

Uracil/Tegafur Plus Cisplatin with Concurrent Radiotherapy for Locally Advanced Non-Small-Cell Lung Cancer: A Multi-institutional Phase II Trial

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ABSTRACT

Purpose: To evaluate the efficacy and toxicity of a novel combination treatment using concurrent radiotherapy with cisplatin plus UFT, which is comprised of uracil and tegafur, in locally advanced non-small cell lung cancer (NSCLC) patients.

Experimental Design: In this Phase II trial, patients with unresectable stage III NSCLC were treated with the oral administration of UFT (400 mg/m²/d tegafur) on days 1–14 and days 29–42 whereas 80 mg/m² cisplatin was administered i.v. on days 8 and 36. Radiotherapy, with a total dose of 60 Gy, was delivered in 30 fractions from day 1.

Results: Seventy patients were enrolled and eligible, as follows: 57 males/13 females; mean age 61 ranging from 36 to 74; performance status 0/1:45/25; stage IIIA/IIIB, 14/56. A complete response was observed in two patients and a partial response in 54 patients, and the overall response rate was 81% (95% confidence interval; 70–89%). The median survival, the 1- and 2-year survival rates were 16.5 months, 67% and 33%, respectively. Grade 3/4 leukopenia occurred in 14%/1% of the patients. Grades 3 non-hematological

toxicities were only reported in three patients with nausea, two with esophagitis and one with pneumonitis whereas no grade 4 non-hematological toxicity was observed.

Conclusions: UFT plus cisplatin with concurrent radiotherapy is considered to be a feasible and effective treatment for locally advanced NSCLC patients. Additional study of this concurrent chemoradiotherapy is warranted.

INTRODUCTION

For non-small cell lung cancer (NSCLC) patients with unresectable stage III disease and a good performance status, combined chemoradiotherapy is the standard treatment (1, 2). Recent randomized Phase III trials have shown that concurrent chemoradiotherapy is superior to chemotherapy followed by radiotherapy in terms of the response and survival in such patients (3, 4). However, concurrent chemoradiotherapy is also associated with an increased rate of bone marrow suppression and acute esophagitis compared with sequential chemoradiotherapy.

Combination chemotherapy comprising cisplatin and the protracted i.v. injection of 5-fluorouracil (5-FU) has been reported to be effective for NSCLC with possibly a lower hematological toxicity than with many other cisplatin-based regimens (5). In this combination chemotherapy, we replaced the protracted infusion of 5-FU that might hamper a quality of life of patients with a oral daily administration of UFT including tegafur (prodrug of 5-FU) and uracil in a 1:4 molar ratio concentration (6). The combination chemotherapy consisting of a daily administration of UFT for 2 or 3 weeks and a bolus injection of cisplatin in advanced NSCLC patients demonstrated a response rate of 29% to 38% and a median survival time of 10 to 13 months (6–8). In addition, the incidence of hematological adverse events is lower than that of those of a platinum-based two-drug combination chemotherapy currently used (9): the frequency of grade 3 or 4 neutropenia/leukopenia was reported to be 1–12% in the former and 63–75% in the latter.

Both cisplatin and 5-FU have been reported to have a radiosensitizing effect in preclinical and clinical studies including NSCLC (10–14). Although there is no information on the suitable combination modality of 5-FU and radiotherapy in NSCLC, continuous 5-FU infusion with concurrent radiotherapy has been reported to be superior to the use of bolus 5-FU schedules because of lower hematological toxicity and improved disease-free and overall survival rates in resected rectal cancer patients (15). Pharmacokinetic studies have shown that the 5-FU plasma levels in patients receiving protracted infusions of 5-FU are similar to those found in patients receiving oral UFT, although peak levels of 5-FU are higher with UFT (16).

On the basis of this background, we conducted a single institutional pilot trial in which the combination chemotherapy of UFT plus cisplatin was performed with concurrent radiother-

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apy for locally advanced NSCLC (17). Among the 23 enrolled patients, 21 (91%) demonstrated a partial response, and the median survival time was 16.6 months. Hematological toxicity was moderate whereas no severe non-hematological toxicities were observed. We thus conducted a multi-institutional Phase II trial to confirm the antitumor effect and toxicity of this concurrent chemoradiotherapy.

