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INFLUENCE OF ETOPOSIDE ON THE LOCAL EFFECT TO RADIATION IN NON-SMALL CELL LUNG CANCER —A RANDOMIZED PROSPECTIVE STUDY—

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Abstract We conducted a prospective randomized study to determine whether or not Etoposide (Et), applied concomitantly with radiation, would be more effective in reducing the tumor sizes of non-small cell lung cancer than radiation alone. Radiation was administered in doses of 1.5-2.0 Gy/day, 5 times a week with targets of a total of 40 Gy or more. Et was administered daily in oral doses of 25 mg/day every day, but 1 hour before radiation on the relevant designated days. The effectiveness of radiation alone was similar in both adenocarcinoma and epidermoid carcinoma. Combined with Et, there was no difference from radiation alone in adenocarcinoma, but a significant difference was evident in epidermoid carcinoma. The number of patients in whom tumors were decreased to less than 50% of the initial sizes by 60 Gy was 16/23 (69.6%) in the concomitant therapy group. In the radiation alone group this rate was 11/29 (37.9%). This difference is statistically significant ($0.02 < P < 0.03$). In terms of tumor size, effects were seen only is the sub-group with tumor sizes of 3.1-5 cm.

Key words: Non-small cell lung cancer, Chemo-radiation therapy, Shrinking rate

INTRODUCTION

The mortality rate of lung cancer patients has been increasing rapidly over the years. For males it increased from 35.3/100,000 in 1985, to 46.3 in 1991, and from 12.7 to 16.3 for females[1]. While surgery is the most effective means of treatment, only 43% of patients are operable, and of those, only 44% can be cured[2]. Some reports[3,4] insist that radiation does not benefit lung cancer patients at all, but there are many [5-11] which claim that, by improving the local control rate, the survival rates of lung cancer patients can be increased. Because of this, treatment of patients with non-small cell lung cancer with radiation is the general rule. It should be noted, however, that conventional radiation alone falls short of

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achieving good local control, and it is essential that particular attention be directed to correct this in rate[3,4,6,12]. Other radiation methods[13–19], combined with systemic chemotherapy[12,20,21], or bronchial artery infusion[22] have been attempted to improve the effects of radiation, but all have yieleded less than satisfactory results. Nevertheless. Cox[23] states that the investigation of different supplemental systemic treatments is justified in view of the frequent occurrence of distant metastases. We concur that these investigations to improve the efficacy of radiation treatment are entirely rational, considering that merely increasing the local control rate improves the prognosis of lung cancer.

Recently, Kubota[24] and Saito[25] showed that Etoposide (Et) significantly reduced the so-called shoulder width of radiation survival curves of tumor cells, indicating suppressed recovery from sublethal radiation damage. Saito[25] showed the existence of dose dependency for Et, and also reported that cells did not recover from sublethal radiation damage in the presence of even low concentration of Et. Kubota[24] suggested that Et kills late S phase cells. Hainsworth[26] concluded that the dose limiting factor of Et is myelosuppression. When administered for 21 consecutive days, the maximum-tolerated oral dose of Et was 50 mg/m^2/day. With this background, we conducted a prospective randomized study using radiation therapy, with and without Et, in non-small cell lung cancer to assess the effect of Et combined with radiation exposure as a means of augmenting the decrease of tumor size.

PATIENTS AND STUDY DESIGN

The following criteria were used in selecting the patients for this study.

Patients

1) with histologically or cytologically confirmed non-small cell carcinoma, 2) with measurable primary lesions or intrathoracic metastatic lymph nodes, 3) with survival expectancies of over 3 months, 4) of age 79 or less, 5) without severe hematologic, liver or renal dysfunctions, 6) which had undergone prior unsuccessful anti-cancer treatment, and with more than a 4 week interval after termination of such treatment, 7) with no other active cancers, 8) considered to have sufficient tolerance to undertake this study, 9) who had given informed consent.

Only those patients satisfying all of these 9 conditions entered into this study. They were assigned to treatment randomly by phone calls to the Statistical Center. After confirmation of eligibility, patients were stratified by histology (epidermoid carcinoma, adenocarcinoma, large cell carcinoma etc.), sex and maximum tumor diameter (−3.0 cm, 3.1–5.0 cm or 5.1 cm+). They were assigned to treatment by A: radiation alone, B: ratiation with Et.

