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文　献

1) Albert FK, Forsting M, Sartor K, Adams HP, Kunze S: Early postoperative magnetic resonance imaging after resection of malignant glioma: Objective evaluation of residual tumor and its influence on regrowth and prognosis. *Neurosurgery* **34**: 45-61, 1994.
2) Berger MS: Functional mapping-guided resection of low-grade gliomas. *Clin Neurosurg* **42**: 437-452, 1995.
3) Brell M, Ibanez J, Caral L, Ferrer E: Factors influencing surgical complications of intra-axial brain tumours. *Acta Neurochir* (Wien) **142**: 739-750, 2000.
4) Catani M, Jones DK, Ffytche DH: Perisylvian language networks of the human brain. *Ann Neurol* **57**: 8-16, 2005.
5) Chung JK, Kim YK, Kim SK, Lee YJ, Paek S, Yeo JS, Jeong JM, Lee DS, Jung HW, Lee MC: Usefulness of 11C-methionine PET in the evaluation of brain lesions that are hypo-or isometabolic on 18F-FDG PET. *Eur J Nucl Med Mol Imaging* **29**: 176-182, 2002.
6) Costello TG, Cormack JR: Anaesthesia for awake craniotomy: A modern approach. *J Clin Neurosci* **11**: 16-19, 2004.
7) Duffau H, Capelle L, Denvil D, Sichez N, Gatignol P, Taillandier L, Lopes M, Mitchell MC, Roche S, Muller JC, Bitar A, Sichez JP, van Effenterre R: Usefulness of intraoperative electrical subcortical mapping during surgery for low-grade gliomas located within eloquent brain regions: Functional results in a consecutive series of 103 patients. *J Neurosurg* **98**: 764-778, 2003.
8) Duffau H, Capelle L, Sichez N, Denvil D, Lopes M, Sichez JP, Bitar A, Fohanno D: Intraoperative mapping of the subcortical language pathways using direct stimulations. An anatomo-functional study. *Brain* **125**: 199-214, 2002.
9) Duffau H, Denvil D, Capelle L: Long term reshaping of language, sensory, and motor maps after glioma resection: A new parameter to integrate in the surgical strategy. *J Neurol Neurosurg Psychiatry* **72**: 511-516, 2002.
10) Goldratt EM: *The haystack syndrome. Sitting information out of data ocean*. New York, North River Press, 1990.
11) Hess KR: Extent of resection as a prognostic variable in the treatment of gliomas. *J Neurooncol* **42**: 227-231, 1999.
12) 星田　徹，榊　寿右：皮質電気刺激による脳機能マッピング．高倉公朋編：脳神経外科の最先端 NO. 2, 21 世紀の新領域とニューテクノロジー．東京，先端医療技術研究所，2000, pp.261-268.
13) Iseki H, Muragaki Y, Taira T, Kawamata T, Maruyama T, Naemura K, Nambu K, Sugiura M, Hirai N, Hori T, Takakura K: New possibilities for stereotaxis. Information-guided stereotaxis. *Stereotact Funct Neurosurg* **76**: 159-167, 2001.
14) Johnson PC, Hunt SJ, Drayer BP: Human cerebral gliomas: Correlation of postmortem MR imaging and neuropathologic findings. *Radiology* **170**: 211-217, 1989.
15) Karim AB, Afra D, Cornu P, Bleehan N, Schraub S, De Witte O, Darcel F, Stenning S, Pierart M, Van Glabbeke M: Randomized trial on the efficacy of radiotherapy for cerebral low-grade glioma in the adult: European Organization for Research and Treatment of Cancer Study 22845 with the Medical Research Council study BRO4: An interim analysis. *Int J Radiat Oncol Biol Phys* **52**: 316-324, 2002.
16) Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, Lang FF, McCutcheon IE, Hassenbusch SJ, Holland E, Hess K, Michael C, Miller D, Sawaya R: A multivariate analysis of 416 patients with glioblastoma multiforme: Prognosis, extent of resection, and survival. *J Neurosurg* **95**: 190-198, 2001.
17) Luyken C, Blumcke I, Fimmers R, Urbach H, Elger CE, Wiestler OD, Schramm J: The spectrum of long-term epilepsy-associated tumors: Long-term seizure and tumor outcome and neurosurgical aspects. *Epilepsia* **44**: 822-830, 2003.
18) Maruyama T, Muragaki Y, Iseki H, Kubo O, Mochizuki M, Seo S, Sakuma I, Hori T, Takakura K: Intraoperative detection of malignant gliomas using 5-Aminolevulic acid induced protoporphyrin fluorescence, openMRI and real-time navigation system. *CARS2001*: 270-275, 2001.
19) Miwa K, Shinoda J, Yano H, Okumura A, Iwama T, Nakashima T, Sakai N: Discrepancy between lesion distributions on methionine PET and MR images in patients with glioblastoma multiforme: Insight from a PET and MR fusion image study. *J Neurol Neurosurg Psychiatry* **75**: 1457-1462, 2004.
20) Moriarity JL, Boatman D, Krauss GL, Storm PB, Lenz FA: Human "memories" can be evoked by stimulation of the lateral temporal cortex after ipsilateral medial temporal lobe resection. *J Neurol Neurosurg Psychiatry* **71**: 549-551, 2001.
21) 村垣善浩，丸山隆志，伊関　洋，堀　智勝：神経膠腫摘出のための覚醒下手術．脳外速報 **14**: 1187-119, 2004.
22) 村垣善浩，平沢研一，山根文孝，今村　強，丸山隆志，久保長生，堀　智勝：長期硬膜下電極埋め込みによる Mapping を利用した Eloquent Area 近傍 Glioma 摘出術．嘉山孝正編：Advanced Technology を用いた脳腫瘍の外科．大阪，メディカ出版，2001, pp.140-148.
23) Muragaki Y, Suzukawa K, Iseki H, Maruyama T, Nambu K, Aramata H, Sugiura M, Naemura K, Hori T, Takakura K: Development of three-dimensional navigation system updated with intraoperative MRI. *CARS2003*: 1360, 2003.
24) Neuloh G, Pechstein U, Cedzich C, Schramm J: Motor evoked potential monitoring with supratentorial surgery. *Neurosurgery* **54**: 1061-1072, 2004.
25) Nimsky C, Ganslandt O, Cerny S, Hastreiter P, Greiner G, Fahlbusch R: Quantification of, visualization, and compen-

sation for brain shift using intraoperative magnetic resonance imaging. *Neurosurgery* **47**: 1070-1080, 2000.
26) Nimsky C, Ganslandt O, Hastreiter P, Wang R, Benner T, Sorensen AG, Fahlbusch R: Intraoperative diffusion-tensor MR imaging: Shifting of white matter tracts during neurosurgical procedures —initial experience. *Radiology* **234**: 218-225, 2005.
27) Ojemann GA: Neurosurgical management of epilepsy: A personal perspective in 1983. *Appl Neurophysiol* **46**: 11-18, 1983.
28) Ojemann JG, Miller JW, Silbergeld DL: Preserved function in brain invaded by tumor. *Neurosurgery* **39**: 253-259, 1996.
29) Pignatti F, van den Bent M, Curran D, Debruyne C, Sylvester R, Therasse P, Afra D, Cornu P, Bolla M, Vecht C, Karim AB: Prognostic factors for survival in adult patients with cerebral low-grade glioma. *J Clin Oncol* **20**: 2076-2084, 2002.
30) Pouratian N, Cannestra AF, Bookheimer SY, Martin NA, Toga AW: Variability of intraoperative electrocortical stimulation mapping parameters across and within individuals. *J Neurosurg* **101**: 458-466, 2004.
31) Proescholdt MA, Macher C, Woertgen C, Brawanski A: Level of evidence in the literature concerning brain tumor resection. *Clin Neurol Neurosurg* **107**: 95-98, 2005.
32) Quinones-Hinojosa A, Ojemann SG, Sanai N, Dillon WP, Berger MS: Preoperative correlation of intraoperative cortical mapping with magnetic resonance imaging landmarks to predict localization of the Broca area. *J Neurosurg* **99**: 311-318, 2003.
33) Report of brain tumor registry of Japan (1969-1993) 10th edition. *Neurol Med Chir (Tokyo)* **40**: 1-106, 2000.
34) Roux FE, Boulanouar K, Lotterie JA, Mejdoubi M, LeSage JP, Berry I: Language functional magnetic resonance imaging in preoperative assessment of language areas: Correlation with direct cortical stimulation. *Neurosurgery* **52**: 1335-1347, 2003.
35) Sartorius CJ, Berger MS: Rapid termination of intraoperative stimulation-evoked seizures with application of cold Ringer's lactate to the cortex. Technical note. *J Neurosurg* **88**: 349-351, 1998.
36) Shi WM, Wildrick DM, Sawaya R: Volumetric measurement of brain tumors from MR imaging. *J Neurooncol* **37**: 87-93, 1998.
37) Taylor MD, Bernstein M: Awake craniotomy with brain mapping as the routine surgical approach to treating patients with supratentorial intraaxial tumors: A prospective trial of 200 cases. *J Neurosurg* **90**: 35-41, 1999.
38) Ulmer JL, Hacein-Bey L, Mathews VP, Mueller WM, DeYoe EA, Prost RW, Meyer GA, Krouwer HG, Schmainda KM: Lesion-induced pseudo-dominance at functional magnetic resonance imaging: Implications for preoperative assessments. *Neurosurgery* **55**: 569-581, 2004.
39) Wada J, Rasmussen T: Intracarotid injection of Sodium Amytal for the lateralization of cerebral speech dominance. Experimental and clinical observations. *J Neurosurg* **17**: 266-282, 1960.
40) Wiedemayer H, Fauser B, Sandalcioglu IE, Schafer H, Stolke D: The impact of neurophysiological intraoperative monitoring on surgical decisions: A critical analysis of 423 cases. *J Neurosurg* **96**: 255-262, 2002.

