TABLE 3. Multivariate-Adjusted Relative Risk (95% CI) for All-Cause and Cardiovascular Disease According to Smoking Habit in Japan, NIPPON DATA80

			Smoker	
Men	Nonsmoker	Ex-Smoker	1–20 Cigarettes/d	≥21 Cigarettes/d
All causes	1	1.17 (0.90–1.52)	1.14 (0.91–1.44)	1.55 (1.17–2.04)*
CVD	1	1.20 (0.76–1.90)	1.49 (1.00–2.20)*	2.00 (1.24–3.31)*
All stroke	1	1.56 (0.84–2.90)	1.60 (0.91–2.79)	2.17 (1.09–4.30)*
Infarction	1	3.06 (1.23–7.63)*	2.97 (1.27–6.98)*	3.26 (1.11–9.56)*
Hemorrhagic	1	0.60 (0.21–1.69)	0.42 (0.16–1.09)	0.68 (0.20–2.33)
All heart disease	1	0.98 (0.48–1.98)	1.40 (0.78–2.51)	2.15 (1.09–4.24)*
Ischemic heart disease	1	1.00 (0.28–3.53)	1.56 (0.54–4.53)	4.25 (1.42–12.8)*
			Smoker	
Women	Nonsmoker	Ex-Smoker	1–20 Cigarettes/d	≥21 Cigarettes/d
All causes	1	1.21 (0.76–1.92)	1.31 (0.99–1.74)	1.32 (0.54–3.22)
CVD	1	1.03 (0.49–2.15)	1.43 (0.92–2.23)	2.35 (0.85–6.50)
All stroke	1	1.31 (0.50–3.39)	1.42 (0.72–2.78)	3.91 (1.18–12.90)*
Infarction	1	1.60 (0.46–5.63)	1.75 (0.71–4.30)	2.31 (0.30–18.10)
Hemorrhagic	1	1.23 (0.15–11.40)	—	—
All heart disease	1	0.89 (0.27–2.93)	1.58 (0.87–2.86)	—
Ischemic heart disease	1	0.87 (0.11–6.70)	1.27 (0.43–3.78)	—

Relative risk were adjusted for age, systolic blood pressure, body mass index, serum total cholesterol, drinking habit, and diabetes.

*Significantly higher than nonsmoker group at alpha=0.05 level.

caused by the 0.026-mmol/L increase in serum total cholesterol.[27]

In conclusion, smoking is a potent risk factor for death from stroke, IHD, all CVD, and all causes of death for both Japanese men and women. We therefore need to more rigorously promote antismoking programs and policy not only in Japan but also in other Asian countries with high smoking rates.

Acknowledgments

This study was supported by a grant-in-aid of the Ministry of Health and Welfare, 7A-2 and H11-Chouju-046, H14-Chouju-003.

References

1. Peto R. Smoking and death: the past 40 years and the next 40. *BMJ.* 1994; 209:937–939.
2. Wolf PA, D'Agostino RB, Kannel WB, Bonita R, Belanger AJ. Cigarette smoking as a risk factor for stroke. The Framingham Study. *JAMA.* 1988;259:1025–1029.
3. Colditz GA, Bonita R, Stampfer MJ, Willett W, Rosner B, Speizer FE, Hennekens CH. Cigarette smoking and risk of stroke in middle-aged women. *N Engl J Med.* 1988;318:937–941.
4. Abbot RD, Yin Y, Reed DM, Yano K. Risk of stroke in male cigarette smokers. *N Engl J Med.* 1986;315:717–720.
5. Hirayama T. An epidemiological study on the relationship between cigarette smoking and arteriosclerosis based on 13 years follow-up of 265 118 adults aged 40 and above in 29 health center districts in Japan. *Saishin Igaku.* 1981;36:798–809. In Japanese.
6. Kiyohara Y, Ueda K, Fujishima M. Smoking and cardiovascular disease in general population in Japan. *J Hypertens.* 1990;8:S9–S15.
7. Ueshima H, Iida M, Shimamoto T, Konishi M, Tsujioka K, Tanigaki M, Nakanishi M, Ozawa H, Kojima S, Komachi Y. Multivariate analysis of risk factors for stroke. Eight-year follow-up of farming villages in Akita, Japan. *Prev Med.* 1980;9:722–740.
8. Yamagishi K, Iso H, Kitamura A, Sankai T, Tanigawa T, Naito Y, Sato S, Imano H, Ohira T, Shimamoto T. Smoking raises the risk of total and ischemic strokes in hypertensive men. *Hypertens Res.* 2003;26:209–217.
9. Tanizaki Y, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Shinohara N, Arima H, Tanaka K, Ibayashi S, Fujishima M. Incidence and risk factors for subtypes of cerebral infarction in a general population. The Hisayama Study. *Stroke.* 2000;31:2616–2622.
10. Ueshima H. Changes in dietary habits, cardiovascular risk factors and mortality in Japan. *Acta Cardiol.* 1990;45:311–327.
11. Okayama A, Ueshima H, Marmot MG, Nakamura M, Kita Y, Yamakawa M. Changes in total serum cholesterol and other risk factors for Cardiovascular disease in Japan, 1980–1989. *Int J Epidemiol.* 1993;22: 1038–1047.
12. Nakayama T, Date C, Yokoyama T, Yoshiike N, Yamaguchi M, Tanaka H. A 15.5-year follow-up study of stroke in a Japanese provincial city. The Shibata Study. *Stroke.* 1997;28:45–52.
13. Okamura T, Kadowaki T, Hayakawa T, Kita Y, Okayama A, Ueshima H, for Nippon Data80 Research Group. What cause of mortality can we predict by cholesterol screening in the Japanese general population? *J Intern Med.* 2003;253:169–180.
14. Goldberg RJ, Burchfiel CM, Benfante R, Chiu D, Reed DM, Yano K. Lifestyle and biologic factors associated with atherosclerotic disease in Middle-aged men. 20-year findings from the Honolulu Heart Program. *Arch Intern Med.* 1995;155:686–694.
15. Ministry of Health, Labor and Welfare. National Nutrition Survey, 2000. Tokyo: Daiichi Shuppan Publisher; 2002.
16. Shimamoto T, Komaci Y, Inada H, Doi M, Iso H, Sato S, Kitamura A, Iida M, Konishi M, Nakanishi N, Terao A, Naito Y, Kijima S. Trends for coronary heart disease and stroke and their risk factors in Japan. *Circulation.* 1989;79:503–515.
17. Kita Y, Okayama A, Ueshima H, Wada M, Nozaki A, Choudhury SR, Bonita R, Inamoto Y, Kasamatsu T. Stroke incidence and case fatality in Shiga, Japan 1989–1993. *Int J Epidemiol.* 1999;28:1059–1065.
18. Kubo M, Kiyohara Y, Kato I, Tanizaki Y, Arima H, Tanaka K, Nakamura H, Okubo K, Iida M. Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: the Hisayama Study. *Stroke.* 2003;34:2349–2354.

19. Robbins AS, Manson JE, Lee IM, Satterfield S, Hennekens CH. Cigarette smoking and stroke in a cohort of U. S. male physicians. *Ann Intern Med.* 1994;120:458–462.
20. Qiu D, Mei J, Tanihata T, Kawaminami K, Minowa M. A cohort study on cerebrovascular disease in middle-aged and elderly population in rural areas in Jianxi province, China. *J Epidemiol.* 2002;13:149–156.
21. Sankai T, Miyagaki T, Iso H, Shimamoto T, Iida M, Tanigaki M, Naito Y, Sato S, Kiyama M, Kitamura A, Konishi M, Terao A, Doi M, Komachi Y. A population-based study of the proportion by type of stroke determined by computed tomography scan. *Nippon Koshu Eisei Zassi.* 1991;38:901–909. In Japanese.
22. Department of Statistics, Ministry of Health, Labor, and Welfare. Survey on facilities in hospitals and clinics. Medical and examination devices in hospitals. No I. Tokyo: Kousei Tokei Kyokai; 1998. In Japanese.
23. Hasuo Y, Ueda K, Kiyohara Y, Wada J, Kawano H, Kato I, Yanai T, Fujii I, Omae T, Fujishima M. Accuracy of diagnosis on death certificates for underlying causes of death in a long-term autopsy-based population study in Hisayama, Japan; with special reference to cardiovascular disease. *J Clin Epidemiol.* 1989;42:577–584.
24. Ron E, Carteer R, Jablon S, Mabuchi K. Agreement between death certificate and autopsy diagnoses among atomic bomb survivors. *Epidemiology.* 1994;5:48–56.
25. Kodama K, Sasaki H, Shimizu Y. Trend of coronary heart disease and its relationship to risk factors in a Japanese population: a 26-year follow-up, Hiroshima/Nagasaki study. *Jpn Circ J.* 1990;54:414–421.
26. Sekikawa A, Kuller LH, Ueshima H, Park JE, Suh I, Jee SH, Lee HK, Pan WH. Coronary heart disease mortality trends in men in the post World War II birth cohort aged 35–44 in Japan, South Korea, and Taiwan compared with the United States. *Int J Epidemiol.* 1999;28:1044–1049.
27. Liu LJ, Choudhury SR, Okayama A, Hayakawa T, Kita Y, Ueshima H. Changes in body mass index and its relationship to the prevalence of hypertension, diabetes mellitus, hypercholesterolemia, smoking, alcohol consumption and daily physical activity in Japanese: Japan 1980 and 1990 National Surveys. *J Epidemiol.* 1999;9:163–174.
28. Ockene IS, Miller NH. Cigarette smoking, cardiovascular disease, and stroke: a statement for healthcare professionals from the American Heart Association. American Heart Association Task Force on Risk Reduction. *Circulation.* 1997;96:3243–3247.

K. Hotta[1]
I. Sekine[1]
K. Suzuki[2]
H. Kondo[2]
H. Asamura[2]
M. Sumi[3]
N. Yamamoto[1]
H. Kunitoh[1]
Y. Ohe[1]
T. Tamura[1]
T. Kodama[1]
N. Saijo[1]
R. Tsuchiya[2]

Distant Failure after Treatment of Postoperative Locoregional Recurrence of Non-Small Cell Lung Cancer

Abstract

Background: The standard treatment for patients with locoregional recurrence of non-small cell lung cancer (NSCLC) after complete resection has not been established. The aim of this study was to evaluate clinicopathologic characteristics, type of locoregional recurrence, pattern of subsequent failure, and survival after the recurrence. **Methods:** Of 743 patients undergoing pulmonary resection for NSCLC in the National Cancer Center Hospital between 1990 and 1995, we retrospectively reviewed the medical charts of the 43 patients (5.8%) found to have locoregional recurrence without distant metastasis or pleural or pericardial involvement. **Results:** The median time to locoregional recurrence was 13.6 months (range: 1.6–85.8 months). The most frequent site of recurrence was the mediastinal nodes in 21 of 43 patients (49%). 33 patients (77%) received further treatment for the recurrence: thoracic irradiation in 26, surgery in two, systemic chemotherapy in two, and a combination of the above in 3 patients. Subsequent distant failure was detected in 26 (68%) of the 38 patients assessable for the analysis of failure pattern: lung in 11, brain in 6, bone in 5, and others in 13. The median interval from the recurrence to distant failure was 8.4 months (range: 1.7–56.4 months). The median survival time after diagnosis of the locoregional recurrence was 10.5 months (range: 0–74.0 months). A multivariate analysis showed that local therapy for the locoregional recurrence had no significant impact on postrecurrent survival or distant failure-free survival. **Conclusions:** Many patients with postoperative locoregional recurrence developed distant metastases early after the first recurrence. Systemic chemotherapy in addition to local therapy may be of benefit in this population.