From among the 140 (A: 69, B: 71) patients entered, 5 (A: 2, B: 3) were later found unsuitable, and 9 (A: 6, B: 3) dropped out. Among the unsuitable cases in the A group was 1 case with an unreliable histopathological confirmation, and 1 case without a measurable lesion. In the B group was 1 case without a measurable lesion, 1 with small cell carcinoma, and 1 without a reliable histopathological confirmation.

Of the cases that did not complete treatment, in the A group were 2 cases in which radiation was terminated at less than 20 Gy, 3 cases had been given incorrect treatment (with Et in group A), and 1 case was disqualified due to incorrect lesion measurement after treatment. In group B, 3 cases were dropped because of incorrect treatment, namely administration of Et before assignment, Et administration after radiation, and administration of a 35% dose of Et.

Treatment

Radiation was administered at 1.5–2.0 Gy/day in 5 fractions/week up to more than 40 Gy, to the primary tumor and mediastinum, to both groups. We could not determine the daily dose, because the optimal daily dose was unknown. To group B, Et was orally administered daily at a dosage of 25 mg/body 1 hour before radiation, throughout the period of treatment. The treatment was discontinued if there was evidence of severe toxicity, which

Table 1. Characteristics of the 126 patients analized Adenoca.: Adenocarcinoma. Epider.: Epidermoid carcinoma. Large.: Large cell carcinoma. P. S.: Performance Status. Stage and Tumor size: 1987 UICC

	radiation alone n=61	radiation with Et n=65	P-value
Sex			
Men	49	60	0.049
Women	12	5	
Age			
-49	6	5	0.801
50-59	11	9	
60-69	19	25	
70-79	25	26	
Histology			
Adenoca.	23	35	0.132
Epider.	33	29	
Large.	3	1	
Other	2	0	
P. S.			
1	16	29	0.057
2	28	22	
3	16	10	
4	1	4	
Stage			
I	3	7	0.536
II	4	2	
IIIA	16	17	
IIIB	22	26	
IV	16	12	
unknown	1	1	
Tumor size			
-3.0 cm	13	10	0.830
3.1-5.0	27	25	
5.1-	34	35	
Dose/ Fraction (Mean±SD)	1.94±0.29	1.88±0.34	0.244

was considered by each investigator, to the radiation or Et.

Characteristics of the Patients

The characteristics of the 126 patients, all with non-small cell lung cancer, entering this trial from October 1989 through September 1990, were analyzed prior to entry. These analyses are summarized in Table 1. Except for sex distribution, no statistically significant difference existed between the groups.

Evaluation of Results

Effects were evaluated by noting differences between the 2 groups in the tumor shrinkage rates. Tumor sizes were measured by chest X-ray or CT, each at 10 Gy, in accordance with the General Rule for Clinical and Pathological Record of Lung Cancer (Japan)[27].

Table 2. Percent of tumor size following irradiation (%) by sex

	n	10 Gy	20 Gy	30 Gy	40 Gy	50 Gy	60 Gy
Men	95	96.1	88.1	78.2	67.9	60.4	54.9
Women	17	100.1	86.5	72.6	66.4	57.0	48.5
P-value		0.95	0.81	0.32	0.82	0.65	0.40

Evaluation of Toxicity

Toxicity indicated by nausea, vomiting, anorexia, alopecia, radiation dermatitis or esophagitis, reduced leucocyte or platelet count or reduced hemoglobin levels was evaluated in accordance with the General Rule for Clinical and Pathological Record of Lung Cancer (Japan)[27].

Statistical Methods

A committee was organized to assess the eligibility of the registerd subjects, and evaluate therapeutic effects and side effects. The distribution of the patients except dose fractions were tested by the χ^2 test. Distribution of the dose fractions between the 2 groups, and differences of shrinkage rates at each radiation dose were tested by the U- or T-test. $P<0.05$ was determined as significant, and $0.05<P<0.1$ was determined as a trend.

