TABLE 2. Multivariate analysis of clinicopathologic factors for positive predictive values of pathologic nodal status

Factors	Odds ratio	95% CI	*P* value
Model 1 (R^2 = 0.236)			
Age	0.998	0.934-1.066	.9424
Sex	2.027	0.585-7.020	.2648
Size	1.205	1.063-1.366	.0036
Pathologic BAC	0.959	0.927-0.992	.0150
Model 2 (R^2 = 0.190)			
Age	0.999	0.938-1.065	.9847
Sex	1.503	0.466-4.843	.4948
Size	1.195	1.065-1.340	.0024
GGO on CT	0.960	0.916-1.006	.0857
Model 3 (R^2 = 0.231)			
Age	0.993	0.929-1.061	.8267
Sex	1.637	0.493-5.438	.4213
Size	1.200	1.061-1.357	.0037
TDR	0.963	0.935-0.993	.0145

CI, Confidence interval; R^2, determination coefficient; *BAC*, bronchioloalveolar carcinoma; *GGO*, ground-glass opacity; *TDR*, tumor disappearance rate.

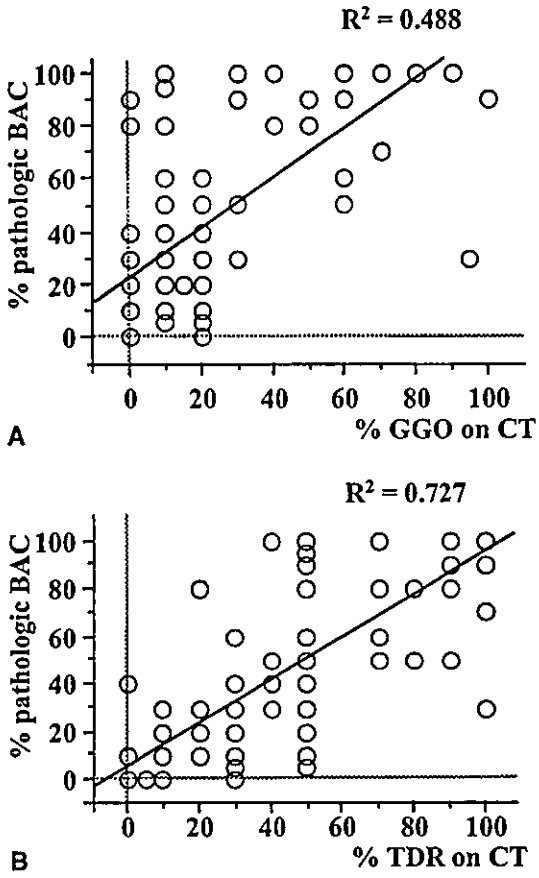


Figure 1. Regression parameters of radiographic findings and pathologic results. A, Correlation of radiographic GGO ratio and pathologic BAC ratio (R^2 = 0.488, P < .0001). B, Correlation of radiographic TDR ratio and pathologic BAC ratio (R^2 = 0.727, P < .0001). *BAC*, Bronchioloalveolar carcinoma; *CT*, computed tomography, *GGO*, ground-glass opacity; *TDR*, tumor shadow disappearance rate.

observed more frequently among patients with a smaller proportion of BAC.

Next, to determine the independent predictors for pathologic nodal status, we performed a multivariate analysis. The tumor size was significant in all multivariable models, but age and gender were not significant in any model (Table 2). TDR (R^2 = 0.231, P = .0145) and BAC components (R^2 = 0.236, P = .0150) were found to be more clinically useful predictors of pN0 disease than GGO ratio (R^2 = 0.190), because their determination coefficients and levels of significance were high. A marginal but not significant correlation was found between GGO ratio and nodal status (P = .0857).

We performed logistic regression analyses to investigate which radiographic parameter correlated better with a pathologic BAC percentage: TDR or GGO ratio (Figure 1). A positive and significant correlation was found between pathologic BAC versus TDR (R^2 = 0.727, P < .0001) and GGO ratios (R^2 = 0.488, P < .0001). These data demonstrated that both TDR and GGO ratios obtained preoperatively from CT were well associated with BAC ratios obtained postoperatively from sections of the specimen and that TDR had a stronger impact as a predictor of pathologic BAC.

Discussion

The recent technologic improvement and extensive use of CT scanning for mass screening allow us to choose among various surgical options to treat small-sized lung cancers, especially adenocarcinomas. We have had great doubts about whether lobectomy, generally accepted as the standard cure for primary lung cancer, is compulsory for managing these small lesions.[17] There are, however, no accurate preoperative indicators of the biologic behavior of a tumor except for tumor size, location, and histology. Choosing lesser pulmonary resections instead of standard lobectomies requires better preoperative methods to distinguish advanced, aggressive cancers from early, indolent cancers. Patient selection is not easy because lymph node metastases are not exceptional in patients with small peripheral adenocarcinomas. Our data showed that among 114 patients with an adenocarcinoma 3 cm or smaller in diameter, 16 (14%) had nodal metastases and 22 (19%) had advanced-stage diseases. The remainder had a tumor that was not biologically aggressive.

Investigators have demonstrated that the degree of BAC component may reflect clinicopathologic and prognostic

characteristics in patients with a small adenocarcinoma.[11,12] In the present study, lung adenocarcinomas accompanied by a higher BAC component showed a more indolent biologic behavior, and the proportion of BAC component on sections of surgical specimens was a significant independent predictor for nodal status. However, because the BAC area can only be defined after surgery, CT characteristics are watched with keen interest to choose surgical approaches preoperatively.

The proportion of GGO on HRCT was associated with the tumor biology and subsequently with the risk for nodal metastases and survival.[8-10,18] Matsuguma and colleagues[10] reported that all the cancers 2 cm or less in which the proportion of GGO was 50% or greater were BACs without nodal involvement and did not recur after resection. In addition, Takamochi and associates[15] proposed TDR as a predictor of the nodal status in patients with lung adenocarcinomas. In general, characterizing and quantifying CT findings used to be relatively subjective and based on visual estimation by individuals, possibly resulting in much discrepancy among the observers. Certainly, the lesions and parts indicating GGO or TDR on CT are not always BAC.[9,19] Therefore, we analyzed the correlation between the pathologic BAC ratio versus radiographic TDR or GGO ratio in small-sized adenocarcinomas 3 cm or less in diameter, which was one of the most crucial analyses in this study. The extent of both TDR and GGO area correlated well with that of BAC growth of adenocarcinomas. It must be emphasized that TDR, rather than GGO ratio, had an even more positive correlation with BAC proportion. In a multivariable analysis, TDR was considered an informative predictor of pathologic nodal status independent of age, sex, and tumor size. These findings can become an essential factor in planning proper management, in particular less invasive surgery for patients with a small adenocarcinoma. Although there were few patients in whom the BAC proportion was overestimated as TDR, BAC proportion was underestimated as TDR in some cases. The underestimation may have occurred because tumor cells induced mucous change at the alveoli and inflammatory cells infiltrated the alveolar lumens. Because patients with lower TDR are not often chosen for a lesser resection, the underestimation could be bypassed in the actual process of surgical intervention.

TDR is a reliable indicator of BAC and can serve to predict the biologic behavior of the tumor. This may be useful in identifying patients for lesser pulmonary resections.

References

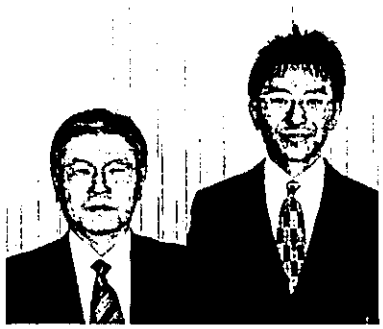
1. Okada M, Yoshikawa K, Hatta T, Tsubota N. Is segmentectomy with lymph node assessment an alternative to lobectomy for non-small cell lung cancer of 2 cm or smaller? *Ann Thorac Surg.* 2001;71:956-60.
2. Read RC, Yoder G, Schaeffer RC. Survival after conservative resection for T1 N0 M0 non-small cell lung cancer. *Ann Thorac Surg.* 1990;49:391-8.
3. Miller JI Jr, Hatcher CR Jr. Limited resection of bronchogenic carcinoma in the patient with marked impairment of pulmonary function. *Ann Thorac Surg.* 1987;44:340-3.
4. Warren WH, Faber LP. Segmentectomy versus lobectomy in patients with stage I pulmonary carcinoma. Five-year survival and patterns of intrathoracic recurrence. *J Thorac Cardiovasc Surg.* 1994;107:1087-93.
5. Kodama K, Doi O, Higashiyama M, Yokouchi H. Intentional limited resection for selected patients with T1 N0 M0 non-small-cell lung cancer: a single-institution study. *J Thorac Cardiovasc Surg.* 1997; 114:347-53.
6. Yoshikawa K, Tsubota N, Kodama K, Ayabe H, Taki T, Mori T. Prospective study of extended segmentectomy for small lung tumors: the final report. *Ann Thorac Surg.* 2002;73:1055-8.
7. Koike T, Terashima M, Takizawa T, Watanabe T, Kurita Y, Yokoyama A. Clinical analysis of small-sized peripheral lung cancer. *J Thorac Cardiovasc Surg.* 1998;115:1015-20.
8. Kuriyama K, Seto M, Kasugai T, Higashiyama M, Kido S, Sawai Y, et al. Ground-glass opacity on thin-section CT: value in differentiating subtypes of adenocarcinoma of the lung. *AJR Am J Roentgenol.* 1999;173:465-9.
9. Kodama K, Higashiyama M, Yokouchi H, Takami K, Kuriyama K, Mano M, et al. Prognostic value of ground-glass opacity found in small lung adenocarcinoma on high-resolution CT scanning. *Lung Cancer.* 2002;33:17-25.
10. Matsuguma H, Yokoi K, Anraku M, Kondo T, Kamiyama Y, Mori K, et al. Proportion of ground-glass opacity on high-resolution computed tomography in clinical T1 N0 M0 adenocarcinoma of the lung: a predictor of lymph node metastasis. *J Thorac Cardiovasc Surg.* 2002; 124:278-84.
11. Noguchi M, Morikawa A, Kawasaki M, Matsuno Y, Yamada T, Hirohashi S, et al. Small adenocarcinoma of the lung. Histologic characteristics and prognosis. *Cancer.* 1995;75:2844-52.
12. Goldstein NS, Mani A, Chmielewski G, Welsh R, Pursel S. Prognostic factors in T1 NO MO adenocarcinomas and bronchioloalveolar carcinomas of the lung. *Am J Clin Pathol.* 1999;112:391-402.
13. Barkley JE, Green MR. Bronchioloalveolar carcinoma. *J Clin Oncol.* 1996;14:2377-86.
14. Koga T, Hashimoto S, Sugio K, Yonemitsu Y, Nakashima Y, Yoshino I, et al. Lung adenocarcinoma with bronchioloalveolar carcinoma component is frequently associated with foci of high-grade atypical adenomatous hyperplasia. *Am J Clin Pathol.* 2002;117:464-70.
15. Takamochi K, Nagai K, Yoshida J, Suzuki K, Ohde Y, Nishimura M, et al. Pathologic N0 status in pulmonary adenocarcinoma is predictable by combining serum carcinoembryonic antigen level and computed tomographic findings. *J Thorac Cardiovasc Surg.* 2001;122:325-30.
16. Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest.* 1997;111:1710-7.
17. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg.* 1995;60:615-22.
18. Jang HJ, Lee KS, Kwon OJ, Rhee CH, Shim YM, Han J. Bronchioloalveolar carcinoma: focal area of ground-glass attenuation at thin-section CT as an early sign. *Radiology.* 1996;199:485-8.
19. Collins J, Stern EJ. Ground-glass opacity at CT: the ABCs. *AJR Am J Roentgenol.* 1997;169:355-67.

