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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 (cm²) 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)

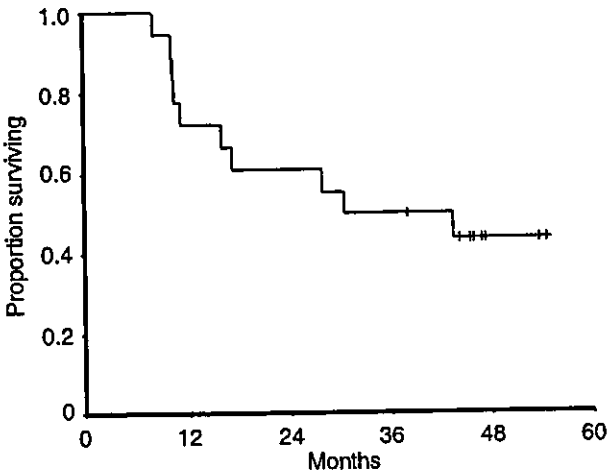

Fig. 1. Overall survival in 18 patients. The median (range) follow-up period of censored cases has been 35.4 (32.0–43.4) months, and the median overall survival time has not yet been reached.

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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CT and MRI Features of Recurrent Tumors and Second Primary Neoplasms in Pediatric Patients with Retinoblastoma

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OBJECTIVE. The aim of our study was to describe the CT and MRI findings of recurrent tumors and second primary (malignant and benign) neoplasms in patients with retinoblastoma and to evaluate imaging features to assist in distinguishing them.

MATERIALS AND METHODS. Records of 445 pathologically confirmed retinoblastomas were retrospectively reviewed. Thirty-four patients with recurrent retinoblastomas and 15 patients with second primary neoplasms who underwent CT and MRI were evaluated by two radiologists with agreement by consensus.

RESULTS. Invasive patterns of recurrent tumors included type A, intraocular tumor ($n = 13$); type B, intraorbital tumor with spread into the optic nerve shown as enlargement and marked enhancement of the optic nerve on contrast-enhanced CT or MRI ($n = 6$); and type C, tumor extending to the lateral aspect of the orbit and invading the brain via the sphenoidal bone ($n = 2$). Thirty-eight percent of patients with recurrent tumors had distant metastases ($n = 7$) or leptomeningeal metastases ($n = 6$). Leptomeningeal metastases were found only in recurrent tumors. Second primary neoplasms included osteosarcoma ($n = 5$), rhabdomyosarcoma ($n = 5$), meningioma ($n = 4$), and other tumors ($n = 3$). A significant difference was seen between the patients' ages at the time of diagnosis of recurrent tumors and second primary neoplasms ($p < 0.0001$). Extraorbital tumors were found more frequently among second primary neoplasms than among recurrent tumors ($p < 0.001$).

CONCLUSION. Both recurrent tumors and second primary neoplasms in patients with retinoblastoma often show characteristic imaging features. The tumor distribution on CT and MRI may help in differentiating recurrent tumors and second primary neoplasms.

Retinoblastoma is the most common primary ocular malignancy of early childhood. The tumor is hereditary in all patients with bilateral retinoblastoma and in 10–15% of those with unilateral disease identified by a family history of retinoblastoma [1, 2]. Although the cure rate of retinoblastoma is excellent after enucleation or irradiation, survivors of hereditary retinoblastoma are at increased risk of developing recurrent tumors or second primary (malignant and benign) neoplasms, most commonly osteosarcoma and other soft-tissue sarcomas [1–10]. Loss or mutation of the retinoblastoma gene, which is a prototypical tumor-suppressor gene located on human chromosome 13q14, has been associated with development of other malignancies, including osteosarcoma and other mesenchymal tumors [11–13].

The incidence of second primary neoplasms after retinoblastoma increases with the length of time from initial diagnosis, with a cumulative incidence of 8.4% 18 years after diagnosis [10]. However, a short latency has been found among patients with recurrent tumors, and the incidence may be overestimated because of difficulties in distinguishing second primary neoplasms from recurrent tumors. Second primary neoplasms often show both high-grade and undifferentiated features on microscopic observation, making them difficult to diagnose and distinguish from the small, undifferentiated round cell tumors that are characteristic of recurrent retinoblastomas [14–21]. Although the CT and MRI findings of patients with retinoblastoma are established, there have been only a few descriptions of second primary neoplasms in patients with retinoblastoma [22]. In our study, we retrospectively reviewed and described CT and MRI findings in recurrent tumors and second primary neoplasms in patients with retinoblastoma.

Materials and Methods

We reviewed cross-referenced records from January 1980 to September 2002 in the divisions of radiation oncology and pathology at the National Cancer

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Center Hospital, Tokyo, and identified 445 patients with pathologically confirmed retinoblastoma. Of these, 34 patients with recurrent retinoblastomas and 15 patients with second primary neoplasms were included in our study. Of the 15 patients with second primary neoplasms, two patients developed two separate second primary tumors. One child had a temporal rhabdomyosarcoma and developed osteosarcoma 12 years later. Another child first developed meibomian carcinoma in the eyelid, followed 5 years later by a meningioma arising in the skull base. Therefore, we reviewed 15 patients with 17 second primary neoplasms for data analysis. Patients seen in consultation were included in the analysis even if they did not receive all primary therapy for retinoblastoma at our institute because some children were referred with recurrent disease after having initial treatment at an outside institution.

Of the 49 patients evaluated, data regarding age at diagnosis; sex; family history; histologic subtype; location; latent period; and all initial treatment for primary tumors including enucleation, chemotherapy, radiation therapy, and treatment of recurrent tumors and second primary neoplasms were documented. Patients with recurrent tumors or second primary neoplasms received combined modality therapy consisting of surgical resection or biopsy, followed by combination chemotherapy either in standard doses or in escalating doses with autologous bone marrow or peripheral blood stem cell transplantation, with or without radiation therapy. The latent period was calculated from the time of initial diagnosis to the time of diagnosis of recurrent tumors or second primary neoplasms. All tumors in the field of radiation were so classified if they appeared to be originating in the eyelids, orbits, paranasal sinuses, temporal bones, or soft tissues overlying the temporal bone region.

CT and MRI examinations were reviewed by two radiologists with agreement by consensus. The images of 49 patients included both CT and MRI (n = 27), only CT (n = 3), or only MRI (n = 19). Unenhanced CT scans were obtained in 30 patients, and contrast-enhanced CT scans were obtained in 24 patients with the use of IV iodinated contrast material. Section thickness ranged between 5 and 10 mm. CT scans were evaluated for predominant attenuation; homogeneity or heterogeneity; and the presence of calcification, bone destruction, surrounding edema, and tumor enhancement.

MRI was performed using 1.5-T systems. Using the spin-echo technique, we obtained T1-weighted images (TR range/TE range, 400–660/12–15) in the axial and coronal planes. T2-weighted spin-echo or fast spin-echo images (3000–5700/80–118) were then obtained in the axial and coronal planes. Whole-brain images were obtained with a field of view of 30–40 cm, an image matrix of 128 × 256, and a slice thickness of 5–10 mm. Locations were judged by the type of margin, extent of tissue involvement, internal architecture, presence of invasion to surrounding tissue, size, and signal characteristics on T1- and T2-weighted images. Tumor size was determined by the largest diameter in the axial plane of CT scans or MRIs. Locations were correlated with the radiation field in all patients. Signal characteristics were described as hypointense, isointense, or hyperintense relative to the surrounding structures: muscle or white matter. MRIs obtained after the IV administration of a gadolinium chelate with T1-weighting (n = 30) were evaluated for the degree and type of enhancement.

For evaluation of recurrent tumors in patients with retinoblastoma, we categorized growth patterns into three types for assessing recurrent retinoblastoma: intraocular tumor (type A), intraorbital tumor with local spread into the optic nerve (type B), and tumor extending to the lateral aspect of the orbit and invading the brain via the sphenoidal bone (type C).

CT and MRI findings were assessed in both recurrent tumors and each histologic type of second primary neoplasms. We also assessed CT and MRI findings to assist in the differentiation of recurrent tumors and second primary neoplasms.

The data obtained related to disease status regarding retinoblastoma and the second primary neoplasms in all patients. Current status was documented by follow-up examination, and follow-up was calculated in months from the date of initial diagnosis to the most recent follow-up. Differences between subgroups were analyzed for correlations with the chi-square test, Fisher's exact probability test, or Spearman's rank correlation coefficient test. The interobserver variation of the extent of various abnormalities was evaluated with the Spearman's rank correlation coefficient test. A p value of less than 0.05 was considered a statistically significant difference.

Results

Clinical Findings

The clinical features of the patients are summarized in Table 1. A significant difference was seen in age at the time of diagnosis between patients with recurrent tumors and those with second primary neoplasms ($p < 0.0001$). Patients with hereditary tumors developed second primary neoplasms more frequently than they developed recurrent tumors ($p < 0.001$). The initial therapy for patients with both tumor types included combination therapy. No significant difference was found in the radiation dose between recurrent tumors and second primary neoplasms.