要　旨

情報誘導によるグリオーマ手術

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グリオーマの積極的摘出はいまだ議論が多い．Selection bias や publication bias，さらに摘出度の評価法が異なることが主な原因と考える．他臓器転移が少なく，約 90%が局所再発であることなどから，われわれは積極摘出の立場を採っているが，最小限の合併症との両立には科学的情報が必要である．神経学的合併症の原因は，①皮質損傷・②白質損傷・③血管損傷であるが，それぞれ，①高次機能に個人差があること，②解剖学的 landmark が欠如しており重要な神経線維同定が困難であること，③皮質動脈は切断による症状が予測困難で，穿通枝は保存する技術的な難易度が高いことなどが原因である．術中 MRI やナビゲーションの解剖学的情報，覚醒下手術でのマッピングやモニタリング（MEP，SEP など）による機能的情報は摘出率向上と合併症予防に有用であるが，各術中情報・検査の特性（偽陽・陰性や誤差）を理解したうえでの判断が必要である．これに組織学的情報や代謝情報を加えた多種情報による手術——情報誘導手術を紹介する．

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Evaluation of Acute Intestinal Toxicity in Relation to the Volume of Irradiated Small Bowel in Patients Treated with Concurrent Weekly Gemcitabine and Radiotherapy for Locally Advanced Pancreatic Cancer

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Abstract. *Background: Treatment of concurrent gemcitabine and radiotherapy for pancreatic cancer was reported to have a higher rate of severe acute intestinal toxicity. This study evaluated the acute intestinal toxicity in relation to the volume of irradiated small bowel and other factors using dosimetric analyses in pancreatic cancer patients treated with gemcitabine-based chemoradiotherapy. Materials and Methods: The patient population was derived from a phase II trial of concurrent weekly gemcitabine and radiotherapy for locally advanced pancreatic cancer. Gemcitabine was administered weekly at a dose of 250 mg/m^2. The total dose was 50.4 Gy in 28 fractions using a four-field conformal technique. A dose-volume histogram was generated for the small bowel, colon and planning target volume (PTV) and dosimetric parameters were recorded. Correlations between the acute intestinal toxicity and the volume of irradiated small bowel and other factors were evaluated. Results: Forty-two patients enrolled between July 2001 and July 2002 were analyzed. Grade 3+ acute intestinal toxicities were observed in twenty-four (62%) patients. There was no correlation between the acute intestinal toxicity and the volume of irradiated small bowel. However, the total volume of PTV was shown to be significantly correlated with the development of Grade 3+ acute intestinal toxicity ($p=0.021$). Conclusion: The volume of irradiated small bowel did not directly influence the acute intestinal toxicity, but only the volume of PTV significantly correlated with severe acute intestinal toxicity.*

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Key Words: Pancreatic cancer, chemoradiotherapy, gemcitabine, intestinal toxicity.

Pancreatic cancer is usually diagnosed as an unresectable locally advanced or metastatic disease in most patients. In patients with locally advanced pancreatic cancer, chemoradiotherapy has been commonly used as a standard treatment since it was recognized that radiotherapy with concurrent 5-fluorouracil (5-FU) prolonged survival when compared to radiotherapy or chemotherapy alone (1-3). Various novel agents and radiation schedules have been examined in clinical trials to improve the efficacy of the treatment (4).

Gemcitabine is a novel deoxycitidine analog with a broad spectrum of antitumor activity against a variety of solid tumors, including pancreatic cancer, which has demonstrated greater clinical benefit and survival compared with 5-FU in patients with advanced pancreatic cancer (5). Gemcitabine has also been shown to be a potent radiosensitizer in human pancreatic cancer (6-8). Therefore, concurrent gemcitabine and radiotherapy are currently being examined in clinical trials, suggesting that the combination of radiotherapy and gemcitabine may improve survival in patients with locally advanced pancreatic cancer (9-13).

However, significant acute intestinal toxicity (AIT) in the treatment of concurrent gemcitabine and radiotherapy was reported compared with concurrent 5-FU and radiotherapy (9, 10, 14). In rectal cancer treated with concurrent chemoradiotherapy, a significant relationship between the intestinal toxicity and the volume of irradiated small bowel is well recognized from the results of examinations using small bowel contrast and orthogonal radiographs to calculate the volume of small bowel in the high-dose volume (15-17) and more accurately three-dimensional (3D) treatment-planning tools (18). However, it has not been reported whether the volume of irradiated small intestine is related to the degree of AIT in patients treated with concurrent chemoradiotherapy for pancreatic cancer. The purpose of this study was to evaluate the AIT in relation to

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the volume of irradiated small bowel and to other factors using dosimetric analyses in patients treated with concurrent weekly gemcitabine and radiotherapy for locally advanced pancreatic cancer.

Materials and Methods

Patient population. The patient population for this study was derived from a phase II trial of concurrent weekly gemcitabine and radiotherapy for unresectable locally advanced pancreatic cancer at the National Cancer Center Hospital (19). Eligibility criteria for this phase II trial included histologically or cytologically confirmed nonresectable adenocarcinoma, 20-74 years of age, an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, no evidence of distant metastasis, adequate hematological function (hemoglobin ≥10 g/dl, leukocytes ≥4000 mm^3, neutrophils >2000 mm^3, and platelets ≥100000 mm^3), adequate hepatic function (serum total bilirubin ≤2.0 mg/dl, and serum transaminase (aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) < 2.5 times the upper normal limit (UNL), adequate renal function (serum creatinine within normal limit) and written informed consent.

Treatment details and dosimetric analysis. Gemcitabine was administered intravenously over 30 min starting 2 h before radiotherapy, weekly for 6 weeks, at a dose of 250 mg/m^2, which had been previously determined in a phase I trial in our hospital (20). When grade 3 hematological toxicity, serum creatinine of 1.5-2.0 times UNL, total bilirubin level of 3.0-5.0 times UNL, serum AST/APT of 5.0-10 times UNL and/or grade 2 non-hematological toxicity (excluding nausea, vomiting, anorexia, fatigue, constipation, alopecia and dehydration) were observed, gemcitabine administration was omitted and postponed to the next scheduled treatment days.

Radiotherapy was delivered *via* a racetrack microtron (MM50, Scanditronix, Uppsala, Sweden) with a 25 MV X-rays. All patients had treatment planning computed tomography (CT) scans (X-vision, Toshiba, Tokyo, Japan), 5 mm thickness with a 5 mm slice interval, with oral small bowel contrast. The clinical target volume (CTV) included the primary tumor, nodal involvement detected by CT scan, and draining and para-aortic lymph nodes. The planning target volume (PTV) was defined as CTV plus a 10 mm margin in the lateral direction and a 10-20 mm margin in the cranio-caudal direction. Four-field techniques (anterior, posterior and opposed lateral fields) were used. The spinal cord dose was maintained below 45 Gy and ≥50% of the liver was limited to ≤30 Gy, ≥50% of both kidneys were limited to ≤20 Gy. The prescription dose was 50.4 Gy, delivered in 1.8 Gy daily fractions. FOCUS (version 3.2.1, CMS, St. Louis, MO, USA) was used as a radiotherapy treatment planning system. The individual loops of small bowel and colon were delineated on each slice of the planning CT scan from the upper end level of the liver to the lower end level of the kidneys. The volumes of small bowel receiving doses between 5 and 45 Gy were recorded from DVH at 5-Gy intervals.

Toxicity assessment. Patients were evaluated at least weekly during radiotherapy, prospectively. National Cancer Institute common toxicity criteria, version 2.0, were used for toxicity assessment. AIT was defined as any toxicity that could be related to the small bowel, which included nausea, vomiting, anorexia and diarrhea, according to the previous report for rectal cancer (17) and ≥grade 3 was considered severe toxicity.

Table I. *Patient characteristics.*

Characteristic	No. of patients (N=42)
Gender	
male	19
female	23
Age, years	
range	43-73
median	59
Performance status	
0	12
1	30
Tumor size, cm	
range	2.0-10.0
median	4.0
Tumor site	
head	20
body-tail	22

Statistical analysis. For each 5-Gy dose level from 5 to 45 Gy, an association between the volume of small bowel irradiated and grade 3+ AIT was analyzed. The differences in mean small bowel volume irradiated to each 5-Gy dose level from 5 to 45 Gy were assessed using the *t*-test for the equality of means. Univariate analysis comparing the clinical and treatment factors and grade 3+ AIT was performed using the Fisher's exact test. *P*-values less than 0.05 were considered to be statistically significant.

Results

Forty-two patients were enrolled in a phase II trial between July 2001 and July 2002, and all patients were entered in this study. The patient characteristics are shown in Table I. Forty patients completed the planned radiotherapy (50.4 Gy). Two patients discontinued radiotherapy. One patient stopped at 30.6 Gy because of duodenal bleeding and another patient stopped at 45.0 Gy because of refusal due to general fatigue. The number of times gemcitabine was administered was 6 times in 17 patients, 5 times in 15 patients, 4 times in 6 patients, 3 times in 2 patients and 2 times in 2 patients. Grade 3 and grade 4 non-hematological toxicities were observed in 31% and 33% of patients, respectively. Overall, the maximum AIT encountered during radiotherapy was grade 0 in 4 patients (9.5%), grade 1 in 9 patients (21.4%), grade 2 in 3 patients (7.2%), grade 3 in 12 patients (28.6%) and grade 4 in 14 patients (33.3%). Median and range values of the dosimetric parameters of small bowel, colon and PTV are shown in Table II. The volume of irradiated small bowel ranged from 43 cm^3 to 552 cm^3, with a median value of 251 cm^3 and the volume of

Table II. *Median and range values of dosimetric parameters.*

Parameter	Median	Range
Small bowel		
total volume, cm^3	274	47-663
irradiated volume, cm^3	251	43-552
max dose, cGy	5072	3079-5229
mean dose, cGy	1485	376-2915
Colon		
total volume, cm^3	403	120-714
irradiated volume, cm^3	397	117-686
max dose, cGy	5028	1975-5221
mean dose, cGy	1516	633-2848
Planning target volume		
total volume, cm^3	555	357-1215
max dose, cGy	5120	3106-5275
mean dose, cGy	4948	3002-5045

Table III. *Volume of irradiated small intestine at each 5-Gy dose level between 5 and 45 Gy vs. the degree of acute intestinal toxicity (mean±SE, cm^3).*

RT dose level (Gy)	Grade 0-2 toxicity	Grade 3-4 toxicity	*p*-value
5	169±99	182±99	0.669
10	150±94	161±92	0.707
15	140±90	148±90	0.787
20	64±41	66±50	0.873
25	53±36	55±42	0.879
30	49±33	50±40	0.910
35	43±27	45±36	0.864
40	38±23	41±32	0.786
45	32±20	35±28	0.715

PTV ranged from 357 cm^3 to 1215 cm^3, with a median value of 555 cm^3, corresponding to a cube of 8.2 cm on a side. The average volume of small bowel irradiated at each 5-Gy dose level between 5 and 45 Gy are shown in Table III.

