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Whole brain radiation dose reduction for primary central nervous system lymphoma patients who achieved partial response after high-dose methotrexate based chemotherapy

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Abstract

Background: The whole brain radiotherapy (WBRT) dose for primary central nervous system lymphoma (PCNSL) patients who achieved complete response after induction chemotherapy was recently reduced to 23.4 Gy, but the optimal radiation dose for patients who achieved partial response (PR) is controversial. The aim of this study was to investigate the feasibility of reduced-dose WBRT for patients who achieved PR.

Method: We retrospectively reviewed the medical records of PCNSL patients who were treated with high-dose methotrexate based chemotherapy. We compared treatment outcomes between the patients who received WBRT at either 36 Gy or 45 Gy.

Results: The overall survival (OS) and intracranial progression-free survival (IC-PFS) was 66.3% and 42.6% at 5 years, respectively. There was no significant difference in treatment outcomes between the patients who received 36 Gy and 45 Gy, especially among patients who achieved PR. Three-year OS was 100% and 83.3% for 36 Gy and 45 Gy group, respectively ($P = 0.313$). Three-year IC-PFS was 60.0% and 66.7% for 36 Gy and 45 Gy group, respectively ($P = 0.916$).

Conclusion: Findings of our study might provide a possibility for dose-reduction in patients achieving PR to induction chemotherapy, which may in turn reduce delayed neurologic sequelae. However, the number of patients included in this study was too small to lead to a concrete conclusion, thus further study is needed.

Key words: lymphoma, non-Hodgkin, primary central nervous system neoplasms, radiation dosage, radiotherapy

Introduction

Whole brain radiotherapy (WBRT) was the sole treatment modality for primary central nervous system lymphoma (PCNSL) before the introduction of methotrexate (1). In the Radiation Therapy Oncology Group (RTOG) 83-15 study, 62% of patients achieved a complete response (CR) with WBRT alone, but the median overall survival (OS) was only 12 months and 61% of patients had intracranial relapse (2). The introduction of methotrexate was the most important advance in PCNSL treatment, and high-dose methotrexate (HD MTX) based chemotherapy followed by WBRT increased the median OS and progression-free survival (PFS) up to 37 months and 24 months, respectively (3).

As survival increased, the delayed neurologic sequelae began to be reported and the 5-year cumulative incidence was reported to be 24% (4,5). WBRT was the major risk factor for delayed neurologic sequelae and there have been two different approaches to reduce the delayed neurologic sequelae without compromising disease control. The first approach was deferring WBRT, and there is a large prospective randomized trial comparing patients who received WBRT and who did not (6,7). The second approach was to reduce WBRT dose. Historically, the recommended WBRT dose was 40–45 Gy, which is close to the upper limit of whole brain radiation tolerance. Several studies reported that reduced dose WBRT is feasible, but they were small sample-sized retrospective studies (8,9). The most recently recommended WBRT dose is 23.4 Gy in 13 fractions based on the result of a Phase II study from Memorial Sloan Kettering Cancer Center (MSKCC) (10,11). However, it was for patients who achieved CR after induction chemotherapy, and the recommended WBRT dose for patients with less than CR was still 45 Gy.

In this study, we reported the 10-year experience of a single institution which has been treating PCNSL patients homogenously and tried to find out whether the reduction of the WBRT dose from 45 Gy to 36 Gy in patients who achieved PR after HD MTX-based chemotherapy is feasible.

Materials and methods

Patients

We retrospectively reviewed PCNSL patients who were treated at Samsung Medical Center from 2002 to 2012. To focus on the effect of radiation therapy, we included patients who were treated using same chemotherapy. A total of 62 patients with pathologically confirmed diffuse large B-cell lymphoma were eligible. Bone marrow biopsy, chest CT scan and abdominopelvic CT scan were done to exclude systemic lymphoma. Since WBRT indication for patients aged 60 years or older was different from that for patients less than 60 years old, the number of patients who received WBRT among patients aged 60 years or older was too small. Thus patients less than 60 years old only were included in this study. This study was approved by the institutional review board (SMC 2016-03-038).

