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Phase I study of cisplatin, vinorelbine, and concurrent thoracic radiotherapy for unresectable stage III non-small cell lung cancer

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To determine the recommended phase II dose of vinorelbine in combination with cisplatin and thoracic radiotherapy (TRT) in patients with unresectable stage III non-small cell lung cancer (NSCLC), 18 patients received cisplatin (80 mg/m^2) on day 1 and vinorelbine (20 mg/m^2 in level 1, and 25 mg/m^2 in level 2) on days 1 and 8 every 4 weeks for 4 cycles. TRT consisted of a single dose of 2 Gy once daily for 3 weeks followed by a rest of 4 days, and then the same TRT for 3 weeks to a total dose of 60 Gy. Fifteen (83%) patients received 60 Gy of TRT and 14 (78%) patients received 4 cycles of chemotherapy. Ten (77%) of 13 patients at level 1 and all 5 patients at level 2 developed grade 3–4 neutropenia. Four (31%) patients at level 1 and 3 (60%) patients at level 2 developed grade 3–4 infection. None developed ≥grade 3 esophagitis or lung toxicity. Dose-limiting toxicity was noted in 33% of the patients in level 1 and in 60% of the patients in level 2. The overall response rate (95% confidence interval) was 83% (59–96%) with 15 partial responses. The median survival time was 30.4 months, and the 1-year, 2-year, and 3-year survival rates were 72%, 61%, and 50%, respectively. In conclusion, the recommended dose is the level 1 dose, and this regimen is feasible and promising in patients with stage III NSCLC. (Cancer Sci 2004; 95: 691–695)

Stage III locally advanced non-small cell lung cancer (NSCLC) accounts for about 25% of all lung cancer cases.[1] Successful treatment of this disease rests on the control of both clinically apparent intrathoracic disease and occult systemic micrometastases, and therefore a combination of systemic chemotherapy and thoracic radiotherapy is indicated in many patients with good performance status and no pleural effusion.[2] Concurrent chemoradiotherapy is superior to the sequential approach, as shown by recent phase III trials in unresectable stage III NSCLC, in which the median survival time was 15.0 to 17.0 months in the concurrent arm and 13.3 to 14.6 months in the sequential arm, although acute esophagitis was more severe in the concurrent arm.[3–5] Chemotherapy regimens combined with simultaneous thoracic radiotherapy have consisted of cisplatin plus etoposide and cisplatin plus vinca alkaloids,[3,4] and a combination of cisplatin plus vindesine, with or without mitomycin, has been widely used in Japan.[5–8]

Vinorelbine, a new semisynthetic vinca alkaloid with a substitution in the catharanthine ring, interacts with tubulin and microtubule-associated proteins in a manner different from the older vinca alkaloids, and it more selectively depolymerizes microtubules in mitotic spindles.[9] Several randomized trials have shown vinorelbine to be more active against advanced or metastatic NSCLC than vindesine as a single agent or in combination with cisplatin.[10–13] Thus, incorporation of vinorelbine into concurrent chemoradiotherapy instead of vindesine is an important strategy for the treatment of locally advanced NSCLC. The objective of this study was to determine the maximum tolerated dose (MTD) and recommended dose of vinorelbine for phase II studies in combination with cisplatin, with or without mitomycin, and thoracic radiotherapy for patients with unresectable stage III NSCLC. We planned to start with the cisplatin and vinorelbine combination and then add mitomycin.

