a major toxicity. Because the efficacy of second-line docetaxel had not been established at the start of this study in 1998, cross-over administration of docetaxel and vindesine was prohibited in both treatment groups and the nature of second-line treatment was recorded.

No routine premedication was given for hypersensitivity reactions during the first cycle of treatment, although in subsequent cycles this was administered if a patient experienced a reaction. All hypersensitivity reactions were identified by the patient's physician and if deemed necessary, premedication drugs were administered by the investigator. However, recombinant human granulocyte colony-stimulating factor was administered when National Cancer Institute Common Toxicity Criteria grade 3 to 4 leukopenia or neutropenia occurred. If grade 4 neutropenia and/or leukopenia lasting for more than 3 days, grade 4 thrombocytopenia, grade 2 neuropathy, or grade 3 to 4 hepatotoxicity was observed, a 25% dose reduction of both drugs was implemented during the subsequent treatment cycle in both arms. If grade 3 stomatitis or renal toxicity occurred, the dose of cisplatin was reduced by 25%. Dose re-escalation was prohibited. Treatment was discontinued in the event of grade 3 neuropathy and again, dose re-escalation was prohibited. When leukocyte and platelet counts were less than 2,000/μL and 100,000/μL, respectively, or if infection developed at day 8 or 15, vindesine was withheld.

Patient Evaluation

Before chemotherapy, each patient underwent a complete medical history and physical examination, blood cell count determinations, biochemistry testing, chest x-ray, ECG, chest and whole-brain computed tomographic scan, abdominal ultrasound and/or computed tomographic scan, and isotope bone scan. Blood cell counts, differential WBC counts, and biochemistry testing were performed weekly during each course of chemotherapy.

Tumor responses were assessed radiographically and all responders were evaluated on extramural review. Treatment arms were blinded at the review. Standard WHO response criteria were used, and all responses were confirmed $\geq$ 28 days after initial documentation of the response.

QoL scores were measured using the validated instrument QoL Questionnaire for Cancer Patients Treated with Anticancer Drugs developed in Japan [27]. The instrument consists of five domains (functional, physical, mental, psychosocial, and global), and it was completed by the patient before treatment began, before the second and third therapy cycles, and 3 months after the last cycle of treatment. Evaluations were not only performed during the course of treatment but also 2 years after study treatment.

Statistical Considerations

Survival from the date of enrollment was the primary end point. The sample size was chosen on the basis of a log-rank test used to compare the two randomized groups. A sample size of 150 patients per group was estimated on the basis of a projected median survival of 42 weeks in the DC group and 30 weeks in the VdsC group, with an α level of 5% (two sided) and a power of 80% to compare both groups. Dynamic balancing factors (ie, prerandomization stratification factors) included ECOG PS and institutions, and these were used to minimize any imbalance in treatment assignment.

Secondary end points included objective tumor response, response duration, rate of adverse drug reactions, and changes in QoL. The survival time and response duration were estimated for each group using the Kaplan-Meier method [28]. Response duration was calculated from the first date of a 50% reduction in the tumor to the last date that tumor reduction was documented. The difference in response duration was evaluated using the generalized Wilcoxon test. Tumor responses in both groups were compared using Fisher's exact test. Other categoric data, such as treatment data and the incidence of adverse events, were compared between treatment groups using the χ^2 test. QoL analyses were performed using repeated-measures analysis of variance between treatment groups on data collected before the second and third treatment cycles, and 3 months after the last cycle of treatment, adjusting for baseline QoL values.

An interim analysis on the basis of overall survival was planned for 1 year after enrollment of the last patient. The predefined early-stopping rule was based on a two-sided significance level of 0.005. The DeMets and Lan method was applied for multiple comparisons [29]. The analysis was monitored by the Independent Data Monitoring Committee. The final analysis was conducted 2 years after enrollment of the last patient and the final significance level was maintained at 0.0491.

RESULTS

Patient Characteristics

From April 1998 to March 2000, 311 previously untreated patients from 58 institutions were randomly assigned to treatment in the trial (Fig 1). However, six patients did not receive any protocol treatment (three in the DC arm and three in the VdsC arm). In the DC arm, one patient withdrew informed consent, another experienced a rapid increase in serum bilirubin beyond levels acceptable for inclusion into the study, and the third patient had an accident causing a thoracic spine pressure fracture; all withdrawals occurred before the first cycle of treatment. Likewise, before the first cycle of treatment, one patient in the VdsC arm had superior vena cava syndrome, one patient contracted pneumonia and the investigator decided against this patient receiving protocol treatment, and one patient (who also had pneumonia) had brain metastases and was therefore excluded from the study. An additional three patients failed to fulfill the eligibility criteria for the following reasons: stage violations (two patients, one per treatment arm) and prior treatment (one patient, DC arm). Because nine patients were deemed ineligible, 302 patients were evaluated—151 in each arm. All 302 patients were evaluated for survival, response, and toxicity. The characteristics of eligible patients are listed in Table 1.

Treatment Delivery

The median number of cycles was three for the DC arm and two for the VdsC arm ($P < .01$; Table 2). One hundred thirty-two patients (87%) in the DC arm and 115 patients (76%) in the VdsC arm received at least two cycles of chemotherapy. The reasons for terminating chemotherapy before the second treatment cycle in the DC and VdsC arms, respectively, were disease progression (7% v 13%), adverse events (5% v 6%), patient refusal (0% v 2%), and adverse event with patient refusal (1% v 3%).

Table 1. Patient Characteristics

Characteristic	Treatment Group: DC (n = 151)	VdsC (n = 151)
Age, years		
Median	63	64
Range	30–74	39–74
Sex, No. of Patients		
Male	97	103
Female	54	48
Histology, No. of patients		
Adenocarcinoma	120	103
Squamous cell	17	33
Large cell	9	11
Adenosquamous	0	2
Other	5	2
ECOG performance status, No. of patients		
0	46	41
1	99	105
2	5	4
3	1	1

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin; ECOG, Eastern Cooperative Oncology Group.

Table 3. Treatment Outcomes

Outcome	Treatment Group: DC (n = 151)	VdsC (n = 151)	P
Tumor response, No. of patients			
Complete	3	0	
Partial	53	32	
No change	63	76	
Progressive disease	27	38	
Not assessable	5	5	
Overall response rate, %	37.1	21.2	< .01
95% CI	29.4 to 45.3	15.0 to 28.6	
Median duration of response, weeks	10.0	8.4	.02
Survival			
Median, months	11.3	9.6	.014
95% CI	10.2 to 13.1	8.4 to 11.4	
1 year, %	47.7	41.4	
95% CI	39.7 to 55.6	33.5 to 49.3	
2 year, %	24.4	12.3	
95% CI	17.5 to 31.2	7.0 to 17.6	

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin.

Response

Patients receiving DC had a significantly higher overall response rate than those receiving VdsC ($P = .0035$; Table 3). There were three complete responses and 53 partial responses, with an overall response rate of 37.1% (95% CI, 29.4% to 45.3%) in the DC arm. The VdsC arm resulted in 32 partial responses, with an overall response rate of 21.2% (95% CI, 15.0% to 28.6%). The median duration of response was 10.0 weeks in the DC arm versus 8.4 weeks in the VdsC arm ($P = .20$).

Survival

The median survival time, 11.3 months (95% CI, 10.2 to 13.1 months) for the DC arm, was significantly greater than the 9.6-month (95% CI, 8.4 to 11.4 months) median survival of the VdsC arm (log-rank test, $P = .014$; Fig 2). The 1- and 2-year survival rates were 47.7% (95% CI, 39.7% to 55.6%) and 24.4% (95% CI, 17.5% to 31.2%) for the DC group, and 41.4% (95% CI, 33.5% to 49.3%) and 12.3% (95% CI, 7.0% to 17.6%) for the VdsC group, respectively (Fig 2).

Table 2. Treatment Delivery

Cycle of Treatment	Received Cycle of Treatment: DC (n = 151) No. of Patients	%	VdsC (n = 151) No. of Patients	%
1	151	100	151	100
2	132	87	115	76
3	84	56	53	35
4	41	27	17	11
5	6	4	1	1
6	2	1	0	0
No. of cycles*				
Median	3		2	
Range	1–9		1–5	

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin.
*$P = .01$.

Toxicity

National Cancer Institute Common Toxicity Criteria grade 3 and 4 hematologic toxicities, anemia, and leukopenia were significantly more severe among patients receiving VdsC compared with those receiving DC ($P < .01$; Table 4). Grade 4 neutropenia also occurred more frequently in the VdsC regimen (50.3%) than in the DC regimen (35.1%), but grade 3 or 4 thrombocytopenia was rare in both arms.