GTS

Sleeve segmentectomy for non–small cell lung carcinoma

Morihito Okada, MD, PhD
Wataru Nishio, MD, PhD
Toshihiko Sakamoto, MD, PhD
Kazuya Uchino, MD
Tsuyoshi Yuki, MD
Akio Nakagawa, MD
Noriaki Tsubota, MD, PhD

GTS



Tsubota and Okada *(left to right)*

Objective: Although sleeve segmentectomy for centrally located lung cancers was originally designed for patients unable to tolerate lobectomy, we have tried it in patients with noncompromised function as well. We evaluated the efficiency of this atypical type of bronchoplasty.

Methods: Of 202 patients for whom we performed bronchoplasty for primary non–small cell lung carcinoma, 16 underwent sleeve segmentectomy.

Results: Sixteen patients were classified into 4 groups according to the mode of bronchial reconstruction: type A, anastomosis between the right intermediate or left main and basal segmental bronchi with removal of the superior segment of the lower lobe (S6; n = 7); type B, anastomosis between the left main and lingular bronchi with removal of the upper division of the left upper lobe (S1+2+3; n = 3); type C, anastomosis between the left main and upper division bronchi with removal of the lingular segments (S4+5; n = 4); and type D, others (n = 2). Nine patients had pulmonary function sufficient to tolerate lobectomy. The tumors were completely resected in all patients. Combined performance of pulmonary angioplasty was carried out in 2 patients. Bronchial reconstruction was successful in all patients, with neither bronchial complications nor local recurrences. Ten patients had stage IA disease, and 6 had more advanced disease. All patients were alive, except 1 who died as a result of distant metastasis and 2 who died of noncancerous causes. Overall 3-year and 5-year survivals were 93.3% and 68.1%, respectively.

Conclusions: Sleeve segmentectomy, which is technically demanding, should be considered in patients with centrally located and possibly curable early non–small cell lung cancer because the prevalence of small-sized or multiple lung tumors has been increasing and because our findings suggest that this lung-saving operation is safe and useful.

From the Department of Thoracic Surgery, Hyogo Medical Center for Adults, Akashi City, Hyogo, Japan.

Received for publication Feb 19, 2004; revisions requested March 26, 2004; accepted for publication April 6, 2004.

Address for reprints: Morihito Okada, MD, PhD, Department of Thoracic Surgery, Hyogo Medical Center for Adults, Kitaohji-cho13-70, Akashi City 673-8558, Hyogo, Japan (E-mail: morihito1217jp@aol.com).

J Thorac Cardiovasc Surg 2004;128:420-4

0022-5223/$30.00

doi:10.1016/j.jtcvs.2004.04.029

The occurrence of lung cancer has recently been increasing, and routine clinical use of spiral or high-resolution computed tomography has made detection of many small pulmonary nodules possible. We have continued to doubt whether lobectomy, which has been generally accepted as a standard form of cure for primary non–small cell lung cancer, is required for treatment of such small-sized lesions. Because lesser removal of lung parenchyma could be beneficial to patients,[1-6] we have always considered pulmonary-saving procedures, even for treatment of malignant lesions.[7-10] We have in fact performed pneumonectomy in only 1.3% of 749 patients treated surgically in our institution for primary lung cancer from 1999 through 2003. In addition, bronchoplastic procedures, which were reported to be usually adequate for around 5% of patients with resectable pulmonary malignancy,[11,12] has been carried out in more than 10% of our patients.[7,8]

TABLE 1. Type of procedure and reconstruction

Class	Lung resection	Anastomosis	Preservation
Type A	S6	Right intermedial bronchi–basal segmental bronchi Left main bronchi–basal segmental bronchi	Basal segments
Type B	Left S1+2+3	Left main bronchi–lingular bronchi	Left S4+5
Type C	Left S4+5	Left main bronchi–upper division bronchi	Left S1+2+3
Type D	Unclassified (others)		

S6, Superior segment of lower lobe; *S1+2+3*, upper division segments; *S4+5*, lingular segments.

The Lung Cancer Study Group's statement that limited resection triggers an increase in locoregional recurrence and death rate compared with lobectomy[13] confirmed the latter to be a standard procedure of choice for tumors of any size. However, to undoubtedly accept their conclusions, of which invited commentators had a poor opinion, is risky and unfair, mainly because their trial included many cases of wedge resection and not segmentectomy as a type of lesser resection. Several studies, including prospectively performed studies, have recently demonstrated the role of segmentectomy for small-sized N0 cancer,[5,14-18] and current influential data thus suggest that segmentectomy for smaller N0 cancers might be an acceptable mode of surgical treatment, even for noncompromised patients. Sleeve segmentectomy was originally designed for patients with compromised lung function who were unable to tolerate lobectomy. If segmentectomy yielded survival results at least equal to those of lobectomy in addition to better functional results, it could become an accepted procedure for patients who have anatomically suitable tumors, regardless of lung function. Functional lung parenchyma can be preserved, and the reimplanted segments will contribute to postoperative quality of life. If a second primary lung cancer develops, subsequent resection might be offered to selected patients. We have aggressively performed various atypical types of bronchial reconstructions at the segmental level in patients with noncompromised as well as compromised lung function. Because there have been very few reports summarizing the results of sleeve segmentectomy for lung cancer, we present here its significance and results obtained on continued careful follow-up.

Patients and Methods

Of 1760 patients who were operated on for primary non–small cell lung cancer from January 1988 through December 2003, 202 (11.5%) underwent bronchoplastic procedures. Of them, 16 patients underwent sleeve segmentectomy, and we classified these patients in 4 groups (A to D) in accordance with the manner of bronchial reconstruction (Table 1).

Preoperative bronchoscopic examination was crucial in revealing the location and extent of the tumor because most of the cases could not be viewed or palpated from outside of the bronchus during the operation. Standard surgical technique was used for segmentectomy until the bronchus was encountered.[14,15] Proximal and distal points of transection at the bronchus were established with at least 1 cm of macroscopically uninvolved distance. On the basis of results of intraoperative frozen section evaluation of both the margins, we possibly removed additional portions of the bronchus, as in case A-6 mentioned below in detail. Bronchial anastomosis was performed with interrupted sutures and full-thickness bites by using 4-0 monofilament absorbable material (polydioxanone suture, PDS-II; Ethicon, Tokyo, Japan), which was placed and tied in order from the deepest point to the lateral direction. In this type of bronchoplasty, there is generally a difference between the proximal diameter of the bronchus and the distal bronchus, which is quite thin and frail. However, the tissues there were flexible enough that careful placement of sutures could compensate for this discrepancy. A few adjusting stitches in the membranous part of the larger stump can help to make the anastomosis simpler to perform at the level of the main or lobar bronchi but not at the level of the segmental bronchi, where there are a couple of knacks for performing anastomosis. To prevent the anastomosis from progressing to stenosis, it is recommended that suturing be done to make the distal stump potentially enlarged as a mainstay of the stronger oral stump and that the bites of suture stitches and the intervals between each stitch, especially at the distal stump, be relatively short, with care being taken that the sutures do not compromise blood flow to the margins. Inside knotting of the deepest stitches is helpful, even at distal levels beyond the lobar bronchus.[7] When combined performance of angioplasty of the pulmonary artery was required, which was occasionally encountered in type C reconstructions, both bronchial and arterial anastomotic sites must be detached. Vascular reconstruction with a continuous 5-0 nonabsorbable polypropylene material (Prolene, Ethicon) was performed after the bronchial reconstruction. Electrocauterization or stapling (Endocutter; Ethicon Endo-Surgery, Cincinnati, Ohio) was used to divide the intersegmental plane.

Dissection or sampling of the hilar and mediastinal nodes was performed in noncompromised or compromised patients, respectively.[19] Resected specimens were examined histopathologically, and histologic typing was performed according to World Health Organization classification. Surgical-pathologic staging was performed by using the New International Staging System for Lung Cancer.[20] For staging and evaluation of recurrence, we carried out a physical examination, biochemical profile, chest radiographic examination, bronchoscopy, bone scintigraphy, and computed tomography of the chest, brain, and upper portion of the abdomen. Routine bronchoscopies were performed 1 and 6 months after the operation to monitor the status of the anastomosis and to rule out

TABLE 2. Case data

Type	No.	Sex	Age (y)	Histologic type	Resected segment	Pathologic T	N	M	Staging	Local recurrence	Prognosis
A	1†	M	74	SQ	Left S6	1	0	0	IA	No	152 mo, alive
	2†	M	58	SQ	Right S6	1	0	0	IA	No	58 mo, dead‡
	3	M	62	AD	Left S6	1	0	0	IA	No	57 mo, alive
	4	M	74	SQ	Right S6	2	0	0	IB	No	53 mo, dead‡
	5	M	70	SQ	Left S6	1	1	0	IIA	No	39 mo, alive
	6†	M	65	SQ	Left S6	1	0	0	IA	No	38 mo, alive
	7	M	59	SQ	Right S6	2	1	0	IIB	No	35 mo, alive
B	1	M	57	SQ	Left S1+2+3	1	1	0	IIA	No	75 mo, alive
	2†	M	54	SQ	Left S1+2+3	1	0	0	IA	No	65 mo, alive
	3†	M	61	SQ	Left S1+2+3	1	0	0	IA	No	35 mo, alive
C	1†	M	63	SQ	Left S4+5	1	0	0	IA	No	103 mo, alive
	2†	M	74	SQ	Left S4+5	1	0	0	IA	No	41 mo, alive
	3*	F	76	SQ	Left S4+5	2	1	0	IIB	No	24 mo, dead§
	4*	F	69	AD	Left S4+5	1	1	0	IIA	No	7 mo, alive
D	1†	M	75	SQ	Left S1+2	1	0	0	IA	No	70 mo, alive
	2†	F	20	ME	Right S3	1	0	0	IA	No	39 mo, alive

SQ, Squamous cell carcinoma; *S6,* superior segment of lower lobe; *AD,* adenocarcinoma; *S1+2+3,* upper division segments; *S4+5,* lingular segments; *S1+2,* apical and posterior segments of upper lobe; *ME,* mucoepidermoid carcinoma; *S3,* anterior segment of upper lobe.
*Double sleeve case (with pulmonary artery reconstruction).
†Patients with an adequate pulmonary function to tolerate lobectomy.
‡Noncancer cause.
§Distant metastasis.

local recurrence. In general, the patients were examined postoperatively at 3-month intervals for 5 years and thereafter at 1-year intervals to check for recurrence and survival.[21]

Results

The clinical characteristics, surgical treatment, pathologic stage, and prognosis of 16 patients in whom sleeve segmentectomy was performed are summarized in Table 2. In addition, illustrations of representative surgical procedures are provided in Figure 1. On the basis of clinical and objective functional assessment, 9 patients were considered to have pulmonary function sufficient to tolerate lobectomy, whereas the remaining 7 patients had poor functional reserve. There were 13 men and 3 women enrolled in the study, with a mean age of 64 years (range, 20-76 years). Overall follow-up ranged from 7 to 152 months, with a median of 46 months. Histologic cell type was squamous cell carcinoma in 13 (81%) patients, adenocarcinoma in 2 (13%) patients, and mucoepidermoid carcinoma in 1 (6%) patient. Complete resection was performed in all patients. Angioplasty of the pulmonary artery, so-called double-sleeve resection, was performed in 2 patients classified as type C. On surgical-pathologic staging, 10 (63%) patients had stage IA disease, 1 had stage IB disease, 3 had stage IIA disease, and 2 had stage IIB disease. There was no operative mortality, which was defined as death within 30 days after the operation. Postoperative complications were infrequent and nonfatal, with bacterial pneumonia and bronchial asthma occurring in 1 patient each. In all patients bronchial reconstruction was successful, and neither stenosis nor local recurrence at the anastomotic site, reimplanted lung, or regional lymph node involvement had developed by the time of this report. However, 1 patient with stage IIB disease died 2 years after the operation as a result of distant metastasis, and 2 patients died of noncancerous causes. Overall 3-year and 5-year survivals were 93.3% and 68.1%, respectively.

