을 분석하였다. 방사선치료후 원발부위에 재발은 드물었으나 전뇌조사에서 불구하고 다른 부위에서 재발하였다. 재발율은 뇌에서 68.7% (11/16)이고 척추에서 25.0%(4/16)이었다. 나이, 성별 발생부위, 병소수, 방사선치료선량등은 각각 생존율과 무관하였다. 이와 같은 결과로 중추신경계 림프종은 방사선 치료의 초기반응은 양호하나 통상적인 방사선치료만으로는 조절이 어려운 질환이다. 따라서 분할치료방법에 의한 방사선량 증가와 항암제의 병용으로 중추신경계 림프종에 대한 치료효과를 향상시키리라 기대한다.