EFFECTS OF POSTOPERATIVE MEDIASTINAL RADIATION ON COMPLETELY RESECTED STAGE II AND STAGE III EPIDERMOID CANCER OF THE LUNG

THE LUNG CANCER STUDY GROUP

Abstract We randomly assigned 230 patients with resected Stage II or III epidermoid (squamous-cell) lung cancer to receive postoperative adjuvant radiotherapy or no adjuvant treatment. Careful intraoperative staging had been performed in all patients. Before randomization, patients were stratified according to stage, weight loss, age, and institution. Prognostic variables, such as stage, weight loss, age, nodal-disease status, and tumor status, were equally distributed between the two groups. The mean time from randomization to analysis was 3.5 years among the 210 eligible patients.

There was no evidence that radiotherapy improved survival, and although recurrence rates appeared to be somewhat reduced among patients assigned to radiotherapy, these decreases were not statistically significant. However, radiotherapy did produce a striking and significant reduction in recurrences to the ipsilateral lung and mediastinum. Moreover, overall recurrence rates were reduced by radiotherapy in patients with N2 disease ($P<0.05$), although even this subgroup had no evidence of improved survival.

We conclude that radiotherapy can reduce local recurrences after resection of epidermoid carcinoma of the lung, but that it does not increase survival rates. (N Engl J Med 1986; 315:1377-81.)

APPROXIMATELY 44 percent of patients with lung cancer present with disease apparently limited to the chest.[1] Radiotherapy has been administered in addition to surgical resection in an effort to improve local disease control and increase survival among these patients. Several retrospective studies have indicated that postoperative radiation benefits the survival of patients with mediastinal[2] and hilar or mediastinal[3] lymph-node metastases from epidermoid carcinoma of the lung. To evaluate these retrospective studies, the Lung Cancer Study Group began a randomized, prospective trial of postoperative mediastinal radiation in patients with Stage II or III epidermoid carcinoma of the lung who had undergone complete resection. These patients were randomly assigned to receive mediastinal radiation or no further therapy. A concurrent, untreated control arm was deemed necessary since the survival benefit of postoperative radiation therapy had not been conclusively demonstrated. A third arm — radiotherapy plus levamisole — was dropped in April 1980, when investigators realized that patient accrual would support only a two-armed study. This report contains data on all patients in the other radiotherapy arm and the control arm, and will not refer further to the third arm, which had only 26 patients.

METHODS

Eligibility

To be eligible, patients had to have undergone complete resection of their tumor, and specimens from the subcarinal, paratracheal, hilar, and bronchopulmonary lymph-node areas were required for pathological staging. Resection margins were required to be microscopically free of tumor. The recommendations of the American Joint Committee for Cancer Staging were followed,[4] and only patients in Stage II or III were eligible. In this classification, Stage II disease is T3 N1 and Stage III is T3 tumor or any N2 nodal disease. Patients with a history of lung, breast, gastrointestinal, or renal-cell carcinoma or melanoma were ineligible. In addition, those with a history of any other cancer except non-melanoma skin cancer or in situ cervical cancer were ineligible unless they had been free of disease for five years without treatment. Patients who had received previous chemotherapy, immunotherapy, or thoracic radiation were also excluded, as were those with any of the following variants of Stage III disease: distant metastases, Pancoast tumor, pleural effusion with malignant cells, or a tumor within 2.0 cm of the carina. In addition, a node proximal or cephalad to the highest mediastinal tumor-bearing node had to have been biopsied and found to be free of tumor, and pathological material was required for review (by the Lung Cancer Study Group Pathology Reference Center, M.D. Anderson Hospital).

Prerandomization evaluation for metastases included chest radiography and measurement of alkaline phosphatase, serum aspartate aminotransferase, and bilirubin. If the alkaline phosphatase concentration was elevated, bone and liver scans had to be negative. If the aspartate aminotransferase or bilirubin concentration was elevated, a liver scan had to be negative. Before entry, each patient was fully informed regarding the risks, possible side effects, limitations, and experimental nature of the treatment approach, and written informed consent was obtained. Patients had to have had a rapid recovery from surgery and not have been on assisted ventilation at the time of randomization.

Experimental Design

Patients were stratified according to clinical center (Illinois Cancer Council, M.D. Anderson Hospital, Mayo Clinic, Seattle Group, Toronto Group, UCLA, or Vanderbilt University), stage (II or III), prior weight loss (10 percent or more vs. less than 10 percent of usual weight), and age (less than 60 vs. 60 or older). They were randomly assigned within 21 days of surgery to receive either radiotherapy or no further treatment (control). A permuted block randomization was used within strata, and treatment was assigned by a central randomization office (Potomac, Md.) after the office had checked the patient's eligibility.

