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# Dose-Escalation Study of Thoracic Radiotherapy in Combination With Pemetrexed Plus Cisplatin in Japanese Patients With Locally Advanced Nonsquamous Non–Small Cell Lung Cancer

## *A Post Hoc Analysis of Survival and Recurrent Sites*

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**Objectives:** We performed a post hoc analysis of progression-free survival (PFS), overall survival (OS), and recurrent sites in patients with locally advanced nonsquamous non–small cell lung cancer who were enrolled in a phase I trial of combination chemotherapy consisting of pemetrexed plus cisplatin with concurrent thoracic radiotherapy.

**Methods:** Patients received pemetrexed (500 mg/m$^2$) plus cisplatin (75 mg/m$^2$) on day 1 every 3 weeks for 3 cycles plus concurrent thoracic radiotherapy consisting of 60 Gy (n = 6) or 66 Gy (n = 12); 4 to 6 weeks thereafter, patients received consolidation treatment with pemetrexed (500 mg/m$^2$) every 3 weeks for up to 3 cycles. We reviewed the medial records to collect data on progression, recurrent sites, late toxicity, and survival.

**Results:** No late radiation morbidity was observed. Thirteen patients (72%) exhibited disease progression: 8 patients had distant metastases, 8 patients had local recurrence (within the radiation field [n = 6], outside the radiation field [n = 2], and both [n = 1]), and 3 patients had local recurrence plus distant metastases. The median PFS was 10.5 months (95% confidence interval [CI], 8.8-12.3), and the 3-year PFS rate was 28% (95% CI, 7.0-48.6). Ten of the 18 patients died of lung cancer. The median follow-up time for the censored cases was 42.8 months (range, 38.1 to 52.9 mo). The median OS was 27.3 months (95% CI, 13.1-41.6), and the 3-year OS rate was 50% (95% CI, 26.9-73.1).

**Conclusions:** The median PFS and OS in our study were comparable to those of historical chemoradiotherapy controls.

**Key Words:** cisplatin, pemetrexed, thoracic radiotherapy, overall survival, progression-free survival

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Platinum-based chemotherapy and concomitant thoracic radiotherapy (TRT) are the standard of care for patients with unresectable locally advanced non–small cell lung cancer (NSCLC). Third-generation anticancer agents, such as paclitaxel, docetaxel, gemcitabine (GEM), and irinotecan cause intolerable esophagitis and/or pneumonitis, if they are concurrently administered with TRT. Therefore, these agents are usually administered weekly at a low dose when used for chemoradiotherapy.[1–4]

Pemetrexed (PEM) is an inhibitor of thymidylate synthase and other folate-dependent enzymes, including dihydrofolate reductase and glycinamide ribonucleotide formyl transferase. PEM plus cisplatin (CDDP) has enabled a statistically superior overall survival (OS) period in chemonaive patients with advanced nonsquamous NSCLC compared with GEM plus CDDP.[5,6] Nowadays, combination chemotherapy consisting of CDDP plus PEM is a standard regimen for patients with advanced nonsquamous NSCLC. In addition, PEM reportedly has a radiosensitizing potential when evaluated in vitro.[7] The tolerability of full-dose chemotherapy consisting of CDDP plus PEM combined with TRT has been confirmed in several phase I/II studies conducted in western countries.[8–13] We conducted a dose-escalation study of TRT used in combination with PEM plus CDDP followed by PEM consolidation therapy in Japanese patients with locally advanced nonsquamous NSCLC. The dose-escalation study was funded by Eli Lilly Japan (K.K.). Concurrent TRT at a total dose of 66 Gy combined with PEM plus CDDP was found to be feasible in the Japanese population.[14] The objectives of the dose-escalation study included the determination of the recommended TRT dose, safety, and response. Here, we report the results of a post hoc analysis of progression-free survival (PFS), OS, recurrent sites, late toxicity, and poststudy treatment in those patients who were enrolled in the above-mentioned dose-escalation study.

## PATIENTS AND METHODS

### Patient Population and Study Treatment

The design and results of the dose-escalation study have been published previously.[14] Briefly, eligible patients had

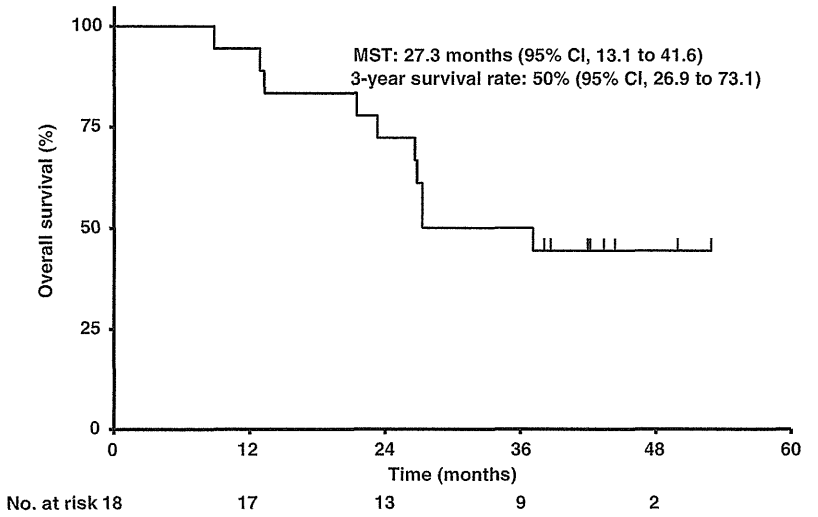


**FIGURE 1.** Overall survival curve for 18 eligible patients. CI indicates confidence interval; MST, median survival time.

nonsquamous NSCLC with unresectable stage IIIA or IIIB disease. The clinical stage was diagnosed according to the 6th edition of the TNM Classification of Malignant Tumors. Patients received PEM (500 mg/m$^2$) plus CDDP (75 mg/m$^2$) on day 1 every 3 weeks for 3 cycles. The first 6 patients were given TRT at a total dose of 60 Gy concurrently, and the next 12 patients were given TRT at a total dose of 66 Gy concurrently. TRT was initiated by anteroposterior opposed fields up to 40 Gy/20 fractions, including elective nodal irradiation to the mediastinum. A booster dose was added to the primary lesion and metastatic lymph nodes by oblique fields at a total dose of 60 or 66 Gy. Treatment planning was based on computed tomography (CT) simulation. The primary lesion and metastatic lymph nodes were defined as gross tumor volume. Subclinical lymph node regions were included as clinical target volume for elective nodal irradiation. The planning target volume was defined as clinical target volume plus appropriate margins (horizontal 0.1 to 1 cm; vertical 1 to 2 cm) in expectation of some setup errors and respiratory motion. Four to 6 weeks after the completion of the chemoradiotherapy, PEM (500 mg/m$^2$) was administered on day 1 every 3 weeks for up to 3 cycles as a consolidation chemotherapy. Safety was assessed until 30 days after the completion of the protocol treatment in the dose-escalation study. After the 30-day follow-up period, physical examinations, toxicity assessments, chest x-rays, and blood tests were conducted every 1 to 3 months, as necessary, as part of our standard clinical practice. For instance, if tumor progression was clinically suspected based on the patient's symptoms, physical examination, chest x-ray, and/or elevation of serum tumor markers, a CT scan of the chest and abdomen, magnetic resonance imaging or CT scan of the brain, bone scan, and/or positron emission tomography were performed.

## Study Design and Statistical Analysis

The endpoint of the dose-escalation study did not include the PFS or OS. Response and safety were assessed until 30 days after the completion of the protocol treatment. We retrospectively reviewed the medical records of patients who were enrolled in the dose-escalation study to collect data on progression, recurrent sites, late toxicity, poststudy treatment, and survival.

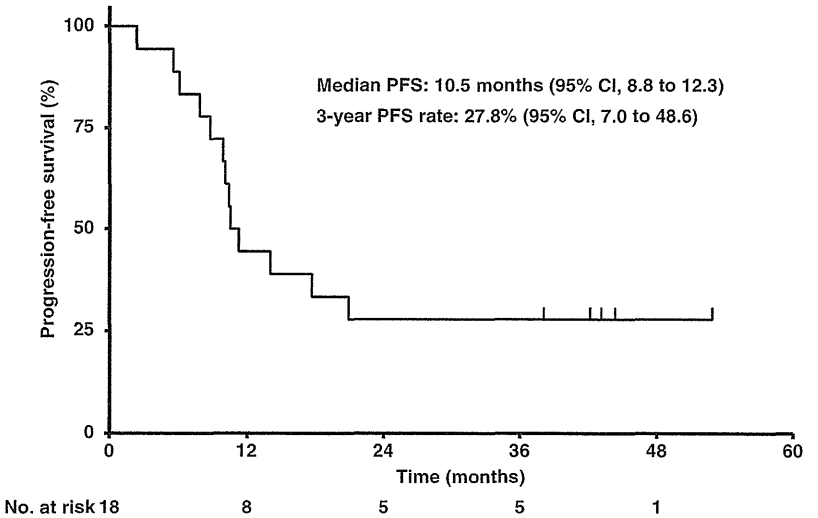


**FIGURE 2.** Progression-free survival (PFS) curve for 18 eligible patients. CI indicates confidence interval.

The OS was defined as the interval between the start of chemoradiotherapy and death or the final follow-up visit. The PFS was defined as the interval between the start of chemoradiotherapy and the first documented evidence of disease progression or death, whichever occurred first. The time-to-event distributions were estimated using the Kaplan-Meier method. The present study was approved by an institutional review board.

## RESULTS

### Recurrent Sites and Late Toxicity

Between November 2008 and December 2010, a total of 20 patients were enrolled in the dose-escalation study, and 18 patients received the protocol treatment. Thirteen patients (72%) had disease progression and recurrence: 8 patients had distant metastases, 8 patients had local recurrence (within the radiation field [n=6], outside the radiation field [n=2], and both [n=1]), and 3 patients had local recurrence plus distant metastases. Distant metastases included the brain (n=3), adrenal gland (n=2), bone (n=2), liver (n=2), and lung (n=2). The sites of distant metastasis overlapped in some cases.

