Local recurrence after complete resection for non-small-cell carcinoma of the lung

Significance of local control by radiation treatment

Of 471 patients undergoing a complete resection for non-small-cell carcinoma of the lung between 1972 and 1989, 40 patients (8.5 %) had local recurrences without extrathoracic distant metastasis. Excluding 8 patients who had malignant pleural effusion, we selected 32 patients (24 with hilar-mediastinal lymph node, 6 with bronchial stump, and 2 with chest wall recurrence) from the 40 patients and assessed the significance of local control by radiotherapy. The median length of survival after disease recurrence for these 32 patients was 19 months. Of 29 patients given radiation treatment, 16 who responded to the treatment survived significantly longer than nonresponders (median survival time 27 months versus 6 months, $p < 0.01$). Univariate analyses of survival after recurrences in relation to various factors revealed that sex and disease-free intervals were significant prognostic factors ($p < 0.05$) other than the effect of radiotherapy. A multivariate analysis showed that the effect of radiotherapy was the predominant prognostic factor. From these results, we conclude that local control with radiation is beneficial in patients with solely locally recurrent tumors in terms of improved survival. (J THORAC CARDIOVASC SURG 1994;107:8-12)

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Operation is the therapy of choice for resectable primary non-small-cell carcinoma of the lung. Unfortunately, the long-term results of operation still remain poor, largely because of the frequent development of distant metastases. Furthermore, despite performance of a radical operation, locoregional recurrences, that is, recurrences in the mediastinum, bronchial stump, and chest wall occur with an incidence of about 30% of the disease recurrences.¹⁻⁴

Does local control of locoregional recurrent disease contribute to the prolongation of survival? In this study, we analyzed the clinical features of local recurrences without extrathoracic distant metastases and identified

the effectiveness of radiation treatment on these diseases.

Patients and methods

We reviewed the hospital charts of 471 patients with non-small-cell carcinoma of the lung that was completely resected at the National Kyushu Cancer Center during the period from April 1972 until December 1989. Complete resections consisted of either a lobectomy or a pneumonectomy together with resection of the regional lymph nodes (ipsilateral hilar and mediastinal system). In all cases, the resection margin was microscopically proved negative for tumor cells. Of the 471 patients, 277 had pathologic stage I disease, 71 had stage II disease, and 123 had stage IIIA disease. A total of 241 patients (51.2%) received postoperative adjuvant chemotherapy with various regimens, whereas 64 patients (13.6%) received radiation treatment to the mediastinum postoperatively. The staging of all patients is reported according to the new International Staging System for Lung Cancer.⁵

Postoperative follow up was done at our outpatient clinic, with patients seen at monthly intervals for the first year, at bimonthly intervals during the second year, and then at 3-month intervals thereafter. Evaluation included a physical examination, chest roentgenography, computed tomographic scans, bone scintigraphy, and bronchoscopy.

In patients treated with either radiation therapy or chemo-

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Table I. Mode of disease recurrence after a complete resection in reference to the initial stages*

Stage	Local	Distant	Combined	Total
I	18 (19.3)	72 (77.4)	3 (3.2)	93
II	7 (17.9)	28 (71.8)	4 (10.2)	39
IIIA	15 (19.0)	55 (69.6)	9 (11.4)	79

*Figures are number of patients with recurrences; parentheses indicate percentages of the total number of patients with recurrences among the same stage.

Table II. Local disease recurrences after a complete resection for non-small-cell lung cancer

Recurrence	No. of cases
Hilar-mediastinal region	24
Bronchial stump	6
Chest wall	2
Pleuritis	8

therapy, tumor response was evaluated at the completion of the therapy. A complete response was defined as complete disappearance of all clinical evidence of the disease. A partial response was defined as a greater than 50% reduction in the sum of the products of the shortest and longest dimensions of all measured lesions for at least 4 weeks. No change indicated neither an objective progression nor regression of the tumor, and progressive disease was classified as a definite progression of the disease.

The Beccel Mark-II statistical package program (version 4.0, Tokyo, Japan) was used in all statistical analyses. Survival after local recurrences was estimated by the method of Kaplan and Meier.⁶ The influence of variables on survival was analyzed with the log-rank test.⁷ The Cox proportional hazards modeling technique was used to identify which independent factors had a jointly significant influence on survival.⁸ All reported *p* values are two-sided.

