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

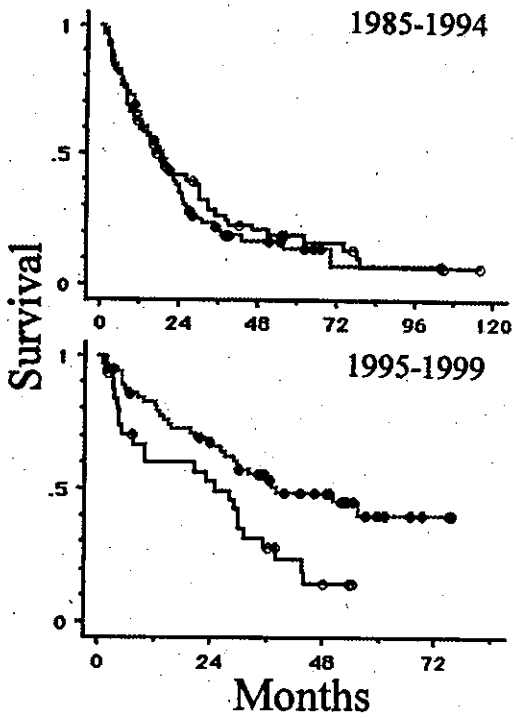

Fig. 2 Survival curves according to the treatment modality. ——○—— : patients treated with radiation alone, - - -●- - - : patients treated with radiation and chemotherapy. The difference was significant in the group of patients treated between 1995 and 1999 (upper panel, $P = 0.63$; lower panel, $P =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

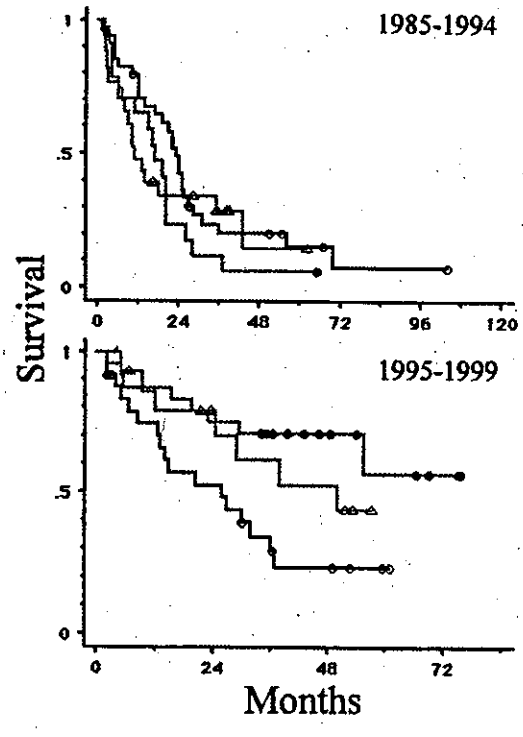

Fig. 3 Survival curves according to chemotherapy regimens. ——○—— : cyclophosphamide, vincristine, prednisolone ± doxorubicin, - - -●- - - : methotrexate-containing regimens, - - -△- - - : other regimens. The difference among the curves was significant in the group of patients treated between 1995 and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

Acknowledgements This study was supported in part by Grants-in-Aid for Scientific Research from the Japanese Ministry of Education, Culture, Sports, Science and Technology (14030042, 14370276, 14657214). The authors wish to thank Drs. Kumiko Karasawa, Atsushi Nishikawa, Naoto Shikama, Koichi Isobe, and Kuniaki Katsui for valuable help in collecting data.

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

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

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(Received April 28, 2004/Revised June 23, 2004/Accepted June 25, 2004)

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)

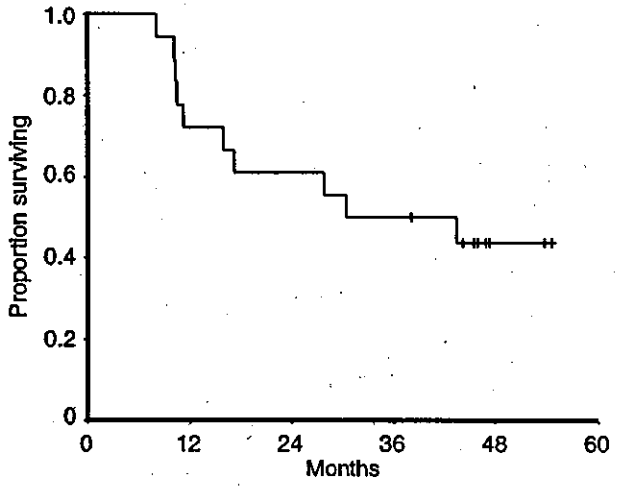

Fig. 1. Overall survival in 18 patients. The median (range) follow-up period of censored cases has been 35.4 (32.0–43.4) months, and the median overall survival time has not yet been reached.