Radiation Therapy

Radiation therapy was delivered by megavoltage equipment (with cobalt-60 or a higher energy source) and directed to the mediastinum. A dose of 50 Gy (5000 rad) was given in a combination of parallel opposed and anterior and posterior oblique fields, or in any combination chosen at the discretion of the radiation oncologist. A daily dose of 1.8 to 2.0 Gy — measured in the central axis at the midplane — was given five days per week until a dose of 50 Gy was reached. The fields were defined superiorly by the suprasternal

Prepared by Thomas H. Weisenburger, M.D., and Mitchell Gail, M.D., Ph.D. Address reprint requests to Information Management Services, 6110 Executive Blvd., Suite 310, Rockville, MD 20852.

Supported by a grant (CA-36045) from the National Cancer Institute.

The principal investigators and institutions participating in the study included E. Carmack Holmes (group chairman) (UCLA, Los Angeles), Mitchell Gail (National Cancer Institute, Bethesda, Md.), Lucius D. Hill (Mason Clinic, Seattle), Paul Thomas (West Side Medical Center, Chicago), Ronald Feld and Robert Ginsberg (University of Toronto, Toronto), Clifton Mountain (M.D. Anderson Hospital, Houston), Anthony Greco (Vanderbilt University, Nashville, Tenn.), and Robert Eagan (Mayo Clinic, Rochester, Minn.); the study chairmen for LCSG 773 were Lucius D. Hill and F.G. Pearson.

notch and inferiorly by a point 5 cm below the carina. The field included the bronchial stump and ipsilateral hilum and vascular shadows of the mediastinum bilaterally. The total dose to the spinal cord was limited to 45 Gy, measured 2 to 3 cm below the superior margin. Radiation treatment was begun approximately 28 days after surgery.

Follow-up

Follow-up examination of both patient groups was performed six weeks after surgery, then every three months for two years, and then every six months thereafter. Examination included a history, physical evaluation (with weight measurement), performance-status evaluation, white-cell and differential counts, measurement of hematocrit, hemoglobin, alkaline phosphatase, aspartate aminotransferase, and bilirubin, and chest radiography.

The number of days from randomization to the detection of the site of first confirmed recurrence or metastasis constituted the length of the disease-free interval. Metastatic or recurrent disease was confirmed by biopsy if clinically feasible. Otherwise, radiographic (x-ray film, CT scan, or nuclear-medicine scan) or laboratory evidence of recurrence or metastasis was accepted. The number of days from randomization to death constituted the period of survival. If death was not observed, observation of a patient was regarded as ending on the date that the patient was last known to be alive.

Statistical Analysis

The Pearson chi-square test was used for contingency-table analyses, with Yates' correction for continuity in the case of 2-by-2 tables.[5] Two-tailed tests for trends in proportions were computed according to Mantel, with equally spaced scores.[6] Survival curves were estimated with the method of Kaplan and Meier,[7] and two-sided tests for significance were based on log-rank statistics as given by Mantel, but without continuity correction.[8] Adjusted survival analyses of stratification variables and other important covariates were designed from the Cox model.[9] Variables were screened for their value in predicting recurrence, by means of a score statistic based on the proportional hazards model with stratification for treatment. A result was considered to be not significant if the P value exceeded 0.05 according to two-sided tests.

Table 1. Distribution of Characteristics among 210 Patients with Epidermoid Cancer (102 Assigned to Radiotherapy and 108 Assigned to No Further Treatment).*

	Radiation	Control		Radiation	Control
	% of group			% of group	
Stage			Sex		
II	63.7	65.7	Female	7.8	10.2
III	36.3	34.3	Male	92.2	89.8
Weight loss			History of heart disease		
<10%	87.3	85.2	No	78.2	83.3
≥10%	12.7	14.8	Yes	21.8	16.7
Age			Preoperative white-cell count		
<60 yr	38.2	39.8	<7100/mm^3	28.4	19.6
≥60 yr	61.8	60.2	7100–9100 mm^3	39.2	38.3
			>9100 mm^3	32.4	42.1
Tumor status			Extent of operation		
T1	1.0	2.8	Sleeve resection	5.9	5.6
T2	81.4	83.3	Lobectomy	44.1	38.0
T3	17.6	13.9	Pneumonectomy	50.0	56.4
Nodal-disease status			Smoking status		
N0	6.9	1.9	Never	2.2	2.0
N1	72.5	76.8	Formerly	41.8	44.9
N2	20.6	21.3	Currently	56.0	53.1
Initial performance status					
9 or 10	92.2	88.0			
≤8	7.8	12.0			

*There were no significant (P<0.05) differences between the groups (either by Pearson chi-square test or by a test for trend for ordered variables, such as tumor status, nodal-disease, or preoperative white-cell count).

