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Appendix. Summarized Characteristics of the Grossarth-Maticek Personality Types and Traits to which they are Prone

Personality	Characteristics	Proneness
Type 1	Dependence on withdrawn objects: - one's well-being is dependent on a withdrawn, highly-valued object (person or situation), - chronically experience hopeless/helpless and depressive feelings, - altruistic behavior and inhibition to express negative emotions and personal needs.	To cancer
Type 2	Dependence on disturbing objects: - one's well-being is constantly threatened by a disturbing, annoying objects (person or situation), - chronically experience feelings of anger, hostility, aggression, and excitement, - feel that frustrating situations are unavoidable.	To cardiovascular disease
Type 3	Ambivalent behavior: - oscillate between the positive and negative aspects of an object (person or situation), - sometimes idealize the object, sometimes devalue it, and fail to reach any integration, - express one's emotion and needs in inadequate and ambivalent ways.	To chronic anxiety
Type 4	Autonomic behavior: - maintain autonomy by flexibly regulating distance to objects (person or situation), e.g., letting a withdrawing object go or keeping distance from an annoying object, - self-regulate behaviors, including expression of emotions and needs, so that they lead to the achievement and maintenance of well-being.	To being healthy
Type 5	Rational and antiemotional behavior: - constantly cope with stress by appeals to reason and logic, never to emotional behaviors, - suppress emotional reactions and behave rationally even in frustrating interpersonal communications.	To cancer, cardiovascular disease, and depression
Type 6	Antisocial behavior: - egocentric, antisocial, and psychopathic behaviors, - express emotions and needs in inadequate and non-conforming ways.	To criminal behaviors and drug addiction

Effect of tumor size on prognosis in patients with non–small cell lung cancer: The role of segmentectomy as a type of lesser resection

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Objective: As a result of increasing discovery of small-sized lung cancer in clinical practice, tumor size has come to be considered an important variable affecting planning of treatment. Nevertheless, there have been no reports including large numbers of patients and focusing on tumor size, and controversy remains concerning the surgical management of small-sized tumors. Therefore, we investigated the relationships between tumor dimension and clinical and follow-up data, as well as surgical procedure in particular.

Methods: We reviewed the records of 1272 consecutive patients who underwent complete resection for non–small cell carcinoma of the lung.

Results: Fifty patients had tumors of 10 mm or less, 273 had tumors of 11 to 20 mm, 368 had tumors of 21 to 30 mm, and 581 had tumors of greater than 30 mm in diameter. The cancer-specific 5-year survivals of patients in these 4 groups were 100%, 83.5%, 76.5%, and 57.9%, respectively. For patients with pathologic stage I disease, they were 100%, 92.6%, 84.1%, and 76.4%, respectively. Multivariate analysis demonstrated that male sex, older age, larger tumor, and advanced pathologic stage adversely affected survival. Lesser resection was performed in 167 (52%) of 323 patients with a tumor of 20 mm or less in diameter but in 156 (16%) of 949 patients with a tumor of greater than 20 mm in diameter. The percentages of lesser resection among all procedures performed were 79%, 56%, 30%, and 15% in patients with pathologic stage I disease with a tumor of 10 mm or less, 11 to 20 mm, 21 to 30 mm, and greater than 30 mm in diameter, respectively. The 5-year cancer-specific survivals of patients with pathologic stage I disease with tumors of 20 mm or less and 21 to 30 mm in diameter were 92.4% and 87.4% after lobectomy, 96.7% and 84.6% after segmentectomy, and 85.7% and 39.4% after wedge resection, respectively. On the other hand, with a tumor of greater than 30 mm in diameter, survivals were 81.3% after lobectomy, 62.9% after segmentectomy, and 0% after wedge resection, respectively.

Conclusions: Tumor size is an independent and significant prognostic factor and important for planning of surgical treatment. Although lobectomy should be chosen for patients with a tumor of greater than 30 mm in diameter, further investigation is required for tumors of 21 to 30 mm in diameter. Segmentectomy should, as a lesser anatomic resection, be distinguished from wedge resection and might be acceptable for patients with a tumor of 20 mm or less in diameter without nodal involvement.

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Of late, as a consequence of advances in diagnostic imaging, such as high-resolution or spiral computed tomography and positron emission tomographic scanning, thoracic surgeons have encountered small-sized lung cancers at an earlier and potentially curable stage. It has thus become increasingly crucial to examine how clinical and oncologic behaviors are related to tumor dimension and thereby to choose the most advantageous treatment strategy, including surgical intervention. Although the traditional TNM staging system exists,[1] it might become obsolete within a few years and should be revised with new findings. As stated by the TNM system, the boundary of T status is a tumor 3 cm in diameter. Recent studies have, however, demonstrated that the postoperative prognosis of patients with non–small cell lung cancer of 2 cm or less in diameter is significantly better than that of patients with a larger tumor.[2-5] Controversy also exists regarding the extent of lung removal necessary for cure, especially for small-sized cancers. Although lobectomy or pneumonectomy has traditionally been considered the standard of care for resectable disease, the significance of lesser resection in the treatment of early non–small cell cancer has attracted increased interest as a minimally invasive operation with the advancement of video-assisted thoracic surgery. Arguments favoring the less-invasive operation include potential preservation of pulmonary function, lower morbidity-mortality, and shorter hospitalization. Surprisingly, there are no reports of large numbers of patients focusing on tumor dimension, one of the most subjective reoperative variables. Thus, newer information for selection of surgical intervention on the basis of tumor size is required.

We evaluated the role of tumor size, which has had increased clinical importance because of the increasing discovery of small-sized lung cancer in clinical practice. The aims of this study were to compare the clinical characteristics and follow-up data of patients subjected to complete resection of non–small cell lung cancer with tumor dimension, with special reference to determination of the appropriate surgical mode of treatment.

Patients and Methods

Between January 1985 and December 2002, a series of 1272 consecutive patients operated on for primary non–small cell carcinoma of the lung were pathologically confirmed to have complete removal with systematic nodal dissection of the hilum and mediastinum. Institutional review board approval was obtained for collection of their data in a secure database and reporting of analyses of that data. The histologic type of the tumor was determined by the World Health Organization classification. Patients with low-grade malignancy of the lung, such as carcinoid, were excluded. Staging was determined according to the international TNM staging system. Patients who had been subjected to preoperative chemotherapy or radiotherapy were excluded.

The maximum dimension of a tumor was measured using resected primary lesion specimens. 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 used physical and biochemical examination, chest radiography, computed tomography of the chest, brain, and upper portion of the abdomen, and bone scintigraphy for evaluation of recurrence.

Survivals were calculated by the Kaplan-Meier method, and differences in survival were determined by log-rank analysis. A multivariate analysis for prognostic factors was carried out by the Cox proportional hazards regression model. We analyzed the prognosis of patients in two fashions, to determine overall and cancer-related survivals. Zero time was the date of pulmonary resection, and the terminal event was death attributable to cancer-related survival, although the terminal point for overall survival was any death due to cancer, noncancerous, or unknown causes.

Results

Patients were divided into 4 groups for comparison by size of resected tumor. Fifty patients had a primary tumor with a diameter of 10 mm or less, 273 patients had a tumor of 11 to 20 mm, 368 patients had a tumor of 21 to 30 mm, and 581 patients had a tumor of greater than 30 mm in diameter. Clinical characteristics, pathologic stage, and surgical mode are summarized in Table 1, which shows that larger lesions had high degrees of association with old age, male sex, squamous cell carcinoma, and advanced-stage disease. Notably, half of the patients with a subcentimeter tumor were female, 70% of the patients had adenocarcinoma, and 96% had pathologic stage IA disease, although 4% had stage III disease. Larger resections were, as a general rule, selected for larger lesions. On the other hand, lesser resections, such as segmentectomy, were preferred for smaller lesions without proof of nodal involvement, as determined by intraoperative pathologic examination. As a result, lesser resections were performed in 167 (52%) of 323 patients with a tumor of 20 mm or less in diameter and in 156 (16%) of 949 patients with a tumor of greater than 20 mm in diameter. Of 50 patients with subcentimeter cancer, 38 (76%) underwent lesser resection, including 27 (54%) with segmentectomy. There were 3 (3/1272 [0.2%]) operative deaths. Causes of death were acute pancreatitis and bleeding during reoperation. The third patient died suddenly at home on the 30th postoperative day as a result of myocardial infarction. Follow-up was almost complete and ranged from 12 to 225 months, with a median of 61 months for surviving patients. The overall 5-year survivals of patients with a tumor of 10 mm or less, 11 to 20 mm, 21 to 30 mm, and greater than 30