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.

This work was supported in part by Grants-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan, and was presented in part at the 42th Annual Meeting of the Japan Lung Cancer Society, Osaka, Japan, November 1–2, 2001. We thank Ms. Yuko Yabe for preparation of the manuscript.

1. Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest* 1997; **111**: 1710–7.
2. Jett JR, Scott WJ, Rivera MP, Sause WT and American College of Chest Physicians. Guidelines on treatment of stage IIIB non-small cell lung cancer. *Chest* 2003; **123**: 221S–5S.
3. Pierre F, Maurice P, Gilles R, Pascal T, Pierre-Jean S, Hervé L, Alain V, Jean-Yves D, Francoise M, Fancoise M. A randomized phase III trial of sequential chemoradiotherapy in locally advanced non-small-cell lung cancer. *Proc Am Soc Clin Oncol* 2001; **20**: 312a (abstr 1246).
4. Curren W Jr, Scott C, Langer C, Komaki R, Lee J, Hauser S, Movsas B, Wasserman TH, Rosenthal S, Byhardt R, Sause W, Cox J. Phase III comparison of sequential vs concurrent chemoradiation for patients with unresectable stage III non-small-cell lung cancer (NSCLC): initial report of the Radiation Therapy Oncology Group (RTOG) 9410. *Proc Am Soc Clin Oncol* 2000; **19**: 484a (abstr 1891).
5. Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, Katagami N, Ariyoshi Y. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999; **17**: 2692–9.
6. Kubota K, Tamura T, Fukuoka M, Furuse K, Ikegami H, Ariyoshi Y, Kurita Y, Saijo N. Phase II study of concurrent chemotherapy and radiotherapy for unresectable stage III non-small-cell lung cancer: long-term follow-up results. Japan Clinical Oncology Group Protocol 8902. *Ann Oncol* 2000; **11**: 445–50.
7. Furuse K, Kubota K, Kawahara M, Kodama N, Ogawara M, Akira M, Nakajima S, Takada M, Kusunoki Y, Negoro S, Matsui K, Masuda N, Takifuji N, Kudoh S, Nishioka M, Fukuoka M. Phase II study of concurrent radiotherapy and chemotherapy for unresectable stage III non-small-cell lung cancer. Southern Osaka Lung Cancer Study Group. *J Clin Oncol* 1995; **3**: 869–75.
8. Atagi S, Kawahara M, Hosoe S, Ogawara M, Kawaguchi T, Okishio K, Naka N, Sunami T, Mitsuoka S, Akira M. A phase II study of continuous concurrent thoracic radiotherapy in combination with mitomycin, vindesine and cisplatin in unresectable stage III non-small cell lung cancer. *Lung Cancer* 2002; **36**: 105–11.
9. Sekine I, Saijo N. Novel combination chemotherapy in the treatment of non-small cell lung cancer. *Exp Opin Pharmacother* 2000; **1**: 1131–61.
10. Furuse K, Fukuoka M, Kuba M, Yamori S, Nakai Y, Negoro S, Katagami N, Takada Y, Kinuwaki E, Kawahara M, Kubota K, Sakuma A, Niitani H. Randomized study of vinorelbine (VRB) versus vindesine (VDS) in previously untreated stage IIIB or IV non-small-cell lung cancer (NSCLC). The Japan Vinorelbine Lung Cancer Cooperative Study Group. *Ann Oncol* 1996; **7**: 815–20.
11. Le Chevalier T, Brisgand D, Douillard JY, Pujol JL, Alberola V, Monnier A, Riviere A, Lianes P, Chomy P, Cigolari S, Gottfried M, Ruffie P, Panizo A, Gaspard MH, Ravaioli A, Besenval M, Besson F, Martinez A, Berthaud P, Tursz T. Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small-cell lung cancer: results of a European multicenter trial including 612 patients. *J Clin Oncol* 1994; **12**: 360–7.