Discussion

Generally, making the decision whether to perform bronchoplasty for malignancy depends on a subtle balance among postoperative quality of life, risk of recurrence, and postoperative complications. One of the greatest concerns about sleeve segmentectomy is the potentially increased rate of local recurrence, although no local recurrence has occurred in this series. In any case, it is essential to ensure a macroscopically sufficient margin of safety, as well as to examine it with rapid frozen sections intraoperatively. The rate of postoperative complications, which were nonfatal and minor respiratory problems, was generally low in the present series, and survival after the operation was not poor. Hilar lung cancer has a tendency to occur multicentrically, and therefore the goal of radical surgical intervention should be to maintain as much lung function as possible because the initial mode of the operation influences the resectability

of secondary disease. We have carried sleeve segmentectomy actively not only in compromised patients but also in noncompromised patients. In the latter group, if an intraoperative pathologic examination points out that the disease can be advanced, the procedure will be modified to the standard one, such as lobectomy or sleeve lobectomy, with complete systematic dissection of the lymph nodes. Most surgeons might have chosen lobectomy for the noncompromised patients and not performed thoracotomy for the compromised patients in this series. Sleeve segmentectomy, for which hilar cancer with negative nodes is the most suitable indication, should be considered, even for noncompromised patients. Two representative cases will be presented. One patient (case A-6; Figure 1, *A*) intentionally underwent left sleeve S6 (superior segment of lower lobe) segmentectomy with partial resection of the upper lobe bronchus because his disease had invaded beyond the second carina. In addition, the distal bronchial stump was trimmed with convex wedge-shaped cutting to complete the anastomosis because the lesion also involved the bronchial wall toward the basal segment. The other patient (case C-4; Figure 1, *B*) underwent sleeve lingulectomy (S4+5) with sleeve angioplasty of the pulmonary artery, so-called double-sleeve resection. To our knowledge, there have been no previous reports concerning double-sleeve resection at the level of the segment. The artery was freed proximally and distally to allow anastomosis without tension and reconstructed with a pericardial patch. Because the patient's preoperative values of forced expiratory volume in 1 second and forced expiratory volume in 1 second/forced vital capacity were 0.85 L and 37%, respectively, high-frequency jet ventilation was applied to inflate the left upper division segments detached during the procedure of anastomosis, accompanied by intermittent positive-pressure ventilation to the right lung.

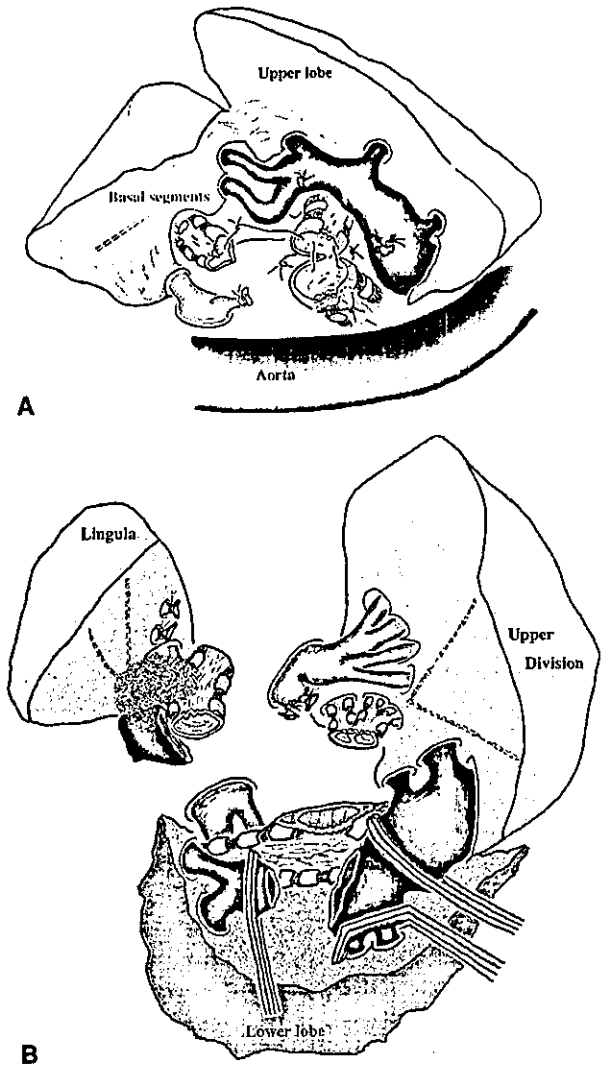


Figure 1. Schematic illustrations of representative surgical findings. A, Case A-6: left sleeve S6 (superior segment of lower lobe) segmentectomy with additional deep wedge resection of the second carina caused by involvement of the lesion. The distal bronchial stump was trimmed with convex wedge-shaped cutting because the lesion also extended to the basal segmental bronchus. B, Case C-4: left sleeve lingulectomy (S4+5) with a side-to-end anastomosis between the left main and the cut end of the upper division of the bronchi, and sleeve resection of the pulmonary artery with subsequent reconstruction using a pericardial patch (so-called double-sleeve resection).

These patients have recovered uneventfully. Endobronchial interventions, such as YAG laser cauterization, brachytherapy, and photodynamic therapy, can be therapeutic options for very early hilar cancer located at sites that can be directly viewed with a bronchoscope. These techniques, however, cannot accurately address the depth of invasion, free margins, or nodal status, and complete remission can be obtained only in carcinoma in situ or microinvasive cancer. We believe that except for selected patients in whom radical treatment can definitely be performed with these endoluminal interventions, thoracotomy is more reliable at present. When segmentectomy, with or without bronchoplasty, is planned in noncompromised patients, dissected lymph nodes should undergo intraoperative frozen-section pathologic examination to confirm the absence of metastasis because this information is needed for a diagnosis of early cancer. The results of this study clearly demonstrate that sleeve segmentectomy is a satisfactory surgical option for hilar lung cancer, as regards both operative risk and curability. The indications for this procedure, which is technically more demanding than lobectomy, need to be thoroughly clarified. We suggest that sleeve segmentectomy should be considered an option for small-sized, centrally located, N0 non–small cell lung cancer when feasible.

GTS

References

1. Read RC, Yoder G, Schaeffer RC. Survival after conservative resection for T1 N0 M0 nonsmall cell lung cancer. *Ann Thorac Surg.* 1990;49:391-8.
2. Jensik RJ, Faber LP, Milloy FJ, Monson DO. Segmental resection for lung cancer. A fifteen-year experience. *J Thorac Cardiovasc Surg.* 1973;66:563-72.
3. Miller JI Jr, Hatcher CR Jr. Limited resection of bronchogenic carcinoma in the patient with marked impairment of pulmonary function. *Ann Thorac Surg.* 1987;44:340-3.
4. Warren WH, Faber LP. Segmentectomy versus lobectomy in patients with stage I pulmonary carcinoma. Five-year survival and patterns of intrathoracic recurrence. *J Thorac Cardiovasc Surg.* 1994;107:1087-93.
5. Kodama K, Doi O, Higashiyama M, Yokouchi H. Intentional limited resection for selected patients with T1 N0 M0 non-small-cell lung cancer: a single-institution study. *J Thorac Cardiovasc Surg.* 1997;114:347-53.
6. Pastorino U, Valente M, Bedini V, Infante M, Tavecchio L, Ravasi G. Limited resection for Stage I lung cancer. *Eur J Surg Oncol.* 1991;17:42-6.
7. Okada M, Tsubota N, Yoshimura M, Miyamoto Y, Matsuoka H, Satake S, et al. Extended sleeve lobectomy for lung cancer: the avoidance of pneumonectomy. *J Thorac Cardiovasc Surg.* 1999;118:710-3.
8. Okada M, Yamagishi H, Satake S, Matsuoka H, Miyamoto Y, Yoshimura M, et al. Survival related to lymph node involvement in lung cancer after sleeve lobectomy compared with pneumonectomy. *J Thorac Cardiovasc Surg.* 2000;119:814-9.
9. Okada M, Sakamoto T, Nishio W, Uchino K, Tsubota N. Characteristics and prognosis of patients after resection of nonsmall cell lung carcinoma measuring 2 cm or less in greatest dimension. *Cancer.* 2003;98:535-41.
10. Okada M, Nishio W, Sakamoto T, Uchino K, Tsubota N. Discrepancy of computed tomographic image between lung and mediastinal windows as a prognostic implication in small lung adenocarcinoma. *Ann Thorac Surg.* 2003;76:1828-32.
11. Lowe JE, Bridgman AH, Sabiston DC Jr. The role of bronchoplastic procedures in the surgical management of benign and malignant pulmonary lesions. *J Thorac Cardiovasc Surg.* 1982;83:227-34.
12. Tedder M, Anstadt MP, Tedder SD, Lowe JE. Current morbidity, mortality, and survival after bronchoplastic procedures for malignancy. *Ann Thorac Surg.* 1992;54:387-91.
13. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg.* 1995;60:615-22.
14. Okada M, Yoshikawa K, Hatta T, Tsubota N. Is segmentectomy with lymph node assessment an alternative to lobectomy for non-small cell lung cancer of 2 cm or smaller? *Ann Thorac Surg.* 2001;71:956-60.
15. Tsubota N, Ayabe K, Doi O, Mori T, Namikawa S, Taki T, et al. Ongoing prospective study of segmentectomy for small lung tumors. Study Group of Extended Segmentectomy for Small Lung Tumor. *Ann Thorac Surg.* 1998;66:1787-90.
16. Yoshikawa K, Tsubota N, Kodama K, Ayabe H, Taki T, Mori T. Prospective study of extended segmentectomy for small lung tumors: the final report. *Ann Thorac Surg.* 2002;73:1055-8.
17. Miller DL, Rowland CM, Deschamps C, Allen MS, Trastek VF, Pairolero PC. Surgical treatment of non-small cell lung cancer 1 cm or less in diameter. *Ann Thorac Surg.* 2002;73:1545-50.
18. Sagawa M, Koike T, Sato M, Oda M, Kondo T, Kato H, et al. Segmentectomy for roentgenographically occult bronchogenic squamous cell carcinoma. *Ann Thorac Surg.* 2001;71:1100-14.
19. Okada M, Tsubota N, Yoshimura M, Miyamoto Y. Proposal for reasonable Mediastinal lymphadenectomy in bronchogenic carcinomas: role of subcarinal nodes in selective dissection. *J Thorac Cardiovasc Surg.* 1998;116:949-53.
20. Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest.* 1997;111:1710-7.
21. Okada M, Nishio W, Sakamoto T, Harada H, Uchino K, Tsubota N. Long-term survival and prognostic factors of five-year survivors with complete resection of non-small cell lung carcinoma. *J Thorac Cardiovasc Surg.* 2003;126:558-62.

Evolution of Surgical Outcomes for Nonsmall Cell Lung Cancer: Time Trends in 1,465 Consecutive Patients Undergoing Complete Resection

Morihito Okada, MD, PhD, Wataru Nishio, MD, PhD, Toshihiko Sakamoto, MD, PhD, Kazuya Uchino, MD, Tsuyoshi Yuki, MD, Akio Nakagawa, MD, and Noriaki Tsubota, MD, PhD

Department of Thoracic Surgery, Hyogo Medical Center for Adults, Akashi City, Hyogo, Japan

Background. Lung cancer is still the most common cause of death due to cancer. Although the 5-year survival rate of patients with lung cancer is reported to be increasing, whether the surgical results have actually been improving or not is controversial. We reviewed our experience to evaluate time trends of surgical outcomes in patients with nonsmall cell lung cancer.

