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Effectiveness of Radical Systematic Mediastinal Lymphadenectomy in Patients With Resectable Non-Small Cell Lung Cancer

Results of a Prospective Randomized Trial

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Objective
To evaluate the effectiveness of lymphadenectomy in the treatment of non-small cell lung cancer (NSCLC).

Summary Background Data
The extent of lymphadenectomy in the treatment of NSCLC is still a matter of controversy. Although some centers perform mediastinal lymph node sampling (LS) with resection of only suspicious lymph nodes, others recommend a radical, systematic mediastinal lymphadenectomy (LA) to improve survival and to achieve a better staging.

Methods
In a controlled, prospective, randomized clinical trial, the effects of LA on recurrence rates and survival were analyzed, comparing LS and LA in 169 patients with operable NSCLC.

Results
After a median follow-up of 47 months, LA did not improve survival in the overall group of patients (hazard ratio: 0.78; 95% confidence interval: 0.47–1.24). Although recurrences rates tended to be reduced among patients who underwent LA, these decreases were not statistically significant (hazard ratio: 0.82; 95% confidence interval: 0.54–1.27). However, analysis of subgroups of patients according to histopathologic lymph node staging revealed that LA appears to prolong relapse-free survival ($p = 0.037$) with a borderline effect on overall survival ($p = 0.058$) in patients with limited lymph node involvement (pN1 disease or pN2 disease with involvement of only one lymph node level); in patients with pN0 disease, no survival benefit was observed.

Conclusions
Radical systematic mediastinal lymphadenectomy does not influence disease-free or overall survival in patients with NSCLC and without overt lymph node involvement. However, a

small subgroup of patients with limited mediastinal lymph node metastases might benefit from a systematic lymphadenectomy.

The usefulness of radical lymph node dissection is still controversial in the field of surgical oncology. One of the best examples is gastric cancer, where randomized trials have been initiated to compare limited lymph node excision with radical systematic lymph node dissection. In the surgical treatment of non-small cell lung cancer (NSCLC), the same controversy exists. Some authors claim that a radical systematic mediastinal lymphadenectomy should be performed in almost every patient with a resectable primary tumor[1-3]; others recommend mediastinal lymph node sampling as the treatment of choice to reduce perioperative morbidity and mortality.[4-6] Postulated arguments for a radical lymphadenectomy are better local tumor control with a prognostic benefit, especially for patients with N2 disease and a complete nodal staging of the disease.

We therefore performed a prospective, randomized, controlled clinical trial to compare the results of conventional lymph node sampling (LS), as recommended by the American Lung Cancer Study Group, with radical systematic lymphadenectomy (LA) in patients undergoing curative resection of NSCLC. Recently, we reported that LA can be performed with an acceptable morbidity and mortality.[7] However, there were complications associated with LA, such as prolonged air leakage and hemorrhage. In this article, we analyze the effect of LA on the long-term results of patients with NSCLC. We observed that the type of lymphadenectomy did not influence the outcome in the overall group of patients with NSCLC. However, a subgroup of patients might benefit from a systematic mediastinal lymph node dissection.

PATIENTS AND METHODS

This trial was approved by the Ethical Research Committee of the Medical Faculty, University of Munich. Patients were evaluated, randomized, treated, and followed at the Department of Surgery, University of Munich, Division of Thoracic Surgery, Central Hospital Gauting, and the Department of Pulmonary Medicine, Central Hospital Gauting.

Eligibility Criteria

Patients of any age and either sex with a curatively resectable NSCLC were eligible for this study. Tumor-associated exclusion criteria were evidence of distant metastasis (M1 disease), contralateral or supraclavicular nodal involvement (N3 disease), and confirmation of extensive mediastinal lymph node involvement (preoperatively, more than one station of the N2 region involved). Patient-associated exclusion criteria were previous or coexistent malignant disease, severe heart failure, renal insufficiency (creatinine > 2× upper normal limit), myocardial infarction less than 6 months ago, liver cirrhosis, and insufficient pulmonary reserve.

