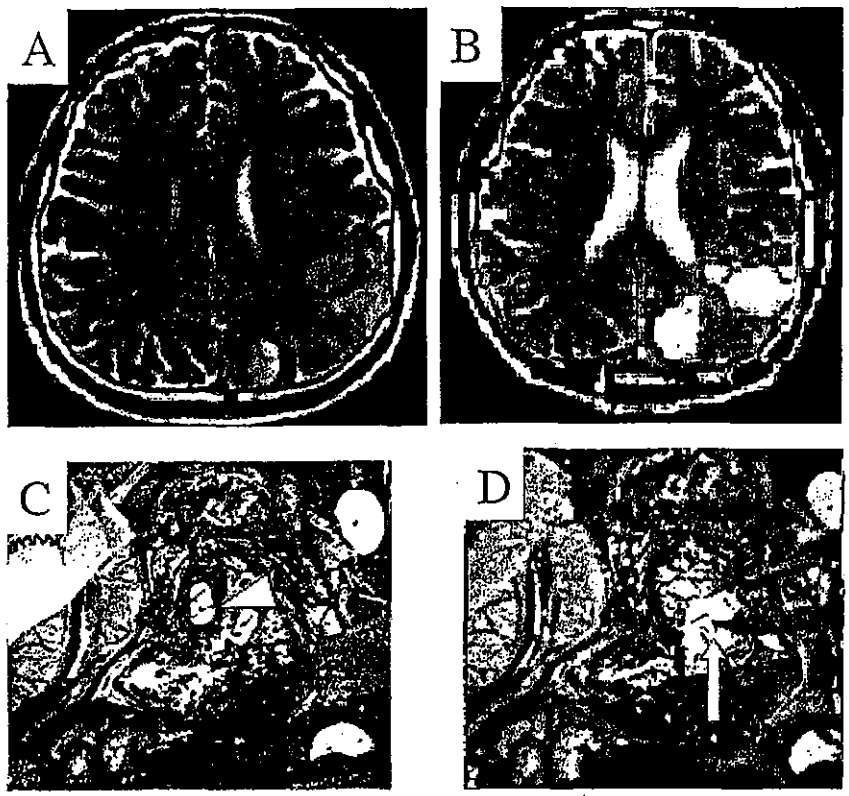

図2　27歳，anaplastic astrocytoma

左頭頂葉縁上回角回と後頭葉の多発性腫瘍（A）．覚醒下手術によるマッピングと術中MRIによるナビゲーションで腫瘍皮質部分に明らかな言語野認めず，言語機能（呼称，復唱，会話）と角回機能（計算，指趾呼称）をモニタリングをしながら摘出．皮質下マッピングにより深部前方で手の運動が誘発された（C矢頭，10mA）．また，シルビウス裂深部後端の下方で刺激後（D矢印，20mA），失語症状が出現したため，摘出を停止した．画像上全摘し，次いで後頭葉腫瘍も全摘した（B）．術直後よりの伝導失語は3ヵ月で軽快し，放射線化学療法後退院．現在復職している．

とは，麻酔科医，手術場Nurse，患者さんの協力である．全麻の手術と異なり覚醒下手術は患者さんが参加する手術であり，外科医と同様疾患に立ち向かう姿勢が肝要であり，その意義を理解できるように十分な術前説明がなされなければならない．また麻酔科医の協力と高度な技術なくしては正確なマッピングやモニタリングは不可能であり，チームとして術前症例検討に十分な時間をかけるべきと考える．

本稿が貴施設における覚醒下手術の一助となり，合併症ない摘出率向上に役立てれば幸いである．

最後になるが，覚醒下手術の広まりを受けて昨年日本AWAKE SURGERY研究会が設立された（山形大学脳神経外科・嘉山孝正教授）．ご興味のある方はぜひご参加いただきたい．

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文 献

1) Albert FK, Forsting M, Sartor K, et al: Early postoperative magnetic resonance imaging after resection of malignant glioma: objective evaluation of residual tumor and its influence on regrowth and prognosis. [see comments]. Neurosurgery 34: 45-60, 1994
2) Berger MS, Kincaid J, Ojemann GA, et al: Brain mapping techniques to maximize resection, safety, and seizure control in children with brain tumors. Neurosurgery 25: 786-792, 1989
3) Fukaya C, Katayama Y, Yoshino A, et al: Intraoperative wake-up procedure with propofol and laryngeal mask for optimal excision of brain tumour in eloquent areas. J Clin Neurosci 8: 253-255, 2001
4) Hess KR: Extent of resection as a prognostic variable in the treatment of gliomas. Journal of Neuro-Oncology 42: 227-231, 1999
5) 星田 徹，榊 寿右：皮質電気刺激による脳機能マッピング，pp261-268（高倉公朋：脳神経外科の最先端 NO.2 21世紀の新領域とニューテクノロジー，先端医療技術研究所，東京，2000）
6) Iseki H, Muragaki Y, Taira T, et al: New Possibilities for Stereotaxis. information-guided stereotaxis. Stereotact Funct Neurosurg 76: 159-167, 2001
7) 隈部俊宏，中里信和，佐藤清貴，他：運動野神経膠腫摘出におけるAwake craniotomyとdirect stimulationによる術中functional brain mapping. No Shinkei Geka 25: 823-828, 1997
8) Lacroix M, Abi-Said D, Fourney DR, et al: A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg 95: 190-198, 2001
9) Larkin M: Neurosurgeons wake up to awake-brain surgery. Lancet 353: 1772, 1999
10) 村垣善浩：脳神経外科における覚醒下手術の経験. Life support and anesthesia 7: 32-40, 2000
11) 村垣善浩，平沢研一，山根文孝，他：長期硬膜下電極埋め込みによるMappingを利用したEloquent Area近傍Glioma摘出術，pp140-148（嘉山孝正：Advanced Technologyを用いた脳腫瘍の外科，メディカ出版，大阪，2001）
12) 村垣善浩，丸山隆志，伊関 洋，他：覚醒下手術（切除率向上のための新技術），pp276-282（高倉公朋：脳腫瘍の最新医療，先端医療技術研究所，東京，2003）
13) Ojemann GA: Neurosurgical management of epilepsy: a personal perspective in 1983. Applied Neurophysiology 46: 11-18, 1983
14) Ojemann JG, Miller JW, Silbergeld DL: Preserved function in brain invaded by tumor. Neurosurgery 39: 253-258, 1996
15) Pignatti F, van den Bent M, Curran D, et al: Prognostic factors for survival in adult patients with cerebral low-grade glioma. J Clin Oncol 20: 2076-2084., 2002
16) Ramesh L, Sahjpaul: Awake Craniotomy: Controversies, Indications and techniques in the surgical Treatment of Temporal lobe Epilepsy. Can J Neurol Sci 27 Suppl 1: S55-S63, 2000
17) Report of brain tumor registry of japan (1969-1993) 10th edition. Neurol Med Chir (Tokyo) 40 (supplement): 1-106, 2000
18) Sartorius CJ, Berger MS: Rapid termination of intraoperative stimulation-evoked seizures with application of cold Ringer's lactate to the cortex. Technical note. J Neurosurg 88: 349-351, 1998
19) Skirboll SS, Ojemann GA, Berger MS, et al: Functional cortex and subcortical white matter located within gliomas. Neurosurgery 38: 678-684, 1996