As we reported previously, 8 patients developed grade 2 or 3 pneumonitis (1 patient developed grade 3 and 7 patients developed grade 2). Five patients required steroid therapy, leading to an improvement in the radiation pneumonitis.[14] None of the patients experienced a recurrence of pneumonitis after the follow-up period of the dose-escalation study. No late radiation morbidity was observed.

### PFS and OS

The median PFS was 10.5 months (95% confidence interval [CI], 8.8-12.3 mo), and the 2- and 3-year PFS rates were both 27.8% (95% CI, 7.0%-48.6%). Ten of the 18 patients died of lung cancer. The median follow-up time for the censored cases was 42.8 months (range, 38.1 to 52.9 mo). The median OS was 27.3 months (95% CI, 13.1-41.6 mo), and the 3-year OS rate was 50% (95% CI, 26.9%-73.1%) (Figs. 1, 2).

### Poststudy Treatment

Of the 13 patients who progressed after the protocol treatment, 8 patients received cytotoxic chemotherapy, 5 patients received epidermal growth factor receptor tyrosine kinase inhibitor, and 3 patients received both treatments. Two patients received only best supportive care including whole brain irradiation. One patient underwent salvage surgery. This patient was a 54-year-old man who had a 4.6 cm mass invading the mediastinum, in the right upper lobe of the lung. The mediastinal (#4R) and hilar (#10R and 11s) lymph nodes were swollen. A transbronchial biopsy revealed NSCLC, not otherwise specified, and transbronchial aspiration cytology revealed an adenocarcinoma, because many malignant cell clusters with papillary structure were observed. We diagnosed this patient as having an adenocarcinoma of the lung with clinical T4N2M0 and stage IIIB. He entered this clinical trial and received 3 cycles of CDDP plus PEM and concurrent TRT of 66 Gy followed by 2 cycles of consolidation chemotherapy with PEM. A partial response was achieved; however, 1 year and 2 months after the start of the chemoradiotherapy, the right hilar mass had increased in size. No other recurrent lesions were observed. He underwent salvage surgery consisting of a right pneumonectomy. The pathologic diagnosis was moderately to poorly differentiated squamous cell carcinoma of the lung. One year and 5 months after the salvage surgery, he developed a right supraclavicular lymph node metastasis

**TABLE 1.** Efficacy Outcomes From Clinical Trials Evaluating Combination Chemotherapy of Cisplatin Plus Pemetrexed Concurrent With Thoracic Radiotherapy in Patients With Locally Advanced Non–Small Cell Lung Cancer

| References | No. Patients | Concurrent Chemoradiotherapy | Consolidation Chemotherapy | Dose of Thoracic Radiotherapy (Gy) | Patients With Squamous Histology (%) | Median PFS (95% CI) (mo) | 2 y PFS Rate (%) | Median OS (95% CI) (mo) | 2 y OS Rate (95% CI) (%) |
|---|---|---|---|---|---|---|---|---|---|
| Brade et al[10] | 39 | CDDP 20 mg/m$^2$ (days 1-5) + PEM 500 mg/m$^2$, q3w, 2 cycles | CDDP 75 mg/m$^2$ (day 1) + PEM 500 mg/m$^2$ (day 1), q3w, 2 cycles | 60-66 | 26 | 11.8 (9.8-21.9) | NA | 19.7 | NA |
| Choy et al[8] | 52 | CDDP 75 mg/m$^2$ (day 1) + PEM 500 mg/m$^2$ (day 1), q3w, 3 cycles | PEM 500 mg/m$^2$, q3w, 3 cycles | 64-68 | 21 | 13.1 (8.3-NA) | NA | 27.0 (23.2-NA) | 58.4 (42.6-71.3) |
| This study | 18 | CDDP 75 mg/m$^2$ (day 1) + PEM 500 mg/m$^2$ (day 1), q3w, 3 cycles | PEM 500 mg/m$^2$, q3w, 3 cycles | 60-66 | 0 | 10.5 (8.8-12.3) | 27.8 | 27.3 (13.1-41.6) | 72.2 (51.4-93.0) |

CDDP indicates cisplatin; CI, confidence interval; NA, not available; OS, overall survival; PEM, pemetrexed; PFS, progression-free survival.

without any other recurrent lesions. The initial TRT field did not include this region. To date, the patient has received radiotherapy to the right supraclavicular lymph node.

## DISCUSSION

Combination chemotherapy consisting of CDDP plus PEM is one of the standard chemotherapy regimens for advanced nonsquamous NSCLC.[6] Our study and previous clinical trials demonstrated that full-dose chemotherapy consisting of CDDP plus PEM could be administered concurrently with TRT.[8–11] Therefore, combination chemotherapy consisting of CDDP plus PEM and concurrent TRT has been considered promising. However, the median PFS was 10.5 months in our study, which is comparable to historical controls for chemoradiotherapy in patients with advanced NSCLC.[1,2] Other phase II studies of CDDP plus PEM and concurrent TRT revealed a median PFS of 12 to 13 months (Table 1).[8,10] These studies included patients with a squamous cell histology (21% to 26%). In contrast, the 2-year OS rate was 72% in our study, which is numerically better than that in the previous studies. Patient accrual for a global phase III study comparing CDDP plus PEM versus CDDP plus etoposide in combination with TRT for locally advanced nonsquamous NSCLC has been completed. However, an official announcement of the results of the global study has not yet been made.

A subset analysis of 3 large-scale randomized studies demonstrated that nonsquamous patients treated with PEM-based therapy experienced a longer survival period than squamous patients.[5,6,15] Since then, PEM has not been recommended for the treatment of squamous cell carcinoma of the lung. In contrast, an exploratory analysis of OS in a randomized phase II study of PEM, carboplatin, and TRT with or without cetuximab revealed no significant difference in OS between the squamous and nonsquamous patients.[16] The eligibility criteria for our study were restricted to a nonsquamous histology; however, pathologic examination of the salvage surgery specimen revealed a squamous cell carcinoma of the lung in 1 patient. Thus, a completely accurate pathologic diagnosis is difficult based only on cytology or small biopsy samples.

No late radiation morbidity was observed in this study; however, 8 of the 18 patients (44%) experienced grade 2 or 3 radiation pneumonitis. Five patients required steroid therapy. In general, pneumonitis sometimes recurs during the tapering of steroids. Fortunately, the recurrence of pneumonitis was not observed in this study. At least, a phase II study on CDDP, PEM, and TRT is warranted to evaluate the safety of this regimen in Japanese patients, as drug-induced pneumonitis, such as that caused by gefitinib and erlotinib, is more frequently observed in Japanese patients than in non-Japanese patients. A randomized phase II study comparing CDDP plus PEM and CDDP plus S-1 in combination with TRT for locally advanced nonsquamous NSCLC is ongoing in Japan (UMIN000009914).

In conclusion, the PFS and OS in our study were comparable to those in historical controls for chemoradiotherapy in patients with locally advanced NSCLC. No late radiation morbidity was observed.

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Original Article

# Analysis of Radiotherapy in 1054 Patients with Primary Central Nervous System Lymphoma Treated from 1985 to 2009

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## Abstract

*Aims:* Data on primary central nervous system lymphoma that had been collected through surveys for four consecutive periods between 1985 and 2009 were analysed to evaluate outcomes according to treatment.

*Materials and methods:* All had histologically proven disease and had received radiotherapy. No patients had AIDS. Among 1054 patients, 696 died and 358 were alive or lost to follow-up. The median follow-up period for surviving patients was 37 months.

*Results:* For all patients, the median survival time was 24 months; the 5 year survival rate was 25.8%. Patients treated with methotrexate-based chemotherapy and radiation had a higher 5 year survival rate (43%) than those treated with radiation alone (14%) and those treated with non-methotrexate chemotherapy plus radiation (20%), but differences in relapse-free survival were smaller among the three groups. The 5 year survival rate was 25% for patients treated with whole-brain irradiation and 29% for patients treated with partial-brain irradiation ($P = 0.80$). Patients receiving a total dose of 40–49.9 Gy had a higher 5 year survival rate (32%) than those receiving other doses (21–25%, $P = 0.0004$) and patients receiving a whole-brain dose of 30–39.9 Gy had a higher 5 year survival rate (32%) than those receiving ≥40 Gy (13–22%, $P < 0.0005$). Patients receiving methotrexate-based chemotherapy and partial-brain radiotherapy (≥30 Gy) had a 5 year survival rate of 49%.

*Conclusions:* The optimal total and whole-brain doses may be in the range of 40–49.9 and <40 Gy, respectively, especially in combination with chemotherapy. Patients receiving partial-brain irradiation had a prognosis similar to that of those receiving whole-brain irradiation. With methotrexate-based chemotherapy, partial-brain radiotherapy may be worth considering for non-elderly patients with a single tumour.


*Key words:* Brain neoplasm; central nervous system; chemotherapy; lymphoma; neurocognitive function; radiotherapy

## Introduction

Treatment strategies for primary central nervous system lymphoma (PCNSL) are gradually changing. Previously, radiotherapy played the most important role. PCNSL responds relatively quickly to radiotherapy, and the complete disappearance of enhancing tumour masses is frequently observed after radiotherapy. However, local recurrence in the irradiated volume as well as remote central nervous system (CNS) recurrence outside the treatment volume are frequently observed, and so the reported outcome of patients treated by radiation alone was relatively poor [1–3]. In addition, a proportion of PCNSL patients treated with radiotherapy develop neurocognitive dysfunction and/or show a reduced performance status [3–6]. These observations led neuro-oncologists to use systemic chemotherapy after the late 1970s.