PATIENTS AND METHODS

Eligibility Criteria. The eligibility requirements were cytologically or histologically confirmed, unresectable stage III NSCLC for which radical dose radiotherapy could be prescribed. All patients were required to meet the following criteria: measurable disease; an Eastern Cooperative Oncology Group performance status of 0 or 1; a projected life expectancy of >3 months; a leukocyte count of $\geq 4,000/\mu\text{l}$; a platelet count of $\geq 100,000/\mu\text{l}$; a blood gas oxygen level of ≥ 70 Torr; a serum bilirubin level < 1.5 mg/dl; serum glutamic oxaloacetic transaminase/glutamic pyruvic transaminase levels of no more than twice the upper limit of normal; a normal creatinine level; and a creatinine clearance level of ≥ 60 ml/min. Other eligibility criteria included no prior treatment and an age ≤ 75 years. All eligible patients underwent computed tomography scans of the thorax and upper abdomen and a radioisotope bone scan.

Any patients who had malignant pleural effusion, malignant pericardial effusion, a concomitant malignancy, or serious concomitant diseases were excluded from the study. Written informed consent was required from all patients, and the protocol was approved by the institutional ethics committee of each participating institute. On entrance to the study, the eligibility of patients was checked via facsimile by the central administration office of the Tokyo Cooperative Oncology Group (Tokyo).

Treatment Schedule. UFT (400 mg/m²/d tegafur) in the form of a 100-mg capsule (100-mg tegafur and 224-mg uracil) was administered p.o. in two divided daily doses, before meals, from days 1 to 14 and from days 29 to 42. The dose was rounded up or down to the nearest 100 mg. If the number of capsules could not be equally divided, then the higher dose was administered in the morning and the lower dose administered in the evening. In practice, most patients received UFT 3 capsules (300 mg of tegafur and 672 mg of uracil) b.i.d. Cisplatin (80 mg/m²) was administered by a 90-minute infusion on days 8 and 36. The patients were also hydrated with ≥ 2500 ml of saline infusion on the day they received cisplatin. After undergoing concurrent chemoradiotherapy, administration of two further cycles of this chemotherapy regimen was recommended to all patients responding to the concurrent chemoradiotherapy. However, the part of this consolidation chemotherapy was not officially included in the present trial.

Radiotherapy was administered in five fractions per week from a megavolt linear accelerator or cobalt 60 at a daily dose of 2 Gy from day 1 up to a total of 60 Gy (30 fractions). One fraction had two beams. Among the 60 Gy, the first 40 Gy was delivered to the isocenter of anteroposterior/posteroanterior fields, which included the primary tumor, ipsilateral hilum, and mediastinum. When no tumor in the supraclavicular fossa was detected by a physical or on radiographic examinations, the area was not irradiated. Shaped custom blocks or multileaf collimator

were used and included a margin of 2 cm between the target and block edge. Thereafter, the last 20 Gy was delivered using a pair of oblique fields that excluded the spinal cord. The oblique fields included gross tumor volume (primary tumor plus metastatic lymph nodes) with a 2-cm margin. Neither posterior spinal cord blocks nor lung inhomogeneity correction was used.

Complete blood cell counts and biochemistry were performed weekly. If the leukocytes decreased to $< 3000/\mu\text{l}$, platelets decreased to $< 100,000/\mu\text{l}$, or abnormal results of hepatic or renal function tests (level higher than eligibility criteria) were observed, then the administration of cisplatin was suspended. Whenever grade 2 diarrhea or stomatitis occurred, a 33% UFT dose reduction was required. When such adverse events were grade 3 or greater, the administration of UFT was suspended. Radiotherapy was suspended if either a grade 4 hematological toxicity or grade 3 or greater esophagitis occurred. When the hematological toxicity and esophagitis recovered to grade 2 and grade 1, respectively, radiotherapy was resumed.

Study Evaluation and Statistical Methods. Patients were evaluated for their response based on the standard WHO criteria (18). Toxicity was graded according to National Cancer Institute common toxicity criteria (version 2.0). The eligibility and response were assessed by extramural reviewers.