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ORIGINAL PAPER

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Primary central nervous system lymphoma in Japan 1995–1999: changes from the preceding 10 years

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Abstract *Purpose*: Previously, we conducted a nationwide survey of primary central nervous system lymphoma (PCNSL) treated between 1985 and 1994 in Japan. In the present study, we conducted further investigations of PCNSL patients treated between 1995 and 1999 to clarify possible changes with time in the clinical features, treatment, and outcome of this disease. *Methods*: Thirteen Japanese institutions were surveyed, and data on 101 patients with histologically-confirmed PCNSL were collected. These data were compared with those of 167 patients treated at the same institutions between 1985 and 1994. *Results*: Regarding patient and tumor characteristics, the proportion of patients with good performance status (PS) was significantly higher in the group treated during 1995–1999 than in that treated during 1985–1994, but other characteristics were not significantly different. Regarding treatment, more patients in the more recent period (66%) received systemic chemotherapy than those in the preceding period (53%, $P = 0.049$). For all patients, including those who did not complete radiotherapy, the median survival time was 17 months and 30 months in patients treated between 1985 and 1994 and those treated between 1995 and 1999, respectively, and the 5-year survival rate was 15% versus 31% ($P = 0.0003$). In both patient groups, higher age and tumor multiplicity were associated with poor prognosis in multivariate analysis. In patients treated between 1995 and 1999, those who received systemic chemotherapy showed significantly better prognosis than those who did not ($P = 0.0049$), but the difference was not significant in multivariate analysis ($P = 0.23$). *Conclusions*: The high survival rates observed in the present survey are comparable with those of recent prospective studies employing intensive chemoradiotherapy. The improvement in prognosis appeared to result, at least in part, from the increase in the proportion of patients with better PS. Since the clinical feature and treatment outcome of patients with PCNSL can thus change with the era, historical control data should not be used in comparing different treatment modalities.

Keywords Brain neoplasm · Lymphoma · Primary CNS lymphoma · Radiotherapy · Chemotherapy

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Introduction

Primary central nervous system lymphoma (PCNSL) is increasing and is becoming one of the most important tumors in neuro-oncology. Radiation therapy has been the standard treatment for PCNSL until recently, but the outcome of patients treated by radiation alone has not necessarily been satisfactory (Shibamoto et al. 1990; Reni et al. 1997; Hayabuchi et al. 1998; Nelson 1999). More recently, the use of high-dose methotrexate (MTX)-containing chemotherapy before radiation appeared to have gained some success in obtaining

long-term survival (Glass et al. 1994; Blay et al. 1998; Brada et al. 1998; Abrey et al. 2000; Ferreri et al. 2000; O'Brien et al. 2000; Reni et al. 2001; Bessel et al. 2001; Caldoni & Aebi 2002; DeAngelis et al. 2002). However, there has been no randomized trial suggesting the superiority of the combined modality treatment over radiation therapy alone, and a recent study by a German group suggested a high rate of progressive disease during treatment with 6 courses of 8 g/m^2 of MTX (Herrlinger et al. 2002). Therefore, the benefit of high-dose MTX appears to remain uncertain. Since the clinical features of PCNSL appear to be changing with time, it may not be reasonable to consider that combined MTX-containing chemotherapy and radiation is superior to radiation alone, by comparing the results of combined treatment with the historical control data in patients treated by radiation therapy alone.

Previously, Hayabuchi et al. (Hayabuchi et al. 1998) conducted a nationwide survey of PCNSL in Japan treated between 1985 and 1994. The findings on 466 patients were previously published. Considering the increasing importance of this disease, we organized a research group consisting of 13 institutions to carry out both retrospective and prospective studies on PCNSL. As a first study of this group, we collected data on PCNSL patients treated between 1995 and 1999 at these institutions. In addition to analyzing these data on 101 patients, we compared the data with those on 167 patients from the previous survey treated between 1985 and 1994 at the same institutions, to investigate changes in the clinical feature, treatment modality, and outcome between these eras.

Materials and methods

Subjects of the present survey were patients with histologically-proven PCNSL who received radiation therapy between 1995 and 1999. Those who did not complete the planned radiotherapy were included. Clinical characteristics, treatment and prognosis of each patient shown in the Results section were asked using a detailed questionnaire. Data on 101 patients were collected from 13 institutions. For comparison, data on 167 patients treated in the preceding 10 years, i.e., between 1985 and 1994, at the same institutions were obtained from the data source of the previous nationwide survey (Hayabuchi et al. 1998) and were analyzed. Data regarding tumor size (maximum diameter at diagnosis and before radiation therapy) was asked for in the present survey, which had not been done in the previous survey. As often happens with such a survey, a number of the items were unanswered by the investigators. Various chemotherapy regimens had been used, and were categorized as follows: (A) cyclophosphamide, vincristine, and prednisolone (COP) or COP plus doxorubicin (CHOP/VEPA); (B) intravenous methotrexate (MTX) alone or MTX-containing regimens. The drugs included in regimen A had often been used in combination with MTX, and such regimens were categorized into this group; (C) cytarabine plus procarbazine; (D) nitrosourea-containing regimens. Some of the drugs in regimen A had been used in combination with nitrosoureas, and such regimens were included in this group. When MTX had been used in combination, the regimen was categorized into group B; (E) cisplatin plus etoposide; and (F) Single use or combination of miscellaneous other agents not included in the above groups. For analysis of treatment results, regimens C–F were grouped together. Differences in patient, tumor, and treatment characteristics between groups were examined by Fisher's exact test.

Survival rates were calculated from the date of starting radiotherapy using the Kaplan-Meier method, and differences in pairs of survival curves were examined by the log-rank test. Multivariate analysis of 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 a computer program, Stat View Version 5 (SAS institute, Cary, NC, USA).

Results

Table 1 shows patient, tumor, and treatment characteristics in the two groups treated between 1985 and 1994 and between 1995 and 1999. There were more patients with better WHO performance status (PS) score in the group treated between 1995 and 1999 than in the

Table 1 Patient, tumor, and treatment characteristics

Characteristic		1985–1994	1995–1999	*P*
Gender	Male/female	97/70	67/34	0.20
Age (years)	< 60/≥ 60	83/84	53/48	0.71
	Median (range)	60 (15–84)	59(15–84)	
Performance status	0–2/3,4	69/95	60/41	0.0078
Lactate dehydrogenase	Normal/high	49/34	50/30	0.75
B symptom	Yes/no	16/133	11/81	0.83
Phenotype	B/T	75/8	79/6	0.59
Tumor number	Single/multiple	103/63	56/43	0.44
Maximum tumor diameter	At diagnosis	–	3 (1.5–9)	
Median (range) (cm)	Before radiation	–	3 (0–9)	
Radiotherapy	Completed/not completed	158/9	97/4	0.77
Radiation field	Whole brain/partial brain	146/21	92/9	0.43
Spinal radiation	Yes/no	15/152	4/97	0.15
Total dose (Gy)	< 50/≥50	54/113	28/73	0.49
	Median (range)	50 (2–70)	50 (6–80)	
Whole-brain dose (Gy)	< 40/≥40	70/97	42/59	1.0
	Median (range)	40 (0–54)	40 (0–60)	
Chemotherapy	Yes / no	78/70	65/34	0.049