TABLE 1. Characteristics of patients with complete resection for non–small cell lung cancer, pathologic findings, and surgical interventions according to tumor size

	Tumor size (mm)				
	≤10 (n = 50)	11-20 (n = 273)	21-30 (n = 368)	≥31 (n = 581)	Total (n = 1272)
Age (y)	62 (40-79)	64 (38-85)	65 (36-85)	65 (30-85)	65 (30-88)
Sex					
Male	25 (50%)	170 (62%)	249 (68%)	455 (78%)	899 (71%)
Female	209 (77%)	254 (69%)	284 (49%)	782 (61%)	
Average size (mm)	7.5	16.7	25.8	47.6	33.1
Histology					
AD	35 (70%)	209 (77%)	254 (69%)	284 (49%)	782 (61%)
SQ	15 (30%)	61 (22%)	105 (29%)	275 (47%)	456 (36%)
LA	0	3 (1%)	9 (2%)	2 (0.3%)	34 (3%)
Pathologic stage					
IA	48 (96%)	208 (76%)	233 (63%)	0	489 (38%)
IB	0	9 (3%)	2 (1%)	258 (44%)	289 (23%)
IIA	0	21 (8%)	42 (11%)	0	63 (5%)
IIB	0	5 (2%)	18 (5%)	141 (24%)	164 (13%)
IIIA	1 (2%)	23 (8%)	39 (11%)	129 (22%)	192 (15%)
IIIB	1 (2%)	7 (3%)	14 (4%)	53 (9%)	75 (6%)
Procedure					
PN	0	2 (1%)	5 (1%)	23 (4%)	30 (2%)
LO	12 (24%)	142 (52%)	268 (73%)	497 (86%)	919 (72%)
SE	27 (54%)	102 (37%)	76 (21%)	53 (9%)	258 (20%)
WE	10 (20%)	27 (10%)	19 (5%)	8 (1%)	64 (5%)
BR	1 (2%)	0	0	0	1 (0.1%)

AD, Adenocarcinoma; *SQ,* squamous cell carcinoma; *LA,* large cell carcinoma; *PN,* pneumonectomy; *LO,* lobectomy; *SE,* segmentectomy; *WE,* wedge resection; *BR,* bronchial resection.

TABLE 2. Multivariate analyses for overall and cancer-specific prognosis in patients with complete resection for non–small cell lung cancer

Factors	Unfavorable	Favorable	Risk ratio	95% CI	*P* value
Prognosis for overall deaths					
Sex	Male	Female	1.772	1.397-2.247	<.0001
Age	Older	Younger	1.030	1.019-1.042	<.0001
Size	Larger	Smaller	1.003	1.001-1.005	.0035
Histology	Non-AD	AD	1.059	0.874-1.284	.5587
P-stage	Advanced	Early	2.027	1.821-2.257	<.0001
Procedure	PN+LO	SE+WE+BR	1.049	0.818-1.345	.7039
Prognosis for cancer-specific deaths					
Sex	Male	Female	1.569	1.184-2.078	.0017
Age	Older	Younger	1.014	1.001-1.027	.0387
Size	Larger	Smaller	1.004	1.002-1.006	<.0001
Histology	Non-AD	AD	1.136	0.894-1.443	.2969
P-stage	Advanced	Early	2.430	2.129-2.773	<.0001
Procedure	PN+LO	SE+WE+BR	1.047	0.761-1.442	.7763

CI, Confidence interval; *AD,* adenocarcinoma; *PN,* pneumonectomy; *LO,* lobectomy; *SE,* segmentectomy; *WE,* wedge resection; *BR,* bronchial resection. Continuous variables for age, size, and p-stage, and categories for gender, histology and procedures are given.

mm in diameter were 87.3%, 75.5%, 68.0%, and 49.0%, respectively (Figure 1, *A*), whereas the corresponding cancer-specific 5-year survivals were 100%, 83.5%, 76.5%, and 57.9%, respectively (Figure 1, *B*). There were significant differences in survivals among the 4 groups. Additionally, for patients with pathologic stage I disease, the overall 5-year survivals of the 4 groups noted above were 86.0%, 83.8%, 75.3%, and 67.0%, respectively (Figure 2, *A*),

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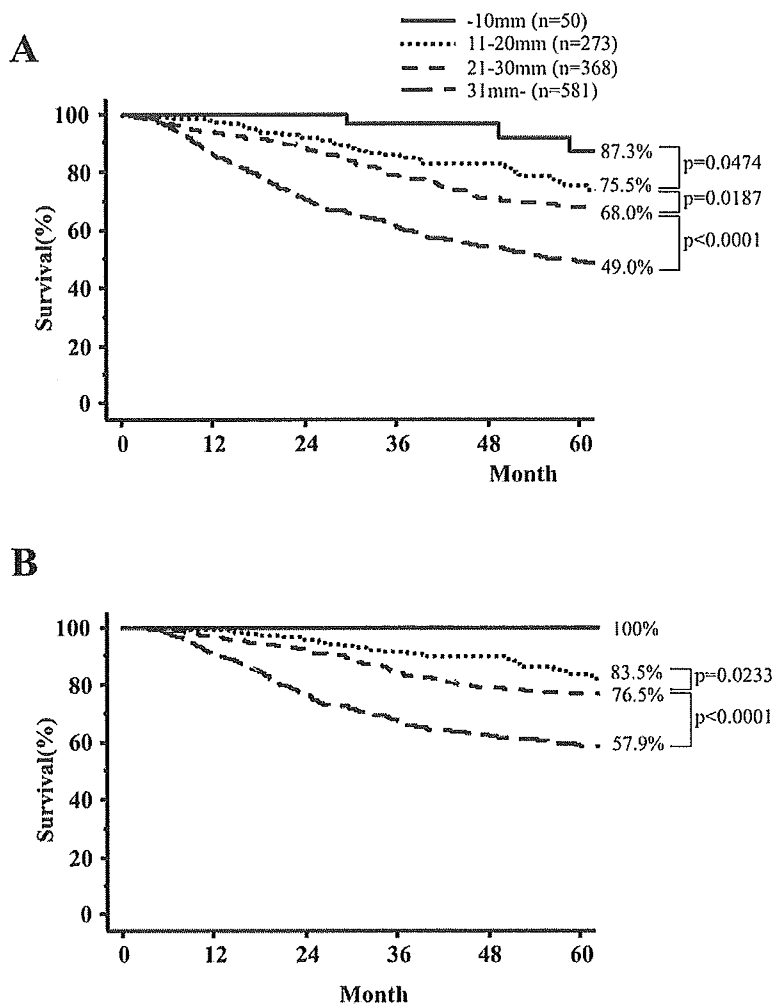

Figure 1. Overall (A) and cancer-specific (B) survival curves for patients with complete resection for non–small cell lung cancer according to tumor size.

whereas their cancer-specific 5-year survivals were 100%, 92.6%, 84.1%, and 76.4%, respectively (Figure 2, *B*). There were significant differences in these survivals between patients with a tumor of 11 to 20 mm in diameter and those with a tumor of 21 to 30 mm in diameter.

Univariate analyses demonstrated that male sex ($P < .0001$), age older than 65 years ($P = .0003$), tumor size larger than 30 mm ($P < .0001$), nonadenocarcinoma ($P = .0004$), advanced pathologic stage ($P < .0001$), and formal resections, including lobectomy and pneumonectomy ($P = .0014$), significantly and negatively affected overall survival. Next we performed multivariate analyses for prognosis by using these key variables (Table 2) and found that male sex, older age, larger tumor, and advanced pathologic stage adversely affected overall and cancer-specific survivals, whereas neither histology nor surgical procedure significantly influenced survival on stratification by other variables.