The average volume of small bowel irradiated at each dose level was not significantly different between the group of grade 3+ AIT and the group of grade 0-2 AIT by the *t*-test for equality of means. The relationships between grade 3+ AIT and clinical factors are shown in Table IVa. No significant correlation was seen between grade 3+ AIT and clinical factors, including age, performance status, tumor size, tumor site, and number of times gemcitabine was administered. The relationships between grade 3+ AIT and the calculated parameters are shown in Table IVb. No significant correlation was seen between grade 3+ AIT and the volume of small bowel irradiated or other parameters regarding the small bowel and the colon. However, the total volume of PTV was shown to be significantly

Table IVa. *Univariate analysis of clinical and treatment factors related to the development of ≥ grade 3 acute intestinal toxicity.*

Characteristic	n	% toxicity	*p*-value*
Gender			
male	19	63.2%	
female	23	60.9%	>0.999
Age, years			
<60	22	54.5%	
≥60	20	70.0%	0.355
PS			
0	12	41.7%	
1	30	70.0%	0.158
Tumor size, cm			
≤4	22	54.5%	
>4	20	70.0%	0.355
Tumor Site			
head	20	65.0%	
body-tail	22	59.1%	0.758
Number of times gemcitabine was administered			
<5	10	80.0%	
≥5	32	56.3%	0.270

*Fisher's exact test.

Table IVb. *Univariate analysis of calculated parameters related to the development of ≥ grade 3 acute intestinal toxicity.*

Characteristic	n	% toxicity	*p*-value*
Small bowel			
irradiated volume, cm^3			
<250	18	66.7%	
≥250	24	58.3%	0.750
max dose, cGy			
<5100	30	60.0%	
≥5100	12	66.7%	0.740
mean dose, cGy			
<1500	22	63.6%	
≥1500	20	60.0%	>0.999
Colon			
irradiated volume, cm^3			
<400	22	59.1%	
≥400	20	65.0%	0.758
max dose, cGy			
<5000	16	68.8%	
≥5000	26	57.7%	0.530
mean dose, cGy			
<1500	21	66.7%	
≥1500	21	57.1%	0.751
Planning target volume			
total volume, cm^3			
<500	16	37.5%	
≥500	26	76.9%	0.021

*Fisher's exact test.

correlated with the development of grade 3+ AIT (p=0.021). The highest incidence of grade 3+ AIT was in patients with the volume of PTV ≥500 cm^3, corresponding to a cube of 7.9 cm on a side.

Discussion

We evaluated the relationship between the AIT and the volume of irradiated small bowel in patients treated with concurrent gemcitabine and radiotherapy for pancreatic cancer and univariate analysis revealed that the volume of irradiated small bowel, which was significantly related to AIT in the treatment of rectal cancer, did not correlate to the AIT here. Minsky *et al.* reported a significant relationship between AIT and the volume of irradiated small bowel in patients with rectal cancer treated with concurrent 5-FU-based chemotherapy and pelvic radiotherapy (17). Orthogonal radiographs were used to calculate the volume of small bowel within the treated volume, using the sum of the anterior-posterior film volume and the lateral film volume. The volume of small bowel in the pelvic radiation field was greater for patients who experienced grade 3+ AIT (441±153 cm^3) compared with those who experienced grade 0-2 acute intestinal toxicity (230±43 cm^3). Baglan *et al.* reported a strong dose-relationship for the development of grade 3+ AIT in patients treated with concurrent 5-FU based chemoradiotherapy for rectal cancer using three-dimensional (3D) treatment planning tools, the same as our method (18). A highly significant association was found between the development of grade 3+ AIT and the average volume of small bowel irradiated to each 5-Gy dose level between 5 and 40 Gy (p<0.001). The volume of small bowel that received at least 15 Gy (V15) was strongly associated with the degree of AIT.

The present report represents the first analysis of AIT using dosimetric analysis in pancreatic cancer treated with chemoradiotherapy. In this study, the patient population and treatment schedule was more homogeneous compared with previous reports for rectal cancer and toxicities were evaluated prospectively, because all patients entered in this analysis were previously enrolled in a clinical trial. The reasons for the different results regarding AIT and the volume of irradiated small bowel between rectal cancer and pancreatic cancer could be several. First, the agent of chemotherapy in the combination of radiotherapy was different between the two groups. In previous reports for rectal cancer, 5-FU based chemotherapy was used, while in our study for pancreatic cancer, gemcitabine was used. An *in vivo* study showed that there was markedly increased normal tissue toxicity, such as jejunal mucosa, when gemcitabine was given more than once a week in combination with radiotherapy (21). Second, the volume of irradiated stomach and duodenum may be related to the AIT in part, since in the treatment of pancreatic cancer the upper abdomen is irradiated and the stomach and duodenum are usually included in the treated volume. However, in this study we did not evaluate the volume of irradiated stomach since it was difficult to evaluate the volume of stomach, exactly, due to the great variation in volume depending on the time of day compared with the small bowel and colon. We also did not evaluate the volume of irradiated duodenum. Because most of the duodenum was included in the radiation field with prophylactic regional lymph node area, the volume of irradiated duodenum was considered similar among the patients.

We found that the PTV was significantly associated with severe AIT. This result indicates that a larger treated volume affects a large volume of normal tissue, not just the small bowel. Recently, in an attempt to decrease the toxicity in the treatment of gemcitabine-based chemoradiotherapy, researchers at the University of Michigan and M.D. Anderson Cancer Center performed and recommended radiation treatment planning, which set only the gross tumor in the target volume without a prophylactic regional lymph node area (11, 14, 22). These authors reported that the PTV ranged from 134 cm^3 to 465 cm^3, with a median value of 255 cm^3, corresponding to a cube of only 6.3 cm on a side, which was much smaller compared with conventional radiotherapy and patients were able to tolerate the treatment (22). Our result that the smaller PTV (<500 cm^3, corresponding to a cube of 7.9 cm on a side) had less acute intestinal toxicity supports their recommendation. However, the efficacy of treatment without prophylactic regional lymph node irradiation should be evaluated in clinical trials and a longer follow-up is needed.

In conclusion, the volume of irradiated small bowel did not directly influence the AIT in patients treated with concurrent weekly gemcitabine and radiotherapy for locally advanced pancreatic cancer. However, only the PTV significantly correlated with severe AIT. Reducing the treated volume, *e.g.,* by omitting prophylactic regional lymph node irradiation, seemed to result in decreased AIT when patients were treated concurrently with gemcitabine-based chemoradiotherapy.

References

1 The Gastrointestinal Tumor Study Group: A multi-institutional comparative trial of radiation therapy alone and in combination with 5-fluorouracil for locally unresectable pancreatic carcinoma. Ann Surg *189*: 205-208, 1979.

2 Moertel CG, Frytak S, Hahn RG *et al*: Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. Cancer *48*: 1705-1710, 1981.

3 The Gastrointestinal Tumor Study Group: Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. J Natl Cancer Inst *80*: 751-755, 1988.
4 Okada S. Non-surgical treatments of pancreatic cancer. Int J Clin Oncol *4*: 257-266, 1999.
5 Burris HA 3rd, Moore MJ, Andersen J *et al*: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol *15*: 2403-2413, 1997.
6 Lawrence TS, Chang EY, Hahn TM *et al*: Radiosensitization of pancreatic cancer cells by 2',2'-difluoro-2'-deoxycytidine. Int J Radiat Oncol Bio Phys *34*: 867-872, 1996.
7 Shewach DS and Lawrence TS: Gemcitabine and radiosensitization in human tumor cells. Invest New Drugs *14*: 257-263, 1996.
8 van Putten JWG, Groen HJM, Smid K *et al*: End-joining deficiency and radiosensitization induced by gemcitabine. Cancer Res *61*: 1585-1591, 2001.
9 Talamonti MS, Catalano PJ, Vaughn DJ *et al*: Eastern Cooperative Oncology Group Phase I trial of protracted venous infusion fluorouracil plus weekly gemcitabine with concurrent radiation therapy in patients with locally advanced pancreas cancer: a regimen with unexpected early toxicity. J Clin Oncol *18*: 3384-3389, 2000.
10 Wolff RA, Evans DB, Gravel DM *et al*: Phase I trial of gemcitabine combined with radiation for the treatment of locally advanced pancreatic adenocarcinoma. Clin Cancer Res *7*: 2246-2253, 2001.
11 McGinn CJ, Zalupski MM, Shureiqi I *et al*: Phase I trial of radiation dose escalation with concurrent weekly full-dose gemcitabine in patients with advanced pancreatic cancer. J Clin Oncol *19*: 4202-4208, 2001.
12 Poggi MM, Kroog GS, Russo A *et al*: Phase I study of weekly gemcitabine as a radiation sensitizer for unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys *54*: 670-676, 2002.
13 Blackstock AW, Tepper JE, Niedwiecki D *et al*: Cancer and leukemia group B (CALGB) 89805: phase II chemoradiation trial using gemcitabine in patients with locoregional adenocarcinoma of the pancreas. Int J Gastrointest Cancer *34*: 107-116, 2003.
14 Crane CH, Abbruzzese JL, Evans DB *et al*: Is the therapeutic index better with gemcitabine-based chemoradiation than with 5-fluorouracil-based chemoradiation in locally advanced pancreatic cancer? Int J Radiat Oncol Biol Phys *52*: 1293-1302, 2002.
15 Herbert SH, Solin LJ, Hoffman JP *et al*: Volumetric analysis of small bowel displacement from radiation portals with the use of a pelvic tissue expander. Int J Radiat Oncol Biol Phys *25*: 885-893, 1993.
16 Gallagher MJ, Brereton HD, Rostock RA *et al*: A prospective study of treatment techniques to minimize the volume of pelvic small bowel with reduction of acute and late effects associated with pelvic irradiation. Int J Radiat Oncol Biol Phys *12*: 1565-1573, 1986.
17 Minsky BD, Conti JA, Huang Y *et al*: Relationship of acute gastrointestinal toxicity and the volume of irradiated small bowel in patients receiving combined modality therapy for rectal cancer. J Clin Oncol *13*: 1409-1416, 1995.
18 Baglan KL, Frazier RC, Yan D *et al*: The dose-volume relationship of acute small bowel toxicity from concurrent 5-FU-based chemotherapy and radiation therapy for rectal cancer. Int J Radiat Oncol Biol Phys *52*: 176-183, 2002.
19 Okusaka T, Ito Y, Ueno H *et al*: Phase II study of radiotherapy combined with gemcitabine for locally advanced pancreatic cancer. Br J Cancer *91*: 673-677, 2004.
20 Ikeda M, Okada S, Tokuuye K *et al*: A phase I trial of weekly gemcitabine and concurrent radiotherapy in patients with locally advanced pancreatic cancer. Br J Cancer *86*: 1551-1554, 2002.
21 Mason KA, Milas L, Hunter NR *et al*: Maximizing therapeutic gain with gemcitabine and fractionated radiation. Int J Radiat Oncol Biol Phys *44*: 1125-1135, 1999.
22 Muler JH, McGinn CJ, Normolle D *et al*: Phase I trial using a time-to-event continual reassessment strategy for dose escalation of cisplatin combined with gemcitabine and radiation therapy in pancreatic cancer. J Clin Oncol *22*: 238-243, 2004.