Table 2 Chemotherapy regimens (COP cyclophosphamide, vincristine and prednisone, CHOP/VEPA COP plus doxorubicin)

Regimen	1985–1994	1995–1999
COP, CHOP/VEPA	35 (45%)	25 (38%)
Methotrexate-containing regimens	18 (23%)	27 (42%)
Cytarabine and procarbazine	0	7 (11%)
Nitrosourea-containing regimens	13 (17%)	2 (3%)
Cisplatin and etoposide	8 (10%)	4 (6%)
Miscellaneous drugs	4 (5%)	0

group treated in the preceding 10 years, but the other patient and tumor characteristics did not differ significantly between the two groups. Radiotherapy characteristics were similar between the two groups. During both study periods, more than 85% of the patients were treated with whole-brain irradiation with or without focal boost, and the median total and whole brain doses were 50 Gy and 40 Gy, respectively. Whole spinal irradiation was employed in less than 10% of the patients. On the other hand, more patients seen between 1995 and 1999 received systemic chemotherapy than those seen between 1985 and 1994 (66% vs 53%, $P = 0.049$). Table 2 shows chemotherapy regimens used in the two groups. The use of MTX-containing regimens appeared to be increasing recently. However, a high dose of MTX (> 2 g/m^2 per administration) was used in only 14 patients (14% of all patients) treated between 1995 and 1999.

Figure 1 shows overall survival curves for all patients in the two groups. Patients in the present survey had significantly better survival rates than those in the previous survey ($P = 0.0003$); median survival time was 30 vs 17 months, and the 3-year survival rate was 46% vs 24%. The 5-year survival was 31% and 15%, respectively. Table 3 summarizes survival data in the two groups according to potential prognostic factors. In both study periods, patients with ages < 60 years, PS 0–2, or a single tumor showed significantly higher survival rates. Patients with normal lactate dehydrogenase (LDH) levels or without B symptom had better prognoses than those with high LDH level or with B symptom, respectively, in the group treated between 1995 and 1999, but not in those treated during 1985–1994.

To analyze the influence of treatment-related factors on outcome, patients who did not complete radiotherapy (and died soon) were excluded. In patients treated between 1985 and 1994, those who received partial-brain radiation, spinal radiation, or whole-brain dose < 40 Gy showed better prognoses, but these phenomena were not observed in patients treated between 1995 and 1999. Figure 2 shows survival curves according to the treatment modality, i.e., radiation alone vs radiation plus chemotherapy. In patients treated between 1985 and 1994, the two groups showed similar prognoses. In patients treated between 1995 and 1999, however, those who received radiation plus chemotherapy showed significantly better survival than those who received radiation alone. Among these patients, 61% of the

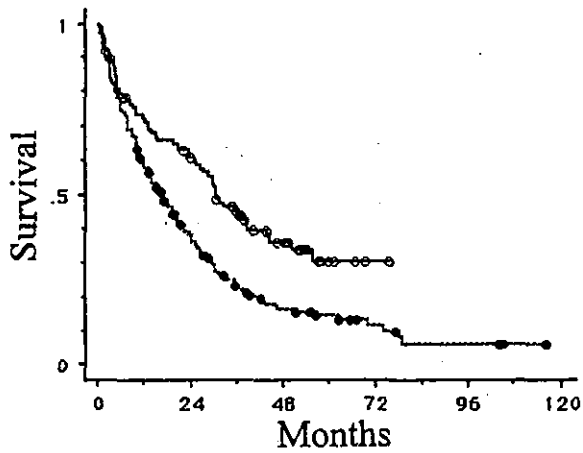

Fig. 1 Survival curves for patients with primary central nervous system lymphoma treated between 1985 and 1994 (- - -●- - -) and for those treated between 1995 and 1999 (____O____). The difference was significant ($P = 0.0003$)

patients who received radiochemotherapy were younger than 60 years, but 39% of those treated with radiation alone were younger than 60 years ($P = 0.050$). Similarly, 64% of the patients who received radiochemotherapy had a PS 0–2, but 55% of those treated with radiation had a PS 0–2 ($P = 0.50$). Figure 3 shows survival curves according to the chemotherapy regimens. In patients treated between 1985 and 1994, there was no significant difference in survival curves according to the regimens. On the other hand, there was an overall difference in those treated between 1995 and 1999 ($P = 0.018$). Patients receiving MTX-containing regimens showed better survival than those treated with CHOP/VEPA or COP ($P = 0.0071$).

Multivariate analyses were performed for potential prognostic factors, which were significant in univariate analyses (Table 4). Factors concerning the radiation field and spinal radiation were not included because of the small number of patients in one of the groups. In both patient groups treated during 1985–1994 and 1995–1999, age and tumor number were suggested to be significant prognostic factors. PS and LDH level did not reach statistical significance. The radiation dose to the whole brain and chemotherapy did not prove significant in patients treated between 1985 and 1994, and in those treated between 1995 and 1999, respectively.

Discussion

The most significant finding of this study appears to be that patients treated between 1995 and 1999 showed a significantly better prognosis than those treated between 1985 and 1994. Comparison of the patient and tumor characteristics revealed that there were more patients with better PS between 1995 and 1999 than between 1985 and 1994. This may be due to the earlier diagnosis of the disease in recent years and improvement in gen-

Table 3 Survival data according to potential prognostic factors (MST median survival time in months, 5-YSR 5-year survival rate)

Prognostic factor		1985–1994				1995–1999			
		n	MST	5-YSR(%)	*P*	*n*	MST	5-YSR(%)	*P*
Gender	Male	97	15	8.7	0.13	67	32	31	0.62
	Female	70	22	23		34	28	33	
Age (years)	<60	83	20	22	0.0057	53	44	45	0.0052
	≥ 60	84	13	6.8		48	23	15	
Performance status	0–2	69	24	18	0.0015	60	37	32	0.024
	3,4	95	11	13		41	12	30	
B symptom	Yes	16	10	7.5	0.30	11	14	18	0.027
	No	133	18	17		81	36	35	
Lactate dehyrdogenase	Normal	49	22	31	0.17	50	55.5	43	0.0084
	High	34	21	5.8		30	20.5	(20)[b]	
Tumor number	Single	103	22	19	0.0021	56	55.5	43	0.0083
	Multiple	63	11	7.9		43	26	17	
Tumor size (cm)[a]	≤ 3 cm	–	–	–	–	51	32	33	0.95
	>3 cm	–	–	–		41	37	31	
Radiation field	Whole brain	139	17	12	0.026	89	30	31	0.99
	Partial brain	19	35	38		8	35	(33)	
Spinal radiation	Yes	15	31	37	0.042	4	-	(50)	0.69
	No	143	17	13		93	30	30	
Total dose (Gy)	<50	45	16	22	0.79	24	29.5	26	0.16
	≥ 50	113	18	13		73	36	32	
Whole-brain dose (Gy)	<40	61	24	22	0.025	38	32	26	0.83
	≥40	97	14	11		59	30	32	
Chemotherapy	Yes	65	18	19	0.63	64	38	40	0.0049
	No	74	19	14		31	25	(14)	