We examined the relationships between surgical mode and tumor size and their association with postoperative survival. The percentages of lesser resection among all procedures completed were 79% (38/48), 56% (121/217), 30% (78/255), and 15% (40/258) in patients with stage I disease with a tumor of 10 mm or less, 11 to 20 mm, 21 to 30 mm, and greater than 30 mm in diameter, respectively. Although only patients without nodal involvement were included in these survival analyses, there were no cancer-specific deaths in patients with a tumor of 10 mm or less in diameter, irrespective of surgical mode. The 5-year cancer-specific survivals of patients with stage I disease with a tumor of 20 mm or less in diameter were 96.7% after segmentectomy, 92.4% after lobectomy, and 85.7% after

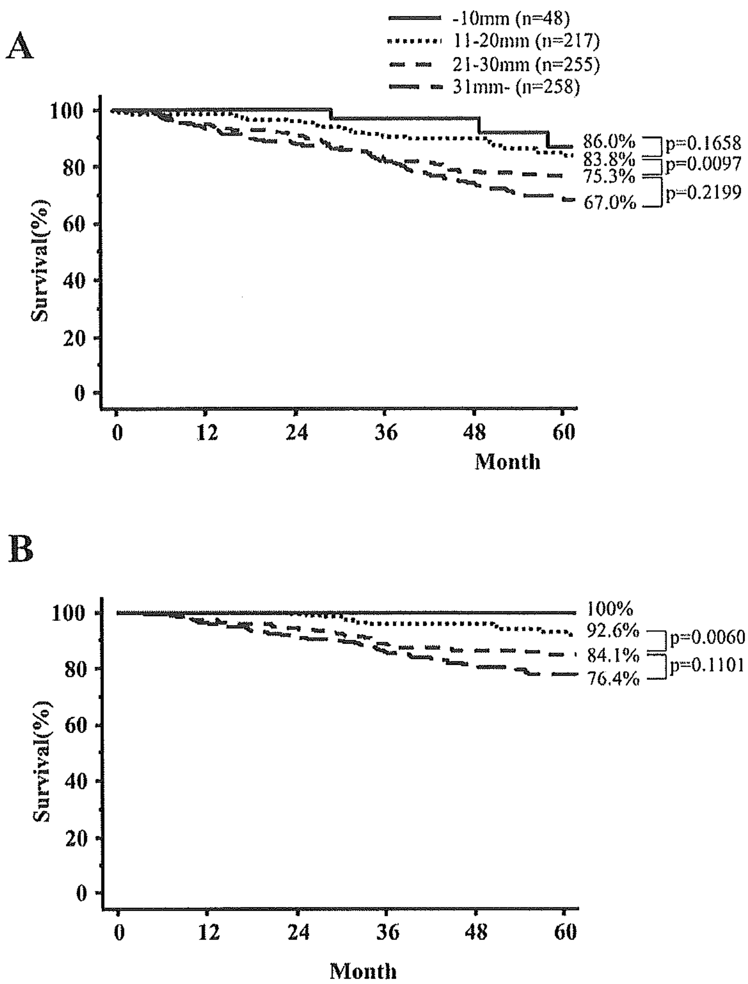

Figure 2. Overall (A) and cancer-specific (B) survival curves for patients with complete resection for pathologic stage I non–small cell lung cancer according to tumor size.

wedge resection (Figure 3, *A*). There were no significant differences between these procedures. In addition, the 5-year cancer-specific survivals of patients with stage I disease with a tumor of 21 to 30 mm in diameter were 87.4% after lobectomy, 84.6% after segmentectomy, and 39.4% after wedge resection (Figure 3, *B*). There were significant differences between wedge resection and the other modes but not between lobectomy and segmentectomy. In patients with stage I disease with a tumor of greater than 30 mm in diameter, the 5-year cancer-specific survivals were 81.3% after lobectomy, 62.9% after segmentectomy, and 0% after wedge resection (Figure 3, *C*). There were significant differences between all matchings.

Discussion

Tumor dimension was clearly shown to be a significant predictor of survival not only by univariate analysis but also by multivariate analysis. In the present international TNM staging system, the cutoff value of T factor (tumor size) is 30 mm,[1] which is a contentious problem. In addition to reports that patients with a tumor of 2 cm or less in diameter had a better survival than those with a tumor of 2.1 to 3.0 cm in diameter,[4,6] we demonstrated that patients with a tumor of 11 to 20 mm in diameter had significantly better overall and cancer-specific survivals than those with a tumor of 21 to 30 mm in diameter among patients with completely resected pathologic stage I tumors excluding lymph node involvement, but there were no significant differences in overall or cancer-specific survivals between patients with a tumor of 21 to 30 mm in diameter and those with a tumor of larger than 30 mm in diameter. These findings suggest that 20 mm is preferable as a cutoff value for T factor in staging.

Tumor size was not the only factor that affected prognosis after complete resection. Additionally, sex, age, histologic type, pathologic stage, and operative procedure significantly affected survival on univariate tests. Surprisingly,

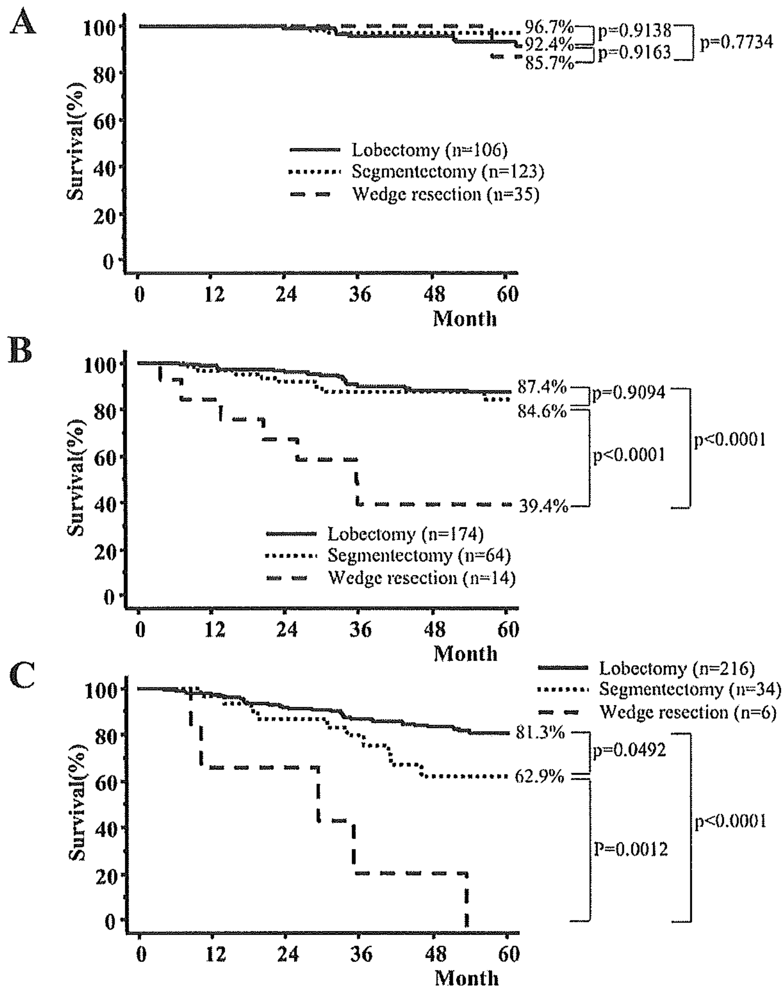

Figure 3. Cancer-specific survival curves for patients with complete resection for pathologic stage I non–small cell lung cancer of 20 mm or less (A), 21 to 30 mm (B), and greater than 30 mm in diameter according to operative procedure.

the prognosis after formal surgical intervention, which included lobectomy and pneumonectomy, was worse than that after lesser operations, probably because we tended to remove less lung parenchyma for earlier-stage cancers. To certify this hypothesis, we evaluated the relationships between operative procedure and survival on multivariate tests, which were unable to correlate the 2 factors. A total of 4% of our patients were found to have any advanced factor, even though tumors measured 10 mm or less in diameter. In our series, tumors of 11 to 20 mm and 21 to 30 mm in diameter had 21% and 36% advanced factors, respectively, whereas 56% of tumors greater than 30 mm in diameter were associated with higher-stage disease. Others have obtained similar results.[3,7] Supporters of lesser resection in noncompromised patients maintain that even for small-sized tumors there is minimal risk of advanced disease, such as nodal involvement, and that it might be essential to identify risks preoperatively or intraoperatively. The proportions of lesser resection in the total procedures were 74% (37/50), 47% (129/273), and 26% (95/368) for patients with a tumor of 10 mm or less, 11 to 20 mm, and 21 to 30 mm in diameter, respectively; when limited to patients with stage I disease, they were 79% (38/48), 56% (121/217), and 30% (78/255), respectively. We have always maintained the policy that removal of lung parenchyma should deliberately be reduced as long as oncologic radicality can be preserved. In this study we analyzed follow-up data in terms of overall survival and cancer-specific survival and believe the latter is probably more appropriate for examination of results. If there is essentially no statistically significant difference in cancer-specific survival between lobectomy and lesser resection, and the 5-year survivals with the 2 types of procedures are equal, on what basis can one conclude that lobectomy is better?