Patients and Methods

Patient selection. The eligibility criteria were: histologically or cytologically proven NSCLC; unresectable stage IIIA or IIIB disease; no previous treatment; measurable disease; tumor within an estimated irradiation field no larger than half the hemithorax; age between 20 years and 74 years; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1[14]; adequate bone marrow function (12.0×10^9/liter ≥white blood cell [WBC] count ≥4.0×10^9/liter, neutrophil count ≥2.0×10^9/liter, hemoglobin ≥10.0 g/dl, and platelet count ≥100×10^9/liter), liver function (total bilirubin ≤1.5 mg/dl and transaminase ≤twice the upper limit of the normal value), and renal function (serum creatinine ≤1.5 mg/dl and creatinine clearance ≥60 ml/min); and a PaO_2 of 70 Torr or more. Patients were excluded if they had malignant pleural or pericardial effusion, active double cancer, a concomitant serious illness, such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonia or lung fibrosis identified by a chest X-ray, chronic obstructive lung disease, infection or other diseases contraindicating chemotherapy or radiotherapy, pregnancy, or breast-feeding. All patients gave their written informed consent.

Pretreatment evaluation. The pretreatment assessment included a complete blood cell count and differential count, routine chemistry determinations, creatinine clearance, blood gas analysis, electrocardiogram, lung function testing, chest X-rays, chest computed tomographic (CT) scan, brain CT scan or magnetic resonance imaging, abdominal CT scan or ultrasonography, and radionuclide bone scan.

Treatment schedule. The dose levels and doses of each anticancer agent are shown in Table 1. Cisplatin and vinorelbine were administered at dose levels 1 and 2. It was planned to give cisplatin, vinorelbine, and mitomycin at dose levels 3–5, but because the MTD was determined to be dose level 2, dose levels 3–5 were not used. Cisplatin was administered on day 1 by intravenous infusion over 60 min together with 2500 to 3000 ml of fluid for hydration. Vinorelbine diluted in 40 ml of normal saline was administered by bolus intravenous injection on days 1 and 8. All patients received prophylactic antiemetic ther-

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apy consisting of a 5HT3-antagonist and a steroid. This chemotherapy regimen was repeated every 4 weeks for 4 cycles.

Thoracic radiotherapy with photon beams from a liniac or microtron accelerator with energy between 6 and 10 MV at a single dose of 2 Gy once daily given 15 times over 3 weeks was begun on day 2 of the first cycle of cisplatin and vinorelbine chemotherapy, and followed by a short rest period of 4 days. The same radiotherapy was begun on day 1 of the second cycle of chemotherapy to a total dose of 60 Gy. The clinical target volume (CTV) was based on conventional chest X-ray and CT scans, and included the primary lesion (CTV1), involved lymph nodes whose short diameter was 1 cm or larger (CTV2), and the ipsilateral pulmonary hilum and bilateral mediastinum area (CTV3). Anterior and posterior parallel opposed fields encompassed the initial planned target volume (PTV), consisting of CTV1–3 with the superior and inferior field margins extended to 1 to 2 cm and the lateral field margins extended to 0.5 cm for respiratory variation and fixation error. The boost PTV included only CTV1–2 based on the second CT scans with the same margins. The spinal cord dose was limited to 40 Gy by using oblique parallel opposed fields.

Toxicity assessment and treatment modification. Complete blood cell counts and differential counts, routine chemistry determinations, and a chest X-ray were performed once a week during the course of treatment. Acute toxicity was graded according to the NCI Common Toxicity Criteria version 2.0 issued in 1998, and late toxicity associated with thoracic radiotherapy was graded according to the RTOG Late Radiation Morbidity Scoring Schema.[15] Vinorelbine administration on day 8 was omitted if any of the following toxicities was noted: WBC count $<3.0\times10^9$/liter, neutrophil count $<1.5\times10^9$/liter, platelet count $<100\times10^9$/liter, elevated hepatic transaminase level or total serum bilirubin ≥grade 2, fever ≥38°C, or performance status ≥2. Subsequent cycles of chemotherapy were delayed if any of the following toxicities was noted on day 1: WBC count $<3.0\times10^9$/liter, neutrophil count $<1.5\times10^9$/liter, platelet count $<100\times10^9$/liter, serum creatinine level ≥1.6 mg/dl, elevated hepatic transaminase level or total serum bilirubin ≥grade 2, fever ≥38°C, or performance status ≥2. The doses of cisplatin and vinorelbine were reduced by 25% in all subsequent cycles if any of the following toxicities was noted: WBC count $<1.0\times10^9$/liter, platelet count $<20\times10^9$/liter, or grade 3 or severer non-hematological toxicity, except for nausea and vomiting. The dose of cisplatin was reduced by 25% in all subsequent cycles if the serum creatinine level was elevated to 2.0 mg/dl or higher. Thoracic radiotherapy was suspended if any of the following toxicities was noted: WBC count $<1.0\times10^9$/liter, platelet count $<20\times10^9$/liter, esophagitis ≥grade 3, fever ≥38°C, performance status ≥3, or PaO_2 <70 Torr. Thoracic radiotherapy was terminated if this toxicity persisted for more than 2 weeks. Granulocyte colony-stimulating factor support was used if the neutrophil count was $<0.5\times10^9$/liter for more than 4 days, the WBC count was $<1.0\times10^9$/liter, or febrile neutropenia ≥grade 3 was noted.