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Treatment of lung damage

Retrospective analysis of steroid therapy for radiation-induced lung injury in lung cancer patients

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Abstract

Purpose: To disclose characteristics of lung cancer patients developing radiation-induced lung injury treated with or without corticosteroid therapy.

Methods and materials: Radiographic changes, symptoms, history of corticosteroid prescription, and clinical course after 50–70 Gy of thoracic radiotherapy were retrospectively evaluated in 385 lung cancer patients.

Results: Radiation-induced lung injury was stable without corticosteroid in 307 patients (Group 1), stable with corticosteroid in 64 patients (Group 2), and progressive to death despite corticosteroid in 14 patients (Group 3). Fever and dyspnea were noted in 11%, 50% and 86% ($p < 0.001$), and in 13%, 44% and 57% ($p < 0.001$) patients in Groups 1–3, respectively. Median weeks between the end of radiotherapy and the first radiographic change were 9.9, 6.7 and 2.4 for Groups 1–3, respectively ($p < 0.001$). The initial prednisolone equivalent dose was 30–40 mg daily in 52 (67%) patients. A total of 16 (4.2%) patients died of radiation pneumonitis or steroid complication with a median survival of 45 (range, 8–107) days.

Conclusion: Development of fever and dyspnea, and short interval between the end of radiotherapy and the first radiographic change were associated with fatal radiation-induced lung injury. Prednisolone 30–40 mg daily was selected for the treatment in many patients.

Keywords: Radiation pneumonitis; Radiotherapy; Lung cancer; Corticosteroid

Thoracic radiotherapy is widely used for the curative and palliative treatment of lung cancer. Radiation-induced lung injury was first described as early as 1922 [1,2], and two types of lung injury, radiation pneumonitis and radiation fibrosis, were recognized in 1925 [3]. Radiation pneumonitis occurs in 5–15% of patients who have received radiation therapy for lung cancer. Its clinical symptoms are characterized by cough, dyspnea and fever developing between 1 and 3 months after the end of radiotherapy. Distinctive radiographic changes of radiation pneumonitis are a ground-glass opacification or diffuse haziness in early phase, and then alveolar infiltrates or dense consolidation in late phase in the region corresponding to the irradiated area [4–7]. Radiation pneumonitis may persist for a month or more and subside gradually. In severe cases, however, pneumonitis progresses to death due to respiratory failure within few weeks [4].

Use of adrenocorticotropic hormone (ACTH) and cortisone for radiation pneumonitis in a case was first reported in 1951 [8], and 9 cases of radiation pneumonitis treated with cortisone therapy in the literature were reviewed in 1968 [9]. Although no case series or clinical trials of corticosteroid therapy have been reported since that time, prednisolone has been given in patients with severe pneumonitis in clinical practice. The initial dose of prednisolone, approximately 30–100 mg daily, and very slow tapering schedule are in agreement among experts [4–6,10], because early withdrawal results in aggravation of pneumonitis [11–13]. There is no consensus, however, about criteria to define when steroids are required for radiation-induced lung injury. The objective of this study is to disclose general characteristics of lung cancer patients developing radiation-induced lung injury treated with or without corticosteroid therapy, to obtain data on the initiation criteria, dose, and taper schedule of corticosteroid therapy for further prospective trials.

Patients and methods

Consecutive lung cancer patients treated with thoracic radiotherapy at a total dose of 50–70 Gy in National Cancer

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Center Hospital between January 1998 and December 2003 were subjects of this study. We retrospectively reviewed all chest X-ray films taken during 6 month period from the end of thoracic radiation to identify the first radiographic change and its progress. History of corticosteroid prescription, symptoms at the time of and one-month period after the first radiographic change in a chest X-ray film, and clinical course of radiation-induced lung injury were obtained from medical charts. The diagnosis of radiation-induced lung injury was defined as radiographic changes including opacification, diffuse haziness, infiltrates or consolidation conforming to the outline of the sharply demarcated irradiated area in a chest X-ray film. During clinical course, scarring (fibrosis) was developed within the irradiated area leading to a reduction in lung volume. In contrast, pulmonary infection spreads through anatomical structure of the lung, and the boundary of infiltrates corresponds to anatomical boundary of the lung. For patients with fever, the radiographical response to antibiotics was also evaluated. Observed differences in the proportions of patients in various patient subgroups were evaluated using Chi-square test. Differences between continuous variables were compared using Mann–Whitney tests. The Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan) was used for all statistical analyses.

Results

Of 544 lung cancer patients receiving thoracic radiotherapy at a total dose of 50–70 Gy, 111 patients were excluded from this study because they were not evaluable: loss of follow-up in 88 patients, early lung cancer progression in 18 patients, chemotherapy-induced neutropenic fever and pneumonia in three patients, death of bleeding from the esophageal stent in one patient, and no chest X-ray films available in one patient. In addition, 48 patients (11% of 433 evaluable patients) were also excluded because no radiation-induced lung injury was noted. Thus, the subject of this study was 385 patients.

Of the 385 patients, 78 (20%) received corticosteroid therapy for radiation-induced lung injury, and 307 did not. Radiation-induced lung injury was stable without corticosteroid in the 307 (80%) patients (Group 1), stable or in remission with corticosteroid in 64 (17%) patients (Group 2), and progressive to death despite corticosteroid in 14 (4%) patients (Group 3). No difference in sex, total dose, intent of radiotherapy, and combination chemotherapy was noted among three Groups, but median age of patients was higher in Group 3 (Table 1). Fever was developed in 50% of patients in Group 3 at the initial radiographic change, and in 86% of them during subsequent clinical course, while it was developed in only 11–12% of patients in Group 1 through their clinical course (Table 2). Dyspnea was developed in 57% of patients in Group 3 and in 44% of patients in Group 2 during clinical course, while it was developed in only 14% of patients in Group 1 (Table 2). A total of 88 patients developed fever at the initial change in chest X-ray and/or during subsequent clinical course. Of these, 43 patients received antibiotics, but no radiographical response was obtained in these patients. Five (2%) and seven (2%) patients in Group 1 developed bloody sputum and chest pain, respectively, but none in Group 2 or 3 developed these symptoms. The average interval of chest X-rays taken between the start of radiotherapy and the first appearance of radiographic change was 1.7 weeks for group 1, 1.3 weeks for group 2, and 0.9 weeks for group 3 ($P < 0.001$, Table 3). Interval between the end of radiotherapy and the first change in a chest X-ray was shorter in Group 3 than in Group 2 or Group 1 (Table 3). Of 57 patients in whom the first radiographic change was noted within three weeks, 9 (16%) died of pneumonitis, while radiation-induced lung injury that occurred 10 weeks or later after the end of radiation was easily managed with or without steroid therapy (Table 3). Oxygen content in the blood at the start of steroid therapy was examined in 70 patients of Groups 2 and 3. Oxygen content

Table 1
Patient demographics and radiotherapy performance

Characteristics	Total *N* (%)	Group 1	Group 2	Group 3	*p*-value
		N (%)	*N* (%)	*N* (%)	
Total	385 (100)	307 (80)	64 (17)	14 (4)	
Sex					
Male	300 (78)	240 (78)	47 (73)	13 (93)	0.28
Female	85 (22)	67 (22)	17 (27)	1 (7)	
Age median (range)	65 (28–87)	63 (28–87)	65 (37–83)	71 (65–84)	0.008
Total dose (Gy)					
Median (range)	60 (50–70)	60 (50–70)	60 (50–61)	60 (50–60)	0.50
Intent of radiotherapy					
Curative	298 (77)	232 (76)	52 (81)	14 (100)	0.074
Palliative	87 (23)	75 (24)	12 (19)	0 (0)	
Chemotherapy					
None	121 (31)	101 (33)	15 (23)	5 (36)	0.48
Sequential	121 (31)	93 (30)	25 (39)	3 (21)	
Concurrent	143 (37)	113 (37)	24 (38)	6 (43)	

Table 2
Symptoms through clinical courses

Symptom	At the initial change in chest X-ray				During subsequent clinical course			
	Group 1	Group 2	Group 3	p	Group 1[a]	Group 2[b]	Group3[b]	p
Cough	96 (31)	35 (56)	5 (36)	0.001	85 (28)	38 (59)	5 (36)	<0.001
Sputum	32 (10)	11 (18)	4 (29)	0.049	30 (10)	11 (17)	3 (21)	0.12
Hemosputum	5 (2)	0 (0)	0 (0)	0.53	4 (1)	0 (0)	0 (0)	0.60
Chest pain	7 (2)	0 (0)	0 (0)	0.40	2 (0.6)	0 (0)	0 (0)	0.78
Fever								
None	269 (88)	35 (56)	7 (50)	<0.001	272 (89)	32 (50)	2 (14)	<0.001
37.0–37.9 °C	18 (6)	11 (18)	2 (14)	24 (8)	16 (25)	5 (35)		
38 °C⩽	13 (4)	14 (22)	5 (36)	8 (3)	13 (20)	7 (50)		
Not specified	7 (2)	3 (4)	0 (0)	3 (1)	3 (4)	0 (0)		
Dyspnea	43 (14)	14 (22)	6 (43)	0.007	40 (13)	28 (44)	8 (57)	<0.001
Fever or dyspnea	75 (24)	37 (58)	10 (71)	<0.001	65 (21)	49 (77)	14 (100)	<0.001
Any	150 (49)	51 (81)	13 (93)	<0.001	118 (38)	60 (94)	14 (100)	<0.001

[a] During one month period following the initial change in the chest X-ray.
[b] At the start of steroid therapy.