[a] Maximum tumor diameter before radiation
[b] Figures in parentheses are 4-year survival rate

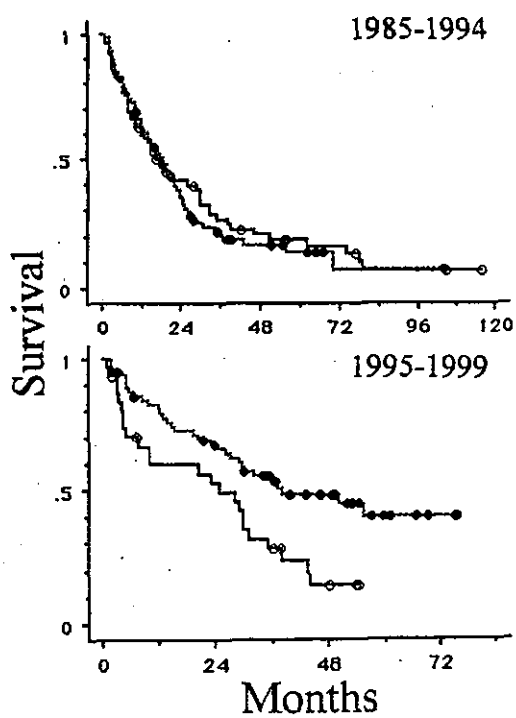

Fig. 2 Survival curves according to the treatment modality. _____O_____ : patients treated with radiation alone, - - -●- - - : patients treated with radiation and chemotherapy. The difference was significant in the group of patients treated between 1995 and 1999 (upper panel, $P = 0.63$; lower panel, $P = 0.0049$)

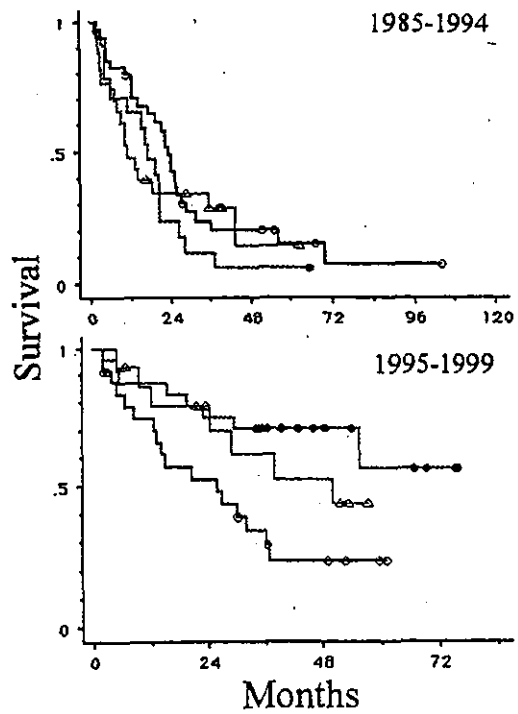

Fig. 3 Survival curves according to chemotherapy regimens. _____O_____ : cyclophosphamide, vincristine, prednisolone ± doxorubicin, - - -●- - - : methotrexate-containing regimens, - - -Δ- - - : other regimens. The difference among the curves was significant in the group of patients treated between 1995 and 1999 (upper panel, $P = 0.32$; lower panel, $P = 0.018$)

Table 4 Multivariate anayses for potential prognostic factors that were significant in univariate analysis

Factor	1985–1994 (n = 154)		1995–1999 (n = 72)	
	P	Relative risk	P	Relative risk
Age (< 60 vs ≥ 60 years)	0.036	1.48 (1.03–2.15)[a]	0.047	2.07 (1.01–4.22)
Performance status (0–2 vs 3,4)	0.13	1.36 (0.92–2.01)	0.13	1.77 (0.85–3.68)
Lactate dehydrogenase (normal vs high)	–	–	0.13	1.70 (0.86–3.34)
Tumor number (single vs multiple)	0.0093	1.67 (1.13–2.45)	0.0032	2.82 (1.42–5.62)
Whole-brain dose (< 40 vs ≥ 40 Gy)	0.22	1.28 (0.86–1.91)	–	–
Chemotherapy (yes vs no)	–	–	0.23	1.53 (0.32–1.31)

[a]Figures in parentheses are 95% confidence intervals

eral care including corticosteroid therapy and less aggressive surgery. Since PS was a significant prognostic factor in univariate analysis, it is suggested that the increase in the proportion of better PS patients may, at least in part, have contributed to the improvement in prognosis in patients treated between 1995 and 1999.

Age, PS, and tumor multiplicity are well-known prognostic factors for PCNSL (Corry et al. 1998; Hayabuchi et al. 1998; O'Brien et al. 2000). The present results of univariate analyses agree with these previous observations, although the influence of PS did not reach a significant level in multivariate analysis. Patients with a high LDH level treated between 1995 and 1999 showed a poorer prognosis than those with a normal LDH level in univariate analysis. However, LDH was not a significant factor in patients treated between 1985 and 1994, as also shown in the multivariate analysis of patients treated between 1995 and 1999. The previous analysis of 466 patients in the nationwide survey suggested an association of high LDH level and poor prognosis in both univariate and multivariate analyses (Hayabuchi et al. 1998), so LDH may be a potential prognostic factor which is certainly weaker than age, PS, and tumor multiplicity. A similar finding was obtained regarding B symptom. In the newer survey, we investigated the influence of tumor size, but it did not appear to have a significant influence on patient outcome.

Regarding the method of radiation therapy, patients who were treated with a partial-brain field showed a better prognosis than those treated with a whole-brain field in the group treated between 1985 and 1994. Shibamoto et al. (Shibamoto et al. 2003) recently discussed the possible benefit of using partial-brain irradiation, especially in patients with a single lesion. Due to the retrospective nature of the present study and the small number of patients who received partial-brain irradiation, no conclusion should be drawn regarding radiation field, but avoiding whole-brain radiation may be a future topic in the treatment of PCNSL. The observation in the earlier period that patients who received spinal radiation and those who received whole-brain doses of less than 40 Gy had a better prognosis are paradoxical, and it is suggested that these observations would represent patient selection bias, which is often seen in retrospective analysis. As has been suggested by previous findings (Nelson et al. 1992; Hayabuchi et al. 1998), a higher dose of radiation did not appear to be associated with survival improvement.

In patients treated between 1985 and 1994, those who received radiation alone and those who received radiation plus chemotherapy showed a similar prognosis. On the other hand, in patients treated between 1995 and 1999, those who received radiation plus chemotherapy had a significantly better prognosis than those who received radiation alone. However, the effect of chemotherapy was not significant in multivariate analysis. Since younger patients were more often treated with combined radiation and chemotherapy, this may be one of the reasons why the effect of chemotherapy was not supported by multivariate analysis. Analysis according to chemotherapy regimens suggested a possible advantage of MTX-containing regimens over conventional CHOP or similar regimens. Several studies have suggested the ineffectiveness of CHOP or similar regimens, especially when given before radiation (Schultz et al. 1996; O'Neill 1999; Mead et al. 2000), although post-radiation CHOP requires further investigation (Shibamoto et al. 1999). The present findings suggest that systemic chemotherapy with weak or moderate intensity may not be beneficial in PCNSL.