RESULTS

Analysis of Effects

Since sex distribution was significantly different between the groups, we compared shrinkage rates by sex, but no significant difference could be found (Table. 2). Therefore, sex differences were ignored in the analyses that followed. There were no differences between the groups in the shrinkage rates of primary lesions and lymph nodes during treatment (Fig. 1). The shrinkage rate from each mode of treatment of the primary lesions were examined histologically, and separately for adenocarcinoma and epidermoid carcinoma (Fig. 2). There was no notable difference in shrinkage rates between adenocarcinoma and epidermoid

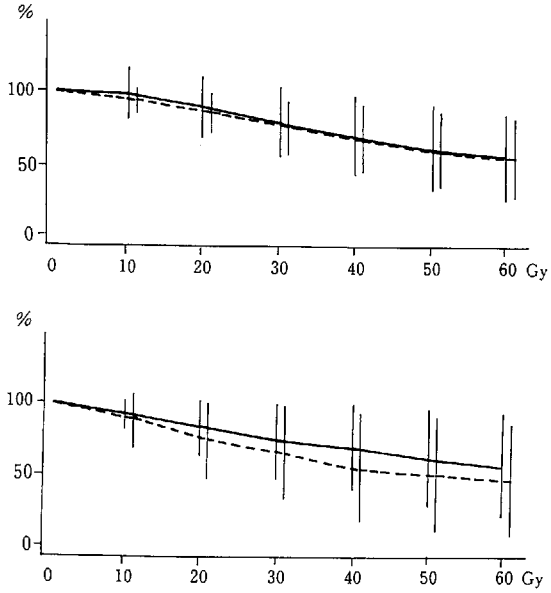

Fig. 1. Percent of tumor size curves.
——: radiation only. ·····: radiation with Etoposide. Vertical axis indicates percent of tumor size(%) and horizontal axis indicates radiation dose (Gy). Vertical bars represent standard deviation in this and following Figures except Fig. 6.
Top: Primary lesion, Bottom: Lymph-node.

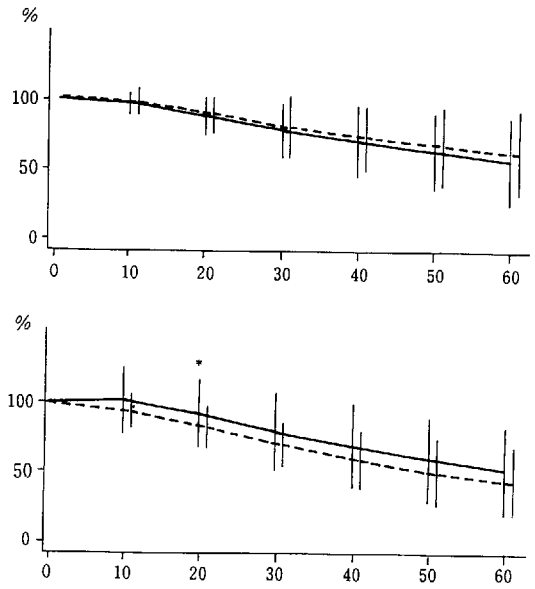

Fig. 2. Percent of tumor size curves, according to histology.
——: radiation only. ·····: radiation with Etoposide. Top: Adenocarcinoma, Bottom: Epidermoid carcinoma.
*: $0.1 > P > 0.05$.

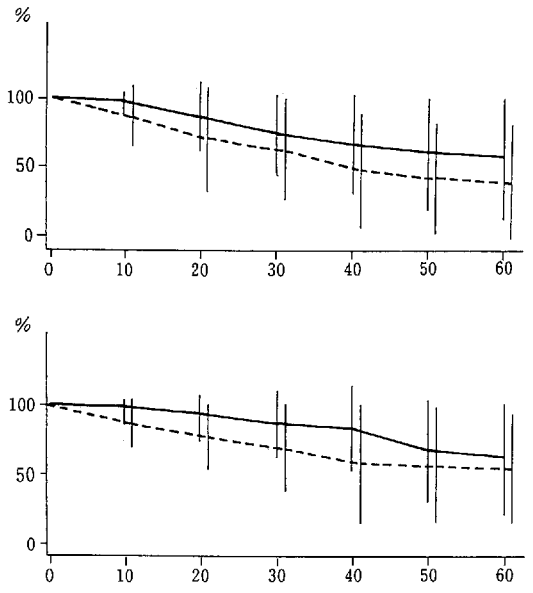

Fig. 3. Percent of size curves in tumors less than 3 cm diameter, according to histology.
——: radiation only. ·····: radiation with Etoposide.
Top: Adenocarcima, Bottom: Epidermoid carcinoma.