Table 3
The chest X-ray intervals and first radiographic change

Weeks	Group 1	Group 2	Group 3	p-value
The average interval of chest X-rays (weeks)[a]				
Median (range)	1.7 (0.7 to 6.0)	1.3 (0.5 to 4.4)	0.9 (0.5 to 3.8)	<0.001
Duration between the end of radiotherapy and the first radiographic change (weeks)				
Median (range)	9.9 (−2.9 to 45.1)	6.7 (0 to 24.9)	2.4 (0.4 to 10.1)	<0.001
<6	82 (27)	26 (41)	11 (79)	<0.001
6–11.9	116 (38)	29 (45)	3 (21)	
12–17.9	71 (23)	7 (11)	0 (0)	
18⩽	38 (12)	2 (3)	0 (0)	

[a] Calculated as follows: the average interval of chest X-rays = (the first radiographic change − the start of radiotherapy)/the number of chest X-rays taken during this period/7).

was slightly decreased (PaO2 = 70–74.9 Torr) in 12 (19%) patients of Group 2 and one (7%) patient of Group 3, and moderately to severely decreased (PaO2 ⩽ 69.9 Torr or SpO2 ⩽ 92%) in 21 (33%) patients of Group 2 and 7 (50%) patients of Group 3 ($p = 0.38$).

Prednisolone was administered as the initial therapy in 69 (88%) patients of Groups 2 and 3. The initial prednisolone equivalent dose of steroid was 30–40 mg daily in 52 (67%), and 60 mg of higher only in 8 (10%) patients (Table 4). The median duration of the initial dose was 10 (range, 2–64) days, and the dose was reduced within 14 days in 57 (77%) patients. The median duration of steroid therapy was 10 (range, 2–28) weeks (Table 4). Steroid pulse therapy (methylprednisolone 1000 mg daily for three days) was administered as the initial therapy in one patient, and as salvage therapy in six patients at the time of pneumonitis aggravation. Among the seven patients, six died of respiratory failure due to progressive radiation pneumonitis.

Outcome of steroid therapy was evaluated in 76 patients (Fig. 1). Symptomatic relief was obtained and the steroid dose was reduced in 71 (93%) of the 76 patients, while no effect was noted in the remaining five patients, who all died of radiation pneumonitis despite escalated steroid administration. Of the 71 patients, 15 (21%) developed recurrent symptoms at the median daily prednisolone dose of 20 mg (range, 10–40 mg) within median 33 days (range, 21–42 days) from the start of the steroid therapy, and required steroids to be escalated. Of the 15 patients, nine died of radiation pneumonitis and one died of complication of steroid therapy. A total of 54 (71%) patients were in remission from pneumonitis and steroid therapy was terminated. The remainder 22 patients died during steroid therapy, 14 of radiation pneumonitis, two of infectious complication (bacterial pneumonia in one, and lung aspergillosis in another patient), five of lung cancer progression, and one of hemoptysis. Thus, 16 patients, who accounted for 4.2% of 385 patients receiving 50–70 Gy of thoracic radiotherapy, and who accounted for 21% of 78 patients treated with steroid therapy, died of radiation pneumonitis or complication associated with steroid therapy. Median survival from the start of steroid therapy in these patients was 45 (range, 8–107) days.

Discussion

Patients with radiation-induced lung injury have been managed in compliance with the expert opinions, because there has been no case series or clinical trial report on clinical course and corticosteroid use for this lung injury. This

Table 4
Corticosteroid, dose and duration of steroid therapy

	N (%)
Corticosteroid	
Prednisolone	69 (88)
Dexamethasone	4 (5)
Betamethasone	4 (5)
Methylprednisolone	1 (1)
Initial dose, mg/body daily (prednisolone equivalent)	
Pulse therapy	1 (1)
60	7 (9)
50	1 (1)
40	10 (13)
30	42 (54)
10–25	17 (22)
Duration of the initial dose, days	
Median (range)	10 (2–64)
⩽14	57 (77)
15–28	9 (12)
29⩽	8 (11)
Not evaluable	4
Total duration of steroid therapy, weeks	
Median (range)	10 (2–28)
⩽6	16 (30)
6.1–12	19 (35)
12.1–18	14 (26)
18.1⩽	5 (9)
Not evaluable	24

study is the first systemic review of these patients both who received corticosteroid therapy and who did not. Comparison between the expert opinions and the results of this study is given below. First, radiation-induced lung injury is severer when a radiographic change appears earlier [5]. In this study, the initial change in a chest X-ray film was observed in 9.9 (range, −3 to 45) weeks in Group 1, in 6.7 (range, 0–25) weeks in Group 2, and 2.4 (range, 0–10) weeks in Group 3 after the end of thoracic radiotherapy. If patients present with symptoms, presumably they receive a chest X-ray. Thus, the patients with symptoms may have radiographic findings seen sooner, since they receive an X-ray when they complain of symptoms. The average interval of chest X-rays taken between the start of radiotherapy and the first appearance of radiographic change was longer in Group 1 than that in groups 2 and 3. The difference, however, was negligibly small when compared with the difference in duration between the end of radiotherapy and the first radiographic change. Second, steroid administration is determined generally based on the severity of symptoms [5]. In this study steroid was used when patients developed dyspnea or fever. Dyspnea has been thought to be the cardinal symptom of radiation pneumonitis but fever to be unusual [5,10]. In this study, however, fever was highly associated with fatal radiation pneumonitis; fever was noted in 12% patients of Group 1, in 58% patients of Group 2, and 86% patients of Group 3. This study failed to show utility of blood gas analysis. An oxygen content in the blood was decreased moderately to severely in only 28 (36%) patients in Groups 2 and 3, and did not differ between the two groups. The oxygen content in Group 1 was measured in only small number of patients, and therefore it was not evaluable in this study. Third, 30–100 mg/day of prednisolone has been recommended as the initial dose [4–6,10]. In our practice, a dose of 30–40 mg was the most frequently used. We selected this relatively low dose of steroid mostly because steroid therapy was started in out patient clinic. Forth, duration of the initial dose was within two weeks in 73% of patients, which is consistent to most expert opinions [6,10]. In contrast, tapering schedules varied between a pa-

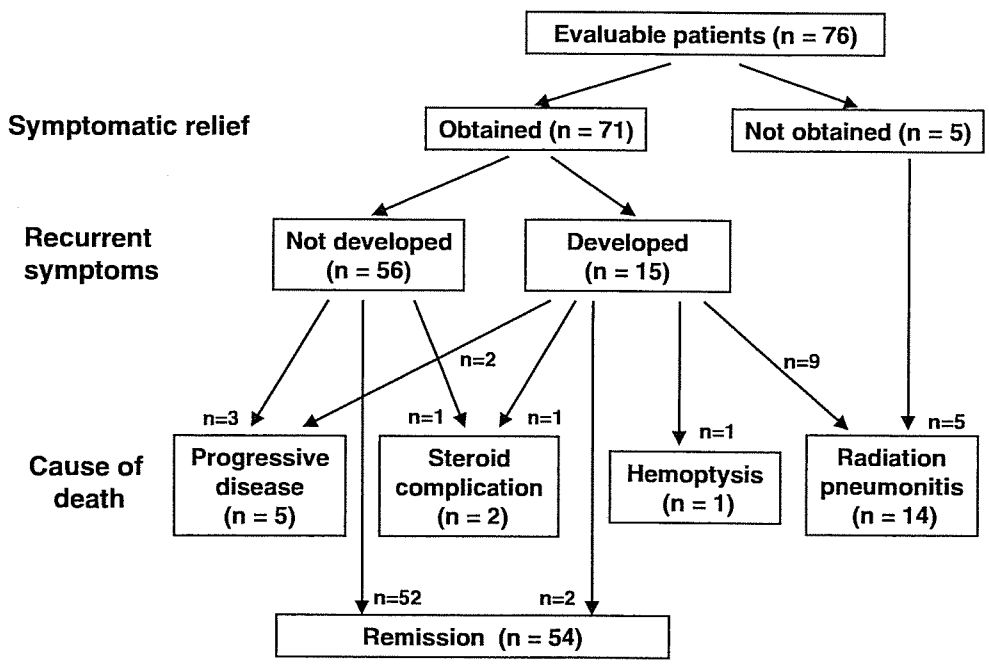

Fig. 1. Outcome of patients who received steroid therapy. Two patients were excluded because of loss of follow-up. Of 76 evaluable patients, 71 (93%) experienced symptomatic relief by steroid therapy.

tient and another in this study. This may be partly due to the diversity in clinical course of radiation pneumonitis, but mostly due to lacking in available recommendation for tapering schedules. In this study, median total duration of steroid therapy was 10 weeks, which may be a tentative guide. A guideline of taper schedule appeared in the latest textbook: the dose should be tapered by 10 mg every two weeks, and be terminated in 12 weeks [10].

Although our clinical practice mostly followed the expert opinions on the management of radiation-induced lung injury as mentioned above, there is little evidence that our steroid use, dose and duration for radiation-induced lung injury were correct. In this study, 21% of patients received steroid therapy and 4% of patients died of radiation pneumonitis among lung cancer patients treated with thoracic radiotherapy at a total dose of 50 Gy or higher. These figures are comparable to the incidence of grade 3 pneumonitis, 3–20%, and that of fatal pneumonitis, 1–4%, in other reports [10].