Key words
Non-small cell lung cancer · postoperative locoregional recurrence · local therapy · distant failure

Introduction

Lung cancer is the leading cause of cancer deaths in many countries. Surgical resection is the preferred treatment for non-small cell lung cancer (NSCLC) and provides the best chance for a definite cure. However, even in pathological stage I disease, as many as 30–40% of the patients experience recurrence after complete resection [1–4]. Although distant metastasis is the main pattern of recurrence after curative resection [1,3–6], locoregional recurrence without manifestations of distant metastases has been reported to occur in 15–35% of resected patients [1,3–7].

Several studies have addressed the role of local therapy, especially thoracic irradiation, in the treatment of patients with postoperative locoregional recurrence of NSCLC [5,8–14]. Most of the authors noted the benefits of local therapy for a favorable an-

Affiliation
[1] Division of Medical Oncology
[2] Division of Thoracic Surgery
[3] Division of Radiation Oncology
National Cancer Center Hospital, Tokyo, Japan

Correspondence
Katsuyuki Hotta, MD · Department of Internal Medicine II, Okayama University Medical School · 2-5-1, Shitaka-cho, Okayama · 700–8558, Japan · Phone: +81–86–235–7227 · Fax: +81–86–232–8226 · E-mail: khotta@md.okayama-u.ac.jp

Received January 1, 2003

Bibliography
Thorac Cardiov Surg 2003; 51: 283–287 · © Georg Thieme Verlag Stuttgart · New York · ISSN 0171-6425

titumor response and relief of symptoms. The optimal therapy for this population, however, has not yet been established since the median survival time after locoregional recurrence remains approximately one year, and long-term survivors are very rare.

Determining patterns of subsequent failure in patients with postoperative locoregional recurrence is essential to further development and improvement in treatment modality. However, since only a few reports have documented and discussed systemic control in addition to local control after local therapy [5,13,14], we have attempted to evaluate the outcome of local therapy, especially in terms of the incidence and pattern of distant failure in patients with postoperative locoregional recurrent NSCLC.

Patients and Methods

In the period from January 1990 to September 1995, 743 patients with NSCLC underwent pulmonary resection in the National Cancer Center Hospital. The extent of pulmonary resection and mediastinal node dissection was left to the discretion of the surgeon. Locoregional recurrence after the operation was diagnosed on the radiological and physical findings of new tumors in the thorax and supraclavicular lymph nodes, and recurrent disease was confirmed by biopsy where clinically feasible. Although not specifically designed for staging the recurrent tumor, the staging procedure included medical history, physical examination, laboratory tests, chest X-rays, computed tomography (CT) scans of the chest and brain, bronchoscopy, ultrasonography or CT scan of the abdomen, and a radionuclide bone scan. Patients with any documented distant metastasis, intrapulmonary metastasis, or pleural or pericardial involvement at the time of the first recurrence were excluded from this analysis. As of April 2001, 43 (5.8%) of the 743 patients had been found to have locoregional recurrence without distant metastasis or effusion. Diagnosis of locoregional recurrence was based on the chest X-ray or chest CT scan in 20 (47%) of the 43 patients, palpable tumor localized in the chest wall, incision, or supraclavicular lymph nodes in 12 (27%), and on bronchoscopic findings in 11 (26%). In the patients treated with radiotherapy for recurrent disease, tumor response was evaluated by chest X-ray, chest CT scan, bronchoscopy, or direct measurement. Favorable response was defined as a reduction greater than 50% in the sum of the products of the longest and shortest dimensions of all measured lesions for at least 4 weeks.

Subsequent distant failure after locoregional recurrence was defined as radiological or physical evidence of new tumor outside the thorax. Documented evidence of intrapulmonary metastasis, pleural involvement, or pericardial involvement was also defined as distant failure.

Of the 43 patients, 5 were lost to follow-up after the detection of the locoregional recurrence, whereas the other 38 patients were followed up until death. The median follow-up time of the 43 patients was 10.5 months with a range of 0–74.0 months. All of the statistical analyses were performed using the STATVIEW 5.0 software package (Brainpower, Calabasas, Calif.). The numbers of days between the detection of the first locoregional recurrent site and the first distant failure and death were recorded as distant failure-free survival and post-recurrent overall survival, respectively. The association between various factors and distant failure-free survival or post-recurrent overall survival was evaluated by Cox's proportional hazards modeling technique. The factors analyzed in this study included gender, type of operation, histology, pathological staging at the time of initial operation, interval between the time of resection and locoregional recurrence, recurrent site, local therapy for locoregional recurrence, age, and performance status at the time of the recurrence. Survival time was estimated using the Kaplan-Meier method.

Results

The characteristics of the 43 patients with postoperative locoregional recurrence are summarized in Table **1**. There were 31 men and 12 women, and their median age at the time of locoregional recurrence was 63 years (range: 40–81 years). Two patients received adjuvant radiation treatment to the mediastinum. Another two patients received preoperative radiotherapy.

Tab. **1** Characteristics of the 43 patients with postoperative locoregional recurrence of non-small cell lung cancer

Age (yr)*	Median (range)	63 (40–81)
Gender	Male/female	31/12
Initial operation	Pneumonectomy	12
	Lobectomy	28
	Segmentectomy	1
	Partial resection	2
Histology	Adenocarcinoma	21
	Squamous cell carcinoma	16
	Adenosquamous carcinoma	4
	Others	2
Pathological staging at initial operation		
	Ia-Ib	9
	IIa-IIb	9
	IIIa-IIIb	25
Performance status *	0–1/2–4	41/2
Median time to locoregional recurrence (range, months)		13.6 (1.6–85.8)

* confirmed at the time of locoregional recurrence

The median interval between the initial resection and locoregional recurrence was 13.6 months (range, 1.6–85.8 months). The most frequent site of recurrence was the mediastinal nodes – mediastinal lymph nodes alone in 14 (33%) of the 43 patients and mediastinal lymph nodes and others in 7 (16%) (Table **2**). 17 patients (40%) had some disease-related symptoms at the time of the recurrence, one of which was hoarseness in 3 patients. Of the 43 patients, 33 (77%) received further treatment for the recurrence, and 10 (23%) received supportive care alone.

The treatment modality consisted of thoracic irradiation in 26 patients, surgery in two, systemic chemotherapy in two, thoracic irradiation and chemotherapy in two, and surgery and radiation

Tab. 2 Sites of locoregional recurrence in the 43 patients

Site	Number of patients	
Mediastinal nodes	14	(33%)
Supraclavicular nodes	8	(19%)
Bronchial stump	8	(19%)
Chest wall	4	(9%)
Hilar nodes	2	(5%)
Mediastinal and supraclavicular nodes	4	(9%)
Mediastinal nodes and bronchial stump	2	(5%)
Mediastinal and supraclavicular nodes and bronchial stump	1	(1%)

in one. Of the 3 patients treated with surgery, the 2 patients recurred in bronchial stump and one in chest wall, and all of them underwent complete tumor resection. In the 28 patients treated with thoracic irradiation, the median treatment interval was 39 days and the median dose delivered was 50 Gy (range: 30–70 Gy). The objective response was assessable in 25 of the 28 patients who underwent thoracic irradiation. Tumor regression was obtained in 13 (52%) of these 25 patients. In the 4 patients that underwent systemic chemotherapy, 3 received a platinum-based regimen. One patient encountered severe drug toxicity, and the treatment was stopped early. The median treatment interval was 54 days, and objective tumor response was obtained in 2 patients. After treating this locoregional recurrence, patients were followed up every one to 6 months.

Only 38 (88%) of the 43 patients were evaluable for analysis of systemic control after recurrence since the other five patients had been lost to follow-up as mentioned above. Distant failure after locoregional recurrence was observed in 26 (68%) of the 38 patients. The median interval between locoregional recurrence and distant failure was 8.4 months (range, 1.7–56.4 months). The most frequent site of distant failure was pulmonary parenchyma (11 patients, Table 3).

Tab. 3 Sites of distant failure in the 26 patients

Site	Number of patients
Lung	11
Brain	6
Bone	5
Pleura	4
Liver	3
Abdominal lymph nodes	2
Adrenal gland	2
Spleen	1
Pericardium	1

The association between several possible risk factors and subsequent distant failure after locoregional recurrence was evaluated using Cox's proportional hazard model (Table 4 and 5). The hazard ratio for a performance status factor could not be calculated with the model. Neither of the two patients with performance status 2 and 4 developed distant failure, but 26 (63%) of the 41 patients with performance status 0 or 1 did. A univariate analysis showed that gender and the addition of local therapy were marginal factors affecting distant failure-free survival (Table 4). Multivariate analysis, however, revealed that neither factor had any significant impact (Table 5).

Tab. 4 Univariate analysis of the hazard ratios for various factors on distant-failure free survival

Factor		Hazard ratio (95% CI)	p
Gender	Male	1	0.058
	Female	5.18 (0.95–28.4)	
Type of operation*	Lobectomy	1	0.854
	Others	1.17 (0.21–6.55)	
Histology*	Squamous cell ca	1	0.132
	Non-squamous cell ca	5.16 (0.61–43.7)	
Pathological staging*	I-II	1	0.767
	III-IV	1.26 (0.27–5.89)	
Interval between resection and locoregional recurrence			
	> 13.6 months	1	0.211
	≤ 13.6 months	3.30 (0.51–21.4)	
Age (yr)**	< 63	1	0.483
	≥ 63	1.62 (0.42–6.16)	
Site of recurrence	Stump	1	0.520
	Others	1.74 (0.32–9.37)	
Local therapy for locoregional recurrence			
	Yes	1	0.080
	No	5.22 (0.82–33.1)	

*confirmed at the initial presentation, **confirmed at the time of locoregional recurrence Abbreviations: ca, carcinoma; CI, confidence interval.

Tab. 5 Multivariate analysis of the hazard ratios for various factors on distant-failure free survival

Factor		Hazard ratio (95% CI)	p
Gender	Male	1	0.183
	Female	3.37 (0.56–20.1)	
Histology*	Squamous cell ca	1	0.286
	Non-squamous cell ca	3.47 (0.35–34.0)	
Interval between resection and locoregional recurrence			
	> 13.6 months	1	0.256
	≤ 13.6 months	3.18 (0.43–23.4)	
Local therapy for locoregional recurrence			
	Yes	1	0.136
	No	4.64 (0.62–34.8)	

*confirmed at the initial presentation. Abbreviations: ca, carcinoma; CI, confidence interval.

The survival curve for the patients of locoregional recurrence is displayed in Fig. 1. The median survival time of the 43 patients was 10.5 months (range: 0–74.0 months). In the univariate analysis, a favorable outcome was obtained in patients that had received local therapy for the recurrence, patients who had a long interval between the initial resection and the recurrence, and patients who had good performance status (Table 6). Multivariate analysis showed that performance status at the time of the initial recurrence influenced post-recurrent survival, but

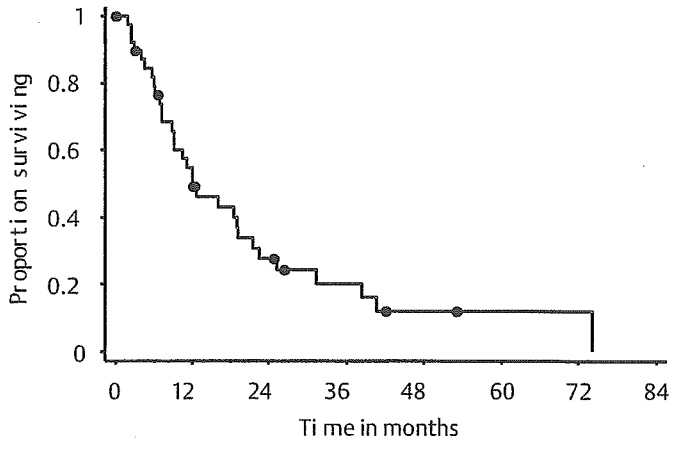

Fig. 1 Survival curve after locoregional recurrence in patients with postoperative non-small cell lung cancer.