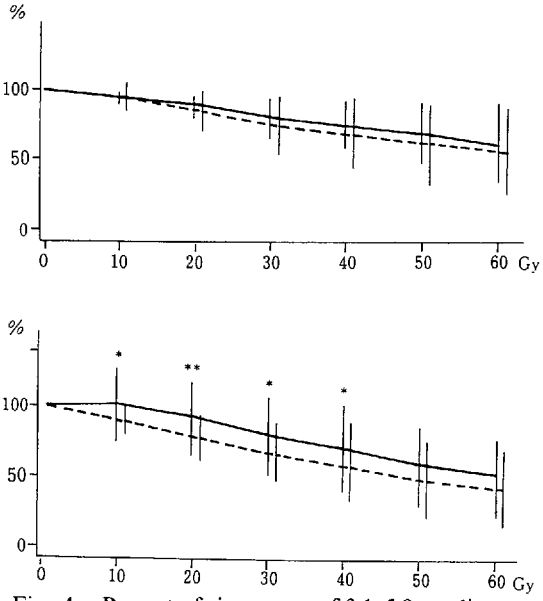

Fig. 4. Percent of size curves of 3.1-5.0 cm diameter tumors, according to histology.
——: radiation only. ·····: radiation with Etoposide.
Top: Adenocarcinoma, Bottom: Epidermoid carcinoma.
*: $0.1 > P > 0.05$. **: $0.05 > P$.

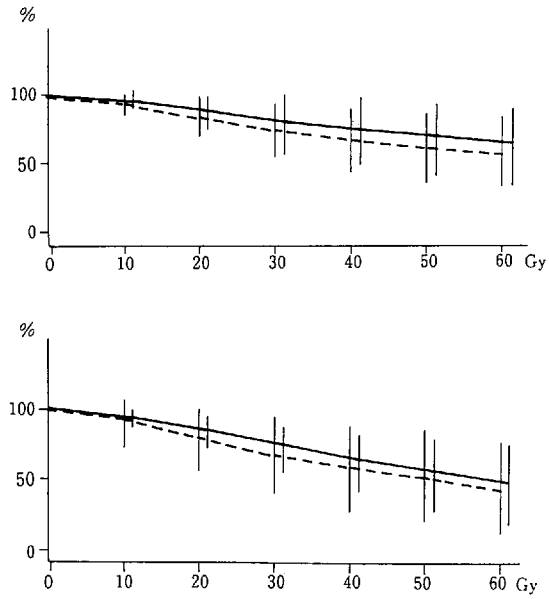

Fig. 5. Percent of tumor size cures in more over 5.1 cm diameter, according to histology. ——: radiation only. ·····: radiation with Etoposide.
Top: Adenocarcinoma, Bottom: Epidermoid carcinoma.

carcinoma. However, a minor difference of effect attributable to the difference in treatment modes was seen in epidermoid carcinoma; group B (radiation with Et) tended to fare better than group A at the radiation dose of 20 Gy; this difference was marked as a trend.

Next, the shrinkage rates of each treatment by tumor size (−3.0 cm, 3.1−5.0 cm, 5.1 cm+) were examined. Tumor sizes 3 cm or less were examined (Fig. 3), but no differences were seen between the groups. In 3.1−5.0 cm tumor sizes (Fig. 4) no difference were observed in adenocarcinoma subjects, but those with epidermoid carcinoma in group B had a higher shrinkage rate than those in group A. Effects of 10, 30 and 40 Gy radiation doses manifested trends with shrinkage rates being higher with Et than with radiation alone. This difference at 20 Gy was significant. In Fig. 5, the shrinkage rates of tumors larger than 5.1 cm are shown; Et shows no effect.

The 29 epidermoid carcinoma subjects in group A, and the 23 in group B, who were given radiation levels of up to 60 Gy, were

Table 3. Cases of each shrinking rates and radiation doses for epidermoid carcinoma, which could be observed up to 60 Gy
A: radiation only B: radiation with Etoposide

		≧50%	50%>, >0%	0%≧	P-value
10 Gy	A	1	11	17	0.734
	B	0	11	12	
20 Gy	A	1	20	8	0.332
	B	0	20	3	
30 Gy	A	2	23	4	0.573
	B	2	19	2	
40 Gy	A	5	21	3	0.191
	B	6	17	0	
50 Gy	A	10	17	2	0.141
	B	12	11	0	
60 Gy	A	11	17	1	0.021
	B	16	7	0	

examined by chest X-ray or by CT for changes in tumor sizes (Table 3). At 60 Gy, significantly more patients (16/23 69.6%) in group B than in group A (11/29 37.9%) had shrinkage rate of 50% or more.