The findings of the present study revealed that the treatment outcome for PCNSL varies greatly with the era. Although most of the chemotherapy regimens used were of mild or moderate intensity and only 14% of the patients received high-dose-MTX-containing chemotherapy, the 5-year survival rate of 31% for all patients treated between 1995 and 1999 (including those who did not complete radiotherapy) were equal to that recently reported by the Radiation Therapy Oncology Group (DeAngelis et al. 2002) or those of other series using intensive combined modality treatment including high-dose MTX (Brada 1998; Bessell et al. 2001). Therefore, it appears to be inappropriate to discuss the usefulness of treatment modality by comparing with the historical control data. There have been no major randomized studies, except for a small one (Mead et al. 2000), regarding the benefit of combining chemotherapy with radiation, but to confirm the efficacy of chemotherapy, randomized studies appear to be necessary.

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References

Abrey LE, Yahalom J, DeAngelis LM (2000) Treatment for primary CNS lymphoma: the next step. J Clin Oncol 18:3144–3150

Bessell EM, Graus F, Lopez-Guillermo A, Villa S, Verger E, Petit J, Holland I, Byrne P (2001) CHOD/BVAM regimen plus radiotherapy in patients with primary CNS non-Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 50:457–464

Blay JY, Conroy T, Chevreau C, Thyss A, Quesnel N, Eghbali H, Bouabdallah R, Coiffier B, Wagner JP, Le Mevel A, Dramais-Marcel D, Baumelou E, Chauvin F, Biron P (1998) High-dose MTX for the treatment of primary cerebral lymphomas: analysis of survival and late neurologic toxicity in a retrospective series. J Clin Oncol 16:864–871

Brada M, Hjiyiannakis D, Hines F, Traish D, Ashley S (1998) Short intensive primary chemotherapy and radiotherapy in sporadic primary CNS lymphoma. Int J Radiat Oncol Biol Phys 40:1157–1162

Calderoni A, Aebi S (2002) Combination chemotherapy with high-dose MTX and cytarabine with or without brain irradiation for primary central nervous system lymphomas. J Neurooncol 59:227–230

Corry J, Smith JG, Wirth A, Quong G, Liew KH (1998) Primary central nervous system lymphoma: age and performance status are more important than treatment modality. Int J Radiat Oncol Biol Phys 41:615–620

DeAngelis LM, Seiferheld W, Schold SC, Fisher B, Schultz CJ (2002) Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93–10. J Clin Oncol 20:4643–4648

Ferreri AJM, Reni M, Villa E (2000) Therapeutic management of primary central nervous system lymphoma: lessons from prospective trials. Ann Oncol 11:927–937

Glass J, Gruber ML, Chef L, Hochberg FH (1994) Preirradiation MTX chemotherapy of primary central nervous system lymphoma: long-term outcome. J Neurosurg 81:188–195

Hayabuchi N, Shibamoto Y, Onizuka Y, JASTRO CNS Lymphoma Study Group members (1999) Primary central nervous system lymphoma in Japan: a nationwide survey. Int J Radial Oncol Biol Phys 44:265–272

Herrlinger U, Schabet M, Brugger W, Kortmann RD, Kuker W, Deckert M, Engel C, Schmeck-Lindenau HJ, Mergenthaler HG, Krauseneck P, Benohr C, Meisner C, Wiestler OD, Dichgans J, Kanz L, Bamberg M, Weller M (2002) German Cancer Society Neuro-Oncology Working Group NOA-03 multi-center trial of single-agent high-dose MTX for primary central nervous system lymphoma. Ann Neurol 51:247–252

Mead GM, Bleehen NM, Gregor A, Bullimore J, Shirley D, Rampling RP, Trevor J, Glaser MG, Lantos P, Ironside JW, Moss TH, Brada M, Whaley JB, Stenning SP (2000) A Medical Research Council randomized trial in patients with primary central non-Hodgkin's lymphoma. Cerebral radiotherapy with and without cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy. Cancer 89:1359–1370

Nelson DF (1999) Radiotherapy in the treatment of primary central nervous system lymphoma (PCNSL). J Neuro-Oncol 43:241–247

Nelson DF, Martz KL, Bonner H, Nelson JS, Newall J, Kerman HD, Thomson JW, Murray KJ (1992) Non-Hodgkin's lymphoma of the brain: can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315. Int J Radial Oncol Biol Phys 23:9–17

O'Brien P, Roos D, Pratt G, Liew K, Barton M, Poulsen M, Olver I, Trotter G (2000) Phase II multicenter study of brief single-agent MTX followed by irradiation in primary CNS lymphoma. J Clin Oncol 18:519–526

O'Neill BP, O'Fallon JR, Earle JD, Colgan JD, Earle JD, Krigel RL, Brown LD, McGinnis WL (1999) Primary central nervous system non-Hodgkin's lymphoma (PCNSL): survival advantages with combined initial therapy? A final report of the North Central Cancer Treatment Group (NCCTG) study 86–72–52. Int J Radiat Oncol Biol Phys 43:559–563

Reni M, Ferreri AJM, Garancini MP, Villa E (1997) Therapeutic management of primary central nervous system lymphoma in immunocompetent patients: results of a critical review of the literature. Ann Oncol 8:227–234

Reni M, Ferreri AJ, Guha-Thakurta N, Blay JY, Dell'Oro S, Biron P, Hochberg FH (2001) Clinical relevance of consolidation radiotherapy and other main therapeutic issues in primary central nervous system lymphomas treated with upfront high-dose MTX. Int J Radiat Oncol Biol Phys 51:419–425

Schultz C, Scott C, Sherman W, Donahue B, Fields J, Murray K, Fisher B, Abrams R, Meis-Kindblom J (1996) Preirradiation chemotherapy with cyclophosphamide doxorubicin, vincristine, and dexamethazone for primary CNS lymphomas: initial report of Radiation Therapy Oncology Group protocol 88–06. J Clin Oncol 14:556–564

Shibamoto Y, Tsutsui K, Dodo Y, Yamabe H, Shima N, Abe M (1990) Improved survival rate in primary intracranial lymphoma treated by high-dose radiation and systemic vincristine-doxorubicin-cyclophosphamide-prednisolone chemotherapy. Cancer 65:1907–1912

Shibamoto Y, Sasai K, Oya N, Hiraoka M (1999) Systemic chemotherapy with vincristine, cyclophosphamide, doxorubicin and prednisolone following radiotherapy for primary central nervous system lymphoma: a phase II study. J Neurooncol 42:161–167

Shibamoto Y, Hayabuchi N, Hiratsuka J, Tokumaru S, Shirato H, Sougawa M, Oya N, Uematsu Y, Hiraoka M (2003) Is whole-brain irradiation necessary for primary central nervous system lymphoma? Patterns of recurrence following partial-brain irradiation. Cancer 97:128–133

