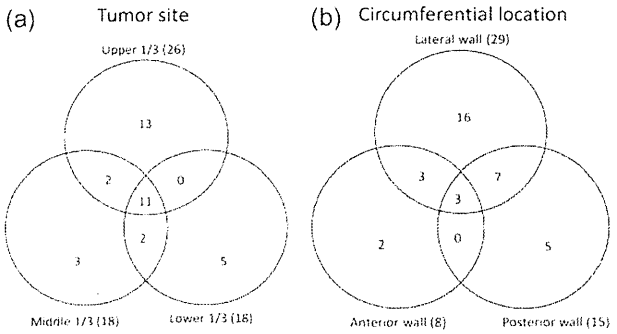

Fig. 1. Distribution of initial location of the tumor in the vagina. (a) Tumor site. (b) Circumferential location.

Table 2. Methods of treatment according to T classification

Treatment methods	T1	T2	T3	T4
EBRT only	0	4	8	2
HDR-ICBT only	2	0	0	0
EBRT + HDR-ICBT	6	4	0	0
EBRT + HDR-ISBT	1	5	4	0
Concurrent chemotherapy	0	2	4	1

EBRT = external beam radiation therapy, HDR-ICBT = high-dose-rate intracavitary brachytherapy, HDR-ISBT = high-dose-rate interstitial brachytherapy.

Table 3. Tumor characteristics and treatment methods according to tumor histology

Treatment methods	Scc (29)	Non-Scc (7)	*P*
Age (mean)	62.5	57.9	0.441
Stage I–II	17	0	0.006*
Stage III–IV	12	7	
T-Stage T1–2	20	2	0.064
T-Stage T3–4	9	5	
N stage N0	22	4	0.37
N stage N1	7	3	
Tumor size (mean)	3.6	5.6	0.148
EBRT only	9	5	0.064
Brachytherapy ± EBRT	20	2	
Concurrent chemotherapy	6	1	0.701

EBRT = external beam radiation therapy, HDR-ICBT = high-dose-rate intracavitary brachytherapy, HDR-ISBT = high-dose-rate interstitial brachytherapy.

rarity of vaginal carcinoma, there have been no randomized clinical trials involving patients with virginal carcinoma and it is difficult to make robust treatment recommendations

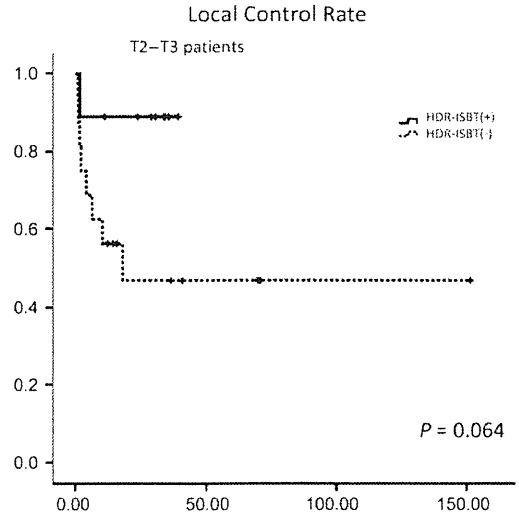

Fig. 2. Local control rate stratified by HDR-ISBT for 25 patients with T2–3 disease.

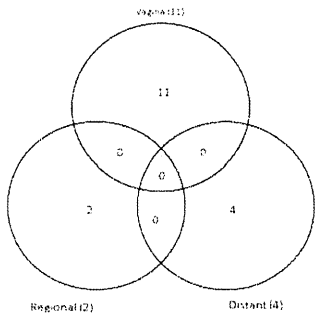

Fig. 3. Patterns of relapse for entire patients. There were 17 relapses in this cohort. There was a local-regional component in 76% of relapses.

Table 4. Vaginal complications according to the administration of brachytherapy

		Brachytherapy		
	Total	yes (18)	no (5)	*P*
Vaginal adhesion	9	5	4	0.056
Vaginal atresia	2	1	1	0.395
Vaginal stricture	2	1	1	0.395
Vaginal ulcer	1	1	0	0.783

for patients with primary vaginal cancer. However, radiation therapy is considered to play a significant role in the management of primary vaginal cancer. In one of the largest series, Frank *et al.* [11] reported the clinical results of 193 patients with primary vaginal squamous cell

