

*CLINICAL STUDY*

# Evaluation of the Effectiveness and Side Effects of Radiotherapy in Patients with Primary Nervous System Lymphoma - A Single Center Experience

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## ABSTRACT

**Aim:** In this study, we aimed to evaluate the overall and progression-free survival, the radiotherapy process and the early and late adverse effects in patients who underwent radiotherapy (RT) for primary nervous system lymphoma in our clinic.

**Method:** Between January 2010 and September 2019, 16 patients who received radiotherapy due to primary central nervous system lymphoma in our clinic were examined according to their statistically significant differences in terms of survival and side effects.

**Results:** The median disease-free survival of the patients was 6 months, and the median overall survival was 12.5 months. 18.75% of the patients could not receive chemotherapy but only radiotherapy. Radiotherapy doses were range from 2600 to 5000 cGy. When patients were evaluated in terms of radiotherapy dose, field size and chemotherapy, no statistically significant difference in overall survival was detected. Cognitive disorders were observed as the most common late side effects while the most common acute side effects in patients were headaches.

**Conclusion:** In the treatment of primary central nervous system lymphoma, changes in radiotherapy portals and radiotherapy doses can be predicted in patients who received high-dose methotrexate chemotherapy or not. Furthermore, it has been considered that more comprehensive studies are needed to increase the success of treatment and provide standardization in treatment, especially in patients with elderly and comorbid diseases.

**KEYWORDS :** Primary Central Nervous System Lymphoma; Non Hodgkin Lymphoma; Radiotherapy; Overall Survival

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## INTRODUCTION

Primary Central Nervous System Lymphoma (PCNSL) is an aggressive non-Hodgkin lymphoma type that can be inhabited in the brain, eye, leptomeninges and spinal cord (NHL) [2]. Primary Central Nervous System Lymphoma (PCNSL) is the most common brain-inhabited and 90% of cases are Diffuse Large B Cell lymphoma [3,4]. PCNSL accounts for about 3-4% of primary intracranial malignancies, with about 1,500 new cases annually seen in the US. Psychomotor disorders, memory problems, behavioral changes, ataxia and urinary incontinence are the most common symptoms [5,6]. In untreated PCNSL patients, prognosis is poor and the average survival after

diagnosis is about 1.5 months [7]. Chemotherapy regimens containing high dose methotrexate are frequently used in PCNSL treatment and the likelihood of late side effects due to treatment increases if all Brain Radiotherapy (WBRT) is applied together with chemotherapy regimens containing high dose methotrexate. 40-45 Gy (1.8-2 Gy) WBRT is applied in the presence of progressive disease and/or recurrence after CT, while 23.4-30 Gy (1.8-2 Gy) WBRT is applied in the presence of complete response. Although the response to radiotherapy of the disease alone is good in cases of WBRT, radiotherapy's contribution to total survival is limited and overall survival is an average of 10-18

months [2]. The main purpose of our study is to evaluate the survival outcomes of PCNSL patients undergoing radiotherapy and the side effects associated with radiotherapy.

#### MATERIAL AND METHODS:

In this study, 16 patients, 14 women and 2 men, who received radiotherapy due to PCNSL between 2010 and 2019 at Akdeniz University Faculty of Medicine Radiation Oncology Clinic, were retrospectively examined. The age range of patients ranges from 51 to 82 (median:65,5). Stereotaxic biopsy was taken from all patients and patients who were diagnosed histopathologically with Diffuse Large B-Cell Lymphoma were included in the study.

Spinal lymphomas, patients younger than 18 years of age, and patients who previously received cranial radiotherapy were not included in the study. Hospital medical records were used to obtain patients' clinical data, radiotherapy information, and post-radiotherapy survival and side effect results. Customized thermoplastic head and neck masks were used to provide immobilization in patient simulations.