Induction chemotherapy

All patients included in this study received HD MTX-based chemotherapy, which was modified from the regimen used in the RTOG 93-10 study (3). Intravenous methotrexate 3.5 g/m^2 and vincristine 1.4 mg/m^2 were administered for five cycles over a 10-week period at fortnight intervals. Procarbazine 100 mg/m^2/day was administered for 7 days on Weeks 1, 5 and 9. Intrathecal methotrexate 12 mg was administered the week after each dose of intravenous methotrexate.

Radiotherapy

WBRT was given 2–4 weeks after the completion of induction chemotherapy. WBRT was indicated for patients who achieved less than CR to induction chemotherapy. In patients who achieved CR, the application of WBRT was personalized by physicians in accordance with the patient's consent. During the early study period, a total dose of 45 Gy in 25 fractions (1.8 Gy daily) was delivered. Since 2008, WBRT dose has been reduced to 36 Gy in 20 fractions (1.8 Gy daily) because of growing bodies of evidence that the reduced-dose WBRT decreased the delayed neurologic sequelae (10,12,13). If ocular involvement was identified, both eyes were included in the radiation field to a total dose of 36 Gy in 20 fractions. Focal boost radiotherapy of 9–10 Gy was selectively delivered to the residual tumor which has contrast enhancement on gadolinium-enhanced magnetic resonance imaging that obtained before WBRT.

Consolidation chemotherapy

Two cycles of consolidation chemotherapy followed 3 weeks after WBRT or HD MTX-based chemotherapy. Cytarabine 3 g/m^2 was administered for 2 days in each cycle.

Response evaluation during and after treatment

The response was evaluated according to the international criteria for PCNSL (14). Gadolinium-enhanced magnetic resonance imaging scans were performed 1 month after the last cycle of induction chemotherapy and WBRT, and were repeated every 3 months for 2 years, every 6 months for 5 years, and every year thereafter. Instead of objective assessment of neurocognitive function, patients were asked if there was a change in memory ability on each visit.

Data analysis

OS was measured from diagnosis of PCNSL until death as a result of any causes. Intracranial progression-free survival (IC-PFS) was measured from diagnosis of PCNSL until intracranial progression or relapse. Pearson's Chi-square test and Fishers's exact test were used to compare the patient characteristics between patients who did and did not receive WBRT, and patients who receive WBRT to 36 Gy and 45 Gy. The Kaplan–Meier method was used to estimate OS and IC-PFS, with comparison by the log-rank test. Statistical analyses were performed using SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA). Values of $P < 0.05$ indicated statistical significance.

Results

Demographics and patient flow

The patient characteristics are summarized in Table 1 and the median age was 47 years (range, 19–59). Figure 1 shows the patient flow according to the response after induction chemotherapy and use of WBRT. Among 62 patients, 54 patients completed induction chemotherapy. After completion of induction chemotherapy, 30 (55.6%) patients had CR, 20 (37.0%) had partial response (PR), and 4 (7.4%) had progressive disease (PD). Among patients who withheld induction chemotherapy, patients who were tolerable to further chemotherapy received second-line chemotherapy and those who were not tolerable received WBRT.

Survival

The median follow-up duration was 61 months (range, 0–165 months). The median OS and IC-PFS of all patients were 93 months and 47 months, respectively. The OS rates were 73.6% and 66.3% at 3 and 5 years, respectively, and the IC-PFS rates were 50.4% and 42.6% at 3 and 5 years, respectively (Fig. 2).