The latent period of second primary tumors ranged between 15 and 400 months (median ± SD, 178.7 ± 28.7 months). There was a significant difference in the latent period between recurrent tumors and second primary neoplasms ($p < 0.0001$). The significant difference was also found in the latent period between histologic subtypes including osteosarcoma, rhabdomyosarcoma, and meningioma (Table 2). Seventy-one percent of patients with recurrent tumors and 73% of patients with second primary neoplasms were still alive, with a median follow-up of 58.2 and 271.3 months, respectively.

Imaging Features in Recurrent Tumors

Sixty-two percent of patients with recurrent tumors had local lesions. Invasive patterns (Fig. 1) of recurrent tumors identified on CT or MRI included type A, intraocular tumor (n = 13, 38%) (Fig. 2); type B, intraorbital tumor with spread into the optic nerve shown as enlargement and marked enhancement of the optic nerve on contrast-enhanced CT or MRI (n = 6, 18%) (Fig. 3); and type C, tumor extending to the lateral aspect of the orbit and invading the brain via the sphenoidal bone (n = 2, 6%) (Fig. 4). Peripherally located intralesional calcification was found in type A (n = 13, 100%) and type B (n = 2, 33%) tumors on unenhanced CT. In addition, no calcification was found in type C tumors. Tumors appeared hypo- to isointense in relation to normal temporal muscle on T1-weighted images and of moderately high signal intensity on T2-weighted images in all patients who underwent MRI. All localized lesions were depicted as heterogeneously enhanced masses with a slightly irregular surface on contrast-enhanced CT or MRI.

Thirty-eight percent of patients with recurrent tumors had distant metastases (n = 7) or leptomeningeal metastases (n = 6) (Fig. 5). Multiple brain metastases were found in three patients. Although the signal characteristics on T1- and

TABLE 1 Characteristics of Patients with Retinoblastoma

Characteristic	Recurrent Tumor	Second Primary Neoplasm	p
No. of patients	34	15	
Age (yr)	2.5 ± 0.4 (0–12)	14.9 ± 2.4 (1–33)	< 0.0001
Sex			NS
Male	21 (62)	7 (47)	
Female	13 (38)	8 (53)	
Family history	7 (21)	1 (7)	NS
Hereditary tumor	6 (18)	12 (80)	< 0.001
Radiation dose (Gy)	40.3 ± 2.1	43.5 ± 2.3	NS
Latent period (mo)	28.5 ± 3.5 (5–79)	178.7 ± 28.7 (15–400)	< 0.0001
Mortality rate	10 (29)	4 (27)	NS

Note.—Numbers in parentheses are percentages or ranges. NS = not significant.

TABLE 2 Second Primary Neoplasms in Patients with Retinoblastoma

Diagnosis	No. of Patients	Size (mm)	Latent Period[a] (mo)
Osteosarcoma	5	50.0 ± 5.4 (45–70)	199.0 ± 54.1 (15–319)
Rhabdomyosarcoma	5	40.0 ± 5.6 (10–80)	55.0 ± 13.8 (15–93)
Meningioma	4	47.5 ± 17.0 (10–80)	291.3 ± 47.3 (169–400)
Malignant fibrous histiocytoma	1	35	192
Meibomian gland carcinoma	1	20	248

Note.—Numbers in parentheses are ranges.

[a]Significant difference was found in latent period among osteosarcoma, rhabdomyosarcoma, and meningioma by Spearman's rank correlation coefficient test ($p < 0.05$).

T2-weighted images were nonspecific, lesions showed heterogeneous enhancement on contrast-enhanced CT or MRI. One patient developed skull metastasis that was seen as focal bone destruction on unenhanced CT and a moderately enhanced mass on contrast-enhanced MRI.

Imaging Features in Second Primary Neoplasms

Seventeen second primary neoplasms included various histologic types of tumors. Malignant tumors consisted of osteosarcoma ($n = 5$), rhabdomyosarcoma ($n = 5$), malignant fibrous histiocytoma ($n = 1$), and meibomian gland carcinoma ($n = 1$), whereas benign tumors were meningioma ($n = 4$) (Table 2).

Osteosarcoma was one of the frequent histologic subtypes (29%). Tumors originated from previously irradiated regions, including the intraorbit ($n = 2$), temporal bone ($n = 1$), and ethmoid bone ($n = 1$). One patient developed a tumor in the distal femur outside the irradiated field. Unenhanced CT scans revealed irregular masses in the orbit, temporal bone, or ethmoid bone with calcification ($n = 4$, 80%) (Fig. 6). Two tumors showed severe bone destruction on unenhanced CT. Contrast-enhanced CT and MRI showed heterogenous enhancement with perifocal edema ($n = 5$, 100%). Fluid–fluid levels, suggestive of hemorrhage, were identified in two tumors on T2-weighted images. Calcification identified on unenhanced CT corresponded in part to areas of signal voids or low signal intensity on both T1- and T2-weighted images.

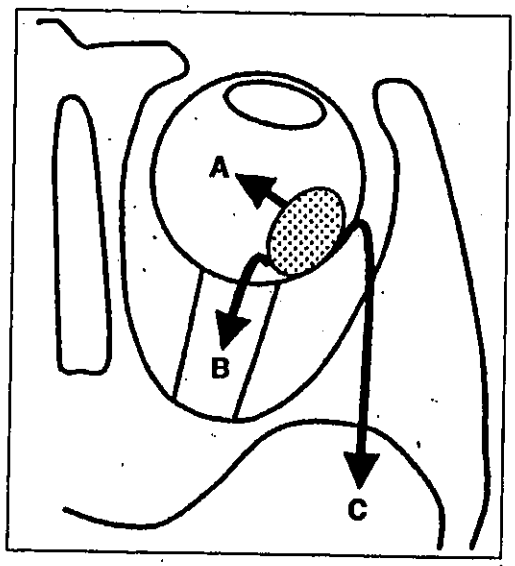

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Fig. 1.—Drawing shows types of tumor extension in recurrent retinoblastoma. Three growth patterns are present in recurrent retinoblastoma: intraocular tumor (type A), intraorbital tumor with local spread into optic nerve (type B), and tumor extending to lateral aspect of orbit and invading brain via sphenoidal bone (type C).

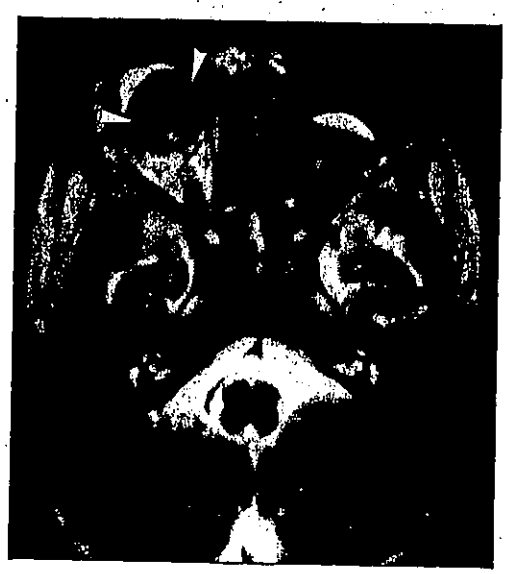

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Fig. 2.—2-year-old boy with recurrent retinoblastoma who underwent enucleation of left eye and irradiation of both eyes. Axial T2-weighted image (TR/TE, 4000/118) shows soft-tissue mass in right globe (type A). Tumor (*arrowheads*) shows heterogeneous high signal intensity relative to temporal muscle.

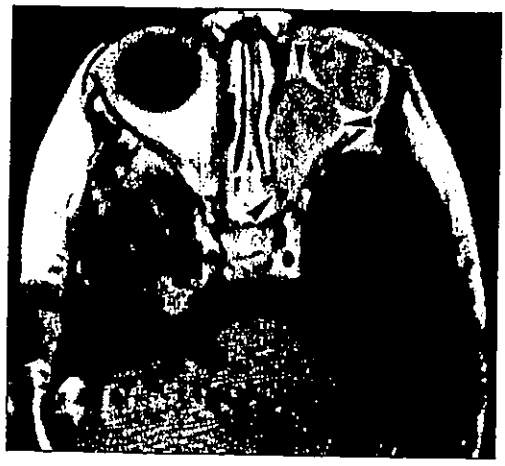

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Fig. 3.—3-year-old boy with recurrent retinoblastoma who underwent irradiation of left eye. Axial contrast-enhanced T1-weighted image (TR/TE, 630/15) shows recurrent tumor (*arrowheads*) that extended into optic nerve (type B) with heterogeneous enhancement.