Computed tomography sections of 2 mm slice thickness were taken from the patients in the supine position and external radiotherapy was applied to the patients with Synergy, Electra<sup>R</sup> brand linear accelerator. During RT planning, brain stem, spinal cord, eyes, lenses, optic nerves, optic chiasm and cochleas were identified as organs at-risk. Whole-brain radiotherapy was planned for all patients, and boost volume was added to patients with localized areas on brain MRI images. Some of the PCNSL patients who were received whole-brain radiotherapy (boosted or not) could not receive chemotherapy due to comorbid diseases. Patients were not received autologous stem cell transplantation as consolidation treatment after chemotherapy. The age, educational status, socioeconomic status, professions, comorbid diseases, smoking and alcohol habits of the patients were learned by phone calls, one-on-one interviews or from archive records. The socioeconomic status of people with an annual income of more than \$ 9042 is medium-high, and the socio-economic status of those with an annual income of less than \$ 9042 is low [1]. The effect of radiation therapy dose and fractionation on disease-free survival and total survival was investigated. Patient characteristics and treatment methods are given in Table 1.

Patients were evaluated once a week during the treatment process in terms of acute reactions. After radiotherapy, the brain was followed up with MRI in the first month and every three months in the first two years thereafter. After the second year, patients were evaluated with brain MRI every six months. Early and late side effects were evaluated according to the Common Terminology Criteria for Adverse Events v3.0 grading system.

IBM SPSS v24.0 is used for statistical comparisons. In the overall survival assessment, the time from biopsy date to the date of death was calculated for all patients. Progression free survival was evaluated as the period

from the date of biopsy to the date of progression in the controlled brain MRI. Kaplan-Meier method was used to compare survival times. Statistically, the p value of 0.05 or smaller has been considered significant.

This study was approved by the Ethics Board of Clinical Research at Akdeniz University Faculty of Medicine on 10.07.2019 (Decision No: 641).

**Table 1. Patient characteristics and treatment methods.**

Variable	N	%
<b>Age</b>		
<60	6	%37,5
≥60	10	%62,5
<b>Sex</b>		
Female	14	%87,5
Male	2	%12,5
<b>Socio-economical status</b>		
Low income	6	%37,5
Medium-High income	10	%62,5
<b>Educational status</b>		
University	1	%6,25
High school	4	%25
Elementary school	11	%68,75
<b>Smoking habit</b>		
Yes	1	%6,25
No	15	%93,75
<b>Comorbid disease</b>		
Yes	8	%50
No	8	%50
<b>Chemotherapy</b>		
Yes	13	%81,25
No	3	%17,5
<b>Radiotherapy portals</b>		
Total cranium	11	%68,75
Total cranium + boost	5	%31,25

#### RESULTS

Radiotherapy fields of the patients included in the study varied as whole brain and whole brain plus boost. 68.75% of patients received radiotherapy as the whole brain, 31,25% whole brain and boost. Radiotherapy doses of the patients ranged from 2600 cGy to 5000 cGy.

Approximately half of the patients have comorbid diseases, mainly hypertension. Three patients included in the study did not receive chemotherapy due to their comorbidities or their own request, and the remaining patients received methotrexate-containing chemotherapy regimens. When the groups that received and did not receive chemotherapy were compared statistically, no significant difference was found in terms of overall survival (p: 0.384). In addition, it was observed that gender, educational status, socioeconomic status do not affect the prognosis of survival. When other survival data are evaluated; The median value of disease-free survival was 6 months, while the median value of total survival was 12.5 months. No significant difference was found between whole brain irradiations with and without boost in terms of survival (p: 0.806). The most common early side effect in patients was headache, and it was seen in

half of the patients. Other early side effects seen in patients were nausea, vomiting, dizziness, and altered consciousness. In two of 16 patients included in the study, impairment was observed in cognitive functions, an expected late effect of radiotherapy. Acute and late side effects in patients are given in Table 2. Statistically, side effects of radiotherapy were found to be independent of radiotherapy dose and field. Corticosteroids were used in the treatment of radiotherapy-induced cerebral edema.