The primary end point of this study was to determine the tumor-response rate produced with this treatment protocol. On the basis of the assumption that a response rate of $> 75\%$ would warrant a further investigation of this combined modality treatment and that a rate $< 60\%$ would make such an investigation unnecessary, a sample size of 62 patients was required with a α error of 0.1 and a β error of 0.1. Therefore, the accrual of 70 patients was planned for a 2-year period because several ineligible patients might be identified in the course of the study.

For comparison of proportions for categorical variables, the χ^2 test was used. The overall survival was defined as the time from the initiation of treatment until death from any cause or last follow-up. Survival was estimated by the Kaplan-Meier method.

RESULTS

Characteristics of Patients. Between May 1999 and March 2001, a total of 70 patients were enrolled in this study, and the all patients were considered eligible. As shown in Table 1, 81% of patients were male with a mean age of 61 years (range, 36–74 years). Adenocarcinoma was the most common histology at 53%, and most patients had clinical stage IIIB disease (IIIA *versus* IIIB; 20% *versus* 80%). Frequently classified Tumor-Node-Metastasis category was T₄N₂M₀ (34%) and T₁₋₃N₃ (29%).

Adverse Events. Adverse events of concurrent chemoradiotherapy are listed in Table 2. Among the hematological toxicities, grade 4 leukopenia was observed only in one patient (1%) and 10 patients (14%) had grade 3 leukopenia. Grade 3 thrombocytopenia was observed only in one patient (1%), and no patient had grade 4 thrombocytopenia. Among the non-hematological toxicities, grade 3 esophagitis was observed in two patients (3%) whose radiotherapy was administered using cobalt-60. Dyspnea of grade 3 possibly attributable to radiation pneumonitis was observed in one patient (1%) who was treated successfully with the oral administration of prednisolone.

Table 1 Patient characteristics

No. of eligible patients		70	(100%)	
Age, yrs.	Mean (range)	61	(36–74)	
Gender	Male	57	(81%)	
	Female	13	(19%)	
ECOG PS ^a	0	45	(64%)	
	1	25	(36%)	
Histology	Adenocarcinoma	37	(53%)	
	Squamous cell ca	30	(43%)	
	Large cell ca	3	(4%)	
TNM	Stage IIIA	T ₃ N ₁ M ₀	1	(1%)
		T _{1–3} N ₂ M ₀	13	(19%)
	Stage IIIB	T _{1–3} N ₃ M ₀	20	(29%)
		T ₄ N _{0–1} M ₀	6	(9%)
		T ₄ N ₂ M ₀	24	(34%)
		T ₄ N ₃ M ₀	6	(9%)
Radiation equipment used	Cobalt-60	8	(11%)	
	Linear accelerator	62	(89%)	

^a ECOG, Eastern Cooperative Oncology Group; PS, performance status; ca, carcinoma; TNM, Tumor-Node-Metastasis.

Treatment Delivered. Sixty-one patients (87%) completed the concurrent treatment consisting of two cycles of chemotherapy and radiotherapy of 60 Gy according to the protocol. Five patients could not complete the scheduled concurrent chemoradiotherapy. Three and one patient could not complete the scheduled radiotherapy and chemotherapy, respectively. The reasons for the discontinuation of the treatment in these nine patients were attributable to adverse events in five patients (grade 3 esophagitis in two; grade 4 leukopenia, grade 2, or grade 3 nausea in one each), concomitant disease in two, withdrawal from the treatment protocol in one, and a poor general condition in one. The dose of cisplatin and UFT was reduced in one patient each attributable to either renal dysfunction or nausea. Among the 56 patients who experienced a response to the concurrent chemoradiotherapy, 17 and 12 patients received one cycle and two cycles of consolidation chemotherapy, respectively.

Response. Among all 70 patients including 4 patients whose response was not evaluable because of insufficient information, 56 patients had responses (80%; 95% confidence interval; 71% to 89%), including two patients (3%) with a complete response and 54 (77%) with a partial response. There were 10 patients (14%) with no change. There were no differences in the response rate by age (>65 *versus* <65, $P = 0.279$), gender (female *versus* male, $P = 0.759$), stage (IIIA *versus* IIIB, $P = 0.100$), performance status (0 *versus* 1, $P = 0.212$), and histology (adenocarcinoma *versus* others, $P = 0.402$).