Since 1992, at our institute we have, as a prospective trial, tried segmentectomy with lymph node dissection in noncompromised patients with stage IA non–small cell lung cancer of 2 cm or smaller in diameter who had undergone lobectomy up to that time.[2,8,9] Continuing controversy exists concerning the role of segmentectomy but not that of wedge resection in noncompromised patients with primary lung cancer, although it is not debated for benign diseases, metastatic tumors, or selected primary cancers in compromised patients. In 1995, lobectomy had been confirmed to be a standard procedure of choice for tumors of any size.[10] However, several sequential studies, including prospective ones, have shown the usefulness of segmentectomy for small-sized N0 cancer.[2,8,9,11-13] Thus, current persuasive data suggest that for smaller N0 cancers, segmentectomy might be an acceptable surgical method, even in noncompromised patients.

In our series the frequency of segmentectomy was 5 times that of wedge resection. It was impossible to overemphasize the percentages of segmentectomy in all lesser resections. Because segmentectomy and wedge resection have thus far been combined and categorized together as types of lesser resection, we cannot evaluate the 2 procedures separately on the basis of results in the literature. We believe that segmentectomy is an anatomic procedure in which lymph nodes can be examined at various levels of N1. Some reports, as well as our own experience, have shown nonanatomic wedge resection to be inferior to anatomic segmentectomy.[12,14] Segmentectomy should be carefully distinguished from wedge resection in practice and clinical research, as in this study. Recently, few segmentectomies are being performed and many thoracic surgeons are not familiar with this useful method.[15] Although technically more challenging than other resections, segmentectomy is valuable and should be kept in mind by younger thoracic surgeons.

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Border between N1 and N2 stations in lung carcinoma: Lessons from lymph node metastatic patterns of lower lobe tumors

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Objective: Distinction of lymph node stations is one of the most crucial topics still not entirely resolved by many lung cancer surgeons. The nodes around the junction of the hilum and mediastinum are key points at issue. We examined the spread pattern of lymph node metastases, investigated the prognosis according to the level of the involved nodes, and conclusively analyzed the border between N1 and N2 stations.

Methods: We reviewed the records of 604 consecutive patients who underwent complete resection for non–small cell lung carcinoma of the lower lobe.

Results: There were 390 patients (64.6%) with N0 disease, 127 (21.0%) with N1, and 87 (14.4%) with N2. Whereas 11.3% of patients with right N2 disease had skip metastases limited to the subcarinal nodes, 32.6% of patients with left N2 disease had skip metastases, of which 64.2% had involvement of N2 station nodes, except the subcarinal ones. The overall 5-year survivals of patients with N0, N1, and N2 disease were 71.0%, 50.8%, and 16.7%, respectively (N0 vs N1 $P = .0001$, N1 vs N2, $P < .0001$). Although there were no significant differences in survival according to the side of the tumor among patients with N0 or N1 disease, patients with a left N2 tumor had a worse prognosis than those with a right N2 tumor ($P = .0387$). The overall 5-year survivals of patients with N0, intralobar N1, hilar N1, lower mediastinal N2, and upper mediastinal N2 disease were 71.0%, 60.1%, 38.8%, 24.8%, and 0%, respectively. Significant differences were observed between intralobar N1 and hilar N1 disease ($P = .0489$), hilar N1 and lower mediastinal N2 disease ($P = .0158$), and lower and upper mediastinal N2 disease ($P = .0446$). Also, the 5-year survivals of patients with involvement up to station 11, up to station 10, and up to station 7 were 41.4%, 37.9% and 37.7%, respectively (difference not significant).

Conclusions: N1 and N2 diseases appeared as a combination of subgroups: intralobar N1 disease, hilar N1 disease, lower mediastinal N2 disease, and upper mediastinal N2 disease. Interestingly, the survivals of patients with involvement up to interlobar nodes (station 11), main bronchus nodes (station 10), and subcarinal nodes (station 7) were identical. These data constitute the basis for a larger investigation to develop a lymph node map in lung cancer.

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In non–small cell lung cancer, metastasis to lymph nodes, the N factor, is one of the most important determinants of prognosis.[1-5] Accurate lymph node staging is therefore imperative to select therapeutic strategies. Currently some variations of the lymph node map can be found, and thus considerable discordance exists regarding the designation of sites among doctors in the United States, Europe, and Japan,[6] which has been causing confusion. Understandably, the survival of patients with N1 disease is between that

TABLE 1. Pattern of N2

	Right lung	Left lung
Total	44	43
Only lower mediastinum	29	33
Skip of N1, station 7	5	5
Skip of N1, station 8	0	3
Skip of N1, station 9	0	2
Skip of N1, stations 7 and 8	0	2
Skip of N1, stations 7 and 9	0	1
N1 and station 7	15	10
N1 and station 8	1	2
N1 and station 9	0	2
N1 and stations 7 and 8	4	5
N1 and stations 7 and 9	0	1
N1 and stations 8 and 9	1	0
N1 and stations 7, 8, and 9	3	0
Upper mediastinum	15	10
Skip of N1, Botallo's node	0	1
N1 and upper mediastinum	2	4
N1, station 7, and upper mediastinum	13	5

Data represent numbers of patients.

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of those with N0 and N2 disease if only the N factor is considered, because N1 lymph nodes are anatomically positioned upstream from N2 nodes. However, both N1 and N2 disease represent heterogeneous groups with variable survivals.[7,8] In each case, the involved nodal levels could probably have different influences on patients' survival. One of the most significant problems concerning lymph node involvement under debate among thoracic oncologists is the definition of the borderline between N1 and N2 stations, which must be absolutely clarified, because otherwise discordance could distort stages reported in different studies. More importantly, in the clinical setting, the potential therapeutic strategies for patients with N1 and N2 disease differ remarkably. In other words, it is difficult to deal with interface nodes at the junction of the hilum and mediastinum, which are around the main bronchus. We should direct our efforts toward defining the border more precisely and reach consensus on the basis of up-to-date evidence.

We reviewed the records of patients with completely resected non–small cell lung cancer to examine the clinical features of lymph nodal involvement. The purposes of this study were to investigate the pattern of lymph node metastases, to analyze survivals of patients according to the level of nodal involvement, and to bring up an unsolved issue on the anatomic border between N1 and N2 stations. To make the anatomic stream of lymph nodes clearly understandable, patients in this study were limited to those with a primary lesion originating from the lower lobe.

Material and Methods

Between July 1984 and December 2003, a total of 604 consecutive patients operated on for primary non–small cell carcinoma in the lower lobes of the lungs had pathologic confirmation of complete removal with systematic nodal dissection of the hilum and mediastinum. Approval of the institutional review board was obtained to collect these patients' data in a secure database and report their outcomes. Histologic type of the tumor was determined according to the World Health Organization classification. Patients with low-grade malignancy of the lungs, such as carcinoid, were excluded. Staging was determined according to the international TNM staging system.[1] All dissected lymph nodes were pathologically examined and classified according to anatomic location by Naruke and colleagues' numbering system.[2] Patients who had been subjected to induction chemoradiotherapy or adjuvant therapy were excluded. For staging, all patients underwent a physical examination; chest radiography; computed tomography of the thorax, brain, and upper abdomen; bone scintigraphy; and bronchoscopy. After surgery, the patients were examined at 3-month intervals for 5 years and thereafter at 1-year intervals in general. The evaluations included physical examination, chest radiography, and tumor markers. Moreover, chest, abdominal, and brain computed tomographic scans and a bone scintiscan were carried out each year.

One hundred sixty-five patients were female and 439 were male, ranging in age from 32 to 83 years with a median of 67 years. The histologic classification was adenocarcinoma in 293 patients, squamous cell carcinoma in 285, adenosquamous carcinoma in 13, and large cell carcinoma in 13. There were 266 patients with left-sided tumors and 338 with right-sided tumors. One hundred ninety-seven patients had pathologic stage IA disease, 164 had IB disease, 33 had IIA disease, 87 had IIB disease, 94 had IIIA disease, and 29 had IIIB disease.

The sites of N2 lymph nodes were grouped as follows: upper mediastinal (highest mediastinal nodes, paratracheal nodes, pretracheal nodes, anterior mediastinal nodes, posterior mediastinal nodes, tracheobronchial angle nodes, Botallo's nodes, para-aortic nodes, and ascending aortic nodes), and lower mediastinal (station 7, subcarinal nodes; station 8, paraesophageal nodes; and station 9, pulmonary ligament nodes) lymph nodes.[2,3] The N1 lymph nodes comprised hilar (station 10, main bronchus nodes; and station 11, interlobar nodes), and intralobar (lobar bronchial nodes, segmental bronchial nodes, and intrapulmonary nodes) ones. Mediastinal metastasis was considered as "skip metastasis" if any of the N2 nodes, but no N1 nodes were involved. In patients with a tumor in the left side, Botallo's nodes, para-aortic nodes, and ascending aortic nodes were invariably removed although removal of pretracheal nodes was optional.