Tab. 6 Univariate analysis of the hazard ratios for various prognostic factors

Factor	*Hazard ratio (95% CI)*		*p*
Gender	Female	1	0.166
	Male	1.89 (0.77–4.65)	
Type of operation*	Lobectomy	1	0.015
	Others	2.63 (1.21–5.75)	
Histology*	Non-squamous cell ca	1	0.202
	Squamous cell ca	1.62 (0.77–3.39)	
Pathological staging*	I–II	1	0.082
	III–IV	2.01 (0.92–4.40)	
Interval between resection and locoregional recurrence			
	> 13.6 months	1	0.023
	≤ 13.6 months	2.35 (1.13–4.91)	
Age (yr) **	< 63	1	0.316
	≥ 63	1.46 (0.70–3.03)	
Performance status**	0–1	1	0.001
	2–4	30.5 (4.22–221.3)	
Recurrent site	Stump	1	0.683
	Others	1.23 (0.46–3.27)	
Local therapy for locoregional recurrence			
	Yes	1	0.012
	No	2.79 (1.26–6.19)	

* confirmed at the initial presentation, ** confirmed at the time of locoregional recurrence. Abbreviations: ca, carcinoma; CI, confidence interval.

that none of the other factors, including the addition of local therapy, had any significant impact (Table 7).

Discussion

We found that 5.8% of the patients who had undergone the initial surgery developed subsequent locoregional recurrence in contrast to the 3–19% range from previous reports [5,8,14]. This wide range was possibly due to the difference of patient population or the definition of local recurrence among the reports.

Tab. 7 Multivariate analysis of the hazard ratios for various prognostic factors

Factor	*Hazard ratio (95% CI)*		*p*
Type of operation*	Lobectomy	1	0.070
	Others	2.20 (0.94–5.14)	
Pathological staging*	I–II	1	0.299
	III–IV	1.58 (0.67–3.76)	
Interval between resection and locoregional recurrence			
	> 13.6 months	1	0.163
	≤ 13.6 months	1.78 (0.79–3.98)	
Performance status*	0–1	1	0.036
	2–4	11.9 (1.18–119.3)	
Local therapy for locoregional recurrence			
	Yes	1	0.219
	No	1.79 (0.71–4.55)	

* confirmed at the time of locoregional recurrence.
Abbreviations: CI, confidence interval

Analysis of treatment failure patterns provides clues as to how to overcome the shortcomings of a treatment program and permits the development of new therapeutic strategies and protocols, and we found a very high incidence of distant failure early after the initial recurrence in patients with postoperative locoregional recurrent NSCLC. The previous reports documented a range of 30–73% in this patient population [5,9,11,13,14]. This wide variability may be attributable to (i) differences in follow-up interval, (ii) patient selection, (iii) differences in staging procedures for recurrent tumors, or (iv) differences in definition of distant failure. This moderate-to-high incidence of distant failure after postoperative locoregional recurrence indicates that these patients should be treated as having systemic disease, even if the site of recurrence is only localized clinically.

Yano et al. reported treating 12 (38%) of 32 patients that had postoperative locoregional recurrence with thoracic irradiation combined with systemic chemotherapy containing cisplatin as opposed to thoracic irradiation alone in the other 20 patients. The authors concluded that median survival time in patients treated with combined modality therapy was comparable to that of patients treated with thoracic irradiation alone [5]. Shaw et al. demonstrated that of 37 patients with postoperative locoregional recurrence, 15 received thoracic irradiation and additional systemic chemotherapy with various regimens, and the others received thoracic irradiation alone. The long-term survival rate of the two groups was similar [13]. In both studies, however, patient selection for chemotherapy was highly biased since the decision as to which patients to treat with systemic chemotherapy in addition to thoracic irradiation was left to the discretion of the physician in charge of the patient. Moreover, these reports included only small numbers of patients. Thus, there was little evaluation of chemotherapy in this population.

The disease distribution of newly diagnosed stage III-NSCLC is also located in the thorax. For many years, radiation therapy alone was considered the treatment of choice for these patients with stage III disease, but the median survival with this treatment modality was only 9–11 months, and the 5-year survival rates were only 3–10%. Long-term observation after treatment

by thoracic irradiation also revealed a high incidence of subsequent extrathoracic failure [15], which led to the investigation into the role of systemic chemotherapy in this population.

Le Chevalier et al. conducted a large randomized trial comparing radiotherapy plus platinum-containing chemotherapy with radiotherapy alone in 353 patients with newly diagnosed stage III-NSCLC [16]. They found that chemotherapy significantly decreased the rate of subsequent distant metastasis, which resulted in a survival advantage of combined modality therapy. Dillman [17] and Sause [18] performed a phase III trial to determine whether the addition of systemic chemotherapy improved survival in patients with primary stage III-NSCLC. Both of them reported that median survival time was superior in the combined modality arm, and an update of Dillman's trial further demonstrated a continued survival benefit with combined modality therapy even for as long as seven years [17].

These results [16–18] strongly indicate the need for both chemotherapy and radiotherapy to achieve the optimal outcome in primary localized NSCLC. Likewise, the addition of systemic chemotherapy to local therapy in patients with postoperative locoregional recurrent NSCLC might be of benefit in achieving substantial further improvements in survival since the clinical behavior and characteristics of the postoperative locoregional recurrent disease seemed very similar to those of newly diagnosed stage III disease in some regards, for example: (i) disease distribution at the time of diagnosis (disease located in the thorax clinically), (ii) subsequent failure pattern after local therapy (moderate-to-high incidence of distant failure), and (iii) median survival time after local therapy (approximately one year).

The current study had several limitations, mainly because all the analyses were performed retrospectively. The problems included the lack of a uniform procedure for patient follow-up and for restaging subsequent recurrent disease. Moreover, this study neither clearly defined how to make a treatment plan for each patient nor how to evaluate the efficacy of treatment. Well-designed prospective trials are warranted in the future to resolve and improve these problems and to investigate the role of systemic chemotherapy for patients with postoperative locoregional recurrent NSCLC. Further, since the large interindividual variability in this population requires a large sample size of patients, multicenter trials should be performed as a means of accruing patients more efficiently.

In conclusion, we found a high incidence of distant failure after postoperative locoregional recurrence in patients with NSCLC. The addition of systemic chemotherapy to local therapy will also be given serious consideration to overcome the high incidence of subsequent distant metastasis, and to improve the postoperative survival in this population.

References

[1] Pairolero PC, Williams DE, Bergstralh EJ, Piehler JM, Bernatz PE, Payne WS. Postsurgical stage I bronchogenic carcinoma: Morbid implications of recurrent disease. Ann Thorac Surg 1984; 38: 331–338

[2] Harpole DH Jr, Herndon JE 2nd, Young WG Jr, Wolfe WG, Sabiston DC Jr. Stage I nonsmall cell lung cancer. A multivariate analysis of treatment methods and patterns of recurrence. Cancer 1995; 76: 787–796

[3] Cangemi V, Volpino P, D'Andrea N, et al. Local and/or distant recurrences in T1–2/N0–1 non-small cell lung cancer. Eur J Cardiothorac Surg 1995; 9: 473–478

[4] Martini N, Bains MS, Burt ME, et al. Incidence of local recurrence and second primary tumors in resected stage I lung cancer. J Thorac Cardiovasc Surg 1995; 109: 120–129

[5] Yano T, Hara N, Ichinose Y, et al. Local recurrence after complete resection for non-small cell carcinoma of the lung. J Thorac Cardiovasc Surg 1994; 107: 8–12

[6] Sawyer TE, Bonner JA, Gould PM, Deschamps C, Lange CM, Li H. Patients with stage I non-small cell lung carcinoma at postoperative risk for local recurrence, distant metastasis, and death: Implications related to the design of clinical trials. Int J Radiat Oncol Biol Phys 1999; 45: 315–321

[7] Kotlyarov EV, Rukosuyev AA. Long-term results and patterns of disease recurrence after radical operations for lung cancer. J Thorac Cardiovasc Surg 1991; 102: 24–28

[8] Green N, Kern W. The clinical course and treatment results of patients with postresection locally recurrent lung cancer. Cancer 1978; 42: 2478–2482

[9] Curran WJJr, Herbert SH, Stafford PM, et al. Should patients with postresection locoregional recurrence of lung cancer receive aggressive therapy? Int J Radiat Oncol Biol Phys 1992; 24: 25–30

[10] Leung J, Ball D, Worotniuk T, Laidlaw C. Survival following radiotherapy for post-surgical locoregional recurrence of non-small cell lung cancer. Lung cancer 1995; 13: 121–127

[11] Kagami Y, Nishio M, Narimatsu N, et al. Radiotherapy for locoregional recurrent tumors after resection of non-small cell lung cancer. Lung cancer 1998; 20: 31–35

[12] Jeremic B, Shibamoto Y, Milicic B, et al. External beam radiation therapy alone for loco-regional recurrence of non-small cell lung cancer after complete resection. Lung cancer 1999; 23: 135–142

[13] Shaw EG, Brindle JS, Creagan ET, Foote RL, Trastek VF, Buskirk SJ. Locally recurrent non-small cell lung cancer after complete surgical resection. Mayo Clin Proc 1992; 67: 1129–1133

[14] Emami B, Graham MV, Deedy M, Shapiro S, Kucik N. Radiation therapy for intrathoracic recurrence of non-small cell lung cancer. Am J Clin Oncol 1997; 20: 46–50

[15] Perez CA, Pajak TF, Rubin P, et al. Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Cancer 1987; 59: 1874–1881

[16] Le Chevalier T, Arriagada R, Quoix E, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer: First analysis of a randomized trial in 353 patients. J Natl Cancer Inst 1991; 83: 417–423

[17] Dillman RO, Herndon J, Seagren SL, Eaton WL, Green MR. Improved survival of stage III non-small-cell lung cancer: Seven-year follow-up of Cancer and Leukemia Group B (CALGB) 8433 trial. J Natl Cancer Inst 1996; 88: 1210–1215

[18] Sause WT, Scott C, Taylor S, et al. Radiation Therapy Oncology Group (RTOG) 88–08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. J Natl Cancer Inst 1995; 87: 198–205

Lung Cancer (2003) 41, 303–309

ELSEVIER

LUNG CANCER
IASLC

www.elsevier.com/locate/lungcan

Histopathological evaluation of fluorescence bronchoscopy using resected lungs in cases of lung cancer

Norihiko Ikeda[a,*], Toshimitsu Hiyoshi[a], Masatoshi Kakihana[a], Hidetoshi Honda[a], Yasufumi Kato[a], Tetsuya Okunaka[a], Kinya Furukawa[a], Takaaki Tsuchida[a], Harubumi Kato[a], Yoshiro Ebihara[b]

[a] *First Department of Surgery, Tokyo Medical University, 6-7-1, Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan*
[b] *Second Department of Pathology, Tokyo Medical University, Tokyo, Japan*

Received 17 February 2003; received in revised form 8 April 2003; accepted 10 April 2003

KEYWORDS
Autofluorescence bronchoscopy;
Dysplasia;
Early cancer;
Lung cancer

Summary Objective evaluation of the performance of autofluorescence bronchoscopy based on analysis of thin sections of the bronchus of resected lungs was performed and compared with the results of preoperative autofluorescence bronchoscopy. Conventional bronchoscopy and autofluorescence bronchoscopy were performed prior to surgery for lung cancer. Thin sections of the bronchus were obtained from the resected specimens. The thin sections were pathologically analyzed and the diagnostic accuracy of endoscopy was calculated. The subjects were 30 consecutive operable lung cancer cases who received white light and autofluorescence bronchoscopy before operation. A total of 163 thin sections of the bronchi in the resected lungs were made. The sensitivity of white light bronchoscopy for cancer was 90 and 31% for dysplasia. The respective figures for autofluorescence bronchoscopy were 97 and 50% for cancer and dysplasia. The specificity of white light and autofluorescence was 88 and 84%, respectively. The diagnostic accuracy of autofluorescence bronchoscopy was objectively confirmed. Autofluorescence examination showed better sensitivity for cancerous/precancerous lesions and the evaluation of the extent of cancer invasion was accurate.