WBRT versus no WBRT

Among the 54 patients who completed induction chemotherapy, a total of 43 patients received WBRT. Eight and three patients did not receive WBRT among patients who achieved CR and PR,

Table 1. Characteristics of all patients included in this study ($n = 62$)

Characteristics	Number of patients (%)
Sex	
Male	39 (62.9)
Female	23 (37.1)
ECOG performance status	
0–1	38 (61.3)
2–4	24 (38.7)
Number of lesions	
Single	20 (32.3)
Multiple	42 (67.7)
Deep location	
No	18 (29.0)
Yes	44 (71.0)
Cerebrospinal fluid cytology	
Negative	51 (82.3)
Positive	6 (9.7)
Not available	5 (8.0)
Cerebrospinal fluid protein (mg/dl)	
≤40	28 (45.2)
>40	20 (32.2)
Not available	14 (22.6)
Serum lactate dehydrogenase (UI/l)	
≤500	47 (75.8)
>500	12 (19.4)
Not available	3 (4.8)
Extent of surgery	
Biopsy	47 (75.8)
Tumor removal	15 (24.2)

ECOG, Eastern Cooperative Oncology Group.

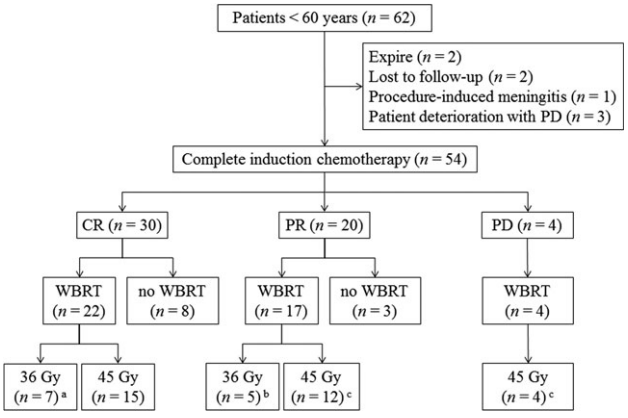

Figure 1. Patient flow diagram. CR, complete response; PR, partial response; PD, progressive disease; WBRT, whole brain radiotherapy. [a]One patient was supposed to receive 36 Gy but withheld at 16.2 Gy. [b]Two patients received focal boost radiation after WBRT. [c]One patient received focal boost radiation after WBRT.

respectively (Fig. 1). When we investigated the patients who achieved CR and PR only ($n = 50$), since all patients who achieved PD received WBRT, there were no differences in patient characteristics between patients who did and did not receive WBRT (Table 2). The median OS for patients who received WBRT was 126 months. The median OS has not been reached in patients who did not receive WBRT and their mean OS was 77 months. The 5-year OS was 78.9% and 51.9% for patients who did and did not receive WBRT,

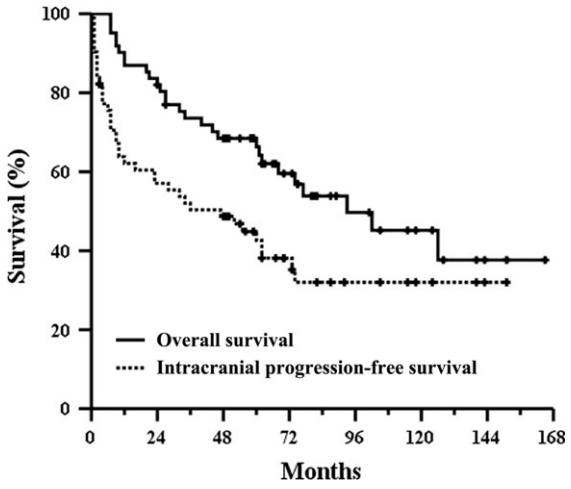

Figure 2. Overall survival and intracranial progression-free survival of all patients ($n = 62$).