12. Perol M, Guerin JC, Thomas P, Poirier R, Carles P, Robinet G, Kleisbauer JP, Paillotin D, Vergnenegre A, Balmes P, Touron D, Grivaux M, Pham E. Multicenter randomized trial comparing cisplatin-mitomycin-vinorelbine versus cisplatin-mitomycin-vindesine in advanced non-small cell lung cancer. 'Groupe Francais de Pneumo-Cancerologie.' *Lung Cancer* 1996; **14**: 119–34.
13. Kawahara M, Furuse K, Nishiwaki Y, Horai T, Saijo N, Hasegawa K, Ohashi Y, Niitani H. Randomized study of vinorelbine (VRB) or vindesine (VDS) with cisplatin (C) and mitomycin (M) as induction chemotherapy in stage IIIB or IV non-small cell lung cancer (NSCLC)-final results. *Proc Am Soc Clin Oncol* 2000; **19**: 489a (abstr 1914).
14. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbonne PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**: 649–55.
15. JCOG Administrational Committee: National Cancer Institute-Common Toxicity Criteria (NCI-CTC Version 2.0, Jan 30, 1998). Japanese edition by JCOG. Available at http://www.med.gunma-u.ac.jp/event/CTCJ_v20.pdf
16. WHO. Handbook for reporting results of cancer treatment. WHO Offset Publication no. 48. Geneva: World Health Organization; 1979.
17. Armitage P, Berry G. Survival analysis. In: Statistical methods in medical research. 3rd ed. Oxford: Blackwell Sci Publ; 1994. p. 469–92.
18. Sekine I, Matsuda T, Saisho T, Watanabe H, Yamamoto N, Kunitoh H, Ohe Y, Tamura T, Kodama T, Saijo N. Bacterial meningitis observed in a phase I trial of vinorelbine, cisplatin and thoracic radiotherapy for non-small cell lung cancer: report of a case and discussion on dose-limiting toxicity. *Jpn J Clin Oncol* 2000; **30**: 401–5.
19. Masters GA, Haraf DJ, Hoffman PC, Drinkard LC, Krauss SA, Ferguson MK, Olak J, Samuels BL, Golomb HM, Vokes EE. Phase I study of vinorelbine, cisplatin, and concomitant thoracic radiation in the treatment of advanced chest,malignancies. *J Clin Oncol* 1998; **16**: 2157–63.
20. Vokes EE, Herndon JE 2nd, Crawford J, Leopold KA, Perry MC, Mikkor AA, Green MR. Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small-cell lung cancer: cancer and leukemia group B study 9431. *J Clin Oncol* 2002; **20**: 4191–8.
21. Zatloukal P, Petruzelka L, Zemanova M, Krejbich F, Havel L. Vinorelbine (VRL) plus cisplatin (CDDP) and concurrent radiotherapy in advanced non-small cell lung cancer. *Proc Am Soc Clin Oncol* 1998; **17**: 505a (abstr 1947).
22. Alcedo J, Gallardo D, Lopez-Mariscal A, Calderillo G, Green L, Correa E, Zamora J, Mohar A. Cisplatin/vinorelbine (CDDP/VNR) and radiotherapy (XRT) in advanced non-small cell lung cancer (ANSCLC): an effective and feasible option with no need for dose reduction. *Proc Am Soc Clin Oncol* 1999; **18**: 494a (abstr 1905).
23. Hotta K, Sekine I, Tamura T, Sawada M, Watanabe H, Kusaba H, Akiyama Y, Inoue A, Shimoyama T, Nokihara H, Ueda Y, Yamamoto N, Kunitoh H, Ohe Y, Kodama T, Saijo N. A phase I/II study of cisplatin and vinorelbine chemotherapy in patients with advanced non-small cell lung cancer. *Jpn J Clin Oncol* 2001; **31**: 596–600.