Table 2. Rates of Recurrence and Death among Patients Assigned to Radiotherapy (102) and to No Further Treatment (108).

Event	No. of Events	Hazard Rate per Person-Year	P Value*
Recurrence			
All cases			
Radiation	41	0.238	0.188
Control	53	0.336	
All cases except 5 2nd primary tumors			
Radiation	38	0.220	0.171
Control	51	0.323	
Death			
Radiation	45	0.227	0.678
Control	51	0.256	

*There were no significant differences between the groups (by two-sided log-rank test).

Study Population

Between February 1978 and May 1985, when patient recruitment ended, 230 patients underwent randomization. One hundred ten patients were assigned to the radiotherapy group, and 120 to the control group. Final pathological review by the Pathology Reference Center was completed for all but 21 patients. Twenty patients were found to be ineligible: 17 were determined to have histologic findings indicating non-squamous cancer, 1 had tumor within 1.5 cm of the carina, 1 had documented residual disease at surgery, and 1 had metastases within one week of randomization. Our analysis therefore focused on the remaining 210 eligible patients. Of these 210 patients, 13 did not receive the assigned treatment: 4 refused any radiotherapy, 3 demanded radiotherapy after they had been assigned to the control group, and 6 did not receive any radiotherapy because of medical complications. To avoid selection bias in the analyses, which can arise if only patients who receive the assigned treatment are compared, we performed most of our analyses on all 210 eligible patients, including the 13 who did not receive the assigned treatment. The mean time since randomization of the 210 patients (through August 28, 1985) was 3.5 years.

Results

Comparability of Groups

No statistically significant imbalances in stratification factors or other base-line covariates were noted between the two study groups (Table 1).

Toxicity

The principal toxic effects in the radiation group were esophagitis (24 percent), other gastrointestinal symptoms (20 percent), dermatologic toxicity (11 percent), and neurologic toxicity (10 percent), which significantly exceeded rates in the control group. Pulmonary toxicity (16 percent) was not significantly higher than among controls (9 percent). Among the 230 patients who underwent randomization, 99 received radiotherapy, and of these, 15 had mild, 6 had moderate, and 3 had severe esophagitis according to the criteria of the Eastern Cooperative Oncology Group.[10] Pulmonary toxicity was severe in two patients in the radiotherapy group and life-threatening in one in the control group. Toxicity was life-threaten-

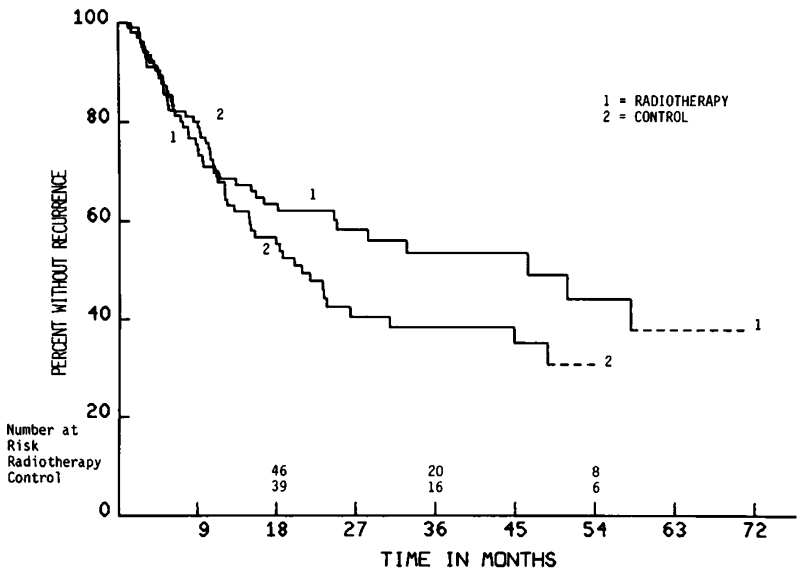

Figure 1. Time to Recurrence of Epidermoid Cancer (Including Second Primary Tumors) among 210 Patients, According to Study Group.
The difference between the groups was not significant (P = 0.188, log-rank test).

ing in three patients: one in the control group had pulmonary failure, as just mentioned; one in the radiotherapy group became paraplegic two years after treatment, and another in this group died of streptococcal pneumonia and portal hypertension with hemorrhage after three weeks of radiotherapy (30 Gy).