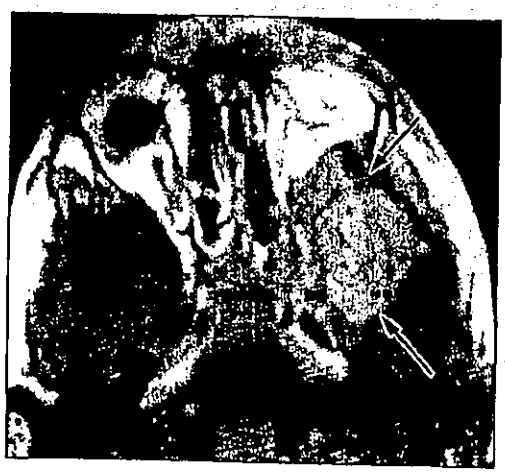

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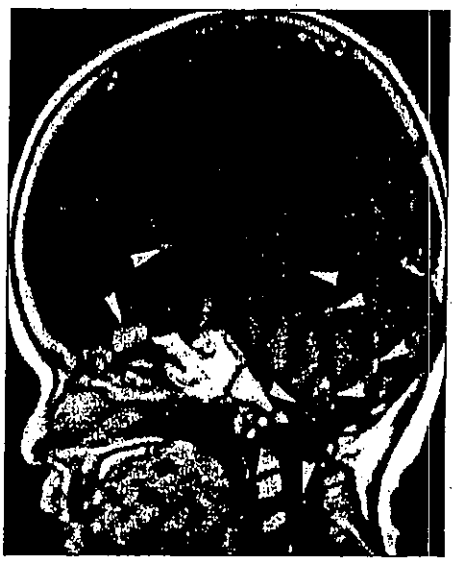
Fig. 4.—6-year-old boy with recurrent retinoblastoma who underwent enucleation and irradiation of left eye. Axial contrast-enhanced T1-weighted image (TR/TE, 600/15) shows tumor extension (*arrows*) through greater wing of sphenoid to middle cranial fossa (type C).



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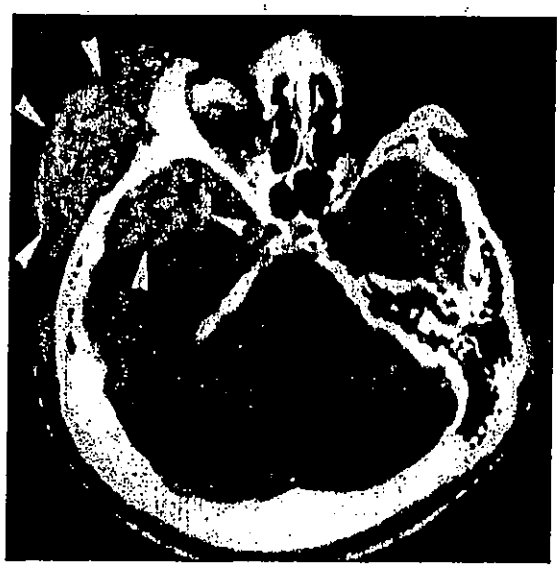

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Fig. 5.—4-year-old boy with recurrent retinoblastoma who underwent enucleation, irradiation, and chemotherapy. Coronal contrast-enhanced T1-weighted image (TR/TE, 400/15) shows multiple leptomeningeal metastases (*arrowheads*).

Fig. 6.—Osteosarcoma in 25-year-old man with hereditary retinoblastoma who underwent enucleation, irradiation, and chemotherapy of both eyes. Axial CT scan shows faintly calcified mass (*arrowheads*) of temporal bone invading both brain and soft tissues.

All rhabdomyosarcomas arose in the region previously irradiated, including five tumors that developed in the temporal muscle within the irradiated field and one that involved the contralateral temporal muscle, which may have received a radiation dose of 50–60% of that in the irradiated field. Unenhanced CT revealed well-defined masses with ovoid contours situated in the temporal muscle ($n = 5$, 100%). Five patients underwent both contrast-enhanced CT and MRI; of these, three tumors (60%) showed heterogeneous and slight enhancement relative to the adjacent muscle (Fig. 7). Fluid–fluid levels were found in one tumor on both T1- and T2-weighted images. Signal characteristics on T1- and T2-weighted images were nonspecific in the other four tumors.

A 16-year-old girl with hereditary retinoblastoma developed malignant fibrous histiocytoma in the orbit, with severe destruction of bone identified on unenhanced CT (Fig. 8). The tumor showed nonspecific signal characteristics on T1- and T2-weighted images, but marked enhancement was found on contrast-enhanced CT scans and MRIs. A 20-year-old woman developed a well-defined mass in the eyelid that was seen on unenhanced CT and diagnosed as a meibomian gland carcinoma after a latent period of 121 months. The tumor showed nonspecific signal characteristics on both T1- and T2-weighted images, but areas of marked enhancement were found on contrast-enhanced MRIs (Fig. 9).

All meningiomas originated from the previously irradiated skull base. Tumors showed hyperattenuation on unenhanced CT ($n = 4$), and marked enhancement was found in all cases on contrast-enhanced CT and MRI (Fig. 10). Punctate calcification was found in one case; this tumor was associated with secondary hyperplastic change of the adjacent bone. Signal characteristics were nonspecific on T1- and T2-weighted images. However, perifocal edema was found in three cases in the adjacent white matter on T2-weighted images.

Differentiation Between Recurrent Tumors and Second Primary Neoplasms

Peripherally located intralesional calcification was found in all type A and in 33% of type B tumors on unenhanced CT. However, this finding was similar to that of osteosarcoma arising in the orbit. Three invasive patterns of recurrent tumors were identified on CT or MRI, whereas only two patients with second primary tumors showed these patterns. However, this configuration of invasive patterns did not assist in the differentiation of recurrent tumors and second primary neoplasms (Table 3). Brain metastases and leptomeningeal metastases were found only in recurrent tumors. A statistically significant difference was found in intra- and extraorbital location of tumors between recurrent tumors and second primary neoplasms (Table 4).

Discussion

In our study, we described the CT and MRI findings of both recurrent tumors and second

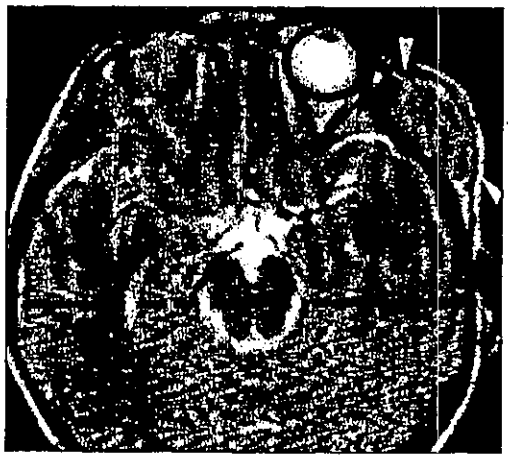

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Fig. 7.—Rhabdomyosarcoma in 5-year-old girl with retinoblastoma who underwent irradiation in right eye. Axial T2-weighted image (TR/TE, 5700/105) shows well-defined soft-tissue mass arising from deep aspect of temporal muscle. Tumor (*arrowheads*) shows high signal intensity relative to muscle.

Fig. 8.—Malignant fibrous histiocytoma in 16-year-old girl with hereditary retinoblastoma who underwent enucleation and irradiation in right eye. Axial contrast-enhanced CT scan shows irregular mass (*arrow*) with bone destruction in orbit.

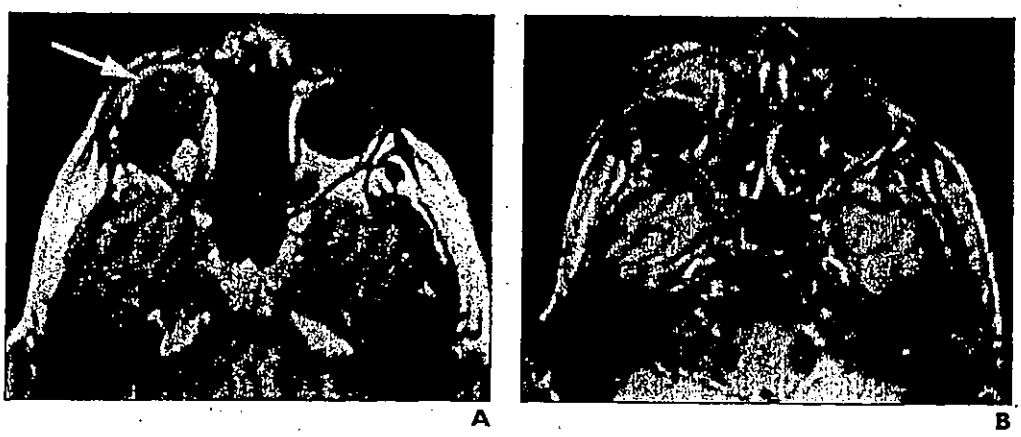

Fig. 9.—Meibomian gland carcinoma in 20-year-old woman with hereditary retinoblastoma who underwent enucleation and irradiation.
A, Axial T1-weighted image (TR/TE, 600/15) shows well-defined soft-tissue mass (*arrow*) in orbit.
B, Axial contrast-enhanced T1-weighted image (600/15) shows marked enhancement of tumor.

primary neoplasms in patients with retinoblastoma. The short latency among patients with retinoblastoma is one factor that encourages us to question whether their new lesions are recurrent tumors or second primary neoplasms. Second primary neoplasms tend to appear after longer intervals, usually showing a latent period of at least 10 years [1, 2]. This finding was mostly in accordance with our results. However, two cases of second primary neoplasms had much shorter latent periods of 15 months. Our results show that both the recurrent tumors and the second primary neoplasms may be seen in the same latent periods. The type of second primary neoplasm appears to be related to the latent period. Rhabdomyosarcoma seems to occur earlier than other tumors, with a relatively short latency ranging from 15 to 93 months. Osteosarcoma is usually considered to be the most frequent second primary tumor in patients with hereditary retinoblastoma. The relatively short follow-up periods in earlier studies probably gave the misleading impression that it is osteosarcoma that preferentially develops in patients who have survived a hereditary tumor at an earlier age than other types of second primary neoplasms.