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一効果関係

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。

Advances in radiation therapy for prostate cancer : Minako Sumi, Division of Radiation Oncology, National Cancer Center Hospital

表1　前立腺のリスク分類

Risk Scoring			
	Seattle[2]	Mt. Sinai[3]	D'Amico[4]
Low	iPSA≦10 GS 2-6 StageT1a-T2b	iPSA≦10 GS 2-6 StageT1a-T2a	iPSA≦10 GS 2-6 StageT1c-T2a
Intermediate	iPSA>10 or GS≧7 or Stage≧T2c	iPSA=10.1-20 or GS 7 or StageT2b	iPSA=10.1-20 and/or GS 7 and/or StageT2b
High	2 or 3 intermediate risk factors	2 or 3 intermediate risk factors or iPSA>20 GS 8-10 or Stage≧T2c	iPSA>20 and/or GS 8-10 StageT2c

外照射によるRTOG第III相試験症例によるリスク分類[5]						
Risk Group	T-Stage	Node Status	Gleason Score	Disease-Specific Survival 5-yr	10-yr	15-yr
1	T1-2	Nx	2-6	96%	86%	72%
2	T1-2	Nx	7	94%	75%	61%
	T3	Nx	2-6			
	T1-3	N+	2-6			
3	T1-2	Nx	8-10	83%	62%	39%
	T3	Nx	7			
	T1-3	N+	7			
4	T3	Nx	8-10	64%	34%	27%
	T1-3	N+	8-10			

iPSA=initial prostate specific antigen
GS= Gleason score

表2　リスク分類と治療方法による5年PSA無再発生存率[2]

Treatment	Seattle Risk Group		
	Low	Intermediate	High
3D-CRT; Zelefsky[6] (, 2001)	90%	70%	47%
Seeds; Blasko[7] (Seattle, 2000)	94%	82%	65%
Seeds+EBRT; Sylvester[8] (, 2002)	85%	77%	45%
Radical Prostatectomy; D'Amico[4] (Univ. Pennsylvania, 2000)	85%	65%	32%
Radical Prostatectomy; D'Amico[4] (B&W, 2000)	83%	50%	28%
Radical Prostatectomy; Kupelian[9] (Cleveland, 1997)	81%	40%	—

前立腺周囲には直腸や膀胱などリスク臓器が隣接しており，従来の放射線治療 (Conventional Radiotherapy) では腫瘍に対する高線量の投与は困難であった。そこで治療成績の向上と有害事象の軽減を目指し，さまざまな放射線治療技術が開発されてきた。本邦では高橋らにより開発された原体照射が以前より応用されており，さらに三次元原体放射線治療 (Three-dimensional conformal radiotherapy; 3D-CRT) が普及してきた。原体照射とは，森田らによれば“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”とされている[13]。最近では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さらに複雑な3D-CRTが可能となっている。

3D-CRTとは永田らによれば[14]，“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の幾何学的配置を決定し，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く正確な放射線治療計画”とされる。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遂げた。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。治療計画の選択においては，従来治療計画を行って線量分布を計算し (forward planning),

表3　外照射による前立腺がんに対するDose Escalation Study

Author	No.	Subset of Pt.	Dose	Local Control	p-value	Biochemical Control	p-value	Cause-specific Survival rate	p-value	Overall Survival rate	p-value
Kupelian[15] (Cleveland)	1041	All subsets	≧72 Gy <72 Gy	95%/8-yr 83%/8-yr	0.026	87%/8-yr 51%/8-yr	<0.001				
Shipley[16] (Harvard)	202	T3-4, poorly diff.	75.6 Gy 67.2 Gy	84%/8-yr 19%/8-yr	0.0014			67%/8-yr 62%/8-yr	NS	55%/8-yr 51%/8-yr	NS
Valicenti[17] (RTOG)	1465	GS 8-10	>66 Gy ≦66 Gy	78%/5-yr 66%/5-yr	0.076			46%/10-yr 31%/10-yr	<0.05	27%/10-yr 18%/10-yr	<0.05
Zelefsky[18] (Memorial Sloan-Kettering C.C.)	828	T1-3	75.6 Gy 70.2 Gy <70.2 Gy	Favolabic 75.6 Gy:83%/10-yr <70.2 Gy:57%/10-yr Intermediate 75.6Gy:50%/10-yr <70.2 Gy:42%/10-yr Unfavolable 75.6Gy:42%/10-yr <70.2 Gy:24%/10-yr		p=0.003 p=0.05 p=0.04					
Hanks[19] (Fox Chase C.C.)	714	GS 7-10	≧74Gy <74Gy					100%/5-yr 89%/5-yr	0.029	88%/5-yr 78%/5-yr	NS
		T2c-T3	≧74Gy <74Gy					95%/5-yr 87%/5-yr	NS	88%/5-yr 73%/5-yr	0.039
Pollack[20] (M. D. Anderson C.C.)	301	T1-3	78 Gy 70 Gy			70%/6-yr 64%/6-yr	p=0.03				

その比較により最適治療計画を選択していたが，IMRTによって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。IMRTは総線量増加を目的とした臨床試験において，近年さかんに前立腺がんに応用されている。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。