The combination of radiation and standard chemotherapy regimens used for systemic lymphoma was attempted, but it did not yield markedly favourable results [7–11]. Subsequently, high-dose methotrexate (MTX)-containing regimens proved to be effective [12–16]. As long-term remission is often achieved with such chemotherapy, a recent trend has been to treat PCNSL with MTX-based chemotherapy first, and reserve radiotherapy for recurrence, especially in elderly patients [17,18]. However, higher

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rates of progression-free survival were noted with the use of radiation in the first-line treatment in a randomised European trial comparing chemotherapy with chemo-radiotherapy [19]. Therefore, the optimal treatment for PCNSL still remains to be determined; the role of radiotherapy should be clarified, especially in non-elderly patients, and optimal forms of radiotherapy, with regard to the treatment volume and radiation dose, should be investigated.

Until very recently, radiotherapy was used in the first-line treatment of PCNSL in Japan, either alone or in combination with chemotherapy, regardless of the patient's age. To evaluate the changes in patient, tumour and treatment characteristics in PCNSL, our group has conducted surveys of Japanese PCNSL patients treated in radiotherapy departments. Data have been collected on patients treated during the four periods of 1985–1994, 1995–1999, 2000–2004 and 2005–2009. Results of respective surveys have been published [20–24]. Through the surveys, data on a total of 1054 patients with histologically proven PCNSL have been accumulated. The purpose of this study was to evaluate the treatment outcome of these patients according to the treatment modality and radiation methods.

## Materials and Methods

This study was approved by the institutional review board of Nagoya City University (approval number 506). Submission of the data was approved by institutional review boards at each institution. Informed consent for the use of data for research purposes was obtained from patients. Methods for the collection of data used for this analysis have been described in detail previously [20–24]. The surveys were carried out by the Japanese Society for Therapeutic Radiology and Oncology Lymphoma Study Group (JLSG), the Chubu Radiation Oncology Group (CROG) and the Japan Radiation Oncology Study Group. Subjects of all surveys were patients with histologically proven PCNSL who received radiotherapy. Patients who were suspected of having secondary CNS lymphoma were excluded. Those who did not complete the planned radiotherapy were included.

Data on 466 patients who started radiotherapy between 1985 and 1994 were collected from 62 institutions. For the period of 1995–1999, 142 patients were accumulated from 25 institutions with the two surveys conducted by the JLSG and CROG. For the period of 2000–2004, 131 patients were accumulated from 17 institutions by JLSG and CROG. Data on 315 patients treated between 2005 and 2009 were collected from 20 institutions. Combining the data, 1054 patients were therefore the subjects of this study. Table 1 summarises the patient and tumour characteristics and treatment details. Among the 1054 patients, 449 (42.6%) and 267 (25.3%) were ≥65 and 70 years old, respectively. Among the patients, 696 died and 358 were alive or lost to follow-up. The median follow-up period for surviving patients was 37 months.

The HIV titre was negative in all patients tested, and no other patients were considered to have AIDS-related PCNSL. The extent of surgical resection had not been ascertained in the survey for 1985–1994, but it was included in the subsequent surveys. Other items were common to all surveys. The performance status before radiotherapy scored with the World Health Organization criteria was used in this analysis. The neurocognitive status of the patients during follow-up periods was asked; all investigators judged neurocognitive function from clinical and neurological symptoms, and a standard battery of neurocognitive tests was not routinely used. Responses to induction chemotherapy and salvage treatment at recurrence were not requested. As expected in such a survey, a number of items were not answered by the investigators.

Although techniques of radiotherapy were not asked, it was confirmed in the group meetings that whole-brain irradiation was delivered using parallel opposing fields,

**Table 1**
Patient and tumour characteristics and treatment details

| | Characteristics | Number (%) |
|---|---|---|
| Gender | Male/female | 630(60)/424(40) |
| Age (years) | Median, range | 62, 5–93 |
| Performance status | 0/1/2/3/4/unknown | 76(8.5)/313(35)/248(28)/215(24)/38(4.3)/164 |
| Lactate dehydrogenase | Normal/high/unknown | 530(66)/276(34)/248 |
| Phenotype | B/T/unknown | 735 (95)/36(4.7)/283 |
| Tumour number | 1/≥2/unknown | 580(55)/466(45)/8 |
| Tumour size (cm) at diagnosis | Mean ± SD | 3.7 ± 1.4 |
| Surgery | Biopsy/resection/unknown | 395(67)/193(33)/466 |
| Brain irradiation field | Whole brain/partial brain | 969(92)/85(8.1) |
| Spinal irradiation | +/−/unknown | 54(5.3)/967(95)/33 |
| Total dose (Gy) | Mean ± SD | 47.8 ± 10.2 |
| Whole-brain dose (Gy) | Mean ± SD | 34.5 ± 12.1 |
| Systemic chemotherapy | +/−/unknown | 643(64)/365(36)/46 |
| Methotrexate-based regimen | +/− | 351(55)/292(45) |
| Intrathecal chemotherapy | +/−/unknown | 98(9.9)/896(90)/60 |

Figures in parentheses indicate percentage of patients, excluding those with unknown data.

and partial-brain irradiation and focal boost after whole-brain irradiation were given using two to four portals from various angles or rotational fields depending on the tumour location. Partial-brain irradiation was defined as non-whole-brain irradiation; the radiation field usually included 2–4 cm margins from a tumour mass [25]. Various chemotherapy regimens were used, but, for the convenience of analysis, they were categorised as high-dose ($\geq$1 g/m$^2$) MTX-containing or other regimens. About two-thirds of non-MTX-containing regimens included vincristine, cyclophosphamide, doxorubicin and prednisolone [5]. Among 643 patients receiving systemic chemotherapy, 351 (54.6%) were treated with high-dose MTX-containing regimens and 292 (45.4%) received non-MTX-containing regimens. In the 351 patients receiving MTX, the MTX dose was unknown in 62. In the remaining 289 patients, the starting dose of MTX was $\geq$4 g/m$^2$ in 29 (10.0%), 3.5 g/m$^2$ in 149 (51.6%), 3 g/m$^2$ in 59 (20.4%) and <3 g/m$^2$ in 52 (18.0%).

Differences in the incidence of neurocognitive decline between paired groups were examined using the chi-squared test. Overall and relapse-free survival rates were calculated from the date of starting radiotherapy using the Kaplan–Meier method, and differences in pairs of survival curves were examined with the Log-rank test. In calculating relapse-free survival, the relapse included both intra- and extra-CNS recurrences; patients who died without tumour recurrence were censored at the time of their death. Multivariate analysis of potential prognostic factors was carried out using the Cox proportional hazards model. In doing multivariate analysis, patients were divided into two groups and all the parameters were entered as dichotomous variables. All statistical analyses were carried out using StatView Version 5 (SAS institute Inc., Cary, NC, USA) and HALWIN (Gendaisuugakusha, Kyoto, Japan).

## Results

### *Overall and Relapse-free Survival*

In all 1054 patients, the median survival time (MST) was 24 months and the 5 year survival rate was 25.8%. The absence or presence of relapse was reported in 987 patients; the median time to relapse was 14 months and the 5 year relapse-free survival rate was 22.8%. Survival rates for the respective periods have been reported previously [23,24]; briefly, the 5 year survival rate was 15.3% for the period 1985–1994, 29.5% for 1995–1999, 30.4% for 2000–2004 and 36.5% for 2005–2009. As the patients treated after 1995 and those treated with high-dose MTX-containing chemotherapy seemed to show a more favourable prognosis, these two groups of patients were separately examined in a number of the following analyses, but, as a result, general trends did not change significantly.

### *Outcome According to Treatment Modality*

Patients were classified into three groups according to treatment modality: (1) radiotherapy alone; (2) non-MTX chemotherapy plus radiation; (3) MTX-based chemotherapy plus radiation. Figure 1A shows overall survival curves for the three groups. The MST was 14, 23 and 40.5 months for groups 1, 2 and 3, respectively, and the 5 year survival rate was 13.8, 20.4 and 42.7%, respectively ($P < 0.0001$). Patients treated with MTX-based chemotherapy plus radiation had markedly high survival rates. As patient selection biases existed among the three groups, patients with an age < 70 years and a performance status 0–2 and receiving radiation doses $\geq$30 Gy were analysed (defined as the favourable-prognosis group). However,

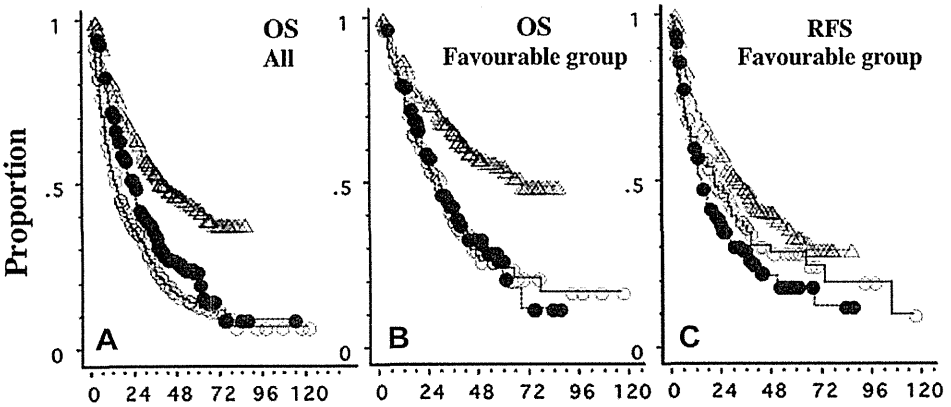


**Fig 1.** Outcome according to treatment modality. ○, radiation alone; ●, non-methotrexate chemotherapy plus radiation; △, methotrexate-based chemotherapy plus radiation. (A) Overall survival: ○, $n = 365$; ●, $n = 292$; △, $n = 351$; $P < 0.0001$. (B) Overall survival for favourable-prognosis patients (age < 70 years, performance status 0–2 and a total radiation dose $\geq$ 30 Gy); ○, $n = 121$; ●, $n = 144$; △, $n = 209$; $P < 0.0001$. (C) Relapse-free survival for favourable-prognosis patients; ○, $n = 113$; ●, $n = 136$; △, $n = 206$; $P = 0.0004$.