Analysis of Toxicity

Special attention was paid to the analyses of nausea, vomiting, anorexia, alopecia, radiation dermatitis, and radiation esophagitis, and there were no differences between the 2 groups. Platelet and hemoglobin levels were the same in both, but the leucocyte counts of group B patients were significantly lower than those in group A at 30 and 50 Gy (Fig. 6). Table 4 lists the 10 patients for whom treatment was interrupted due to toxicity. There were 5 patients with leucopenia and 4 with radiation pneumonia or fibrosis in group B.

DISCUSSION

At the present time, most technically or medically non-resectable patients without distant metastases, and in generally good condition are treated with radiation. On radiation techniques, Haas[28] stated in 1957 that he believed future progress in radiotherapy techniques would significantly improve its response rate. 11 years later, in 1968, Roswit[29] was to say,"radiation therapy appeares to have

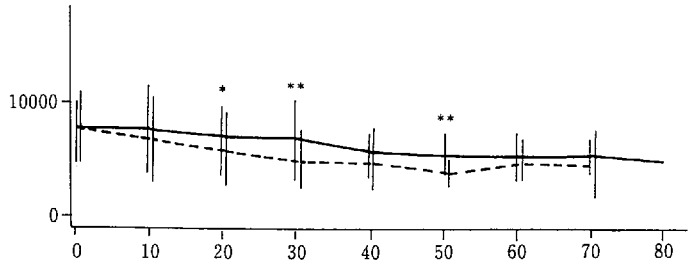

Fig. 6. Leucocyte counts during radiation or radiation with Etoposide.
——: radiation only. ·····: radiation with Etoposide. Vertical axis indicates leucocyte counts (/mm³) and horizontal axis indicates radiation dose (Gy). Vertical bars represent standard deviation.
*: $0.1 > P > 0.05$. **: $0.05 > P$.

Table 4. List of interrupted treatment cases

	Side effect	Treat.	Result	Relation
B	WBC: 4,900→2,400	ended radiation at 30 Gy	recovered WBC→3,700	provably positive
B	WBC: 10,300→400	ended radiation and Et at 24 Gy	recovered by blood transfusion	provably positive
B	WBC: 9,381→1,740 Pneumonia	ended radiation at 40 Gy	died from ARDS	provably positive
B	Radiation pneumonia	ended radiation and Et at 39 Gy	died from ARDS like disease	unclear
B	Radiation pneumonia	ended Et at 60 Gy	Whole lung pneumonia	provably positive
B	Radiation fibrosis	ended Et at 50 Gy	No change	unclear
B	Nausea Vomiting	ended Et at 36 Gy	recovered	provably positive
B	Nausea Vomiting WBC: 8,100→3,270	ended Et at 39 Gy	recovered	provably positive
B	Allergy WBC: 8,100 → 2,600	ended Et at 20 Gy	recovered	provably positive
A	rt. cardiac incomplete failure Dyspnea	ended radiation at 25 Gy	died from DIC	nothing

a significant influence on the improvement of survival". However, radiation therapy still cannot be described as satisfactory. In this connection, Durrant[3] stated that, "the mean survival in the wait-and-see group was 8.4 months, while after irradiation it was 8.3 months", thus affording no hope at all in radiation therapy. However Namer[6] experiences a 12.5% complete tumor remission (CR) rate, and 25% incomplete remission (<50%)

rate. Perez[12] notes a CR of 16% at 40 Gy, and 21 - 31% at 50-60 Gy in tumors with diameters of 3 cm or less. Cox[5] observes that "complication of the local tumor (infection, hemorrhage and respiratory failure) caused death in 50% of patients with squamous, and in 1/3 with large cell carcinoma".

Although the Japan Radiation-ACNU Study Group[30] reports that, even though radiation with ACNU increases the local control rate, it does not affect the survival rate; on the other hand, Perez[31], Petrovich[7], Schaake-Konig[9], Umsawasdi[10], Kawamura[11] and Okazaki[17] report that responders have good prognoses. Stanley[8] considers that "efforts to improve local control—by more extensive use of surgery, higher doses of irradiation, combined cytotoxic chemotherapy etc.—appear to be warranted". Thus, although there are many authors investigating radiation therapy per se[13-19], so far, no concrete progress is very much in evidence.

On the other hand, Le Chevalier[21], and Umsawasdi[10] reported that radiation combined chemotherapy resulted in more CR+PR (partial response) than radiation alone. However, Le Chevalier[32] backed away later from this position rejecting his earlier belief in the efficacy of radiation therapy in conjunction with chemotherapy.