Survivals were calculated by the Kaplan-Meier method, and differences in survival were determined by log-rank analysis. Zero time was the date of pulmonary resection, and the terminal event was death attributable to cancer, noncancerous cause, or unknown causes.

Results

Lymph node involvement was recognized in 214 (35.4%) of the 604 patients evaluated; of them 127 patients (21.0%) showed N1 node involvement and 87 (14.4%) showed N2 node involvement. Among 127 patients with N1 disease, 54 had metastasis of intralobar nodes but not hilar nodes. In addition, patients with hilar N1 node metastases were fur-

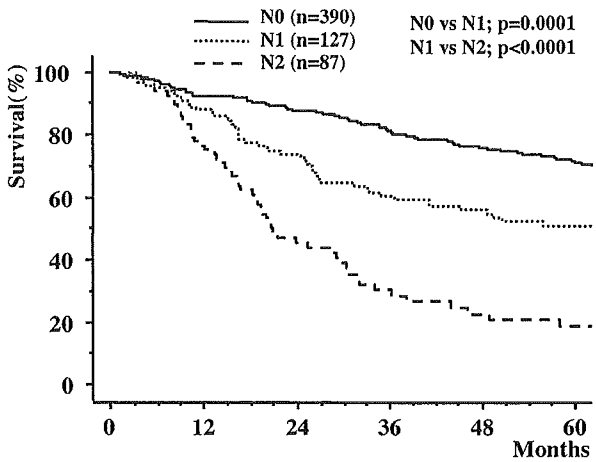

Figure 1. Overall survival curves of patients subjected to complete resection for non–small cell lung cancer according to pathologic nodal status.

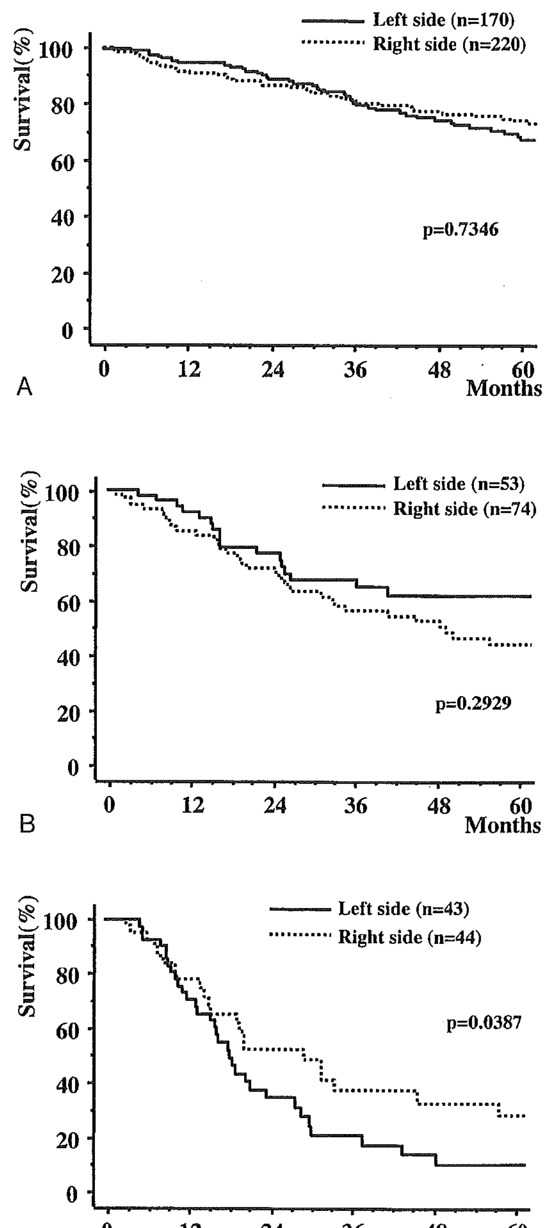

Figure 2. Overall survival curves of patients subjected to complete resection for pN0 (A), pN1 (B), and pN2 (C) non–small cell lung cancer according to side of primary lesion.

ther categorized as those with (n = 16) and those without (n = 57) main bronchus node (station 10) involvement. The spread patterns of N2 lymph node metastases according to the side of the primary tumor are presented in Table 1. Of 44 patients with a right tumor involving the N2 region, 5 (11.3%) had skip metastases, all of which were limited to station 7. On the other hand, among 43 patients with a left tumor involving the N2 region, 14 (32.6%) had skip metastases, of whom 9 showed involvement of any N2 node except station 7. To our surprise, skip metastasis to the upper mediastinal node but not the lower mediastinal nodes was found in only 1 patient, who had a bronchioloalveolar cancer 80 mm in diameter as the primary lesion, with node station 5 metastasis. Except for that patient, all the patients with nodal involvement reaching the upper mediastinum showed involvement of N1 nodes.

Follow-up ranged from 3 to 203 months, with a median of 92 months for surviving patients. The overall 5-year survivals of patients with N0, N1, and N2 disease were 71.0%, 50.8%, and 16.7%, respectively (Figure 1). There were statistically significant differences in survival among these groups (N0 vs N1 $P = .0001$, N1 vs N2 $P < .0001$). Next, we investigated the survivals of patients with N0, N1, or N2 disease according to the side of the primary tumor (Figure 2). Although there were no significant differences in survival according to the side of the tumor among patients with N0 or N1 disease, patients with a left N2 tumor had a worse prognosis than those with a right N2 tumor ($P = .0387$). Their 5-year survivals were 6.9% and 28.2%, respectively.

In addition, we examined survivals after classifying patients with N1 disease into those with and without hilar node (stations 10, 11) metastasis, and patients with N2 disease as those with and without upper mediastinal node metastasis. Overall 5-year survivals of patients with N0, intralobar N1, hilar N1, lower mediastinal N2, and upper mediastinal N2 disease were 71.0%, 60.1%, 38.8%, 24.8%, and 0%, respectively (Figure 3, *A*). Significant differences were observed between intralobar N1 and hilar N1 disease ($P = .0489$), between hilar N1 and lower mediastinal N2 disease ($P =$

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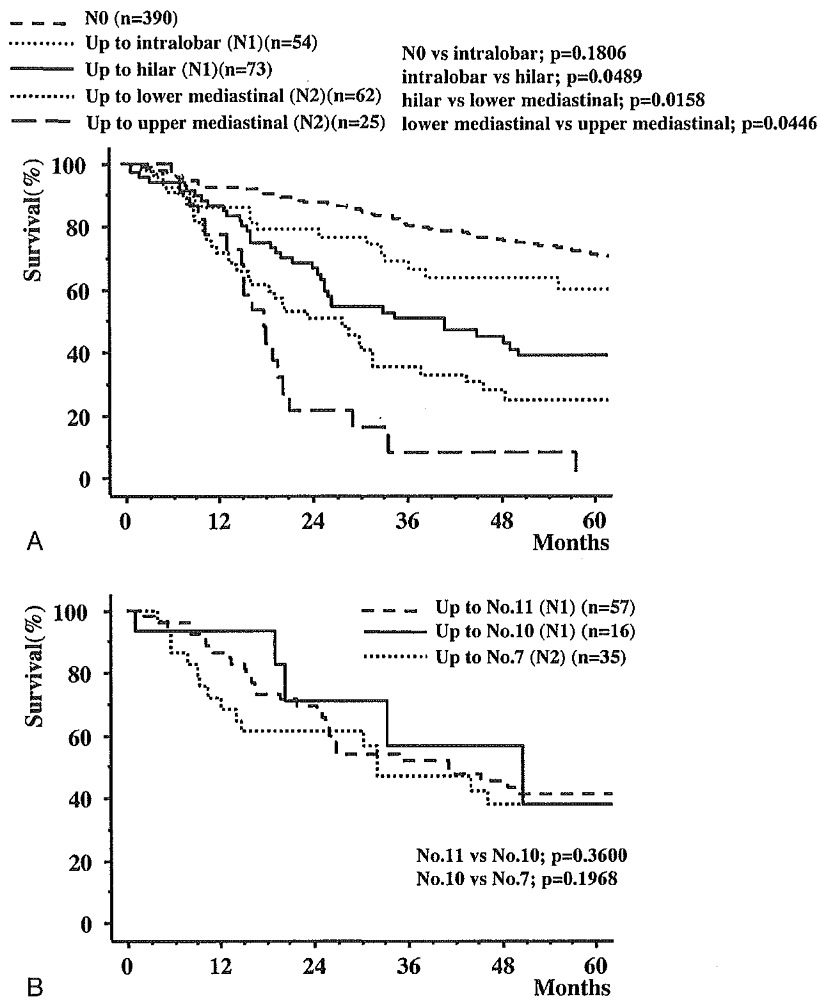

Figure 3. Overall survival curves of patients subjected to complete resection for non–small cell lung cancer according to pathologic nodal status. (A) Disease was classified as N0 disease, intralobar N1 disease, hilar N1 disease, lower mediastinal N2 disease, and upper mediastinal N2 disease. (B) Disease was further classified tumor involving up to either interlobar (station 11), main bronchus (station 10), or subcarinal (station 7) nodes.