Dose-limiting toxicity, MTD, and recommended dose for phase II studies. The dose-limiting toxicity (DLT) was defined as a neutrophil count $<0.5\times10^9$/liter lasting 4 days or longer, febrile neutropenia ≥grade 3, platelet count $<20\times10^9$/liter, grade 3 or more severe non-hematological toxicity other than nausea and vomiting, and patient's refusal to receive subsequent treatment. Doses were escalated according to the frequency of DLT evaluated during the first and second cycles of chemotherapy and thoracic radiation. Six patients were initially enrolled at each dose level. If one or none of them experienced DLT, the next cohort of patients was treated at the next higher dose level. If 2 of the 6 patients experienced DLT, then 6 additional patients were enrolled at the same dose level to make a total of 12 patients. If 4 or fewer patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If 5 or more of the 12 patients experienced DLT, that level was considered to be the MTD. If 3 of the initial 6 patients experienced DLT, that level was considered to be the MTD. The recommended dose for phase II trials was defined as the dose preceding the MTD.

Response evaluation. Objective tumor response was evaluated according to the WHO criteria issued in 1979.[16] A complete response (CR) was defined as the disappearance of all known disease for at least 4 weeks with no new lesions appearing. A partial response (PR) was defined as an at least 50% decrease in total tumor size for at least 4 weeks without the appearance of new lesions. No change (NC) was defined as the absence of a partial or complete response with no progressive or new lesions observed for at least 4 weeks. Progressive disease was defined as a 25% or greater increase in the size of any measurable lesion or the appearance of new lesions.

Study design, data management, and statistical considerations. This study was designed as a phase I study at two institutions, the National Cancer Center Hospital and Kanagawa Cancer Center. The protocol and consent form were approved by the Institutional Review Board of each institution. Registration was conducted at the Registration Center. Data management, periodic monitoring, and the final analysis were performed by the Study Coordinator. A patient accrual period of 24 months and a follow-up period of 18 months were planned. Overall survival time and progression-free survival time were estimated by the Kaplan-Meier method.[17] Survival time was measured from the date of registration to the date of death due to any cause. Progression-free survival time was measured from the date of registration to the date of disease progression or death. Patients who were lost to follow-up without event were censored at the date of their last known follow-up.

Table 1. Dose level and the dose of each anticancer agent

Dose level	Cisplatin (mg/m²)	Vinorelbine (mg/m²)	Mitomycin (mg/m²)
−1	80	15	—
1	80	20	—
2	80	25	—
3	80	15	8
4	80	20	8
5	80	25	8

Results

Registration and characteristics of the patients. From October 1999 to August 2000, 13 patients were registered at dose level 1 and 5 patients at dose level 2. The detailed demographic characteristics of the patients are listed in Table 2. All patients had unresectable IIIA-N2 or IIIB disease. One of the 6 patients enrolled at dose level 1 developed bacterial meningitis during the second cycle of chemotherapy, and that case is described in detail elsewhere.[18] We did not include it in the assessment of DLT, because the bacterial meningitis was not specifically related to treatment. We registered another patient at the same dose level, and 2 cases of DLT were noted among the initial 6 patients evaluable for DLT. We added another 6 patients, and DLT was noted in 4 of the 12 patients registered at the dose level 1. Of the 5 patients registered at level 2, 3 patients developed DLT. This dose level was determined to be the MTD, and patient accrual to this study was terminated.