respectively ($P = 0.249$). The median IC-PFS was 73 and 7 months in patients who did and did not receive WBRT, respectively. The 5-year IC-PFS was 61.0% and 15.0% for patients who did and did not receive WBRT, respectively ($P = 0.006$). Subgroup analyses according to the response to induction chemotherapy were performed (Table 3). Among patients who achieved CR, there was no difference in IC-PFS between those who did and did not receive WBRT (73 versus 47 months, $P = 0.179$). On the other hand, among patients who achieved PR, patients who did not receive WBRT had a poor IC-PFS than those who receive WBRT. The median IC-PFS for patients who did not receive WBRT was 7 months. The median IC-PFS has not been reached in patients who received WBRT and mean IC-PFS for these patients was 97 months ($P = 0.001$). However, the number of patients who did not receive WBRT was only three. Among them, one patient refused WBRT. Another patient who had subtle tumor enhancement on brain magnetic resonance imaging obtained after induction chemotherapy was assigned to CR group and did not receive WBRT. The other patient had vitreous opacity in pre-evaluation but underwent treatment without confirmation. After induction chemotherapy, the brain lesion had disappeared but vitreous opacity was still present. Thus diagnostic vitrectomy was performed and lymphomatous involvement was confirmed. He was treated with intraocular methotrexate without WBRT. These patients had intracranial progression at 4, 7 and 7 months, respectively, and received salvage chemotherapy consisting of ifosfamide, carboplatin and etoposide.

WBRT 36 Gy versus 45 Gy

We selected a total of 38 patients among 43 patients who received WBRT after induction chemotherapy. Four patients who achieved PD were not included since they all received 45 Gy and there was no comparison group receiving 36 Gy. One patient who was supposed to receive 36 Gy, but did not complete WBRT, was also excluded. A total of 11 and 27 patients received 36 Gy and 45 Gy, respectively, and there were no differences in patient characteristics between patients who received 36 Gy and 45 Gy (Table 4). Figure 3 shows OS and IC-PFS according to WBRT dose and there were no statistically significant differences between patients who received 36 Gy and

45 Gy (Fig. 3a and b). Three-year OS was 100% and 81.5% for 36 Gy and 45 Gy group, respectively. Five-year OS was 72.7% and 77.8%, respectively ($P = 0.970$). Three-year IC-PFS was 63.6% and 70.4% for 36 Gy and 45 Gy group, respectively. Five-year IC-PFS was 63.6% and 62.6%, respectively ($P = 0.980$). Subgroup analyses according to the response to induction chemotherapy were performed, and the treatment outcomes of 36 Gy and 45 Gy were not different (Fig. 3c–f). Especially in patients who achieved PR, there was no difference in OS or IC-PFS between two radiation doses. Three-year OS was 100% and 83.3% for 36 Gy and 45 Gy group, respectively ($P = 0.313$). Three-year IC-PFS was 60.0% and 66.7% for 36 Gy and 45 Gy group, respectively ($P = 0.916$).

Change in memory ability

To exclude the change of neurocognitive function caused by disease progression, our investigation was limited to the patients who maintained a no-evidence-of-disease (NED) status during follow-up period. A total of 25 patients maintained NED status. Among them, 10 patients had a change in memory ability and they all received

Table 2. Comparison of patient characteristics between patients who did and did not receive WBRT among patients who achieved complete or partial response to induction chemotherapy ($n = 50$)

Characteristics	Number of patients		*P* value
	WBRT (+) ($n = 39$)	WBRT (−) ($n = 11$)	
Mean age	47	50	0.305
Sex			
Male	24	7	>0.999
Female	15	4	
ECOG performance status			
0–1	25	7	>0.999
2–4	14	4	
Number of lesions			
Single	12	6	0.147
Multiple	27	5	
Deep location			
No	12	4	0.728
Yes	27	7	
Cerebrospinal fluid cytology			
Negative	31	11	0.313
Positive	6	0	
Not available	2	0	
Cerebrospinal fluid protein (mg/dl)			
≤40	22	4	0.434
>40	11	4	
Not available	6	3	
Serum lactate dehydrogenase (UI/l)			
≤500	30	10	0.318
>500	7	0	
Not available	2	1	
Extent of surgery			
Biopsy	32	6	0.059
Tumor removal	7	5	
Response to induction chemotherapy			
Complete response	22	8	0.489
Partial response	17	3	

WBRT, whole brain radiotherapy; ECOG, Eastern Cooperative Oncology Group.