1. Introduction

Lung cancer is a solid tumor with poor prognosis, mainly due to its progressive nature as well as the fact that most lung cancer cases are detected at an advanced stage. However, favorable prognosis may be expected if lung cancer is detected and treated at an early stage, especially in the in situ stage. Also these types of early cancers can be treated by minimally invasive methods, such as endoscopic photodynamic therapy (PDT) [1,2], brachytherapy [3] and so on. Advances in endoscopy and the expanding prevalence of sputum cytology have helped to increase the detection of central type

*Corresponding author. Tel.: +81-3-3342-6111x5072; fax: +81-3-3349-0326.
E-mail address: ikeda@wd5.so-net.ne.jp (N. Ikeda).

0169-5002/03/$ - see front matter © 2003 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/S0169-5002(03)00231-9

early lung cancer in number, but these lesions usually show only subtle changes of the bronchial mucosa [4] and are, therefore, sometimes difficult to localize by conventional bronchoscopy [5]. Woolner showed that the finding rate of carcinoma in situ in patients with abnormal sputum cytology findings was only 29% [5]. It is not very difficult to detect early lesions which are located at a bronchial bifurcation and possessing a polypoid or nodular appearance. However, if slightly edematous change is located at sites other than bifurcations, it is difficult to detect such lesions because the only findings may be loss of luster or subtle granular change of the mucosa [4]. Sato reported that a total of 527 bronchoscopic sessions were needed to diagnose 180 patients with 200 occult cancers [6]. To improve the detection rate of early bronchial lesions, fluorescence diagnosis has been investigated and used clinically in several facilities [6–13]. The principle of this diagnostic procedure is that normal bronchial tissue emits green autofluorescence (500–600 nm) excited by blue light, while tumor or dysplasia lack green autofluorescence because of differences in tissue architecture and autofluorescence fluorophores [6,14,15]. Lam et al. developed the Lung Imaging Fluorescence Endoscope (LIFE, Xillix Technology, Richmond, Canada) which employs a helium–cadmium laser as an excitation light source and the autofluorescence generated by the tissue is amplified by the highly-sensitive CCD camera. By means of a sophisticated algorithm of the analysis of reflected light, a real time fluorescence image is displayed on the monitor in pseudo-color [14,15]. Also autofluorescence diagnosis is reported to be useful in localizing the lesions of cases with abnormal sputum cytology findings as well as deciding the resection line before lung cancer operation [8].

Several clinical trials proved the usefulness of autofluorescence bronchoscopy [6–10,12,13] in detecting early cancer and preneoplastic lesions. All the reports highly evaluated the performance of autofluorescence diagnosis based on the correlation between endoscopic findings and pathological results of biopsy specimens. Sensitivity and specificity were calculated based on the endoscopic findings and biopsy results of areas with abnormal fluorescence findings and areas with normal fluorescence (control biopsy). The main purpose of this study was to objectively evaluate the performance of autofluorescence bronchoscopy. The whole bronchial tree should be examined to obtain unbiased sensitivity and specificity. We analyzed the whole bronchus of lungs resected due to lung cancer by making continuous thin sections of the bronchi. Therefore, only lung cancer patients who received surgery as well as preoperative white light and fluorescence bronchoscopy were studied.

2. Material and methods

2.1. Patients

A total of 30 consecutive subjects who received both an operation for lung cancer as well as preoperative fluorescence endoscopy with the LIFE system were studied (Table 1).

All 20 men and ten women (mean age, 67, range 42–78) were smokers or ex-smokers. There were 11 cases in which the tumors were visible endoscopically, but in the other 19 cases, tumors could not be recognized due to their peripheral location. All patients were current or former smokers.

The operation method was lobectomy in 25 cases, pneumonectomy in four cases and sleeve lobectomy in one case. There were ten squamous cell carcinomas, 18 adenocarcinomas, one large cell carcinoma and one metastatic pulmonary tumor from colon cancer.

2.2. Endoscopy

White light bronchoscopy (Olympus BF-20, Olympus, Co. Ltd., Tokyo, Japan) was performed followed by fluorescence examination using the LIFE system. With this system, normal sites show green color images but abnormal sites lack this green fluorescence and show dark images. Two or three experienced bronchoscopists performed LIFE procedures and judged the image. We employed only two criteria of LIFE images, normal or abnormal. The bronchoscopy was performed under local anesthesia as a part of preoperative examination.

Table 1 Characteristics of cases

Location of primary lesions	
Central	11
Peripheral	19
Histologic type	
Squamous cell carcinoma	10
Adenocarcinoma	18
Large cell carcinoma	1
Metastatic carcinoma	1
Surgical procedure	
Lobectomy	25
Pneumonectomy	4
Sleeve lobectomy	1

Number of cases, 30; number of slices, 163 (range 4–12 per case).

All procedures were videotaped and areas with abnormal findings were recorded and biopsied. However, the biopsies taken from the lungs to be preserved was out of the scope of the present study. Control biopsies or random sampling were not performed.

2.3. Pathology

The resected lungs were immediately carried to the bronchoscopic suite and white light as well as fluorescence examination was performed once more by the same bronchoscopists and pathologists. This procedure was performed to help pathologists to create topographically accurate three dimensional structures of the bronchus and be able to recognize the precise location of suspected areas. We did not change the judgement of bronchoscopic image in this procedure. Resected lungs were then carried to the pathology department and fixed in formalin in routine manner. After fixation, 3 mm slices of the bronchi were made; lobar and segmental bronchi through subsegmental bifurcations in every case and the main bronchus also in pneumonectomy cases. The sections were stained with hematoxylin–eosin staining and interpreted by an experienced pathologist (Y.E.). The pathological results were basically classified into five categories based on WHO criteria; invasive cancer, early cancer, dysplasia, inflammation and normal. The pathological results were compared with preoperative endoscopic findings and the diagnostic accuracy rate was calculated.

3. Results

A total of 163 thin sections (3 mm thick) of the bronchus were made from the resected lungs of 30 subjects. The diagnosis of each section was derived from the highest degree of abnormality observed: normal in 97, inflammation in 19, squamous dysplasia in 16 and cancer in 31, respectively. Table 2 shows the pathological results of the lesions (sections).

Table 2 Pathological diagnosis of each slice of the bronchus

Normal	97 slices
Chronic inflammation	19
Dysplasia	16
Cancer	31
	163 slices

Sensitivity, specificity and positive predictive value were calculated as shown below.

$$\text{Sensitivity} = (\text{True Positive}/\text{True Positive} + \text{False Negative}) \times 100(\%)$$

$$\text{Specificity} = (\text{True Negative}/\text{True Negative} + \text{False Positive}) \times 100(\%)$$

$$\text{Positive Prediction value} = (\text{True Positive}/\text{True Positive} + \text{False Positive}) \times 100(\%)$$

Table 3 shows the diagnostic rate of the endoscopy and pathological results.

3.1. Cancer

There were 31 sections proven to be cancer. White light bronchoscopy yielded a correct diagnosis in 28 of these 31 sections (90%) while the LIFE system was correct in 30 of 31 (97%) sections. The sensitivity of LIFE was better than that of conventional bronchoscopy but there was no statistical difference (χ^2-test, $P = 0.61$).

3.2. Dysplasia

A total of 16 slices were considered to show dysplasia. Conventional bronchoscopy correctly identified five of 16 slices (31%) while the fluorescence identified eight of 16 (50%). However, there was no statistical difference between two methods ($P = 0.28$). Table 4 shows the clinicopathological characteristics of 16 lesions of squamous dysplasias. Dysplasias located in bronchial bifurcations tended to be detected more easily than those located in other sites.

3.3. Inflammation/normal

In 116 slices diagnosed as inflammation or normal, white light bronchoscopy and fluorescence endoscopy correctly diagnosed 102 and 97 slices, which means the specificity of white light and fluorescence was 88 and 84%, respectively. The

Table 3 Endoscopic findings and pathological results

	WL (%)	AF (%)
Sensitivity (cancer)	90	97
Sensitivity (dysplasia)	31	50
P.P.V. (cancer + dysplasia)	70	67
Specificity	88	84

WL, White light bronchoscopy; AF, Autofluorescence bronchoscopy; P.P.V., Positive predictive value.

Table 4 Clinicopathological characteristics of squamous dysplasias in this study

	Overlooked		Detected	
	WL	AF	WL	AF
Location				
Bifurcation	2	0	4	6
Non-bifurcation	10	8	0	2
Degree of atypia				
Mild	9	7	0	2
Moderate	2	1	3	4
Severe	0	0	2	2

WL, white light; AF, autofluorescence.

main reasons for false positive diagnosis with the fluorescence examination were basal cell hyperplasia and thickened basement membrane due to chronic inflammation.

3.4. Case presentation

3.4.1. Case 1 (Figs. 1 and 2)

Fig. 1 shows the white light and fluorescence endoscopic findings of the right upper lobe bronchus of a 74-year-old man. He had received PDT due to central type early cancer in right B3 and complete remission was obtained. Local recurrence occurred at the same site 24 months after PDT and right upper lobectomy was performed. Fluorescence endoscopy using the LIFE system was performed preoperatively, and cold spots were found at the site of the tumor in right B3 and the bifurcation of B1a and B1b. Histological analysis of the resected lung revealed squamous cell carcinoma originating in the orifice of right B3 and also small skip lesions at the bifurcation of B1a and B1b and the orifice of right B2. The skip lesion in B1 was preoperatively identified only by fluorescence endoscopy, it was not recognizable by white light endoscopy. The other lesion at the orifice of B2 was not visible by either white light or fluorescence examination. The pathology of these three lesions and the "map" of the extent of the lesion is shown in Fig. 2.