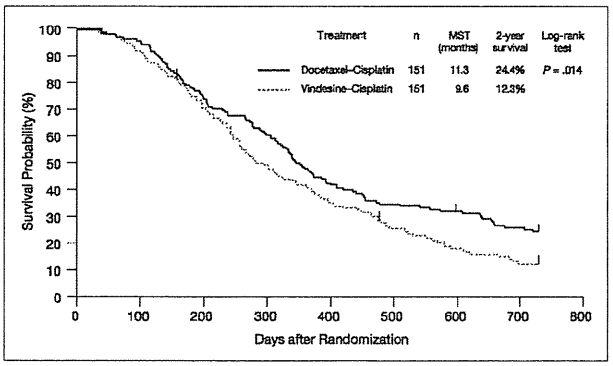

Fig 2. Kaplan-Meier survival estimates for patients treated with docetaxel plus cisplatin and patients treated with vindesine plus cisplatin. MST, median survival time.

Table 4. Grade 3 or 4 Hematologic Toxicities

Toxicity (grade)	Treatment Group: DC (n = 151) No. of Patients	DC (n = 151) %	VdsC (n = 151) No. of Patients	VdsC (n = 151) %	P
Anemia					< .01
3	15	10	34	23	
4	0		0		
Thrombocytopenia					
3	1	1	0	0	
4	0		0		
Leukopenia					< .01
3	66	46	92	68	
4	3		10		
Neutropenia					
3	59	74	41	77	
4	53		76		

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin.

Table 6. Poststudy Treatment

Therapy	Treatment Group (% of patients): DC (n = 151)	VdsC (n = 151)
Chemotherapy	52	46
Platinum	29	23
Gemcitabine	26	19
Vinorelbine	15	15
Irinotecan	9	7
Paclitaxel	8	11
Gefitinib	3	1
Other	11	12
Docetaxel	23	5
Vindesine	0	7
Radiation	51	48
Surgery	2	2

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin.

Grade 3 and 4 nonhematologic toxicities are listed in Table 5. The incidences of the majority of grade 3 or 4 nonhematologic toxicities were similar in both arms, with no significant differences between treatments. However, the incidences of grade 3 or 4 nausea and vomiting, anorexia, and diarrhea were significantly more frequent in the DC arm compared with the VdsC arm ($P < .05$, $P < .01$, and $P < .01$, respectively). There were two deaths in the DC arm that probably were related to treatment. One patient had acute myocardial infarction and died on day 2 of the first cycle of treatment; the second patient had obstructive pneumonia in the same lobe as the primary tumor and died on day 25 of the first course of therapy.

Table 5. Grade 3 or 4 Nonhematologic Toxicities*

Toxicity (grade)	Treatment Group: DC (n = 151) No. of Patients	DC (n = 151) %	VdsC (n = 151) No. of Patients	VdsC (n = 151) %	P
Nausea and vomiting					< .05
3	13	9	7	5	
4	0		0		
Anorexia					< .01
3	30	21	14	9	
4	1		0		
Diarrhea					< .01
3	6	9	2	1	
4	8		0		
Malaise					
3	6	4	3	3	
4	0		1		
Dysrhythmia					
3	3	2	2	1	
4	0		0		
AST elevation					
3	0		3	2	
4	0		0		
ALT elevation					
3	2	1	4	3	
4	0		0		
Bilirubin					
3	3	2	3	2	
4	0		0		

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin.
*Occurring in ≥ 2% patients in at least one arm.

Poststudy Treatment

A total of 52% of patients receiving DC and 46% of patients receiving VdsC also received second-line chemotherapy. The agents used as second-line therapy in both arms were similar without usage of docetaxel and vindesine. Although cross-over treatments were considered to be protocol deviations, 5% of patients receiving first-line vindesine received second-line docetaxel, and these patients were included in survival analyses. Palliative radiotherapy was used in 51% of patients in the DC arm and 48% of patients in the VdsC arm (Table 6).

QoL

QoL questionnaires were completed at baseline, before the second and third treatment cycles, and 3 months after the last cycle of treatment by 82.1%, 83.1%, 76.6%, and 54.9% of patients in the DC arm (n = 151) and 82.8%, 89.6%, 61.6%, and 55.4% of patients in the VdsC arm (n = 151), respectively. Least squares mean scale values for the functional, physical, and mental domains tended to improve among patients receiving DC, but the difference only achieved statistical significance for the functional (nonphysical) domain ($P = .02$; Fig 3). A separate, more detailed analysis of QoL data currently is ongoing.

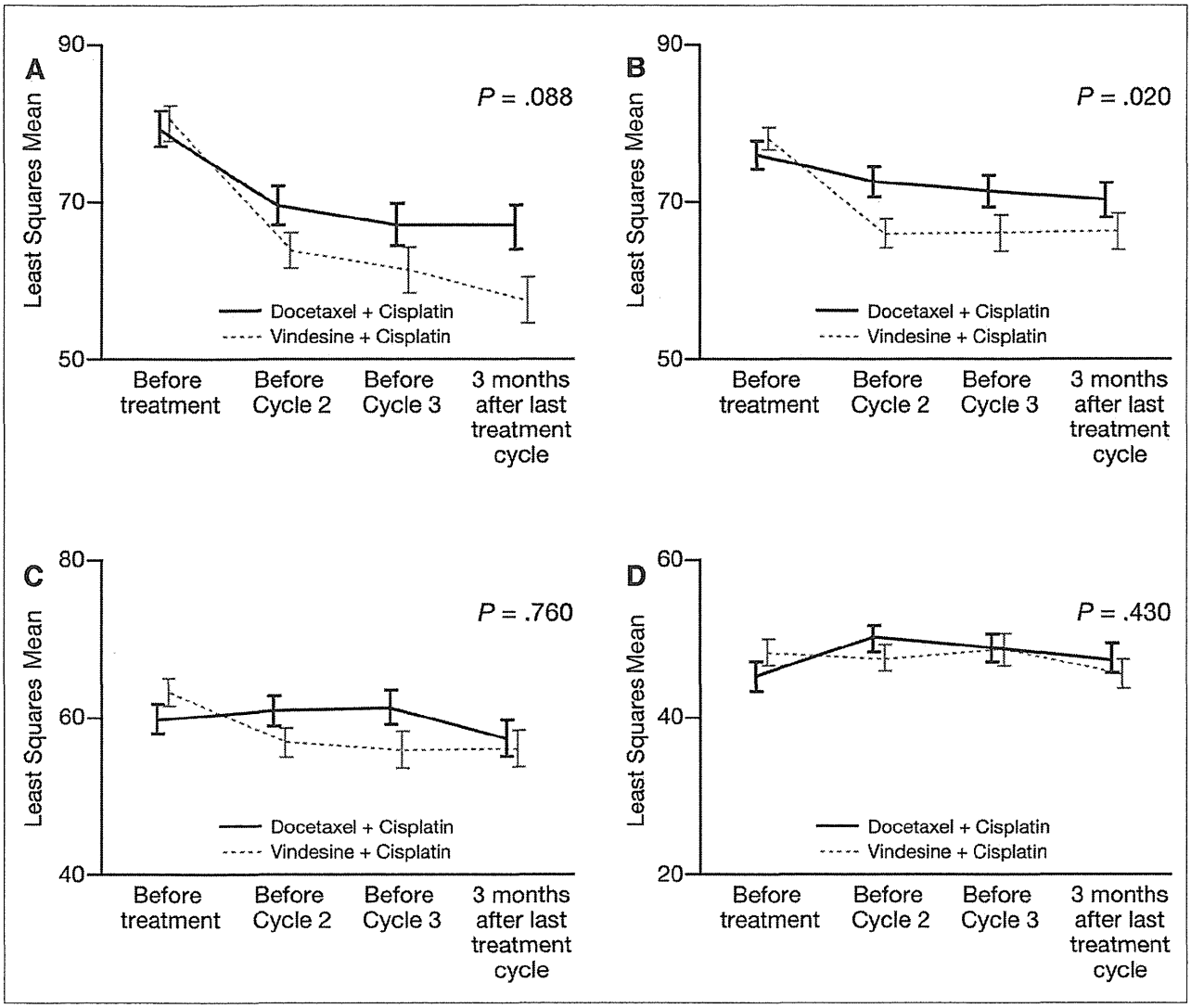

Fig 3. Quality-of-life assessments across four domains of the Quality of Life Questionnaire for Cancer Patients Treated with Anticancer Drugs instrument, among patients treated with docetaxel plus cisplatin and vindesine plus cisplatin. (A) Functional; (B) physical; (C) mental; and (D) psychosocial. Vertical bars represent least square means ± SE. Higher score indicates better quality of life.