前立腺がんにおいては総線量の増加により，局所制御率やPSA無再発生存率が向上することが示されている。表3に外照射によるDose escalation studyの結果を示す。Zelefskyらの Memorial Sloan-Kettering Cancer Centerにおける828症例の検討によると[18]，10年PSA無再発生存率はFavolable・Intermediate・Unfavolable riskの各々で70.2Gy未満に比較し75.6Gyで良好であった。Pollackらによる M. D. Anderson Cancer Centerの報告では[20]，T1-3症例に対する第Ⅲ相比較試験の結果，6年PSA無再発率は70Gy群で64%に対し78 Gy群で70%と有意差を認めていた (p=0.03)。特に治療前のPSAが＞10ng/mlの症例では6年PSA無再発率は70Gy群で43%に対し78Gy群では62%と良好であった (p=0.01)。6年後のGrade2以上の直腸の遅発性放射線反応は，70Gy群で12%に対し78Gy群で26%と78Gy群で有意に多く認められており注意が必要である (p= 0.001)。膀胱の遅発性放射線反応は，両群で10%であり差がなかった。現在RTOGでは3D-CRTによる72.93Gyと82.28Gyの第Ⅲ相比較試験 (RTOG P-0126) を施行中であり，結果が注目される。

2．粒子線治療

粒子線治療は腫瘍制御率の向上と周囲正常組織の有害反応軽減を目的として，前立腺がん治療に利用されてきた。陽子線や重粒子線は物理的特徴としてBragg peakを有し，線量のpeak-plateau ratioが高いために線量分布に優れる。この特徴を応用し周囲正常組織に対する影響を増加せずに前立腺の総線量の増加を図ることが可能となると考えられる。放射線医学総合研究所重粒子治療センターでは重粒子線の1つである炭素線を用いて，1995年より前立腺がんに対する臨床研究が開始されている。第I/II相試験の結果，その後の第II相試験では炭素線治療66GyEを行っている。

陽子線治療ではMassachusetts General Hospitalにおいて1970年代より前立腺がんに対する陽子線治療が開始された。Loma Linda大学では1991

年より局所進行前立腺がんに対して陽子線ブースト照射を用いた治療を行っている。X線照射45Gyと陽子線ブースト照射30GyEを行い5年生存率89%，5年生化学的無病生存率79%と良好な成績を報告している[21]。日本においては，筑波大学陽子線医学利用センターにおいて1985年より前立腺がんに対する陽子線治療が行われ，国立がんセンター東病院では2001年より病院設置型陽子線治療装置による前立腺がんの治療が開始されている。多施設共同臨床試験としては，アメリカでProton Radiation Oncology Group (PROG) が，早期前立腺がん (T1b-T2b, PSA ≦ 15) に対し70.2GyEと79.2GyEの第Ⅲ相比較試験を行っており，本邦でもT1b-T3bN0M0を対象とする多施設共同第Ⅱ相試験が計画されており，今後の成果が期待されている。

3．組織内照射

前立腺がんに対する組織内照射には^{125}Iや^{103}Pd等の核種を密封したシード線源による永久挿入密封小線源治療や低線量率^{192}Ir線源による一時装着法，高線量率^{192}Ir線源による高線量率組織内照射がある（表4）。永久挿入密封小線源治療は限局性の前立腺がんの中，特にLow Risk群で以前より欧米では広く応用されてきた。古くは1914年に^{226}Raを用いた報告があるが[31]，1980年代より経直腸的超音波ガイドによるアプローチにより発展を遂げリアルタイムに三次元的表示が可能となった。アメリカでは標準的治療の一環として1998年には23,000件が施行され，症例の増加により年間50,000件以上の実施が想定されている。表3に^{125}Iや^{103}Pdでの永久挿入密封小線源治療単独治療および外照射との併用による治療成績を示す。

日本では，厚生労働省の定める「診療用放射線照射器具を永久的に挿入された患者の退出について」平成15年3月3日医薬安第0313001号通知および「患者に永久的に挿入された診療用放射線照射器具（ヨウ素125シード，金198グレイン）の取扱いについて」平成15年7月15日医政指発第0715002号が出され，^{125}Iシード線源の供給が開始されたことにより永久挿入密封小線源治療は標準治療の選択肢の一つとして普及することが予想される。日本放射線腫瘍学会・日本泌尿器科学会・日本医学放射線学会では「シード線源による前立腺永久挿入密封小線源治療の安全管理に関するガイドライン」を作成し，安全性の確保と放射線治療の質の向上を目指している。^{125}Iシードは，軌道電子捕獲により崩壊し平均エネルギーは28.5keVと低く，半減期は59.4日であり周囲への正常組織への影響を低く抑えることが可能である。