.0158), and between lower and upper mediastinal N2 disease (P = .0446), but not between N0 and intralobar N1 disease (P = .1806). Finally, we debated whether the survivals of patients with nodal involvement up to either station 11, station 10, or station 7, differed. The 5-year survivals were 41.4%, 37.9%, and 37.7%, respectively. Comparison of the survivals among the three subgroups demonstrated no significant differences, and their curves were overlaid (Figure 3, *B*).

Discussion

Even now, optimal lymph node dissection remains controversial among thoracic surgical oncologists. On the one hand, lymphadenectomy can improve the accuracy of lung cancer staging and decrease locoregional recurrence; on the other, it increases operative time, blood loss, and the frequencies of recurrent laryngeal nerve injury, chylothorax, and bronchopleural fistula. Thus it is important to develop a more reasonable approach for dissecting mediastinal lymph nodes.

In this series, we acknowledged so-called skip metastasis to mediastinal lymph nodes in approximately 22% of our patients with N2 disease. This percentage is close to those of previous reports: 27% by Martini and colleagues[9] and 28.6% by Ishida and colleagues.[10] Skip metastasis may possibly develop as a result of the existence of lymphatic channels opening directly to the mediastinum. Subpleural lymphatics have been reported to have straight passages to the mediastinal lymph nodes in 22% of the segments in the right lung and in 25% of the segments in the left lung.[11]

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Consistent with these data, we found skip metastases more frequently and at more complicated modes in the left lung than in the right lung, suggesting that dissection of mediastinal lymph nodes on the left side requires more careful handling. In addition, survival of patients with a right N2 lesion was significantly better than that of patients with a left N2 lesion, although no significant difference in survival according to the side of disease was observed in patients with N0 or N1 disease. Drainage patterns of lymph nodes and quicker operative access to the right side of mediastinal lymph nodes may explain restriction of the better survival results to patients with right-sided lesions. Although paratracheal, pretracheal, and tracheobronchial angle nodes can be dissected through a right thoracotomy without difficulty, it is hard to reach some of these nodes from the left side. Moreover although right-sided tumors generally spread to the ipsilateral mediastinal lymph nodes, tumors in the left lower lobe are recognized to metastasize passing through the subcarinal nodes not only to the ipsilateral (left) but also to the contralateral (right) mediastinum. We should understand the importance of the left side in lymphadenectomy.

Metastatic spread may occur in nonregional mediastinum without involving lymph nodes of the regional mediastinum. Because the extent and the mode of nodal spread are affected by location of the tumor, we classified the mediastinum into an upper region, including the aortic region, and a lower region. All patients with skip N2 metastasis from a lower-lobe lesion showed no involvement of upper mediastinal nodes, except for 1 patient who had a huge primary tumor. In patients with a lower-lobe tumor without N1 node involvement, very little prevalence of upper mediastinal node involvement can exist. Therefore if N1 nodes are found to be free of tumor by an adequate use of frozen sections, upper mediastinal lymphadenectomy is basically dispensable. An exception is when the patients have advanced disease suspected on the basis of findings such as size of tumor and extent of invasion; in such cases complete hilar and mediastinal lymphadenectomy should be routinely done as long as the patient is considered able to tolerate the procedure. In addition, fluorodeoxyglucose positron emission tomography, reported to be superior to computed tomography in assessing lymph node metastasis,[12] can help to decide the extent of lymphadenectomy.

There are ongoing controversies concerning lymph node stations as a result of the lack of a universally widespread map. One of the biggest problems is the distinction between N1 and N2 stations. In general, pleural reflection has been accepted as an anatomic border between N1 and N2 regions, as the American Joint Committee established in 1973 and Mountain[1] revised in 1997. Management of nodes around the main bronchus (stations 7, 10, 11), is the point, because the main bronchus is positioned partially within the pleural envelope and partially outside it. Indeed, one of the most important problems is to decide whether the main bronchus nodes belong to the N1 or N2 station in relation to prognosis as well as anatomy. In this study, we found no differences in survival among patients with nodal metastases up to either station 11, station 10, or station 7, suggesting that these nodes could be designated as intermediate between N1 and N2 and that there might be no borderline between N1 and N2 nodes around the main bronchus. Some reports have also shown the prognoses of patients with hilar N1 disease and single-station N2 disease to be identical.[13,14] Those data suggest that pleural reflection is not a suitable anatomic border between N1 and N2 stations in lung cancer.

Another important finding of this study was that patients with intralobar metastasis had a significantly better prognosis than those with hilar metastasis, who in turn had a significantly better prognosis than those with lower mediastinal metastasis. In addition, patients with lower mediastinal metastasis had a significantly better prognosis than those with upper mediastinal metastasis. Upper mediastinal nodes might be considered as representing an N3 station for a lower-lobe lesion, although clearer and more extensive evidence is required. The map for lymph node stations in lung cancer is still under development. We fervently hope to have a single, accurate map of lymph node stations that can be used universally. Otherwise, it will be impossible to make progress in therapeutic strategies for lung cancer.

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Hybrid Surgical Approach of Video-Assisted Minithoracotomy for Lung Cancer: Significance of Direct Visualization on Quality of Surgery

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Hybrid Surgical Approach of Video-Assisted Minithoracotomy for Lung Cancer*

Significance of Direct Visualization on Quality of Surgery

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Study objectives: Controversy regarding the most suitable surgical approach for treating malignancies of the lung is a matter of continuous discussions. "Complete" video-assisted thoracic surgery (VATS) that is performed using only the vision of a monitor is generally limited to lung resections of minimal difficulty. With the great interest in minimally invasive techniques for treating various pathologies, we have widely applied an integrated surgical approach that combines muscle-sparing minithoracotomy (incision, 4 to 10 cm) and video assistance using mainly direct visualization of the lung resection, which we have called _hybrid VATS_. The aim of this study is to evaluate the usefulness of hybrid VATS.

Design: Retrospective single-center study.

Interventions: From January 1998 to October 2004, 405 of 678 lobectomies (60%) and 165 of 226 segmentectomies (73%) were performed for primary lung cancer using hybrid VATS.

Results: Bronchoplasty was performed in 93 of the 678 patients (14%) who underwent lobectomy and in 11 of the 226 patients (5%) who underwent segmentectomy. Hybrid VATS was utilized in 33% of sleeve lobectomy procedures and in 27% of sleeve segmentectomy procedures. The mean (± SD) surgical time using hybrid VATS was 164 ± 48 min for lobectomy and 158 ± 35 min for segmentectomy, and the mean blood loss was 166 ± 120 and 109 ± 80 mL, respectively. There was one operative mortality (0.2%) secondary to cardiogenic shock. Postoperative complications developed in 11% of patients with p-stage IA disease after undergoing hybrid VATS, in contrast to 19% of patients after undergoing open thoracotomy. The prognosis of patients treated by hybrid VATS was equivalent to that obtained with open thoracotomy.

Conclusions: Minithoracotomy combined with video support that is performed predominantly via direct visualization is a secure, integrated, minimally invasive approach to performing major resection for lung cancer, including atypical procedures such as bronchoplasty. This hybrid VATS can be an acceptable and satisfactory option whenever the performance of complete VATS is considered to be challenging. **_(CHEST 2005; 128:2696–2701)_**

Key words: lung cancer; surgery; thoracotomy; video-assisted thoracic surgery

Abbreviation: VATS = video-assisted thoracic surgery

In the last decade, thoracic surgeons have been forced somewhat to accept video-assisted thoracic surgery (VATS) as an innovation that can improve the overall quality of a patient's life following surgery for lung cancer. Indeed, at present patients understand that VATS is less invasive than standard thoracotomy. The advantages of VATS are reduced pain, decreased production of various cytokines, and shorter hospital stay.[1,2] In addition, several authors[3–6] have demonstrated that VATS can be performed safely without affecting survival, but many surgeons have questioned its safety, its adequacy as a cancer operation, and any benefit of VATS.[7,8] Besides, two prospective randomized studies[8,9] failed to

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conclusively prove the advantages of lobectomy performed by the VATS approach compared with that performed by standard thoracotomy.