CT and MRI can show tumor extension by three types of growth patterns in primary retinoblastoma: the endophytic type, in which the tumor projects anteriorly and grows into the vitreous; the exophytic type, in which the tumor arises intraretinally and subsequently grows into the subretinal space; and the diffuse infiltrating type, in which tumor growth in the retina appears as a plaquelike mass [14–16]. Our results also suggested that three growth patterns might exist in recurrent retinoblastoma, and that CT and MRI can detect tumor extension: intraocular tumor (type A), intraorbital tumor with local spread into the optic nerve (type B), and tumor extending to the lateral aspect of the orbit and invading the brain via the sphenoidal bone (type C).

Different types of second primary neoplasms have also been documented in previous studies, with most of the second primary neoplasms being soft-tissue sarcomas, followed by melanomas, brain tumors, leukemias, and other epithelial tumors [1–9]. In our study, the most common types of second primary neoplasms in patients with retinoblastoma were osteosarcoma and rhabdomyosarcoma.

Osteosarcoma is one of the most frequent second primary neoplasms originating from a previously irradiated region. Calcification within the tumor that depends on the amount of mineralization is observed on CT. Four of our patients showed central calcification within the mass on unenhanced CT. An important feature to diagnose osteosarcoma on CT may be central calcification within the mass situated in the irradiated field, including the intraorbit, temporal bone, and ethmoid bone. Extraskeletal osteosarcoma presents nonspecific signal characteristics on MRI: a mass with mixed low signal intensity on T1-weighted images and mixed but predominantly high signal intensity on T2-weighted images [23–25]. Fluid–fluid levels, suggestive of hemorrhage, were identified in two of our patients on T2-weighted images; this finding was consistent with a previous report [23].

Rhabdomyosarcoma also presents with rather nonspecific CT and MRI findings, but some characteristic findings were discovered in our patients. All rhabdomyosarcomas arose within the region previously irradiated. As a rule, rhabdomyosarcomas in the head and neck region grow rapidly, often in an infiltrative and destructive manner [26, 27]. However, all of our patients presented with well-defined masses with ovoid contours situated in the temporal muscle on both CT and MRI. The MRI

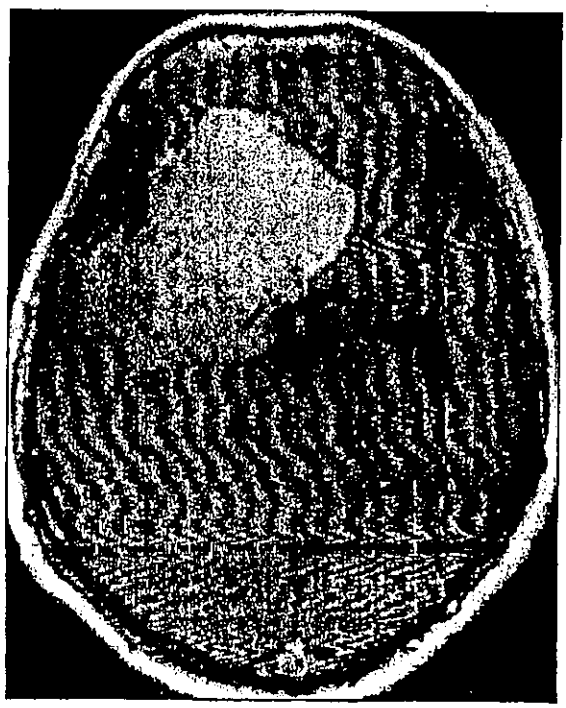

Fig. 10.—Meningioma in 24-year-old man with hereditary retinoblastoma who underwent enucleation and irradiation. Axial contrast-enhanced T1-weighted image (TR/TE, 600/15) shows extraaxial mass with marked enhancement adjacent to sphenoid bone.

TABLE 3 Invasive Patterns in Recurrent Tumors and Second Primary Neoplasms

Invasive Types	Type A		Type B		Type C	
	No.	%	No.	%	No.	%
Recurrent tumor (n = 21)	13	62	6	29	2	9
Second primary neoplasm (n = 2)	0		1	50	1	50

Note.—Patients with distant metastases are excluded. Invasive patterns do not help to distinguish recurrent tumors and second primary neoplasms by Spearman's rank correlation test (p = 0.11). Type A = intraocular tumor, type B = intraorbital tumor with spread into optic nerve, type C = tumor extending to lateral aspect of orbit and invading brain via sphenoidal bone.

TABLE 4 Intra- and Extraorbital Tumor Location

Characteristics	Intraorbital		Extraorbital	
	No.	Range	No.	Range
Recurrent tumor (n = 34)	21	62	13	38
Second primary neoplasm (n = 17)	2	11	15	88

Note.—Significant difference was found between two groups by Fisher's exact probability test (p < 0.001).

signal characteristics and enhancement patterns identified on both contrast-enhanced CT and MRI were nonspecific. Few characteristic imaging findings reflect the degree of cellularity; the relative amounts of collagen; and the presence and extent of secondary changes such as hemorrhage, necrosis, and ulceration.

The initial therapy for primary tumors has been enucleation of the most severely affected eye and irradiation of the contralateral eye to preserve vision. Patients with hereditary retinoblastoma may have an increased susceptibility to the induction of second primary neoplasms by radiation [28].

Radiation increases the total risk in addition to the already high incidence because more second primary tumors develop in the irradiated field than outside the irradiated field [2]. Sarcomas can be categorized as radiation-induced if they meet the following criteria: tumor must develop within the boundaries of a previously irradiated area, a relatively long asymptomatic latent period (≥ 4 years) must have elapsed, the tumor must have a different histology from the original lesion, and the tumor must be histologically confirmed [28]. Most of our cases of second primary neoplasms arose in the irradiated field. However, some tumors occurred with relatively short latency and outside the irradiation field. Similar findings have suggested that nearly all second primary neoplasms occur among hereditary retinoblastoma tumors, and that many second primary tumors occur outside the irradiation field, with some among nonirradiated tumors [2, 28]. Second primary neoplasms in patients with retinoblastoma may occur both as a result of, and independently of, radiation therapy. However, the follow-up period and the number of patients with second primary neoplasms in our study are not sufficient for conclusive analysis. Further follow-up study is necessary to evaluate the relationship between irradiation and the occurrence of second primary neoplasms in patients with retinoblastoma.

In conclusion, several kinds of imaging features were present both in recurrent tumors and in second primary neoplasms in patients with retinoblastoma. The tumor distribution on CT and MRI may help in differentiating recurrent tumors and second primary neoplasms.

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complications of SNAD. The axillary failure rate (AFR) in patients with breast cancer treated with lumpectomy, SNAD, and radiation therapy (RT) with breast tangents alone has been reported to be less than 3%. This has resulted in the elimination of the axillary radiation field in patients with negative lymph nodes thus reducing the toxicity profile. In this study, we compared the rates and patterns of AFR in patients treated with SND only versus SNAD followed by local breast tangent RT while excluding the axillary field.

Materials/Methods: 193 consecutive patients with AJCC stages I and II breast cancer treated with either SND or SNAD followed by RT to the breast tangents only to a median dose 65 Gy (range, 50–74 Gy) between 1997 and 2001 were evaluated in a serial retrospective manner. There were 121/193 (63%) patients treated with SND alone, and 72/193 (37%) treated with SNAD. All patients were planned using CT stimulation, and the majority of patients' levels I and II axillary nodes were either partially or completely encompassed by the standard tangents. The two cohorts of breast cancer patients were similar for age, stage, technique of sentinel lymph node examination, adjuvant systemic therapy, follow-up, grade, margins, and menopausal status. Patients were seen in our clinics every 3–6 months for the first five years following completion of the breast conserving therapy. Fischer's exact tests were used in comparing the outcomes of two groups for the rates of AFR, ipsilateral breast tumor recurrence (IBTR), and metastatic disease. A 5-year progression free survival (PFS) was compared using logrank test.

Results: The median follow-up of the entire patient population was 34 months (range, 14–70 months). The incidence of metastatic disease in axillary lymph nodes in patients treated with SND followed by breast tangent RT only was 0/121 (0%). Similarly, we found 0/72 (0%) patients treated with SNAD experienced a local AFR following the completion of breast conserving therapy. The results of rates of AFR, ipsilateral breast tumor recurrence (IBTR), metastatic disease, and a 5-year progression free survival (PFS) are summarized in the table.

The rate of complications - seroma formation, wound infection, hematoma, numbness, loss of strength, loss of range of motion, impaired use of arm, and chronic lymphedema - was increased when SND was followed by SNAD. In contrast, no patients undergoing SND alone experienced numbness, tingling or paresthesia.