Survival. The overall median follow-up time for all patients was 33 months (range, 18–45 months). As shown in Fig. 1, the median survival time of all 70 patients was 16.5 months, and the survival rates at 1 and 2 years were 67% (95% confidence interval; 56–78%) and 33% (95% confidence interval; 22–45%), respectively.

Sites of First Failures. With respect to the sites of first failure among 59 recurrent patients, 29 (49%) were distant, 25 (42%) were local (primary tumor site and/or regional lymph nodes including supraclavicular lymph nodes), and 3 (5%) were

both local and distant (Table 3). Of a total of 28 patients with local recurrence, 18 patients had a recurrence within an irradiated field. In addition, isolated brain metastasis was reported in five patients.

DISCUSSION

The goals of chemoradiotherapy in NSCLC with stage III disease are to achieve local control, for which radiotherapy plays the main role, and eradicate occult distant metastases by chemotherapy. Therefore, the administration of the full doses of both chemotherapy and radiotherapy is ideal. Recent randomized trials comparing concurrent chemoradiotherapy with sequential chemoradiotherapy as a standard treatment have shown that the former is superior to the latter when chemotherapy and radiotherapy are given at full dose (19, 20). The chemotherapy regimen and total dose of radiotherapy was mitomycin, vindesine plus cisplatin, and 56 Gy (28 fractions of 2 Gy each for 6 weeks including a rest of 10 days at the first 28 Gy in the concurrent arm and 28 fractions of 2 Gy each for 5 weeks in the sequential arm) in the trial of the West Japan Lung Cancer Group (3) and vinblastine plus cisplatin and 60 Gy (30 fractions of 2 Gy each for 6 weeks in both arms) in the trial of the Radiation Therapy Oncology Group (4), respectively. The median survival time of the concurrent and sequential treatment groups was 16.5 *versus* 13.3 months in the Japanese trial and 17 *versus* 14.6 months in the Radiation Therapy Oncology Group trial. In the present study, the chemotherapy regimen using UFT plus cisplatin was demonstrated to be capable of being given at full dose with concurrent radiotherapy at full dose. As a result, this regimen achieved a survival comparable with the concurrent treatments reported previously.

The other well-known chemotherapy regimen that can be administered at full dose with concurrent radiotherapy is etoposide plus cisplatin. Because this regimen is considered to be a safe and active regimen, it is currently most often concurrently used with radiotherapy for both small and NSCLC with localized disease (19, 20). However, toxicity is well known to in-

Table 2 Hematologic and non-hematologic adverse events

	Grade ^a			Frequency of
	1	2	3 or 4 (%)	
Toxicity ($n = 70$)	1	2	3	4
Leukopenia	4	14	10	1
Neutropenia	4	7	4	1
Thrombocytopenia	9	4	1	0
Anemia	16	7	4	0
Bilirubin	2	1	0	0
Glutamic-oxaloacetic transaminase	8	0	0	0
Glutamic-pyruvic transaminase	7	1	0	0
Creatinine	5	0	0	0
Proteinuria	5	2	0	0
Hematuria	5	0	0	0
Nausea	16	11	3	0
Vomiting	11	8	0	0
Diarrhea	1	2	0	0
Stomatitis	3	0	0	0
Alopecia	5	0		0
Esophagitis	20	7	2	0
Pulmonary	24	8	1	0
Dermatitis	7	0	0	0

^a National Cancer Institute common toxicity criteria.