carcinomas treated with carefully tailored primary radiation therapy as showing excellent pelvic control. The 5-year pelvic disease control rate was 86% for Stage I, 84% for Stage II, and 71% for combined Stages III and IVA. The study published by Frank *et al.* [11], however, had several limitations, which are as follows: the retrospective nature of the study; the small number of patients; the heterogeneity of the patient's backgrounds; the treatment modalities used, which presumably included selection bias; and the short follow-up period. Therefore, the results have to be interpreted with caution. However, after careful analysis, several findings were derived from the current study. In the current study, the use of HDR-ISBT in patients with T2–T3 primary vaginal cancer was associated with favorable local control. This result was consistent with the report by Leung *et al.* [12], in which the addition of interstitial brachytherapy to EBRT was shown to have a significant favorable effect on clinical outcome. Seeger *et al.* [13] also reported favorable results for ISBT for primary carcinoma of the vagina and vulva, with no local recurrences of vaginal cancer with a median follow-up period of 27 months. In contrast, Nonaka *et al.* [14] reported the results of 26 patients with primary vaginal carcinoma who were treated mainly with HDR-ICBT with or without EBRT. Specifically, the 5-year pelvic control rate (PCR) for Stage I was 86%, whereas the 5-year PCR for Stages II and III was 50% and 57%, respectively [14]. Similarly, Hegemann *et al.* [15] reported the results of EBRT with or without ICBT for primary vaginal cancer and found that the median survival for Stage III/IV was unfavorable compared to Stage I/II (26.8 months and 58.1 months, respectively), suggesting that it is difficult to control thicker tumors with HDR-ICBT. In the current study, there was no difference in the LCR between HDR-ICRT and HDR-ISBT in patients withT1–T3 tumors, most likely because patient selection was performed properly; indeed, HDR-ICBT was applied only for thin tumors. The recently published American Brachytherapy Society guidelines for vaginal cancer recommend using ISBT for vaginal tumors ≥0.5 cm thick at the time of brachytherapy [16]. However, the follow-up period for those patients treated with HDR-ISBT in the current study was rather short, thus it is important to interpret this result with caution. Unfortunately, the treatment results did not differ significantly between treatment periods in this study, presumably because of the small number of patients analyzed and the short follow-up period for patients treated after 2008 (Table 1).

In seven patients with non-squamous cell carcinoma, six had Stage III and one had Stage IV disease, and only one of the patients received a combination of EBRT and HDR-ISBT, which was a relatively favorable factor for advanced disease in this analysis, while the remaining patients underwent only EBRT. As shown in Table 3, the treatment modality did not differ significantly between tumor pathologies, although non-squamous cell carcinomas were more likely to be treated by EBRT alone. The administration of chemotherapy did not differ significantly between tumor pathologies. However, non-squamous cell carcinomas were significantly more advanced at the time of initial presentation compared with squamous cell carcinomas ($P = 0.06$, Table 3). This observation explains, in part, the reason why patients with non-squamous cell carcinomas had such poor outcomes. In the current retrospective study, non-squamous cell carcinoma histology was shown to be a strongly negative factor for local control, which was consistent with the largest retrospective analysis of 301 patients with primary vaginal cancer that included 30 adenocarcinomas [17]. Specifically, the analysis showed that adenocarcinomas have twice the rates of local and metastatic relapse compared with squamous cell carcinomas. Whether or not the routine application of HDR-ISBT in patients with advanced non-squamous cell carcinomas can improve outcomes warrants an additional study.

Because of the small number of patients in the current study, it is difficult to discuss the role of chemotherapy in patients with primary vaginal carcinoma. Distant metastases were frequent in the current study, and the addition of chemotherapy concurrent with radiotherapy might add survival benefit in patients with advanced primary vaginal cancer, as occurs in patients with cervical cancer. In contrast, in vaginal cancer patients the perineum is more likely to be included in the radiation field compared with cervical cancer patients. Therefore, skin toxicities caused by chemoradiation should be prospectively assessed as well as the survival benefits.

Only a small number of patients had late complications in the current study; even HDR-ISBT and the administration of brachytherapy for vaginal cancer did not increase the incidence of complications (Table 4); however, further observation is required.

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CLINICAL STUDY

Risk factors for early death after surgery in patients with brain metastases: reevaluation of the indications for and role of surgery

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Abstract Surgical resection remains an important option for the treatment of brain metastases despite recent advancements in radiotherapy and systemic therapy. When selecting surgical candidates, it is important to exclude terminal cases who will receive neither a survival benefit nor an improvement in their quality of life. We reviewed a total of 264 surgical cases of brain metastases and analyzed the clinical characteristics of early death in order to clarify the indication for and the role of surgery. The median survival time (MST) after surgery in all cases was 12.4 months. Early death was defined as death within 6 months, and 23 % (62 cases) of this series were succumbed to this. A decrease in postoperative Karnofsky performance status (KPS) (<70) ($P = 0.041$), lack of systemic therapy after surgery ($P < 0.0001$), and uncontrolled extracranial malignancies ($P = 0.0022$) were significantly related to early death in multivariate analysis, while preoperative KPS (<70) and recursive partitioning analysis (RPA) class were related to early death only in univariate analysis ($P < 0.05$). When analyzing patients with uncontrolled extracranial malignancies and those with a postoperative KPS score of 70 or greater (who were generally candidates for systemic therapy), the MST was significantly longer in the systemic therapy (+) group compared with the systemic therapy (−) group (12.5 vs. 5.6 months; $P = 0.0026$). Our data indicate that the postoperative RPA class and treatment strategy were associated with early death. Deterioration of patients by surgery should be avoided in the treatment of brain metastases.