Table 4. Comparison of patient characteristics between two different radiation doses ($n = 38$)

Characteristics	Number of patients		*P* value
	WBRT 36 Gy ($n = 11$)	WBRT 45 Gy ($n = 27$)	
Mean age	50	45	0.237
Sex			
Male	8	16	0.488
Female	3	11	
ECOG performance status			
0–1	7	18	>0.999
2–4	4	9	
Number of lesions			
Single	2	9	0.452
Multiple	9	18	
Deep location			
No	5	7	0.240
Yes	6	20	
Cerebrospinal fluid cytology			
Negative	9	21	0.655
Positive	1	5	
Not available	1	1	
Cerebrospinal fluid protein (mg/dl)			
≤40	7	15	0.380
>40	1	9	
Not available	3	3	
Serum lactate dehydrogenase (UI/l)			
≤500	10	19	0.400
>500	1	6	
Not available	0	2	
Extent of surgery			
Biopsy	11	20	0.084
Tumor removal	0	7	
Response to induction chemotherapy			
Complete response	6	15	0.955
Partial response	5	12	

WBRT, whole brain radiotherapy; ECOG, Eastern Cooperative Oncology Group.

Table 3. Comparison of treatment outcomes according to WBRT among patients who completed induction chemotherapy

	Response to induction chemotherapy			
	CR + PR	CR	PR	PD
Number of patients (WBRT/no WBRT)	50 (39/11)	30 (22/8)	20 (17/3)	4 (4/0)
Median OS time (WBRT/no WBRT, months)	126/NR ($P = 0.249$)	126/NR ($P = 0.517$)	102/46 ($P = 0.216$)	12
Median IC-PFS time (WBRT/no WBRT, months)	73/7 ($P = 0.006$)	73/47 ($P = 0.179$)	NR/7 ($P = 0.001$)	2

CR, complete response; PR, partial response; PD, progressive disease; WBRT, whole brain radiotherapy; OS, overall survival; IC-PFS, intracranial progression-free survival; NR, not reached.