DISCUSSION

Platinum-based combination chemotherapy is the treatment of choice for stage IV NSCLC patients with good performance status. The Big Lung Trial recently conducted in England confirmed the survival advantage of platinum-based combination chemotherapy in this setting [30]. The results of the present multicenter randomized trial reveal a significant survival advantage for DC when compared with VdsC in the treatment of patients with stage IV NSCLC. It is noteworthy that the 2-year survival rate in the DC arm was 24.3%—double that observed in the control arm. This is comparable to results for patients with stage III NSCLC who were treated with sequential chemoradiotherapy [4].

VdsC was chosen as the control arm because this regimen showed significant survival advantage over BSC in a Canadian trial [31]. In addition, this combination has long been the standard regimen for advanced NSCLC [22,31,32]. For instance, two randomized trials conducted in Japan, which compared the more recently developed agent irinotecan plus cisplatin with VdsC, failed to show an overall survival advantage for the irinotecan-containing regimen in advanced NSCLC [33,34]. In the European study, 612 patients were randomly assigned to receive vinorelbine plus cisplatin, vindesine plus cisplatin, or vinorelbine alone. In this study, the unadjusted log-rank test comparing the survival of patients who received vinorelbine plus cisplatin versus VdsC yielded a *P* value of .085 in favor of vinorelbine

plus cisplatin. Patients with both stage III and local recurrence (41%), or metastatic NSCLC (59%) were included, and nearly half of the patients received thoracic irradiation after chemotherapy [22]. The treatment strategy of locally advanced NSCLC is different from that of metastatic disease. Thus, the advantage of vinorelbine plus cisplatin over VdsC in patients with stage IV NSCLC has not been clearly defined.

Despite undergoing more treatment cycles, fewer patients on the DC arm experienced severe hematologic toxicities (including anemia and leukopenia) than patients treated with VdsC. Although diarrhea, nausea and vomiting, and anorexia were more frequently observed in the DC arm, such toxicities were easily managed with standard care.

DC has been evaluated in other phase III trials. In the ECOG trial, 1,207 patients were randomly assigned to paclitaxel plus cisplatin, gemcitabine plus cisplatin, docetaxel plus cisplatin, or paclitaxel plus carboplatin [35]. The response rate and median survival were similar among the four regimens for eligible patients at 19% and 7.9 months, respectively. In a large international trial (TAX-326), 1,218 chemotherapy-naive patients were randomly assigned to docetaxel plus cisplatin, docetaxel plus carboplatin, or vinorelbine plus cisplatin [36]. The DC arm favored a longer median survival time compared with the vinorelbine plus cisplatin arm (11.3 *v* 10.1 months) and response (31.6% *v* 24.5%). Although we must be careful when making retrospective comparisons, both survival figures and response data of the present study and TAX-326 were virtually identical and were better than those of the ECOG trial [35]. It is suggested that patients with more favorable prognostic factors entered in TAX-326 and the current study.

More recently, attention has focused on improving QoL as a goal of therapy for patients with advanced NSCLC [37]. One trial of docetaxel as second-line therapy versus BSC showed that chemotherapy resulted in significantly better control of pain and fatigue than did BSC [20]. In a similar comparative phase III trial, docetaxel, administered as first-line in chemotherapy-naive patients, was significantly better than BSC in controlling not only pain but also dyspnea and emotional functioning [19]. In the present study, QoL measures demonstrated that the physical domain was significantly better in the DC arm over the VdsC arm ($P = .020$). This finding of a QoL benefit with a docetaxel plus platinum combination is also supported by the results of TAX-326 [38]. This investigation indicated that patients in receipt of a docetaxel plus platinum combination reported greater global QoL benefit in terms of patient pain or less Karnofsky performance status deterioration than patients receiving vinorelbine plus cisplatin when the EuroQol and Lung Cancer Symptom Scale instruments were used [39,40].

In this study, we used 60 mg/m^2 of docetaxel on the basis of the phase II study conducted in Japan [26]. The dose of docetaxel is lower than the doses used in ECOG1594 and TAX-326 (docetaxel and cisplatin 75 mg/m^2) [35,36]. In a randomized trial comparing docetaxel alone with BSC in patients previously treated with platinum-based chemotherapy, docetaxel 100 mg/m^2 was not tolerated but docetaxel 75 mg/m^2 demonstrated significant survival benefit [20]. Therapeutic index was also better for the lower dose of docetaxel in another randomized trial of second-line chemotherapy, which compared 100 or 75 mg/m^2 of docetaxel against a control regimen of vinorelbine or ifosfamide [21]. The docetaxel dose of 60 mg/m^2 might be optimal when it is combined with a standard dose of cisplatin. Additional study is warranted regarding this dose issue.

In summary, this randomized phase III trial demonstrates that DC is superior, in terms of response rate and survival, to VdsC in the treatment of previously untreated patients with stage IV NSCLC. A doubling in the 2-year survival rate is reported for DC compared with the classic standard regimen. Given the results of this trial, DC should be considered as a standard regimen for the first-line treatment of stage IV NSCLC, and it is suggested that the classic combination regimen should no longer be regarded as a suitable control arm in future randomized studies of patients with stage IV NSCLC.

Appendix

The appendix is included in the full-text version of this article, available on-line at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Performed contract work within the last 2 years: Kaoru Kubota, Aventis Pharma Ltd; Koshiro Watanabe, Aventis Pharma Ltd; Hideo Kunitoh, Aventis Pharma Ltd; Kazumasa Noda, Aventis Pharma Ltd; Yukito Ichinose, Aventis Pharma Ltd; Nobuyuki Katakami, Aventis Pharma Ltd; Takahiko Sugiura, Aventis Pharma Ltd; Masaaki Kawahara, Aventis Pharma Ltd; Akira Yokoyama, Aventis Pharma Ltd; Soichiro Yokota, Aventis Pharma Ltd; Shuichi Yoneda, Aventis Pharma Ltd; Kaoru Matsui, Aventis Pharma Ltd; Shinzo Kudo, Aventis Pharma Ltd; Masahiko Shibuya, Aventis Pharma Ltd; Takeshi Isobe, Aventis Pharma Ltd; Yoshihiko Segawa, Aventis Pharma Ltd; Yutaka Nishiwaki, Aventis Pharma Ltd; Yasuo Ohashi, Aventis Pharma Ltd; Hisanobu Niitani, Aventis Pharma Ltd.

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A Randomized Trial of Adjuvant Chemotherapy with Uracil–Tegafur for Adenocarcinoma of the Lung

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ABSTRACT

BACKGROUND

In a previous phase 3 trial of adjuvant chemotherapy after resection of non–small-cell lung cancer, a combination of uracil and tegafur (often referred to as UFT) taken orally was shown to prolong survival. A subgroup analysis disclosed that most patients who benefited had pathological stage I adenocarcinoma.

METHODS

We randomly assigned patients with completely resected pathological stage I adenocarcinoma of the lung to receive either oral uracil–tegafur (250 mg of tegafur per square meter of body-surface area per day) for two years or no treatment. Randomization was performed with stratification according to the pathological tumor category (T1 vs. T2), sex, and age. The primary end point was overall survival.

RESULTS

From January 1994 through March 1997, 999 patients were enrolled. Twenty patients were found to be ineligible and were excluded from the analysis after randomization; 491 patients were assigned to receive uracil–tegafur and 488 were assigned to observation. The median duration of follow-up for surviving patients was 73 months. The difference in overall survival between the two groups was statistically significant in favor of the uracil–tegafur group (P=0.04 by a stratified log-rank test). Grade 3 toxic effects occurred in 10 of the 482 patients (2 percent) who actually received uracil–tegafur.

CONCLUSIONS

Adjuvant chemotherapy with uracil–tegafur improves survival among patients with completely resected pathological stage I adenocarcinoma of the lung.