**Table 2.** Acute and late side effects.

Side effect	N	%
<b>Acute side effects</b>		
Headache	8	%50
Neusea and vomiting	2	%12,5
Dizziness	2	%12,5
Fluctuation of consciousness	2	%12,5
<b>Late side effects</b>		
Cognitive Function Impairment	2	%12,5

When the final status of the patients was evaluated, it was determined that 7 patients (43.75%) died and 9 patients (56.25%) were still alive.

## DISCUSSION

Chemotherapy containing high-dose methotrexate is considered the standard treatment in PCNSL patients. Autologous stem cell transplantation or low dose WBRT may also be included in the treatment in addition to chemotherapy applications containing high dose methotrexate. However, optimal treatment is not yet clear. PCNSL is sensitive to radiotherapy, but the use of radiotherapy alone is inadequate in control of the disease and leads to neurotoxicity, especially in older patients [8,9].

In the RTOG 8315 study, 41 patients received a total of 60 Gy radiotherapy with a 40 Gy WBRT and 20 Gy boost dose, and the median overall survival was reported as 12.2 months [10]. In our study, although the radiotherapy fields differ, the mean value of radiotherapy dose is 4081.25 cGy and the median overall survival was found to be 12.5 months. Neuhauser et al, reported that the use of rituximab with chemotherapy regimens containing high methotrexate has become widespread, but treatment becomes difficult in elderly patients due to toxicity [11]. Yoo Kang Kwak and colleagues reported that radiotherapy may be an alternative treatment in patients who cannot receive chemotherapy. In their study, only radiotherapy

was applied to the 32 patients and the median overall survival was reported as 16.3 months [12].

Tali Siegal et al. Stated that the incidence of PCNSL increased with age and reported that it became difficult for elderly patients to tolerate high-dose chemotherapy because of their comorbidities and that whole-brain radiotherapy could be used in patients who cannot tolerate chemotherapy. However, they stated that optimal treatment is still an unresolved issue, especially in elderly patients, and studies should be conducted on this subject [13]. In our study, radiotherapy was (only) applied to patients who could not tolerate chemotherapy.

According to a phase 2 study in which PCNSL patients who underwent whole-brain radiotherapy after immunochemotherapy or autologous stem cell transplantation after intensive chemotherapy were evaluated, it was reported that radiotherapy and autologous stem cell transplantation as a consolidative treatment in PCNSL patients were effective [14]. In our study, patients were not received autologous stem cell transplantation and only radiotherapy was applied to patients.

In another study evaluating the addition of WBRT to patients treated with high-dose methotrexate chemotherapy, it was reported that adding WBRT to high-dose methotrexate-containing chemotherapy did not create a significant difference in overall survival, but increased progression-free survival, but the risk of neurotoxicity increased in the group in which WBRT was added. [15].

Correa D et al, reported that administration of WBRT with chemotherapy regimens containing high-dose methotrexate reduced cognitive functions [16]. Also, in the case of combined use of WBRT and chemotherapy in PCNSL treatment, the neurotoxicity rates were reported to be approximately 20-30% [17]. In our study, cognitive dysfunction was detected in 12.5% of the patients.

## COMMENTS

This manuscript reflects a single center experience. In the treatment of primary central nervous system lymphoma, changes in radiotherapy sites and radiotherapy doses can be predicted in patients who received high-dose methotrexate chemotherapy or not. In addition, it is thought that more comprehensive studies are needed to increase the success of the treatment and to provide standardization in the treatment, especially in the elderly and patients with comorbid diseases.

## REFERENCES

- [1] GDP per capita (current US\$), <https://data.worldbank.org/indicator/NY.GDP.PCAP.CD>
- [2] Hoang-Xuan K, Bessell E, Bromberg J, et al. Diagnosis and treatment of primary CNS lymphoma in immunocompetent patients: Guidelines from the European Association for Neuro-Oncology. *Lancet Oncol* 2015; 16: e322–e332
- [3] Current management of primary central nervous system lymphoma. *Oncology* 9:63–71, 1995.
- [4] Camilleri-Broët S, Martin A, Moreau A, et al: Primary central nervous system lymphomas in 72 immunocompetent patients: Pathologic findings and clinical correlations. *Groupe Ouest Est d'étude des Leucémies et Autres Maladies du Sang (GOELAMS)*. *Am J Clin Pathol* 110:607-612, 1998.
- [5] Nakamura H, Makino K, Yano S et al (2011) Epidemiological study of primary intracranial tumors: a regional survey in Kumamoto prefecture in southern Japan—20-year study. *Int J Clin Oncol* 16:314–321.
- [6] Grommes C, DeAngelis LM. Primary CNS lymphoma. *J Clin Oncol*. 2017; **35** (21): 2410-2418.