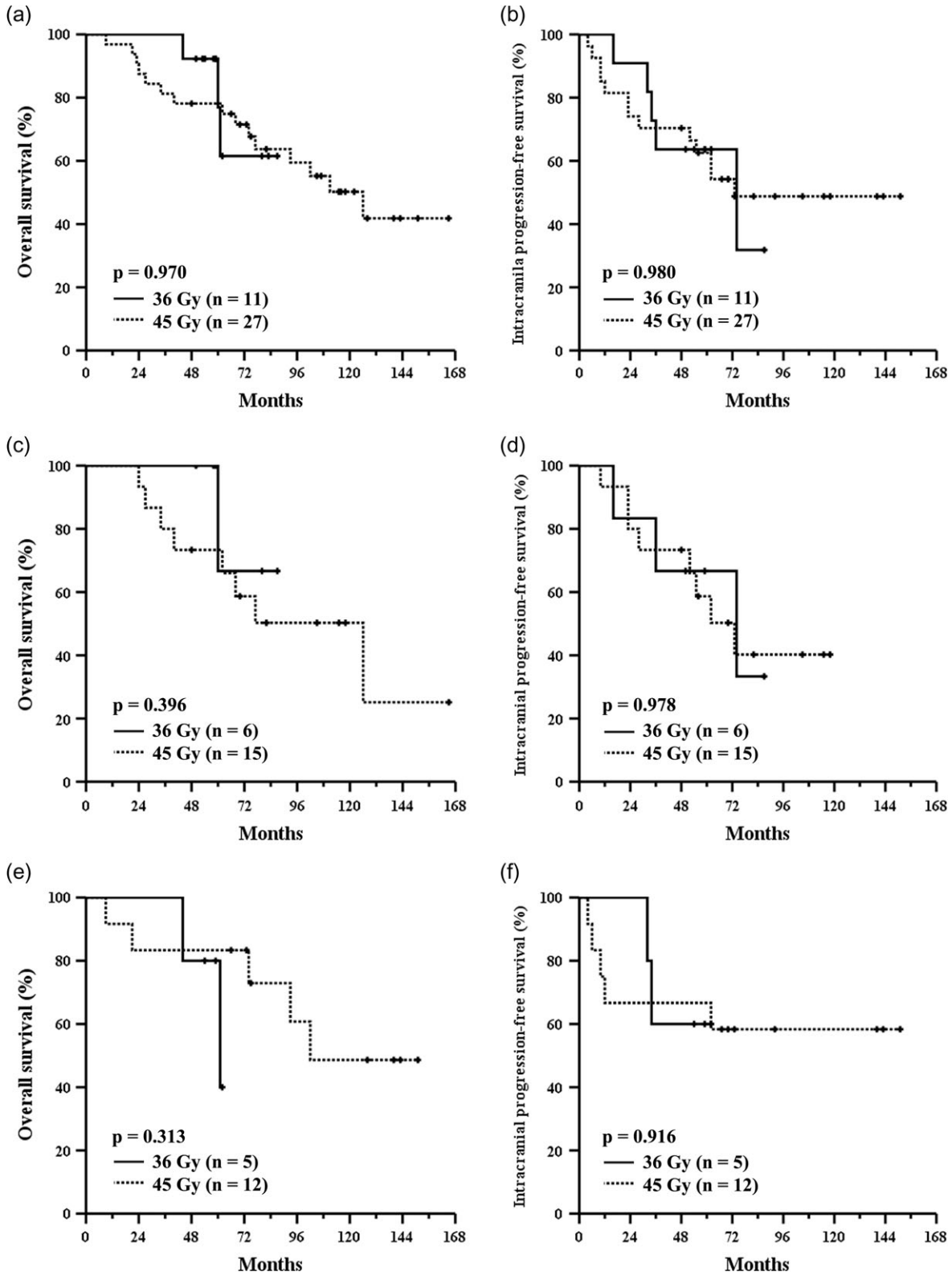

Figure 3. Overall survival and intracranial progression-free survival according to radiation dose in 38 patients who received whole brain radiotherapy (a and b), 21 patients who achieved complete response to induction chemotherapy (c and d), and 17 patients who achieved partial response to induction chemotherapy (e and f), respectively.

WBRT of 45 Gy. The other 15 patients who did not have a change in memory ability were as follows: six patients received 36 Gy, six patients received 45 Gy, and three patients did not receive WBRT.

Discussion

After the introduction of HD MTX-based chemotherapy, WBRT is primarily being used as a consolidation treatment after induction chemotherapy. However, there are concerns of radiation-induced brain damage and some efforts have been suggested to decrease treatment-related neurotoxicity. The first effort to decrease radiation-induced neurotoxicity was to treat elderly patients with chemotherapy alone without WBRT. Although recurrences occurred more frequently, the survival outcomes were satisfactory (15–17). In contrast to studies of elderly patients, there have been few studies on deferring WBRT in younger patients. Omuro et al. reviewed the medical records of patients less than 60 years old who were treated in institutions from the French Association of Neuro-Oncology (18). Patients who achieved CR to induction chemotherapy proceeded to maintenance chemotherapy without WBRT, and their 3-year OS and PFS were 69% and 28%, respectively. The PFS was much shorter than that of other studies in which the treatment outcomes of patients less than 60 years old were presented separately (3,8,13,15). Shortening of PFS by deferring WBRT also has been proven in the German Primary Central Nervous System Lymphoma Study Group 1 trial (6,7). In intention-to-treat analysis, WBRT significantly prolonged PFS (15.4 versus 9.9 months, $P = 0.034$), but without OS prolongation (32.4 versus 36.1 months, $P = 0.980$). When patients who achieved CR and less than CR were considered separately, WBRT prolonged PFS in patients with less than CR (4.7 versus 2.9 months, $P = 0.004$), but not in patients with CR (29.9 versus 25.7 months, $P = 0.350$). Likewise, a small number of patients who achieved PR after induction chemotherapy did not receive WBRT and had a poor IC-PFS in our study. The median IC-PFS for patients who did not receive WBRT was 7 months. The median IC-PFS has not been reached in patients who received WBRT and mean IC-PFS for these patients was 97 months ($P = 0.001$). However, the number of patients was too small to present statistical significance.