Treatment Compliance

Among the patients assigned to radiotherapy, 13 percent received no radiation, 5 percent received 1 to 20 Gy in a midplane dose, 5 percent received 20 to 40 Gy, 1 percent received 40 to 45 Gy, none received 45 to 47.5 Gy, 74 percent received 47.5 to 52.5 Gy, none received 52.5 to 55 Gy, and 2 percent received 55 to 60 Gy. Thus, 74 percent received within 5 percent of the intended dose of 50 Gy.

Three control patients insisted on receiving radiotherapy.

Analysis of Recurrences

There were 94 cases of recurrence among eligible patients, including 5 second primary tumors with distinct histopathology (Table 2). The hazard rate of recurrence was about 1.4-fold higher in the control group (Table 2 and Fig. 1), but this difference was not statistically significant. Adjustment with the Cox model[9] of the four stratification factors and adjustment for age, stage, and weight loss, plus any one of the following factors, had no appreciable influence on estimates of treatment effect: white-cell count, neutrophil count, serum calcium level, extent of resection, performance status, sex, or smoking status. Results were similar when all patients undergoing randomization were included in the analysis. Thus, we could not demonstrate convincingly that radiation prolonged the overall disease-free interval.

Although radiation had no statistically significant effect on overall recurrence rates, it had an undeniable effect on local recurrence, defined as a first recurrence in the ipsilateral lung or mediastinum (Table 3). The log-rank comparison of rates of local recurrence showed a significant difference ($P<0.001$); it is striking that only 1 first recurrence was local in the radiation group, as compared with 21 in the control group. This result is not obvious in the analyses in Table 2 because it is obscured by the large numbers of systemic recurrences. Quite possibly, a larger, longer study would demonstrate an overall reduction in recurrence rate. When patients with multiple sites of first recurrence were counted several times, unlike the case in Table 3, the predominant systemic first sites of recurrence were bone (13 patients in the radiotherapy group and 7 in the control group), contralateral lung (5 and 10), brain (5 and 6), and liver (7 and 2).

Analysis of Survival

Data on survival (Table 2 and Fig. 2) provided no evidence in favor of radiotherapy. This was also true when adjustments were carried out with the Cox model, as described above, and when all patients were included in the analysis. Fourteen eligible patients given radiotherapy died without recurrence, as compared with 7 eligible controls. Thirty-one eligible patients in the radiotherapy group died after recurrence, as compared with 44 eligible controls. Six of the deaths in the radiotherapy group that were not due to cancer were associated with respiratory failure, five with cardiac failure, and two with undocumented

Table 3. Site of First Recurrence (Excluding Second Primary Tumors) in the Study Groups.

Site	Radiation (102)		Control (108)		P Value*
	No. (%)	Rate per Person-Year	No. (%)	Rate per Person-Year	
Only local (ipsilateral lung or mediastinum)	1 (3)	0.006	21 (41)	0.144	<0.001
Only brain	5 (13)	0.029	6 (12)	0.038	0.850
All other†	32 (84)	0.180	24 (47)	0.152	0.337
	38		51		

*By two-sided log-rank test.

†"All other" includes single sites other than brain or "local" (defined as ipsilateral pulmonary or mediastinal, or a combination thereof) as well as any combination of multiple sites detected on the common date of first recurrence — e.g., liver only, brain plus "local," or liver plus "local."

causes, as compared with three with respiratory failure, two with cardiac failure, and two from other causes among controls. Thus, the slight excess of deaths with cancer among control patients was offset by a slight deficit in the deaths without cancer, but none of these differences were statistically significant.

Analysis of Subgroups

We compared recurrence and survival among the 92 eligible patients who received radiotherapy with outcomes among the 105 eligible control patients who did not receive radiotherapy. No substantial differences were evident from the data, shown in Table 2. This comparison of the "pure" radiotherapy group with the "pure" control group, which is not fully protected by the randomization and may be subject to selection bias, nonetheless confirms the analyses including all eligible patients (Table 2).