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特集：固形腫瘍の新しい治療

小児固形腫瘍・脳腫瘍の放射線治療

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要旨

放射線治療の技術的進歩としての三次元放射線治療（Three-dimensional conformal radiotherapy：3D-CRT）について，その構成要素および治療計画について紹介する．さらに，応用としての脳腫瘍や軟部組織腫瘍に対する臨床試験における放射線治療の実際を紹介する．

Key Words

radiation therapy
three-dimensional conformal radiotherapy
clinical trial
pediatric

はじめに

放射線治療の歴史は1895年のレントゲンによるX線の発見に始まるとされる．その後の放射線生物学・物理学の研究の発展と治療技術・装置の開発により，悪性腫瘍治療の3本柱のひとつとして広く応用されている．その特徴としては，①機能・形態の温存，②治療対象部位の制限が少ない，③合併症を有する患者や高齢者など対象患者の制限が少ない，の3点があげられている．しかし，これらの特徴はさらなる局所制御率の向上と有害反応の軽減があってこそ，臨床においてその有用性を発揮すると考えられる．

本稿では，放射線治療の技術的進歩として三次元放射線治療（Three-dimensional conformal radiotherapy，以下3D-CRTと略す）について述べる．さらに，その応用としての脳腫瘍や，軟部組織腫瘍に対する臨床試験における放射線治療の実際を紹介する．

三次元放射線治療計画

3D-CRTとは，放射線腫瘍医の追究する理想をCTやMRI，PETなどの放射線診断学と治療装置に関するテクノロジーの進歩が支え，実現した治療方法といえよう．その応用と成果は重

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要臓器に囲まれた，従来の二次元放射線治療では正常組織の有害反応ゆえに，放射線治療にとって困難の多かった領域，脳腫瘍・頭頸部腫瘍や骨盤腫瘍などの治療で，まずその成果が報告され，諸臓器の治療でその応用が進行している．

3D-CRTとは，永田らによれば[1]“薄い間隔で撮像された複数のCT画像に基づいて，正確なターゲット領域とリスク臓器体積（organs at risk volume）の幾何学的配置を決定する．それらを画像処理した種々の三次元画像を用いたうえで，適切な三次元線量計算に基づき正確な放射線治療計画を行う”と定義している．従来の放射線治療が“照射方向と照射野辺縁の設定をしてからターゲット内の線量分布を確認する”のに対し，“ターゲットと関連正常臓器の輪郭を設定してから，計算された三次元画像を利用することによって，照射方向や照射門数を決定する”ように，治療計画は大きな変化をとげた．

さらに，強度変調放射線治療（Intensity-Modulated Radiotherapy：IMRT）では“ターゲットの内部の詳細な照射線量と各種関連リスク臓器の詳細な容積線量を定義（prescribe）した後に，治療計画装置によって最適な照射方法を決定する”こととなり，望ましい線量分布の実現が，治療計画装置の進歩により可能となりつつある．

もっとも重要であるターゲットの決定において，治療計画を施行する放射線腫瘍医間における認識の差異を最小化するために，国際的な用語の統一が行われてきた．現在使用されているICRU Report 62[2]による表記では表1に示す用語が使用されている．放射線治療にかかわるターゲットの決定においては，ICRU Report 62に従い対象を決定していくが（図），その容積はGTV＜CTV＜ITV＜PTVの順に大きくなり，対象とする疾患やその組織型・分化度，臨床病期などにより異なる設定が必要となった．たとえば，聴神経腫瘍など良性腫瘍や動静脈奇形，転移性脳腫瘍に対する定位放射線照射においては，CTVはGTVに限りなく近づくこととなる．ターゲットの決定において重要な役割を果すのは画像診断であり，CTやMRI，PETにとどま

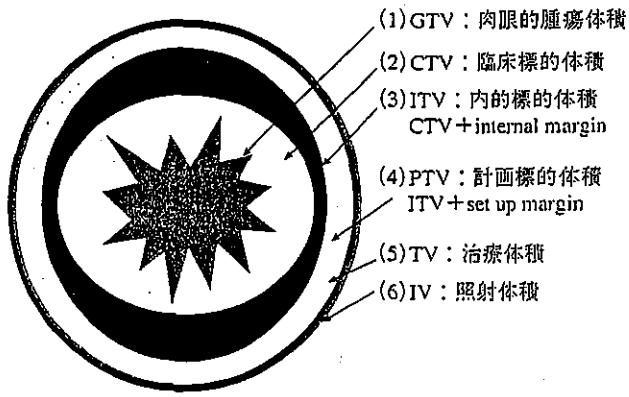

図　ICRU Report 62に基づく放射線治療にかかわるターゲットの決定

表1　放射線治療にかかわるターゲットの決定

GTV：Gross Tumor Volume 肉眼的腫瘍体積	画像や触診で明らかに腫瘍が存在すると判断される領域の体積
CTV：Clinical Target Volume 臨床標的体積	GTV＋顕微鏡的進展範囲
ITV：Internal Target Volume 内的標的体積	CTVに臓器移動に対するmarginを加えた標的体積 CTV＋IM
PTV：Planning target volume 計画標的体積	ITVに患者およびビームの位置合わせに関する不正確さを考慮した領域 ITV＋SM

IM：internal margin：呼吸移動や腸管のガスによる影響など体内臓器の移動にかかわるmargin
SM：set up margin：毎回の治療における設定誤差にかかわるmargin

らずMolecular ImagingやFunctional Imagingの応用で腫瘍の浸潤・残存範囲や正常組織の機能を考慮した治療計画の可能性が実現されている．

治療計画の選択においては，従来は治療計画を行って線量分布を計算し（forward planning），その比較により最適治療計画を選択していた．近年，線量を設定したあとに治療計画を最適化するinversed planningが実現している．治療計画の比較には，線量分布図以外に容積線量ヒストグラム（Dose-Volume Histogram：DVH）が使用され，ターゲットや周囲の重要なリスク臓器の全容積中の照射線量が表示されている．TCP（tumor control probability）やNTCP（normal tissue complication probability）の計算も可能である．

3D-CRTは，ターゲットへの線量の集中を可能とし有害反応の軽減をもたらしうるが，総線量の増加により局所制御率の向上が望みうる領域においては，局所制御率をも期待させることとなった．3D-CRTには日本で開発された原体照射や，定位放射線照射，non-coplanar固定多門三次元照射，わが国で開発された歳差運動照射，アメリカで開発されたCyber-knifeなども含まれる．森田ら[3]によれば原体照射とは，“光子線ないし粒子線ビームを用いた二次元ないし三次元方向からの回転運動照射で，どの照射方向から見ても照射野形状がターゲット形状に一致している照射法”と定義されている．CT-simulator，治療計画装置，照射野形状を作成するためのマルチリーフコリメーター（Multi-leaf Collimator：MLC）を搭載した治療装置とネットワークの構築により，原体照射は可能となり，多くの施設に普及している．non-coplanar固定多門三次元照射は，体軸と垂直な方向以外から照射する三次元照射方法で，体軸にそって重要な臓器がとりまくように存在する脳腫瘍や骨盤内腫瘍では，リスク臓器体積の照射線量の軽減に有用である．