At present, even the definition of VATS is being debated. Some medical communities have insisted that VATS must be defined as thoracic surgery that is performed completely by visualization through a television monitor, the so-called *complete VATS*, and that employing direct vision, even partially, should exclude a procedure from being defined as VATS.

Complete VATS offers the same approach for cancer surgery as that of open thoracotomy, in some cases, such as in standard lobectomy of low difficulty, results in more or less sacrificing the completeness of oncologic radicality, and therefore cannot be applied to all cancer operations, including segmentectomy and bronchoplasty. Until now, we have aggressively tried a minimally invasive approach that is reasonable as a lung cancer operation. Consequently, we have established an integrated surgical approach consisting of muscle-sparing minithoracotomy with television monitoring and direct visualization. Because this approach is somewhere between the two outlined approaches, we have called it *hybrid VATS*.

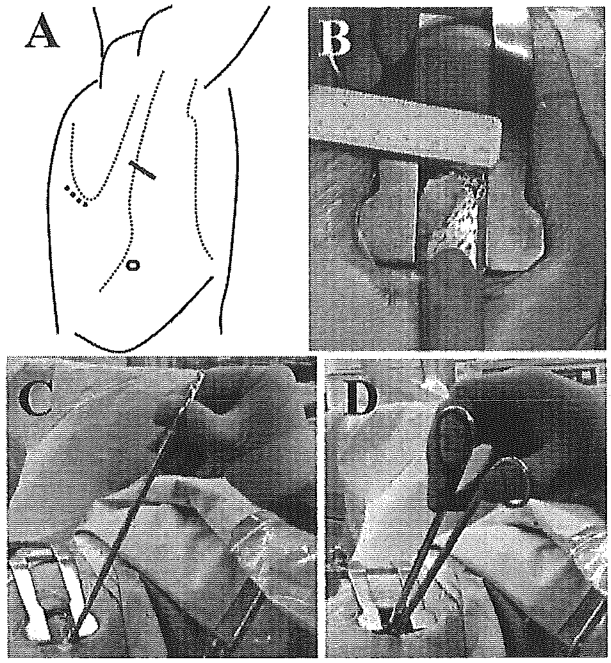

FIGURE 1. *Top left, A*: Skin incisions for one access port for a thoracoscope (circle) and for an access thoracotomy (solid line), which is made over the midaxillary line in the fourth interspace for upper or middle lobe tumors. Lower lobe tumors are approached through the auscultatory triangle in the fifth interspace (dotted line). An operative exposure about 2-cm-wide is made using a thoracic opener (*top right, B*), and dissection through direct vision is performed using an upside-down grip of 30-cm-long scissors, which the surgeon can maneuver at will by turning up the wrist (*bottom left, C*, and *bottom right, D*).

Materials and Methods

We began using hybrid VATS in January 1998, and, up to October 2004, 678 patients underwent lobectomy and 226 underwent segmentectomy for primary non-small cell carcinoma of the lung. Since, where feasible, we have always tried to perform minimally invasive surgery for any patients with lung cancer, we have not designed a fixed indication for performing VATS. Therefore, we flexibly extended the wound or converted to standard thoracotomy whenever we judged that it would be difficult to curatively and safely resect the lesions. The extent of the incision was decided by the surgeons according to their preferences. The common exclusion criteria were tumor size > 10 cm, extensive invasion of the chest wall identified by preoperative imaging findings, and repeat resection. Generally, cN2 disease, induction chemotherapy or radiation therapy, centrally located tumors, and lobar or hilar nodes adherent to pulmonary vessels were not necessarily contraindications to performing the hybrid VATS approach.

Operative Technique

Use of a headlamp is recommended. Under general anesthesia, double-lumen endotracheal intubation with selective contralateral lung ventilation is achieved. One access port for the insertion of a thoracoscope is normally placed with a 2-cm-long incision in the eighth or ninth intercostal space over the midaxillary line (Fig 1, *top left, A*). An additional transverse skin incision 4 to 10 cm long for access thoracotomy is made over the midaxillary line in the fourth interspace for upper lobe and middle lobe tumors. Basically, no other port is built for access. The serratus anterior muscle is divided not transected, and no extracostal muscles or ribs are cut. The intercostal muscle of the fourth interspace is then incised, and the pleura is opened 2 to 3 cm wide using a thoracic opener (Fig 1, *top right, B*). Lower lobe tumors are accessed through the auscultatory triangle, for which a transverse incision is made below the tip of the scapula, and the chest is entered through the fifth intercostal space without cutting any ribs. More recently, the minithoracotomy has been opened to approximately 2×4 cm with a chest retractor or a silicon rubber instrument (Lap-Protector; Hakko; Nagano, Japan). It is important to note that the skin incision should be extended without hesitation if the surgeon during the procedure that the surgery would be too difficult to perform without such extension.

Through the minithoracotomy, the surgeon can directly observe the hilum of the diseased lobe, and can dissect the bronchi and vessels using standard surgical instrumentation. We prefer 30-cm-long scissors (model 101-8098-30; Mayo-Harrington; Stille, Sweden) with a backhand grip, holding them upside-down, for sharp dissection (Fig 1, *bottom left, C, bottom right, D*) and forceps covered with a nonconducting material. As well, lengthy needle holders and forceps are usually used for suturing with synthetic material (Vicryl and PDS-II; ETHICON; Tokyo, Japan), and, especially, long, curved dissecting forceps are our favorite instruments for individually ligating the vessels. Also, coaxial endosurgical instruments may be employed to assist the retraction of the parenchyma during the dissection. Television monitor guidance is variably utilized during the procedure when dissecting an area out of direct view such as the mediastinal lymph nodes, the lower lung ligament, and adhesions. The lower access port established primarily for a thoracoscope is usually used to subsequently introduce the stapler (Endocutter; Ethicon Endo-Surgery Inc; Cincinnati, OH) for pulmonary vascular or bronchial closure, while the stapler can be inserted directly through the thoracotomy if the angle is more appropriate. In general, we use a stapler to completely cut and close the lobar bronchi in the case of standard lobectomy, although we prefer to suture bronchi manually during the course of the segmentectomy. When the intersegmental plane is being cut during segmentectomy or the fissure is absent or incomplete even during lobectomy, direct vision in hybrid VATS is extremely significant. In these cases, the three-dimensional understanding of pulmonary anatomy is crucial to avoid ambiguous procedures. The segmental plane can be stapled, which makes the adjacent remaining portion severely distorted and restricted from full expansion, and therefore we commonly use electrocautery or a combination.[10,11] Using a commercially available fibrin sealant (Bolheal; Chemo-Sero Therapeutic Institute; Kumamoto, Japan) that is composed of fibrinogen and thrombin and an absorbable polyglycolic acid felt (Neoveil; Japan Medical Planning Co; Kyoto, Japan), the raw surface of the remaining lung allows minimum or no air leakage following the procedure. The affected lung tissue is wrapped in a surgical bag whenever there is a fear of increased risk of cancer dissemination due to the difficulty of removing it through the small wound. Routinely, the chest is drained using a single chest tube under a water seal, which is put through the incision that was initially established for a thoracoscope.

Institutional review board approval was obtained for collecting the data in a secure database and for reporting them. Staging was determined according to the international TNM staging system.[12] Survival was calculated by the Kaplan-Meier method, and differences in survival were determined by the log-rank analysis. Zero time was the date of pulmonary resection, and the terminal event was death attributable to cancer, noncancer, or unknown causes.

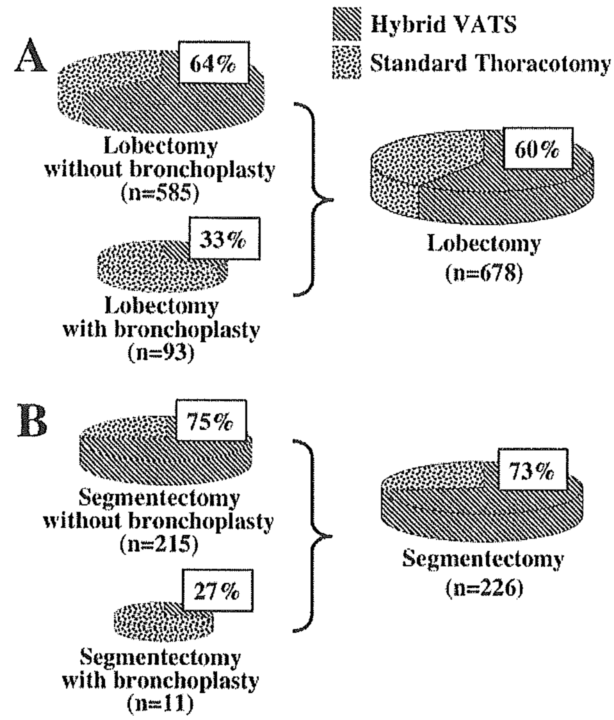

FIGURE 2. The distribution of surgical approaches performed using hybrid VATS and standard thoracotomy for lobectomy (*top*, *A*) or segmentectomy (*bottom*, *B*).