American Brachytherapy Society (ABS) は1999年に発表した前立腺永久挿入密封小線源治療に関する勧告のなかで[32]，単独治療の場合は①T1-T2aで，②Gleason sum 2-6かつ，③PSA＜10ng/mlという選択基準を示している。また，外照射に加え追加治療として行うべき症例としては，①T2b, T2cまたは，②Gleason sum 8-10または，③PSA＞20ng/mlという選択基準を示している。会陰浸潤例や生検で陽性多数である場合，両葉で陽性であった症例およびMRI上被膜浸潤が陽性の症例では外照射のboostとしての前立腺永久挿入密封小線源治療の選択を勧めている。さらに，前立腺体積が60cc以上の症例ではホルモン療法による体積の減少後に検討されるべきである。臨床的除外基準としては，期待寿命5年未満の症例やTURPによる大きな，または治癒前の欠損のある症例，施術に関する危険の高い症例および遠隔転移症例を挙げている。また合併症のリスクの高い症例として，大きな中葉，骨盤既照射例，AUA Scoreの高い症例，骨盤内手術の回数が多い症例および重症糖尿病症例が指摘されている。また，TURPの既往，前立腺体積が60cc以上の症例，大きな中葉，精嚢が生検陽性の症例で技術的に十分な照射が困難であると述べている。1995年に American

表4　前立腺永久挿入密封小線源治療症例のPSA

	No.	Treatment	T Stage	Definition	Follow-up	PSA Outcome by Pretreatment PSA 0～4	4～10	10～20	20～
Beyer (1997)[22]	489	I-125	T1-2	≧4.0	5 yr	93%	72%	42%	38%
Blasko (2000)[7]	230	Pd-103	T1-2	2 rises	9 yr	90%	87%	80%	67%
Critz (1998)[23]	689	I-125+EBRT	T1-2	≧0.5	5 yr	94%	93%	74%	69%
Dattoli (2003)[24]	102	Pd-103+EBRT	T2a-T3	≧1.0	4 yr		82%	85%	75%
Grado (1998)[25]	490	I-125/ Pd-103±EBRT	T1-3	2 rises	5 yr		88%	72%	57%
Grimm (2001)[26]	125	I-125	T1-2b	2 rises	10 yr	97%	78%	86%	55%
Ragde (2000)[27]	147	I-125/ Pd-103	T1-3	3 rises	12 yr			66%	
	82	I-125/ Pd-103+EBRT		3 rises	12 yr			79%	
Stock (1997)[28]	258	I-125/ Pd-103	T1-2	2 rises	4 yr		75%	74%	34%
Sharkey (2000)[29]	65	Pd-103		≧1.5	4 yr	90%	75%	57%	—
Zelefsky (2000)[30]	248	I-125	T1c-2b	3 rises	5 yr	96%	84%	62%	

Association of Physics and Medicine (AAPM) のTask Group No. 43 (TG-43) により線量計算アルゴリズムの変更が勧告されており[33]，^{125}Iシードによる前立腺永久挿入密封小線源治療に関するABSによる処方線量のガイドラインも単独治療で160Gyより144Gyへ変更された。40-50Gyの外照射を併用する場合は110～120Gyより100～110Gyへ変更されている。挿入後の線量評価の実施も勧告されているが最適な時期は明らかでなく，挿入後4週間頃のCT実施が報告されている。記載すべき線量としては①処方線量，②前立腺体積を100%含む線量であるD_{100}，③前立腺体積を90%含む線量であるD_{90}，④処方線量を照射される前立腺体積の比率V_{100}が勧告されている。

高線量率^{192}Ir線源による高線量率組織内照射は，本邦では永久挿入密封小線源が使用できなかった為，前立腺がんに応用されてきた。従来の報告の多数は欧米での放射線物理学的・生物学的利点を利用した検討であり，ほとんどが外照射との併用である。

4．前立腺全摘術後のPSA再発

根治的前立腺全摘術後25-35%に再発を生じるとされ[34-35]，局所再発例には放射線治療，遠隔転移例には内分泌療法が施行されている。再発形式のひとつとして，術後の経過観察中に局所再発が画像上は明らかでないもののPSAの上昇を認めるPSA再発がある。表5に根治的前立腺全摘術後のPSA再発に対する放射線治療成績を示す。PSA倍加時間が短いほど，早期に臨床的再発が生じることが指摘されており[46]，局所再発か遠隔転移かを予測する因子としては，術後PSA再発までの期間が2年以内，PSA倍加時間が6ヵ月未満，Gleason scoreが8以上のものが遠隔転移と相関する因子とする報告がある[47]。根治的前立腺全摘術後のPSA再発に対する標準的治療法は確立されていないが，1997年ASTRO (American Society for Therapeutic Radiology and Oncology) Consensus Panelにおいて根治的前立腺摘出後PSA上昇に対する放射線治療の解析がおこなわれ，1999年にConsensus Panel Statementとして報告された[48]。Massachusetts General Hospital (Zietman)・Washington University (Hudson)・Mayo Clinic (Schild)・Wayne State University (Forman) のデータの解析より総線量64Gy以上で通常分割照射（1回線量1.8～2.0Gy）が推奨された。治療のタイミングについては，Parkerらの分析より早期の放射線治療の有効性が示されつつある[49]。