Conclusions: This study provides early evidence that patients with early stage breast cancer treated with SND followed by tangent breast RT only while omitting the axillary field have low AFR. Furthermore, these findings should reassure physicians that eliminating the treatment of the axillary field in patients with negative sentinel lymph nodes without a complete axillary dissection may provide excellent long-term cure rates while avoiding morbidities, and ongoing prospective randomized trials will definitively answer this question.

	SND	SNAD	p-value
Percent AFR at 3 years	0% (0/121)	0% (0/72)	NS
Percent IBTR at 3 years	0.8% (1/121)	0% (0/72)	1.0
Percent metastases at 3 years	0.8% (1/121)	2.8% (2/72)	0.56
5-year actuarial PFS	92%	94%	0.70

2075 Patterns of Care Study: Comparison of Process of Post-Mastectomy Radiotherapy in Two Surveys in Japan and That in USA

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Purpose/Objective: The Patterns of Care Study (USPCS) by the American Collage of Radiology has made significant contributions to improvements in the process of care for patients with breast cancer in the United States. The Japan Patterns of Care Study Group (JPCS) started its national survey from 1998. The first goal of this study was to identify changes associated with the process of care for patients undergoing post-mastectomy radiotherapy (PMRT) by comparing Japanese two surveys. The second goal was to compare problems with PMRT identified in the JPCS and compare them with those identified in the USPCS.

Materials/Methods: JPCS conducted two national surveys. The first survey (JPCS-1) collected the data of patients treated between 1995 and 1997 and the second (JPCS-2) those of patients treated between 1999 and 2001. The patients and institutions were selected by means of two-stage cluster sampling. JPCS-1 included 40 large academic (A1) or large non-academic (B1) institutions and 39 small academic (A2) or small non-academic (A2) institutions, while JPCS-2 has collected data from 38 A1 or B1 institutions only. However, JPCS-2 is still being conducted, and it has not completed collection of the data from A2 and B2 institutions. JPCS-1 included 693 patients who were treated with conservative therapy or PMRT in academic institutions, and JPCS-2 included 431 corresponding patients. We compared the process of care for the patients undergoing PMRT in A1 and B1 institutions in the two surveys. The USPCS collected the data of patients with breast cancer who were treated at 55 institutions between 1998 and 1999.

Results: JPCS-1 included 128 patients (18%) who received PMRT, while JPCS-2 included 37 patients (8%) ($p < 0.0001$). In comparison, the USPCS included 407 such patients. Modified radical mastectomy was performed for 66% of the patients in JPCS-1, for 81% in JPCS-2, and for 93% in USPCS, while axillary node dissection was performed for 99% in JPCS-1, 100% in JPCS-2, and 98% in USPCS. T3-4 stage accounted for 29% of the patients in JPCS-1, for 25% in JPCS-2, and for 23% in the USPCS. Of the patients in JPCS-1, 55% had more than three axillary positive nodes and 75% in JPCS-2 did ($p = 0.028$). In the USPCS, 46% of the patients had multiple axillary nodes. Chest wall irradiation was performed for 26% of the patients in JPCS-1 and 72% in JPCS-2 ($p < 0.0001$), supraclavicular irradiation for 83% of the patients in JPCS-1 and 78% in JPCS-2

(p = 0.242), and parasternal irradiation for 66% of the patients in JPCS-1 and 59% in JPCS-2 (p = 0.435). The iso-dose curve was calculated for 50% of the patients in JPCS-1, and 58% of those in JPCS-2 (p = 0.145). According to the USPCS, chest wall, supraclavicular, and parasternal irradiation were performed for 97%, 98%, and 19% of the patients, respectively. The iso-dose curve was calculated for 90% of patients in the USPCS.

Conclusions: There was little difference regarding surgical management between the two JPCS surveys. JPCS-2 made it clear that the administration of PMRT has been reduced, but PMRT used for patients with multiple axillary positive nodes frequently. More complex radiation techniques including chest wall, supraclavicular and parasternal irradiation were used in JPCS-2 than in JPCS-1, but the iso-dose curve was calculated for only half of the patients in JPCS-1 and -2. Acceptance of the USPCS as a desirable model indicates that calculation of iso-dose curves should be performed for all patients.

2076 Patterns of Care Study of Breast Conserving Therapy in Japan: Comparison of the Treatment Process Between 1995-1997 and 1999-2001 Surveys

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Purpose/Objective: The number of the patients with breast cancer who undergo breast conserving therapy (BCT) has been rapidly growing in Japan, and approximately 40 % of the patients received BCT in the year of 2000. However, it was not until 1999 that the Japanese Breast Cancer Society (JBCS) published its treatment guideline for BCT. The purpose of the study is to compare the results from 1995–1997 national survey and 1999–2001 national survey, and evaluate the impact of the treatment guideline published meanwhile.

Materials/Methods: The first national survey on the process of BCT collected the data of 865 patients from 72 institutions who were treated between 1995–1997. Similarly, the second national survey collected the data of 665 patients from 62 institutions who were treated between 1999 and 2001. The data was collected by external audit in which the patients' clinical records were retrospectively reviewed by visiting radiation oncologists. The extent of surgery, prescription and technique of radiation therapy, and the regimen of systemic chemo-endocrine therapy were compared between two surveys.

Results: There was a significant reduction in the extent of breast surgery and more patients received wide excision in 1999–2001 survey. This resulted in significantly increased ratio of patients with positive/close margin in 1999–2001 survey. Consequently, the ratio of the patients who received boost to the tumor bed was significantly higher in 1999–2001 survey. Use of a simulator, fixation system such as cast or shell, and wedge filters were significantly more common in 1999–2001 survey. Although the ratio of node-positive patients who received any form of chemotherapy was not significantly different in two series, the ratio of the patients who received intensive chemotherapy was significantly increased in 1999–2001 series. (Table 1.)

Conclusions: 1999–2001 survey thus demonstrated the trend in the treatment process of BCT in Japan. In the surgical aspect, there was a clear movement towards smaller surgery although lumpectomy was still seldom employed. Radiation therapy correspondingly increased its role by increasing the dose to tumor bed. Systemic chemo-endocrine therapy also became more consistent with international guidelines. These treatment guidelines for BCT seem to have great impact on the patterns of care in Japan, considering the rapid change in this short interval.

	1995-1997 survey n=865	1999-2001 survey n=655	p value
Extent of final breast surgery:			
Lumectomy	47/865 (5.4%)	55/655 (8.4%)	p<0.001
Wide excision	325/865 (37.6%)	414/655 (63.2%)	
Quadrantectomy	493/865 (57.0%)	186/655 (28.4%)	
Pathologic margin status:			
Positive	65/865 (7.5%)	85/655 (13.%)	p<0.001
Close (2mm or less)	40/865 (4.6%)	37/655 (5.6%)	N.S.
Negative	663/865 (76.6%)	507/655 (77.4%)	N.S.
Unknown / Missing	97/865 (11.2%)	24/655 (3.7%)	p<0.001
Boost was given to:			
Margin positive	35/65 (53.9%)	69/85 (81.2%)	p<0.001
Margin close (2mm or less)	18/40 (45.0%)	23/37 (62.2%)	N.S.
Margin negative	80/663 (12.1%)	69/499 (13.8%)	N.S.
Margin unknown	14/97 (14.4%)	8/26 (30.8%)	p=0.05
Simulator used	776/863 (89.9%)	633/654 (96.8%)	p<0.001
Cast or Shell was used	282/864 (32.6%)	373/653 (57.1%)	p<0.001
Wedge was used	388/781 (49.7%)	380/626 (60.7%)	p<0.001
Chemotherapy was given to node positive:	103/159 (64.8%)	108/146 (74.0%)	N.S.
Intensive chemotherapy* was given to node positive:	37/159 (23.3%)	53/146 (36.3%)	p=0.01

*includes chemotherapy which incorporates at least one of the following: Doxorubicin, Cyclophosphamide, Methotrexate, Mitomycin, Mitoxantrone, Paclitaxel, Vinblastine, and Vincristine.

2133 Radiation-Induced Liver Disease in Three-Dimensional Conformal Radiotherapy for Primary Liver Carcinoma

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Purpose/Objective: To identify the risk factors of radiation-induced liver disease (RILD) in three-dimensional conformal radiotherapy (3DCRT) for primary liver carcinoma (PLC) and find a dosimetric threshold for RILD.

Materials/Methods: Between April 1999 and August 2003, 128 patients with PLC were treated by 3DCRT at Cancer Hospital, Guangxi Medical University. All of the patients were technical unresectable or medical inoperable due to poor liver function or cardiovascular diseases. The clinical characteristics of these patients were as follows: 113male, 15 female; median age of 48.2(27–72); with portal vein thrombosis (PVT) in 34 cases, without in 94 cases; liver cirrhosis of Child-Pugh grade A in 108 cases, Child-Pugh grade B 20 cases. 3DCRT was carried out by 8MV x-ray with Topslane treatment planning system. In 48 patients transarterial chemoembolization (TACE) was performed prior to 3DCRT with DDP, ADM and MMC.