Methods. We reviewed the clinical records of 1,465 consecutive patients with proven primary nonsmall cell carcinoma who underwent complete removal of the primary tumor together with hilar and mediastinal lymph nodes from 1985 to 1995 (early era) and from 1996 to 2002 (late era). The clinical characteristics, surgical outcome, and overall survival of the patients were analyzed, and data from the two eras were compared.

Results. There were 694 patients in the early era and 771 in the late era. As for their characteristics, elder age, female sex, adenocarcinoma, earlier stage of disease and smaller size of tumor were more frequently encountered in the late era. Lobectomy was the most common procedure performed during both periods, and in the late era, the rate of segmentectomy was doubled (11% to 25%) whereas that of pneumonectomy was much less (6% to 1%). Although the frequency of operative deaths in the two eras did not differ (0.3%), that of in-hospital deaths and of postoperative complications decreased significantly in the late era (2% to 0.5% and 28% to 12%, respectively). A significant improvement in survival probability was observed in patients with pathologic stage IA ($p < 0.0001$), IB ($p = 0.0477$), and III disease ($p = 0.00120$) but not in those with pathologic stage II disease ($p = 0.5353$). Also, the multivariate analysis of patients with pathologic stage I or III demonstrated that age, sex, and size of the tumor were significant prognostic determinants, and confirmed that the recent prolonged survivals remained significant even after simultaneous adjustment for other factors.

Conclusions. These data indicate a significant recent improvement in surgical outcomes after stratification of various prognostic variables although careful consideration should be given to the retrospective nature of this study.

(Ann Thorac Surg 2004;77:1926–31)

Recent progress in the therapy for cancer is one of the best examples of the successful evolution of clinical medicine. Cancer has been the leading cause of death since 1981 in Japan, where the average life expectancy is one of the highest in the world. Likewise, in the United States, it is estimated that 1,334,100 new cases of cancer will be diagnosed and 556,500 people will die of cancer in 2003 [1]. In the United States, lung cancer continues to be the most common cause of cancer death in both men and women; the 5-year survival has significantly increased from 12% in the 1970s to 15% in the 1990s, while the estimated number of deaths from lung cancer remains relatively stable at 157,200 patients per year [1].

Among patients with primary lung cancer, approximately 80% have nonsmall cell lung cancer. Although pulmonary resection is the most effective treatment of choice whenever possible for patients with nonsmall cell lung cancer who are presumed to have no disseminated disease, the assessment of surgical results is still hampered by insufficient follow-up and the small number of patients studied. The actual impact of advances in surgical treatment on the outcome of patients with nonsmall cell lung cancer is of great interest to us but it remains unclear. There have been few reports on time trends in surgical outcomes for nonsmall cell lung cancer [2]. Even meta-analyses based on reports from many institutions or literatures have seldom been published. The limitation of such analyses is that pooled data collected from multiple institutions over many years lack uniformity with regard to diagnosis and treatment, and in reporting outcomes. Therefore, we reviewed our data on surgical treatment provided by a single team to evaluate the changes with the times regarding the survival of patients with nonsmall cell lung cancer.

Accepted for publication Dec 10, 2003.

Address reprint requests to Dr Okada, Department of Thoracic Surgery, Hyogo Medical Center for Adults, Kitaohji-cho 13-70, Akashi City 673-5885, Hyogo, Japan; e-mail: morihito1217jp@aol.com.

Published by Elsevier Inc

0003-4975/04/$30.00
doi:10.1016/j.athoracsur.2004.01.002

Patients and Methods

Between January 1985 and December 2002, 1,465 consecutive patients with proven primary nonsmall cell lung carcinoma underwent complete removal of the tumor together with ipsilateral hilar and mediastinal lymph nodes. Patients who had evidence of residual tumor at the surgical margin, malignant effusion, or N3 disease verified by intraoperative findings or postoperative pathologic examination, were defined as having undergone incomplete surgery and were excluded from this study. Patients whose tumors were subsequently classified as small cell carcinoma or low-grade malignant tumor were also excluded. The criteria, based on and modified from those of Martini and Melamed [3] have been used for the designation of multiple primary lung cancers [4]. Tumors with minute satellite nodules that were found incidentally within the same lobe of the resected specimen were not excluded from this study, because we were not certain whether these lesions should be considered local tumor spread or not. Tumors with satellite lesions in another lobe were excluded. One hundred sixty-four patients who received induction chemoradiotherapy were included.

Surgical-pathologic staging was carried out according to the New International Staging System for Lung Cancer [5]. Routine systematic dissection of all the hilar and mediastinal lymph nodes was performed in every case, even if the preoperative evaluation was N0 or N1 [6]. Every node dissected was examined by more than one pathologist to be diagnosed as microscopically positive or negative during and after the operation. In general, the patients were examined after surgery at 3-month intervals for 5 years and thereafter at 1-year intervals. The evaluation included physical examination, chest roentgenography, and tumor markers. Moreover, chest, abdominal and brain computed tomographic (CT) scans and a bone scinti scan were carried out each year. Whenever any symptoms or signs of recurrence were detected, further examinations to detect the disease were performed. Minor complications as well as major ones were taken into account for the analyses of data in this study.

In this study we evaluated our institutional experience in the surgical treatment of nonsmall lung cancer from 1985 to 1995 (early era) and from 1996 to 2002 (late era). These historical periods selected were determined as the number of patients surgically treated was roughly equal on the two groups. The clinicopathologic characteristics, surgical outcomes, and overall survival of the patients were analyzed, and data from the two eras were compared.

The survival probabilities were calculated by the Kaplan-Meier method, and differences in survival were determined by the log-rank analysis. A multivariable analysis of several independent prognostic factors was carried out using Cox's proportional hazards regression model. Zero time was the date of surgery, and the terminal event was death attributable to cancer, noncancer or unknown causes. Patients with operative or in-hospital mortality, defined as death occurring within 30 days after the operation or during hospitalization, respectively, were included in this study. Factors potentially influencing the prognosis for a proportion of the patients' population were analyzed by the Mann-Whitney *U* test. A value of p less than 0.05 was considered to indicate statistical significance, and all resulting p values were two-tailed.

Table 1. Clinicopathologic Characteristics

Factor	Early Era	Late Era	p Value
Number	694	771	
Mean age (years)	63.3 (30–88)	65.0 (15–85)	0.0004
Male/female	523/171	539/232	0.0197
Histology			0.0666
AD	381 (55%)	459 (60%)	
SQ	273 (39%)	268 (35%)	
LA	18 (3%)	23 (3%)	
AS	14 (2%)	11 (1%)	
CA	8 (1%)	9 (1%)	
Pathologic-stage			<0.0001
IA	213 (31%)	320 (42%)	
IB	148 (21%)	178 (23%)	
IIA	40 (6%)	32 (4%)	
IIB	102 (15%)	96 (12%)	
IIIA	130 (19%)	113 (15%)	
IIIB	60 (9%)	32 (4%)	
Mean size (mm)	35.8	30.1	<0.0001
Procedure			<0.0001
Pneumonectomy	39 (6%)	9 (1%)	
Lobectomy	557 (80%)	517 (67%)	
Segmentectomy	76 (11%)	195 (25%)	
Wedge resection	20 (3%)	49 (6%)	
Bronchial resection	2 (0.3%)	1 (0.1%)	
Bronchoplasty	87 (13%)	90 (12%)	0.6130
Induction therapy	86 (12%)	78 (10%)	0.1948
Operative death	2 (0.3%)	2 (0.3%)	
Death at hospitalization	14 (2%)	4 (0.5%)	<0.0001
Complication	192 (28%)	89 (12%)	<0.0001

AD = adenocarcinoma; AS = adenosquamous carcinoma; CA = carcinoid; LA = large cell carcinoma; SQ = squamous cell carcinoma.

Results

There were 694 patients in the early era and 771 in the late era. Median follow-up periods for the early and late eras (for patients still alive) were 103 and 41 months, respectively. The clinicopathologic characteristics, types of procedure, and surgical outcomes are presented in Table 1. Elder age, female sex, adenocarcinoma, earlier stage of disease and smaller size of the tumor were encountered more frequently in the late era. On the basis of the international staging system, there was a remarkable increase in the number of patients with stage IA disease in the late era (42%) compared with the early era (31%). Lobectomy was by far the most common procedure performed during both periods, and the frequency

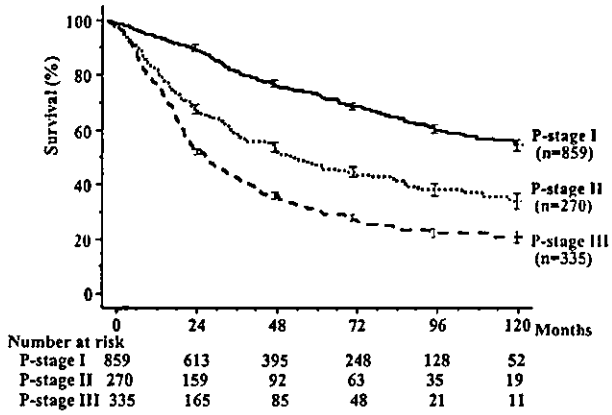


Fig 1. Survival of patients who underwent complete resection for nonsmall cell lung cancer by pathologic stage. Significant differences in survival among pathologic stages were found (pathologic stage I versus II, and II versus III; p < 0.0001).

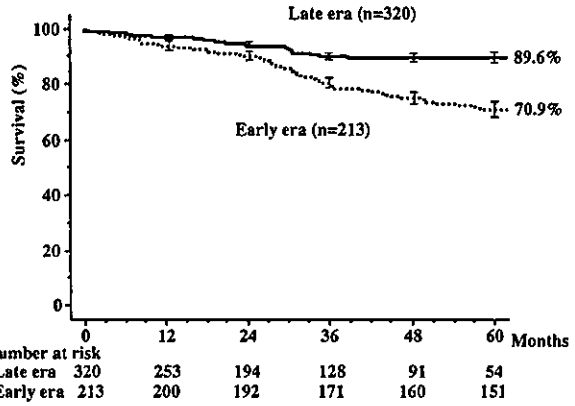


Fig 2. Survival of patients who underwent complete resection for pathologic stage IA nonsmall cell lung cancer. The survival in the late era (1996 to 2002) was significantly higher than that in the early era (1985 to 1995; p < 0.0001).

of segmentectomy was doubled in the late era (11% to 25%). Because we always kept in mind the possibility of lung-saving procedures [7, 8], the ratio of broncoplasties was relatively high (12% to 13%) through both periods while that of pneumonectomies was much less in the late era (6% to 1%). Although the frequency of operative deaths in the two eras did not differ (0.3%), that of in-hospital deaths and of postoperative complications decreased significantly in the late era (2% to 0.5% and 28% to 12%, respectively).