- [7] Gerard, L.M., Imrie, K.R., Mangel, J. High-dose methotrexate based chemotherapy with deferred radiation for treatment of newly diagnosed primary central nervous system lymphoma. *Leuk Lymphoma*. 2011; 52(10): 1882–90.
- [8] Han CH, Batchelor TT. Diagnosis and management of primary central nervous system lymphoma. *Cancer*. 2017; 123(22): 4314-4324. DOI:[10.1002/cncr.30965](https://doi.org/10.1002/cncr.30965)
- [9] Seidel S, Schlegel U. Have treatment protocols for primary CNS lymphoma advanced in the past 10 years. *Expert Rev Anticancer Ther*. 2019; 19(10): 909-915. DOI: [10.1080/14737140.2019.1677157](https://doi.org/10.1080/14737140.2019.1677157)
- [10] Nelson DF, Martz KL, Bonner H, et al. Non-Hodgkin's lymphoma of the brain: can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315. *Int J Radiat Oncol Biol Phys*. 1992;23(1):9-17. DOI: [10.1016/0360-3016\(92\)90538-s](https://doi.org/10.1016/0360-3016(92)90538-s)
- [11] Neuhauser M, Roetzer T, Oberndorfer S, et al. Increasing use of immunotherapy and prolonged survival among younger patients with primary CNS lymphoma: a population-based study. *Acta Oncol*. 2019;58(7):967-976. DOI: [10.1080/0284186X.2019.1599137](https://doi.org/10.1080/0284186X.2019.1599137)
- [12] Kwak YK, Choi BO, Choi KH, Lee JH, Sung SY, Lee YH. Radiotherapy as an alternative treatment option for primary central nervous system lymphoma patients who are noncandidates for chemotherapy. *Oncotarget*. 2017;8(63):106858-106865. Published 2017 Nov 10. DOI: [10.18632/oncotarget.22427](https://doi.org/10.18632/oncotarget.22427)
- [13] Siegal T, Bairey O. Primary CNS Lymphoma in the Elderly: The Challenge. *Acta Haematol*. 2019;141(3):138-145. DOI: [10.1159/000495284](https://doi.org/10.1159/000495284)
- [14] Houillier C, Taillandier L, Dureau S, et al. Radiotherapy or Autologous Stem-Cell Transplantation for Primary CNS Lymphoma in Patients 60 Years of Age and Younger: Results of the Intergroup ANOCEF-GOELAMS Randomized Phase II PRECIS Study. *J Clin Oncol*. 2019;37(10):823-833. DOI: [10.1200/JCO.18.00306](https://doi.org/10.1200/JCO.18.00306)
- [15] Thiel E, Korfel A, Martus P, et al. High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. *Lancet Oncol*. 2010;11(11):1036-1047. DOI: [10.1016/S1470-2045\(10\)70229-1](https://doi.org/10.1016/S1470-2045(10)70229-1)
- [16] Correa DD, Shi W, Abrey LE, et al. Cognitive functions in primary CNS lymphoma after single or combined modality regimens. *Neuro Oncol*. 2012;14(1):101-108. DOI: [10.1093/neuonc/nor186](https://doi.org/10.1093/neuonc/nor186)
- [17] Omuro AM, Ben-Porat LS, Panageas KS, et al. Delayed neurotoxicity in primary central nervous system lymphoma. *Arch Neurol*. 2005;62(10):1595-1600. DOI: [10.1001/archneur.62.10.1595](https://doi.org/10.1001/archneur.62.10.1595)