おわりに

前立腺がんの放射線治療の選択肢は，外照射や永久挿入密封小線源治療および粒子線治療な

表5　根治的前立腺全摘術後のPSA failureに対する放射線治療

Author	No.	Median pre-RT PSA	Gleason score 8-10	Seminal Vesicle+ or LN+	Dose Median	Follow-up Median	Biochemical Control
Leventis[45]	49	2.1	7%	27%	66Gy	29 mos	24%/5-yr
Catton[46]	43		15%	35%	60Gy	43 mos	20%/5-yr
Pisansky[47]	166	0.9	16%	31%	64Gy	52 mos	46%/ 5-yr
Anscher[48]	89	1.4	26%	34%	66Gy	48 mos	50%/ 4-yr
Nudell[49]	69	0.1-29.3	22%	10%	60-74Gy	37 mos	47%/4-yr
Cadeddu[50]	82	2.8(mean)	15%	15%	64Gy (mean)	8.3 years (mean)	10%/ 5-yr
Garg[51]	78	1.2	35%	38%	66Gy	25 mos	57/78
Do[52]	60		17%	37%	64.8Gy	36 mos (mean)	30/60
Morris[53]	48	1.7	34%	25%	60-64Gy	32 mos (mean)	47%/3-yr
Crane[54]	41	2.7	35%	29%	60Gy	55 mos	8/41

ど多岐にわたり，その最適な選択については今後の検討課題となっている。外照射は3D-CRTやIMRTの応用により，永久挿入密封小線源治療および粒子線治療はその物理学および生物学的特性により，正常組織の線量軽減による有害事象の制御と総線量の増加による治療効果の向上を目指している。治療の選択にあたっては，臨床病期や治療前PSA，Gleason Scoreおよび前立腺の容積や形態，合併症の有無などの総合的な検討が必要である。