Next, we analyzed overall survival probability in all patients according to pathologic stages (Fig 1). There were marked differences between stage I versus stage II and between stage II versus stage III ($p < 0.0001$). Survivals by age, sex, size of the tumor, histologic type, surgical procedure, pathologic stage, and era were summarized (Table 2). Statistical differences were found in the probability of survival in favor of the late era as well as younger, female, smaller tumor, adenocarcinoma, lesser resection, and early stage. In the late era, there were significant increases in the probability of survival of patients with pathologic stage IA disease (89.6% versus 70.9% at 5 years, $p < 0.0001$; Fig 2) as well as in that of patients with pathologic stage IB disease (74.9% versus 62.8% at 5 years, $p = 0.0477$; Fig 3). However, no significant difference was found in the survival of patients with pathologic stage II disease between the two eras ($p = 0.5353$; Fig 4). The survival of patients with pathologic stage III disease was 44.3% at 5 years in the late era and significantly better than that of patients in the early era (26.2% at 5 years, $p = 0.0120$; Fig 5). Thus, the improvement in overall survival probability was observed in patients with pathologic stage I or III disease.

Finally, we performed Cox proportional hazards regression analysis not only to determine independent prognostic variables but also to remove any bias as much as possible because of the retrospective nature of the study. The results of multivariate analyses were same as those of univariate analyses except for surgical mode (Table 3). Interestingly, after stratified by various possible variables, no difference was found in survival between standard and lesser resections. The analysis of patients with pathologic stage I (n = 859) or stage III (n = 336) demonstrated that age, sex, and size of the tumor

Table 2. Univariate Analysis of Prognostic Factors

Factors	Unfavorable	Favorable	*p* Value
Age (years)	≥65	≤64	0.0006
Sex	Male	Female	<0.0001
Size (mm)	≥30	≤31	<0.0001
Histology	non-AD	AD	0.0082
Procedure	Pne + Lob	Wed + Seg	<0.0001
Pathologic stage	I	II + III	<0.0001
Era	Early	Late	<0.0001

AD = adenocarcinoma; Lob = lobectomy; Pne = pneumonectomy; Seg = segmentectomy; Wed = wedge resection.

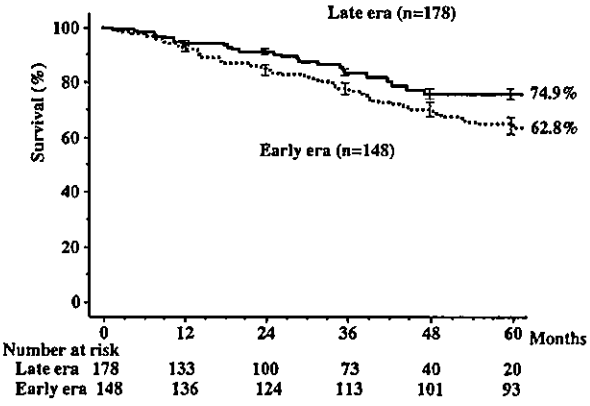


Fig 3. Survival of patients who underwent complete resection for pathologic stage IB nonsmall cell lung cancer. The survival in the late era (1996 to 2002) was significantly higher than that in the early era (1985 to 1995; p = 0.0477).

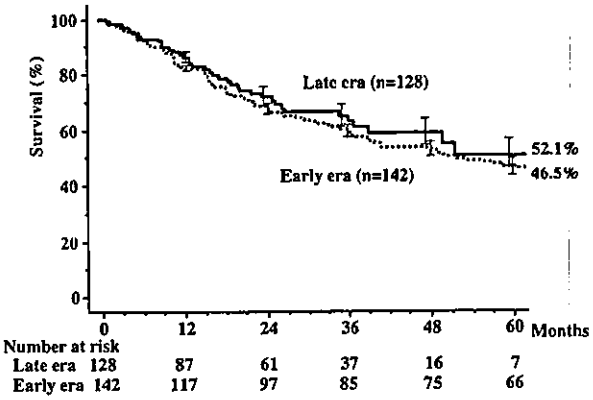


Fig 4. Survival of patients who underwent complete resection for pathologic stage II nonsmall cell lung cancer. There was no significant difference in the survival between the early (1985 to 1995) and the late era (1996 to 2002; p = 0.5353).

were the factors with stronger influence on the postoperative prognosis, and confirmed that the improvement in survival in the late era remained significant even after simultaneous adjustment for age, sex, size, and histology of the tumor (Table 4). It is interesting to note that in terms of histology adenocarcinoma was a significantly independent worse determinant among patients with pathologic stage III disease although it was associated with a relatively better prognostic tendency in patients with pathologic stage I disease.

Comment

One of the most important findings in the present series was a significant improvement in postoperative survival from the early to the late period. Univariate comparisons of the prognosis according to pathologic stage revealed an improvement in all patients except those with pathologic stage II disease. In particular, the overall survival rate of patients with pathologic stage IA disease in the late era was extremely high (89.6%). Multivariate analyses performed after adjustment for age, sex, size of the tumor, and histology also showed a significant increase in the survival of patients with pathologic stage I or III disease. In both periods, lobectomy was the most common procedure, but the rate of sublobar resection including segmentectomy significantly increased in the late era. The ratio of patients who underwent pneumonectomy markedly decreased from 6% to 1%, which was in part the reason the incidence of in-hospital deaths and postoperative complications decreased significantly in the late era [8]. In recent times, more patients prefer a lesser resection to preserve as much lung function as possible [7, 9, 10]. Additional reasons for the decrease in occurrence of postoperative complications and operation-related deaths were not entirely clear in the present series.

There were differences in the distribution of patients between the two eras concerning age, sex, histology, stage of the disease, and size of the tumor. Elder age, female sex, adenocarcinoma, and early stage of the disease were more frequent in the late era; and these were independent prognostic determinants as shown by the multivariate analyses. It is of interest to note the marked increase in the proportion of patients with stage I disease, particularly of stage IA disease, which was a strong factor for the better prognosis of patients treated surgically because of an increase in the rate of early detected lung tumors as a result of our extended screening system and improved diagnostic techniques. Besides, advances in diagnostic ability such as speed and high resolution of computed tomographic images have allowed the detection of patients with inoperable disease and those who could undergo complete resection of the tumor. Preoperative care for patients with other morbidities has improved, and patients have routinely been transferred to the intensive care unit postoperatively. In addition, surgeons in the department might have become more experienced. Thus, the improvement may be attributable to many factors, including comprehensive screening and evolution of diagnostic methods, but there is little doubt that meaningful advances have also taken place in surgical techniques and supportive care. Surgical results depend on two major factors, which are oncologic radicality to prevent recurrences and quality of postoperative status, that is, preservation of lung function and preclusion of perioperative complications. The surgeons should advocate less invasive surgery because we have reached the limit of pursuing radicality of the disease by extensive surgical procedures.

Survival data could be biased due to selection bias, lead-time bias, and length bias [11, 12]. Selection bias is a major determinant of participation in surgical intervention. Although in a nonrandomized study it is impossible to avoid selection bias, the surgical procedures in this study had been performed by the same team, so that the criteria to select patients for surgery were the same throughout the periods of this study. On the other hand, the phenomena called lead-time bias and length bias more recently occurs when a suitable diagnostic practice

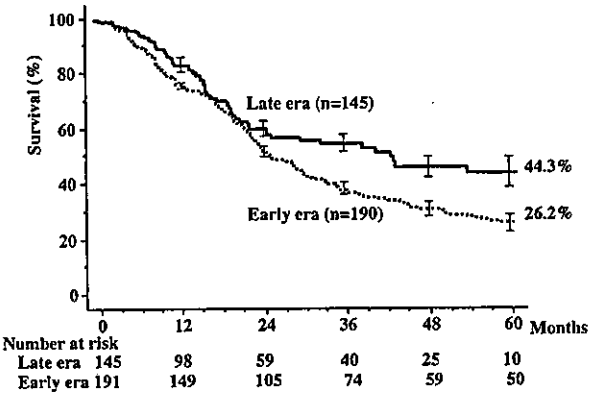


Fig 5. Survival of patients who underwent complete resection for pathologic stage III nonsmall cell lung cancer. The survival in the late era (1996 to 2002) was significantly higher than that in the early era (1985 to 1995) (p = 0.0120).

Table 3. Multivariate Analysis of Prognostic Factors

Factors	Unfavorable	Favorable	Risk Ratio	95% CI	*p* Value
Age	Older	Younger	1.030	1.020–1.040	<0.0001
Sex	Male	Female	1.691	1.347–2.123	<0.0001
Size (mm)	Larger	Smaller	1.014	1.009–1.019	<0.0001
Histology	AD	non-AD	1.199	1.004–1.432	0.0449
Procedure	Pne + Lob	Wed + Seg	1.027	0.799–1.321	0.8349
Pathologic stage	Advanced	Earlier	1.795	1.622–1.986	<0.0001
Era	Early	Late	1.558	1.275–1.903	<0.0001

Continuous variables for age, size, pathologic stage; and categories for sex, histology, procedure, and era.

AD = adenocarcinoma; CI = confidence interval; Lob = lobectomy; Pne = pneumonectomy; Seg = segmentectomy; Wed = wedge resection.

or a screening test leads to exposure of a disease before symptoms have developed. The advance in the time of diagnosis without moving back the time of death creates lead-time bias in survival comparison. Moreover, the attempt to discover a tumor results in detection of more biologically indolent tumors, which is named length bias. Even if therapy is ineffectual, the period of survival will increase because of the increment provided by presymptomatic detection of the disease.

Both the lead-time and length problems are pertinent, but we were concerned about another problem regarding the comparison of survival in each of the constituent stages [13, 14]. If innovative systems of diagnostic imaging routinely found silent or early metastases, the stages for the more recent patients would not be assigned to the same data as in the older era. The new data would allow patients with silent metastases to migrate from lower stages into higher ones, which would improve survival both in the lower and higher stages, although the total survival rate would be unaffected. Therefore, we must always pay careful attention to the extent to which known biases may have influenced the observed results.

Table 4. Multivariate Analysis of Prognostic Factors in Patients With Pathologic Stage I or III Disease

Factors	Unfavorable	Favorable	Risk Ratio	95% CI	*p* Value
Among patients with pathologic stage I disease (n = 859)					
Age	Older	Younger	1.035	1.019–1.051	<0.0001
Sex	Male	Female	1.616	1.146–2.280	0.0062
Size (mm)	Larger	Smaller	1.018	1.010–1.026	<0.0001
Histology	Non-AD	AD	1.064	0.797–1.421	0.6715
Era	Early	Late	2.031	1.449–2.846	<0.0001
Among patients with pathologic stage III disease (n = 336)					
Age	Older	Younger	1.024	1.008–1.041	0.0039
Sex	Male	Female	1.843	1.259–2.698	0.0017
Size (mm)	Larger	Smaller	1.013	1.006–1.020	0.0001
Histology	AD	non-AD	1.477	1.105–1.976	0.0085
Era	Early	Late	1.397	1.023–1.907	0.0356

Continuous variables for age and size; and categories for sex, histology, and era.

AD = adenocarcinoma; CI = confidence interval.