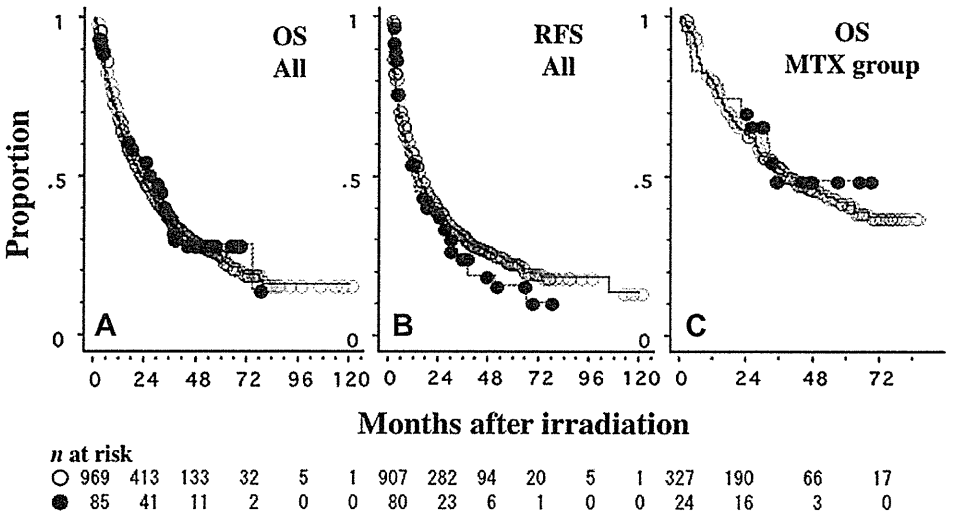


**Fig 2.** Outcome according to radiation treatment volume. ○, whole-brain irradiation; ●, partial-brain irradiation. (A) Overall survival for all patients (○, $n = 969$; ●, $n = 85$; $P = 0.80$); (B) relapse-free survival for all patients (○, $n = 907$; ●, $n = 80$; $P = 0.35$); (C) overall survival for patients receiving methotrexate-based chemotherapy plus radiation (○, $n = 327$; ●, $n = 24$; $P = 0.77$).

results were similar, as shown in Figure 1B. Relapse-free survival curves for the three groups in the favourable-prognosis group are shown in Figure 1C. Differences among the three groups were smaller compared with overall survival curves.

*Outcome According to Radiation Treatment Volume*

As an initial radiation field, 969 patients (91.9%) received whole-brain irradiation and 85 patients received partial-brain irradiation; 46% of the patients with whole-brain and 25% of those with partial-brain irradiation had multiple tumours. Figure 2 shows overall and relapse-free survival curves according to the treatment volume. The MST and 5 year survival rates were 23 months and 24.8%, respectively, for the patients treated with whole-brain radiotherapy and 25.5 months and 29%, respectively, for those treated with partial-brain radiotherapy ($P = 0.80$). No difference was found between the two groups, even when an analysis was carried out of the 588 patients treated between 1995 and 2009 ($P = 0.63$; data not shown). Relapse-free survival also did not differ between the two groups (Figure 2B). The observation was the same in patients treated with MTX-based chemotherapy plus radiation (Figure 2C), and patients treated with MTX-based chemotherapy plus partial-brain radiation had a 5 year survival rate of 49%.

When only patients with a single tumour were analysed, the overall survival did not differ between the whole-brain irradiation-treated and partial-brain irradiation-treated patients (5 year survival rate: 28.6 versus 29%, respectively; $P = 0.54$). However, relapse-free survival rates were higher in the former than in the latter (5 year relapse-free survival: 31.0 versus 14%, respectively; $P = 0.022$). When only patients with a single tumour treated with MTX-based chemotherapy were analysed, overall and relapse-free survival did not differ between the whole-brain irradiation-treated and partial-brain irradiation-treated patients (5 year survival rate: 52.6 versus 47%, respectively, $P = 0.53$; 5 year relapse-free survival: 45.0 versus 33%, respectively, $P = 0.33$).

*Outcome According to Total Radiation Dose*

Patients were divided into four groups according to the total radiation dose: (1) 30–39.9 Gy; (2) 40–49.9 Gy; (3) 50–53.9 Gy; (4) ≥54 Gy. Patients receiving < 30Gy were not included, as planned radiotherapy did not seem to be completed in most of these patients (most of them died soon thereafter, and they had a MST of only 1 month and a median time to progression of 2 months). The MST and 5 year survival rate were significantly more favourable in the group receiving 40–49.9 Gy than in the other groups (Figure 3A; 5 year survival rate 24, 31.6, 24.7 and 20.6% for groups 1–4, respectively; all $P < 0.05$ against group 2 receiving 40–49.9 Gy). Relapse-free survival data were similar to overall survival data (Figure 3B). Even when the analysis was limited to patients receiving high-dose MTX-based chemotherapy and radiation, the survival rate was similarly the highest in the group receiving 40–49.9 Gy (Figure 3C; 5 year survival rate 41, 51.1, 36.8 and 37% for groups 1–4, respectively).

*Outcome According to Whole-brain Dose*

Patients were divided into four groups according to the whole-brain dose: (1) 0–29.9 Gy; (2) 30–39.9 Gy; (3) 40–49.9 Gy; (4) ≥50 Gy. Patients receiving a total dose of <30 Gy were excluded, because they otherwise belong to group 1 and had an extremely short MST (as stated above). The MST and 5 year survival rate were significantly more favourable in the group receiving 30–39.9 Gy than in the other groups (Figure 4A; 5 year survival rate 28.0, 32.0, 21.7 and 9.4% for groups 1–4, respectively; all $P < 0.05$ against

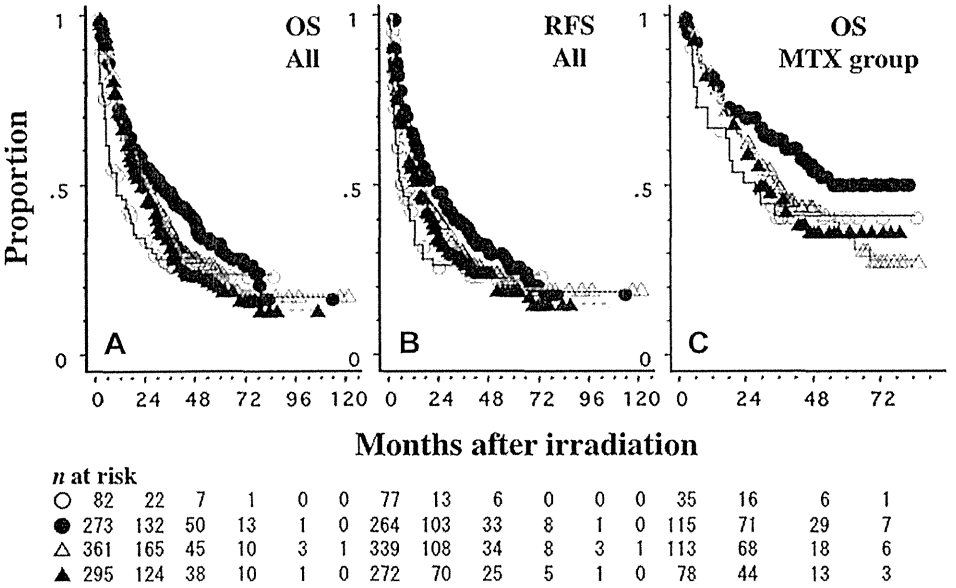


**Fig 3.** Outcome according to total radiation dose. ○, 30–39.9 Gy; ●, 40–49.9 Gy; △, 50–53.9 Gy; ▲, ≥54 Gy. (A) Overall survival for all patients (○, $n = 82$; ●, $n = 273$; △, $n = 361$; ▲, $n = 295$; $P = 0.0004$); (B) relapse-free survival for all patients (○, $n = 77$; ●, $n = 264$; △, $n = 339$; ▲, $n = 272$; $P = 0.0046$); (C) overall survival for patients receiving methotrexate-based chemotherapy plus radiation (○, $n = 35$; ●, $n = 115$; △, $n = 113$; ▲, $n = 78$; $P = 0.093$).

group 2 receiving 30–39.9 Gy). Relapse-free survival curves were similar (Figure 4B). However, when the analysis was limited to patients receiving MTX-based chemotherapy and radiotherapy, the survival rate was similarly higher in the groups receiving 0–29.9 Gy and those receiving 30–39.9 Gy than in the other groups (5 year survival rate 53, 45.5, 37.9 and 0% for groups 1–4, respectively).