We analyzed the rates of recurrence and death separately according to nodal-disease status (Table 4). Overall recurrence rates were significantly reduced among patients with N2 disease. However, no survival benefits of radiotherapy were found in any nodal-disease subgroup. Such subgroup analyses are suggestive but not convincing, because if enough subgroups are examined, often some spurious indication of treatment efficacy will appear.[11] Moreover, the numbers of recurrences (19) and deaths (24) in the N2 subgroup were small. Nonetheless, this analysis suggests a useful hypothesis for further study — namely, that radiotherapy may prolong the disease-free interval in patients with N2 disease.

Table 4. Rates of Recurrence and Death According to Nodal-Disease Status.*

	No. of Events	Rate per Person-Year	P Value†
Recurrence (without 2nd primary)			
N0			
Radiation	1	0.062	0.351
Control	1	0.290	
N1			
Radiation	31	0.264	0.917
Control	37	0.294	
N2			
Radiation	6	0.155	0.031
Control	13	0.453	
Death			
N0			
Radiation	2	0.120	0.306
Control	2	0.426	
N1			
Radiation	31	0.223	0.951
Control	37	0.240	
N2			
Radiation	12	0.285	0.805
Control	12	0.296	

*There were 9 patients with N0 status (7 in the radiation group and 2 in the control group), 157 with N1 status (74 and 83), and 44 with N2 status (21 and 23).

†By two-sided log-rank test.

Discussion

The rationale for postoperative radiation is to prevent local or regional relapse. Our data demonstrate that postoperative radiation does indeed protect against local recurrence of epidermoid carcinoma, but this effect does not translate into a demonstrable overall survival benefit, largely because 75 percent of recurrences were outside the radiation field (Table 3) and, possibly, because radiation may slightly increase the risks of disease other than cancer. It is clear that significant improvements in the survival of patients with resectable epidermoid carcinoma require more effective systemic therapy.

Data on five-year survival in three retrospective studies are summarized in Table 5. The main difficulty in interpreting such data is that since the investigators do not describe how patients were selected to receive radiation, in a given study it is quite possible that the radiotherapy group was systematically selected to be healthier, or sicker, than the group not given radiation. Although the numbers of patients are small, the data of Green[3] and Kirsh[2] and their colleagues on epidermoid carcinoma suggest that radiation therapy benefits survival. This finding was not confirmed by Choi et al.[12] The findings regarding adenocarcinoma, though less relevant for comparison with our study, suggest a possible survival benefit from radiation and would seem to justify a controlled randomized trial for evaluation. However, the established tendency of adenocarcinoma to recur systemically[13,14] indicates that

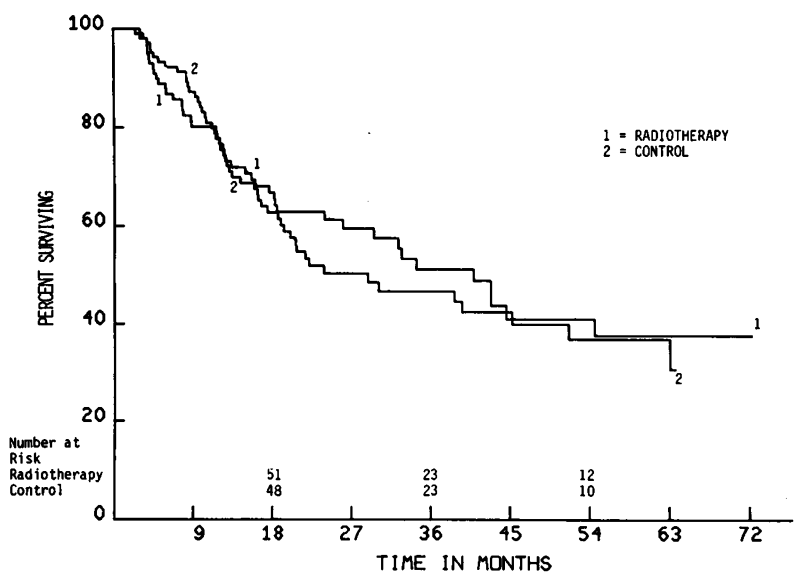

Figure 2. Time to Death (from Any Cause), According to Study Group. The difference between the groups was not significant (P = 0.678, log-rank test).

Table 5. Five-Year Survival Rates in Three Retrospective Studies of Radiation and Surgery for Carcinoma.