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THE COMBINATION OF URACIL AND tegafur (also referred to as UFT) at a molar ratio of 4:1 is an oral anticancer agent with good absorption in the small intestine.[1] Tegafur is a prodrug that is gradually converted to fluorouracil in the liver by the cytochrome P-450 enzyme. Uracil enhances the serum concentration of fluorouracil by competitive inhibition of dihydropyrimidine dehydrogenase, the enzyme responsible for fluorouracil catabolism.[2] Oral uracil–tegafur generates a higher maximal plasma level of fluorouracil than the protracted intravenous injection of fluorouracil given in a dose that is equimolar to the amount of tegafur in uracil–tegafur.[3]

In patients with advanced non–small-cell lung cancer, the rate of response to treatment with uracil–tegafur ranges from 6 percent to 8 percent,[4,5] and a regimen of daily uracil–tegafur for 2 or 3 weeks plus a bolus injection of cisplatin yields a response rate of 29 to 38 percent and a median survival of 8 to 13 months.[6-8] In two trials of uracil–tegafur plus cisplatin with concurrent radiotherapy in patients with locally advanced non–small-cell lung cancer, the response rates were 80 percent[9] and 94 percent,[10] with a median survival of 16.5 months.[9] The results with uracil–tegafur plus cisplatin are similar to the results of other regimens of cisplatin-based combination chemotherapy.[11,12]

The West Japan Study Group for Lung Cancer Surgery reported that survival was significantly longer in patients assigned to adjuvant treatment with uracil–tegafur than in patients assigned to observation alone after complete resection of stage I, II, or III non–small-cell lung cancer.[13] The five-year survival rate was 64 percent in the uracil–tegafur group and 49 percent in the control group (P=0.02). In a subgroup analysis, there was no significant difference in overall survival between the uracil–tegafur group and the control group among patients with squamous-cell carcinoma (P=0.24). In contrast, patients with adenocarcinoma in the uracil–tegafur group had a significantly better survival than those in the control group (P=0.009).[14] In addition, most patients with adenocarcinoma had stage I disease. These results prompted us to conduct a randomized trial of uracil–tegafur as a postoperative adjuvant treatment for patients with completely resected stage I adenocarcinoma.

METHODS

PATIENTS

Enrollment began in January 1994. Eligible patients had undergone a complete surgical resection of a pathologically documented stage I (T1N0M0 or T2N0M0) adenocarcinoma of the lung (according to the 1986 classification of the American Joint Committee on Cancer).[15] Visceral pleural involvement was classified according to the rules of the Japan Lung Cancer Society,[16] and a tumor that was larger than 3 cm in diameter or a tumor of any size that was exposed on the visceral pleural surface was classified as a pathological T2 tumor. Other inclusion criteria were an age of 45 to 75 years; the absence of preoperative anticancer treatment, previous cancer, and synchronous multiple cancers; an Eastern Cooperative Oncology Group (ECOG) performance status[17] of 0, 1, or 2; a leukocyte count of at least 4000 per cubic millimeter; a platelet count of at least 100,000 per cubic millimeter; a hemoglobin level of at least 100 g per liter; serum aspartate aminotransferase and alanine aminotransferase levels that were no more than twice the upper limit of the normal range; and an absence of severe postoperative complications, such as pneumonia or empyema. Written or oral informed consent was obtained from all patients or their representatives, and the study was approved by the institutional review board of each participating center.

Confirmation of eligibility and randomization were performed by telephone or fax at a central site within 28 days after each patient's operation. All eligible patients were stratified according to age (less than 65 years vs. 65 years or older), sex, and pathological tumor category (T1 vs. T2).[18]

TREATMENT

Patients assigned to the control group were observed, with no treatment after surgery. In the treatment group, uracil–tegafur (250 mg of tegafur per square meter of body-surface area per day) in the form of 100-mg capsules (100 mg of tegafur plus 224 mg of uracil) was given orally before meals twice daily for two years, starting four weeks postoperatively. The dose was rounded up or down to the nearest 100 mg. Most patients received two capsules of uracil–tegafur (200 mg of tegafur and 448 mg of uracil) twice daily. The patients were asked at each follow-up visit whether they had taken the capsules as prescribed.

Toxic effects of uracil–tegafur were graded according to the criteria of the Japan Society of Clinical Oncology, which consist of the World Health Organization criteria with minor modifications.[19] If a grade 2 adverse reaction occurred, the dose of uracil–tegafur was reduced to 200 mg per square meter. Treatment was stopped if there was a grade 3 or higher adverse reaction, a leukocyte count of less than 3000 per cubic millimeter, a platelet count of less than 70,000 per cubic millimeter, a hemoglobin level of less than 9.5 g per deciliter, or an aspartate aminotransferase or alanine aminotransferase level that was more than three times the upper limit of the normal range.

FOLLOW-UP

A follow-up evaluation was performed every three months for the first two years after the operation and every six months thereafter. The evaluation included a physical examination, a complete blood count, blood chemical tests, screening for serum tumor markers, and chest radiography. A computed tomographic (CT) scan of the thorax and brain and either a CT scan or a sonogram of the upper abdomen were obtained every six months for the first two years after the operation and at least twice during the subsequent three years. Whenever possible, a biopsy of any new lesion suspected of being a recurrence or a second primary cancer was performed. A final diagnosis of such lesions was made by the physician in charge.

STATISTICAL ANALYSIS

The primary end point was overall survival; secondary end points were cancer-free survival and safety. All eligible patients were included in the analysis of overall survival and cancer-free survival, and all patients who were given uracil–tegafur were included in the safety assessment.

The sample size was calculated by the method of Schoenfeld and Richter[20] according to the following assumptions: a five-year survival rate of 70 percent in the no-treatment group, a hazard ratio for death of 0.67 in the uracil–tegafur group, a two-year accrual period, a five-year follow-up, a one-sided significance level of 0.05, and a statistical power of 80 percent. Since these calculations resulted in a sample size of 518 patients, the sample size was determined to be 600, with an allowance of about 15 percent for ineligible patients or patients who were lost to follow-up. In May 1995, the sample size was expanded to 984 patients after it became clear that the five-year survival rate for those in the control group was better than expected. The newly adopted five-year survival rate was 83 percent, and the accrual period was extended to three years. A committee for efficacy and safety provided independent monitoring of the study. Haybittle–Peto horizontal boundaries,[21] with a criterion of $P<0.001$, were used in the interim analyses conducted to determine whether the study should be terminated early.

Overall survival was defined as the time from surgery until death from any cause, and cancer-free survival was defined as the time from surgery until the appearance of the first recurrence of cancer, a second cancer, or death from any cause. Survival was estimated by the Kaplan–Meier method, and any differences in survival were evaluated with a stratified log-rank test. Multivariable analyses with the Cox proportional-hazards model were used to estimate the simultaneous effects of prognostic factors on survival.[22] Interactions with prognostic factors were also examined with the Cox proportional-hazards model. The SAS statistical software package (version 6.09, SAS Institute) was used for all calculations. Differences were considered to be statistically significant when the P value was 0.05 or less. All statistical tests were two-sided.

The protocol committee of the Japan Lung Cancer Research Group designed the study. Taiho Pharmaceutical Company collected and analyzed the data, and the authors interpreted the data and wrote the report. The authors had access to the primary data.

RESULTS

CHARACTERISTICS OF THE PATIENTS

From January 1994 through March 1997, 999 patients were enrolled and randomly assigned to receive uracil–tegafur (498 patients) or no treatment (501 patients). Seven patients in the uracil–tegafur group and 13 patients in the control group were ineligible for the following reasons: pathological N1 or M1 disease in 7 patients, histologic findings other than adenocarcinoma in 6, no laboratory data at registration in 2, and miscellaneous reasons in 5. Therefore, there were 491 eligible patients in the uracil–tegafur group and 488 in the control group. Table 1 lists the base-line clinical characteristics of the two groups, which did not differ significantly. All but one patient in each group underwent lobectomy.

Table 1. Base-Line Characteristics of the Patients.

Characteristic	Uracil–Tegafur Group (N=491)	Control Group (N=488)
Age		
Mean (yr)	62	62
Range (yr)	45–75	45–75
<65 yr (no.)	274	275
≥65 yr (no.)	217	213
Female sex (no.)	253	249
ECOG performance status (no.)*		
0	376	369
1	105	113
2	10	6
Pathological tumor stage (no.)		
T1	362	354
T2	129	134
Invasion of pleura (no.)†		
0	340	346
1	120	114
2	29	28
Unknown	2	0
Tumor size (no.)		
≤2 cm	208	204
>2 to ≤3 cm	174	170
>3 cm	109	114
Location of the tumor (no.)		
Right upper lobe	182	189
Right middle lobe	41	34
Right lower lobe	102	87
Right lobes	2	2
Left upper lobe	107	114
Left lower lobe	54	60
Left lobes	3	2
Type of surgery (no.)		
Lobectomy	490	487
Pneumonectomy	1	1

* ECOG denotes Eastern Cooperative Oncology Group. Higher performance-status numbers indicate greater impairment.

† 0 indicates a tumor with no pleural involvement or a tumor that reaches the visceral pleura but does not extend beyond the elastic layer, 1 a tumor that extends beyond the elastic layer of the visceral pleura but is not exposed on the pleural surface, and 2 a tumor that is exposed on the pleural surface but does not involve the parietal pleura.

ADVERSE REACTIONS AND COMPLIANCE

Of the 498 patients originally assigned to the uracil–tegafur group, 482 actually received uracil–tegafur. Few severe adverse reactions were associated with uracil–tegafur. A grade 3 adverse reaction developed in 10 of 482 patients (2 percent), and no grade 4 adverse reactions occurred (Table 2).