Treatment delivery. Treatment delivery was generally well maintained, and it did not differ between the two dose levels (Table 3). Full dose (60 Gy) thoracic radiotherapy was completed in 77% and 100% of the patients at dose levels 1 and 2,

Table 2. Patients' characteristics

		Median (range)	N (%)
Number of patients			18
Gender	male		16 (89)
	female		2 (11)
Age	median (range)	59 (48–69)	
PS	0		4 (22)
	1		14 (78)
Body weight loss	<5%		12 (67)
	5–9%		4 (22)
	≥10%		2 (11)
T-factor	1		1 (6)
	2		6 (33)
	3		7 (39)
	4		4 (22)
N-factor	2		11 (61)
	3		7 (39)
Clinical stage	IIIA		9 (50)
	IIIB		9 (50)
Histology	adenocarcinoma		14 (78)
	squamous cell carcinoma		3 (17)
	adenosquamous carcinoma		1 (6)

Table 3. Treatment delivery

	Dose level 1 (N=13)	Dose level 2 (N=5)
	N (%)	N (%)
Initial irradiation field (cm^2) median (range)	171 (128–529)	182 (128–248)
Total dose of radiotherapy (Gy)		
60	10 (77)	5 (100)
50–59	1 (8)	0
<50	2 (15)	0
Delay of radiotherapy (days)[1)]		
<5	6 (60)	3 (60)
5≤	4 (40)	2 (40)
Number of chemotherapy cycles		
4	10 (77)	4 (80)
3	0	1 (20)
2	2 (15)	0
1	1 (8)	0
Omission of vinorelbine administration on day 8		
0	9 (69)	2 (40)
1	4 (31)	2 (40)
3	0	1 (20)

1) Evaluated in patients who received 60 Gy radiotherapy (N=15).

respectively. Delays in radiotherapy evaluated in patients who completed the full course of radiotherapy amounted to less than 5 days in 60% of the patients at both levels. Full cycles (4 cycles) of chemotherapy were administered to 77% and 80% of the patients at dose levels 1 and 2, respectively, but vinorelbine administration on day 8 was more frequently omitted at dose level 2 (Table 3).

Toxicity, MTD, and the recommended dose for phase II trials. Acute severe toxicity was mainly hematological (Table 4). Grade 3–4 leukopenia and neutropenia were noted in 77% and 100% of the patients at dose levels 1 and 2, respectively. Grade 3 anemia was observed in 23% and 20% of the patients at dose levels 1 and 2, respectively, but no blood transfusions were required. Thrombocytopenia was mild. Grade 4 transaminase elevation was observed in 1 patient during the first cycle of chemotherapy, but no subjective manifestations associated with liver dysfunction were noted. Chemotherapy was discontinued and the transaminases quickly decreased to within their normal ranges. Transient asymptomatic grade 3 hyponatremia was noted in 1 patient. Grade 3–4 infection was noted in 7 patients. Bacterial meningitis unassociated with neutropenia developed on day 6 of the second cycle of chemotherapy in 1 patient.[18] The other grade 3–4 infections were all associated with neutropenia. Esophagitis was mild in this study, and no grade 3–4 esophagitis was noted. No deaths occurred during or within 30 days of therapy.

DLT was noted in 4 of the 12 (33%) evaluable patients at dose level 1, and in 3 of the 5 (60%) at dose level 2. Six of these 7 DLTs were grade 3–4 infection associated with neutropenia, and the other 1 was grade 4 transaminase elevation. Thus, we determined that dose level 2 was the MTD, and dose level 1 was recommended as the dose for phase II trials.