So far, no investigation reported shows that extensively improved local control results in significantly improved survival rates, except one by Bergsael[20]. He reported that high dosage cyclophosphamide administered intermittently, combined with radiotherapy significantly improved local control, as well as the survival rates of lung cancer patients, including those with oat cell carcinoma. In our investigation, because we wished to detect some signs of the effects of this combined therapy very early, the General Rule for Clinical and Pathological Record of Lung Cancer[27], in which effects are evaluated only after continuous shrinkage for more than 4 weeks, was not used. In our study, shrinkage rates at each radiation dose were examined. Here, the difference of Et effects depended on histomorphology, with no effect on adenocarcinoma detected. In a study using radiation with or without ACNU Trial[30], radiation with ACNU (30~mg/m^2×4 times) did improve the CR+PR in adenocarcinoma, and similarly in epidermoid carcinoma. Since Et effects are dose dependent[25], it is more likely that the dosage of Et administered in adenocarcinoma in our study were not adequate, rather than that concomittant drug therapy is generally not effective. The effect of Et in epidermoid carcinoma, however, was evident.

By tumor size, effects were detectable only in tumors with diameters of 3.1-5.0 cm. In tumors of 3 cm or less, the effects of Et could not be detected, probably because of the pronounced effects of radiation, and in tumors of 5.1 cm or more, its effect could not be detected, either, probably because of central necrosis. This was probably also true in adenocarcinoma. Without reference to absolute tumor sizes, in patients in which radiation was measured up to 60 Gy, those with tumors that decreased to 50% or less were 11/29 (37.9%) in group A, and 16/23 (69.6%) in group B (Table 3), a statistically significant difference. Since these results were noted immediately after radiation therapy at doses of 60 Gy, and in epidermoid carcinoma only, we are unable to accurately compare them with the experiences of other studies. Although our investigation with radiation alone did not reach the results achieved by Perez[12], in which CR+PR was reported at 46-51% at 40 Gy, and 61-66% at 50-60 Gy, our experience was similar to Namer's[6], in which CR+PR was 37.5%. In addition, our results of radiation together with Et were similar to Umsawasdi's report, it which CR+PR was 65%. He had administered two courses of cyclophosphamide, adriamycin and cisplatin (CAP) over a 6-week period, followed by 5 weeks of low weekly doses of CAP combined with radiation of 50 Gy. In this study, severe nausea and vomiting occurred in 12% of the patients, and severe esophagitis in 30%.

Thus, if the results to be obtained are similar, then the oral and low dose administration of Et can be said to be better than the reference trials cited earlier in terms of side effects and duration of treatment.

On the other hand, even with less than half the dose of Hainsworth's maximum of Et of 50 mg/m^2, which was well tolerated, leucopenia of less than 3000/mm^3 occurred in 32% of our patients, and in 12% with radiation alone. He reported that myelosupression occurred between days 21 and 28, but recovered adequately by day 35. Even at 25 mg/body/day, the administration of Et for 6-8 weeks may not be well tolerated. Also, increases in radiation pneumonia or fibrosis were seen. Kataoka[33] reported delayed-onset pneumonitis as a result of the administration of oral Et. As with all cytotoxic drugs the physician should be alert to the onset of the relevant side effects, not only after radiation, but also during such therapy.

Because high survival rates can be achieved by controlling the intrathoracic lesions of lung cancer[34], continued investigations to reduce toxicity, without sacrificing the local control rate, are deemed necessary.

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要旨：原発性非小細胞肺癌に対して，Etoposide（Et）併用放射線照射が放射線照射単独より腫瘍縮小率を向上させるか否かを確認する為に，無作為試験を行なった．放射線は一回 1.5 ないし 2 Gy で週 5 回，計 40 Gy 以上を目的とし，Et は 25 mg を連日経口投与とし，照射日には照射 1 時間前投与とした．登録され分析可能な症例は 126 例であった．放射線照射単独では，腫瘍縮小率は腺癌と扁平上皮癌で差は無かった．腺癌では Et 併用効果は見られなかったが，扁平上皮癌では Et 併用群が 60 Gy の時点で，当初の腫瘍の 50%以下になった症例が 16/23(69.6%)で，放射線照射単独群の 11/29(37.9%)より有意に多かった(0.02＜P＜0.03)．その効果を扁平上皮癌の腫瘍径別に検討すると，3.1-5 cm 径のみで見られ，3 cm 以下および 5.1 cm 以上の腫瘍では見られなかった．