Compliance with instructions to take uracil–tegafur was calculated on the basis of the number of patients who actually took uracil–tegafur and the number of patients who were assigned to it, excluding those with a recurrence or second cancer and those who died. The rate of compliance was 80 percent (95 percent confidence interval, 77 to 84 percent) at 6 months, 74 percent (95 percent confidence interval, 70 to 78 percent) at 12 months, 69 percent (95 percent confidence interval, 65 to 73 percent) at 18 months, and 61 percent (95 percent confidence interval, 57 to 66 percent) at 24 months. The main reasons for discontinuation of uracil–tegafur were an adverse reaction (in 123 patients), the patient's decision (52 patients), and the doctor's judgment (34 patients).

OVERALL SURVIVAL

The median follow-up among surviving patients was 72 months in the uracil–tegafur group and 73 months in the control group. Data were censored for 426 patients in the uracil–tegafur group and 399 in the control group. At the last follow-up visit, 65 patients in the uracil–tegafur group and 89 in the control group had died, and the overall survival rates in the two groups differed significantly on the basis of the stratified log-rank test (Fig. 1A). The five-year overall survival rate was 88 percent (95 percent confidence interval, 85 to 91 percent) in the uracil–tegafur group and 85 percent (95 percent confidence interval, 82 to 89 percent) in the control group. When the survival analysis was performed with the inclusion of all 999 randomized patients, the result did not change (P=0.047).

The predetermined covariates were age (<65 years vs. ≥65 years), sex, ECOG performance status (0 vs. 1 or 2), pathological T status (T1 vs. T2), and the assigned treatment. The covariates were selected according to multivariate analysis with the use of a stepwise procedure. All P values were less than 0.05. The selected covariates were as follows: age (hazard ratio for patients ≥65 years, 2.02; 95 percent confidence interval, 1.46 to 2.80; P<0.001), sex (hazard ratio for women, 0.66; 95 percent confidence interval, 0.48 to 0.91; P=0.01), T category (hazard ratio for T2, 1.95; 95 percent confidence interval, 1.41 to 2.69; P<0.001), and treatment group (hazard ratio for the uracil–tegafur group, 0.72; 95 percent confidence interval, 0.53 to 1.00; P=0.05).

Table 2. Adverse Reactions to Uracil–Tegafur.

Adverse Reaction	Grade of Toxicity*			
	1	2	3	4
	% of patients			
Leukopenia	2	1	0	0
Thrombocytopenia	<1	0	0	0
Anemia	1	<1	0	0
Increase in bilirubin	1	<1	0	0
Increase in aspartate aminotransferase	6	2	<1	0
Increase in alanine aminotransferase	6	2	0	0
Increase in alkaline phosphatase	2	<1	0	0
Anorexia	9	8	1	0
Nausea or vomiting	10	3	1	0
Diarrhea	2	1	<1	0
Alopecia	<1	0	0	0

* Toxicity was graded according to criteria of the Japan Society of Clinical Oncology. Grades range from 1 to 4, with a higher grade indicating a more severe reaction.

We also evaluated interactions between the four prognostic factors (sex, age, pathological tumor category, and size of the tumor) (Fig. 2) and the treatment. We included tumor size in the analysis because the tumor category is determined mainly by the maximal diameter of the primary tumor. As Figure 2 shows, there were significant interactions between the tumor category and size of the tumor and the treatment.

The survival rate among patients with T2 disease in the uracil–tegafur group was significantly higher than that in the control group, whereas among patients with T1 disease, there was no significant difference in survival between the uracil–tegafur and control groups. The five-year survival rate among patients with T2 disease was 85 percent (95 percent confidence interval, 79 to 91 percent) in the uracil–tegafur group and 74 percent (95 percent confidence interval, 66 to 81 percent) in the control group (Fig. 1B). The difference in overall survival between the two groups was statistically significant (P=0.005 by the log-rank test). The five-year survival rate among patients with T1 disease was 89 percent in the uracil–tegafur group and 90 percent in the control group (Fig. 1C). In the subgroups of patients with a tumor that was less than 2 cm in diameter, 2 to 3 cm, and greater than 3 cm, the five-year survival rate was 89 percent, 89 percent, and 85 per-

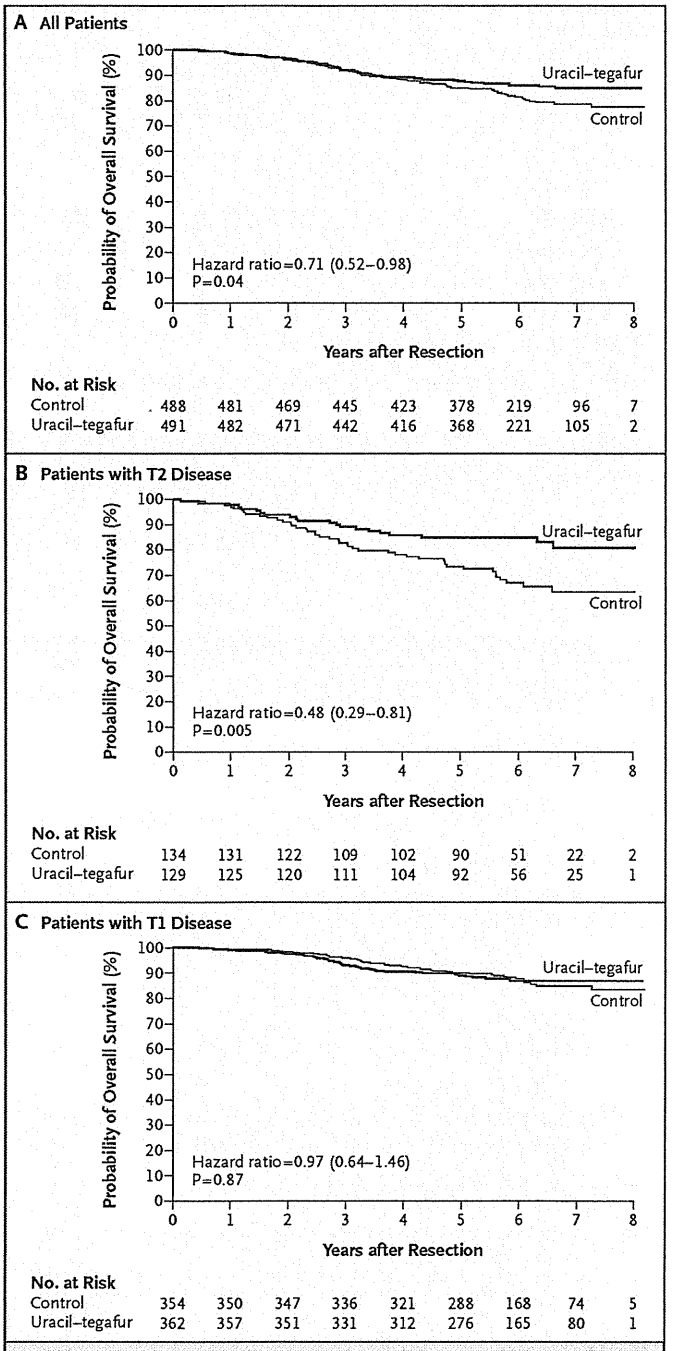

Figure 1. Overall Survival among All 979 Eligible Patients (Panel A), 263 Patients with T2 Disease (Panel B), and 716 Patients with T1 Disease (Panel C) Who Were Randomly Assigned to the Uracil–Tegafur Group and the Control Group.

The hazard ratios indicate the risk of death in the uracil–tegafur group as compared with the control group; 95 percent confidence intervals are shown in parentheses. P values were calculated with the use of the stratified log-rank test.

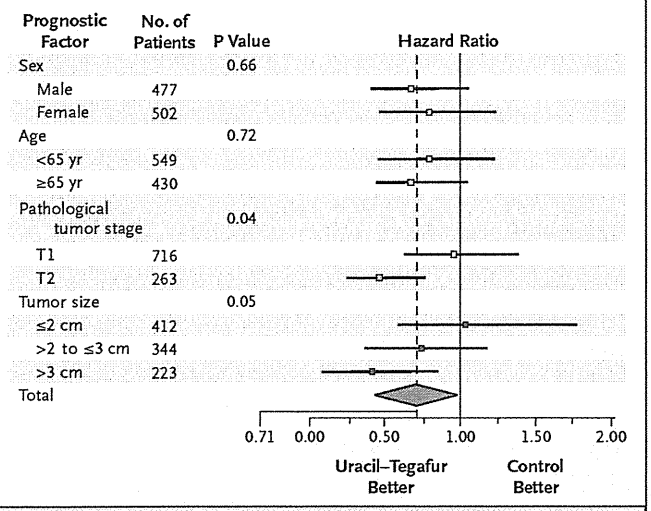

Figure 2. Hazard Ratios for Death in Patients in the Uracil–Tegafur Group as Compared with the Control Group, According to Four Prognostic Factors.