*Prognostic Factor Analysis*

The 5 year survival rate according to various patient or tumour characteristics and treatment factors is summarised in Table 2. For patients ≥65 years old, the 5 year survival rate was 13.7% and the 5 year relapse-free survival rate was 20.3%. For patients ≥70 years old, these rates were 7.7% and 16.8%,

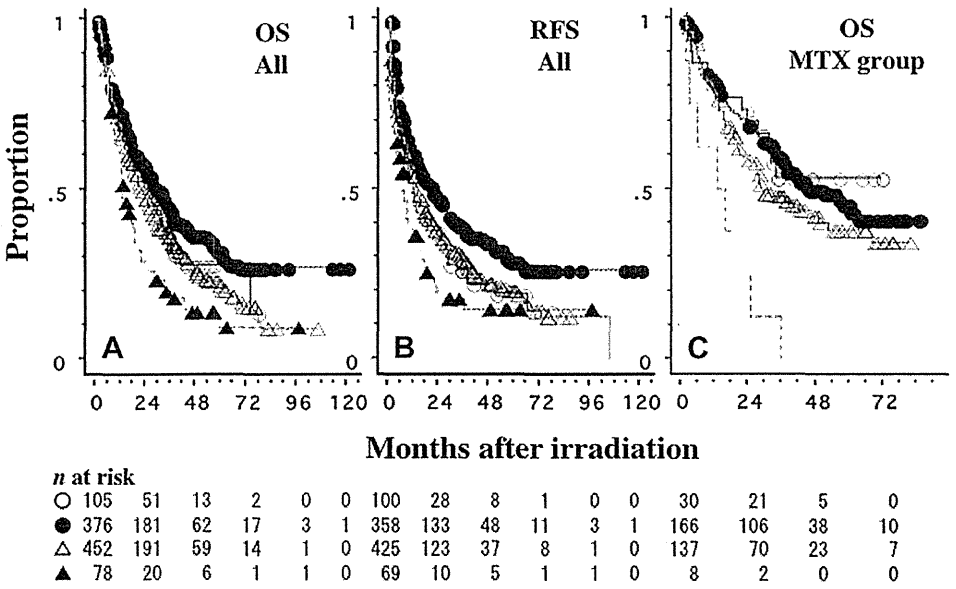


**Fig 4.** Outcome according to whole-brain dose. ○, 0–29.9 Gy; ●, 30–39.9 Gy; △, 40–49.9 Gy; ▲, ≥50 Gy. (A) Overall survival for all patients (○, $n = 105$; ●, $n = 376$; △, $n = 452$; ▲, $n = 78$; $P < 0.0001$); (B) relapse-free survival for all patients (○, $n = 100$; ●, $n = 358$; △, $n = 425$; ▲, $n = 69$; $P = 0.0001$); (C) overall survival for patients receiving methotrexate-based chemotherapy plus radiation (○, $n = 30$; ●, $n = 166$; △, $n = 137$; ▲, $n = 8$; $P = 0.0004$).

**Table 2**
Five year survival rate according to patient/tumour characteristics and treatment factors

| | Characteristics | 5 year survival (%) | *P* |
|---|---|---|---|
| Gender | Male/female | 26.6/22.8 | 0.30 |
| Age (years) | <60/60–69/≥70 | 37.6/19.3/7.7 | <0.0001 |
| Performance status | 0/1/2/3/4 | 47/35.9/24.2/15.4/5.6 | <0.0001 |
| Lactate dehydrogenase | Normal/high | 35.6/17.9 | <0.0001 |
| Phenotype | B/T | 26.8/29 | 0.62 |
| Tumour number | 1/≥2 | 28.8/21.0 | 0.0029 |
| Tumour size at diagnosis (cm) | <4/≥4 | 27.4/25.8 | 0.21 |
| Surgery | Biopsy/resection | 35.9/29 | 0.24 |
| Brain irradiation field | Whole brain/partial brain | 24.8/29 | 0.80 |
| Spinal irradiation | +/− | 23/24.0 | 0.97 |
| Total dose (Gy) | 30–49.9/≥50 | 29.6/22.9 | 0.22 |
| Whole-brain dose (Gy) | 0–34.9/≥35 | 32.9*/21.0* | 0.0023 |
| Systemic chemotherapy | +/− | 32.5/13.8 | <0.0001 |
| Methotrexate-based regimen | +/− | 42.7/20.4 | <0.0001 |
| Intrathecal chemotherapy | +/− | 43/24.2 | 0.025 |

* Patients receiving a total dose of <30 Gy were excluded.

respectively. Multivariate analysis was carried out for the factors listed in Table 2, excluding the three factors with $P > 0.5$. For this analysis, patients receiving <30 Gy were excluded, because of the reason stated above. The influence of chemotherapy was analysed for a MTX-containing one versus other or no chemotherapy. Figure 5 shows hazard ratios for the 11 factors. Among them, younger age, better performance status, single tumour, normal lactate dehydrogenase level and use of MTX-based chemotherapy were associated with better overall survival.

*Neurocognitive Function*

The presence of a decline in the neurocognitive function during the course of follow-up was asked, irrespective of its reason. Answers were obtained for 379 cases and 109 (28.8%) were reported to have developed neurocognitive decline. The percentage was 26% (19/74) for patients receiving radiotherapy alone, 27.2% (70/257) for those receiving MTX-based chemotherapy plus radiation and 42% (20/48) for those receiving non-MTX chemotherapy and radiation. The proportion tended to be higher in the last group than in the former two groups ($P = 0.10$). The proportion of patients developing neurocognitive decline was 29.5% (103/349) for those receiving whole-brain irradiation and 20% (6/30) for those treated with partial-brain irradiation ($P = 0.27$). The proportion was 23.9% (39/163) for those receiving a total dose of 30–49.9 Gy and 33.0% (69/209) for those receiving ≥50 Gy ($P = 0.055$).

## Discussion

This study analysed patient data collected over 25 years; during the period, marked changes occurred regarding patient characteristics and the treatment policy. Therefore, some biases need to be taken into account when evaluating the treatment outcome according to modalities and methods. Patients treated with high-dose MTX-containing chemotherapy plus radiation had the highest overall survival rates. This group consisted of many patients treated in the newest era. Patient care and second-line treatment have improved over the years, and more recent patients tend to show better overall survival. Even when patients who were expected to have a favourable prognosis were compared, differences among the treatment modalities existed, but they became smaller when relapse-free survival was compared (Figure 1C). Randomised trials of radiation versus radiation plus MTX-based chemotherapy have not been and will not be conducted in the future, so the data in the present study will be helpful to understand the issue. In addition, this study suggested that non-MTX chemotherapy might be of no merit when combined with radiotherapy.

As PCNSL is often multiple and the margin of PCNSL lesions is obscure, whole-brain irradiation is safe in terms of not missing viable tumour cells and it has been commonly used to treat PCNSL. This was especially so in the era before magnetic resonance imaging or computed tomography. However, the toxicity of whole-brain irradiation has been

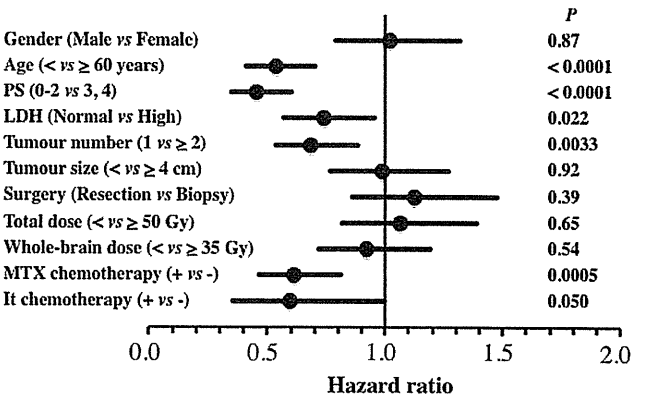


**Fig 5.** Hazard ratios and multivariate *P* values for the potential prognostic factors. Bars represent 95% confidence intervals. LDH, lactate dehydrogenase; It, intrathecal.

stressed [3–5]. We speculate that PCNSL grows invasively against normal brain tissue so that such normal cells, even if they retain their function at the diagnosis of PCNSL, are more vulnerable to radiation than in other tumours. Brain metastases and other tumours might invade normal tissue less aggressively, and normal cells are considered to be more resistant to the adverse effects of radiation, so that neurocognitive decline is less frequent in patients with these tumours [26,27]. Even when the whole brain is not irradiated, the critical region for neurocognitive function retention might not be outside the treatment volume, but we expect that avoiding whole-brain irradiation will contribute to retaining the overall neurological function in PCNSL patients. The results of the present study suggest that partial-brain irradiation may be considered in patients with a single tumour, especially when combined with high-dose MTX-containing chemotherapy, as high-dose MTX is expected to eradicate microscopic diseases. When employing partial-brain irradiation, the addition of wide margins up to 4 cm from a tumour mass is recommended [25].

No randomised studies have been conducted regarding the optimal total and whole-brain irradiation doses, and few non-randomised studies have addressed the issue of the optimal radiation dose. The RTOG 8315 study, with 41 patients, investigated an increase in the total dose to 60 Gy (40 Gy to the whole brain followed by a 20 Gy focal boost), but the results were not considered superior to those obtained with lower doses of radiation (e.g. 50 Gy) [1]. The results agree in part with ours, but lower doses have not been investigated. In our study, 64% of the patients had received chemotherapy, and patients receiving a total dose of 40–49.9 Gy showed the most favourable survival. Patients receiving higher doses might have had more advanced disease, leading to poorer survival, but our data, as well as the RTOG 8315 data, suggest that the effects of radiotherapy might saturate at a certain dose. In the era of MTX-based chemotherapy, we postulate that 40–45 Gy may be a reasonable radiation dose to be used in first-line treatment.

Regarding the whole-brain dose, reduction of the dose from 45 to 30.6 Gy seemed to be associated with an increased recurrence rate in a phase II study involving 57 patients [28]. On the other hand, in a phase II study of 30 patients, only 23.4 Gy was given to patients who achieved a complete response after chemotherapy, and disease control was reported to be satisfactory [29]. As the use of boost irradiation after whole-brain radiotherapy is common in Japan, our study suggested the optimal whole-brain dose to be 30–39.9 Gy. When combined with MTX-containing chemotherapy, patients receiving 0–29.9 Gy had similarly favourable prognoses. This observation supports our policy of using partial-brain irradiation combined with MTX-based chemotherapy.