Table 4. Acute toxicity

Toxicity	Dose level 1 (N=13), Grade					Dose level 2 (N=5), Grade				
	1	2	3	4	3–4 (%)	1	2	3	4	3–4 (%)
Hematological										
Leukopenia	0	2	9	1	(77)	0	0	4	1	(100)
Neutropenia	1	1	7	3	(77)	0	0	1	4	(100)
Anemia	4	6	3	0	(23)	2	2	1	0	(20)
Thrombocytopenia	1	2	0	0	(0)	1	0	0	0	(0)
Non-hematological										
AST	2	0	0	1	(8)	1	0	0	0	(0)
ALT	7	0	0	1	(8)	0	1	0	0	(0)
Total bilirubin	2	1	0	0	(0)	2	0	0	0	(0)
Creatinine	2	2	0	0	(0)	1	0	0	0	(0)
Hyponatremia	6	0	1	0	(8)	1	0	0	0	(0)
Infection	1	3	2	2	(31)	0	0	3	0	(60)
Nausea	4	1	0	0	(0)	3	0	0	0	(0)
Diarrhea	0	1	0	0	(0)	0	0	0	0	(0)
Stomatitis	2	0	0	0	(0)	0	2	0	0	(0)
Esophagitis	6	1	0	0	(0)	4	0	0	0	(0)
Sensory neuropathy	2	0	0	0	(0)	0	0	0	0	(0)

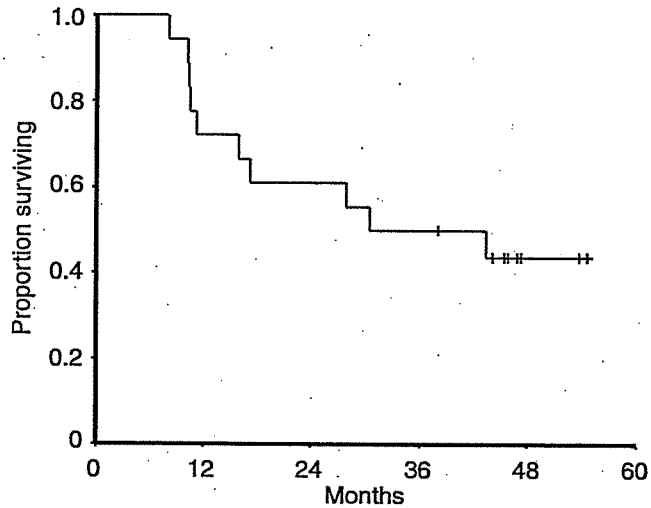

Fig. 1. Overall survival in 18 patients. The median (range) follow-up period of censored cases has been 35.4 (32.0–43.4) months, and the median overall survival time has not yet been reached.

Late lung toxicity associated with thoracic radiotherapy was grade 3 in 1 (6%) patient, grade 2 in 4 (22%) patients, and grade 1 in 8 (44%) patients. No late esophageal toxicity was noted.

Objective responses, relapse pattern, and survival. All patients were included in the analyses of tumor response and survival. No CR, 15 PRs, and 1 NC were noted, and the overall response rate (95% confidence interval) was 83% (59–96%). Relapse was noted in 12 (67%) of 18 patients. Initial relapse sites were locoregional alone in 5 (28%) patients, locoregional and distant in 3 (17%) patients, and distant alone in 4 (22%) patients. Brain metastasis was detected in 5 patients, and the brain was the most frequent site of distant metastasis. The median progression-free survival time was 15.6 months, and the median overall survival time was 30.4 months. The 1-year, 2-year, and 3-year survival rates were 72%, 61%, and 50%, respectively (Fig. 1).