定位放射線照射（stereotactic irradiation：STI）とは，小病変に対し多方向から放射線を集中させる方法であり，通常の放射線治療に比較し周囲正常組織の線量を極力減少させつつ，病巣に高線量を集中させる治療である．定位放射線治療は，ガンマナイフに代表される1回で照射する定位手術的照射（stereotactic radiosurgery：SRS）と，分割して照射する定位放射線治療（stereotactic radiotherapy：SRT）に大別される．定位的であるという条件としては，①患者あるいはそれに固定された座標系において照射中心を固定精度内に納めるシステムであること，②定位型手術枠または着脱式固定具を用いた方法であること，③固定装置の照射中心精度が1～2 mm以内であること，④治療中を通じて上記固定精度を保つこと，などが考えられている．脳以外の体幹部定位放射線治療に関しては，①照射装置の照射中心精度が±1 mm以内であること，②治療セットアップの精度が左右，背腹方向それぞれに±5 mmを保ち，頭尾方向に±10 mmを保つ機能を有することが，体幹部定位放射線照射研究会から提言されている．

ガンマナイフは201個のCo^{60}より出るγ線がその中心に集束するよう設計されている．頭部固定用のLeksell stereotactic frameを用い，機械的精度を0.1 mmとする高精度の放射線治療である．SRSは一般放射線治療用の直線加速器（Linac）を用いることにより普及し，より均一な線量分布や大きな照射野が可能となった．Lars Leksellらの治療体積が小さければ逆比例して耐容線量が上り，高線量1回投与が可能となる[4]という理論がSRSの裏づけとなっている．よってその特徴を活かすためにも，対象病変は3 cm以下とされる場合が多い．

SRTは分割照射により治療可能比（正常組織の耐容線量/腫瘍の致死線量）が高まるという放射線生物学のLQ（linear quadratic）モデルを背景としている．1回線量や照射回数などの治療

スケジュールが腫瘍により適切に設定可能であるが，精度がSRSより劣る可能性があり，さまざまな工夫が精度管理のためになされている．

定位放射線照射の治療成績は，局所制御において手術と同等と考えられている．有害反応はFlickingerら[5]の動静脈奇形に関する検討より，その発生頻度が照射部位によることが明らかとなり，照射部位や脳神経との位置関係により1回線量の低減が推奨されている．脳転移の治療は，全脳照射と手術に加え定位放射線照射の登場により，その選択の多様性と妥当性に関する検討がさまざまに行われている．

脳腫瘍の三次元放射線治療計画

小児の脳腫瘍ではAstrocytoma星細胞腫がもっとも多く，ついでMedulloblastoma髄芽腫，上衣腫やGerm Cell Tumorが続く．小児の脳腫瘍においては，手術や化学療法の併用による集学的治療の一環として放射線治療が応用されるが，遅発性放射線反応の軽減が重要な課題である．神経機能と神経内分泌機能の発達への影響を軽減するために，照射体積と照射線量の最適化をめざした試みがなされている．

Children's Oncology Group（COG）のLow-

表2 Intergroup Rhabdomyosarcoma Study Groupの臨床試験における横紋筋肉腫の放射線治療 *Guidelines*

臨床試験	総線量	1回線量/ターゲット/タイミング	化学療法と結果
IRS I (1972～78)	age < 3yrs = 40 Gy age < 6yrs and < 5 cm = 50 Gy age > 6 yrs or > 5 cm = 55 Gy age > 6 yrs and > 5 cm = 60 Gy	1.5～2.25 Gy/Fr/day whole muscle bundle or tumor + margin *no difference in local control* Immediately: Groups I and II Week 6: Groups III and IV	VAC, VA, VACA Overall 5-year survival 55%
IRS II (1978～84)	Group I = no RT. Group II = 40-45 Gy. Group III : age < 6yrs and < 5 cm = 40-45 Gy age > 6 yrs or > 5 cm = 45-50 Gy age > 6 yrs and > 5 cm = 50-55 Gy	1.5～2.25 Gy/Fr/day GTV + 2 cm *Week 0: Group II* Week 6: Groups III and IV	VAC, VA, VadrC-VAC Overall 5-year survival 63% Botryoid89%, Embryonal 68%, Alveolar 52%, Other 55%
IRS III (1984～88)	Grp I FH-no RT. Grp I UH/II-41.4 Gy. Group III varied by age, size but all < 50.4 Gy.	GTV + 2 cm Day 0: PM with CN palsy, BOS erosion, intracranial extension. Week 2: Group II FH/Group III orbit and H/N. Week 6: all others	VAC, VA, VadrC-VAC, *VAadr* CDDP/VP16 VadrC-VAC + CDDP Overall 5-year survival 71%
IRS IV (1991～97)	Group I, Stage 1/2-no RT. Group I, Stage3/II-41.4 Gy CRT. Group III randomized to 50.4 Gy CRT vs 59.4 Gy HRT (1.1 Gy BID)	GTV + 2 cm Day 0: PM with CN palsy, BOS erosion, intracranial extension. Week 12: all others	VA, VAC, VAI, VIE Overall 3-yr FFS 77% No difference in local control with CRT vs HRT.
IRS V (1999～04)	Experimental dose reductions for selected patients: Group I alveolar/undifferentiated 36 Gy Group II N0: 36 Gy Group III orbit/eyelid: 45 Gy Group III second look surgery negative margins: 36 Gy microscopically + margins: 41.4 Gy Group III requiring 50.4Gy: volume reduction to initial GTV + 5 mm at 36 Gy if N0, and at 41.4 Gy if N+	GTV + 2 cm Day 0: PM with intracranial extension only Week 3: low risk, week 12: intermediate, week 15: high risk	Low risk: VA, VAC Intermediate Risk: VAC vs VAC/VTC

Grade Glioma に対する臨床試験においては[6)~7)]，3D-CRT が応用され線量分布の改善による遅発性放射線反応の軽減が図られている．小児の Glioma の治療においては，発達への影響を考慮して放射線治療の適応を躊躇する傾向にあったが，3D-CRT による正常組織への影響の軽減によって，放射線治療のより積極的な応用が検討されており，今後の臨床試験結果が注目される．

Medulloblastoma の集学的治療においては，Craniospinal Irradiation（CSI）が標準治療であり，high risk 群で 36 ～ 40 Gy，average risk 群で 18 ～ 24 Gy 程度の CSI と，54 Gy 前後の後頭蓋窩への照射が組み合せて施行されている．Children's Cancer Group（CCG）で施行された CCG9892 では，化学療法の併用により CSI の線量を低減する臨床試験が施行され，その効果が確認された[8)]．その後の CCG9961 では average risk 群では，化学療法併用で 23.4Gy の CSI と 54 ～ 55.8 Gy の後頭蓋窩への照射が施行された．さらに COG では，average risk 群で CSI の線量の低減とともに，3D-CRT を応用して原発巣への追加照射の照射野を，後頭蓋窩より腫瘍床＋margin へ限局する臨床試験が提案されている．総線量や照射野以外に考慮されるべき放射線治療因子として，治療期間の延長が治療効果に与える影響が delCharco らにより報告されている[9)]．5 年後頭蓋窩制御率が照射期間 45 日以内で 89％であったのに対し，45 日を超えると 68％と低下し（$p = 0.01$），5 年無再発生存率が照射期間 45 日以内で 76％であったのに対し，45 日を超えると 43％と低下していた（$p = 0.004$）．放射線治療の中断の治療効果への影響は，International Society of Paediatric Oncology（SIOP）と United Kingdom Children's Cancer Study Group（UKCCSG）の臨床試験でも指摘されており[10)]，今後臨床試験を検討する際に十分認識すべきと考える．