Keywords Brain metastases · Surgery · Early death · Leptomeningeal metastases

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Introduction

Brain metastasis is a life-threatening event for cancer patients and indicates that cancer has reached the advanced stages. Surgical resection remains an important option for treatment despite recent advancements in radiotherapy and chemotherapy. The aims of surgical resection are mass reduction and rapid improvement of neurological status.

Knowledge regarding the prognosis of extracranial lesions is important when making decisions about surgery. Several studies have attempted to identify prognostic factors, and various classification systems including recursive partitioning analysis (RPA) classification and graded prognostic assessment (GPA) have been developed [1, 2]. These classification systems have mainly been validated in patient populations treated with radiotherapy; however, some reports have indicated that these systems are useful for predicting survival time after surgery [3–9]. Considering the risks associated with treatment, terminal cases who receive neither a survival benefit nor an improvement in their quality of life (QOL) should be excluded during the selection of surgical candidates.

Herein, we describe a retrospective analysis of the relationship between clinical characteristics and the

outcome of surgery for brain metastases, and we discuss the indications for and the role of surgery.

Materials and methods

Patients

In total, we included 264 cases (156 men and 108 women) who underwent resection as their first surgery for brain metastases at the National Cancer Center Hospital in Japan between January 2000 and December 2011. The mean age of the included patients was 57.5 years (range 19–87), and their clinical characteristics were extracted from their medical records. Overall survival was calculated from the first resection surgery to death. The Karnofsky performance status (KPS) was determined as recorded or was retrospectively estimated from information obtained from the clinical chart by three neurosurgeons (Y.N., Y.M., and S.S.) who performed surgery on the patients. RPA classification of each patient was performed using published criteria [1]. Preoperative status, including performance status and RPA, was evaluated at the time of surgery, while postoperative status was evaluated approximately 1 month after surgery. The performance status and RPA class of patients who died within 1 month after surgery were recorded as 0 and III, respectively. Information regarding the RPA class and status of extracranial malignancy was not available for 1 case.

The cause of death was determined by clinical evaluation. Neurological deaths were defined as cases with neurological deterioration and stable extracranial disease as well as cases with apparent fatal progression of intracranial lesions or leptomeningeal metastases (LMM) regardless of systemic conditions.

The analysis in this study was approved by the local institutional review board (reference no. NCC16-066).

Treatment

Our basic surgical indications for brain metastases were described in a previous report [10]. Surgical candidates included patients with the following characteristics: (1) a post-surgery life expectancy of 6 months or more based on information from medical oncologists, (2) no clinical symptoms or apparent radiological findings indicating LMM, and (3) single metastases measuring $\geqq 3$ cm, or multiple or smaller tumors associated with severe neurological symptoms such as cerebellar metastases. In principle, adjuvant radiotherapy usually began 8 days after surgery. Adjuvant stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) was undergone only for the treatment of the surgical remnant or unresected lesion(s) in patients with multiple metastases. After brain metastases were controlled, patients received further systemic therapy or best supportive care (BSC) according to decisions made by medical oncologists.

A total of 37 patients received RT prior to surgery. In patients who experienced tumor recurrence after radiotherapy, surgical indication was judged via discussion with senior radiologists.

Early death

Early death was defined as death within 6 months after the first surgery for brain metastases, and the clinical profiles between the early death group and the non-early death group were compared. This definition is based on a comparison between the outcome of whole brain radiation therapy (WBRT) and surgery. The median survival time (MST) after WBRT alone is approximately 6 months [11–13]; therefore, if surgery confers a survival benefit, it should extend this time period.

Statistical analysis

Statistical analysis was performed using JMP version 10 (SAS Institute, Cary, NC, USA). The data for survival time were analyzed using the Kaplan–Meier method. A P value below 0.05 was considered statistically significant.

Results

Analysis for all cases

When all cases were analyzed, the median follow-up, MST, 1-year overall survival rate, and 5-year overall survival rate were 11.2, 12.4 months, 52, and 12 %, respectively. The 3 and 6-month overall survival rates were 89 and 75 %, respectively. When patients were divided according to preoperative RPA class, we determined that MST was 21.8 months for class I (59 cases, 22 %), 12.4 months for class II (148 cases, 56 %), and 6.5 months for class III (56 cases, 21 %) (Fig. 1a). When we reevaluated the data using postoperative RPA classification, MST was 20.8 months for class I (66 cases, 25 %), 11.2 months for class II (176 cases, 67 %), and 4.3 months for class III (21 cases, 8 %) (Fig. 1b). Both of pre- and postoperative RPA class were significantly related with survival ($P < 0.0001$, log-rank test). The relationships between preoperative and postoperative RPA class are shown in Supplementary Table 1.