Discussion

The combination of cisplatin, vindesine, and mitomycin with concurrent thoracic radiotherapy has been shown to yield an encouraging survival outcome, a median survival time of 17–19 months, and a 5-year survival rate of 16% in patients with unresectable stage III NSCLC.[5,7,8] A Japanese randomized trial revealed that replacement of vindesine by vinorelbine in combination with cisplatin and mitomycin yielded a promising response rate (57% versus 38%, $P=0.025$) and median survival time (15 months versus 11 months, $P<0.01$) in patients with stage IIIB or IV NSCLC.[13] Thus, the combination of cisplatin, vinorelbine, and mitomycin is a chemotherapy regimen with potential for combination with concurrent thoracic radiotherapy. The present study, however, showed that a DLT developed in 60% of patients who received cisplatin and vinorelbine 25 mg/m^2 days 1 and 8 (level 2), and since the DLTs were associated with myelosuppression, which is the major critical toxicity of mitomycin, we concluded that it would be impossible to incorporate mitomycin into this regimen.

The recommended doses of vinorelbine of 20 mg/m^2 on days 1 and 8 and cisplatin of 80 mg/m^2 on day 1 repeated every 4 weeks in this study are comparable to the doses used in the CALGB (vinorelbine 15 mg/m^2 on days 1 and 8 and cisplatin 80 mg/m^2 on day 1 repeated every 3 weeks),[19,20] and the Czech Lung Cancer Cooperative Group (vinorelbine 12.5 mg/m^2 on days 1, 8, and 15 and cisplatin 80 mg/m^2 on day 1, repeated every 4 weeks),[21] but lower than in a Mexican study (vinorelbine at 25 mg/m^2 on days 1 and 8 and cisplatin 100 mg/m^2 on day 1, repeated every 3 weeks).[22] These recommended doses are also lower than expected when compared with the recommended vinorelbine dose combined with cisplatin for metastatic NSCLC (vinorelbine 30 mg/m^2 on days 1 and 8 and cisplatin 80 mg/m^2 on day 1, repeated every 3 weeks),[23] and when compared with the results of vindesine, cisplatin, and mitomycin combined with thoracic radiotherapy, where the full doses can be administered concurrently.[8] Thus, vinorelbine can be safely administered with cisplatin and concurrent thoracic radiotherapy at a maximum dose of two-thirds the optimal dose without radiotherapy.

The results for response and survival in this study, however, were very encouraging. This may have been attributable to patient selection bias, but the percentage of patients who had stage IIIB disease in this study was similar to the percentage in the CALGB randomized phase II study.[20] In addition, 33% of the patients in this study had ≥5% body weight loss, whereas only 7% of the patients did in that study.[20] The median survival time was 30.4 months and exceeded the results of concurrent

chemoradiotherapy with old drug combinations that yielded a median survival time of 15–19 months.[3–8] Thus, it could be argued that the combination of cisplatin and vinorelbine is more active for locally advanced NSCLC than the older drug combinations, although there have not been any randomized trials comparing this regimen with old drug combinations in combination with thoracic radiotherapy in patients with stage III NSCLC. Our results also seem better than those of other trials using concurrent cisplatin, vinorelbine, and thoracic radiotherapy, in which the median survival time was 13 to 18 months.[20,22] Those trials used induction chemotherapy followed by chemoradiotherapy. Since the response rate to induction chemotherapy is no more than 40%, induction chemotherapy may be disadvantageous. This issue is being evaluated in an on-going CALGB phase III trial.

Severe esophagitis and pneumonitis have been DLTs in many trials of concurrent chemoradiotherapy, but neither was observed in this study. Nevertheless, since the occurrence of these non-hematological toxicities associated with thoracic radiotherapy is sporadic, the sample size in this study may have been too small to detect them. Thus, careful observation for these toxicities is needed in further phase II and phase III trials to definitely establish the safety profile of this regimen.

In conclusion, cisplatin and vinorelbine chemotherapy combined with concurrent full-dose thoracic radiotherapy is feasible, and the recommended dose of vinorelbine for phase II trials is 20 mg/m^2 on days 1 and 8 repeated every 4 weeks. This regimen was highly active in patients with stage III NSCLC.