Study	Patient Registration Dates	Scheduled Radiation (Gy)	Percentage Surviving (Number)			
			Epidermoid Carcinoma		Adenocarcinoma	
			Radiation + Surgery	Surgery Alone	Radiation + Surgery	Surgery Alone
Green[3]	1954–1966	50–60	21 (28)	6 (16)	50 (24)	14 (22)
Kirsh[2]	1959–1969	Not defined	34 (32)	*	12 (34)	*
Choi[12]	1971–1977	40–60	33 (46)	33 (29)	43 (40)	8 (21)

*Histology not described, but none of 20 survived for five years.

an effective regimen should include systemic therapy in addition to efforts at local control.

The five-year survival rate in our study was about 38 percent (Fig. 2), which is marginally higher than most of the rates for survival of epidermoid carcinoma in Table 5. This difference may reflect a difference in criteria for eligibility. In addition, diagnostic procedures to detect distant metastases have been improved and may have excluded from our study population patients who would have been included in the earlier studies.

Several factors may have diminished the apparent benefits of radiotherapy in the present study. The control group may have benefited from delayed radiation, since 12 of the control patients in whom local disease developed as the only site of first recurrence were subsequently treated with radiation. However, the results in Table 2 and Figures 1 and 2 address the therapeutic decision whether to begin radiotherapy shortly after surgery. In addition, only 43 of the 210 eligible patients had N2 disease — a subgroup in which radiation may prove beneficial. Although it is possible that a favorable effect of radiation will emerge with continued follow-up, we think that this is unlikely because the mean time from randomization is already 3.5 years.

It is important to ask what beneficial effects of radiation may have been obscured by random variation. The power of the log-rank test depends mainly on the total number of observed events,[15] and our study was designed to include at least 90 events in order to have a chance of 90 percent of detecting a twofold reduction in the hazard rate with a two-sided log-rank test. More than 90 recurrences and deaths were observed (Table 2). In terms of two-year survival rates, this study had a 90 percent power to detect an improvement of more than 17 percent above the control two-year survival rate of 60 percent. If the trends in Figure 2 and Table 2 persist, there is virtually no chance that a statistically significant survival benefit from radiotherapy will emerge from continued follow-up of this cohort.

We are indebted to Bill Lake Jr., Sherrill Long, and Marilyn Bossenga for assistance in data management and manuscript preparation.

References

1. Cancer patient survival. Report no. 5. Bethesda, Md.: Department of Health, Education, and Welfare, 1977. (DHEW publication no. (NIH) 77-992.)
2. Kirsh MM, Rotman H, Argenta L, et al. Carcinoma of the lung: results of treatment over ten years. Ann Thorac Surg 1976; 21:371-7.
3. Green N, Kurohara SS, George FW III, Crews QE Jr. Postresection irradiation for primary lung cancer. Radiology 1975; 116:405-7.
4. Manual for staging of cancer 1978. Chicago: American Joint Committee For Cancer Staging and End Results Reporting, 1978:59-64.
5. Snedecor GW, Cochran WG. Statistical methods. 6th ed. Ames, Iowa: Iowa State University Press, 1967.
6. Mantel N. Chi-square tests with one degree of freedom: extensions of the Mantel–Haenszel procedure. J Am Stat Assoc 1963; 58:690-700.
7. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457-81.
8. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966; 50:163-70.
9. Cox DR. Regression models and life-tables. J R Stat Soc (B) 1972; 34: 187-220.
10. Oken MM, Creech RJ, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649-55.
11. Lee KL, McNeer JF, Starmer CF, Harris PJ, Rosati RA. Clinical judgment and statistics: lessons from a simulated randomized trial in coronary artery disease. Circulation 1980; 61:508-15.
12. Choi NCH, Grillo HC, Gardiello M, Scannell JG, Wilkins EW Jr. Basis for new strategies in postoperative radiotherapy of bronchogenic carcinoma. Int J Radiat Oncol Biol Phys 1980; 6:31-5.
13. Feld R, Rubinstein LV, Weisenburger TH. Lung Cancer Study Group. Sites of recurrence in resected stage I non–small-cell lung cancer: a guide for future studies. J Clin Oncol 1984; 2:1352-8.
14. Holmes EC, Gail M. Surgical adjuvant therapy for stage II and stage III adenocarcinoma and large-cell undifferentiated carcinoma. J Clin Oncol 1986; 4:710-5.
15. Lininger L, Gail MH, Green SB, Byar DP. Comparison of four tests for equality of survival curves in the presence of stratification and censoring. Biometrika 1979; 66:419-28.