The management of neurocognitive function decline after treatment is an important issue in the treatment of PCNSL. In a retrospective setting, it is difficult to evaluate neurocognitive status and, indeed, this study did not address the issue in detail, and the reported neurocognitive function decline may not necessarily be a sequela of treatment. Nevertheless, there were trends towards decreased rates of developing dementia in patients treated with partial-brain irradiation and those treated with lower total or whole-brain irradiation doses. Patients treated with MTX-based chemotherapy and radiation did not show higher rates than those with other treatments. This might be related to the use of relatively low doses of MTX; as this study included many patients treated before 2000, nearly 40% of the patients received doses <3.5 g/m$^2$. All these observations may also support the abovementioned treatment strategy.

## Conclusions

This large retrospective analysis suggested future directions regarding radiotherapy in PCNSL treatment. If radiotherapy is integrated into primary treatment, especially for non-elderly PCNSL patients, partial-brain irradiation with less than 50 Gy doses may be worthy of consideration when the tumour occurs singly. If the long-term outcomes of currently ongoing chemotherapy-alone studies prove to be unsatisfactory, prospective randomised studies on MTX-based chemotherapy with and without partial-brain irradiation with 40 Gy should then be considered.

### Acknowledgements

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ORIGINAL ARTICLE

# Primary CNS lymphoma treated with radiotherapy in Japan: a survey of patients treated in 2005–2009 and a comparison with those treated in 1985–2004

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**Abstract**
*Background* The aim of our study was to analyze changes over time in the characteristics, treatment, and outcome of patients with primary central nervous system lymphoma (PCNSL).
*Methods* Data on 315 patients with histologically proven PCNSL undergoing radiotherapy between 2005 and 2009 were collected from 20 Japanese institutions using a questionnaire. These data were then compared with data on 273 patients treated during the period 1995–2004 and those on 466 patients treated during the period 1985–1994.
*Results* In terms of patient and tumor characteristics, we found a significant increase in mean patient age in the 2005–2009 period compared to the 1985–2004 period (63 vs. 58–59 years, respectively) and in the percentage of patients with better performance status (PS) during the 2005–2009 period compared with the 1995–2004 period (World Health Organization PS 0–2: 73 vs. 65 %, respectively). Regarding treatment, relative to the 1995–2004 period, significant changes in the 2005–2009 period were (1) decreased rate of attempting tumor resection (23 vs. 44 %); (2) increased use of chemotherapy (78 vs. 68 %), and (3) increased use of methotrexate (MTX)-containing regimens (84 vs. 53 %). The 5-year overall survival rates were 15.3, 30.1, and 36.5 % for patients seen during the 1985–1994, 1995–2004, and 2005–2009 periods,

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respectively, but relapse-free survival did not improve between the 1995–2004 and 2005–2009 periods (26.7 vs. 25.7 % at 5 years, respectively). Patients receiving MTX-containing chemotherapy had 5-year survival rates of 19, 50, and 44 % during these three periods, respectively.
*Conclusions* Although patient backgrounds differed among the study periods, recent trends were a high patient age, better PS, avoidance of extensive tumor resection, more frequent use of chemotherapy, and improved survival. The recent improvement in survival may be due to improvements in second-line treatment and supportive care.

**Keywords** Lymphoma · Primary CNS lymphoma · Radiotherapy · Chemotherapy · Soluble interleukin-2 receptor

## Introduction

Primary central nervous system lymphoma (PCNSL) is increasing in incidence and is currently one of the most important primary brain tumors. As a consequence, the clinical features of the disease as well as diagnostic procedures, recognition guidelines, and treatment policies have changed considerably. With the widespread recognition of the disease and improvement in diagnostic modalities, patient status, tumor characteristics, and treatment policy appear to be changing gradually [1–7]. Unfortunately, however, randomized studies on the treatment of PCNSL have been scarce, and uncertainties still remain regarding appropriate management [1–7].

In view of the relative rarity of PCNSL coupled with its increasing incidence and importance, we have been conducting nationwide surveys aimed at analyzing changes in the clinical features of the disease, treatment characteristics, and outcomes of the patients. The first study was conducted by Hayabuchi et al. [8] on patients seen between 1985 and 1994. The following two studies were conducted independently by the Japanese Society for Therapeutic Radiology and Oncology (JASTRO) Lymphoma Study Group (JLSG) and the Chubu Radiation Oncology Group (CROG) [9, 10] and included patients seen between 1995 and 1999. The fourth study was conducted by the JLSG and CROG and included those patients seen between 2000 and 2004 [11]. Data on a total of 739 patients were collected from the four previous studies. Given the time span of >5 years since the 2000–2004 survey, the Japan Radiation Oncology Study Group (JROSG) collected data on patients seen between 2005 and 2009. In the study reported here, we analyzed all of the patients in the previous and most recent surveys. Follow-up information was updated whenever possible for patients reported in the earlier studies.

## Materials and methods

The study design was approved by the institutional review board (IRB) of Nagoya City University (Approval Number 506). Submission of the data was approved by the IRBs at each participating institution. Subjects of all of the surveys were patients with histologically proven PCNSL who had received radiation therapy. Patients who were suspected of having secondary CNS lymphoma were excluded from enrolling in the survey by each institution. Those patients who did not complete the planned radiotherapy were included. The clinical characteristics of the patients, their treatment, and the prognosis, shown in the Results, were obtained using a detailed questionnaire.

For our survey, we collected data on 315 patients from 20 Japanese medical institutions who started radiation therapy between 2005 and 2009. In the previous surveys, data on 466 patients from 62 institutions seen between 1985 and 1994 were collected [8], and for the period of 1995–1999, a total of 142 patients from 25 Japanese medical institutions were surveyed within the framework of the surveys conducted by JLSG and CROG, respectively

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[9, 10]. For the period of 2000–2004, 131 patients from 17 institutions were surveyed by the JLSG and CROG. The results of these previous surveys were published separately [8–11]. Since the number of patients included in the 1995–1999 and 2000–2004 surveys is relatively small compared to the preceding and current surveys, patient data for these two time periods were combined for this analysis ($n = 273$ for the period of 1995–2004). Thus, we compared data on 466, 273, and 315 patients receiving treatment for PCNSL in the periods 1985–1994, 1995–2004, and 2005–2009, respectively.

A total of 1,054 patients with histologically proven PCNSL therefore constituted the study population (subjects). Human immunodeficiency virus titer was negative in all patients who had received the test, and none of the other patients were considered to have acquired immunodeficiency syndrome-related PCNSL. Of the 20 institutions that participated in the most recent survey, eight (40 %) had also participated in the 2000–2004 survey; 76 % of the institutions which participated in the 2000–2004 survey had also participated in the 1995–1999 survey, and 68 % of the institutions participating in the 1995–1999 survey had also been included in the1985–1994 survey.

The extent of surgical resection had not been ascertained in the 1985–1994 survey, but it had been determined in the subsequent surveys. All other items were common to all surveys. Only one new item was added to the most recent survey: the soluble interleukin-2 receptor (sIL-2R) level before treatment. The performance status (PS) was scored using the World Health Organization (WHO) criteria, and the pre-surgery PS was used for this analysis. A number of items for which data were unclear in the previous surveys were included in the newest survey, and updated information was obtained. As is expected in such a survey, a number of items were unanswered by the investigators. Various chemotherapy regimens had been used, but for the convenience of analysis, these were categorized as either a high-dose ($\geq$1 g/m$^2$) methotrexate (MTX)-containing regimen, or others; about two-thirds of non-MTX-containing regimens were vincristine–cyclophosphamide–doxorubicin–prednisolone or similar regimens [12].

Differences in patient, tumor, and treatment characteristics between groups were examined using the Fisher's exact test. Survival rates were calculated from the date of the patient starting radiotherapy using the Kaplan–Meier method, and differences in pairs of survival curves were examined with the log-rank test. All statistical analyses were carried out using StatView ver. 5 (SAS institute, Cary, NC) and HALWIN (Gendaisuugakusha, Kyoto, Japan). The median length of follow-up for living patients was 33, 40.5, and 35 months for the 1985–1994, 1995–2004, and 2005–2009 periods, respectively.

## Results

Table 1 shows patient and tumor characteristics in the three patient groups treated during the three survey periods. Several marked changes were noted. The mean patient age and proportion of patients with PS 0–2 have increased over time. The proportion of patients with multiple tumors was 52 % in the most recent series, while it was 38 and 47 % in the previous series. Other patient and tumor characteristics did not differ significantly between the pairs of groups, except that the proportion of T cell PCNSL was relatively higher in patients surveyed in the 1985–1994 study.

Table 2 shows the changes in treatment that occurred over time. As a surgical procedure, biopsy alone was performed in 77 % of the patients in the most recent series, whereas it had been performed in 56 % of the patients during 1995–2004. Over 90 % of the patients were treated with whole-brain irradiation with or without a focal boost throughout all study periods. The use of spinal irradiation decreased from 4.6 % during the 1995–2004 period to 1.6 % during the 2005–2009 survey. Mean total doses did not differ significantly among the three periods survey. Whole-brain doses were lower in 1995–2004 and 2005–2009 than in 1985–1994. In contrast, there were steady increases in the proportion of patients undergoing systemic chemotherapy over time. In particular, MTX-containing regimens steadily increased (in 84 % of patients undergoing chemotherapy in the most recent period).

Figure 1 shows the overall survival curves for the three groups. Patients treated between 1995 and 2004 and those treated between 2005 and 2009 showed significantly better survival rates than those treated between 1985 and 1994 (both $P < 0.0001$); the median survival time increased from 18 to 26 to 35 months, respectively. The 5-year survival was 15.3, 30.1 and 36.5 % for the 1985–1994, 1995–2004, and 2005–2009 periods, respectively. The $P$ value between 1995–2004 and 2005–2009 was 0.062. Figure 2 shows the relapse-free survival curves for the patients with known data on recurrence in these three periods. Relapse-free survival of the patients was also better in the two more recent periods than in the period of 1985–1994 (both $P < 0.0001$). The median time to recurrence was 9, 20, and 21 months, and the 5-year relapse-free survival was 17.8, 26.7, and 25.7 % for 1985–1994, 1995–2004, and 2005–2009, respectively. There was no difference between the two most recent periods ($P = 0.62$).