In conclusion, development of fever and dyspnea, and short interval between the end of radiotherapy and the first radiographic change were associated with fatal radiation-induced lung injury. Prednisolone 30–40 mg daily for two weeks followed by slow taper was selected for the treatment in many patients.

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References

[1] Groover TA, Christie AC, Merritt EA. Observations on the use of the copper filter in the roentgen treatment of deep-seated malignancies. South Med J 1922;15:440–4.
[2] Hines LE. Fibrosis of the lung following roentgen-ray treatments for tumor. JAMA 1922;79:720–2.
[3] Evans WA, Leucutia T. Intrathoracic changes induced by heavy radiation. Am J Roentgenol 1925;13:203–20.
[4] Gross NJ. Pulmonary effects of radiation therapy. Ann Intern Med 1977;86:81–92.
[5] Stover D, Kaner R. Pulmonary toxicity. In: DeVita Jr V, Hellman S, Rosenberg S, editors. Cancer: principles and practice of oncology. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 2894–904.
[6] McDonald S, Rubin P, Phillips TL, Marks LB. Injury to the lung from cancer therapy: clinical syndromes, measurable endpoints, and potential scoring systems. Int J Radiat Oncol Biol Phys 1995;31:1187–203.
[7] Inoue A, Kunitoh H, Sekine I, et al. Radiation pneumonitis in lung cancer patients: a retrospective study of risk factors and the long-term prognosis. Int J Radiat Oncol Biol Phys 2001;49:649–55.
[8] Cosgriff SW, Kligerman MM. Use of ACTH and cortisone in the treatment of post-irradiation pulmonary reaction. Radiology 1951;57:536–40.
[9] Rubin P, Casarett GW. Clinical Radiation Pathology. Philadelphia: WB Saunders Co; 1968.
[10] Machtay M. Pulmonary complications of anticancer treatment. In: Abeloff M, Armitage JO, Niederhuber JE, Kastan MB, McKenna WG, editors. Clin. Oncol.. Philadelphia: Elsevier Churchill Livingstone; 2004. p. 1237–50.
[11] Pezner RD, Bertrand M, Cecchi GR, et al. Steroid-withdrawal radiation pneumonitis in cancer patients. Chest 1984;85:816–7.
[12] Parris TM, Knight JG, Hess CE, Constable WC. Severe radiation pneumonitis precipitated by withdrawal of corticosteroids: a diagnostic and therapeutic dilemma. Am J Roentgenol 1979;132:284–6.
[13] Castellino RA, Glatstein E, Turbow MM, et al. Latent radiation injury of lungs or heart activated by steroid withdrawal. Ann Intern Med 1974;80:593–9.

Docetaxel Consolidation Therapy Following Cisplatin, Vinorelbine, and Concurrent Thoracic Radiotherapy in Patients with Unresectable Stage III Non-small Cell Lung Cancer

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Background: To evaluate the feasibility and efficacy of docetaxel consolidation therapy after concurrent chemoradiotherapy for unresectable stage III non–small cell lung cancer (NSCLC).

Patients and Methods: The eligibility criteria included unresectable stage III NSCLC, no previous treatment, age between 20 and 74 years, and performance status 0 or 1. Treatment consisted of cisplatin (80 mg/m^2 on days 1, 29, and 57), vinorelbine (20 mg/m^2 on days 1, 8, 29, 36, 57, and 64), and thoracic radiotherapy (TRT) (60 Gy/30 fractions over 6 weeks starting on day 2), followed by consolidation docetaxel (60 mg/m^2 every 3 to 4 weeks for three cycles).

Results: Of 97 patients who were enrolled in this study between 2001 and 2003, 93 (76 males and 17 females with a median age of 60) could be evaluated. Chemoradiotherapy was well tolerated; three cycles of chemotherapy and 60 Gy of TRT were administered in 80 (86%) and 87 (94%) patients, respectively. Grade 3 or 4 neutropenia, esophagitis, and pneumonitis developed in 62, 11, and 3 patients, respectively. Docetaxel consolidation was administered in 59 (63%) patients, but three cycles were completed in only 34 (37%) patients. The most common reason for discontinuation was pneumonitis, which developed in 14 (24%) of the 59 patients. During consolidation therapy, grade 3 or 4 neutropenia, esophagitis, and pneumonitis developed in 51, 2, and 4 patients, respectively. A total of four patients died of pneumonitis. We calculated a V_{20} (the percent volume of the normal lung receiving 20 Gy or more) on a dose–volume histogram in 25 patients. Of these, five patients developed grade 3 or more severe radiation pneumonitis. A median V_{20} for these five patients was 35% (range, 26–40%), whereas the median V_{20} for the remaining 20 patients was 30% (range, 17–35%) (p = 0.035 by a Mann–Whitney test). The response rate was 81.7% (95% confidence interval [CI], 72.7–88.0%), with 5 complete and 71 partial responses. The median progression-free survival was 12.8 (CI, 10.2–15.4) months, and median survival was 30.4 (CI, 24.5–36.3) months. The 1-, 2-, and 3-year survival rates were 80.7, 60.2, and 42.6%, respectively.

Conclusion: This regimen produced promising overall survival in patients with stage III NSCLC, but the vast majority of patients could not continue with the docetaxel consolidation because of toxicity.

Key Words: Non-small cell lung cancer, Chemoradiotherapy, Consolidation, Docetaxel.

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Locally advanced unresectable non–small cell lung cancer (NSCLC), stage IIIA with bulky N2 and stage IIIB disease without pleural effusion, is characterized by large primary lesions and/or involvement of the mediastinal or supraclavicular lymph nodes and occult systemic micrometastases. A combination of thoracic radiotherapy and chemotherapy is the standard medical treatment for this disease, but the optimal combination has not been established.[1] Although the available data are insufficient to accurately define the size of a potential benefit,[2] concurrent chemoradiotherapy using a platinum doublet has been shown to be superior to the sequential approach in phase III trials of this disease.[3–5] However, third-generation cytotoxic agents, which have provided better patient survival with extrathoracic spread than the old-generation agents, must be reduced when administered concurrently with thoracic radiotherapy.[6] Thus, it has been hypothesized that the addition of systemic dose chemotherapy with a new cytotoxic agent to concurrent chemoradiotherapy, either as induction or as consolidation chemotherapy, might further improve patient survival.[1]

The consolidation chemotherapy with docetaxel was based on the observation that this drug was highly active in the primary treatment of metastatic NSCLC, producing a response rate (RR) as high as 20% after platinum-based chemotherapy failed.[7–9] Highly encouraging results of a me-

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dian survival time (MST) of more than 2 years and a 3-year survival rate of nearly 40% were obtained in a phase II trial of docetaxel consolidation after chemoradiotherapy with cisplatin and etoposide in patients with stage IIIB NSCLC (SWOG study S9504).[10]

We have developed a combination chemotherapy schedule with cisplatin and vinorelbine concurrently administered with thoracic radiotherapy at a total dose of 60 Gy in 30 fractions in patients with unresectable stage III NSCLC. The results of a phase I study in 18 patients were very promising, with a RR of 83%, a MST of 30 months, and a 3-year survival rate of 50%.[6] Thus, addition of docetaxel consolidation to this regimen is a particularly interesting therapeutic strategy. The objectives of the current study were to evaluate the feasibility of docetaxel consolidation therapy after concurrent chemoradiotherapy with cisplatin and vinorelbine and to evaluate the efficacy and safety of the whole treatment regimen including both the chemoradiotherapy and consolidation therapy in patients with unresectable stage IIIA and IIIB NSCLC.

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 and 74 years; Eastern Cooperative Oncology Group performance status (PS) of 0 or 1; adequate bone marrow function (12.0×10^9/liter $\geq$ white blood cell [WBC] count $\geq 4.0 \times 10^9$/liter, neutrophil count $\geq 2.0 \times 10^9$/liter, hemoglobin ≥ 10.0 g/dl, and platelet count $\geq 100 \times 10^9$/liter), liver function (total bilirubin ≤ 1.5 mg/dl and transaminase no more than twice the upper limit of the normal value), and renal function (serum creatinine ≤ 1.5 mg/dl and creatinine clearance ≥ 60 ml per minute); and a PaO_2 of 70 torr or more under room air conditions. 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 if they were 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

Treatment consisted of a chemoradiotherapy phase with three cycles of cisplatin and vinorelbine followed by a consolidation phase with three cycles of docetaxel (Figure 1). Cisplatin 80 mg/m^2 was administered on days 1, 29, and 57 by intravenous infusion for 60 minutes with 2500 to 3000 ml of fluid for hydration. Vinorelbine diluted in 50 ml of normal saline was administered intravenously on days 1, 8, 29, 36, 57, and 64. All patients received prophylactic antiemetic therapy consisting of a $5HT_3$-antagonist and a steroid.

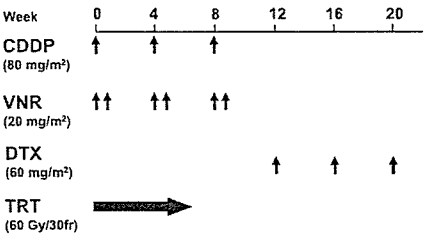

FIGURE 1. Treatment schema. CDDP, cisplatin; DTX, docetaxel; TRT, thoracic radiotherapy; VNR, vinorelbine.

Radiation therapy was delivered with megavoltage equipment ($\geq$6 MV) using anterior/posterior opposed fields up to 40 Gy in 20 fractions including the primary tumor, the metastatic lymph nodes, and the regional nodes. A booster dose of 20 Gy in 10 fractions was given to the primary tumor and the metastatic lymph nodes for a total dose of 60 Gy using bilateral oblique fields. A CT scan–based treatment planning was used in all patients. The clinical target volume (CTV) for the primary tumor was defined as the gross tumor volume (GTV) plus 1 cm taking account of subclinical extension. CTV and GTV for the metastatic nodes (>1 cm in shortest dimension) were the same. Regional nodes, excluding the contralateral hilar and supraclavicular nodes, were included in the CTV, but the lower mediastinal nodes were included only if the primary tumor was located in the lower lobe of the lung. The planning target volumes for the primary tumor, the metastatic lymph nodes, and regional nodes were determined as CTVs plus 0.5- to 1.0-cm margins laterally and 1.0- to 2.0-cm margins craniocaudally, taking account of setup variations and internal organ motion. Lung heterogeneity corrections were not used.