Each square represents the estimated treatment effect, the horizontal lines represent the 95 percent confidence intervals, and the diamond corresponds to the 95 percent confidence intervals for the entire group of patients. The P value for the tumor size is for the comparison of patients who had tumors that were 2 cm or less in diameter with patients who had tumors that were more than 3 cm.

cent, respectively, in the uracil–tegafur group and 91 percent, 86 percent, and 74 percent, respectively, in the control group.

PATTERN OF FAILURE AND CANCER-FREE SURVIVAL

A recurrence or a second primary cancer as the first treatment failure after surgery was documented in 23 percent of the uracil–tegafur group and 26 percent of the control group (Table 3). Among the 716 patients with T1 disease, recurrence or a second primary cancer was observed in 69 of 362 patients (19 percent) in the uracil–tegafur group and 76 of 354 patients (21 percent) in the control group; among the 263 patients with T2 disease, 42 of 129 patients (33 percent) in the uracil–tegafur group and 53 of 134 patients (40 percent) in the control group had recurrence or a second primary cancer as the first treatment failure. On the basis of a Kaplan–Meier analysis, the difference in cancer-free survival between the two groups was not statistically significant (P=0.25 by the stratified log-rank test). The survival of patients after the diagnosis of a recurrence or a second primary cancer did not differ significantly between the groups (P=0.14 by the log-rank test): the one-year and two-year survival rates after diagnosis were 65 percent and 50 percent, respectively, in the uracil–tegafur group and 65 percent and 42 percent, respectively, in the control group.

DISCUSSION

The Japanese Association for Chest Surgery and Japan Lung Cancer Society recently reported the long-term survival rate of 7408 patients with lung cancer who had undergone a surgical resection in 1994, the year that our trial started.[23] The main histologic types were adenocarcinoma (in 56 percent of the patients) and squamous-cell carcinoma (in 33 percent). Among patients with pathological stages T1N0M0 and T2N0M0, the five-year survival rates were 79 percent and 60 percent, respectively. In our study of adenocarcinoma, the five-year survival rate in the control group was 90 percent among patients with T1N0M0 disease and 74 percent among those with T2N0M0 disease. Although the figures in the two studies cannot be directly compared, owing to different histologic patterns and times when the data were collected, the excellent five-year survival rate for the control patients in our study[24,25] indicates that our collaborative group has made improvements in the quality of the surgical treatment and the accuracy of surgical staging.

Our study shows that adjuvant chemotherapy with uracil–tegafur has a beneficial effect on the survival of patients with resected stage I adenocarcinoma of the lung. This benefit, however, was not observed in patients with T1N0 disease. In the past few years, the number of patients in whom small adenocarcinomas have been discovered has increased owing to the increased use of computed tomography. In our study, 412 of 979 patients (42 percent) had an adenocarcinoma that was less than 2 cm in diameter. Adenocarcinomas of this size often include bronchoalveolar carcinoma, which is unlikely to recur after resection.[26] Therefore, a small adenocarcinoma usually has a very good prognosis[26,27]: in our study, the five-year survival rate of patients with tumors that were 2 cm or less in diameter was 91 percent. For this reason, we believe that patients with small tumors should be excluded from adjuvant trials unless a subgroup with a poor prognosis is identified.

In contrast, treatment with uracil–tegafur tended to improve the survival rate among patients with a tumor that was 2 to 3 cm in diameter and provided

a definitive survival benefit for patients with a tumor that was more than 3 cm in diameter. These findings indicate that the effect of uracil–tegafur may be related to certain biologic factors. In a retrospective study, Tanaka et al.[28] found that the prognosis was good for patients with non–small-cell lung cancer characterized by a high apoptotic index and no aberrant expression of p53 who received postoperative uracil–tegafur.

Patient compliance is usually a problem in trials of adjuvant chemotherapy. In trials of cisplatin-based chemotherapy, which was scheduled to be administered in three or four cycles postoperatively, only 50 to 70 percent of the planned treatment was given.[29-32] In our trial, we planned to give uracil–tegafur daily for two years. However, only 61 percent of patients assigned to the treatment completed the two-year course. The main reasons for discontinuing uracil–tegafur were adverse reactions (which were infrequent and usually mild) and the patient's decision, which suggests that compliance in trials of adjuvant chemotherapy may not be related to the severity of adverse events.

The main difference between trials of cisplatin-based adjuvant chemotherapy and trials of adjuvant chemotherapy with uracil–tegafur is the duration of the treatment. The cisplatin-based regimens entail three or four cycles (9 to 16 weeks) of chemotherapy,[29-32] whereas uracil–tegafur is taken daily for 1 or 2 years.[13,33-36] Fluorouracil is not a dose-dependent drug but a time-dependent agent. Therefore, a daily regimen of uracil–tegafur is an effective way of maintaining the blood level of fluorouracil. In addition, uracil–tegafur and its metabolites have an inhibitory effect on tumor angiogenesis in mice.[37] If this effect occurs in humans, then the daily, long-term administration of uracil–tegafur may be beneficial.

So far, six randomized trials,[13,33-36] including the present one, have been conducted that compare surgery alone with adjuvant chemotherapy with uracil–tegafur. Among them, three trials have shown a survival benefit from treatment with uracil–tegafur.[13,34] A meta-analysis of those six trials showed that adjuvant chemotherapy with uracil–tegafur improved the overall survival (hazard ratio for death, 0.77; 95 percent confidence interval, 0.63 to 0.94; P=0.01).[38] It is unclear whether patients with stage II or stage III disease benefit from treatment with uracil–tegafur and whether treatment for one year is equivalent to treatment for two years. However, our study indicates that patients with completely resected stage I disease, especially T2N0 adenocarcinoma, will benefit from adjuvant chemotherapy with uracil–tegafur.

Table 3. Pattern of Treatment Failure.

Pattern	Uracil–Tegafur Group (N=491)	Control Group (N=488)
	no. of patients (%)	
Intrathoracic only		
Local recurrence	17	8
Pulmonary metastases	36	38
Local recurrence plus pulmonary metastases	3	12
Second cancer	11	11
Extrathoracic only		
Recurrence	23	33
Second cancer	14	18
Intrathoracic plus extrathoracic recurrence	7	9
Total	111 (22.6)	129 (26.4)

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APPENDIX

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Prognostic value of visceral pleural invasion in resected non–small cell lung cancer diagnosed by using a jet stream of saline solution

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Objective: Visceral pleural invasion caused by non–small cell lung cancer is a factor in the poor prognosis of patients with that disease. We investigated the relationship between the diagnosis of visceral pleural invasion by using a jet stream of saline solution, which was previously reported as a new cytologic method to more accurately detect the presence of visceral pleural invasion, and prognosis.

Methods: From January 1992 through December 1998, 143 consecutive patients with peripheral non–small cell lung cancer that appeared to reach the visceral pleura underwent a surgical resection at the Department of Thoracic Oncology, National Kyushu Cancer Center. The surface of the visceral pleura in patients undergoing lung cancer resection was irrigated with a jet stream of saline solution. The diagnosis of visceral pleural invasion was determined by means of either a pathologic examination or by means of a jet stream of saline solution. In addition, a cytologic examination of the pleural lavage fluid obtained immediately after a thoracotomy was evaluated.

Results: Forty-nine (34%) resected tumors were identified as having visceral pleural invasion. The diagnosis of visceral pleural invasion in 31, 6, and 12 patients was determined by using a jet stream of saline solution alone, pathologic examination alone, or both, respectively. The visceral pleural invasion and positive findings of intrapleural lavage cytology were linked. Although there was no significant difference between the incidence of distant metastases in the patients with visceral pleural invasion and those without visceral pleural invasion, the incidence of local recurrence, especially regarding carcinomatous pleuritis (malignant pleural effusion, pleural dissemination, or both), in the patients with visceral pleural invasion was significantly higher than in those without visceral pleural invasion. The recurrence-free survival of patients with visceral pleural invasion was significantly shorter than that of patients without visceral pleural invasion ($P = .004$), even patients with stage I disease ($P = .02$). There was also a significant difference between the patients with or without visceral pleural invasion in the overall survival ($P = .02$). Visceral pleural invasion was independently associated with a poor recurrence-free survival on the basis of multivariate analyses ($P = .03$), as were sex ($P = .03$), age ($P = 002$), and the stage of the disease ($P < .0001$).

Conclusions: This study confirmed that the jet stream of saline solution method in addition to ordinary pathologic examination was useful for detecting visceral pleural invasion, which is considered to be one of the causes of local recurrence, especially in carcinomatous pleuritis.