Results

Postoperative cancer recurrence was observed in 211 of the 471 patients. Locoregional recurrences occurred in 40 of the 211 patients (19.0%), distant metastases in 155 patients (73.4%), and combined recurrences in 16 patients (7.6%). The mode of recurrence was not different among the various stages of the disease (Table I). As shown in Table II, the 40 patients with local disease recurrences had hilar-mediastinal lymph node metastases (24 patients), bronchial stump recurrences (6), chest wall extensions (2), and carcinomatous pleuritis (8). Excluding the 8 patients with carcinomatous pleuritis, we selected the 32 patients with local disease recurrences for a retrospective evaluation in this study. Of those, 17 patients had received postoperative adjuvant chemotherapy and 6 patients had received radiation treatment postoperatively.

Table III. Patient characteristics

	No. of cases
Sex	
Male	22
Female	10
Performance status (ECOG)	
0-1	28
2-3	4
Symptoms	
+	19
-	13
Pathologic stage	
I	14
II	6
IIIA (N2)	12 (10)
Histology	
Squamous cell	15
Adenocarcinoma	13
Large-cell	4
Disease-free interval	
≥2 yr	19
<2 yr	13
Treatments	
Radiotherapy	
+	29
-	3
Chemotherapy	
+	12
-	20

ECOG, Eastern Cooperative Oncology Group.

Table IV. Symptoms caused by local disease recurrences

	No. of cases (%)
Hemoptum	9 (28.1)
Cough	5 (15.6)
Hoarseness	3 (9.4)
Dysphagia	2
Supraclavicular nodes	1
SVC syndrome	1
Total	19*

SVC, Superior vena cava.

*Two patients had two symptoms (hemoptum and cough).

The selected study group of 32 patients consisted of 22 men and 10 women with a mean age of 61.3 years (range 42 to 76 years). The performance status (Eastern Cooperative Oncology Group), histologic classifications, pathologic stages of the disease, disease-free intervals, and treatment modalities after recurrence were noted and are listed in Table III. Of 32 patients, 19 patients had some disease-related symptom, listed in Table IV, at the time of diagnosis. All patients but one died of the disease by the time of the last follow-up.

Fig. 1. Survival curve after local recurrences for completely resected non-small-cell carcinoma of lung. Numbers in parentheses indicate number of patients still being followed up at each time point; bars indicate standard errors.

Fig. 2. Effect of radiotherapy on survival after local disease recurrences. CR, Complete response; PR, partial response; NC, no change; PD, progressive disease.

The median survival time after disease recurrence for all patients was 19 months with cumulative survivals of 56%, 38%, and 8.5% at 12, 24, and 60 months, respectively (Fig. 1). For the control of local lesions, 29 patients received a radiation treatment with a total dose of 50 through 60 Gy given in multiple fractions (1.6 to 2 Gy per day). Three patients achieved a complete response, whereas 13 patients had a partial response. There was no significant difference in the response according to site of recurrence. As shown in Fig. 2, those 16 responders survived significantly longer than non-responders (median survival time 27 months versus 6 months, $p < 0.01$).

Systemic chemotherapy with various regimens containing cisplatin was administered in 12 patients with a

partial response in one patient, but this did not contribute to the survival (Fig. 3). In 14 patients, extrathoracic distant metastases appeared after local recurrences. However, the survival of those 14 patients was not different from that of 18 patients without extrathoracic metastases (Fig. 4). The association of other prognostic variables, that is, sex, stage of the disease, histologic type, disease-free intervals, and presence of symptoms, were all examined and are summarized in Table V. Significant differences existed with respect to sex and disease-free intervals. Patients who were female or who had a disease-free interval longer than 2 years had a significantly better survival. Multivariate analysis showed that the effect of radiotherapy was the predominant prognostic factor for patients with local recurrences (Table VI).

Fig. 3. Influence of chemotherapy on survival after local disease recurrences.

Fig. 4. Influence of extrathoracic distant metastases on survival after local disease recurrences.

Discussion

In our series, solely local recurrences, including malignant effusion, occurred in 8.5% of 471 patients undergoing a complete resection for non-small-cell lung cancer and accounted for 19.0% of all postoperative recurrences. The incidence of local recurrences seemed slightly lower than that in other series,^{1-4,9} but is not so different. As in other reports, lymph node metastases in the hilum and mediastinum were the most common mode of local recurrences.^{2,9} This implies a possibility that despite systematic lymph node dissection, occult residual disease was persistent in the hilar and mediastinal tissues, probably in the small lymphatic vessels. Iacone and associates¹ reported that local recurrences accounted for 75% of all recurrences in N0 disease, 28.6% in N1 disease, and 15.4% in N2 disease. However, we did not observe any

differences in the modes of recurrences among the initial stages of the disease (Table I).