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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

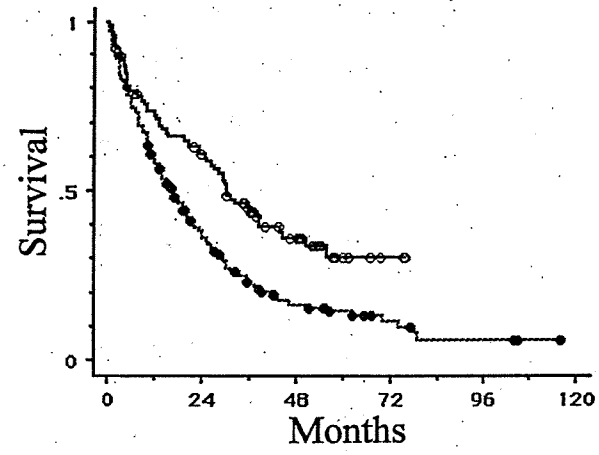

Fig. 1 Survival curves for patients with primary central nervous system lymphoma treated between 1985 and 1994 (- - -●- - -) and for those treated between 1995 and 1999 (____○____). The difference was significant ($P = 0.0003$)

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	Normal	49	22	31	0.17	50	55.5	43	0.0084
dehyrdogenase	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	< 40	61	24	22	0.025	38	32	26	0.83
(Gy)	≥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

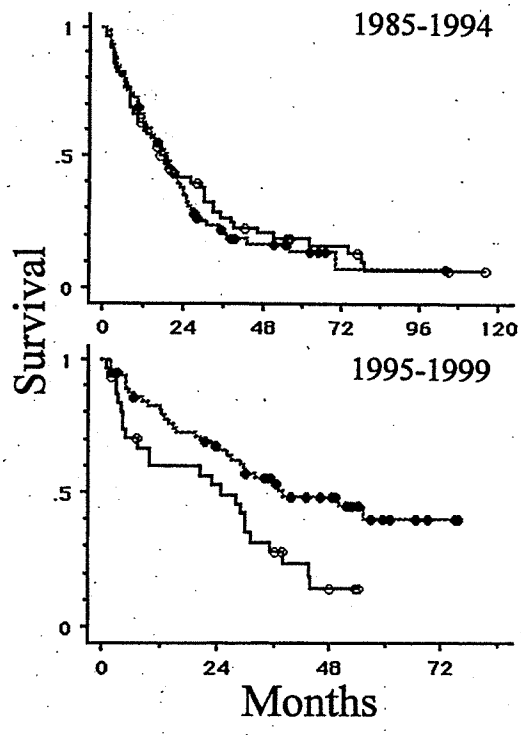

Fig. 2 Survival curves according to the treatment modality. _____O_____ : patients treated with radiation alone, - - -●- - - : patients treated with radiation and chemotherapy. The difference was significant in the group of patients treated between 1995 and 1999 (upper panel, $P = 0.63$; lower panel,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

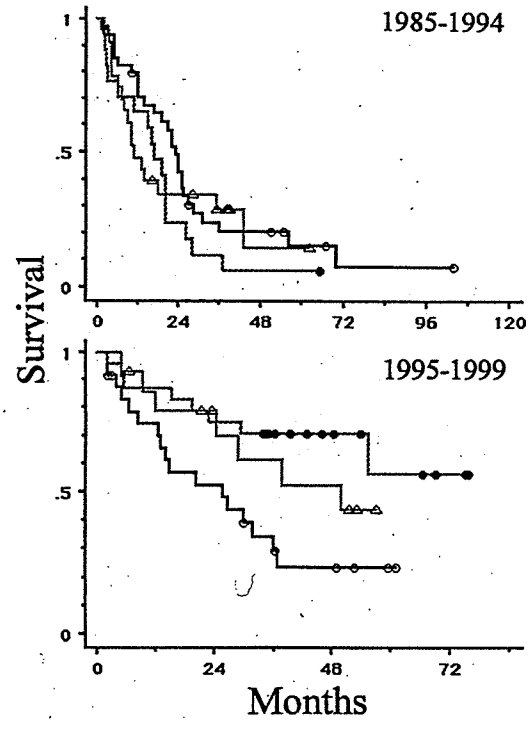

Fig. 3 Survival curves according to chemotherapy regimens. _____O_____ : cyclophosphamide, vincristine, prednisolone ± doxorubicin, - - -●- - - : methotrexate-containing regimens, - - -△- - - : other regimens. The difference among the curves was significant in the group of patients treated between 1995 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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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