KPS improved in 53 %, was unchanged in 40 %, and worsened in 7 % of all cases after surgery. Surgical complications were observed in 20 cases (7.6 %) including 8 instances of neurological deterioration due to surgical

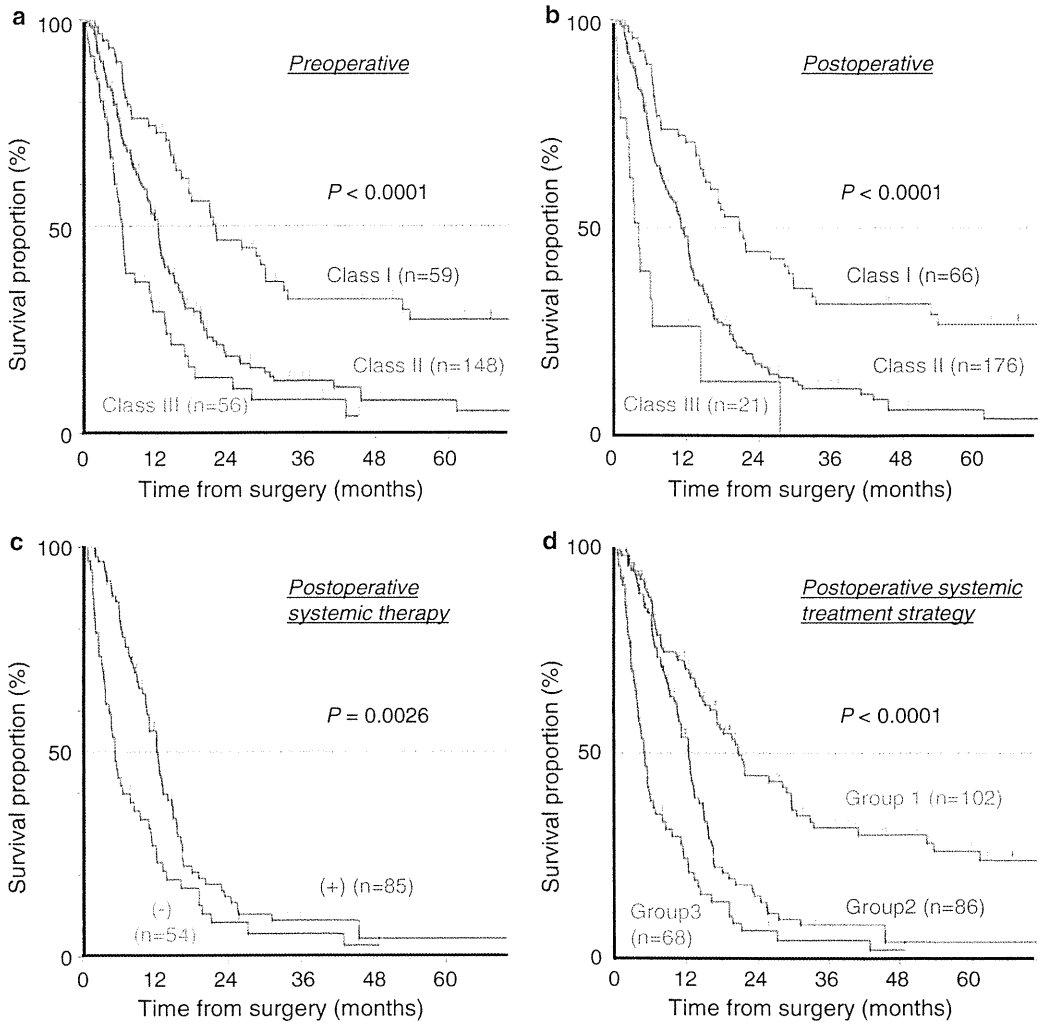

Fig. 1 Survival analysis. **a** Survival curves according to preoperative RPA class. MST was 21.8 months for class I, 12.4 months for class II, and 6.5 months for class III. **b** Survival curves according to postoperative RPA class. MST was 20.8 months for class I, 11.2 months for class II, and 4.3 months for class III. **c** Survival curves according to type of adjuvant therapy in patients with high KPS (70 or more) and uncontrolled extracranial malignancies. MST was 12.5 months for the systemic therapy (+) group and 5.6 months for the systemic therapy (−) group. **d** Survival curves according to postoperative systemic therapy. Group 1 consisted of patients without systemic disease, group 2 consisted of patients undergoing systemic therapy for uncontrolled extracranial disease, and group 3 consisted of patients who had extracranial disease but did not receive systemic therapy. MST was 20.8 months for group 1, 12.4 months for group 2, and 5.1 months for group 3

manipulation, 3 cerebral infarctions, 2 cases requiring evacuation of intraparenchymal hemorrhage, 1 case requiring evacuation of epidural hematoma, 1 case treated conservatively for intraparenchymal hemorrhage, 1 case requiring ventricular drainage for obstructive hydrocephalus, 1 instance of pulmonary embolism, 1 instance of surgical site infection, 1 sudden cardiopulmonary arrest, and 1 instance of vocal paralysis related to intubation. A permanent neurological deficit occurred in 11 (4.2 %) patients, but did not lead to early death in any case. Four patients (1.5 %) succumbed to surgery-related death (i.e., death within 30 days after surgery). Of these, two died of advanced systemic diseases 22 and 30 days after surgery, respectively. The other patients experienced neurological death: 1 died of LMM 23 days after surgery, while the other died of brainstem infarction 17 days after surgery for frontal lobe metastases.