RESULTS

The number and distribution of surgical approaches performed according to hybrid VATS or standard thoracotomy are shown in Figure 2. From January 1998, 405 of the 678 patients (60%) who underwent lobectomy and 165 of the 226 patients (73%) who underwent segmentectomy were operated on using hybrid VATS. The distribution of patients by clinical and pathologic stage in the lobectomy and segmentectomy group is demonstrated in Table 1. Among the 405 patients who underwent hybrid VATS lobectomy, 177 (44%) had c-stage IA disease, 163 (40%) had c-stage IB disease, 32 (8%) had c-stage II disease, and 33 (8%) had c-stage III disease. In contrast, 15%, 33%, 27%, and 25% of the patients, respectively, who needed open thoracotomy for lobectomy had c-stage IA, IB, II, and III disease. Of the patients who underwent hybrid VATS segmentectomy, 92% were clinically staged as having IA disease.

Since less removal of the lung parenchyma can be beneficial to patients, we have always employed pulmonary-saving procedures even for the treatment of malignant lesions.[10,13,14] Further analysis revealed that bronchoplasty was performed in 93 of the 678 patients (14%) who underwent lobectomy and in 11 of the 226 patients (5%) who underwent segmentectomy (Fig 2). Hybrid VATS was employed in 33% of sleeve lobectomies and in 27% of sleeve segmentectomies. Over the years, hybrid VATS has been applied more frequently. When analysis is restricted to the last 2 years, hybrid VATS was found to have been utilized in 70% of lobectomies and in 83% of segmentectomies. The mean (± SD) total time of surgery using hybrid VATS was 164 ± 48 min for lobectomy and 158 ± 35 min for segmentectomy, while that using standard thoracotomy was 163 ± 32 min for lobectomy and 147 ± 38 min for segmentectomy. During lobectomy and segmentectomy per-

Table 1—*Surgical and Staging Data*

Disease Stage	Lobectomy: Hybrid VATS (n = 405)	Lobectomy: Thoracotomy (n = 273)	Segmentectomy: Hybrid VATS (n = 165)	Segmentectomy: Thoracotomy (n = 61)
Clinical				
IA	177 (44)	41 (15)	151 (92)	41 (67)
IB	163 (40)	89 (33)	11 (7)	11 (18)
II	32 (8)	74 (27)	3 (2)	7 (11)
III	33 (8)	69 (25)	0 (0)	2 (3)
Pathologic				
IA	127 (31)	44 (16)	128 (78)	32 (52)
IB	123 (30)	60 (22)	17 (10)	13 (21)
II	62 (15)	85 (31)	8 (5)	8 (13)
III	93 (23)	84 (31)	12 (7)	8 (13)

formed through hybrid VATS, the estimated mean intraoperative blood loss was 166 ± 120 mL and 109 ± 80 mL, respectively. With the standard thoracotomy procedure, the mean blood loss was 187 ± 122 mL for lobectomy and 119 ± 86 mL for segmentectomy. There was one operative death (0.2%) from cardiogenic shock among the 570 patients who underwent hybrid VATS. Postoperative complications developed in 28 of the 255 patients (11%) with p-stage IA disease who underwent hybrid VATS, and in 47 of the 254 patients (19%) with p-stage IA disease who underwent open thoracotomy. Atrial fibrillation was the most common morbidity following surgery by either approach.

In a median follow-up period of 63 months (range, 2 to 145 months), the overall survival curves of patients with p-stage IA disease who were stratified by the surgical approach are shown in Figure 3. The prognosis of patients who were operated on using hybrid VATS was as good as that of those who underwent open thoracotomy, whether it was lobectomy or segmentectomy. In addition, the overall survival curves of patients with p-stage IB to III disease who underwent lobectomy showed that performing surgery with hybrid VATS did not affect prognosis even in patients with advanced disease compared with standard thoracotomy (Fig 4). These data suggested that there should be wide application of the hybrid VATS approach for lung cancer surgery.

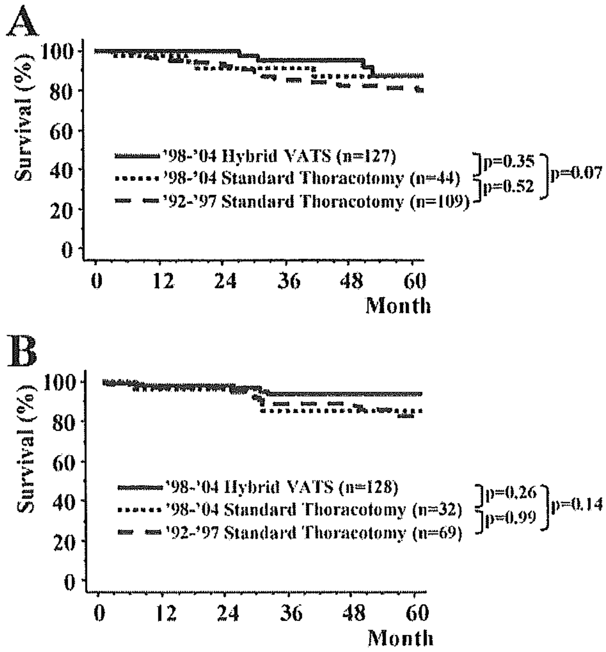

FIGURE 3. Overall survival curves of patients with pathologic stage IA disease who underwent lobectomy (*top*, *A*) or segmentectomy (*bottom*, *B*) stratified by the surgical approach.

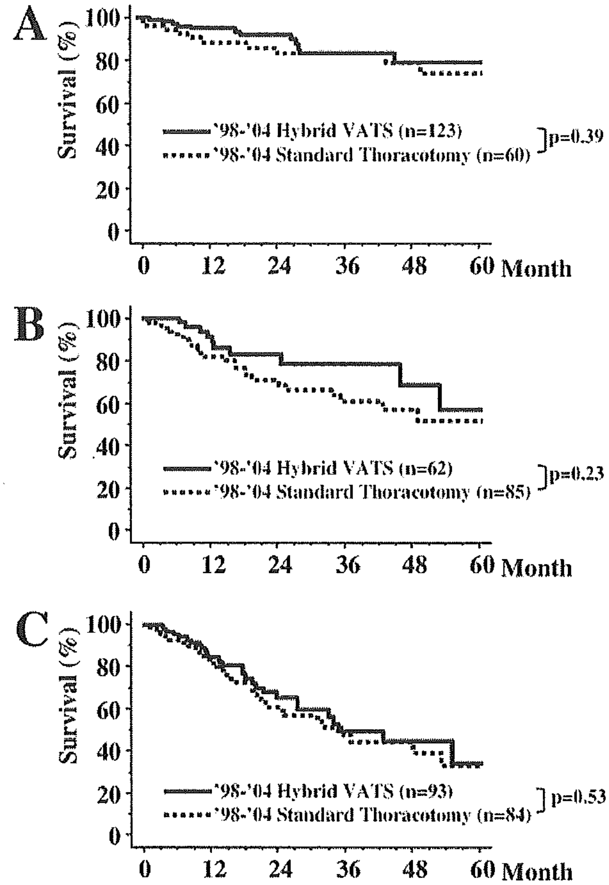

FIGURE 4. Overall survival curves of patients with pathologic stage IB disease (*top*, *A*), stage II disease (*middle*, *B*), and stage III disease (*bottom*, *C*) who underwent lobectomy stratified by the surgical approach.

DISCUSSION

Complete VATS can now be used safely in lobectomy for resecting selected lung lesions, as we know from accumulated experience. Since we have been confronted relatively frequently with the need to perform atypical surgical procedures for the treatment of lung cancer, such as bronchoplasty, reconstruction of the pulmonary artery, and segmentectomy,[10,11,13,14] we have tried to find a new minimally invasive surgical approach for various types of resections.

Recently, Szwerc and colleagues[15] reported their experience with minithoracotomy combined with mechanically stapled bronchial and vascular ligation for lung resection. We agree with their principles regarding the surgical approach. In practice, however, there are some differences between their technique and ours. For example, video assistance is mandatory for our procedure, and we often utilize manual ligation and suturing of the bronchi and vessels in the hilum. Bronchoplasty by hybrid VATS is typical of the latter.