References

1. Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ. Cancer statistics, 2003. CA Cancer J Clin 2003;53:5–26.
2. Jie C, Wever AM, Huysmans HA, Franken HC, Wever-Hess J, Hermans J. Time trends and survival in patients presented for surgery with non-small-cell lung cancer 1969–1985. Eur J Cardiothorac Surg 1990;4:653–7.
3. Martini N, Melamed MR. Multiple primary lung cancers. J Thorac Cardiovasc Surg 1975;70:606–12.
4. Okada M, Tsubota N, Yoshimura M, Miyamoto Y. Operative approach for multiple primary lung carcinomas. J Thorac Cardiovasc Surg 1998;115:836–40.
5. Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997;111:1710–7.
6. Okada M, Tsubota N, Yoshimura M, Miyamoto Y. Proposal for reasonable mediastinal lymphadenectomy in bronchogenic carcinomas: role of subcarinal nodes in selective dissection. J Thorac Cardiovasc Surg 1998;116:949–53.
7. Okada M, Tsubota N, Yoshimura M, et al. Extended sleeve lobectomy for lung cancer: the avoidance of pneumonectomy. J Thorac Cardiovasc Surg 1999;118:710–3.
8. Okada M, Yamagishi H, Satake S, et al. Survival related to lymph node involvement in lung cancer after sleeve lobectomy compared with pneumonectomy. J Thorac Cardiovasc Surg 2002;119:814–9.
9. Okada M, Yoshikawa K, Hatta T, Tsubota N. Is segmentectomy with lymph node assessment an alternative to lobectomy for non-small cell lung cancer of 2 cm or smaller? Ann Thorac Surg 2002;71:956–60.
10. Tsubota N, Ayabe K, Doi O, et al. Ongoing prospective study of segmentectomy for small lung tumors. Study Group of Extended Segmentectomy for Small Lung Tumor. Ann Thorac Surg 1998;66:1787–90.
11. Strauss GM, Gleason RE, Sugarbaker DJ. Chest X-ray screening improves outcome in lung cancer. A reappraisal of randomized trials on lung cancer screening. Chest 1995; 107(6 Suppl):270S-9S.
12. Cole P, Morrison AS. Basic issues in population screening for cancer. J Natl Cancer Inst 1980;64:1263–72.
13. Feinstein AR. Symptoms as an index of biological behaviour and prognosis in human cancer. Nature 1966;209:241–5.
14. Richert-Boe KE, Humphrey LL. Screening for cancers of the lung and colon. Arch Intern Med 1992;152:2398–404.

GENERAL THORACIC

Prognostic Significance of Perioperative Serum Carcinoembryonic Antigen in Non-Small Cell Lung Cancer: Analysis of 1,000 Consecutive Resections for Clinical Stage I Disease

Morihito Okada, MD, PhD, Wataru Nishio, MD, PhD, Toshihiko Sakamoto, MD, PhD, Kazuya Uchino, MD, Tsuyoshi Yuki, MD, Akio Nakagawa, MD, and Noriaki Tsubota, MD, PhD

Department of Thoracic Surgery, Hyogo Medical Center for Adults, Akashi City, Hyogo, Japan

Background. The prognostic implication of serum carcinoembryonic antigen (CEA) has yet to be comprehensively analyzed since the reports available so far have comprised small patient populations. We evaluated perioperative CEA values with regard to surgical results in a large number of patients to clarify its merit.

Methods. We measured serum CEA levels before and after surgery in 1,000 consecutive patients with clinical stage I non-small cell lung cancer who underwent resection of tumor. High CEA value was greater than 5.0 ng/mL.

Results. Three hundred and sixty-eight patients (36.8%) had high preoperative CEA levels. The CEA levels after surgery were normalized in 242 patients (24.2%) and persistently elevated in 126 patients (12.6%). High CEA levels were seen more frequently in patients with older age, male gender, larger size of tumor, incomplete resection, and advanced pathologic stage. Patients with a high preoperative CEA level had a poor survival. Among these patients, even worse survival was seen for those with a high postoperative CEA level. These prognostic trends were still observed for patients with pathologic stage I disease. Multivariate analysis demonstrated that both preoperative and postoperative CEA levels were independent prognostic determinants ($p = 0.0243$ and $p < 0.0001$, respectively).

Conclusions. Perioperative measurement of serum CEA concentrations yields information valuable for detecting patients at high risk of poor survival. Normalization of CEA levels after surgery was a significant favorable prognostic sign in patients with an elevated CEA level before surgery. Even after apparently successful surgical therapy, patients with a high CEA level should be carefully followed up, and might represent a suitable target for neoadjuvant clinical trials.

(Ann Thorac Surg 2004;78:216–21)

Although the international TNM classification system is the key to planning therapy options in patients with non-small cell lung cancer and is considered the best available prognostic predictor, its power is limited. Among patients within the same TNM group of risk, we have often encountered differences between expected and real surgical results following curative resection. Owing to the possible concept that response to treatment or prognosis may be based on inherent biological characteristics of cancer cells, we should rapidly expand methods for the description of biological tumor aggressiveness.

Presently, the idea that serum biomarkers are helpful in the management of lung cancer is not uniformly accepted. In 1997, the American Thoracic Society and The European Respiratory Society jointly published guidelines [1] for assessment of non-small cell lung cancer, indicating that no serum tumor markers had sensitivity and specificity sufficient to reliably detect occult disease or influence treatment. Finally, they did not recommend routine measurement of any biomarkers in the screening, staging, or evaluation of disease progression.

Carcinoembryonic antigen (CEA) represents a heterogeneous group of oncofetal glycoprotein antigens, which circulate in high concentrations in patients with certain malignancies. Because of reports of its low sensitivity and specificity as a tumor marker, CEAs have played a less valuable role in the diagnosis, management, and prognosis of non-small cell lung cancer than has been the case with most other common cancers [2]. Routine measurement of serum CEA levels is not widely performed before or after resection for non-small cell lung cancer, particularly in the United States. However, several reports suggested that increased preoperative serum CEA levels were associated with more advanced disease and with poor survival after presumptively curative resection

Accepted for publication Feb 3, 2004.

Address reprint requests to Dr Okada, Department of Thoracic Surgery, Hyogo Medical Center for Adults, Kitaohji-cho13-70, Akashi City 673-8558, Hyogo, Japan; e-mail: morihito1217jp@aol.com.

Published by Elsevier Inc

0003-4975/04/$30.00
doi:10.1016/j.athoracsur.2004.02.009

Table 1. Characteristics of Patients With Clinical Stage I Non-Small Cell Lung Cancer (n = 1,000)

		Serum CEA Value (ng/mL)			
	Total	N Group	HN Group	HH Group	*p* Value
Number	1000	632	242	126	
Age (years)	64.5 ± 10.1	63.2 ± 10.4	64.5 ± 9.7	68.2 ± 8.5	<0.0001
Gender					<0.0001
Male	644	373	169	102	
Female	356	259	73	24	
Size (mm)	28.4 ± 15.1	27.0 ± 14.3	30.1 ± 14.3	32.2 ± 19.0	<0.0001
Histology					0.1897
Adenocarcinoma	694	449	167	78	
Squamous cell carcinoma	260	151	65	44	
Large cell carcinoma	18	11	5	2	
Anosquamous carcinoma	13	8	3	2	
Carcinoid	15	13	2	0	
Procedure					0.0011
Pneumonectomy	4	3	1	0	
Lobectomy	660	404	181	75	
Segmentectomy	261	178	49	34	
Wedge resection	75	47	11	17	
Resectability					0.0003
Complete	933	599	227	107	
Incomplete	67	33	15	19	

According to serum CEA values before and after surgery, patients were classified into three groups: continuously normal (N group), returned to normal range (HN group), and continuously high (HH group).

CEA = carcinoembryonic antigen.

[3–7]. Carcinoembryonic antigen assay may be a useful serum test that could correlate with aspects of tumor biological aggressiveness not measured by conventional modalities. This capacity has yet to be intensively investigated since reports published thus far have dealt with small patient populations. The present study, which consisted of consecutive series of numerous patients, was undertaken to analyze the biology plausibility of CEA as a predictive method by associating increase in its levels with clinical characteristics of patients and pathologic findings, and to evaluate the independent prognostic significance of perioperative CEA values. In addition, some reports indicated that non-small cell lung cancer patients, with a serum CEA level higher than 50 ng/mL, all died within a few years, even if apparently curative surgery was performed [3, 7, 8]; we examined follow-up data for such patients in our series.

Material and Methods

From January 1985 to December 2002, we measured serum CEA levels before and after surgery in 1,000 consecutive clinical stage I patients who underwent resection for primary non-small cell lung cancer. Institutional review board approval was obtained for collecting the data in a secure database and reporting on its analyses. Patients who had preoperative chemotherapy or radiotherapy were excluded. For preoperative evalua-

Table 2. Pathologic TNM Stage of Patients With Clinical Stage I Non-Small Cell Lung Cancer (n = 1,000)

		Serum CEA Value (ng/mL)			
	Total	N Group	HN Group	HH Group	*p* Value
Number	1000	632	242	126	
P-stage					<0.0001
IA	479	339	98	42	
IB	216	133	56	27	
IIA	45	27	16	2	
IIB	74	40	18	16	
IIIA	87	43	30	14	
IIIB	80	42	19	19	
IV	19	8	5	6	
P-T status					<0.0001
T1	570	393	129	48	
T2	305	173	84	48	
T3	41	23	7	11	
T4	84	43	22	19	
P-N status					<0.0001
N0	785	526	169	90	
N1	112	57	36	19	
N2	103	49	37	17	
P-M status					0.0313
M0	981	624	237	120	
M1	19	8	5	6	

According to serum CEA values before and after surgery, patients were classified into three groups: continuously normal (N Group), returned to normal range (HN Group), and continuously high (HH Group).

CEA = carcinoembryonic antigen.

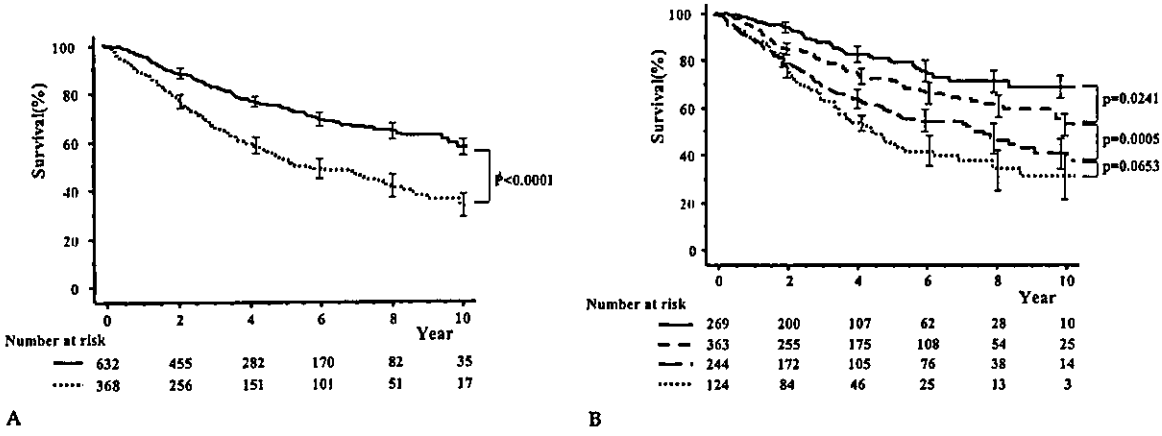


Fig 1. Cumulative survival curves for patients with clinical stage I non-small cell lung cancer according to preoperative serum CEA values (A) (— = CEA ≤ 5.0 ng/mL [n = 632]; · · · = CEA ≥ 5.1 ng/mL [n = 368]). In addition, the study groups were subdivided by serum CEA levels (B) (— = CEA; ≤ 2.5 ng/mL [n = 269]; – – = CEA; 2.6 to 5.0 ng/mL [n = 363]; –· = CEA; 5.1 to 10.0 ng/mL [n = 244]; · · · = CEA; ≥ 10.1 ng/mL [n = 124]). (CEA = carcinoembryonic antigen.)

tion or clinical staging, we used a detailed history and physical examination, biochemical profile, chest roentgenogram examination, bronchoscopy, computed tomography of the chest, brain, and upper portion of the abdomen, and bone scintigraphy. Staging was determined according to the international TNM staging system [9]. Intraoperative staging was performed by dissecting intrapulmonary, hilar, and mediastinal lymph nodes, and careful postoperative examination was carried out by pathologists. The histologic type of the tumor was determined using the World Health Organization classification. There were 644 males and 356 females, ranging in age from 15 to 88 years (mean, 64.5 ± 10.1 years). The average size of tumor was 28.4 ± 15.1 mm. Histologic diagnosis was adenocarcinoma in 694 patients, squamous cell carcinoma in 260, large cell carcinoma in 18, carcinoid in 15 and adenosquamous carcinoma in 13. The surgical procedure was lobectomy in 660 patients, segmentectomy in 261, wedge resection in 75, and pneumonectomy in 4, and the rate of curative resection reached 93.3%. Pathologic stage was I in 695 patients, II in 119, III in 167, and IV in 19. Patient characteristics and pathologic stage are summarized in Tables 1 and 2, respectively.

