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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

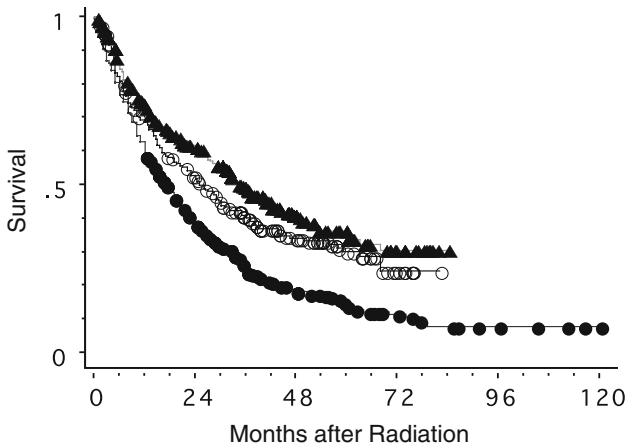

Fig. 1 Survival curves for patients with primary central nervous system lymphoma (PCNSL) seen in 1985–1994 (*filled circle*, $n = 466$), 1995–2004 (*open circle*, $n = 273$), and 2005–2009 (*filled diamond*, $n = 315$). Patients surveyed in 1995–2004 and 2005–2009 showed significantly better survival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

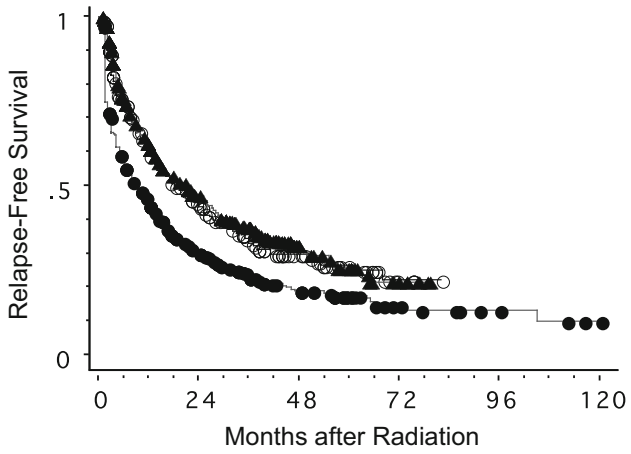

Fig. 2 Relapse-free survival curves for patients with PCNSL seen in 1985–1994 (*filled circle*, $n = 408$), 1995–2004 (*open circle*, $n = 264$), and 2005–2009 (*filled diamond*, $n = 315$). The patients surveyed in 1995–2004 and 2005–2009 showed significantly better relapse-free survival rates than 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

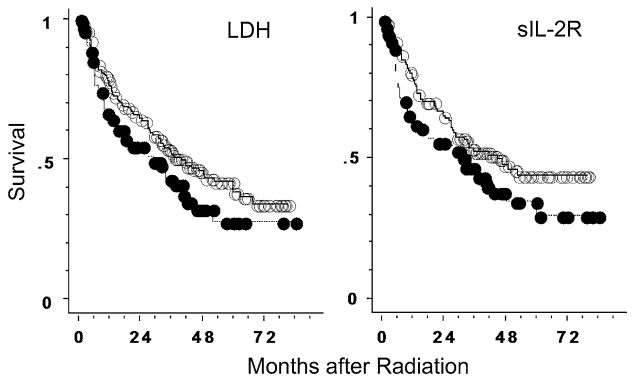

Fig. 3 Survival curves for patients treated between 2005 and 2009 according to the serum lactate dehydrogenase (*LDH*) and soluble interleukin-2 receptor (*sIL-2R*) levels. *Open circle* Normal level ($n = 206$ for LDH and 135 for sIL-2R), *filled circle* elevated level ($n = 99$ for LDH and 95 for sIL-2R).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