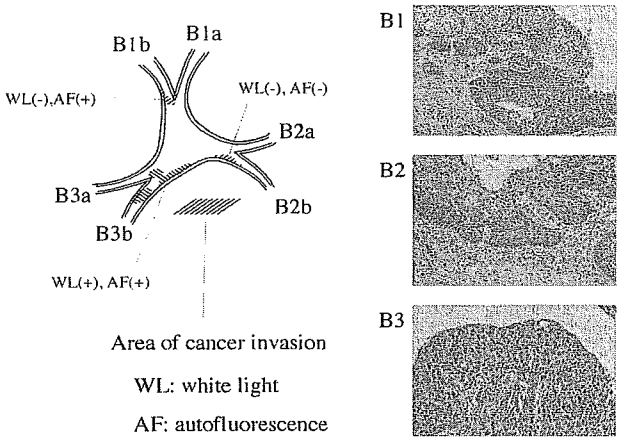

Fig. 2 A map of tumor extent and endoscopic findings. The lesion in B1 was diagnosed only by fluorescence examination. The lesion in B2 was diagnosed neither by white light bronchoscopy nor fluorescence bronchoscopy.

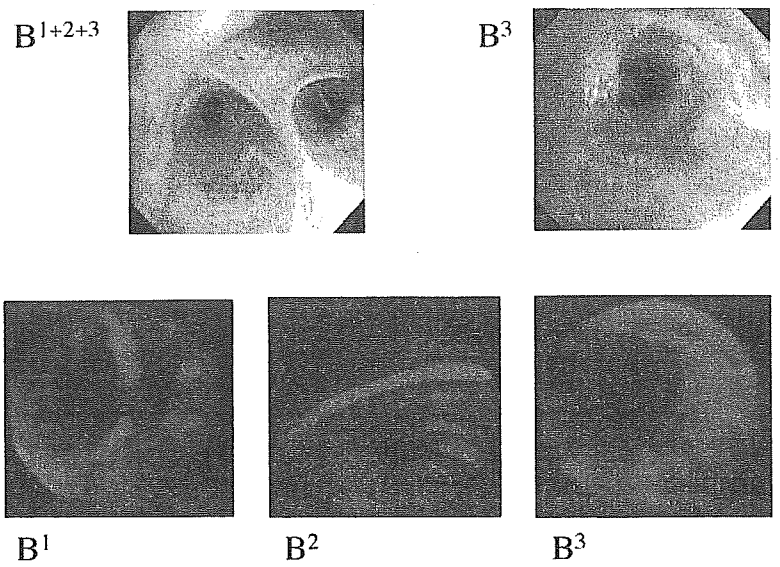

Fig. 1 White light and fluorescence endoscopic findings of the right upper lobe bronchus of a 74-year-old man. A recurrent tumor was observed in the orifice of right B3. Fluorescence examination revealed abnormal findings in B1 (bifurcation of B1a and B1b) and B3, however, normal image was observed in B2.

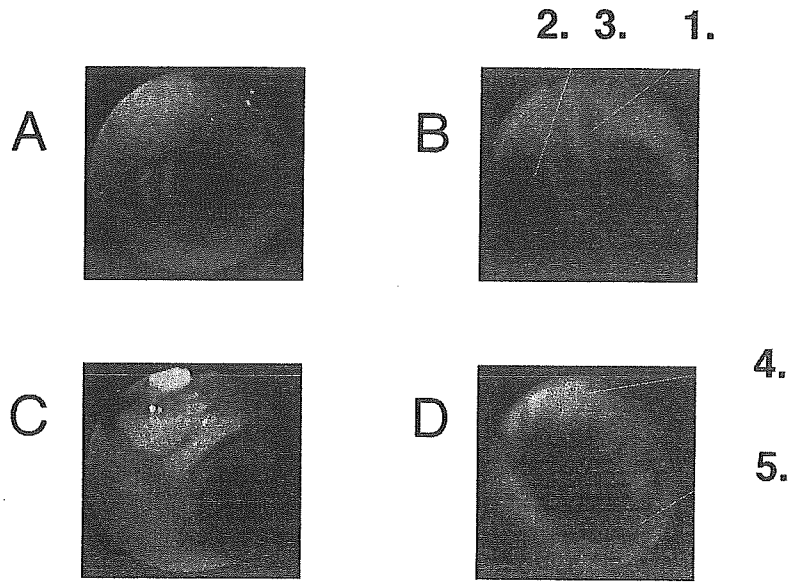

Fig. 3 White light and fluorescence endoscopic findings of the left basal bronchus of a 55-year-old man. A protruding tumor was observed in the orifice of left B6. The numbers indicated (1–5) correspond to the section slices in Fig. 4.

3.4.2. Case 2 (Figs. 3 and 4)

Fig. 3 shows the endoscopic findings of the left lower lobe of a 55-year-old man. This patient was referred due to an abnormal shadow on chest X ray located in left S6. White light bronchoscopy revealed a protruding tumor in left B6 and biopsy revealed squamous cell carcinoma. Left lower lobectomy was performed and the pathological stage was stage Ib. Fluorescence examination was performed before surgery and cold spots were detected at the site of the tumor in B6 and at the orifice of the basal bronchus. Fig. 4 demonstrated the results of the fluorescence endoscopy and the pathological findings. The numbers indicated in Fig. 3 correspond to the section slices in Fig. 4. Pathology revealed the site and extent of the tumor was correctly diagnosed by preoperative fluorescence examination. Two small areas of dysplasia were found by histological analysis of the resected specimen (slices 1 and 4 in Fig. 4). One of these lesions (area 1 in Fig. 3) was diagnosed as abnormal by LIFE before operation, however, the other site (area 4 in Fig. 3) could not be identified by LIFE (false negative). The cold spot

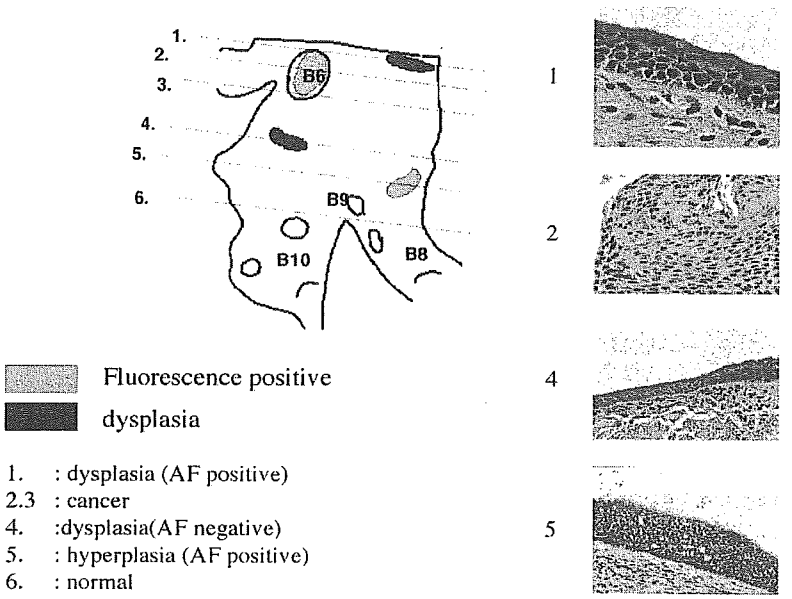

Fig. 4 The map demonstrated the relationship between endoscopic findings and pathological results. The number (1–6) shows the section slices.

at the orifice of the basal bronchus (area 5 in Fig. 3) was histologically recognized to be hyperplasia (false positive).

Precise evaluation of endoscopic findings and pathological results was performed in all other cases in the same manner as done in the representative two above cases.

4. Discussion

The increase in the number of lung cancer deaths is mainly because it is detected at a late stage. However, central type early stage lung cancer has shown a good response to endoscopic treatment [1–3]. Sputum cytology is the primary method to detect central type early stage lung cancer, however, such lesions may show only subtle changes in the bronchial mucosa making it difficult to detect the lesions endoscopically [4,5]. In order to reduce the mortality rate of lung cancer a new approach is needed to detect the disease at an early stage. Fluorescence diagnosis of the bronchial tree was initially reported by Lam et al. and this diagnostic procedure (LIFE system) has been adopted at several sites in recent years, resulting in increased detection rates of cancerous or precancerous lesions by conventional bronchoscopy plus additional fluorescence examination [6–10,12,13]. The mechanism of fluorescence diagnosis has not yet been fully defined. It is probable that extracellular matrix, internal fluorophores and blood flow influence the autofluorescence captured by fluorescence endoscopy [6,14–16]. Also, it has been reported that accumulative genetic abnormalities result in differences in autofluorescence patterns [17]. Lam reported that the relative sensitivity of white light endoscopy and LIFE versus white light alone was 6.3 for intraepithelial neoplastic lesions [7]. Venman reported that LIFE is slightly more sensitive (89%) than white light alone (78%) in the diagnosis of dysplasia and CIS [13]. However, in their report the specificity and positive predictive value of LIFE was lower (61 and 14%) than white light bronchoscopy (88 and 32%). We found that the sensitivity for cancer and dysplasia detection was 72% by white light and 95% by the LIFE system. The positive predictive value of white light endoscopy and the LIFE system were 64 and 73% [9]. On the contrary, Kurie et al. reported low sensitivity in detecting preneoplastic bronchial lesions using the LIFE system [11]. This may be due to all subjects in their study were not high risk individuals. We believe lung cancer patients have high risk for synchronous/metachronous multiple cancers. Considering the concept of field cancerization and the fact that genetic disorders can be observed in ostensibly normal bronchial tissue of lung cancer patients, we perform autofluorescence bronchoscopy for surgical evaluation as well as for screening intraepitheklial lesions at other sites. The sensitivity and specificity of fluorescence diagnosis were calculated by correlation with biopsy histology previously. However, we postulated that it should be necessary to survey not just the target lesion but the whole bronchial tree in order to obtain an unbiased evaluation of the sensitivity and specificity. No study to date has analyzed the whole bronchial tree in detail. We made sagittal continuous thin sections of the bronchus of resected specimens and compared the fluorescence findings and pathological results by making a bronchial "map". In interpreting endoscopically harvested biopsy specimens, diagnostic discrepancy among pathologists is sometimes unavoidable, especially when the specimen is small or crushed [18]. However, interobserver disagreement might be less using histopathological diagnosis of resected specimens. The sensitivity for cancer was 90% with conventional white light bronchoscopy and 97% with the LIFE system. For dysplasia detection, the sensitivity was 31% with white light and 50% with the LIFE system. The performance of fluorescence diagnosis was superior to that of conventional endoscopy in detecting intraepithelial lesions, but no statistical difference was obtained. The total number of dysplastic lesions was only 16, which is insufficient to yield a stastistical difference. The materials of this study were all obtained from operable lung cancer cases. The cohort which received fluorescence bronchoscopy in a previous report contained large number of cases with abnormal sputum cytology findings and high risk heavy smokers, therefore, the incidence of dysplasia was relatively high. A total of nine sites (one cancer and eight dysplasia) were not detected by the LIFE system. The overlooked cancer lesion was a tiny skip lesion in the vicinity of CIS in the right upper lobe. We speculate that the lesion may have been located at a site where the illumination by the laser light was insufficient. There might be several reasons for overlooking dysplastic lesions by autofluorescence diagnosis: the location and size of the lesions, histological interpretation of the pathologists, diagnostic ability of the device, or differences in the biological characteristics of each dysplastic lesion. The dysplastic lesions which could not be detected by LIFE were all very small (1–2 mm in maximum dimension) and tended to be located in the membranous portion of the bronchus, thus the lesions might

have been hidden in the shade of longitudinal folds. Also seven of the eight dysplastic lesions were mild atypia and the other was mild to moderate atypia. There is, therefore, the possibility that the overlooked dysplasias might have had different biological characteristics and different optical properties. The characteristics of the autofluorescence may be influenced by various fluorophores (flavin derivatives, NADH, etc.), extracellular matrix (collagen, fibronectin, etc.) and blood flow. Molecular genetic changes such as cumulative gene losses during the progression of precancerous lesions have been reported [17,19]. The fluorescence image may reflect some molecular events, which are not observed microscopically. Further investigations are needed to determine the reason for these false negatives. However, the histological analysis of the resected lung confirmed the improvement of diagnostic accuracy of cancer and dysplasia detection by fluorescence diagnosis compared with that of conventional bronchoscopy. The reasons for false positives in fluorescence diagnosis were mainly due to the thickened mucosal and submucosal layer due to chronic inflammation, such as basal cell hyperplasia. Autofluorescence emission was blocked by the thickened layer of the bronchus in subjects with chronic inflammation. For this reason, the extent of the tumor might be overestimated under fluorescence if there is chronic inflammation in the vicinity of the tumor, however, the pathology of the resected lung revealed the extent of the tumor was correctly diagnosed preoperatively by fluorescence examination.