3DCRT was delivered by4.88 ± 0.47Gy(4-8Gy)/fraction, three fractions per week (Mon., Wed. Fri.) with a median total dose of 53.6Gy. The mean value of gross target volume (GTV) was 458.92 ± 429.8 cm3.

RILD was defined as either anicteric elevation of alkaline phosphatase level of at least twofold and non-malignant ascites (classic RILD), or elevated transaminases of at least fivefold the upper limit of normal or of pre-treatment level(non-classic RILD). The diagnosis of RILD should be distinguished from the progression of PLC, which occurred within 4 months.

Parameters evaluated for the occurrence of RILD included: gender, age, GTV, AFP level, HBV, PVT, TACE, Child-Pugh grade of liver cirrhosis. Among 128 patients, 84 patients had complete 3-dimensional dose-volume data, and these dosimetric parameters, including DVH were also analyzed.

Results: During a median follow-up time of 17.2 months (4–56) after 3DCRT, 19 patients were diagnosed as RILD with the incidence of 14.8%(19/128). Classic RILD 13cases,non-classic RILD 6 cases. 16 cases died of hepatic failure, 8 of them died within 4 months after completion of radiation with the median survival time of 5.2 (1–14) months.

GTV, PVT and Child-Pugh grade of liver cirrhosis had correlation with occurrence of RILD, in favor of small GTV, without PVT and Child-Pugh grade A ($p = 0.000, 0.002, 0.001$, respectively). The Grade of hepatic toxicity of Common Toxicity Criteria (Version 2.0) during 3DCRT also related to RILD ($p = 0.000$).

Ten of 84 patients, who had 3DCRT dosimetric data developed RILD after treatments. When whole liver volume was taken as a single organ, which included normal liver and tumors, the mean whole liver dose was significantly higher in patients with RILD than those without (27.5Gy ± .8.5Gy vs.33.9Gy ± 5.9Gy,$p = 0.027$). Multivariate analysis demonstrated that only Child-Pugh grade of liver cirrhosis played an independent factor ($p = 0.000$, RR = 29.7) for occurrence of RILD with much high incidence for Child-Pugh B patients. In Child-Pugh grade A patients, the threshold of dosimetric parameters, which would not produce >5% of RILD was 81% for V5, 69% fqr V10, 51% for V15, or 42% for V20.For Child-Pugh A patients, when mean normal liver (excluding tumors) dose was ≤19Gy(33 cases), there was no case of RILD (0%),whereas, when mean normal liver dose was over 19Gy,the incidence of RILD was 2/36(5.6%).The incidence of RILD were 0/38(0%) and 2/31(6.5%), respectively for mean whole liver dose of ≤28Gy and >28Gy. In Child-Pugh grade B patient, the probability of developing RILD was 53% (8/15),which implied that the doses used in this study was not tolerable.

Conclusions: Liver cirrhosis was the most critical risk factor for occurrence of RILD when PLC was treated by irradiation. For Child-Pugh grade A patients, the safe threshold dose could be 81% for V5, 69% for V10, 51% for V15, or 42% for V20, and mean normal liver dose of 19Gy or mean whole liver dose of 28Gy when 3DCRT was carried out by fractionation used in this study. The fractionation and total doses implemented in this study was not tolerable for PLC patients with liver cirrhosis of Child-Pugh grade B, and not recommended for the further clinical trials.

2134 Radiation Therapy for Elderly Esophageal Cancer Patients; Results of the Patterns of Care Study in Japan

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Purpose/Objective: To examine the treatment process and outcome of elderly patients with esophageal cancer treated by radiation therapy (RT).

Materials/Methods: A national survey of 52 facilities including both academic and nonacademic institutions was conducted using the original two-stage cluster sampling. Detailed information was accumulated on 470 patients with cancer in the thoracic esophagus who had received RT between 1999 and 2001. The median age was 68 years old. Thirty-seven percent were aged 64 years old or less (YG), 34% were aged between 65 and 74 years old (MG) and 29% were aged 75 years old or more (EG). According to a modified 1983 American Joint Committee on Cancer staging system, 21 percent of all patients had clinical stage (CS) I disease, 33% had CS II and 44% had CS III. In EG, 78% percent were male and 22% were female. All patients had squamous cell carcinoma histology and 53% had main tumor in mid thoracic esophagus. Performance status, accompanied medical complications, use of chemotherapy and esophagectomy, survival and complication were analyzed and compared between EG and other age groups.

Results: Karnofsky performance score (KPS) less than equal 70 identified in YG, MG, EG were 15%, 19%, 36%, respectively ($p = 0.007$). Frequencies of accompanied pulmonary disease in YG, MG, EG were 10%, 17%, 17% ($p = .210$), cardiovascular disease were 19%, 35%, 48% ($p = 0.001$), and diabetes were 11%, 13%, 15% ($p = 0.593$). Esophagectomy was applied to 52%, 27%, 4% in YG, MG, EG ($p = .001$). Chemotherapy was used for 73%, 74%, 33% in YG, MG, EG ($p = 0.001$). Esophagectomy and chemotherapy were significantly less used in EG. Cisplatin and 5FU were used for 17% and 25% of EG. Completion rates of planned treatment were not significantly differ on age groups (84%, 88%, 90% in YG, MG, EG ($p = .278$)). Median total external RT dose for patients who did not receive esophagectomy was 60Gy, 60Gy, 61Gy in YG, MG, EG, respectively ($p = 0.089$). The average longitudinal field size in EG was 16.4cm whereas 20.6cm in YG and 18.0cm in MG. EG

patients were treated with significantly smaller field than YG (p = 0.001) and MG (p = 0.016). The median follow up period from radiation therapy was 10 months. Two-year overall survival rates for all patients of CS I, II and III were 73%, 60% and 43%, respectively (p = 0.001). Two-year overall survival rates for YG, MG and EG were 58%, 54% and 49% (YG vs. EG; p = 0.057, MG vs. EG; p = 0.323). Significant variables for overall survival in multivariate analysis include CS I or II disease, KPS equal 90 or 100 and receiving esophagectomy. Age, sex, institution type and receiving chemotherapy were not significant prognostic factors. Acute toxicities with RTOG grade 2 or more were not significantly correlated with age groups (26%, 28%, 18% in YG, MG, EG (p = 0.325)).

Conclusions: Although elder esophageal cancer patients treated by RT less frequently receive esophagectomy or chemotherapy than younger patients, age was not the significant prognostic factor and did not affect the acute toxicities. Elder patients may take considerable benefit from definitive RT.

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Univariate and Multivariate Analysis of Survival					
	Univariate			Multivariate	
	2-Year Survival Rates		p-value	p-value	Risk Ratio
Stage, I and II vs. III	0.652	0.434	0.001	0.001	2.196
Age, <=74 vs. >=75	0.560	0.491	0.099	0.993	1.002
KPS, 90-100 vs. 60-80	0.651	0.475	0.003	0.022	1.645
Sex, male vs. female	0.528	0.650	0.169	0.230	0.694
Institution, academic vs. non-ac.	0.560	0.523	0.760	0.486	0.868
Chemotherapy, yes vs. no	0.534	0.549	0.805	0.823	0.949
Esophagectomy, yes vs. no	0.627	0.504	0.001	0.015	0.555

2135 Real-Time Monitoring of a Digestive-Tract Marker to Reduce Adverse Effects of Moving Organs at Risk (OAR) in Radiotherapy for Thoracic and Abdominal Tumors

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Purpose/Objective: For the majority of thoracic and abdominal tumors, moving serial organs such as the esophagus and duodenum are the organs at risk (OAR). The aim of the present study was to evaluate the feasibility of real-time monitoring of a fiducial marker in the digestive tract and to analyze the motion of the OAR so as to determine a reasonable internal margin.

Materials/Methods: A fluoroscopic real-time tumor-tracking radiotherapy (RTRT) system was used to monitor the position of a metallic fiducial marker in or near the digestive tract every 0.03 s by means of two sets of diagnostic fluoroscopy in the treatment room. We developed two methods to insert a fiducial marker into or near the digestive tract adjacent to the target volume. One method involves an intra-operative insertion technique using a thread and a bead, a 2.0-mm gold marker with a 0.5-mm pinhole. The bead can be fixed by suturing the thread into or near the organs at risk. The other technique involves endoscopic insertion of the marker into the submucosal layer of the normal digestive tract with the aid of a special long needle (Olympus, Tokyo) to avoid dropping the fiducial markers from the mucosal surface. The feasibility of inserting the submucosal marker and the stability of the marker were evaluated in this study. The motion of the esophagus and duodenum was evaluated using tracking data from the RTRT system. The position of the marker in the OAR was monitored during irradiation so as to not irradiate the tumor when the marker in the OAR was moving into the high-dose region.