After randomization, patients were excluded if they had evidence of intrapulmonary metastases. Patients whose resection specimen exhibited residual tumor at the resection margin were also excluded, as were patients whose tumor was subsequently classified as small cell lung cancer.

Diagnostic Evaluation

Each patient was assessed by plain chest x-ray, bronchoscopy with perbronchial or intraluminal biopsies, computed tomography scan of the thorax and abdomen, abdominal ultrasound, and bone scan. Only patients with enlarged mediastinal lymph nodes (>1 cm in short-axis diameter[8]) underwent a preoperative mediastinoscopy and biopsy. For assessment of functional operability, body plethysmography, preoperative arterial blood gas analysis, and bicycle ergonometry were performed.

Randomization and Surgical Technique

At thoracotomy, eligible patients were randomly allocated into two groups: regional lymphadenectomy with mediastinal lymph node sampling (LS) or radical systematic lymphadenectomy (LA).

The surgical approach was via anterolateral thoracotomy in the fourth intercostal space. The technique of resection of the primary lung tumor was the same in both groups, consisting of a classic lobectomy or pneumonectomy, in some cases combined with bronchoplastic or sleeve-resecting procedures. Tumors that exhibited adherence to neighboring structures or organs (*e.g.*, pericardium, thoracic wall, diaphragm, pulmonary artery) were treated by extended resections with *en bloc* removal of the lobe or lung with adhering structures. Confirmation of tumorous invasion of these structures was not attempted intraoperatively. The bronchial stump was routinely closed with a linear stapler (TA 30; United States Surgical Instruments, Norwalk, CT) and covered with a pericardial or pleural flap.

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In the LS group, the resection was combined with a regional lymphadenectomy of interlobular, peribronchial, and hilar nodes representing nodes 10, 11, and 12 according to the lymph node mapping of the American Thoracic Society.[1] A mediastinotomy was performed via longitudinal incision of the mediastinal pleura, and nodes of regions 2 to 9 were explored. Any nodes suspicious of cancer were removed and submitted for pathohistologic analysis. Nodes of regions 4, 5, and 7 were removed routinely in all patients.

In the LA group, resection was combined with a radical systematic *en bloc* mediastinal lymphadenectomy as described by Naruke[9] and Martini[11] and by our group previously.[7] Briefly, in right-sided tumors, the superior mediastinal compartment, contained between the trachea, the superior vena cava from the level of the azygos vein to the right subclavian artery, and the right recurrent laryngeal nerve, was dissected and the trachea, azygos vein, superior vena cava, and ascending aorta were completely freed from all tissue. The azygos vein and the vagus nerve were generally spared, and the right laryngeal nerve was exposed. As a modification of the technique described by Martini,[11] the anterior mediastinum anteriorly to the superior vena cava was routinely included in the dissection, including thymectomy and dissection of the left and right brachiocephalic vein, the phrenic nerve, and the ascending aorta. Subcarinal, paraesophageal, and inferior pulmonary lymph nodes were removed *en bloc*, exposing the entire thoracic esophagus and the vagal nerve. The thoracic duct usually was ligated at the height of the main carina. For sampling reasons, contralateral hilar nodes were also excised.

In left-sided cancers, the subaortic compartment, contained between the left pulmonary artery, the aortic arch, the left recurrent laryngeal, and the phrenic nerve, was dissected by completely freeing the left vagal nerve and the recurrent laryngeal nerve. Thereafter, the aortopulmonary ligament of Botalli was ligated and divided and the aortic arch was mobilized anteriorly to facilitate dissection of paratracheal nodes (nodes 2, 3, and 4). Routinely, contralateral hilar nodes were removed for sampling.

Pathohistologic Analysis and Postoperative Adjuvant Therapy

Tumors were classified according to the staging classification suggested by the UICC.[12] Each lymph node was sectioned at three different levels and classified as positive or negative for tumor. Frozen-section analysis of lymph nodes was not employed as a routine procedure during surgery.