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GTS

Visceral pleural invasion (VPI) is a factor in the poor prognosis of patients with non–small cell lung cancer (NSCLC).[1,2] The diagnosis of VPI is usually confirmed by means of a pathologic examination (PE) alone. PE is based on 1 or 2 cut slices of the resected tumor. Although PE can easily confirm VPI when the tumor is clearly visible on the visceral pleura, such cases are relatively rare. Therefore it remains unclear as to whether a tumor can be reliably considered to have no VPI on the basis of PE alone. To resolve this problem, we previously reported a simple method involving a cytologic examination of cells desquamated from the visceral pleura by using a jet stream of saline solution (JSS). This method is considered to be significantly more sensitive and accurate than ordinary PE in detecting VPI by lung cancer.[3]

We retrospectively investigated the relationship between a diagnosis of VPI in patients with resected NSCLC by using the JSS method and recurrent site and the prognosis.

Methods

Patients and Methods

From January 1992 through December 1998, 143 consecutive patients with peripheral NSCLC that appeared to reach the visceral pleura and that either did not adhere to or did not invade the surrounding tissue underwent a surgical resection at the Department of Thoracic Oncology, National Kyushu Cancer Center. This study included the 90 cases of a former report about JSS.[3] Any patients with diffuse pleural adhesions, distant metastases, and T4 disease were excluded. The patients consisted of 81 men and 62 women. The median age of the patients was 64 years, with a range of 24 to 90 years. A complete surgical resection consisted of a lobectomy (n = 132), bilobectomy (n = 5), pneumonectomy (n = 3), or segmentectomy (n = 3). The JSS method was performed as previously described.[3] Briefly, the surface of the visceral pleura in patients with resected lung cancer was irrigated twice with a jet stream of heparinized saline solution by using a 20-mL syringe with a 21-gauge needle immediately after performing a surgical resection. The distance between the tip of the needle and the pleural surface was kept at approximately 2 cm, and a total of 40 mL of saline solution containing cells desquamated from the visceral pleural surface was collected and then centrifuged at 1000 rpm for 10 minutes. Thereafter, the obtained sediment was stained by using the Giemsa and Papanicolaou method for cytologic examination. When it was necessary to distinguish cancer cells from reactive mesothelial cells, anticarcinoembryonic antigen staining, alcian blue staining, and periodic acid–Schiff reactions were performed. In addition, a cytologic examination of pleural lavage fluid obtained immediately after a thoracotomy was evaluated in all but 5 patients. The pathologic stage of the disease was based on the TNM classification of the Union Internationale Contre Cancer.[4] The pathologic stage of the tumors in this series was IA in 49 patients, IB in 46 patients, IIA in 3 patients, IIB in 14 patients, IIIA in 28 patients, and IIIB in 3 patients. The histologic analysis of the tumor was based on the World Health Organization classification for cell types.[5] One hundred sixteen patients had adenocarcinoma, 19 had squamous cell carcinoma, 6 had adenosquamous cell carcinoma, and 2 had large cell carcinoma. After the operation, the patients were re-examined once every 3 months for 5 years and thereafter at 6-month intervals. The evaluations included a physical examination and chest roentgenography at each visit and computed tomography of the chest, magnetic resonance imaging of the brain, and a bone scan every year.

TABLE 1. Rate of positive findings of VPI classified by means of JSS, PE, or either method according to the tumor stage

Pathologic stage	No. of positive findings		Total no. of positive findings
	JSS	PE	
IA (n = 49)	11 (22%)	—	11 (22%)
IB (n = 46)	17 (37%)	9 (20%)	21 (46%)
II (n = 17)	3 (18%)	3 (18%)	4 (24%)
III (n = 31)	12 (39%)	6 (19%)	13 (42%)
Total (n = 143)	43 (30%)	18 (13%)	49 (34%)

VPI, Visceral pleural invasion; *JSS,* jet stream of saline solution; *PE,* pathologic examination.

TABLE 2. Rate of positive findings of VPI classified by means of JSS, PE, or either method according to N status

N status	No. of positive findings		Total no. of positive findings
	JSS	PE	
n0 (n = 95)	28 (29%)	9 (9%)	32 (34%)
n1 (n = 17)	3 (18%)	3 (18%)	4 (24%)
n2 or more (n = 31)	12 (39%)	6 (19%)	13 (42%)

VPI, Visceral pleural invasion; *JSS,* jet stream of saline solution; *PE,* pathologic examination.

TABLE 3. Relationship between pleural lavage cytologic findings and VPI as diagnosed with either diagnostic method

Cytologic findings on intrapleural lavage	VPI	
	Present	Absent
Positive (n = 13)	13	0
Negative (n = 125)	33	92

VPI, Visceral pleural invasion.

Statistical Analysis

Statistical analyses were performed by using either χ^2 analysis or the Fisher exact test for various clinicopathologic factors. The duration of the recurrence-free survival was calculated from the date of operation until either the first evidence of recurrence or death of any cause. Survival was calculated from the date of operation until death of any cause or the date of the last follow-up (censored). The recurrence-free interval and survival curves were determined by using the Kaplan-Meier method, and differences in

TABLE 4. Incidence of recurrent disease in the patients with or without VPI as diagnosed with JSS, PE, or either method

	JSS VPI		PE VPI		Either method VPI	
Recurrent site	Present (n = 43)	Absent (n = 100)	Present (n = 18)	Absent (n = 125)	Present (n = 49)	Absent (n = 94)
Local recurrence	12 (28%)*	4 (4%)	4 (22%)	12 (10%)	12 (24%)§	4 (4%)
Carcinomatous pleuritis	7 (16%)†	0	3 (17%)‡	4 (3%)	7 (14%)‖	0
Other sites	5 (12%)	4 (4%)	1 (6%)	8 (6%)	5 (10%)	4 (4%)
Distant metastases	8 (19%)	26 (26%)	7 (39%)	27 (22%)	12 (24%)	22 (23%)

VPI, Visceral pleural invasion; *JSS,* jet stream of saline solution; *PE,* pathologic examination.
*P = .0001.
†P = .0002.
‡P = .04.
§P = .0003.
‖P = .0004.

their distribution were evaluated by means of the log-rank test.[6,7] The Cox proportional hazards models were applied for the multivariate analysis.[8] All data were analyzed with Abacus Concepts, Survival Tools for StatView (Abacus Concepts, Inc, Berkeley, Calif).

Results

Of the 143 tumors evaluated that were located peripherally and suspected of reaching the visceral pleura, 49 (34%) were diagnosed to invade the visceral pleura by means of PE, the JSS method, or both. The diagnosis of VPI was made on the basis of the JSS method in 43 tumors and on the basis of PE in 18 tumors. Twelve tumors were found to have invaded the visceral pleura by means of both the JSS method and PE. The presence of VPI for the 49 resected tumors diagnosed by using the JSS method, PE, or both was considered to be true positive in this study. There were 6 false-negative results with the JSS method and 31 with PE. The sensitivity and accuracy of the JSS method for the diagnosis of VPI were 88% and 96%, respectively. In contrast, the sensitivity and accuracy of PE were 37% and 78%, respectively. The JSS method was significantly more sensitive and accurate than PE for the diagnosis of VPI. Table 1 shows the incidence of VPI as diagnosed with the JSS method and with PE according to pathologic stage. The presence of VPI for 11 (22%) patients with stage IA disease was diagnosed with the JSS method. As shown in Table 2, there was no significant relationship between the extensive N2 involvement and VPI. VPI and a positive finding on intrapleural lavage after a thoracotomy was linked, as shown in Table 3. No positive finding in the intrapleural lavage was found in our series in cases without VPI diagnosed on the basis of either the JSS method or PE. During a more than 5-year observation, we experienced 16 cases of local recurrence (metastases of hilar or mediastinal lymph nodes in 9 cases and carcinomatous pleuritis in 7 cases) and 34 cases of recurrence at distant organs. We defined malignant pleural effusion, pleural dissemination, or both as carcinomatous pleuritis in this study. Although there was no significant difference between the incidence of distant metastases in the patients with VPI and those without VPI, the incidence of local recurrence, especially regarding carcinomatous pleuritis, in the patients with VPI was significantly higher than in those without VPI, as shown in Table 4. Patients who otherwise were classified as having stage I disease had a significantly shorter recurrence-free survival if their VPI was present compared with that in patients with stage I disease without VPI, as shown in Figure 1, *A* (P = .02). All stages of patients with VPI had significantly shorter recurrence-free survivals than the patients without VPI, as shown in Figure 1, *B* (P = .004). As shown in Figure 2, there was also a significant difference between the patients with or without VPI in terms of overall survival (P = .02). In a multivariate analysis model that included sex, age, histologic type, pathologic stage, VPI, and positive cytologic finding on intrapleural lavage, VPI was an independent prognostic factor (P = .03), as were sex (P = .03), age (P = .002), and the stage of the disease ($P < .0001$; Table 5).