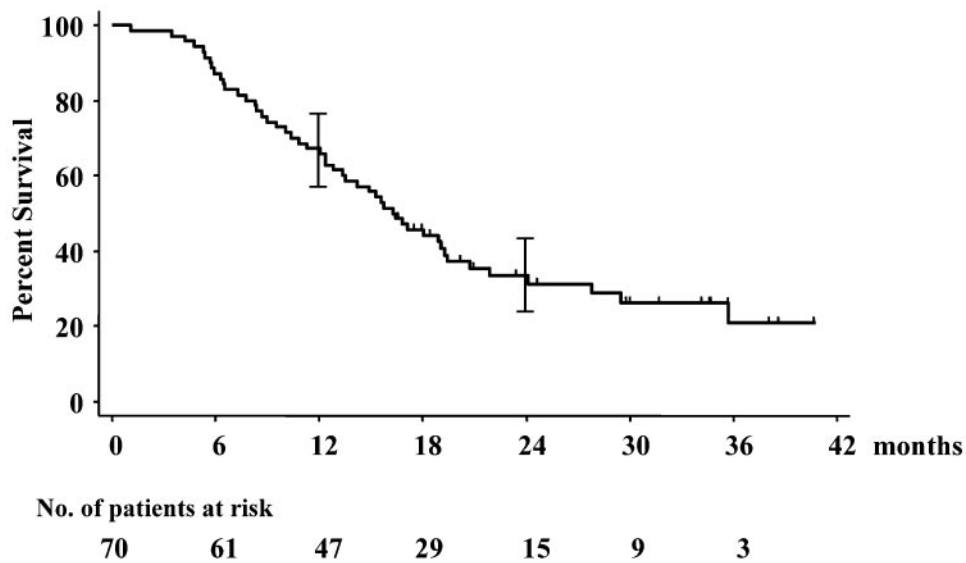


Fig. 1 Survival. Each tick mark represents a patient who is alive. The bars represent the 95% confidence interval of the survival rate at 1 and 2 years after treatment.

crease with greater myelotoxicity and esophagitis in such a concurrent treatment modality. Even in a safe regimen such as etoposide plus cisplatin, grade 3/4 esophagitis was observed in 20% of the patients, and grade 4 neutropenia occurred in 32%, when it was used with concurrent radiotherapy (20). In the present study, grade 4 neutropenia and grade 3 esophagitis were observed only in one (1%) and two patients (3%), respectively, whereas there was no grade 4 esophagitis. Although the difference in the frequency of those adverse events may be partly attributable to differences in the racial background of the patients, no severe hematological toxicity was observed in any trials including UFT with concurrent radiotherapy for rectal cancer, trials which were performed in the United States (21) and Europe (22).

Whether there is any benefit to be obtained by administering induction or consolidation chemotherapy in addition to concurrent chemoradiotherapy remains to be determined. In the present study, two cycles of consolidation chemotherapy were recommended but not mandated in the patients who responded to concurrent chemoradiotherapy. Regardless of the rather low degree of toxicity observed with this concurrent regimen, only 29 patients (52%) received consolidation chemotherapy. This

low figure may be partly attributable to the still unclear role of consolidation chemotherapy.

The Southwest Cooperative Oncology Group conducted a Phase II trial using cisplatin plus etoposide with concurrent radiotherapy followed by docetaxel, which is known to be the most active second-line agent in NSCLC (23). The median survival was 26 months, and the 3-year survival rate was 37%. Grade 4 neutropenia (57%) was the most common toxicity observed during consolidation, and it was manageable and expected based on the profile of adverse events related to docetaxel. We are now gathering unresectable stage III NSCLC patients to enter them into a randomized Phase III trial to compare UFT plus cisplatin with docetaxel as a consolidation chemotherapy after UFT plus cisplatin with concurrent radiotherapy.

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APPENDIX

The following principal investigators and institutions also participated in this study: Yoshinobu Ohsaki, M.D., First Department of Internal Medicine, Asahikawa Medical College, Hokkaido; Saburo Sone, M.D., Ph.D., Third Department of Internal Medicine, The University of Tokushima School of Medicine, Tokushima; Ushijima Sunao, M.D., Department of Pulmonology, Kumamoto Chuou Hospital, Kumamoto; Hideki Yokoyama, M.D., Department of Chest Surgery, National Beppu Hospital, Oita; Tokujiro Yano, M.D., Department of Thoracic Surgery, Nakatsu Municipal Hospital, Oita; and Hiroo Nishijima, M.D., Department of Surgery, Kagoshima Kouseiren Hospital, Kagoshima.

REFERENCES

1. Clinical practice guidelines for the treatment of unresectable non-small-cell lung cancer. Adopted on May 16, 1997 by the American Society of Clinical Oncology. *J Clin Oncol* 1997;15:2996–3018.