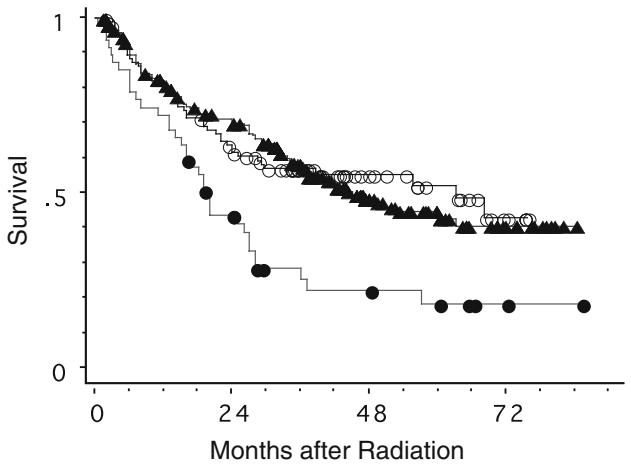

Fig. 4 Survival curves for patients treated with high-dose methotrexate-containing chemotherapy plus radiation in 1985–1994 (*filled circle*, $n = 46$), 1995–2004 (*open circle*, $n = 92$), and 2005–2009 (*filled diamond*, $n = 203$). The *P* value was 0.0030 for 1985–1994 vs. 1995–2004, 0.0002 for 1985–1994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

radiotherapy between the different surveys. Shibamoto et al. [21] suggested the possible use of partial-brain radiation for solitary lesions, but such a policy has yet to spread nationwide. Reducing total as well as whole-brain radiation doses using chemotherapy has not become popular in Japan. The increased use of systemic chemotherapy and, in particular, MTX-based regimens appear to be a worldwide trend, as was also shown in our study.

The prognosis of PCNSL patients has improved recently. Improvement in supportive care may at least in part have contributed to these changes. The 5-year survival was 30.1 and 36.5 % in 1995–2004 and 2005–2009, respectively. However, relapse-free survival rates did not differ between these two periods, suggesting that although second-line treatment at recurrence has prolonged survival, the cure rate has not yet improved. This trend was also true for patients treated with high-dose MTX and radiation; no improvement was seen for the most recent period, suggesting that, in terms of cure, more than half of PCNSLs are resistant to currently available treatment. New treatments are therefore urgently needed.

Many prognostic factors of PCNSL, such as age, PS, and tumor multiplicity, have been reported [8, 11, 17, 19, 22], and the results of the univariate analyses we conducted in our study agree with previously published data. Consequently, we did not present the multivariate analysis data. In the most recent survey, we paid attention to sIL-2R as a prognostic marker and observed that patients with a high sIL-2R level tended to have a poorer prognosis. The prognostic value of sIL-2R has been reported for extracranial lymphoma [23, 24], but, to our knowledge, its role in PCNSL has not been reported. The serum sIL-2R level reflects the total amount of activated T lymphocytes and is correlated with disease activity [25]. It can also be elevated in cancers other than lymphoma, collagen disease, and infection [25, 26]. Since sIL-2R and LDH levels do not necessarily correlate with each other, sIL-2R may be another useful prognostic marker for PCNSL.

Very recently, a few Japanese groups have started to treat PCNSL patients with chemotherapy alone, following the trend set in Western countries. A randomized European study of chemotherapy alone versus chemotherapy + radiation indicated that chemotherapy alone was associated with a decreased progression-free survival, although overall survival was similar, partly due to the use of radiotherapy as a second-line treatment [27]. Since most studies are conducted in phase II settings, the data presented in our study may serve as a basis for studying the treatment and prognosis of PCNSL patients in Japan.

In conclusion, the results of our study reveal that recent trends in PCNSL are increased patient age, better PS, tumor multiplicity, avoidance of extensive tumor resection, more frequent use of high-dose MTX-containing chemotherapy, and improved survival, with no improvement in relapse-free survival. Newer strategies are therefore necessary to further improve the prognosis of PCNSL patients, and the present data may serve as a basis for designing new studies.

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Conflict of interest The authors declare that they have no conflict of interest.

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