Another approach to decrease delayed neurologic sequelae was reducing the radiation dose. Bessell et al. reduced the WBRT dose from 45 Gy to 30.6 Gy in patients who achieved CR after induction chemotherapy (19). The induction chemotherapy consisted of cyclophosphamide, doxorubicin, vincristine, dexamethasone, carmustine, vincristine, methotrexate and cytarabine, which was different from the HD MTX-based chemotherapy widely used in recent years. The result was disappointing, especially in patients less than 60 years old (3-year OS, 92% versus 60%, $P = 0.04$). However, after the introduction of HD MTX-based chemotherapy, several retrospective studies have reported that reduced-dose WBRT does not compromise disease control, and radiation dose was successfully reduced to 23.4 Gy in a Phase II study conducted by the MSKCC (10,11). They integrated rituximab into induction chemotherapy and reduced the WBRT dose from 45 Gy to 23.4 Gy for patients who achieved CR to induction chemotherapy; however, the WBRT dose for patients who achieved less than CR was still 45 Gy. Two-year PFS for patients who received reduced-dose WBRT was 77% and median PFS was 7.7 years.

There are several differences between our study and the study conducted by the MSKCC. First, we administered conventional HD MTX-based induction chemotherapy without rituximab. Second, our WBRT dose was reduced from 45 Gy to 36 Gy, which is higher than that of the MSKCC study. However, we delivered the reduced-dose of WBRT to both complete and partial responders. And we performed subgroup analysis to investigate the effect of dose reduction in complete and partial responders separately. In brief, a total dose of 36 Gy did not compromise the treatment outcomes compared with 45 Gy in both complete and partial responders (Fig. 3c–f).

Our study has several limitations. First, while treatment-related toxicity is an important factor that determines radiation dose, we did not perform the objective assessment of neurocognitive function before and after the treatment. Second, the subgroup that received 36 Gy had a shorter follow-up period and smaller number of patients than the subgroup that received 45 Gy, since radiation dose was amended during study period. Third, the number of each group was too small to lead to a concrete conclusion. Also, there might be a selection bias since we included patient less than 60 years old only which is known as favorable prognostic factor in PCNSL (20–22). However, there was no significant difference between our results and previous papers that reported the treatment outcomes of patients less than 60 years old (3-year OS 63–85% and 3-year PFS 53–58%) (3,8,13,15).

On the other hand, there is a strong point in our study that 62 patients were not a few numbers and they all were treated with same chemotherapy that makes us focus on the effect of WBRT. Unlike many studies had sought to reduce the WBRT dose for patients who achieved CR to induction chemotherapy and prescribed a higher dose to patients who achieved PR, our results showed that it is possible to reduce the WBRT dose for patients who achieved PR to HD MTX-based chemotherapy.

As is well known, WBRT prolongs IC-PFS in patients who achieved PR to induction chemotherapy. However, if we weigh this benefit against the risk of delayed neurologic sequelae, it may not be the best choice that delivering WBRT to 45 Gy for these patients as the two large prospective studies did (6,10). In our study, radiation dose reduction from 45 Gy to 36 Gy did not compromise treatment outcomes. Also, although it was not objective assessment, changes in memory ability were reported only in patients who received 45 Gy, not in those who received 36 Gy. These results may provide a possibility for dose-reduction in patients who achieved PR, which may in turn reduce delayed neurologic sequelae. To confirm our results, a well-designed prospective study that involves systematic assessment of neurocognitive function is needed.

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None.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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