Table 3 Sites of first failure (n = 59)

Site	Patients	
	No.	%
Local	25	42
Local + Distant	3	5
Distant	29	49
Lung	6	
Liver	6	
Bone	6	
Brain	5	
Others	6	
Unknown	2	3

2. Jett JR, Scott WJ, Rivera MP, Sause WT. Guidelines on treatment of stage IIIB non-small cell lung cancer. *Chest* 2003;123(Suppl 1):221S-55S.
3. 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;17:2692-9.
4. Curran W, Scott C, Langer C. Phase III comparison of sequential vs concurrent chemoradiation for patients with unresected stage III non-small cell lung cancer: Report of Radiation Therapy Oncology Group (RTOG) 9410. *Lung Cancer* 2000;29(Suppl 1):93.
5. Heim W, Wampler GL, Lokich JJ, et al. A study of infusional cisplatin and infusional fluorouracil for locally advanced or metastatic non-small-cell lung cancer: a Mid-Atlantic Oncology Program study. *J Clin Oncol* 1991;9:2162-6.
6. Ichinose Y, Takanashi N, Yano T, et al. A phase II trial of oral tegafur and uracil plus cisplatin in patients with inoperable nonsmall cell lung cancer. *Cancer (Phila)* 1995;75:2677-80.
7. Ichinose Y, Yosimori K, Yoneda S, Kuba M, Kudoh S, Niitani H. UFT plus cisplatin combination chemotherapy in the treatment of patients with advanced nonsmall cell lung carcinoma: a multiinstitutional phase II trial. For the Japan UFT Lung Cancer Study Group. *Cancer (Phila)* 2000;88:318-23.
8. Saito J, Nakai Y, Saijo Y, et al. A phase II trial of oral UFT plus cisplatin (CDDP) in patients with non-small cell lung cancer (NSCLC). *Lung Cancer* 2001;31:285-93.
9. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92-8.
10. Douple EB, Richmond RC. Enhancement of the potentiation of radiotherapy by platinum drugs in a mouse tumor. *Int J Radiat Oncol Biol Phys* 1982;8:501-3.
11. Byfield JE, Calabro-Jones P, Klisak I, Kulhanian F. Pharmacologic requirements for obtaining sensitization of human tumor cells in vitro to combined 5-Fluorouracil or ftorafur and X rays. *Int J Radiat Oncol Biol Phys* 1982;8:1923-33.
12. Schaake-Koning C, van den Bogaert W, Dalesio O, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *N Engl J Med* 1992;326:524-30.
13. Lo TC, Wiley AL Jr, Ansfield FJ, et al. Combined radiation therapy and 5-fluorouracil for advanced squamous cell carcinoma of the oral cavity and oropharynx: a randomized study. *Am J Roentgenol* 1976;126:229-35.
14. Segawa Y, Ueoka H, Kiura K, et al. A phase II study of cisplatin and 5-fluorouracil with concurrent hyperfractionated thoracic radiation for locally advanced non-small-cell lung cancer: a preliminary report from the Okayama Lung Cancer Study Group. *Br J Cancer* 2000;82:104-11.
15. O'Connell MJ, Martenson JA, Wieand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. *N Engl J Med* 1994;331:502-7.
16. Ho DH, Pazdur R, Covington W, et al. Comparison of 5-fluorouracil pharmacokinetics in patients receiving continuous 5-fluorouracil infusion and oral uracil plus N1-(2'-tetrahydrofuryl)-5-fluorouracil. *Clin Cancer Res* 1998;4:2085-8.
17. Yoshino I, Yohena T, Kitajima M, et al. UFT plus cisplatin with concurrent radiotherapy for locally advanced non-small-cell lung cancer. *Proc Am Soc Clin Oncol* 2000;19:506a.
18. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer (Phila)* 1981;47:207-14.
19. Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 1999;340:265-71.
20. Albain KS, Crowley JJ, Turrisi AT 3rd, et al. Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: a Southwest Oncology Group phase II study, SWOG 9019. *J Clin Oncol* 2002;20:3454-60.
21. Hoff PM, Janjan N, Saad ED, et al. Phase I study of preoperative oral uracil and tegafur plus leucovorin and radiation therapy in rectal cancer. *J Clin Oncol* 2000;18:3529-34.
22. de la Torre A, Ramos S, Valcarcel FJ, et al. Phase II study of radiochemotherapy with UFT and low-dose oral leucovorin in patients with unresectable rectal cancer. *Int J Radiat Oncol Biol Phys* 1999;45:629-34.
23. 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;21:2004-10.