Patients whose primary tumor was classified by the pathologist as T3 or T4 tumor (stage IIIA and IIIB) received adjuvant postoperative percutaneous radiation therapy of the tumor bed with 50 Gy. All patients with involvement of nodes of the N2 region by conventional histopathology (stage IIIA and IIIB) received percutaneous radiation therapy of the entire mediastinum using megavoltage equipment. A dose of 50 Gy (4 × 2.5 Gy or 5 × 2.0 Gy/week) was given in a combination of parallel opposed and anterior and posterior oblique fields, or any combination chosen at the discretion of the radiation oncologist. This adjuvant therapeutic regimen was followed in both groups.

Follow-Up and Definitions of Tumor Recurrence

Patients were followed up at 6-month intervals. Routine examinations included a plain chest x-ray, computed tomography scan of the thorax and abdomen, abdominal ultrasound, bone scan, and bronchoscopy with biopsy if warranted. The median follow-up time was 47.5 months (range 25–67).

Local recurrence was defined as evidence of tumor within the same lung, at the bronchial stump, or manifest disease in ipsilateral mediastinal lymph nodes. Distant metastatic disease was defined as disease in the contralateral lung or outside the hemithorax, including supraclavicular lymph node metastases as well as metastases to distant organs (*e.g.*, brain, adrenal glands).

Statistical Analysis and Study Population

The primary objective of this prospective randomized trial was to investigate whether LA increases the probability of 5-year survival over conventional node dissection with a difference of 20%. To show a difference of 20% between the procedures with a type I error of 0.05 and a type II error of 0.10 by a two-tailed test, 100 patients per group were required. Secondary end points were local recurrence-free and distant metastasis-free survival, as well as the effect of radical lymphadenectomy on tumor staging, morbidity, and mortality.

Differences in baseline characteristics of binary and ordinal variables were tested with Fisher's exact test and chi square tests. Probability of cumulative cancer-related survival inclusive 30-day mortality, metastasis-free interval, and local recurrence-free interval were assessed by the Kaplan-Meier method, and differences were compared using the log-rank test. A proportional hazards regression model was fitted to determine the influence of various factors on survival.

Two hundred one patients were recruited for the study and randomly assigned to be treated either by LA (n = 100) or by LS (n = 101). After randomization, 32 patients were excluded from analysis due to residual tumor (n =

12) or classification as small cell lung cancer (n = 10), involvement of contralateral nodes (N3 disease; n = 5), or metastatic disease in the resected lobe or lung (M1 disease; n = 5). Hence, 169 patients (LS, 93; LA, 76) remained for survival analysis. Three patients in each group were lost to follow-up during the observation period and were censored at the respective time intervals.

RESULTS

Comparability of Groups

There were no statistically significant differences between patients treated by LA or LS with respect to age, sex, tumor site, T or N classification, and type of primary tumor resection. However, there were more squamous cell carcinomas in the LA group than in the LS group (52.7 *vs.* 31.6%; Table 1).

Analysis of Overall Survival

After median follow-up of 47.5 months, there were 26 (34.2%) deaths in the LA group and 42 deaths (45.2%) in the LS group. Cox proportional hazards analysis did not reveal a statistically significant treatment effect (Table 2, Fig. 1).

Table 1. DISTRIBUTION OF CHARACTERISTICS AMONG 169 ELIGIBLE PATIENTS WITH NSCLC TREATED BY RADICAL SYSTEMATIC LYMPHADENECTOMY (LA) OR LYMPH NODE SAMPLING (LS)

	LS (n = 93)	LA (n = 76)
Age		
<60 yr	40 (43.0)	35 (46.1)
≥60 yr	53 (57.0)	41 (53.9)
Sex		
Female	20 (21.5)	24 (31.6)
Male	73 (78.5)	52 (68.4)
Tumor typing		
Squamous cell carcinoma	49 (52.7)	24 (31.6)*
Adenocarcinoma	28 (30.1)	39 (51.3)
Large cell carcinoma	9 (9.7)	5 (6.6)
Adenosquamous carcinoma	4 (4.3)	3 (3.9)
Other types	3 (3.2)	4 (6.6)
T stage		
1	13 (14.0)	18 (23.7)
2	64 (68.8)	47 (61.8)
3	10 (10.8)	10 (13.2)
4	6 (6.5)	1 (1.2)
N stage		
0	54 (58.1)	49 (64.5)
1	16 (17.2)	9 (11.8)
2	23 (24.7)	18 (23.7)

Values are number (%) of patients.
NSCLC = non-small cell lung cancer.
* Difference between LA and LS is significant at p = 0.032.