Results: Thirty-two patients were entered into this study. Fourteen markers (two in the mediastinum and 12 in the abdomen) in 14 patients were implanted intra-operatively without any displacement. Nineteen markers (13 in the esophagus, 2 in the stomach, and 4 in the duodenum) in 18 patients were implanted into the submucosal layer using endoscopy. The marker was successfully implanted into the submucosal layer and maintained in the same place in 12/13 cases in the esophagus, 1/2 in the stomach, and 3/4 in the duodenum. No symptomatic adverse effects related to insertion of the marker were demonstrated. The mean/standard deviation of the range of motion (median, 95% confidence interval of the marker position) of the esophagus was 3.5/1.8 (3.3, 1.5 - 6.8) mm, 8.2/3.8 (8.4, 1.3 - 15.4) mm, and 3.8/2.6 (2.6, 2.0 - 10.8) mm for lateral (R-L), cranio-caudal (C-C), and antero-posterior (A-P) directions, respectively. Respiratory and cardiac motion was detected in the frequency analysis. The magnitude of the motion varied individually and changed during the delivery of irradiation in the same patient. The range of motion was the largest in the C-C direction in 9 patients, the A-P direction in 2 patients, and in the R-L direction in none. The median range of motion (95% confidence interval of the marker position) of the duodenum was 10.4 (6.8 - 11.6) mm, 22.2 (11.2 - 25) mm, and 10.5 (10.4 - 16.2) mm for the R-L, C-C, and A-P directions, respectively. The frequency analysis showed the duodenal motion to be influenced by involuntary bowel movement as well as respiratory motion.

Conclusions: Intra-operative and endoscopic insertion of a fiducial marker into the gastro-intestinal tract for the monitoring of organs at risk is safe and feasible. The motion analysis suggested that the internal margin should be determined to cover a mean range of 4, 8, and 4 mm for the esophagus and 10, 22, and 11 mm for the duodenum in R-L, C-C, and A-P directions, respectively. Using fluoroscopic individual verification of the marker every treatment day, the margin for internal motion can be individualized, and unnecessary irradiation of these digestive tracts can be significantly reduced.

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綜　説

がん診療における医学判断
—標準治療とはなにか—

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Standard Care of Cancer Treatment

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Key words: cancer treatment, standard therapy, guideline
がん治療，標準治療，診療ガイドライン

I　はじめに

近年，がん診療における集学的治療の重要性が注目され，各種治療法が診療科枠を超え合理的に連携することが求められている。また，エビデンス・ベースの医療（科学的根拠に基づく医療：Evidence Based Medicine, EBM）が注目され，個人の経験のみから成り立つ診療ではなく科学的根拠に基づく診療が求められている[1]。世界中で数多くの臨床試験が行われ信頼性の高い知見が次々と報告されているが，すべてを把握し臨床の現場に生かしていくことは容易ではない。一方，EBMを中心とした診療は個々の患者の意向が考慮されにくいとの指摘もあり，ナラティブ・ベースの医療（患者自身によって語られる医療：Narrative Based Medicine, NBM）の重要性も指摘されている。EBMとNBMとが車の両輪のような形で機能し日常臨床が行われることが望ましい。誰もがどこででもある一定水準以上の医療を受けられることは国民の健康を守る上で重要であり，がん診療においても治療法の標準化が進められている。一方，個別化した診療も重要と考えられているが，臨床の現場において「患者個別の治療」や「オーダーメイド治療」と称される診療の中に科学的根拠のないものが含まれているという現状は見逃せない。

ここ数年来，本邦においても厚生労働省や各学会が挙って診療ガイドラインを作成しており，診療レベルの底上げを図ろうとしている。近年の診療ガイドライン・ブームは，診療レベルの施設間格差が大きいことや，質の悪い診療が少なからず行われていることを物語っている。診療ガイドラインの作成が即根本的な解決策にはならないまでも，本邦の診療レベルがわずかずつではあるが底上げされるものと期待されている。診療ガイドラインの利用に当たっては，ガイドラインは規則でもマニュアルでもないということを十分に意識していることが重要である。これさえ守っていればよいというものではなく，利用方法を誤った場合には悪影響さえ及ぼしかねない。本稿では，筆者が乳がん診療ガイドラインの作成や臨床試験の作成に携わる中考えてきた，がん診療における標準治療について述べる。また，より良い医学判断を下すために，いかにEBMの手法を活用し，診療ガイドラインで推奨される診療や臨床試験の結果を実臨床の現場に反映させるべきかを概説する。

II　医学判断とは

「医学判断」という言葉は一般には馴染みのない言葉であるが，がん診療に限らずすべての診療において重要なキーワードである。久道　茂氏が「医学判断学入門」の中で様々な例をあげわかりやすく解説している[2]。人間という非常に個体差の大きな生き物を対象とした場合には，行った医療行為（介入）により起こりうる結果を事前に的確に予測することは困難である。久道氏は起こりうる結果の予測がいかに難しいかを，天候が悪化しやすい冬の旅行や，ゴルフのアプローチ

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ショットにたとえてわかりやすく説明している。その例を一つ紹介する。ゴルフのアプローチショットをする際，プレーヤーは天候や芝の状況を考慮し最適なクラブ（がん治療における治療方針）を選択する。ゴルフの腕の悪いプレーヤー（医者としての技量の低い者）が打っても偶然グリーンにボールを乗せられることもある。また，技術が非常に高いプレーヤーが適切なクラブを選択し，またその日のコンディションを正確に読み取り，すばらしい技術でショットを打っても必ずグリーンに乗るとは限らない。風や気温，芝の状態など無数の条件が不規則に絡み合っているため予想された結果が必ず出るとは限らないのである。これを「不確実性下の判断」という。また，たとえボールがグリーンに乗ったとしても，悪い判断や技術ではあったが偶然成功した場合と，良い判断と技術で成功している場合とを，「ボールがグリーンに乗った」という結果だけからでは区別することはできないのである。初心者がプレーするより，テレビでお馴染みのプロゴルファーがプレーした方が成功する可能性が高く，より良い判断と技術を持ち合わせていることは誰もが疑わない。しかし，実力が僅差であるプロ選手同士の場合には，その実力の差を評価するには実際にプレーして成績を比較するしかない。ましてやその実力が僅差であればあるほど，厳密なルールと同一の状況下で何回もプレーを競うことで比較しなければならない。個々のプレーにおいて良好な成績をあげるのは毎回同一のプレーヤーではなく，一回ごとの勝者は入れ替わることもあろう。総合成績で選手Aが勝ったとしても，ある場面の一回のプレーだけを見た場合には選手Bが勝っていることもある。この状況を医療の現場に当てはめると，多数の症例を解析した際にはある一つの治療法が他の治療法に勝ることが示されたとしても，患者個々の診療においてどちらの治療法が適正であるかは判断できない。厳密な状況で比較を行っても個体差の大きい人間を対象とした医療を行う場合には，性別，体格，遺伝子，合併症の有無，疾患の性質のばらつきなど様々な因子が絡み合っており，不確実性下の判断は困難を極める。より良い医学判断とより良い技術を身につけるため，心ある医師は常に己を磨くのである。

医療における意志決定においてもう一つ重要なキーワードは「ヒューリスティック（heuristic）」である。この言葉も聞き慣れないものと思われるが，これは「人間が頭の中で情報を処理する際，必ずしも理論的・定量的に考えるのではなく，複雑な情報をまぜこぜにして処理するプロセス（近道思考）をとる」ということである（表1）。この情報処理と意志決定のプロセスは，類似や典型例からの発想（Representative ness heuristic），印象深い例からの発想（Availability heuristic），固定観念と修正不十分な発想（Anchoring and adjustment heuristic）に分けられる。類似や典型例からの発想とは，最も陥りやすい思考プロセスであり，「かつて，こんな症例があった」，「教科書にこんなことが書いてあった」など，類似や典型例などからの発想により意志決定がなされるものである。日常臨床の現場でよく遭遇する発想である。二つ目の印象深い例からの発想は，過去の印象深い経験によるものであり，非常にうまくいった経験や辛い経験，また最近の新しい記憶として残っている知識（最近聞いた講演の内容など）により意志決定が左右されるというものである。めずらしい疾患に遭遇し症例報告として論文を書いた際などには，その後もめったにお目にかかることがないはずの疾患にまた遭遇するのではないかと日々頭に思い浮かべてしまう。三番目の固定観念と修正不十分な発想は，人間は誰しも最初に下した判断に固執しやすく，後から収集した様々な情報から軌道修正をする際にも，最初に下した判断に固執してしまい十分な軌道修正ができないことが多いということである。これを船の錨にたとえると，船（判断）の位置を修正する際に，最初に下ろした錨の位置により修正できる船の範囲に限りが生じてくるという現象である。

このように人間を扱う医療を行う際，不確実性下の判断は避けられない問題であり，ヒューリスティックな意志決定をいかに排除し，理論的・定量的に判断できるかが重要である。

表1　ヒューリスティック(heuristic)の種類

1	Representative ness heuristic　代表性：類似，典型例からの発想 → 「かつて，こんな症例があった」 「教科書にこんなことが書いてあった」
2	Availability heuristic　利用しやすさ：印象深い例からの発想 → 「昨日の講演で同じような話があった」 「昔，この方法でうまくいって，上司に褒められた」
3	Anchoring and adjustment heuristic　投錨と調整：固定観念と修正不十分な発想 → 第一印象からの修正が不十分である場合 固定観念から脱却し，正しい修正が行えない状態