Clinical characteristics of the early death group

A total of 62 patients (23 %) were included in the early death group. The early death rates were 10, 22, and 41 % in preoperative RPA class I, II, and III patients. When patients were divided according to postoperative RPA class, the

Table 1 Patient characteristics

	Total	Early death	Non-early death	*P* value[a]
Patients no.	264	62	202	
Multiple BM	67	24	43	0.0058
Infra-tentorial lesions	79	18	61	0.86
Age 65 or more	82	16	66	0.31
Preoperative KPS <70	57	24	33	0.0002
Postoperative KPS <70	22	13	9	<0.0001
ECM and/or uncontrolled primary lesion[b]	161	50	111	0.0003
Preoperative RPA[b]				0.0059[c]
I	59	6	53	
II	148	33	115	
III	56	23	33	
Postoperative RPA[b]				0.0041[c]
I	66	7	59	
II	176	43	133	
III	21	12	9	
Primary cancer				
Lung	102	24	78	
Breast	48	11	37	
GI	46	14	32	
Malignant melanoma	13	5	8	
Renal	8	2	6	
Others	47	6	41	
GTR	232	53	179	0.51
Any RT prior to surgery	37	11	26	0.33
Adjuvant RT(+)	216	46	170	0.075
Systemic therapy after operation for BM				
(+)	119	16	103	<0.0001
(−)	129	46	83	

BM brain metastases, *ECM* extra-cranial metastases, *GI* gastrointestinal, *GTR* gross total removal, *KPS* Karnofsky performance status, *RPA* recursive partitioning analysis, *RT* radiation therapy, *WBRT* whole brain radiation therapy

[a] Pearson's Chi square test

[b] Data of one case was absent

[c] Analyzing with dividing into RPA I and II-III

early death rates were 11, 24, and 57 % in class I, II, and III patients, respectively.

Table 1 shows the results of univariate analysis of data from the early death group and the non-early death group. The early death group contained a significantly higher ratio of patients with multiple brain metastases, KPS <70, uncontrolled primary cancers, and advanced RPA (II or III). The distribution of primary cancers did not differ significantly between these 2 groups. Fewer patients received systemic therapy after the resection of brain metastases in the early death group than in the non-early death group (26 vs. 55 %).

Table 2 Multiple logistic regression analysis for early death

	Odds ratio	*P* value
Postoperative systemic therapy (−)	4.91	<0.0001
Uncontrolled extra-cranial malignancy (+)	5.22	0.0022
Postoperative poorer KPS (<70)	3.61	0.041
Multiple brain metastases	(2.04)	0.051
Preoperative poorer KPS (<70)	(1.84)	0.18
Preoperative advanced RPA (class II or III)	(0.79)	0.84
Postoperative advanced RPA (class II or III)	(0.96)	0.98
Adjuvant radiotherapy (not performed)	(1.69)	0.21

KPS Karnofsky performance status, *RPA* recursive partitioning analysis

Multivariate logistic regression analysis was performed to identify which factors were most closely related with early death. Only clinical factors with $P < 0.1$ in univariate analysis (as described above) were used for this analysis. As shown in Table 2, uncontrolled primary tumors or extracranial metastases, lack of postoperative systemic therapy, and a postoperative decrease in KPS (<70) were significantly related to early death.

The impact of postoperative systemic therapy on the survival of patients with uncontrolled extracranial disease

The impact of treatment strategy on survival was further analyzed because postoperative systemic therapy was significantly related with early death in the univariate and multivariate analyses described above. Survival analysis using the Kaplan–Meier method did not reveal a difference in survival between patients in the systemic therapy (+) group (119 cases) and the (−) group (129 cases) (12.9 vs. 10.7 months; $P = 0.68$, log-rank test). Because systemic therapy is not usually administered to patients with poor performance status or without extra-cranial malignancies, we performed a further analysis including only patients with uncontrolled extracranial malignancies and those with a postoperative KPS of 70 or more. Based on this analysis, the MST was significantly longer in the systemic therapy (+) group (85 cases) than in the systemic therapy (−) group (54 cases) (12.5 vs. 5.6 months; $P = 0.0026$, log-rank test) (Fig. 1c).