Discussion

VPI is a factor of poor prognosis.[1,2] PE alone usually confirms the diagnosis of VPI. However, it remains questionable as to whether a tumor can be considered reliably to have no VPI on the basis of PE findings alone. We previously reported a simple method involving a cytologic examination of cells desquamated from the visceral pleura by using the JSS method, which was significantly more sensitive and accurate than ordinary PE in detecting VPI caused by lung cancer.[3] This is a sequel report about JSS, which is a useful method to detect VPI. This study accumulated over 140 cases, and the follow-up period was sufficient to analyze the relationship between the presence of VPI detected

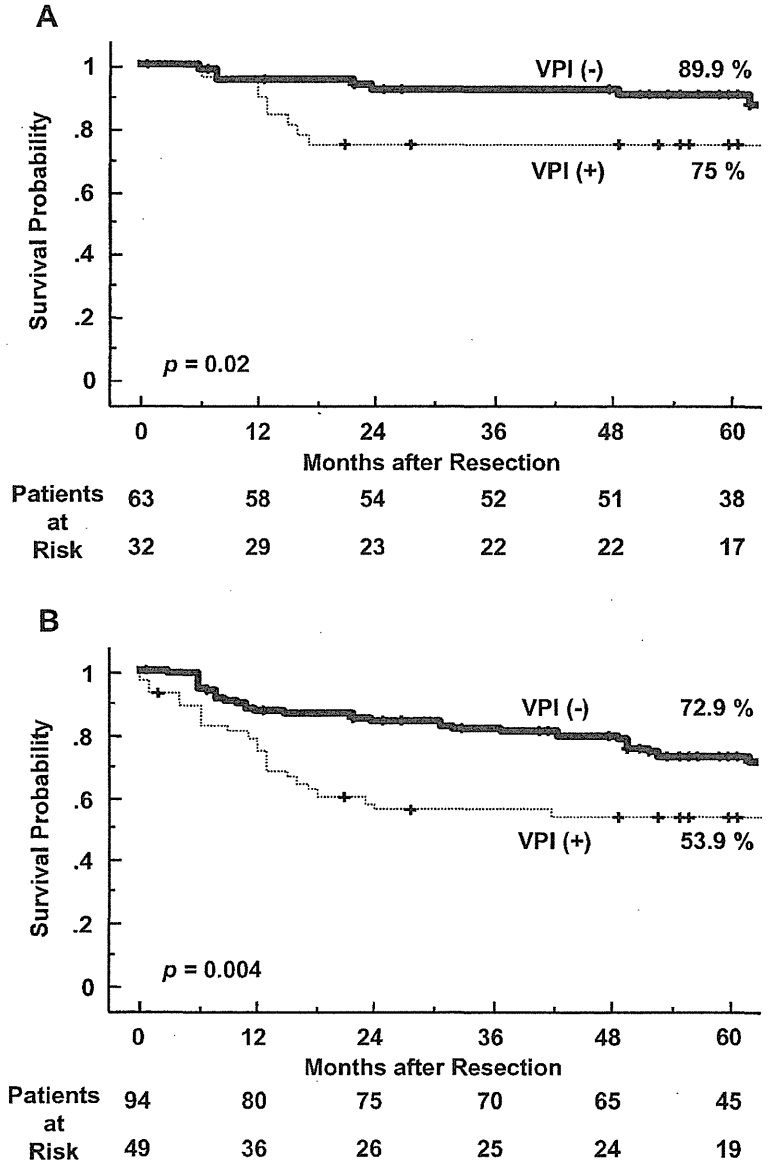

Figure 1. A, Recurrence-free survival in patients with stage I disease with or without VPI, as diagnosed by means of JSS or PE. B, Recurrence-free survival in all stages with or without VPI, as diagnosed by means of JSS or PE.

by means of our method and the prognosis. Bunker and associates[9] reported that an evaluation of VPI by means of hematoxylin and eosin examination alone might be indeterminate, and Verhoeff-Van Gieson elastic stains can be helpful in the diagnosis of VPI. However, there are limitations in making a diagnosis of VPI on the basis of PE alone because the diagnosis of VPI by PE usually is based on 1 or 2 cut slices of the resected tumor. Our findings reconfirmed that the JSS method is significantly more sensitive and accurate than ordinary PE in detecting VPI. The methodology for the JSS after resection for tumor close to the pleura is simple to complete and thus could affect the ultimate staging of patients. Unfortunately, the results are dependent on the ability of the cytologic team, which might not be universally available. Recently, the Cancer and Leukemia Group B trial demonstrated micrometastatic tumor cells in the lymph nodes of patients with stage I NSCLC by using standard and quantitative real-time reverse transcriptase–polymerase chain reaction for carcinoembryonic antigen.[10] Newer molecular techniques like this also might increase the yield of positivity. After our report on the usefulness of the JSS method, Saito and colleagues[11] reported on the diagnosis of

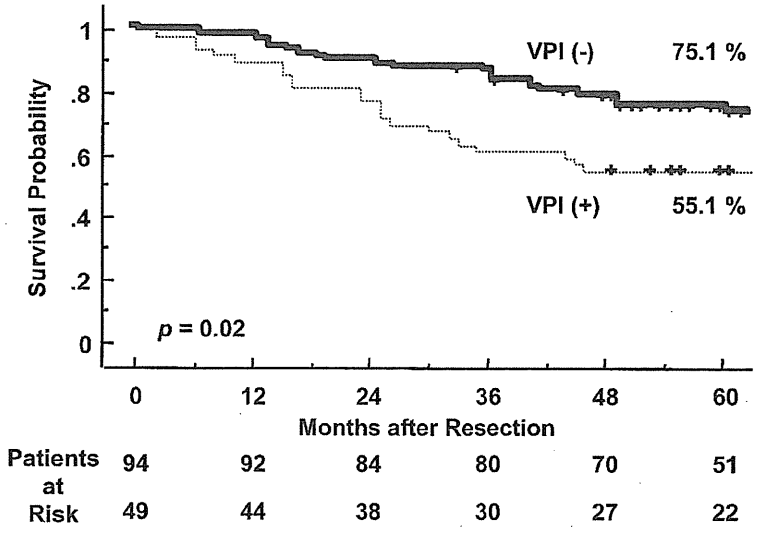

Figure 2. Overall survival with or without VPI, as diagnosed by means of JSS or PE.

VPI by using intraoperative touch cytology. Their method was simple and useful for detecting VPI; however, their follow-up was too short to fully analyze the prognosis. Manac'h and coworkers[2] reported that VPI was associated with a higher frequency of N2 involvement, and cancer-related death was mainly caused by distant metastases rather than local recurrence. Their results support the hypothesis that exfoliated tumor cells are drained through the pleural lymphatics to the mediastinal lymphatic pathways and then into the bloodstream. There was no relationship between the findings of VPI and the N status in our series. The prognosis of patients with positive cytologic findings on intrapleural lavage was poor compared with that in patients with negative findings.[12,13] Therefore they suggested that patients with positive cytologic findings on intrapleural lavage were considered to be in a prestage of carcinomatous pleuritis and thus should be upstaged. It was important that positive cytologic findings on intrapleural lavage were never present in cases without VPI in our series. Ichinose and associates[14] reported that intraoperative intrapleural hypotonic cisplatin treatment was found to effectively suppress the appearance of malignant pleural effusion, pleural dissemination, or both in selected patients who demonstrated positive pleural lavage cytology findings.

Our JSS method in addition to ordinary PE is therefore useful in detecting VPI, which is considered to be one of the causes of local recurrence, especially in patients with carcinomatous pleuritis. VPI is therefore considered to be an important prognostic factor and index for better selecting patients who can most benefit from adjuvant therapy consisting of hypotonic cisplatin treatment.

TABLE 5. Multivariate findings of the recurrence-free survival

Variable	Hazard ratio	95% Confidence interval	*P* value
Sex: female/male	1.96	1.08–3.57	.03
Age*: Elderly (>64 y)/ younger (<64 y)	2.76	1.45–5.24	.002
Histologic type: nonsquamous/squamous	1.44	0.49–4.21	.51
Pathologic stage†:			
IB/IA	3.69	1.19–11.5	.02
II/IA	7.65	2.26–25.9	.001
III/IA	22.0	7.36–65.7	<.0001
VPI	2.15	1.06–4.33	.03
Positive cytologic finding on intrapleural lavage	1.95	0.79–4.83	.15

VPI, Visceral pleural invasion.
*The number of elderly and younger patients was 71 and 72, respectively.
†The pathologic stage of the tumors was IA in 49 patients, IB in 46 patients, II in 17 patients, and III in 31 patients.

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