This study attempted an unbiased evaluation of the accuracy of fluorescence bronchoscopy by precise histological analysis of the resected lungs. The authors concluded that autofluorescence diagnosis is an acceptable method in conjunction with conventional bronchoscopy to increase the detection of subtle cancer and precancerous lesions of the bronchus.

Acknowledgements

The authors thank Professor J.P. Barron, International Medical Communications Center, Tokyo Medical University, for his support in reviewing this manuscript. This study was partly supported by a grant from the Japanese Foundation for Research and Promotion of Endoscopy.

References

[1] Cortese DA, Edell ES, Kinsey JH. Photodynamic therapy for early stage squamous cell carcinoma of the lung. Mayo Clin Proc 1977;72:595–602.
[2] Kato H, Okunaka T, Shimatani S, et al. Photodynamic therapy for early stage bronchogenic carcinoma. J Clin Laser Med Surg 1996;14:235–8.
[3] Sutedja G, Postmus PE. Review article. Bronchoscopic treatment of lung tumors. Lung Cancer 1994;11:1–7.
[4] Kato H, Horai T. A color atlas of endoscopic diagnosis in early stage lung cancer. Wolfe: Aylesbury, UK, 1992:35.
[5] Woolner LB, Fontana RS, Cortese DA, et al. Roentgenographically occult lung cancer pathologic findings an frequency of multicentric during a 10 year period. Mayo Clin Proc 1983;59:435–66.
[6] Sato M, Saito Y, Usuda K, Takahashi S, Sagawa M, Fujimura S. Occult lung cancer beyond bronchoscopic visibility in sputum cytology positive patients. Lung Cancer 1998;20:17–24.
[7] Lam S, Kennedy T, Unger M, et al. Localization of bronchial intraepithelial neoplastic lesions by fluorescence bronchoscopy. Chest 1998;113:696–702.
[8] Ikeda N, Honda H, Katsumi T, et al. Early detection of bronchial lesions using Lung Imaging Fluorescence Endoscope. Diagn Ther Endosc 1999;5:85–90.
[9] Kato H, Imaizumi T, Aizawa K, et al. Photodynamic diagnosis in respiratory tract malignancy using an excimer dye laser system. J Photochem Photobiol 1990;6:189–96.
[10] Kakihana M, Kim K, Okunaka T, et al. Early detection of bronchial lesions using system of autofluorescence endoscopy (SAFE) 1000. Diagn Ther Endosc 1999;5:99–104.
[11] Kurie JM, Lee JS, Morice RC, et al. Autofluorescence bronchoscopy in the detection of squamous metaplasia and dysplasia in current and former smokers. J Natl Cancer Inst 1998;90:991–5.
[12] Thiberville L, Sutedja G, Vermijlen P. A multicenter European study using the light induced fluorescence endoscopy system to detect precancerous lesions in high risk individuals. Eur Resp J 1999;14:2475.
[13] Venmans BJ, Boxem TJ, Smit EF, et al. Results of two years experience with fluorescence bronchoscopy in detection of preinvasive bronchial neoplasia. Diagn Ther Endosc 1999;5:77–84.
[14] Qu J, MacAulay C, Lam S, et al. Laser-induced fluorescence spectroscopy at endoscopy: tissue optics, Monte Carlo modeling and in vivo measurements. Optical Eng 1995;34:3334–43.
[15] Hung J, Lam S, LeRiche J, et al. Autofluorescence of normal and malignant bronchial tissue. Laser Surg Med 1991;11:99–105.
[16] Richards-Kortum R, Sevick-Muraca E. Quantitative optical spectroscopy for tissue diagnosis. Annu Rev Phys Chem 1996;47:555–606.
[17] Thiberville L, Payne P, Vielkinds J, et al. Evidence of cumulative gene losses with progression of premalignant epithelial lesions to carcinoma of the bronchus. Cancer Res 1995;55:5133–9.
[18] Venmans BJ, Linden van der JC, Elbers JRJ, et al. Observer variability in histopathological reporting of bronchial biopsy specimens: influence on the results of autofluorescence bronchoscopy in detection of bronchial neoplasia. J Bronchol 2000;7:210–4.
[19] Gazdar A, Park I, Sood S, et al. Clonal patches of molecular changes in smoking damaged respiratory epithelium. Lung Cancer 2000;29:S7.

A Clinicopathological Study of Resected Adenocarcinoma 2 cm or Less in Diameter

Norihiko Ikeda, MD, PhD, Junichi Maeda, MD, Koichi Yashima, MD, Masahiro Tsuboi, MD, Harubumi Kato, MD, PhD, Soichi Akada, MD, PhD, and Shinya Okada, MD, PhD

Departments of Thoracic Surgery, Radiology, and Pathology, Tokyo Medical University, Tokyo, Japan

Background. The biological behavior of small adenocarcinoma is different in each patient and these are especially enormous differences when evaluating solid tumors and nonsolid tumors.

Methods. A total of 159 adenocarcinomas 2 cm or less in diameter were studied. Several clinicopathological factors were retrospectively analyzed.

Results. The diameter of the primary tumors was less than 1 cm in 47 patients, 1–1.5 cm in 49 patients, and 1.5–2 cm in 63 patients, respectively. Almost all patients (147) were pathologic N0 and there were 12 node-positive patients (7.5%). Lymph-node involvement was observed in 1 patient with a tumor diameter measuring less than 1 cm and in 11 patients with a tumor diameter measuring 1–2 cm. According to Noguchi' s classification, 33 patients belonged to class A or B, 71 patients belonged to class C, and 55 patients belonged to class D, E, or F. The ratio of ground-glass opacity (GGO) area in the main tumor in high resolution computed tomography was classified into two groups with a threshold of 50%. There were 44 patients with a GGO ratio of equal to or greater than 50%, none of which indicated lymph-node metastasis or tumor recurrence during follow-up (5-year survival = 100%). On the contrary among 115 patients with a GGO ratio less than 50%, lymph-node involvement was indicated in 12 patients (10.4%) and the 5-year survival rate was 83.9%.

Conclusions. The biological malignancy of small adenocarcinomas might be accurately evaluated by the proportion of GGO area as well as the Noguchi classification.

(Ann Thorac Surg 2004;78:1011–6)

Lung cancer is the greatest cause of cancer-related death in the world because most lung cancers are detected at a late stage and curative treatment is not an option. Nevertheless a cure rate of greater than 70% was obtained in completely resected patients of stage I cancer [1]. Prevention and early detection are thus essential with regard to the reduction of lung cancer mortality. Adenocarcinoma is the most common type of lung cancer arising from the peripheral lung parenchyma. Chest x-ray surveys have been considered useful for early detection. However if the lesions are located in a "dead angle" on the chest roentgenogram film, such as behind the aorta or heart, abnormalities may be overlooked. Bronchioloalveolar carcinoma (BAC) seldom reveals abnormalities on chest roentgenogram because it grows without destroying alveolar structure [2]. Helical computed tomography (CT) screening has greatly increased the sensitivity of cancer detection compared with that of conventional chest roentgenogram screening [3–7]. A prospective randomized trial comparing the lung cancer mortality rate of a CT screening group with that of a conventional chest roentgenogram screening group has been conducted by the National Cancer Institute [8]. In this respect, the biggest issue facing thoracic surgeons is the treatment strategy for small cancers detected by CT screening, including the possibility of limited resection. BAC is known to exhibit a relatively nonaggressive nature, therefore a favorable outcome can be expected after curative operation [2, 9–12]. However patients with solid images on chest CT tend to have invasive adenocarcinomas and their survival is definitely worse than that of BAC [9–11]. Pathologic classification of the tumor is essential regarding the evaluation of the aggressiveness of each patient [2] but postoperative pathologic findings cannot exhibit a strong impact on the choice of treatment.

There are several reports indicating that the ratio of the size of ground-glass opacity (GGO) and that of consolidation on high resolution CT (HRCT) is strongly related to the stage and prognosis of the cancer [10, 13–15]. Lung cancers with a large GGO component tend to be BAC or minimally invasive adenocarcinomas that exhibit favorable prognoses [10, 13–15]. If a definition of peripheral early cancer could be established, it would be useful with regard to selecting optimal treatment for individual patients. For this purpose we retrospectively analyzed clinicopathological features of adenocarcinomas with a diameter of 2 cm or less resected in our hospital between 1997–2002.

Patients and Methods

Patients

A total of 983 lung cancer operations were performed from January 1997 to December 2002 at the Department

Accepted for publication March 15, 2004.

Address reprint requests to Dr Ikeda, 6-7-1, Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan; e-mail: ikeda@wd5.so-net.ne.jp.

Published by Elsevier Inc

0003-4975/04/$30.00
doi:10.1016/j.athoracsur.2004.03.048

Ann Thorac Surg
2004;78:1011–6

Table 1. Patient Characteristics

Character	
Age	
Average	63
Minimum	40
Maximum	84
Sex	
Male	67
Female	92
Smoking habit	
Non-smoker	89
Smoker	70
Operative procedure	
Lobectomy	112
Segmantectomy	20
Wedge resection	27

of Thoracic Surgery, Tokyo Medical University Hospital (Tokyo, Japan). Among these, there were 168 patients with peripheral adenocarcinomas less than 2 cm in diameter as well as a total of 159 patients who had undergone high-resolution computed tomography (HRCT) and in whom complete records were available for study (Table 1). There were 67 men and 92 women ranging in age from 40–84. There were 89 nonsmokers and 70 smokers. The primary lesions were detected by chest x-ray in 115 patients: detection was determined by mass survey or private general check-up in 81 patients, follow-up for other diseases in 18 patients, and respiratory symptoms in 16 patients. The other 44 patient's lesions were detected by chest CT performed by mass survey program or private general check-up.

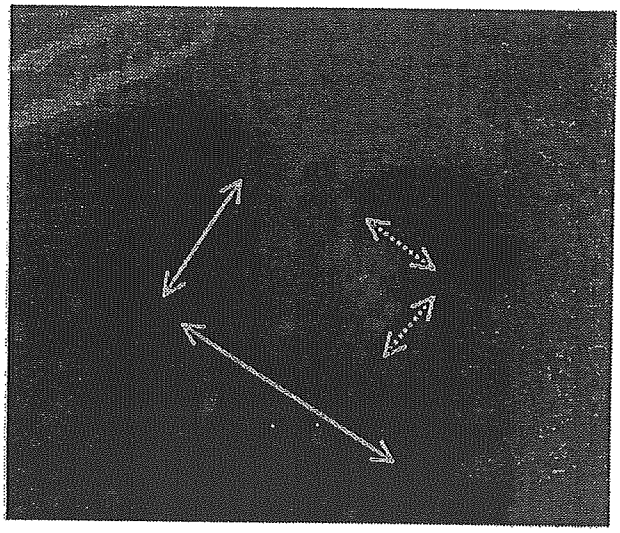

Fig 1. Thin section computed tomographic scan of lung cancer depicting solid attenuation and ground-glass opacity (GGO). The largest area of tumor (solid line) *and solid attenuation* (dotted line) *were decided based on this film. The proportion of GGO area to the entire tumor was defined; GGO ratio = (maximum GGO − maximum consolidation)/maximum GGO. Max GGO* (solid arrow); *Max consolidation* (dotted arrow).