The impact of postoperative treatment strategy on survival

All patients were divided into 3 groups according to treatment course after surgery for brain metastases: group 1

(102 cases) included patients without systemic disease, group 2 (89 cases) included patients who underwent systemic therapy for uncontrolled extracranial disease, and group 3 (65 cases) included patients who had extracranial disease but did not receive systemic therapy. Group 3 patients were treated with best supportive care. The MSTs of groups 1, 2, and 3 were 20.8, 12.4, and 5.1 months, respectively, and the difference among the groups was significant ($P < 0.0001$, log-rank test) (Fig. 1d). The early death rate was 12 % in group 1, 16 % in group 2 and 55 % in group 3, and the early death rate of group 3 was significantly higher than that of the other groups ($P < 0.0001$, Pearson's Chi square test).

Cause of death

Data regarding cause of death was available for 55 of the early death cases. Twenty patients (32 %) died from neurological causes, while 35 patients (56 %) died from systemic diseases. Thirteen of the neurological deaths were attributed to LMM. The adjuvant radiation therapies used in LMM cases were WBRT in 5 and local brain radiation therapy in 3 cases. Five cases did not receive either therapy. Other neurological deaths were due to progression of brain metastases after RT (6 cases) and brain stem infarction (1 case).

Postoperative status and survival time in preoperative RPA class III patients

Patients assessed as preoperative RPA class III ($n = 56$) typically have shorter survival times; therefore, the clinical courses of these patients were further analyzed in order to evaluate the potential treatment benefit. Of these patients, 8 (14 %), 31 (55 %), and 17 (30 %) were postoperative RPA class I, II, and III, respectively. When patients were divided according to postoperative RPA class, MST was 13.6, 6.5, and 3.6 months in class I, II, and III patients, respectively. MST was significantly longer in patients who experienced an improvement in postoperative RPA class ($n = 39$) compared with patients who remained in class III ($n = 17$) (6.9 vs. 3.6 months; $P = 0.019$, log-rank test). KPS was improved in 43 (77 %), unchanged in 10 (18 %), and worsened in 3 (5.4 %) preoperative RPA class III cases after surgery.

We further analyzed the cases showing RPA class III preoperatively but better RPA class postoperatively (I, 8 cases; II 31 cases) in order to discuss the operative indication for preoperative RPA class III patients (Supplementary Table 1). Twelve cases (31 %) of this cohort (39 cases) succumbed to early death after surgery, and their postoperative RPA class was I in one and II in 11. The causes of their early death were mainly consisted of systemic death; systemic disease in 8 cases, leptomeningeal metastasis in 2 cases and unknown in 2 cases. To identify what factor contributed to the early death in this cohort (39 cases), the postoperative treatment strategy was compared between the early death cases (12 cases) and the non-early death cases (27 cases). Eight of the 12 early death cases received best supportive care while 7 of the 25 non-early death cases (2 cases lacked the data) did. Thus, lack of postoperative systemic therapy was also statistically related with the early death in this cohort despite improvement in RPA class (8/12 vs. 7/25; $P = 0.025$, Pearson's Chi square test).

Discussion

In this study, we reviewed a surgical series from a single center and focused on the clinical characteristics of cases with poorer prognosis. Comparing with the recent studies presenting their surgical outcome, our series showed the comparable survival time [3, 6, 7, 9] according to RPA class and the comparable complication rate (7.6 vs. 4.5–14 %) despite the high ratio of RPA class III (21 vs. 5.7–6.8 %) [6, 14, 15]. We showed that postoperative treatment strategy and performance status were the significant factors for early death in multivariate analysis.

Systemic therapy after surgery was previously reported as being significantly related to survival time, but this was contradicted by the result in multivariate analysis [6]. This result simply seems to reflect the bias of the analysis: systemic therapy is usually avoided in patients with poorer performance status or patients without uncontrolled extracranial malignancy. We further analyzed only patients with favorable postoperative KPS scores and uncontrolled extracranial malignancies to ensure that we were only analyzing patients who truly needed further treatment for primary cancer. We showed that postoperative systemic therapy had a significant effect on survival in this population (Fig. 1c). Similarly, multivariate analysis showed that a lack of postoperative systemic therapy was a significant factor for early death, which was mainly analyzed in this study (Table 2). Thus, the treatment strategy for extracranial malignancies should be considered when determining operative indication, and this is supported by the results described in Fig. 1d. In other words, patients who cannot undergo chemotherapy (e.g., due to multidrug resistance to systemic therapy) are at high risk of early death after surgery. We also subjected our cohort to further analysis for survival by dividing three groups time according to the operative period (2000–2003, 2004–2007 and 2008–2011), but the difference in OS or early death rate was not apparent (data not shown). Despite the recent advances in systemic therapeutic agents, brain metastases