The present study demonstrates that local treatment with radiation is beneficial in patients with locoregional recurrent disease after a complete resection. Half of the patients who received radiation treatment achieved a good local response and a prolonged survival with a median survival time of 27 months. On the other hand, the median survival time of patients with uncontrolled disease was only 6 months. The subsequent appearance of extrathoracic metastases did not affect the survival time after local recurrences. This implies that locoregional spreading of the disease is likely to be critical and that local control is important even if temporary. As far as we know, there has been only one report referring to the treatment results of postoperative local recurrences.

Table V. Univariate analysis of various prognostic factors in patients with local disease recurrences

Variable	Category	n	p Value
Sex	Female	10	<0.05
	Male	22	
Symptoms	+	19	NS
	-	13	
Pathologic stage	I	14	NS
	II	6	
	IIIA	12	
Histology	Squamous	15	NS
	Nonsquamous	17	
Disease-free interval	<2 yr	13	<0.05
	≥2 yr	19	
Effect of radiotherapy	CR, PR	16	<0.01
	NC, PD	13	
Chemotherapy	-	3	NS
	+	12	
	-	20	
Distant metastasis	-	18	NS
	+	14	

NS, Not significant; CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

Table VI. Cox proportional hazards model for factors associated with survival after local recurrences

Variable	p Value	Relative risk
Radiotherapy (CR + PR, NC + PD, none)	0.0210	2.96 (1.18, 7.43)
Sex (female, male)	0.158	1.92 (0.78, 4.7)
DFI (<2 yr, ≥2 yr)	0.357	1.53 (0.60, 3.81)

CR, Complete response; PR, partial response; NC, no change; PD, progressive disease; DFI, disease-free interval. Parentheses indicate 95% confidence interval of relative risk.

Green and Kern⁹ observed a propensity for locally recurrent tumors to remain limited to the site of origin and an improved survival of patients with such disease with radiotherapy. Similarly in our series, 19 of 32 patients were disease-free for more than 2 years until local recurrence finally manifested itself. Such patients also had a longer survival than others.

From the present results, we do not mean to suggest that there is advantage in postoperative adjuvant radio-

therapy. In fact, The Lung Cancer Study Group demonstrated that postoperative adjuvant radiotherapy could reduce local recurrence but that the effect did not translate into a survival benefit, largely because most of the recurrences were systemic.^{10,11} In terms of improved survival, local control by radiation seems to benefit only patients with solely locally recurrent tumors.

At present, we surgeons must carefully consider the necessity for radiotherapy when we find local recurrences after resection.

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REFERENCES

1. Iacone C, DeMeester TR, Albertucci M, Little AG, Golomb HM. Local recurrence of resectable non-oat cell carcinoma of the lung. *Cancer* 1986;57:471-6.
2. Kotlyarov EV, Rukosuyev AA. Long-term results and patterns of disease recurrence after radical operations for lung cancer. *J THORAC CARDIOVASC SURG* 1991;102:24-8.
3. Little AG, DeMeester TR, Ferguson MK, et al. Modified stage I (T1N0M0, T2N0M0), nonsmall cell lung cancer: treatment results, recurrence patterns, and adjuvant immunotherapy. *Surgery* 1986;100:621-8.
4. The Lung Cancer Study Group. Postoperative T1 N0 non-small cell lung cancer: squamous versus nonsquamous recurrences. *J THORAC CARDIOVASC SURG* 1987;94:349-54.
5. Mountain CF. A new international staging system for lung cancer. *Chest* 1986;89:225S-33S.
6. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
7. Peto R, Peto J. Asymptotically efficient rank and invariant procedures. *J R Stat Soc (A)* 1972;135:185-207.
8. Cox DR. Regression models and life tables. *J R Stat Soc (B)* 1972;34:187-220.
9. Green N, Kern W. The clinical course and treatment results of patients with postresection locally recurrent lung cancer. *Cancer* 1978;42:2478-82.
10. The Lung Cancer Study Group. Effects of postoperative mediastinal radiation on completely resected stage II and stage III epidermoid cancer of the lung. *N Engl J Med* 1986;315:1377-81.
11. Sadeghi A, Payne D, Rubinstein L, Lad T, The Lung Cancer Study Group. Combined modality treatment for resected advanced non-small cell lung cancer: local control and local recurrence. *Int J Radiat Oncol Biol Phys* 1988;15:89-97.