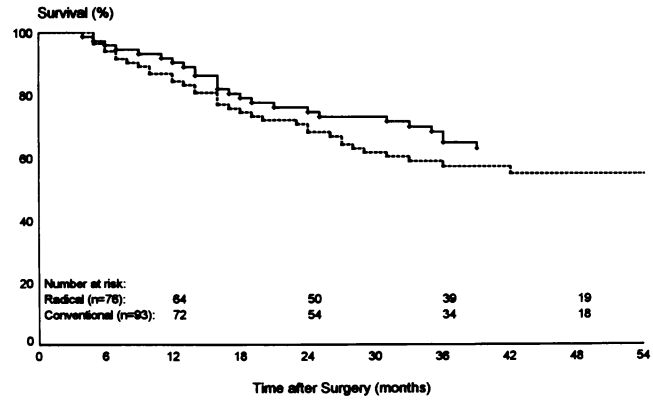

Figure 1. Kaplan-Meier plots of overall survival in patients with non-small cell lung cancer treated by systematic radical lymphadenectomy (n = 76; solid line) or conventional lymphadenectomy (n = 93; dashed line). The difference between the two groups is not significant (p = 0.256, log-rank test).

Analysis of Relapse-Free Survival and Pattern of Recurrence

The median disease-free interval was 48 months (range 2–54) in the LA group and 24 months (range 3–53) in the LS group (Fig. 2). Because extensive lymphadenectomy might be especially useful in controlling local recurrences, we examined the pattern of tumor relapse (*e.g.*, local recurrences and distant metastases) separately. Distant metastases as the only manifestation of tumor relapse were observed in 20 (26.3%) patients in the LA group

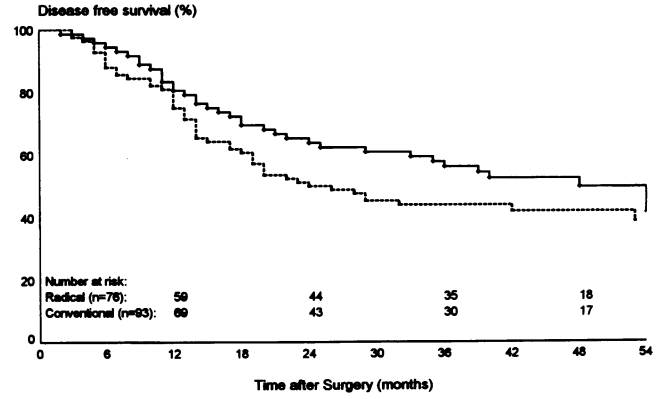

Figure 2. Kaplan-Meier plots of disease-free survival in patients with non-small cell lung cancer treated by systematic radical lymphadenectomy (n = 76; solid line) or conventional lymphadenectomy (n = 93; dashed line). The difference between the two groups is not significant (p = 0.204, log-rank test).

Table 2. COX REGRESSION MODELS OF DISEASE-FREE AND OVERALL SURVIVAL IN PATIENTS WITH NSCLC TREATED BY LYMPH NODE SAMPLING (LS) OR SYSTEMATIC LYMPHADENECTOMY

		Overall Survival			Disease-Free Survival		
Factor	Level	p Value	Hazard Ratio	95% CI	p Value	Hazard Ratio	95% CI
Treatment	LS						
	LA	0.273	0.76	0.47–1.24	0.338	0.82	0.54–1.27
pT stage	pT1–2						
	pT3–4	0.005	2.28	1.28–4.08	0.004	2.20	1.29–3.78
pN stage	pN0						
	pN1–2	0.026	1.80	1.07–3.03	0.007	1.88	1.18–3.00
Age (yr)	≤60						
	>60	0.101	1.50	0.92–2.46	0.024	1.67	1.07–2.60

NSCLC = non-small cell lung cancer; CI = confidence interval.

and 29 (31.2%) patients in the LS group. Local tumor recurrences (including patients in whom a local tumor recurrence and a distant metastasis were recorded at the same time) were noted in 22 (28.9%) patients in the LA group and 32 (34.4%) patients in the LS group. None of these differences were significant.