Table 3 summarizes the survival data on the three groups according to patient- and tumor-related potential prognostic factors. In all study periods, patients aged <65 years and those with WHO PS of 0–2 had significantly higher survival rates. In one or two of the three series, patients without B symptoms, those with a normal lactate dehydrogenase (LDH) level, those with a single

**Table 1** Patient and tumor characteristics

| Characteristic | Survey period (years) | | | $P^a$ |
|---|---|---|---|---|
| | 1985–1994 ($n$ = 466) | 1995–2004 ($n$ = 273) | 2005–2009 ($n$ = 315) | |
| Gender | | | | |
| Male | 276 (59) | 163 (60) | 191 (61) | 0.90 |
| | | | | 0.82 |
| Age (years) | | | | |
| Mean ± SD | 58 ± 13 | 59 ± 11 | 62 ± 11 | 0.016 |
| Median (range) | 60 (5–86) | 61 (15–93) | 63 (17–85) | 0.024 |
| Performance status (PS) | | | | |
| 0–2 | 229/438 (52) | 174/266 (65) | 226/309 (73) | 0.0006 |
| | | | | 0.012 |
| Lactate dehydrogenase | | | | |
| High | 103/267 (39) | 74/234 (32) | 99/305 (32) | 0.11 |
| | | | | 0.84 |
| B symptoms[b] | | | | |
| Yes | 33/418 (7.9) | 19/249 (7.6) | 30/299 (10) | 0.90 |
| | | | | 0.33 |
| Phenotype | | | | |
| T cell | 20/234 (8.5) | 8/235 (3.4) | 8/302 (2.6) | 0.020 |
| | | | | 0.61 |
| Tumor number | | | | |
| Multiple | 175/460 (38) | 128/271 (47) | 163/315 (52) | 0.015 |
| | | | | 0.28 |
| Tumor size at diagnosis (cm) | | | | |
| Mean ± SD | 3.8 ± 1.4 | 3.8 ± 1.4 | 2.7 ± 1.9 | 1.0 |
| | | | | 0.30 |
| CSF dissemination | | | | |
| Yes | 56/422 (13) | 43/248 (17) | 29/308 (9.4) | 0.15 |
| | | | | 0.83 |

Data are presented as the number of patients with the percentage given in parenthesis, unless indicated otherwise

*CSF* cerebrospinal fluid

[a] First and second $P$ values are for comparison between the 1985–1994 and 1995–2004 surveys, and between the 1995–2004 and 2005–2009 surveys, respectively

[b] B symptoms: fever (>38 °C for 3 consecutive days), weight loss (>10 % in 6 months), and/or drenching night sweats

tumor, and those without CSF dissemination on diagnostic imaging had better prognoses, but the tumor size was not associated with the prognosis. Figure 3 shows survival curves according to the LDH and sIL-2R levels in the most recent series. Patients with an elevated sIL-2R level tended to have a poorer prognosis ($P = 0.054$). Regarding the association between LDH and sIL-2R levels, 51 % of patients with a high LDH level also had a high sIL-2R level, while the remaining 49 % had a normal sIL-2R level.

To analyze the influence of treatment-related factors on the outcome, patients who did not complete radiotherapy (receiving <30 Gy) and those who died soon after completing radiotherapy were excluded from the analysis. Table 4 shows survival data according to the treatment-related factors; no factors were found to be associated with an improved prognosis throughout all three periods. In the groups treated during 1995–2004 and 2005–2009, patients receiving systemic chemotherapy had better survival rates than those treated with radiation alone, and those who received MTX-containing chemotherapy had or tended to have a better prognosis than those who received other regimens. However, these phenomena were not observed in patients treated during the preceding decade. No radiotherapy-related factors were found to be associated with the prognosis, except that five patients receiving spinal irradiation had a poorer prognosis in the 2005–2009 series. Figure 4 shows the survival curves for patients treated with high-dose MTX-containing chemotherapy and radiation during the three survey periods; the patients seen during 1995–2004 and those seen during 2005–2009 had significantly better survival rates than those treated during 1985–1994 ($P = 0.0030$ and 0.0002, respectively), but there was no difference between the two most recent periods ($P = 0.95$).

## Discussion

Given the increasing importance of PCNSL tumor in neuro-oncology, medical organizations in Japan consider it

**Table 2** Treatment characteristics

| Characteristic | Period (year) | | | $P^a$ |
|---|---|---|---|---|
| | 1985–1994 ($n$ = 466) | 1995–2004 ($n$ = 273) | 2005–2009 ($n$ = 315) | |
| Surgery | | | | |
| Biopsy | – | 154/273 (56) | 241/315 (77) | – |
| | | | | 0.000 |
| Radiotherapy course | | | | |
| Not completed | 25/466 (5.4) | 11/273 (4.0) | 5/315 (1.6) | 0.42 |
| | | | | 0.070 |
| Brain radiation field | | | | |
| Partial brain | 37/466 (7.9) | 27/273 (9.9) | 21/315 (6.7) | 0.36 |
| | | | | 0.16 |
| Spinal radiation | | | | |
| Yes | 37/445 (8.3) | 12/261 (4.6) | 5/315 (1.6) | 0.061 |
| | | | | 0.034 |
| Total dose (Gy) | | | | |
| Mean ± SD | 48.4 ± 11.2 | 47.9 ± 10.0 | 46.9 ± 8.6 | 0.61 |
| | | | | 0.35 |
| Whole-brain dose (Gy) | | | | |
| Mean ± SD | 35.6 ± 13.7 | 33.3 ± 13.0 | 33.9 ± 8.1 | 0.02 |
| | | | | 0.57 |
| Iv chemotherapy | | | | |
| Yes | 212/420 (50) | 186/273 (68) | 245/315 (78) | 0.000 |
| | | | | 0.008 |
| MTX-containing regimen | | | | |
| Yes | 47/212 (22) | 98/186 (53) | 206/245 (84) | 0.000 |
| | | | | 0.000 |
| It chemotherapy | | | | |
| Yes | 42/415 (10) | 24/273 (8.8) | 32/306 (11) | 0.56 |
| | | | | 0.50 |

Data are presented as the number of patients with the percentage given in parenthesis, unless indicated otherwise

*Iv* intravenous, *MTX* methotrexate, *It* intrathecal

[a] First and second *P* values are for comparison between the 1985–1994 and 1995–1999 surveys, and between the 1995–2004 and 2005–2009 surveys, respectively

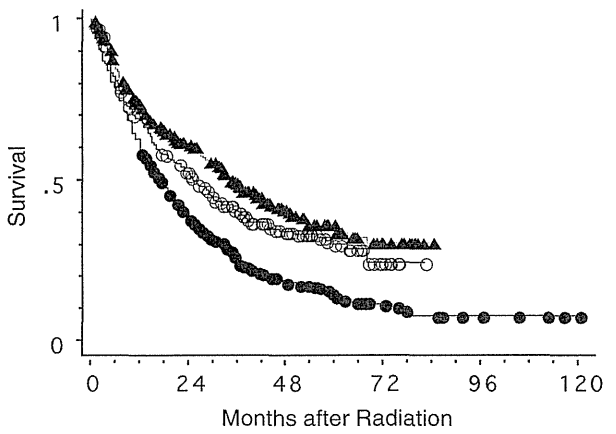


**Fig. 1** Survival curves for patients with primary central nervous system lymphoma (PCNSL) seen in 1985–1994 (*filled circle*, $n$ = 466), 1995–2004 (*open circle*, $n$ = 273), and 2005–2009 (*filled diamond*, $n$ = 315). Patients surveyed in 1995–2004 and 2005–2009 showed significantly better survival rates than those surveyed in 1985–1994 ($P < 0.0001$), but there was no difference between the 1995–2004 and 2005–2009 groups ($P = 0.062$)

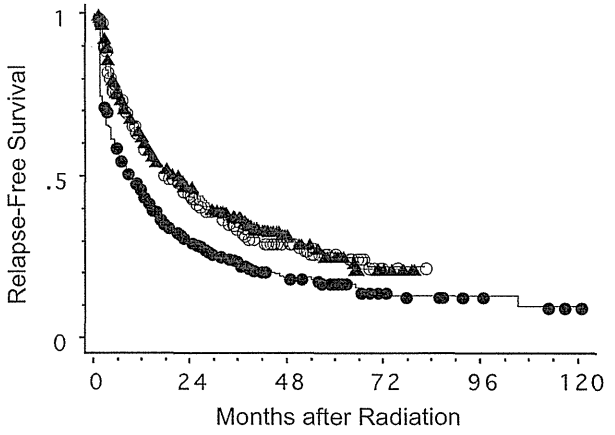


**Fig. 2** Relapse-free survival curves for patients with PCNSL seen in 1985–1994 (*filled circle*, $n$ = 408), 1995–2004 (*open circle*, $n$ = 264), and 2005–2009 (*filled diamond*, $n$ = 315). The patients surveyed in 1995–2004 and 2005–2009 showed significantly better relapse-free survival rates than those surveyed in 1985–1994 ($P < 0.0001$), but there was no difference between the 1995–2004 and 2005–2009 groups ($P = 0.62$)