III　科学的根拠に基づく医療（EBM）

信頼できる臨床データとは何か？一般的にはバイアス（偏り）が少なく，より多くの症例数を検討したデータがより信頼性の高いデータとされる。公表されたデータが他の施設・国でも同様の結果が得られた場合にはさらにその信頼性は増し，再現性の良いデータとして評価される。しかし，ここで注意しておかなければならないのは，信頼性が高いとされるランダム化比較試験の結果においても対象となった症例やスタディ・デザインにより得られる結果が変わってしまうこともあり，大規模なランダム化比較試験の結果が普遍性のある事実とは必ずしも言えないということである。公表された報告の信頼性をレベル分けする方法として，オックスフォード・EBM センターの評価法がよく用いられる（表2）。表2には治療，予防，病因に関するエビデンスレベルを示しているが，この他，診断，鑑別診断・症状有病率研究および決断分析に関するエビデンスレベルもある。

A　臨床試験

過去に遡って臨床データを解析する際には，治療法のばらつきとさまざまなバイアス（偏り）が混入しており，このばらつきやバイアスを完全に除去した解析を行うことは不可能である。このバイアスを取り除くためにランダム割付を行い，偶然がもたらす賢さによって人が認識できないバイアスも各群に均等に振り分けることができ，試験治療の効果や安全性をより正確に評価することができる。標準治療と試験治療を直接比較するのが第III相試験であるが，その前段階として第III相試験の試験治療の候補となりうる治療法を検証する第II相試験があり，奏功率や短期の生存率，生存期間の中央値などをエンドポイントとして試験が組まれる。さらにその前段階として，試験治療の安全性を評価するため毒性から見た至適容量を決定する第I相試験がまず行われ，適正な第II相試験の試験デザインを決定していく。このようなステップを一つ一つ積み上げ，個々のデータを正確に収集するためには多くの労力を要し，臨床試験全体の運用にあたってはコーディネータやデータセンターの存在は不可欠となる。なんでも二つの治療法をランダム割付して比較すればランダム化比較試験として成り立つと考える風潮があるが，これは大きな過ちである。当たり前のことであるが，臨床試験は多額の費用と労力を費やしてでも解決すべき臨床的問題を取り扱うものでなければならず，立案に当たっては事前に算定される症例数を集められるかという実行可能性や，結果が予想に反した場合の解釈なども考慮しなくてはならない。多数の患者にボランティアとして参加していただき，長期の経過を追うことで初めて結果が出されるものであり，試験管を用いたデータより遥かに手間がかかっており，なおかつ得られる結果は主たる目的（プライマリー・エンドポイント）ただ一つである。副次的に検討されるセカンダリー・エンドポイントは多重比較の問題もあり，プライマリー・エンドポイントとして得られた結果に比べ信頼性は落ちる。現在，世界中であらゆる分野の臨床試験が行われ次々と結果が報告されているが，そのデータの信頼性を吟味する能力を身につけなければEBM を実践することはできない。ここで多くを述べることは困難であるが，症例数は少なくないか，Intension to treat analysis（意図した通りの治療に基づく解析）が行われているか，算出された数値の信頼区間（95%信頼区間）はどうか，実臨床で実行可能な治療法であるのかなどを吟味してデータを検証する必要がある。一方，有名な学術雑誌に掲載されたランダム化比較試験の論文ばかりを精読したからといって，バイアスのない真実だけが身に付いたとは言えないので注意が必要である。ネガティブデータ（予測した結果が得られなかった場合や，新規治療の有用性が示されなかった場合など）が論文に掲載されにくいというバイアス（パブリケーション・バイアス）も無視することはできず，このバイアスを避けるために世界規模のプロジェクト（コクラン・プロジェクト）が組まれ

表2　オックスフォード・EBM センターのエビデンスレベル（2001）

レベル	研究内容
1a	ランダム化比較試験の系統的レビュー
1b	信頼区間の狭い個別のランダム化比較試験
1c	全か無の結果
2a	コホート研究の系統的レビュー
2b	個別のコホート研究 低質なランダム化比較を含む：例えば追跡が80%に満たない
2c	アウトカム調査：生態学的研究
3a	症例対照研究の系統的レビュー
3b	個別の症例対照研究
4	症例集積（と低質なコホート症例対照研究）
5	明白な批判的吟味のない専門家の意見，もしくは生理学，実験調査あるいは根本原理に基づくもの

ており，世界中で行われた臨床試験の結果を言語にかかわらず，また論文化されたものおよびされていないものもすべてを集積し，膨大なデータを系統的にレビューすることで真実に近いものを探る活動が進められている[1]。このプロジェクトはヒトゲノム解析の世界的プロジェクトと並ぶものと称されているが，がんの臨床研究を行う研究者たちはこのコクラン・プロジェクトの方がより意義の大きなものと注目している。コクラン・プロジェクトにより集められたデータと系統的レビューの一部はインターネットで入手可能であり，有料ではあるがその全体を入手することもできる。

公表された臨床試験の結果をどう解釈するかは最も重要な作業である。エビデンスレベル1bのランダム化比較試験の結果であっても，実臨床に適応するに当たっては注意が必要である。1例をあげる。限局期非ホジキンリンパ腫に関する臨床試験として，短期化学療法（3サイクル）と放射線治療の併用療法と，化学療法単独治療（8サイクル）を比較したランダム化比較試験（SWOG 8736）がある[3]。この試験により短期化学療法と放射線治療の併用療法が無病生存率および生存率において有意に化学療法単独に勝ることが示され，多くの放射線腫瘍医の励みとなった。しかし，9年の長期経過観察を行っていくとこの二つの生存率曲線は重なってしまい，前者の優越性は認められなくなった。一見，短期化学療法と放射線治療の併用療法が否定されたかのようにも取られがちであるが，長期経過を追ってみると二つの治療法には差がないことが示されたにすぎず，サブセット解析ではあるが予後不良因子の少ない症例では短期化学療法と放射線治療とを組み合わせた治療法の成績は依然良好な成績を示している。我々が現在行っている高齢者リンパ腫を対象とした短期化学療法と放射線治療の併用療法の有用性を検討する第II相臨床試験において，SWOG 8736のデータが問題となり試験の続行が検討された。我々は70歳以上の高齢者を対象としており，特に75歳を超えた患者にとって10～15年先の予後を改善するより，5～8年の経過においてより成績が良好であり，また高齢者にとって負担が少ない治療法を開発することが重要であるとの判断から試験は続行されることとなった。単なる治療法の優劣を論評するのではなく，その治療法が持つ臨床的意義を考慮した治療の選択が必要である。

B　メタ解析

一つのランダム化比較試験では解決できない臨床的問題も多々あり，それを解決する一つの方法としてメタ解析がある。メタ解析は，多数のランダム化比較試験をある一定の手法で収集し膨大な症例数を解析する。肺小細胞がんにおける予防的全脳照射の意義や，頭頸部腫瘍における化学療法の有用性などがこのメタ解析の手法により示された[4][5]。この手法により一つのランダム化比較試験では検出できなかった2～5％のわずかな治療成績の差を検出することができる。また，一つのランダム化比較試験では集積できないような多数の症例数を解析することで，より信頼性の高い知見を得ることができる。乳房温存療法における術後放射線治療の意義については1970年代から80年代にかけて複数のランダム化比較試験で放射線治療の有効性と乳房温存療法の安全性が示され，さらに最近，20年の長期経過観察を行った結果でも乳房切除術の成績と同等であることが示された[6]。さらに，メタ解析やpooled analysisの手法を用い，9,000例を超えるデータを解析し，乳房部分切除後に照射を行わないことで生存率の低下は招かないものの，術後照射は乳房内再発を1/3に減少させることが示された[7]。このように一つ一つのランダム化比較試験，および複数の試験を解析したメタ解析による検討を行い，一つの治療法が標準治療として相応しいかを一つ一つ階段を上るようにして長い時間をかけて確認していくことが必要である。

メタ解析は最も信頼性の高いエビデンスに値するとされているが，メタ解析の結果も注意深い解釈が必要である。ここで注意しておかなければならないことがある。治療成績においてたとえ1％の差であっても，5,000例から10,000例を対象とした解析を行うことで統計学的有意差を証明することができることがある。しかし，「1％の差」の持つ臨床的意味を考えなくてはならない。つまり，ある一人の医師がこの新規の治療で100人治療するとそのうちの1人がその恩恵を受けた計算になる。一生のうちにこの新規の治療法を用いて50人程度しか治療することがないとすると，この新規の治療の恩恵を受けた患者は一人もいない可能性がある。Number needed to be treated（NNT）の考えである。ここで重要なことは，この新規の治療法の毒性や，医療従事者側の労力などが問題となり，従来の治療法と毒性が変わらないものであれば新規の治療法を選択するのは当然であるが，新規治療法の毒性が強い場合などには，わずかな治療成績の向上と毒性とを天秤にかけ慎重に選択する必要がある。患者の負担と利益を中心に治療法を選択すべきである。

メタ解析も万能ではない。同じ目的で行われたメタ