Analysis of Subgroups

To investigate whether LA might be beneficial for certain subgroups of patients with NSCLC, we stratified the patients according to conventional clinicopathologic parameters such as T status, N status, tumor histology (adenocarcinoma *vs.* squamous cell carcinoma), and patient age and sex. There were no significant differences in any of these subgroups between patients treated by LA or LS, including patients with no lymph node involvement (pN0) or extensive mediastinal disease (pN2).

However, in patients who had either regional nodal involvement (pN1 disease) or limited mediastinal involvement (pN2 disease with involvement of only one lymph node level of the N2 region), LA tended to improve survival (p = 0.058) and to prolong relapse-free survival (p = 0.037) and it seemed to reduce distant (p = 0.059) and local (p = 0.066) recurrences (Table 3, Fig. 3).

Table 3. RATES OF DEATH AND RECURRENCE IN PATIENTS WITH LIMITED MEDIASTINAL LYMPH NODE INVOLVEMENT*

	Treatment Group	Number (%) of Events	p Value†
Death	LA (n = 17)	5 (29.4)	
	LS (n = 29)	18 (62.1)	0.058
Recurrence	LA	7 (41.2)	
	LS	23 (79.3)	0.037
Only distant metastases	LA	2 (11.8)	
	LS	10 (34.5)	0.059
All other‡	LA	5 (29.4)	
	LS	13 (44.8)	0.066

LA = lymphadenectomy; LS = lymph node sampling.
* Patients with pN1 disease or pN2 disease with involvement of only one lymph node level of the N2 region.
† Log rank test.
‡ "All other" includes local recurrences as well as patients in which local recurrences and distant were detected at the same time.

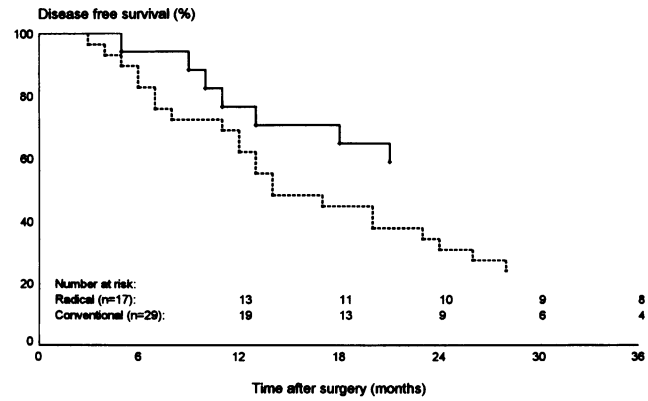

Figure 3. Disease-free survival in patients with non-small cell lung cancer and limited mediastinal lymph node involvement (N1 disease or involvement of only one lymph node level of the N2 region) treated by systematic radical lymphadenectomy (n = 17; solid line) or conventional lymphadenectomy (n = 29; dashed line). The difference between the two groups is significant (p = 0.037, log-rank test).