**Table 3** Survival data according to patient or tumor-related potential prognostic factors

| Prognostic factor | 1985–1994 | | | | 1995–2004 | | | | 2005–2009 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | MST | 5-YSR (%) | *P* | *n* | MST | 5-YSR (%) | *P* | *n* | MST | 5-YSR (%) | *P* |
| Gender | | | | | | | | | | | | |
| Male | 276 | 17 | 17 | 0.92 | 163 | 26 | 30 | 0.76 | 191 | 37 | 38 | 0.31 |
| Female | 190 | 20 | 13 | | 110 | 25 | 30 | | 124 | 31 | 36 | |
| Age (years) | | | | | | | | | | | | |
| <65 | 294 | 20 | 21 | 0.0001 | 158 | 36 | 40 | <0.0001 | 153 | 42 | 47 | 0.0009 |
| ≥65 | 172 | 14 | 5.4 | | 115 | 17 | 15 | | 162 | 29 | 23 | |
| Performance status (PS) | | | | | | | | | | | | |
| 0–2 | 229 | 24 | 20 | <0.0001 | 149 | 37 | 37 | <0.0001 | 226 | 48.5 | 44 | 0.0001 |
| 3, 4 | 209 | 12 | 10 | | 74 | 13 | 14 | | 83 | 11.5 | 14 | |
| B symptoms | | | | | | | | | | | | |
| Yes | 33 | 10 | 0 | 0.030 | 19 | 15 | 15 | 0.028 | 30 | 31 | 30 | 0.26 |
| No | 385 | 18 | 17 | | 232 | 29 | 35 | | 269 | 36 | 39 | |
| Lactate dehydrogenase | | | | | | | | | | | | |
| Normal | 164 | 22 | 26 | 0.0007 | 160 | 35 | 37 | 0.0001 | 206 | 40 | 42 | 0.050 |
| High | 103 | 14 | 5.7 | | 74 | 16 | 21 | | 99 | 29 | 28 | |
| Tumor number | | | | | | | | | | | | |
| Single | 285 | 22 | 18 | 0.0012 | 143 | 29 | 37 | 0.065 | 152 | 40 | 43 | 0.096 |
| Multiple | 175 | 12 | 11 | | 128 | 23 | 23 | | 163 | 31 | 31 | |
| Tumor size (cm)[a] | | | | | | | | | | | | |
| ≤3.5 | 196 | 19 | 15 | 0.60 | 125 | 28 | 28 | 0.93 | 160 | 37 | 42 | 0.45 |
| >3.5 | 197 | 17 | 18 | | 137 | 26 | 34 | | 131 | 33.5 | 29 | |
| CSF dissemination | | | | | | | | | | | | |
| Yes | 56 | 10 | 14 | 0.039 | 43 | 43.5 | 36 | 0.45 | 29 | 15 | 26 | 0.022 |
| No | 366 | 19 | 16 | | 205 | 26 | 32 | | 279 | 37 | 39 | |

*MST* Median survival time in months, *5-YSR* 5-year survival rate

[a] Maximum tumor diameter at diagnosis

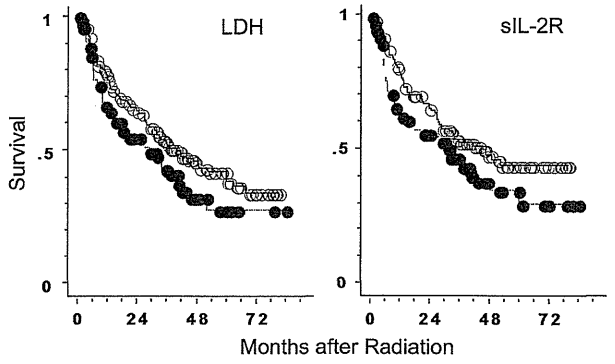


**Fig. 3** Survival curves for patients treated between 2005 and 2009 according to the serum lactate dehydrogenase (*LDH*) and soluble interleukin-2 receptor (*sIL-2R*) levels. *Open circle* Normal level ($n = 206$ for LDH and 135 for sIL-2R), *filled circle* elevated level ($n = 99$ for LDH and 95 for sIL-2R). The *P* value was 0.050 for LDH and 0.054 for sIL-2R

meaningful to survey data on PCNSL every 5 years. To date, these surveys have been conducted by radiation oncology groups (JASTRO-JLSG, CROG, and JROSG) and, therefore, patients undergoing radiotherapy have been the subjects of these surveys. Consequently, data on patients treated with chemotherapy alone are unavailable, which is a limitation of our study. Although treatment with chemotherapy alone seems to be increasing in use in Western countries [13–15], such a treatment strategy was not popular in Japan before 2010—and was in fact exceptional. Therefore, we are confident that these survey data represent the status of PCNSL treatment up to and including 2009 in Japan. More recently, the strategy of primary chemotherapy with deferred radiotherapy appears to be gaining acceptance in Japan also, so these data might serve as a control for the evaluation of different treatment modalities in the future. Another limitation of our study is the long study period; patient backgrounds may considerably differ among the study periods, and comparison among patients in the different eras may be inappropriate for some items.

Various changes have been noted with regard to patient and tumor characteristics. The recent increase in aged patients may be related to the fact that subjects of these

**Table 4** Survival data according to treatment-related factors

| Prognostic factor | 1985–1994 | | | | 1995–2004 | | | | 2005–2009 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | MST | 5-YSR (%) | *P* | *n* | MST | 5-YSR (%) | *P* | *n* | MST | 5-YSR (%) | *P* |
| Surgical resection | | | | | | | | | | | | |
| Extensive | – | – | – | – | 53 | 24.5 | 30 | 0.66 | 40 | 40.5 | 12 | 0.63 |
| Non-extensive | – | – | – | | 209 | 26 | 29 | | 270 | 34 | 38 | |
| Radiation field | | | | | | | | | | | | |
| Whole brain | 405 | 19 | 15 | 0.72 | 236 | 24.5 | 28 | 0.21 | 289 | 36 | 37 | 0.67 |
| Partial brain | 34 | 16 | 17 | | 26 | 35 | 43 | | 21 | 32 | 28 | |
| Spinal radiation | | | | | | | | | | | | |
| Yes | 36 | 24 | 19 | 0.16 | 11 | NR | 55 | 0.30 | 5 | 5 | – | 0.0091 |
| No | 384 | 18 | 15 | | 251 | 26 | 28 | | 302 | 36 | 37 | |
| Total dose (Gy) | | | | | | | | | | | | |
| <50 | 134 | 18 | 17 | 0.97 | 80 | 28.5 | 34 | 0.98 | 141 | 42 | 41 | 0.38 |
| ≥50 | 305 | 8 | 16 | | 182 | 25 | 28 | | 169 | 32.5 | 31 | |
| Whole-brain dose (Gy) | | | | | | | | | | | | |
| <40 | 156 | 18 | 18 | 0.43 | 109 | 32 | 34 | 0.91 | 216 | 35.5 | 40 | 0.43 |
| ≥40 | 283 | 18 | 14 | | 153 | 23 | 25 | | 94 | 32 | 28 | |
| Iv chemotherapy | | | | | | | | | | | | |
| Yes | 202 | 20 | 16 | 0.30 | 180 | 36 | 39 | <0.0001 | 242 | 42 | 41 | <0.0001 |
| No | 192 | 16 | 17 | | 82 | 14 | 10 | | 68 | 12.5 | 13 | |
| Iv chemotherapy regimen | | | | | | | | | | | | |
| MTX | 46 | 20 | 19 | 0.66 | 92 | 55.5 | 50 | 0.061 | 203 | 45 | 44 | 0.0031 |
| Other | 156 | 21 | 15 | | 88 | 29 | 30 | | 39 | 27 | 23 | |
| It chemotherapy | | | | | | | | | | | | |
| Yes | 39 | 16 | 20 | 0.78 | 22 | NR | 53 | 0.10 | 32 | NR | 59 | 0.097 |
| No | 350 | 19 | 16 | | 232 | 24.5 | 26 | | 269 | 34 | 34 | |

*NR* Not reached

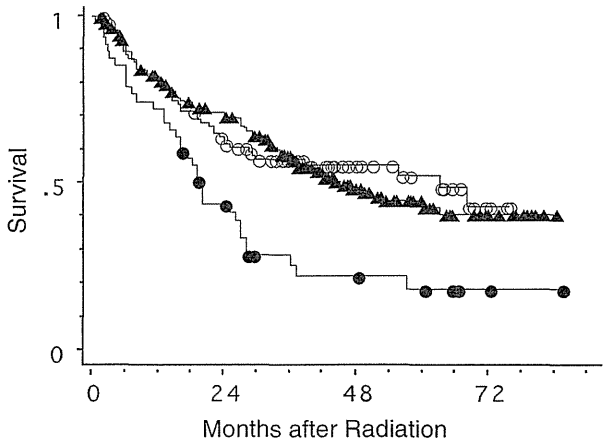


**Fig. 4** Survival curves for patients treated with high-dose methotrexate-containing chemotherapy plus radiation in 1985–1994 (*filled circle*, $n = 46$), 1995–2004 (*open circle*, $n = 92$), and 2005–2009 (*filled diamond*, $n = 203$). The *P* value was 0.0030 for 1985–1994 vs. 1995–2004, 0.0002 for 1985–1994 vs. 2005–2009, and 0.95 for 1995–2004 vs. 2005–2009

surveys are histologically proven PCNSL patients. One possible explanation is the increasing acceptance in recent years of biopsy—even in aged patients—to confirm the diagnosis. The incidence of multiple tumors appears to be increasing, being 52 % in the most recent period compared to 38 and 47 % in the two earlier surveys, respectively; most previous reports suggest an incidence of between 30 and 40 % [16–19]. The improvement in imaging modalities and techniques, including the more frequent use of magnetic resonance imaging, may have contributed to the improved detection of small tumors. The proportion of T-cell lymphoma was high (8.5 %) in the 1985–1994 period, possibly reflecting the difficulty in determining the phenotype of lymphoma in that era.

In terms of treatment, attempts at tumor resection have decreased because it is now clear that surgical resection does not contribute to an improved prognosis [2, 11]. The results of our survey also supports this conclusion. However, Weller et al. [20] recently stated that resection of PCNSL might play a beneficial role provided that surgery is safely conducted. We noted no major changes in