参考文献

1) がんの統計編集委員会編．癌の臨床統計（Cancer Statistics in Japan 2003）．財団法人がん研究振興財団，p.36-47, 2003.
2) Sylvester JE, *et al.*: Int J Radiat Oncol Biol Phys. 57: 944-952, 2003.
3) Lee LN, *et al.*: Int J Radiat Oncol Biol Phys. 52: 444-452, 2002.
4) D'Amico AV, *et al.*: J Clin Oncol. 18: 1164-1172, 2000.
5) Roach M, *et al.*: Int J Radiat Oncol Biol Phys. 47: 609-615, 2000.
6) Zelefsky MJ, *et al.*: J Urol. 166: 876-881, 2001.
7) Blasko JC, *et al.*: Int J Radiat Oncol Biol Phys. 46: 839-850, 2000.
8) Sylvester JE, *et al.*: Int J Radiat Oncol Biol Phys. 54(Suppl): 38, 2002.
9) Kupelian PA, *et al.*: Int J Radiat Oncol Biol Phys. 37: 1043-1052, 1997.
10) Hanks GE, *et al.*: Int J Radiat Oncol Biol Phys. 13: 499-505, 1987.
11) Zeitman AL.: Seminar Radiat Oncol. 8: 81-86, 1998.
12) Kupelian PA, *et al.*: Int J Radiat Oncol Biol Phys. 58: 25-33, 2004.
13) Morita K: Int. J. Radiation Oncology Biol. Phys. 48: 431-434, 2000.
14) 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，45-60, 2001, 中外医学社，東京．
15) Kupelian PA, *et al.*: Int J Radiat Oncol Biol Phys. 46: 567-574, 2000.
16) Shipley WU, *et al.*: Int J Radiat Oncol Biol Phys. 32: 3-12, 1995.
17) Valicenti R, *et al.*: J Clin Oncol. 18: 2740-2746, 2000.
18) Zelefsky M, *et al.*: Int J Radiat Oncol Biol Phys. 57 (Suppl): S45, 2003.
19) Hanks GE, *et al.*: Cancer J Sci Am. 5: 152-158, 1999.
20) Pollack A, *et al.*: Int J Radiat Onocl Biol Phys. 53: 1097-1105, 2002.
21) Slater JD, *et al.*: Int J Radiat Oncol Biol Phys. 42: 299-304, 1998.
22) Beyer DC, Priestley JB Jr.: Int J Radiat Oncol Biol Phys. 37: 559-563, 1997.
23) Critz FA,*et al.*: Cancer J Sci Am. 4: 359-363, 1998.
24) Dattoli M, Cancer. 97: 979-983, 2003.
25) Grado GL, *et al.*: Int J Radiat Oncol Biol Phys. 42: 289-298, 1998.
26) Grimm PD, *et al.*: Int J Radiat Oncol Biol Phys. 51: 31-40, 2001.
27) Ragde H, *et al.*: Cancer. 89: 135-141, 2000.
28) Stock RG, Stone NN.: Semin Surg Oncol. 13: 454-460, 1997.
29) Sharkey J, *et al.*: J Endourol. 14: 343-350, 2000.
30) Zelefsky MJ, *et al.*: Int J Radiat Oncol Biol Phys. 47: 1261-1266, 2000.
31) Pasteau O, *et al.*: Arch Roentg Ray. 28: 396-410, 1914.
32) Nag S, *et al.*: Int J Radiat Oncol Biol Phys. 44: 789-799, 1999.
33) Bice WS, *et al.*: Int J Radiat Oncol Biol Phys. 40: 1237-1241, 1998.
34) Carroll P.:Eur Urol. 40 Suppl 2: 9-16, 2001.
35) Pound CR, *et al.*: JAMA. 281: 1591-7, 1999.
36) Leventis AK, *et al.*: J Clin Oncol. 19: 1030-1039, 2001.
37) Catton C, *et al.*: Radiother Oncol. 59: 51-60, 2001.
38) Pisansky TM, *et al.*: J Urol. 163: 845-850, 2000.
39) Anscher MS, *et al.*: Radiat Oncol Biol Phys. 48: 369-375, 2000.
40) Nudell DM, *et al.*: Urology. 54: 1049-1057, 1999.
41) Cadeddu JA, *et al.*: J Urol. 159: 173-177, 1998.
42) Garg MK, *et al.*: Urology. 51: 998-1002, 1998.
43) Do T, *et al.*: Sci Am. 4: 324-330, 1998.
44) Morris MM, Int J Radiat Oncol Biol Phys. 38: 731-736, 1997.
45) Crane CH, *et al.*: Int J Radiat Oncol Biol Phys. 39: 681-686, 1997.
46) Patel A, *et al.*: J Urol. 158: 1441-1445, 1997.
47) Partin AW, *et al.*: Urology. 43: 649-659, 1994.
48) ASTRO Consensus Panel.: J Clin Oncol. 1: 1155-1163, 1999.
49) Parker C, *et al.*: Radiotherapy Oncol. 61: 107-116, 2001.

小児科診療〔第67巻・第4号〕別刷

2004年4月1日発行

発行所 株式会社 診断と治療社

特集

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

0386-9806/04/¥100/頁/JCLS

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

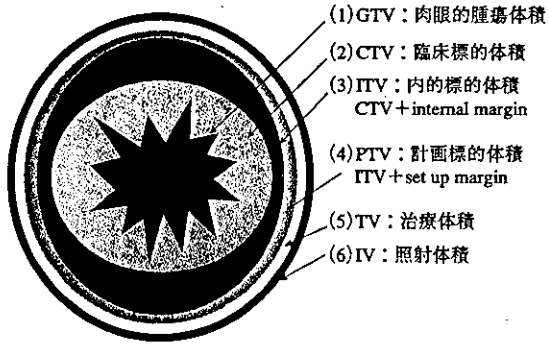

図　ICRU Report 62に基づく放射線治療にかかわるターゲットの決定

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	総照射線量	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 脳幹	全脳 3 歳未満 23.4Gy	不要
	全脳 3 歳以上 30.6Gy	不要
眼 水晶体		必要
眼 網膜	46.8Gy	必要
眼 視神経	46.8Gy	必要
眼 視神経交叉		必要
下垂体	41.4Gy	不要
耳 蝸牛	14.4Gy	不要
耳 外耳道	41.4Gy	不要
耳 鼓膜		必要
頭部 甲状腺		必要
胸部 肺	両肺 14.4Gy	必要
胸部 心臓	全心臓 30.6Gy	必要
腹部 肝臓	全肝 23.4Gy	必要
腹部 腎臓	両側で 14.4Gy	必要
腹部 消化管	一部 45Gy	不要
腹部 全腹～骨盤	30Gy（1.5Gy/回）	不要
骨盤 膀胱		必要
骨盤 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