Table 3 Review of previous clinical studies: cause of death

Treatment		Pt no.	MST (months)	Neurological death (%)[c]	Systemic death[c]	Unknown[c]
Hashimoto et al. [17]	Surgery + WBRT	66	11.5	37	35 %	31 %
	Surgery + LBRT	64	9.7	36	36 %	29 %
Muacevic et al.[a] [18]	Surgery + WBRT	33	9.5	29	53 %	N.A.
	SRS	31	10.3	11	53 %	N.A.
Aoyama et al. [19]	WBRT + SRS	65	7.5	19	N.A.	N.A.
	SRS alone	67	8.0	23	N.A.	N.A.
Manon et al. [20]	SRS	31	8.3	19	30 %	16 %
Serizawa et al. [21]	SRS	521	9.0	18	N.A.	N.A.
Jawahar et al. [22]	SRS	44	7.0	25	36 %	39 %
Andrews et al. [11]	WBRT + SRS	137	6.5	28	62 %	9 %
	WBRT alone	149	5.7	31	64 %	5 %
Petrovich et al. [23]	SRS for MM	231	8	42	50 %	8 %
	SRS for others	227	6–17[b]	23	70 %	7 %
Agboola et al. [5]	Surgery + RT	125	9.5	25	37 %	6 %
Mintz et al. [13]	Surgery + WBRT	41	5.6	15	46 %	5 %
	WBRT	43	6.3	28	35 %	0 %
Wronski et al. [24]	Surgery ± WBRT	231	13	39	30 %	12 %
Bindal et al. [25]	Surgery ± WBRT	82				
	Multiple lesions	56	10	36	32 %	23 %
	Single lesion	30	14	25	45 %	15 %
Vecht et al. [16]	Surgery + WBRT	32	10	32	N.A.	N.A.
	WBRT	31	6	33	N.A.	N.A.

LBRT local brain radiation therapy, *MM* malignant melanoma, *MST* median survival time, *RT* radiation therapy, *SRS* stereotactic radiosurgery, *WBRT* whole brain radiation therapy

[a] The ratio was evaluated with 1-year rate

[b] The ratio was described in each cancer

[c] Deaths of combined cause of systemic and neurological were not included in any groups. When unknown cause were excluded from analysis in the original articles, the ratios were re-estimated including deaths of unknown causes

may arise after acquiring drug resistance even for newly developed agents, and the survival after brain metastases might depend largely on whether further systemic therapy can be available or not.

One of the challenges in our study was evaluating both preoperative and postoperative status. The prognostic significance of pre- and postoperative RPA class was previously analyzed, and the multivariate analysis showed that only preoperative RPA was significant [9]. This observation was, however, based simply on the analysis of survival time. Our analysis differed from the previous study because we evaluated the factor related to early death and specifically analyzed the group with the poorest prognosis: preoperative RPA class III patients. In the present study, postoperative RPA class was related to survival and a higher early death rate, and the early death rate was extremely high in preoperative RPA class III patients without postoperative improvement. Because RPA class III simply indicates a poor KPS score (<70), improvement in performance status is a significant factor for survival in preoperative RPA class III patients. Therefore, when determining the indications for surgery in preoperative RPA class III patients, it is important to consider whether surgery is likely to improve KPS. Patients who are not likely to experience an improvement in performance status are also not likely to obtain a survival benefit. However, it is important to remember that the postoperative treatment strategy is also significant factor for survival as shown in our analysis for RPA class III patients.

Finally, we analyzed the cause of death. Previous studies have reported a neurological death rate of 15–37 % after surgery for brain metastases [5, 11, 13, 16–25] (Table 3). Our results were in line with this, although one limitation of our study was that the cause of death was available only for early death cases. Of note, 21 % (13/62) of early death cases were attributed to LMM in this study. Recent large studies reported a 5–16 % incidence of LMM after surgical removal [14, 17, 26, 27]. Considering these results, LMM

appears to occur early after surgery and may be a significant cause of early death. An increased incidence of early death might be attributed to either (1) preoperative undiagnosed LMM without apparent radiological findings because of a lack of routine cerebrospinal fluid cytology [26] or (2) LMM caused by the surgery itself. In fact, several previous reports have shown an increased risk of LMM after surgery compared with SRS alone [14, 26–28]. In order to reduce early deaths due to LMM, adjuvant therapies will need to be developed. The protective effect of adjuvant radiation therapy for LMM remains controversial, and recent studies have failed to demonstrate this effect [14, 26]. Further studies are needed to clarify the efficacy of radiation therapy.

In summary, early death after resection of brain metastases can be attributed to neurologic factors and systemic factors. Of the neurological factors, LMM is a critical factor that is related to early death. Further studies exploring the prevention and treatment of LMM are necessary. Of the systemic factors, a poor performance status after surgery (rather than before surgery), uncontrolled extracranial malignancies, and a lack of systemic therapy after surgery are related to early death. The limitation of our retrospective study lies in the possibility of the bias derived from patient selection. Further analysis including non-surgically treated cases may confirm our observations. When making decisions regarding surgery for brain metastases, physicians should be aware of the importance of a systemic treatment strategy after surgery, while surgeons should recognize that a poor performance status deprives patients of QOL and a chance for systemic therapy. The role of surgery for brain metastases is not only to improve the QOL and prevent neurological death but also to give patients a chance for further systemic therapy.