The criteria for starting consolidation chemotherapy were completion of three cycles of cisplatin and vinorelbine and a full dose of thoracic radiotherapy, the absence of progressive disease, adequate general condition within 6 weeks of the start of the third cycle of cisplatin and vinorelbine (PS 0 or 1, WBC count $\geq 3.0 \times 10^9$/liter, neutrophil count $\geq 1.5 \times 10^9$/liter, hemoglobin ≥ 9.0 g/dl and platelet count $\geq 100 \times 10^9$/liter, total bilirubin ≤ 1.5 mg/dl and transaminase no more than twice the upper limit of the normal value, and a PaO_2 of 70 torr or more at room air). Docetaxel (60 mg/m^2) was administered intravenously for 1 hour every 3 to 4 weeks for three cycles.

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, and late toxicity associated with thoracic radiother-

apy was graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme. Vinorelbine administration on day 8 was omitted if any of the following were noted: WBC count $<3.0 \times 10^9$/liter, neutrophil count $<1.5 \times 10^9$/liter, platelet count $<100 \times 10^9$/liter, elevated hepatic transaminase level or total serum bilirubin of at least grade 2, fever ≥38°C, or PS ≥2. Subsequent cycles of cisplatin and vinorelbine chemotherapy were delayed if any of the following toxicities were noted on day 1: WBC count $<3.0 \times 10^9$/liter, neutrophil count $<1.5 \times 10^9$/liter, platelet count $<100 \times 10^9$/liter, serum creatinine level ≥1.6 mg/dl, elevated hepatic transaminase level or total serum bilirubin of at least grade 2, fever ≥38°C, or PS ≥2. The dose of cisplatin was reduced by 25% in all subsequent cycles if the serum creatinine level rose to 2.0 mg/dl or higher. The dose of vinorelbine or docetaxel was reduced by 25% in all subsequent cycles if any of the following toxicities were noted: WBC count $<1.0 \times 10^9$/liter, platelet count $<10 \times 10^9$/liter, or grade 3 or 4 infection or liver dysfunction. Thoracic radiotherapy was suspended if any of the following were noted: fever ≥38°C, grade 3 esophagitis, PS of 3, or PaO_2 <70 torr. Thoracic radiotherapy was terminated if any of the following were noted: grade 4 esophagitis, grade 3 or 4 pneumonitis, PS of 4, or duration of radiotherapy of over 60 days. The use of granulocyte colony-stimulating factor during radiotherapy was not permitted unless radiotherapy was on hold. The criteria for termination of docetaxel consolidation were not defined in the protocol.

Response Evaluation

Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumor.[11] Local recurrence was defined as tumor progression in the primary site and in the hilar, mediastinal, and supraclavicular lymph nodes after a partial or complete response; regional recurrence as the development of malignant pleural and pericardial effusions; and distant recurrence as the appearance of a distant metastasis.

Study Design, Data Management, and Statistical Considerations

This study was conducted at three institutions: the National Cancer Center Hospital, National Cancer Center Hospital East, and Tochigi 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.

The primary objective of the current study was to evaluate the feasibility of docetaxel consolidation therapy. The secondary endpoints were toxicity observed during chemoradiotherapy and consolidation therapy, the best response, and overall survival in all patients eligible to participate in this study. Because no standard method to evaluate consolidation chemotherapy after chemoradiotherapy has been established, we arbitrarily defined the primary endpoint of this study as a ratio (R) of the number of patients receiving docetaxel without grade 4 nonhematological toxicity or treatment-related death to the total number of patients receiving docetaxel. The sample size was initially estimated to be 34 patients with a power of 0.80 at a significance level of 0.05, under the assumption that a R of 0.95 would indicate potential usefulness, whereas a R of 0.8 would be the lower limit of interest, and that 85% of patients would move into the consolidation phase. An analysis of the first 13 patients, however, showed that only 8 (61%) patients advanced into the consolidation phase. The reasons for not receiving docetaxel were disease progression in one, delay in completion of chemoradiotherapy in two, grade 3 esophagitis in one, and death due to hemoptysis in one patient. Considering that the SWOG trial S9504 included 83 patients, we decided to revise the number of patients in the current study. According to Simon's two-stage minimax design, the required number of patients was calculated to be 59 with a power of 0.80 at a significance level of 0.05, under the assumption that a R of 0.85 would indicate potential usefulness, whereas a R of 0.7 would be the lower limit of interest.[12] Assuming that 61% of registered patients would move into the consolidation phase, the sample size was determined to be 97 patients.

Overall survival time and progression-free survival time were estimated by the Kaplan–Meier method, and confidence intervals (CI) were based on Greenwood's formula.[13] Overall survival time was measured from the date of registration to the date of death (from any cause) or to the last follow-up. Progression-free survival time was measured from the date of registration to the date of disease progression, death (from any cause), or the last follow-up. Patients who were lost to follow-up without event were censored at the date of their last known follow-up. A CI for RR was calculated using methods for exact binomial CIs. The Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan) was used for statistical analyses.

RESULTS

Registration and Characteristics of the Patients

A total of 97 patients were enrolled in this study between April 2001 and June 2003. Four patients were excluded from this study before the treatment was started because the radiation treatment planning disclosed that their tumors were too advanced for curative thoracic radiotherapy. Thus, 93 patients who received the protocol-defined treatment were the subjects of this analysis (Figure 2). There were 76 males and 17 females, with a median age of 60 (range 31–74). Body weight loss was less than 5% in 77 patients; adenocarcinoma histology was noted in 57 patients, and stage IIIA disease was noted in 41 patients (Table 1).

Treatment Delivery

Treatment delivery was generally well maintained in the chemoradiotherapy phase (Table 2). Full cycles of cisplatin and vinorelbine and the full dose of thoracic radiotherapy were administered in 80 (86%) and 87 (94%) patients, respectively. Delay in radiotherapy was less than 5 days in 61 (66%) patients. In contrast, the delivery of docetaxel was poor (Table 2). A total of 59 (63%) patients could enter the consolidation phase, and only 34 (37%) patients completed three cycles of docetaxel chemotherapy. The reasons for not

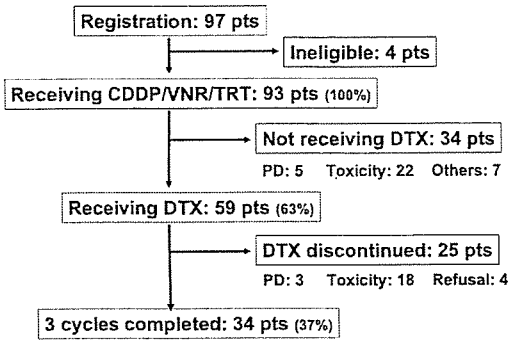

FIGURE 2. Patient registration. CDDP, cisplatin; DTX, docetaxel; TRT, thoracic radiotherapy; VNR, vinorelbine.

receiving consolidation were toxicity in 22 (65%) patients including pneumonitis in seven patients, myelosuppression in five patients, esophagitis in four patients, liver dysfunction in two patients, infection in two patients, other toxicity in two patients, progressive disease in five (15%) patients, patient refusal in three (9%) patients, early death due to hemoptysis in one (3%) patient, and other reasons in three (9%) patients. Of the 59 patients, 18 (31%) discontinued docetaxel consolidation because of toxicity, including pneumonitis (n = 14) and esophagitis, infection, gastric ulcer, and allergic reaction (n = 1 each), four (7%) because of patient refusal, and three (5%) because of progressive disease.

Toxicity

Acute severe toxicity in the chemoradiotherapy phase was mainly leukopenia and neutropenia, whereas grade 3 or 4 thrombocytopenia was not noted (Table 3). Severe nonhematological toxicity was sporadic, and grade 3 esophagitis and pneumonitis were observed in only 11 (12%) and 3 (3%) patients, respectively. Acute severe toxicity in the consolidation phase also consisted of neutropenia and associated infection (Table 4). In addition, grade 3 or 4 pneumonitis developed in 4 (7%) patients. The R observed in this study was 0.05 (3 out of 57 patients), which was much lower than the hypothetical value. Grade 3 or 4 late toxicities were included lung toxicity in four patients, esophageal toxicity in two patients, renal toxicity in one patient, and a second esophageal cancer that developed 35.4 months after the start of the chemoradiotherapy in one patient. Treatment-related

TABLE 1. Patient Characteristics

Characteristics	n	%
Gender		
Male	76	82
Female	17	18
Age median (range)	60	31–74
Weight loss		
<5%	76	81
5–9%	12	13
≥10%	3	3
Unknown	2	2
Histology		
Adenocarcinoma	57	61
Squamous cell carcinoma	23	25
Large cell carcinoma	12	13
Others	1	1
Stage		
IIIA	41	44
IIIB	52	56

TABLE 2. Treatment Delivery

Variables	n	%
Cisplatin and vinorelbine chemotherapy		
Total number of cycles		
3	80	86
2	10	11
1	3	3
Number of vinorelbine skips		
0	63	68
1	25	27
2–3	5	5
Thoracic radiotherapy		
Total dose (Gy)		
60	87	94
50–59	4	4
<50	2	2
Delay (days)		
<5	61	66
5–9	20	22
10–16	6	6
Not evaluable (<60 Gy)	6	6
Docetaxel consolidation		
Number of cycles		
3	34	37
2	12	13
1	13	14
0	34	34

TABLE 3. Acute Toxicity in Chemoradiotherapy (n = 93)

	Grade			
Toxicity	3	4	3 + 4	%
Leukopenia	54	18	72	77
Neutropenia	33	29	62	67
Anemia	21	0	21	23
Infection	15	1	16	17
Esophagitis	11	0	11	12
Hyponatremia	11	0	11	12
Anorexia	9	1	10	11
Nausea	5	—	5	5
Pneumonitis	3	0	3	3
Syncope	2	0	2	2
Hyperkalemia	2	0	2	2
Ileus	0	1	1	1
Cardiac ischemia	1	0	1	1

TABLE 4. Acute Toxicity in Consolidation Therapy (n = 57)

	Grade			
Toxicity	3	4	3 + 4	%
Leukopenia	33	11	44	77
Neutropenia	24	26	50	88
Anemia	5	0	5	9
Infection	5	1	6	11
Esophagitis	2	0	2	3
Anorexia	1	0	1	2
Pneumonitis	2	2	4	7

death was observed in four (4%) patients. Of these, three received docetaxel, and one did not. The reason for death was pneumonitis in all patients. We calculated a V_{20} (the percent volume of the normal lung receiving 20 Gy or more) on a dose–volume histogram in 25 patients. Of these, five patients developed grade 3 or severer radiation pneumonitis. A median V_{20} for these five patients was 35% (range, 26–40%), whereas that for the remaining 20 patients was 30% (range, 17–35%) (p = 0.035 by a Mann–Whitney test).