All patients underwent a physical examination and blood examination, respiratory function test, electrocardiogram, and chest radiography. Also, all patients received helical CT of the chest preoperatively with 10-mm thick continuous sections. HRCT images with 1–2 mm slices of the primary tumors were then performed to obtain the precise findings of GGO and consolidation of the tumors. Histologic typing was diagnosed based upon the classification of the World Health Organization (WHO) and we also classified all of the patients into six subtypes using the Noguchi classification. The staging of patients was determined by the thoracic wall, node involvement, and metastases (TNM) classification of the International Union Against Cancer (UICC).

Lobectomy combined with systemic mediastinal lymph-node dissection was performed in 112 patients and limited surgery was performed in 47 patients. Of these 47 patients, 37 received intentionally limited operation because of the nonaggressive appearance on HRCT and the remaining 10 patients because of impaired condition. Segmentectomy with mediastinal sampling was performed in 27 patients and wedge resection without nodal dissection was performed in 20 patients. All patients that underwent wedge resection indicated pure GGO or enormously GGO-dominant findings on HRCT as well as being clinically node negative.

CT Findings

In this study the ratio of the size of solid attenuation to that of GGO was extensively analyzed. GGO was defined as a hazy increase in lung attenuation without obscuration of the underlying vascular marking. At least two experienced chest surgeons and radiologists reviewed the hard-copy films of HRCT and determined the maximal area of GGO and tumor. Discrepancies between reviewers were resolved by consensus. The ratio area of GGO to the area of primary tumor was calculated as illustrated in Figure 1. Patients were divided into two groups: those with a GGO ratio greater than 50% and those with a GGO ratio less than 50%.

Pathology

Resected lungs were fixed in formalin and stained by hematoxylin and eosin staining in a routine manner and also stained with elastica van Gieson. Experienced pathologists diagnosed the subtypes of primary tumors according to the Noguchi classification as well as the nodal status. The Noguchi classification is presented in Table 2. Types A and B are considered to be noninvasive cancers and types D, E, and F are considered to be invasive cancer.

Statistics

We examined the relation of the proportion of GGO area to maximal tumor size, stage, Noguchi classification, and other prognostic factors. The χ^2 test using StatView 5.0 (SAS Institute Inc., Cary, NC) was performed and the differences were considered to be statistically significant

Table 2. Tumor Size and Nodal Status

Tumor Size	N0	N1	N2
1.0 cm or less (n = 47)	46	0	1
1.0–1.5 cm (n = 49)	46	1	2
1.5–2.0 cm (n = 63)	55	2	6

when the p value was less than 0.05. All patients were periodically examined and the average length of follow-up was 40 months. The 5-year survival curve was obtained using the Kaplan–Meier method.

Results

A total of 159 patients were studied. The size was classified into three categories: 1 cm or less, 1–1.5 cm, and 1.5–2 cm. There were 47, 49, and 63 patients, respectively. There were 147 pathologic N0 patients and lymph-node metastasis was recognized in 12 patients (7.5%); N1 in 3 patients and N2 in 9 patients. Table 3 lists the rate of lymph-node involvement according to tumor size. Lymph-node involvement was not indicated in 98% of patients who had a tumor size of 1 cm or less, however even in patients with tiny tumors, 2% indicated N2 disease. In patients who had a tumor size of 1 and 1.5 cm, 94% indicated no metastasis but 6% were either N1 or N2. In patients who had a tumor size of 1.5 and 2 cm, lymph-node involvement was recognized in 13%.

In this study the proportion of the size of GGO to that of the tumor was extensively analyzed. We divided patients into two categories according to how much of the lesion consisted of GGO findings. According to these criteria, 44 tumors consisted of greater than 50% of GGO and 115 tumors consisted of less than 50% of GGO. Patients with a GGO ratio of greater than 50% indicated no lymph-node metastases. On the contrary all node-positive patients indicated a GGO ratio of less than 50% (Table 3). The relationship between the proportion of GGO area on HRCT and the Noguchi classification is indicated in Table 4.

Twenty-five out of 44 patients (76%) of types A and B indicated a GGO component of greater than 50% on HRCT. Seventeen out of 71 patients (24%) of type C indicated greater than 50% GGO and the remaining 54 patients (76%) indicated less than 50% GGO. Fifty three out of 55 patients (96%) of types D, E, and F tumors indicated less than 50% GGO. A favorable correlation between CT findings and the Noguchi classification was recognized.

Table 3. GGO Area and T,N Status

GGO%	$T \leqq 1$	$1 < T \leqq 5$	$1.5 < T \leqq 2$	
50 ↑	18	16	10	44
50 ↓	29 (1)[a]	33 (3)[a]	53 (8)[a]	115 (12)[a]

[a] The number in parentheses corresponds to the number of node-positive cases.

GGO = ground-glass opacity.

Table 4. GGO Area and Noguchi Classification

GGO%	A, B	C	D, E, F	
50 ↑	25	17	2	44
50 ↓	8	54	53	115

GGO = ground-glass opacity.

The relationship between representative clinicopathological factors and the proportion of GGO area is indicated in Table 5. According to the χ^2 test, the ratio of GGO area to that of the tumor is related to the tumor size ($p = 0.0135$) and pathologic stage ($p = 0.04$). In particular a significant relationship was obtained regarding the pathologic features including Noguchi classification ($p = 0.0001$), vascular invasion, and lymphatic invasion .

Patients were followed-up in the outpatient clinic and periodically received blood examinations, chest roentgenogram, and chest CT. The median follow-up period for all patients was 40 months. The overall 5-year survival rate of patients studied was 88.0% (Fig 2), but it was 96.7% in patients with tumors less than 1 cm in diameter, 81.6% in patients with tumors between 1 and 1.5 cm, and 84.4% in patients with tumors between 1.5 and 2 cm (Fig 3).

The 5-year survival rate according to how much of the lesion consisted of GGO findings was also analyzed. In patients with tumors greater than 50% GGO, a 100% 5-year survival rate was obtained, but in patients with tumors less than 50% GGO an 83.9% 5-year survival rate was obtained (Fig 4)

The survival rate according to the Noguchi classification is illustrated in Figure 5. A 100% 5-year survival rate was obtained in types A and B, 97.4% in type C, and 67.1% in types D, E, and F, respectively, which was statistically lower than the results of types A, B, and C.

Comment

Because of the increasing widespread application of helical CT, the detected number of small lung peripheral nodules has enormously increased [3–7]. In addition the size of peripheral type adenocarcinomas has been smaller on average when they were detected. This has raised several issues: discerning how to discriminate

Table 5. Relationship Between Prognostic Factors and GGO Ratio on HRCT

Prognostic Factor	χ^2	p Value
Gender	0.162	0.687
Tumor size	8.616	0.0135
p stage		
I or II–IV	4.168	0.0412
Noguchi classification		
A, B, C or DEF	14.442	0.0001
Vascular invasion	6.76	0.0093
Lymphatic invasion	5.326	0.0206

GGO = ground-glass opacity; HRCT = high resolution computed tomography.

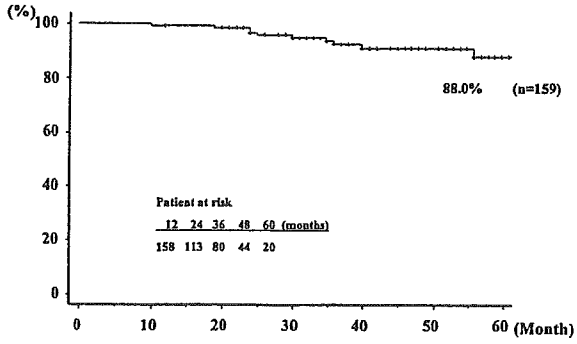

Fig 2. Five-year survival rate of adenocarcinoma less than or equal to 2 cm was 88.0%.

malignant from benign nodules, the usefulness of CT screening in diminishing lung cancer mortality, the optimal intervention in patients who have small nodules, and so on [16, 17]. The management of small cancers is a particular concern of thoracic surgeons, because some of these small cancers might be managed appropriately by limited resection. As previously reported adenocarcinoma tends to metastasize to the regional lymph nodes even if small in size. Nearly 20% of adenocarcinomas less than 2 cm in diameter were reported to be node positive and 5% of adenocarcinomas less than 1 cm were also considered as N1 or N2 disease [18–20]. The Lung Cancer Study Group failed to demonstrate positive results with regard to limited resection for clinical T1 lung cancers. The limited surgery group indicated a local recurrence rate of 5–6 times higher than the lobectomy group [21]. Thus lobectomy and locoregional lymph-node dissection have been recommended as standard lung cancer procedures. However if peripheral early cancer is properly defined, such patients could be managed by lesser resection, which would be useful with regard to decreasing the operative mortality and morbidity as well as enhancing the performance status of the patients.

In our study 12 out of 159 patients (7.5%) exhibited lymph-node metastasis and even tumors measuring 1 cm or less indicated lymph-node metastasis in 2% of patients. The 5-year survival rate did not indicate a statistically significant difference between the three groups

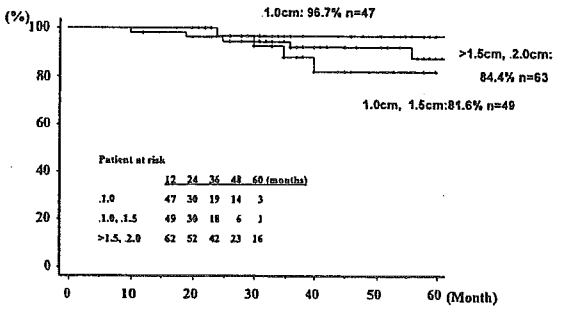

Fig 3. Five-year survival rate according to tumor size. Less than or equal to 1 cm = 96.7%, 1.0–1.5 cm = 81.6%, 1.5–2.0 cm = 84.4%.

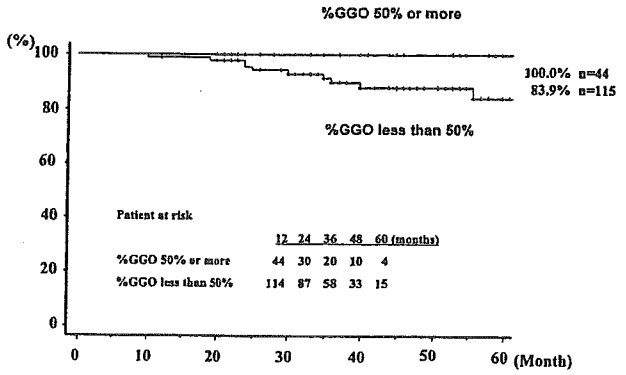

Fig 4. Five-year survival rate according to the proportion of ground-glass opacity (GGO) area. A GGO dominant patient indicated a 100% 5-year survival, whereas patients exhibiting a GGO area less than 50% indicated an 83.9% 5-year survival.

according to tumor size in this study. There are reports that 5%–8% of such tiny adenocarcinomas indicated lymph-node metastasis [18, 22]. Kondo reported 57 adenocarcinomas measuring 1 cm or less, none of which indicated lymph-node metastasis, and 49 revealed BAC without destructive growth that were categorized as nonaggressive tumors [23]. This demonstrates that the indications of limited surgery cannot be determined by size alone. In our study, 47 patients received limited resection. Out of these, mediastinal lymph node or sampling were performed in 20 patients and the rest of 27 patients received wedge resection without nodal dissection. Of these 27 patients stage migration may occur because nodal status was not evaluated pathologically. However these patients indicated pure GGO or overwhelmingly dominant GGO findings on chest CT as well as being clinically node negative. Such patients have been reported to be free from lymph-node metastasis [10, 12–15, 20] and recurrence was not observed in any of these patients by chest CT examination during follow-up.