Effect of Radical Lymphadenectomy on Tumor Staging

The strategy in conventional lymphadenectomy is to remove the superior mediastinal, para- and pretracheal, paraesophageal, and pulmonary ligament lymph node levels (levels 2, 3, 6, 8) only if they are macroscopically suspicious of cancer. Thus, metastatic involvement might be underestimated because involved lymph nodes can be missed by the surgeon. To investigate this hypothesis, we analyzed the incidence of lymph node metastases in the LA group of patients in which all lymph node levels had been resected. In this group, lymph node metastases in regions 2, 3, 6, or 8 were detected by histopathology in 13 (17.1%) of 76 patients. In nine patients, only one of these levels was affected; in three patients, two levels were involved; and in one patient, three levels were positive. In 4 of these 13 patients (5.3% of all LA patients), lymph node involvement of the N2 region was limited to lymph nodes that were resected only in the LA group. In the other nine patients, N2 disease was already diagnosed in lymph nodes that were routinely resected in all patients. Thus, only a small number of patients were understaged due to the limited mediastinal lymph node sampling.

DISCUSSION

As in other types of solid carcinomas, the significance of lymphadenectomy on the long-term outcome is controversial in patients with apparently resectable NSCLC. In addition to a potential prognostic benefit, advocates of radical mediastinal lymph node dissection claim a better tumor staging.[1,3,11,13,14] Opponents of the radical approach postulate higher morbidity and mortality due to the extent of the operation and even a negative effect on long-term prognosis due to an impaired local immune response. For staging reasons, they recommend a mediastinal lymph node sampling.[4,5] We therefore performed a prospective randomized trial comparing the influence of a radical mediastinal lymphadenectomy with a conventional sampling of mediastinal lymph nodes in patients with resectable (R0) NSCLC.

Recently, we reported the short-term results of this trial by analyzing the effect of systematic lymphadenectomy on intraoperative complications and postoperative morbidity and mortality.[7] We observed that the radical approach was associated with a longer operation time (LA, 207 min; LS, 185 min), but the rate of intraoperative complications (*e.g.*, recurrent laryngeal nerve lesions) was not influenced by the type of lymphadenectomy. The postoperative course was essentially the same in both groups, except for a higher need of postoperative blood transfusions and a prolonged air leakage in patients with systematic lymph node dissection. However, these parameters did not influence the length of the hospital stay or the duration of stay in the intensive care unit. Similarly, the 30-day mortality was not statistically different between patients with conventional or systematic lymphadenectomy.

In the present study, we observed no significant effect of systematic mediastinal lymph node dissection on long-term survival and recurrence rates. However, a subgroup of patients with limited nodal involvement (pN1 disease or pN2 disease with only one lymph node level involved; see Table 3) might benefit from systematic mediastinal lymphadenectomy. This is supported by data provided by the immunohistochemical staining of lymph nodes. In addition to the routine histopathologic staining, the extent of lymphatic tumor cell dissemination was examined in a subgroup of 94 patients by applying an immunohistochemical assay; this allows the detection of even single tumor cells in lymph nodes staged as free of metastases by conventional hematoxylin and eosin staining.[10,15] In patients in whom immunohistochemistry revealed no additional lymphatic tumor cell spread, rates of overall recurrence and especially local recurrence were significantly reduced in the LA group (data not shown). Therefore, there might be patients even with macroscopic lymph node metastases but without additional regional lymphatic tumor cell spread who will benefit from a radical resection of the primary tumor with a complete removal of all resectable lymph nodes.

To predict which patients may profit from radical lymphadenectomy, the biologic behavior of the individual primary tumor must be taken into consideration. Our recent analysis of the expression pattern of immunoregulatory molecules such as MHC molecules and ICAM-1 provides first evidence that there might be biologic differences between primary tumors with or without a widespread lymphatic dissemination.[16] In patients with an early lymphatic spread, we observed a significant downregulation of the molecules that mediate an effective immune response.

A major criticism of our study might be the so-called Will Rogers phenomenon, or the stage migration of patients due to an improved lymph node staging by a more extensive lymphadenectomy,[17,18] meaning that in a substantial number of patients in whom only a limited lymphadenectomy was performed, the true N stage remains unrecognized because the relevant lymph nodes were not removed and consequently not examined by histopathology. This might result in a downstaging of some of the patients of the lymph node sampling group. In 5.5% of the patients in the LA group, N2 disease was detected only in lymph node levels that would not have been routinely included in the lymph node sampling group. Therefore, the postulated beneficial effect of LA in patients with limited mediastinal lymph node involvement might be

due at least in part to an imbalance within the groups with respect to the number of patients with lymph node involvement at multiple levels of the N2 region.