Blood sampling was performed within the 1-month period preceding surgery and 1 month after surgery. The serum CEA level of all blood samples was measured by the enzyme immunoassay method (Fuji Rebio, Tokyo, Japan). According to the manufacturer, the average for this assay in healthy individuals is 1.93 ng/mL and the upper limit of normal is 5.0 ng/mL. Patients were categorized according to shift of CEA levels by surgery as follows: continuously normal (N group), continuously high (HH group), or returned to normal range (HN group).

After surgery, the patients were in general examined at

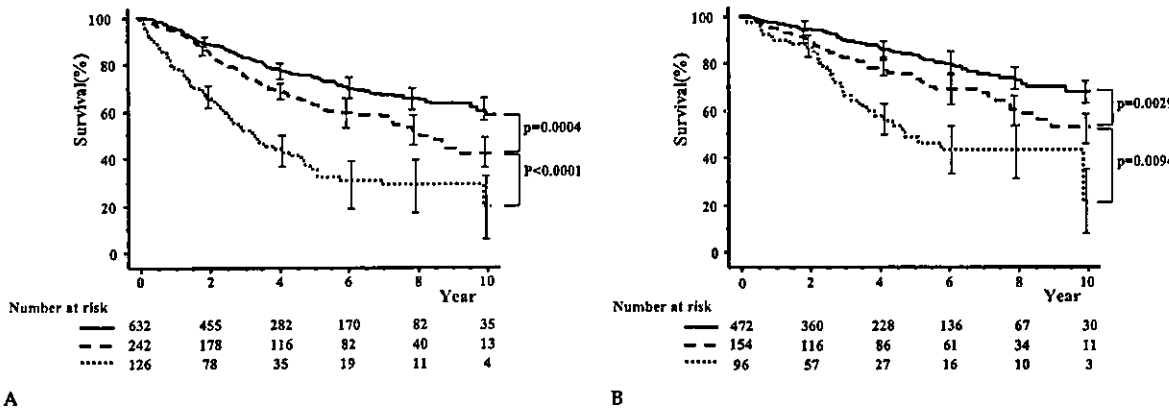


Fig 2. Cumulative survival curves for patients with clinical stage I non-small cell lung cancer (A) (— = N group [n = 632]; – – = HN group [n = 242]; · · · = HH group [n = 126]), and of patients with pathologic stage I non-small cell lung cancer (B) (— = N group [n = 472]; – – = HN group [n = 154]; · · · = HH group [n = 69]). According to change in serum CEA values before and after surgery, patients were classified into three groups; continuously normal (N group), returned to normal range (HN group), and continuously high (HH group). (CEA = carcinoembryonic antigen.)

Table 3. Multivariate Analysis of Prognostic Factors With Preoperative Determined Variables (n = 1,000)

Factors	Unfavorable	Favorable	Risk Ratio	95% CI	p Value
Gender	Male	Female	1.633	1.254–2.128	0.0003
Age	Higher	Lower	1.027	1.014–1.040	<0.0001
Size	Larger	Smaller	1.022	1.016–1.027	<0.0001
Preoperative CEA	Higher	Lower	1.004	1.000–1.007	0.0243

Continuous variables for age, size, CEA level, and categories for gender.

CEA = carcinoembryonic antigen; CI = confidence interval.

3-month intervals for 5 years and thereafter at 1-year intervals. The evaluations included physical examination, chest roentgenography, and tumor markers. Moreover, chest, abdominal, and brain computed tomographic scans and a bone scintiscan were carried out each year. Whenever any symptoms or signs of recurrence appeared in these examinations, further evaluations to detect disease were performed.

The statistical significance of differences between the classified groups and several clinical-pathologic factors was assessed by the Kruskal-Wallis test. Survival was calculated by the Kaplan-Meier method, and differences in survival were determined by log-rank analysis. A multivariate analysis of several prognostic factors was carried out using Cox's proportional hazards regression model. Zero time was the date of pulmonary resection, and the terminal event was death attributable to cancer, noncancer, or unknown cause. Significance was defined as p less than 0.05.

Results

Among 1,000 patients with clinical stage I non-small cell lung cancer, 632 (63.2%) had a normal preoperative CEA level (N group) and 368 (36.8%) had a high one. Of the latter 368 patients, postoperative evaluations of CEA revealed a return to normal range in 242 patients (HL group) and unchanged at a high level in 126 (HH group). The distributions of the previously mentioned groups according to age, gender, size of tumor, histologic type, surgical procedure, and resectability are shown in Table 1. Older age, male gender, larger size of tumor, and incomplete resection were frequently observed in patients with a high postoperative CEA level, particularly in the HH group. Moreover, the HH group exhibited more advanced disease than not only the N group but also the HN group (Table 2).

Next, we analyzed the affect of serum CEA level on survival. Overall follow-up ranged from 8 to 224 months, with a median of 61 months for surviving patients. The 5-year survival rates were 75.2% and 53.8% for patients with normal and high preoperative CEA levels, respectively (Fig 1A). The survival rate was significantly poorer for patients with a high preoperative CEA level ($p < 0.0001$). In addition, we investigated the survival rates for groups subdivided by preoperative CEA levels (Fig 1B). The higher the preoperative CEA level, the poorer survival was, even within the normal range. When we also considered postoperative CEA levels, the survival rates for 5 years in the HH group and HN group were 35.2% and 62.6%, respectively ($p < 0.0001$, Fig 2A). In general, patients with pathologic stage I disease are assumed to have been cured following complete resection of the tumor because lymph nodes are not involved. However, we found that a considerable number of patients with still elevated CEA levels had poor survival despite being postoperatively diagnosed as having pathologic stage I disease. The 5-year survival rates of pathologic stage I patients of the N group, the HL group, and the HH group were 84.2%, 74.2%, and 48.6%, respectively (Fig 2B). These data suggested that failure to normalize CEA levels after surgery was associated with a significantly worse prognosis, and that the survival, even of patients with pathologic stage I disease for 5 years, was less than 50%.

Univariate analyses demonstrated that not only male gender ($p < 0.0001$), age older than 65 years ($p = 0.0001$), tumor size larger than 30 mm ($p < 0.0001$), advanced pathologic stage ($p < 0.0001$), and incomplete resectability of the tumor ($p < 0.0001$), but also a high CEA level before ($p < 0.0001$) and after surgery ($p = 0.0001$) significantly and negatively affected survival. Using these variables we performed multivariate analyses for the prognostic significance of CEA values to be strongly emphasized. Multivariate Cox analysis for preoperative determined factors demonstrated that CEA level ($p = 0.0243$) as well as gender ($p = 0.0003$), age ($p < 0.0001$),

Table 4. Multivariate Analysis of Prognostic Factors With Postoperative Determined Variables in Patients With a High Preoperative CEA Value (n = 368)

Factors	Unfavorable	Favorable	Risk Ratio	95% CI	p Value
Pathological stage	Higher	Lower	1.497	1.249–1.795	<0.0001
Resectability	Incomplete	Complete	1.968	1.008–1.022	0.0097
Postoperative CEA	Higher	Lower	1.015	1.051–2.539	<0.0001

Continuous variables for stage, CEA level, and categories for resectability.

CI = confidence interval; CEA = carcinoembryonic antigen.

Ann Thorac Surg
2004;78:216–21

Table 5. Characteristics and Surgical Results of C-stage I Patients with Preoperative CEA Values Greater than 50 ng/mL (n = 13)

No.	Age	Sex	CEA (ng/mL) Pre	CEA (ng/mL) Post	Size (mm)	Hist	Resec	pTNM, Stage	Rec	Prognosis (month)
1.	72	M	62.6	169.9	18	AD	Incomplete	pT4N2M0, 3B	Distant	15m Death (Cancer)
2.	78	F	63.2	7.8	65	LA	Incomplete	pT2N0M1, 4	Distant	4m Death (Cancer)
3.	75	M	72.7	4.5	40	SQ	Complete	pT2N0M0, 1B	(-)	106m Alive
4.	75	F	74.6	10.5	43	AD	Complete	pT2N0M0, 1B	Distant	54m Alive
5.	69	M	75.5	9.9	25	AD	Complete	pT1N0M0, 1A	Local	27m Death (Cancer)
6.	69	F	81.0	3.3	37	AD	Complete	pT2N0M0, 1B	(-)	106m Alive
7.	68	M	81.4	152.7	32	AD	Incomplete	pT2N0M1, 4	Distant	5m Death (Cancer)
8.	68	M	102.5	13.8	35	AD	Complete	pT2N0M0, 1B	Distant	17m Death (Cancer)
9.	80	M	120.0	23.1	34	AD	Complete	pT2N1M0, 2B	Distant	19m Death (Cancer)
10.	50	F	134.5	17.2	34	AD	Incomplete	pT4N0M0, 3B	Distant	61m Death (Cancer)
11.	66	M	182.1	14.8	75	AD	Complete	pT4N0M0, 3B	Distant	23m Death (Cancer)
12.	65	M	188.9	120.0	90	AD	Incomplete	pT3N0M1, 4	Distant	4m Death (Cancer)
13.	74	F	427.8	45.2	31	AD	Complete	pT2N0M0, 1B	(-)	64m Alive

Hist = histologic type; Rec = resurrence; Resec = resectability.

and size of tumor ($p < 0.0001$) were independent, significant prognostic determinants (Table 3). Furthermore, analysis for postoperative determined factors revealed that CEA level ($p < 0.0001$) as well as pathologic stage ($p < 0.0001$), and resectability of the tumor ($p = 0.0097$) were independent, significant prognostic variables (Table 4).

Last, we examined the follow-up data for patients with preoperative CEA level greater than 50 ng/mL (Table 5). There were 13 patients (1.3%) belonging to this category among 1,000 patients diagnosed as having clinical stage I disease. Of them, 9 (69%) had distant metastasis as initial recurrence, and had already died of cancer. Interestingly, 3 patients (23%) in this category are alive more than 5 years without recurrence.

Comment

The genuine question examined in this study was whether patients who otherwise appeared to have curable tumors would have a worse prognosis if serum CEA value was high. In our series, the results yielded by univariate and multivariable analyses demonstrated that both preoperative and postoperative serum CEA values had a strong impact on survival. In addition, multivariate analysis for postoperative factors showed that CEA values as well as pathologic TNM stage and resectability of tumor were significant, important predictive variables affecting survival. Results suggested that CEA values did not simply reflect tumor load but were independent prognostic factors per se and might serve to stratify patients within the same TNM stage after complete resection. One of the most interesting issues is to the prognosis of patients with only a serum high CEA value, particularly of those who otherwise underwent curative surgery for proven early-stage cancer. It was surprising that 5-year survival rate was less than 50% for patients with a still elevated postoperative CEA level diagnosed as having pathologic stage I disease after apparently complete resection of tumor.

We have provided powerful evidence that completeness of removal of the tumor is essential. It would be of concern if patients whose disease was judged to be incompletely resected actually had similar survival to those with completely resected disease. As well as the prognostic advantage seen in completely resected patients, a higher proportion of patients with elevated CEA levels before surgery had a return to normal range in CEA level. In our series, CEA levels returned to normal range in approximately 66% of patients, which we believe will get better with further experience and practice. We suspect that failure to achieve normal levels of CEA is caused either by unrecognized extrapulmonary disease or failure to eradicate all pulmonary disease.