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

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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

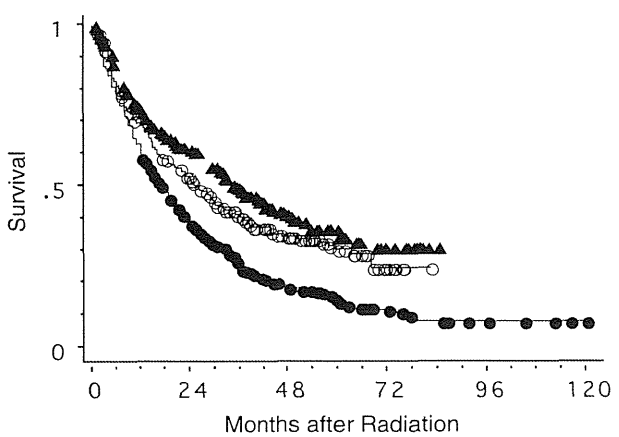

Fig. 1 Survival curves for patients with primary central nervous system lymphoma (PCNSL) seen in 1985–1994 (*filled circle*, n = 466), 1995–2004 (*open circle*, n = 273), and 2005–2009 (*filled diamond*, n = 315). Patients surveyed in 1995–2004 and 2005–2009 showed significantly better survival rates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

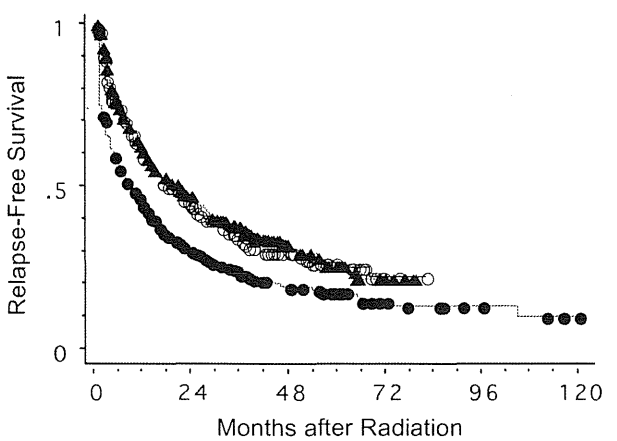

Fig. 2 Relapse-free survival curves for patients with PCNSL seen in 1985–1994 (*filled circle*, n = 408), 1995–2004 (*open circle*, n = 264), and 2005–2009 (*filled diamond*, n = 315). The patients surveyed in 1995–2004 and 2005–2009 showed significantly better relapse-free survival rates than those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

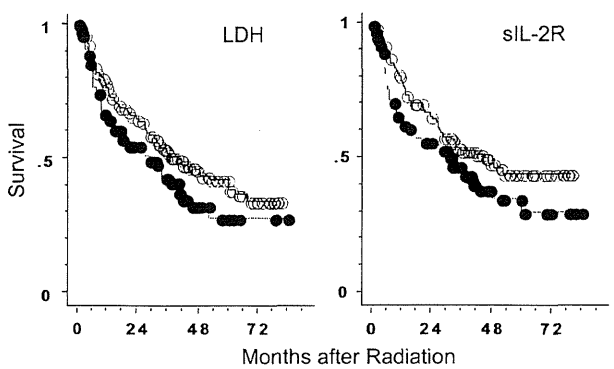

Fig. 3 Survival curves for patients treated between 2005 and 2009 according to the serum lactate dehydrogenase (*LDH*) and soluble interleukin-2 receptor (*sIL-2R*) levels. *Open circle* Normal level ($n = 206$ for LDH and 135 for sIL-2R), *filled circle* elevated level ($n = 99$ for LDH and 95 for sIL-2R).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

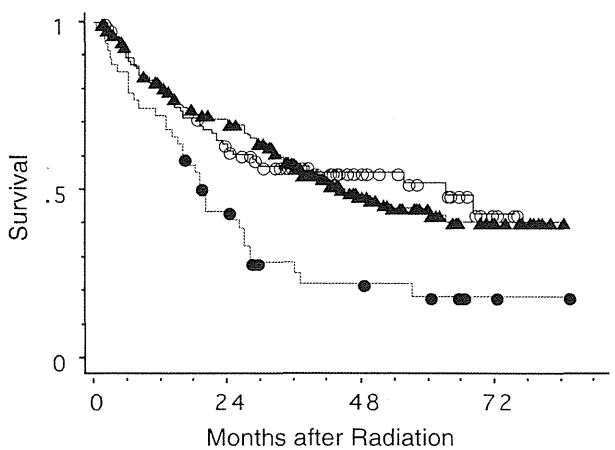

Fig. 4 Survival curves for patients treated with high-dose methotrexate-containing chemotherapy plus radiation in 1985–1994 (*filled circle*, $n = 46$), 1995–2004 (*open circle*, $n = 92$), and 2005–2009 (*filled diamond*, $n = 203$). The *P* value was 0.0030 for 1985–1994 vs. 1995–2004, 0.0002 for 1985–1994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