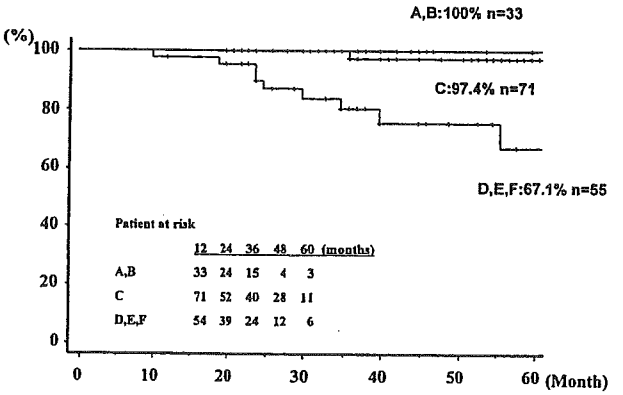

Fig 5. Five-year survival rate according to the Noguchi classification. Noguchi A, B indicated a 100% 5-year survival, type C indicated a 97.4% 5-year survival, and types D, E, and F, indicated a 67.1% 5-year survival, respectively.

Therefore we classified these patients as N0 in this study. Noguchi classified small adenocarcinomas into six categories (types A–F) and this classification indicated a favorable correlation with the biologically aggressive nature of the tumor [2]. Types A and B are localized BAC with or without foci indicating a collapse of alveolar structures that are recognized to be noninvasive. Types D, E, and F are poorly differentiated, tubular, papillary type, respectively, and are invasive. Pathologic analysis revealed that all type A and B patients were N0, however 25%–56% of type D, E, and F patients indicated lymph-node metastasis [2]. Many thoracic surgeons postulated that certain types of adenocarcinomas might be candidates for limited resection and have sought for criteria of "peripheral early cancer." The Noguchi classification is useful with regard to evaluating the aggressive nature in individual patients, but this criteria is based on postoperative pathologic findings and could not have a strong impact on the choice of treatment. Therefore we require criteria that are available preoperatively to define early minimally invasive cancers.

Increased amounts of collagenization or hyalinization microscopically detected in the central fibrotic focus in adenocarcinoma have been reported to influence the prognosis and the smaller the central fibrosis, the more favorable the prognosis [24, 25]. Suzuki reported that central fibrosis in a tumor corresponds to consolidation on HRCT. Thus the ratio of the area of GGO and that of consolidation seems to be strongly related to nodal status and stage [25].

In our study there were 12 N1 or N2 out of 159 patients, in all of whom the proportion of the area of GGO to the entire tumor was less than 50%. All patients with a ratio of GGO greater than 50% survived without recurrence during the follow-up period, although patients with GGO less than 50% indicated an 83.9% 5-year survival rate. The proportion of the GGO area correlates well with the Noguchi classification [26]. There were 33 Noguchi type A and B patients, 25 of which indicated a GGO area of greater than 50% and 8, of which indicated a GGO area of less than 50%. As for type D, E, and F patients, 53 out of 55 indicated a low GGO% and only 2 patients belonged to the high GGO ratio group. A statistically significant correlation was obtained between GGO% and Noguchi classification but types A and B could be completely diagnosed by HRCT findings as they should be the suitable indication of limited surgery. The 5-year survival rate of the high GGO group was 100% and the 5-year survival rate of the low GGO group was 83.9%. Similar results were obtained by Matsuguma who compared the preoperative HRCT findings with pathologic results in 96 patients who underwent surgical resection because of stage Ia cancers [14]. They determined that patients in whom the proportion of GGO to the whole tumor on CT was equal to or greater than 50% exhibited no nodal metastasis or postoperative recurrence. Small cancers with a high GGO ratio might be candidates for limited resection and a large multicenter study is necessary to confirm this postulate.

Limited resection has mostly been performed on patients with poor pulmonary reserve. Intentional limited surgery has not been common, particularly because lobectomy has been considered to be the standard treatment, which was confirmed by a randomized trial of the Lung Cancer Study Group [21]. However some successful results regarding limited surgery for T1 N0 tumors were published by Yamato who proposed limited resection for BAC by employing intraoperative pathological examination to confirm the absence of nodal metastasis [27]. They planned to convert limited resection to lobectomy if some invasive signs were recognized by frozen section. Tsubota performed extended segmentectomy for 55 patients with peripheral cancers measuring less than 2 cm in diameter and only 1 patient locally recurred in whom N2 disease was not indicated during operation [28]. Nakata performed thoracoscopic wedge resection for 33 pure GGO patients with tumors measuring less than 1 cm and no recurrence or metastasis was indicated during the follow-up period [12]. However well-differentiated adenocarcinomas or GGO-dominant tumors are considered to be indolent and slow-growing, therefore a long-term observation period is necessary to evaluate whether limited surgery could be an alternative to lobectomy.

In this study the ratio of GGO and consolidation on chest CT allows for the evaluation of the aggressive nature of small adenocarcinomas. However further investigation is required in this area, especially to characterize GGO on HRCT. Also genomic or proteomic studies are necessary to provide the clues to discriminate tumors with an indolent nature from those with an aggressive nature. Comprehensive research including pathology and molecular analysis will alter the conventional method of management regarding tiny cancers, which will be of great importance in daily practice.

The authors are indebted to Professor James Patrick Barron and Assistant Professor Raoul Breugelmans of the International Medical Communications Center at Tokyo Medical University (Tokyo, Japan) for their review of this manuscript.

References

1. Naruke T, Goya T, Tsuchiya R, et al. Prognosis and survival in resected lung carcinoma based on the new international staging system. J Thorac Cardiovasc Surg 1988;96:440–7.
2. Noguchi M, Morikawa A, Kawasaki M, et al. Small adenocarcinoma of the lung. Histologic characteristics and prognosis. Cancer 1995;75:2844–52.
3. Henschke C, McCauley D, Yakelevitz D, et al. Early Lung Action Project. Overall design and findings from baseline screening. Lancet 1999;354:99–105.
4. Sobue T, Moriyama N, Kaneko M, et al. Screening for lung cancer with low-dose helical computed tomography: anti-lung cancer association project. J Clin Oncol 2002;20:911–20.
5. Sone S, Takashima S, Li F, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. Lancet 1998;351:1242–5.
6. Kaneko M, Eguchi K, Ohmatsu H, et al. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. Radiology 1996;201:798–802.
7. Nawa T, Nakagawa T, Kusano S, et al. Lung cancer screening using low-dose spiral CT- results of baseline and one-year follow-up studies. Chest 2002;122:15–20.

8. Marcus PM. Lung cancer screening: an update. J Clin Oncol 2001;19(Suppl 18):83S–6.
9. Suzuki K, Asamura H, Kondo H, et al. Clinical predictors of minimally invasive peripheral adenocarcinoma of the lung: possible indications for limited surgical resection. Lung Cancer 2000;29:142.
10. Suzuki K, Asamura H, Kusumoto M, et al. "Early" peripheral lung cancer: Prognostic significance of ground glass opacity on thin-section computed tomographic scan. Ann Thorac Surg 2002;74:1635–9.
11. Higashiyama M, Kodama K, Yokouchi H, et al. Prognostic value of bronchiolo-alveolar carcinoma component of small lung adenocarcinoma. Ann Thorac Surg 1999;68:2069–73.
12. Nakata M, Sawada S, Saeki H, et al. Prospective study of thoracoscopic limited resection for ground-glass opacity selected by computed tomography. Ann Thorac Surg 2003; 75:1601–6.
13. Aoki T, Tomoda Y, Watanabe H, et al. Peripheral lung adenocarcinoma correlation of thin-section CT findings with histologic prognostic factors and survival. Radiology 2001; 220:803–9.
14. Matsuguma H, Yokoi K, Anraku M, et al. Proportion of ground grass opacity on high-resolution computed tomography in clinical T1N0M0 adenocarcinoma of the lung: A predictor of lymph node metastasis. J Thorac Cardiovasc Surg 2002;124:278–84.
15. Takashima S, Li F, Maruyama Y, et al. Discrimination of subtypes of small adenocarcinoma in the lung with thin-section CT. Lung Cancer 2002;36:175–82.
16. Warner E, Mulshine J. Surgical considerations with lung cancer screening. J Surg Oncol 2003;84:1–6.
17. Rusch V. High-resolution computed tomography in clinical T1N0M0 adenocarcinoma of the lung. J Thorac Cardiovasc Surg 2002;124:221–2.
18. Asamura H, Nakayama H, Kondo H, et al. Lymph node involvement, recurrence, and prognosis in resected small, peripheral, non-small-cell lung carcinomas: are these carcinomas candidates for video-assisted lobectomy? J Thorac Cardiovasc Surg 1996;111:1125–34.
19. Konaka C, Ikeda N, Hiyoshi T, et al. Peripheral non-small cell lung cancers 2.0 cm or less in diameter: proposed criteria for limited pulmonary resection based upon clinicopathological presentation. Lung Cancer 1998;21:185–91.
20. Suzuki K, Nagai K, Yoshida J, et al. Predictors of lymph node and intrapulmonary metastasis in clinical stage IA non-small cell lung carcinoma. Ann Thorac Surg 2001;72:352–6.
21. Lung Cancer Study Group. Randomized Trial of lobectomy versus limited resection for T1N0 non-small cell lung cancer. Ann Thorac Surg 1995;60:615–23.
22. Yoshida J, Nagai K, Yokose T, et al. Primary peripheral lung carcinoma smaller than 1 cm in diameter. Chest 1998;114: 710–2.
23. Kondo D, Yamada K, Kitayama Y, et al. Peripheral lung adenocarcinomas. 10 mm or less in diameter. Ann Thorac Surg 2003;76:350–5.
24. Shimosato Y, Suzuki A, Hashimoto T, et al. Prognostic implications of fibrotic focus (scar) in small peripheral lung cancers. Am J Surg Pathol 1980;4:365–73.
25. Suzuki K, Yokose T, Yoshida J, et al. Prognostic significance of size of central fibrosis in peripheral adenocarcinoma of the lung. Ann Thorac Surg 2000;69:893–7.
26. Ikeda N, Tsuboi M, Hiyoshi T, et al. A clinicopathological study of resected adenocarcinoma less than 2 cm in size. Lung Cancer 2003;41:S51.
27. Yamato Y, Tsuchida M, Watanabe T, et al. Early results of a prospective study of limited resection for bronchioloalveolar adenocarcinoma of the lung. Ann Thorac Surg 2001;71:971–4.
28. Tsubota N, Ayabe K, Doi O, et al. Ongoing prospective study of segmentectomy for small lung tumors. Ann Thorac Surg 1998;66:1787–90.