Objective Responses, Relapse Pattern, and Survival

All 93 patients were included in the analyses of tumor response and survival. Complete and partial responses were obtained in 5 (5%) and 71 patients (76%), respectively, for an overall RR of 81.7% (95% CI, 72.7–88.0%). Stable and progressive diseases occurred in 12 (13%) and 5 (5%) patients, respectively. With a median follow-up period of 29.7 months, 38 patients developed locoregional recurrence, 32 developed distant recurrence, 4 developed both locoregional and distant recurrences, and 19 did not. The median progression-free survival time was 12.8 (95% CI, 10.2–15.4) months (Figure 3). Two patients underwent salvage surgery for a recurrent primary tumors. Conventional chemotherapy and gefitinib monotherapy were administered after recurrence in 20 and 25 patients, respectively. The median overall survival time was 30.4 (95% CI, 24.5–36.3) months. The 1-, 2-, and 3-year survival rates were 80.7, 60.2, and 42.6%, respectively. (Figure 4).

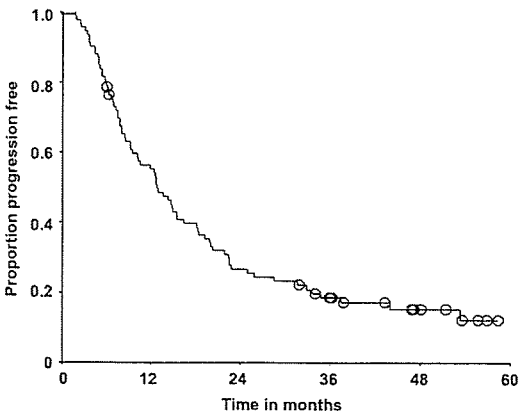

FIGURE 3. Progression-free survival (n = 93). The median progression-free survival time was 12.8 (95% CI, 10.2–15.4) months.

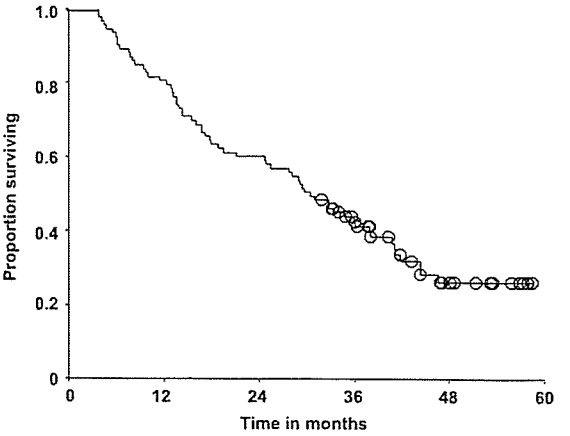

FIGURE 4. Overall survival (n = 93). The median overall survival time was 30.4 (95% CI, 25.4–35.4) months. The 1-, 2-, and 3-year survival rates were 80, 60, and 40%, respectively.

DISCUSSION

This study showed that concurrent chemoradiotherapy with cisplatin, vinorelbine, and standard thoracic radiotherapy was well tolerated, with a high completion rate exceeding 80%. The incidence of acute toxicity, including 67% (62/93) of grade 3 or 4 neutropenia, 12% (11/93) of grade 3 esophagitis, and 3% (3/93) of grade 3 pneumonitis, were comparable with other reports of concurrent chemoradiotherapy.[3,4,10] In contrast, consolidation docetaxel could be administered in only 59 of 93 (63%) patients eligible to participate in this study. Of the remaining 34 patients, 22 (65%) patients did not receive consolidation chemotherapy because of toxicities affecting various organs. Other studies also showed that not all patients proceeded to the consolidation phase after completion of concurrent chemoradiotherapy: 61 to 78% of patients after two cycles of cisplatin and etoposide with radiotherapy,[3,10] and 54 to 75% of patients after weekly carboplatin and paclitaxel with radiotherapy.[14,15] Thus, for 20 to 40% of the patients, concurrent chemoradiotherapy was as much as they could undergo, and the additional chemotherapy was not practical.

Furthermore, the number of patients who fulfilled the three cycles of consolidation docetaxel was only 34 (58%) of the 59 patients, which corresponded to only 37% of those eligible in this study. The reason for the termination of docetaxel in the 25 patients was toxicity in 18 (72%) patients, especially pneumonitis in 14 (56%) patients. The grade of pneumonitis during the consolidation phase was within grade 2 in most cases, and this was probably because docetaxel was discontinued early. Considering that pneumonitis associated with cancer treatment is more common in Japan, docetaxel consolidation is not thought to be feasible in the Japanese population. The MST and the 3-year survival rate in all eligible patients were 33 months and 44% in this study, but docetaxel consolidation was unlikely to contribute to these promising results because only 37% of patients received full cycles of docetaxel. This contrasts clearly with the result of

the SWOG study S9504, a phase II trial of two cycles of cisplatin and etoposide with thoracic radiation followed by three cycles of docetaxel. In this trial, 75% of patients starting consolidation and 59% of those entering the trial received full cycles. In addition, docetaxel consolidation seemed to prolong survival, although this was drawn from a retrospective comparison of the results between the two SWOG studies S9504 and S9019.[10]

There is no widely used definition of consolidation therapy following chemoradiotherapy. Given that consolidation therapy is arbitrarily defined as chemotherapy with three cycles or more after the completion of concurrent chemoradiotherapy, only one randomized trial is available in the literature. The randomized phase III trial of standard chemoradiotherapy with carboplatin and paclitaxel followed by either weekly paclitaxel or observation in patients with stage III NSCLC showed that only 54% of patients proceeded to randomization, and overall survival was worse in the consolidation arm (MST, 16 versus 27 months).[15] Thus, there have been no data supporting the use of consolidation therapy, especially when a third-generation cytotoxic agent such as paclitaxel and vinorelbine is incorporated into concurrent chemoradiation therapy.

The low complete-response rate of 5% in this study may be explained partly by an inability to distinguish between inactive scarring or necrotic tumor and active tumor after radiotherapy. Positron emission tomography (PET) using 18F-fluorodeoxyglucose showed a much higher rate of complete response than conventional CT scanning and provided a better correlation of the response assessment using PET with patterns of failure and patient survival.[16] In addition, the high locoregional relapse rate in this study clearly showed that the conventional total dose of 60 Gy was insufficient. Three-dimensional treatment planning, omission of elective nodal irradiation, and precise evaluation of the gross tumor volume by PET may facilitate the escalation of the total radiation dose without enhanced toxicity.

In conclusion, cisplatin and vinorelbine chemotherapy concurrently combined with standard thoracic radiotherapy and followed by docetaxel consolidation produced promising overall survival in patients with stage III NSCLC, but the vast majority of patients could not continue with the docetaxel consolidation because of toxicity.

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REFERENCES

1. Vokes EE, Crawford J, Bogart J, et al. Concurrent chemoradiotherapy for unresectable stage III non-small cell lung cancer. *Clin Cancer Res* 2006;11:5045s–5050s.
2. Auperin A, Le Pechoux C, Pignon JP, et al. Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. *Ann Oncol* 2006;17:473–483.
3. Fournel P, Robinet G, Thomas P, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupeqqfrancaisqqqq de Pneumo-Cancerologie NPC 95-01 Study. *J Clin Oncol* 2006;23:5910–5917.
4. Furuse K, Fukuoka M, Kawahara M, et al. 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;17:2692–2699.
5. Curran W, Scott CJ, Langer C, et al. Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemo-radiation for patients with unresected stage III NSCLC: RTOG 9410. *Proc Am Soc Clin Oncol* 2003;22:621 (abstr 2499).
6. Sekine I, Noda K, Oshita F, et al. Phase I study of cisplatin, vinorelbine, and concurrent thoracic radiotherapy for unresectable stage III non-small cell lung cancer. *Cancer Sci* 2004;95:691–695.
7. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol* 2000;18:2354–2362.
8. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000;18:2095–2103.
9. Fossella FV, Lee JS, Shin DM, et al. Phase II study of docetaxel for advanced or metastatic platinum-refractory non-small-cell lung cancer. *J Clin Oncol* 1995;13:645–651.
10. Gandara DR, Chansky K, Albain KS, et al. Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: phase II Southwest Oncology Group Study S9504. *J Clin Oncol* 2003; 21:2004–2010.
11. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92: 205–216.
12. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989;10:1–10.
13. Armitage P, Berry G, Matthews J. Survival analysis. In Armitage P, Berry G, Matthews J (eds.), *Statistical Methods in Medical Research* (4th ed.). Oxford: Blackwell Science Ltd, 2002, pp. 568–590.
14. Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol* 2006;23:5883–5891.
15. Carter D, Keller A, Tolley R, et al. A randomized phase III trial of combined paclitaxel, carboplatin, and radiation therapy followed by either weekly paclitaxel or observation in patients with stage III non-small cell lung cancer. *Proc Am Soc Clin Oncol* 2006;22:635s (abstr 7076).
16. Mac Manus MP, Hicks RJ, Matthews JP, et al. Metabolic (FDG-PET) response after radical radiotherapy/chemoradiotherapy for non-small cell lung cancer correlates with patterns of failure. *Lung Cancer* 2006; 49:95–108.