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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

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

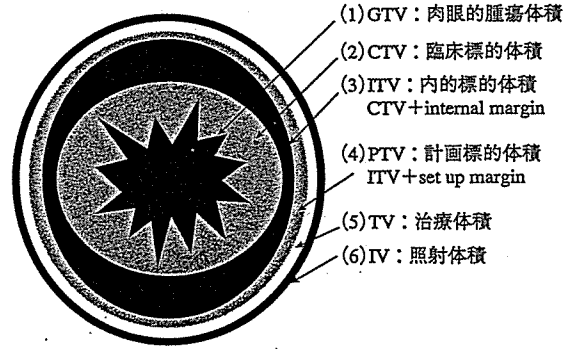

図　ICRU Report 62に基づく放射線治療にかかわるターゲットの決定

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
耳		必要
頭部：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．

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5 放射線治療の新しい展開

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Key words : Prostate Cancer, Radiation Therapy, Dose escalation, Brachytherapy

はじめに

前立腺がんは本邦の男性悪性新生死亡の4.2%を占め（平成13年），年齢別罹患率は年齢とともに増加し，70-74歳で152，80-84歳では294となる[1]。治療方法に関しては，根治的治療として放射線治療・手術・ホルモン療法が単独あるいは集学的に応用されている。前立腺がんにはさまざまな放射線治療が応用されており，治療方法の選択にはその特徴をよく理解しインフォームドコンセントを行う必要がある。

前立腺がんに関してはさまざまなリスク分類が提唱されているが（表1），治療開始前のProstate Specific Antigen (PSA)，Gleason Score，臨床病期（T因子・N因子）による予後の差異が報告されており，治療方法選択にも応用されている[1-5]。外照射症例の予後因子解析としては，Roachらによる Radiation Therapy Oncology Group (RTOG) の臨床試験結果の解析が報告されている[5]。外照射による放射線単独の治療を受けた1,557症例の解析より，Gleason Score，T-Stage，病理学的骨盤リンパ節転移を予後因子とする4群のリスクグループを設定し，Disease-Specific Survivalを報告している。5年で96%～64%，15年では72%～27%とリスクグループにより予後には大きな差異が認められる。Sylvesterらは根治的前立腺全摘術・三次元原体放射線治療 (3D-CRT)・シードによる組織内照射およびシードと外照射の組み合わせによる治療結果を，5年PSA無再発生存率のSeattle Risk Groupによるリスク別比較を行っている[2]。Low Risk群ではいずれの治療方法でも94%～81%の5年PSA無再発生存率であるが，High Risk群では65%～28%と差があり治療方法の選択が迫られる。

1．前立腺がんにおける放射線治療の線量ー効果関係

欧米においては，早期前立腺がんに対する根治的放射線治療と根治的前立腺全摘術は局所制御率において同等の成績であるされている[10-12]。Cleveland Clinic FoundationとMemorial Sloan Kettering at Mercy Medical Centerで1990年より98年に治療したT1-2症例の検討で[12]，72Gy以上の外照射による放射線治療と前立腺全摘でPSA無再発生存率に有意差のないことが示されている（7年PSA無再発生存率：前立腺全摘76%，72Gy未満の外照射48%，72Gy以上の外照射81%，永久挿入密封小線源治療75%，外照射と永久挿入密封小線源治療77%）。予後因子として治療前PSA ($p<0.001$)・Gleason Score ($p<0.001$) とともに，放射線治療における総線量が指摘されている。

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