軟部組織腫瘍の三次元放射線治療計画

横紋筋肉腫の治療は，1970 年代より集学的治療が積極的に進められており，臨床試験の結果により治療成績の改善が進められてきた分野の一つである．表 2 に，Intergroup Rhabdomyosarcoma Study Group により計画されてきた集学的治療の経過を示す[11)~15)]．放射線治療は，化学療法の併用薬剤の変化とともに総線量の軽減が図られた．一方で，IRS-Ⅳ では Group Ⅲ において，50.4 Gy の通常分割照射と 59.4 Gy の多分割照射（1.1 Gy を 1 日 2 回照射）が比較検討された．Donaldson らの報告では[16)]，failure-free survival（FFS）および overall survival（OS）と

表 3　IRS-V 放射線治療 Guidelines による正常組織の耐容線量と DVH による評価

正常組織		通常照射による上限	DVH
頭部	脳	全脳 3 歳未満 23.4Gy	不要
		全脳 3 歳以上 30.6Gy	不要
	左右網膜		必要
	左右視神経	46.8Gy	必要
	視神経交叉	46.8Gy	必要
	下垂体		必要
	角膜	41.4Gy	不要
	水晶体	14.4Gy	不要
	涙腺	41.4Gy	不要
	蝸牛		必要
頸部	甲状腺		必要
胸部	肺	両肺 14.4Gy	必要
	心臓	全心臓 30.6Gy	必要
腹部	肝臓	全肝 23.4Gy	必要
	腎臓	両側で 14.4Gy	必要
	消化管	一部 45Gy	不要
	全腹—骨盤	30Gy（1.5Gy/回）	不要
骨盤	膀胱		必要
	直腸		必要
脊髄	脊髄	45Gy	必要

この耐容線量は化学療法と併用した場合の有害事象の増強することが考慮されていない．大量化学療法併用時の耐容線量はさらに低いことが予想され，両側腎，肝臓全体，両側肺，全脳，脊髄，心臓全体への照射の場合はさらに 5 Gy 程度低い線量を上限とすることが望ましいと考えられる

もに通常分割照射と多分割照射で有意差を認めなかった．現在進行中のIRS-Vでは，1日1回1.8 Gy/回の通常分割照射が採用され，新たにIMRTを含む3D-CRTが推奨されており，小線源治療や陽子線治療を含む正常組織の線量を軽減した放射線治療が，放射線治療ガイドラインに取り入れられている．表3にIRS-Vの放射線治療Guidelinesにおいて示されている正常組織の耐容線量とDVHによる評価が必要な正常組織を示す．今後，臨床試験の結果によるevidenceの蓄積により，さらに適切な照射線量の設定が可能となることが期待されている．

おわりに

小児の悪性腫瘍において，放射線治療の技術的進歩により応用範囲が拡大してきている．小児に対する放射線治療は，リスク臓器の線量に細心の注意をはらった治療が実施されるべきであり，さらに有害事象の経過観察が長期に必要である．

今後，線量分布の最適化による治療成績の向上と有害事象の軽減や，分割照射方法や化学療法や手術との併用の工夫に関するevidenceの蓄積が求められている．

●文　献

1) 永田　靖，平岡真寛：三次元放射線治療計画(IMRTを含む)．平岡真寛，笹井啓資，井上俊彦・編，放射線治療マニュアル，中外医学社，東京，45-60, 2001
2) International Commission on Radiation Units and Measurements Report 62; Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU Report 50). ICRU Publications, 1999
3) Morita K: Conformal RT and conformation RT. Int J Radiation Oncology Biol Phys 48: 431-434, 2000
4) Leksell L: Stereotactic radiosurgery. J Neurol Neurosurg Psychiatry 46 (9): 797-803, 1983
5) Flickinger JC, Kondziolka D, Maitz AH et al.: Analysis of neurological sequelae from radiosurgery of arteriovenous malformations: how location affects outcome. Int J Radiat Oncol Biol Phys 40 (2): 273-278, 1998
6) Wisoff JH, Sanford A, Sposto R et al.: Low grade gliomas of childhood: Impact of surgical resection-A report from the Children's Oncology Group protocol CCG-9891/POG-9130. J Neurosurg 96: 427-428, 2002
7) Shaw EG, Wisoff JH: Prospective clinical trials of intracranial low-grade glioma in adults and children. Neuro-Oncology, (in Press)
8) Packer RJ, Goldwein J, Nicholson HS et al.: Treatment of children with medulloblastomas With Reduced-Dose craniospinal radiation therapy and adjuvant chemotherapy: A Children's Cancer Group Study J Clin Oncol 17: 2127-2136, 1999
9) DelCharco JO, Bolek TW, McCollough WM et al.: Medulloblastoma: Time-dose relationship based on a 30-year review. Int J Radiation Oncology Biol Phys 42: 147-154, 1998
10) Taylor RE, Bailey CC, Robinson K et al.: Results of a randomized study of preradiation chemotherapy versus radiotherapy alone for nonmetastatic medulloblastoma: The International Society of Paediatric Oncology/United Kingdom Children's Cancer Study Group PNET-3 Study J Clin Oncol 21: 1581-1591, 2003
11) Wolden SL, Anderson JR, Crist WM et al.: Indications for radiotherapy and chemotherapy after complete resection in Rhabdomyosarcoma: A Report From the Intergroup Rhabdomyosarcoma Studies I to III. J Clin Oncol 17: 3468-3475, 1999
12) Maurer H, Beltangady M, Gehan E et al.: The Intergroup Rhabdomyosarcoma Study-I: A final report. Cancer 61: 209-220, 1988
13) Maurer H, Gehan E, Beltangady M et al.: The Intergroup Rhabdomyosarcoma Study-II. Cancer 71: 1904-1922, 1993
14) Crist W, Gehan EA, Ragab AH et al.: The third Intergroup Rhabdomyosarcoma Study. J Clin Oncol 13: 610-630, 1995
15) Crist WM, Anderson JR, Meza JL et al.: Intergroup

rhabdomyosarcoma study-Ⅳ: Results for patients with nonmetastatic disease. J Clin Oncol 19: 3091-3102, 2001

16) Donaldson SS, Meza J, Breneman JC et al.: Results from the IRS-IV randomized trial of hyperfractionated radiotherapy in children with rhabdomyosarcoma-A report from the IRSG. Int J Radiation Oncology Biol Phys 51: 718-728, 2001

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