Icard and colleagues [7] reported that all patients with preoperative CEA levels higher than 50 ng/mL who underwent seemingly curative resection for non-small cell lung cancer died within 2 years. Earlier, Concannon and colleagues [3] demonstrated that all 47 patients who had resected lung cancer and high CEA levels failed to survive longer than 3 years. The most interesting inquiry was whether a preoperative CEA level higher than 50 ng/mL always indicated metastatic carcinoma, or whether thoracic surgeons would accept the validity of CEA testing to exclude patients who have such an abnormally elevated level from undergoing lung resections. In our analysis, it should be emphasized that 69% (9 of 13) of clinical stage I patients with preoperative CEA greater than 50 ng/mL developed distant metastasis and died of cancer. Despite these poor survival data, we still have concern about giving up surgical therapy in clinical stage I lesions even if they have an excessively high CEA level. To our surprise, among patients with preoperative CEA higher than 50 ng/mL, 3 (23%) were long-term survivors with no recurrence. One patient had a 427.8 ng/mL CEA level before surgery but a remarkable drop after surgery. The CEA levels of the other 2 patients normalized postoperatively. It is of great interest to note that normalization of serum CEA level after surgery was an important

prognostic sign even in patients with an abnormally elevated CEA level before surgery.

A point will be reached when the risk signaled by serum CEA value may be greater than the risk indicated by a more advanced TNM stage. In other words, when a patient has had extremely high CEA levels, the influence of CEA on prognosis might be more crucial than the influence of TNM stage. This emphasizes the need to avoid dichotomous results (positive vs negative) at least in cases in which CEA is employed to estimate prognosis. It seems more satisfactory to use CEA as a continuous variable since this would enable any predictive information to be more effectively utilized. Although a cutoff point is usually used to define a high or low risk group of patients, this method tends to oversimplify and even distort the associations between variables and results.

At present, perioperative measurement of serum CEA is not commonly performed during the staging or resection of tumors in patients with non-small cell lung cancer. This study describes the significant independent value of serum CEA in patients undergoing stage determination, undergoing resection, or considering adjuvant therapy for non-small cell lung cancer. Unfortunately, this has not gained universal acceptance with physicians or surgeons, particularly in the United States.

References

1. Pretreatment evaluation of non-small-cell lung cancer. Official statement of The American Thoracic Society and The European Respiratory Society. Am J Respir Crit Care Med 1997;156:320–2.
2. Carcinoembryonic antigen: its role as a marker in the management of cancer. Br Med J 1981;282:373–5.
3. Concannon JP, Dalbow MH, Hodgson SE, et al. Prognostic value of preoperative carcinoembryonic antigen (CEA) plasma levels in patients with bronchogenic carcinoma. Cancer 1978;42:1477–83.
4. Ford CH, Stokes HJ, Newman CE. Carcinoembryonic antigen and prognosis after radical surgery for lung cancer: immunocytochemical localization and serum levels. Br J Cancer 1981; 44:145–53.
5. Dent PB, McCulloch PB, Wesley-James O, et al. Measurement of carcinoembryonic antigen in patients with bronchogenic carcinoma. Cancer 1978;42:1484–91.
6. Sawabata N, Ohta M, Takeda S, et al. Serum carcinoembryonic antigen level in surgically resected clinical stage I patients with non-small cell lung cancer. Ann Thorac Surg 2003;74:174–9.
7. Icard P, Regnard JF, Essomba A, et al. Preoperative carcinoembryonic antigen level as a prognostic indicator in resected primary lung cancer. Ann Thorac Surg 1994;58:811–4.
8. Sadoff L. The usefulness of carcinoembryonic antigen testing in the overall management of patients with non-small-cell lung cancer. Am J Clin Oncol 1998;21:284–6.
9. Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997;111:1710–7.

GENERAL THORACIC

Effect of Histologic Type and Smoking Status on Interpretation of Serum Carcinoembryonic Antigen Value in Non–Small Cell Lung Carcinoma

Morihito Okada, MD, PhD, Wataru Nishio, MD, PhD, Toshihiko Sakamoto, MD, PhD, Kazuya Uchino, MD, Tsuyoshi Yuki, MD, Akio Nakagawa, MD, and Noriaki Tsubota, MD, PhD

Department of Thoracic Surgery, Hyogo Medical Center for Adults, Akashi City, Hyogo, Japan

Background. Serum carcinoembryonic antigen (CEA) has all of the properties desired for a biologic measure to be used as a prognostic indicator in the clinical evaluation of lung cancer. Carcinoembryonic antigen value appears to be related to tumor histologic type and patients' smoking status, which has yet to be intensively analyzed as reports available thus far have consisted of a limited number of patients. This study was undertaken to determine whether the prognostic value of CEA differs according to histologic type in a large group of patients with clinical early-stage lung cancer, and how smoking influences its value.

Methods. Two series of 694 and 260 consecutive patients who underwent resection for clinical stage I lung adenocarcinoma and squamous cell carcinoma, respectively, were evaluated. We measured serum CEA before and after surgery, and analyzed its prognostic significance in relation to histologic type and its correlation with smoking status.

Results. We found significantly higher CEA levels in patients with adenocarcinomas than in those with squamous cell carcinomas (7.8 versus 5.5 ng/mL; $p = 0.0018$), but a higher percentage of CEA-positive patients among those with squamous cell carcinoma (109 of 260, 41.9%) than those with adenocarcinoma (245 of 694, 35.3%). Clinical stage I patients with a high preoperative CEA level had a poor prognosis, and for pathologically confirmed stage I patients with a high postoperative CEA level the prognosis was worse. The prognostic value of serum CEA level was thus significantly greater for adenocarcinoma than for squamous cell carcinoma. This was probably because of a much higher proportion of smokers among patients with squamous cell carcinoma. In adenocarcinoma, the growth of which was generally less influenced by smoking, the proportion of CEA-positive smokers (49.3%, 170 of 345) was greater than that of CEA-positive nonsmokers (21.5%, 75 of 349, $p < 0.0001$). Additionally, in patients with adenocarcinoma, survival of nonsmokers was more greatly influenced by CEA level than that of smokers.

Conclusions. Although serum CEA values measured before and after surgery are important in identifying patients at high risk of poor survival, its specificity is higher for adenocarcinoma than for squamous cell carcinoma. When serum CEA levels are checked, smoking status of patients, particularly of those with squamous cell carcinoma, should be taken into account.

(Ann Thorac Surg 2004;78:1004–10)

In 1997, the American Thoracic Society and the European Respiratory Society jointly stated the guidelines for evaluation of non–small cell lung cancer [1]. It was noted that no serum tumor marker was sensitive and specific enough to identify occult disease or influence treatment, and that routine measurement of biomarkers was not recommended for screening or staging of disease. Thus, the role of serum carcinoembryonic antigen (CEA) levels measured before or after resection of non–small cell lung cancer is not widely accepted. However, several studies have indicated that CEA in patients with non–small cell lung cancer provides information useful for determining survival independent of the stage of the disease [2–7].

Non–small cell lung cancer constitutes a histologically heterogeneous group of lung cancers, among which the two major subtypes are adenocarcinoma and squamous cell carcinoma. The majority of studies done thus far on the prognostic value of serum CEA involved a patient population not stratified by histologic type. There are few reports examining the differences in CEA prognostic values between adenocarcinoma and squamous cell carcinoma. Occasionally serum CEA levels are elevated in patients with nonmalignant diseases such as chronic bronchitis, emphysema, or colitis [8, 9]. In addition, cigarette smoking is one of the most powerful variables associated with increased serum CEA levels [10, 11]. We undertook this study to evaluate the prognostic value of CEA levels in patients with adenocarcinoma and squa-

Accepted for publication March 8, 2004.

Address reprint requests to Dr Okada, Department of Thoracic Surgery, Hyogo Medical Center for Adults, Kitaohji-cho13-70, Akashi City, 673-8558, Hyogo, Japan; e-mail: morihito1217jp@aol.com.

Published by Elsevier Inc

0003-4975/04/$30.00
doi:10.1016/j.athoracsur.2004.03.019

Table 1. Characteristics and Pathologic Findings of Patients With Clinical Stage I Disease

Variable	Total	Histologic Type		*p* Value
		AD	SQ	
Number	954	694	260	
Age (y)	64.6 ± 9.9	63.5 ± 9.9	67.9 ± 9.1	<0.0001
Sex				<0.0001
Male	611	376	235	
Female	343	318	25	
Size (mm)	28.3 ± 15.1	27.5 ± 15.3	30.6 ± 14.3	<0.0001
Preoperative CEA	7.2 (0.5–427.8)	7.8 (0.6–427.8)	5.5 (0.5–72.7)	0.0018
Procedure				0.0884
Pneumonectomy	4	2	2	
Lobectomy	634	473	161	
Segmentectomy	251	180	71	
Wedge resection	65	39	26	
Resectability				0.1173
Complete	890	635	255	
Incomplete	64	59	5	
P stage				0.0933
IA	455	345	110	
IB	204	128	76	
IIA	44	31	13	
IIB	69	32	37	
IIIA	82	68	14	
IIIB	83	74	9	
IV	17	16	1	

AD = adenocarcinoma; CEA = carcinoembryonic antigen; SQ = squamous cell carcinoma.

mous cell carcinoma, as well as to investigate how the significance of serum CEA is affected by smoking.

Material and Methods

From January 1985 through December 2002, two series of 694 and 260 consecutive patients with clinical stage I disease were operated on for proven primary adenocarcinoma and squamous cell carcinoma of the lung, respectively. The histologic type of tumor was determined by applying the World Health Organization classification. In all patients, we measured serum CEA before and after surgery and resected the primary tumor. The tumor was measured directly in the surgical specimens. For preoperative clinical staging, we used a detailed history and physical examination, biochemical profile, chest roentgenogram, bronchoscopy, computed tomography of the chest, brain, and upper portion of the abdomen, and bone scintigraphy. Stage was determined according to the international TNM staging system [12]. Patients who had undergone preoperative chemotherapy or radiotherapy were excluded.

All thoracotomies were performed within 1 month of the preoperative CEA measurement, and postoperative CEA was measured 1 month after surgery. The serum CEA was determined by an enzyme immunoassay (Fuji Rebio, Tokyo, Japan). According to the manufacturer, the average for this assay in healthy individuals is 1.93 ng/mL and the upper limit of normal is 5.0 ng/mL. Generally, the patients were postoperatively examined at 3-month intervals for 5 years and thereafter at 1-year intervals to check for recurrence and survival. We defined smokers as patients who were smoking at the time of diagnosis of lung cancer. The nonsmokers group thus included ex-smokers as well as patients who had never smoked.

The statistical significance of differences among the subdivided groups and several clinicopathologic variables was analyzed by Mann-Whitney *U* test. Survival was calculated by the Kaplan-Meier method, and differences in survival were determined by log-rank analysis. A multivariable analysis of several prognostic factors was carried out using Cox's proportional hazards regression model. Zero time was the date of pulmonary resection, and the terminal event was death attributable to cancer, noncancer, or unknown causes. Significance was defined as p less than 0.05.

Results

Clinical characteristics, surgical treatment, and pathologic stage are summarized in Table 1. Compared with squamous cell carcinoma patients, adenocarcinoma patients were younger ($p < 0.0001$), included a higher number of women ($p < 0.0001$), had a smaller tumor ($p < 0.0001$), and had higher levels of preoperative serum CEA ($p = 0.0018$). However, the percentage of preoperative CEA-positive patients was higher in the squamous cell