In conclusion, the type of lymphadenectomy may not have a strong influence on the long-term clinical outcome in patients with apparently no lymph node involvement (pN0). However, some patients with a limited mediastinal tumor cell spread might benefit from a more radical approach. Because current preoperative staging procedures cannot precisely identify these patients, and because radical lymphadenectomy is not associated with higher morbidity and mortality,[7] we recommend that all patients with apparently resectable NSCLC should undergo systematic mediastinal lymphadenectomy.

References

1. Martini N, Flehinger BJ, Zaman MB, Beattie EJ. Results of resection of non-oat cell carcinoma of the lung with mediastinal lymph node metastases. Ann Surg 1983;198:386–397.
2. Martini N, Flehinger BJ, Zaman MB, Beattie EJ. Results of surgical treatment in N2 lung cancer. World J Surg 1981;5:663–666.
3. Naruke T, Goya T, Tsuchiya R, Suemasu K. The importance of surgery to non-small cell carcinoma of the lung with mediastinal lymph node metastasis. Ann Thorac Surg 1988;46:603–609.
4. Thomas PA, Piantadosi S, Mountain CF, the Lung Cancer Study Group. Should subcarinal lymph nodes be routinely examined in patients with non-small cell lung cancer? J Thorac Cardiovasc Surg 1988;95:883–887.
5. Thomas P, Rubinstein L, the Lung Cancer Study Group. Cancer recurrence after resection: T1N0 non-small cell lung cancer. Ann Thorac Surg 1990;49:242–247.
6. Sorensen JB, Badsberg JH. Prognostic factors in resected stages I and II adenocarcinoma of the lung. J Thorac Cardiovasc Surg 1990;99:218–226.
7. Izbicki JR, Thetter O, Habekost M, et al. Radical systematic lymphadenectomy in non-small cell lung cancer: A prospective controlled randomized clinical trial. Br J Surg 1994;81:229–235.
8. Izbicki JR, Thetter O, Karg O, et al. Accuracy of computed tomography and of surgical assessment for staging of bronchial carcinoma: A prospective study. J Thorac Cardiovasc Surg 1992;104:413–420.
9. Naruke T, Suemasu K, Ishikawa S. Surgical treatment for lung cancer with metastasis to mediastinal lymph nodes. J Thorac Cardiovasc Surg 1975;71:279–285.
10. Pantel K, Koprowski H, Riethmüller G. Conference on cancer micrometastasis: Biology, methodology, and clinical significance. Int J Oncol 1993;3:1019–1022.
11. Martini N, Flehinger BJ. The role of surgery in N2 lung cancer. Surg Clin North Am 1987;67:1037–1049.
12. UICC. TNM classification of malignant tumors, 4th ed. Berlin/Heidelberg/New York: Springer; 1987.
13. Naruke T, Goya T, Tsuchiya R, Suemasu K. Prognosis and survival in resected lung carcinoma based on the new international staging system. J Thorac Cardiovasc Surg 1988;96:440–447.
14. Hata E, Hayakawa K, Miyamoto H, Hayashida R. Rationale for extended lymphadenectomy in lung cancer. Theor Surg 1990;5:19–25.
15. Passlick B, Izbicki JR, Kubuschok B, et al. Detection of disseminated lung cancer cells in lymph nodes: Impact on staging and prognosis. Ann Thorac Surg 1996;61:177–183.
16. Passlick B, Pantel K, Kubuschok B, et al. Expression of MHC molecules and ICAM-1 on non-small cell lung carcinomas: Association with early lymphatic tumor cell spread. Eur J Cancer 1996;32A:141–145.
17. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon: Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. N Engl J Med 1985;312:1604–1608.
18. Bunt AMG, Hermans J, Smit VTHBM, et al. Surgical/pathological stage migration confounds comparison of gastric cancer survival rates between Japan and Western countries. J Clin Oncol 1995;13:19–25.