Mediastinal lymph node dissection improves survival in patients with stages II and IIIa non-small cell lung cancer

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Mediastinal Lymph Node Dissection Improves Survival in Patients With Stages II and IIIa Non-Small Cell Lung Cancer

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Background. **Mediastinal lymph node dissection (MLND) is an integral part of surgery for non-small cell lung cancer (NSCLC). To compare the impact of systematic sampling (SS) and complete MLND on the identification of mediastinal lymph node metastases and patient survival, the Eastern Cooperative Oncology Group (ECOG) stratified patients by type of MLND before participation in ECOG 3590 (a randomized prospective trial of adjuvant therapy in patients with completely resected stages II and IIIa NSCLC).**

Methods. **Eligibility requirements for study entry included a thorough investigation of the mediastinal lymph nodes with either SS or complete MLND. The former was defined as removal of at least one lymph node at levels 4, 7, and 10 during a right thoracotomy and at levels 5 and/or 6 and 7 during a left thoracotomy, while the latter required complete removal of all lymph nodes at those levels.**

Results. **Three hundred seventy-three eligible patients were accrued to the study. Among the 187 patients who underwent SS, N1 disease was identified in 40% and N2 disease in 60%. This was not significantly different than the 41% of N1 disease and 59% of N2 disease found among the 186 patients who underwent complete MLND. Among the 222 patients with N2 metastases, multiple levels of N2 disease were documented in 30% of patients who underwent complete MLND and in 12% of patients who had SS ($p = 0.001$). Median survival was 57.5 months for those patients who had undergone complete MLND and 29.2 months for those patients who had SS ($p = 0.004$). However, the survival advantage was limited to patients with right lung tumors (66.4 months vs 24.5 months, $p < 0.001$).**

Conclusions. **In this nonrandomized comparison, SS was as efficacious as complete MLND in staging patients with NSCLC. However, complete MLND identified significantly more levels of N2 disease. Furthermore, complete MLND was associated with improved survival with right NSCLC when compared with SS.**

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The role of mediastinal lymphadenectomy in the staging and treatment of non-small cell lung cancer (NSCLC) remains controversial. Accurate intraoperative staging of NSCLC requires some assessment of the mediastinal lymph nodes. However, the degree to which the mediastinal lymph nodes should be sought and the extent of their removal remains controversial. Current surgical practice varies from mere visual inspection of the unopened mediastinum to radical lymphadenectomy. Furthermore, the therapeutic effect of extensive mediastinal lymphadenectomy is the subject of debate.

Critical assessment of the published literature relating survival to pathologic stage and type of lymph node dissection requires knowledge of the operative technique. In general, "sampling" means that only those lymph nodes that were obviously abnormal were removed. "Systematic sampling" refers to routine biopsy of lymph nodes at levels specified by the author. "Complete mediastinal lymph node dissection" indicates that all lymph node-containing tissue was routinely removed at those levels indicated by the investigators.

The recently completed Intergroup Trial 0115 (Eastern Cooperative Oncology Group [ECOG] 3590) of adjuvant therapy in patients with completely resected stages II and IIIa NSCLC [1] provided the opportunity to compare the merits of systematic sampling (SS) and complete mediastinal lymph node dissection (MLND) with regard to staging and patient survival. Among the study eligibility criteria was the requirement for either a thorough SS or a complete MLND. Patients were stratified by the type of lymph node dissection before randomization to one of the two treatment arms.

Material and Methods

Study Design

The ECOG initiated a randomized prospective trial of adjuvant therapy in patients with completely resected

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stages II and IIIa NSCLC in April 1991. The objectives of the study were to determine if combination chemotherapy and concomitant thoracic radiotherapy (TRT) were superior to TRT alone in preventing local recurrence and prolonging survival in patients with completely resected stages II and IIIa NSCLC. The Radiation Therapy Oncology Group joined the trial at the time of activation, the North Central Cancer Treatment Group activated the study in November 1991, and the Cancer and Leukemia Group B and the Southwest Oncology Group opened the trial in December 1993. The National Cancer Institute designated the study as "high priority."

Patients were enrolled from April 1991 through February 1997. Randomization was accomplished via telephone communication with the operations office of the cooperative group with which the investigator was associated. The protocol was reviewed and approved by the institutional review board or ethics committee at each site. Written informed consent was obtained from either the patient or his surrogate.

Randomization was required within 42 days of surgery. Patients were stratified by histology (squamous vs other), weight loss within the past 6 months ($< 5\%$ vs $\geq 5\%$), nodal status (N1 vs N2), and type of lymph node dissection (SS vs complete MLND). Patients randomized to the control arm received 50.4 Gy in 28 daily 1.8-Gy fractions. The initial portion of the treatment was given with AP-PA portals to 36 to 42 Gy. The remainder of the treatment was given to the same target volume, but with a lateral/oblique field arrangement that prevented the spinal cord from receiving more than 45 Gy. An additional 10.8 Gy (1.6-Gy fractions) was administered to those nodal levels in which histologic documentation of extracapsular extension of nodal metastases was present. The treatment arm consisted of identical TRT administered concomitantly with VP-16 (120 mg/m^2 IV, days 1 to 3) and cisplatin (60 mg/m^2 IV, day 1). Chemotherapy was initiated within 24 hours of beginning TRT and was repeated every 28 days for a total of four cycles.

Eligibility Criteria

Patients who had undergone complete resection of pathologic stages II (T1-2N1M0) or IIIa (T1-2N2M0, T3N1-2M0) NSCLC were eligible for study participation. Patients with multifocal bronchoalveolar tumors within the same lobe or different ipsilateral lobes were not eligible. The international lung cancer staging system accepted by the American Joint Committee on Cancer and the Union Internationale Contre Cancer during the years 1986 to 1997 was utilized [2]. Lymph node levels were defined according to the American Thoracic Society [3]. Level 10 was considered an N1 lymph node.

To assure accurate histologic documentation, a complete MLND or SS was mandated. The former was defined as resection of all lymph nodes at specified levels. The latter entailed removal of a representative lymph node at those same levels. Complete MLND or SS of levels 4, 7, and 10 was required during a right thoracotomy and levels 5 and/or 6 and 7 during a left thoracotomy. Each operative note and pathology report was reviewed (S.M.K.) to ensure uniform lymph node labeling and staging. A videotape illustrating the technique of complete MLND was made available to all participating institutions.

Cervical mediastinoscopy was required beginning in December 1993 if the preoperative computed tomography scan demonstrated mediastinal lymph nodes greater than 1.5 cm in short-axis diameter. Patients found to have multilevel metastases, contralateral mediastinal disease, or extranodal disease were ineligible. Lymph node levels biopsied during cervical mediastinoscopy did not require rebiopsy during thoracotomy for the patient to have been stratified to the SS group. However, complete removal of all nodal tissue at those previously biopsied levels was required in order for the patient to have been stratified to the complete MLND group. Patients must have undergone either lobectomy or pneumonectomy. Segmental or wedge resections were permitted during the early months of the study, but later rendered the patient ineligible for study participation. Additional eligibility requirements included a postoperative ECOG performance status of 0 or 1 and a postoperative forced expiratory volume in 1 second (FEV_1) sufficient to tolerate the proposed TRT.

Statistical Methods

Survival time was computed as follows: patients who are dead are considered as events and survival time is the time to death from date of registration. Patients who are alive were censored as of last known follow-up.

UNIVARIATE ANALYSIS. Fisher's exact test [4] was used to compare groups with respect to categorical endpoints (eg, recurrence). Survival distributions for survival time, time to recurrence, and disease-free survival were estimated with the Kaplan-Meier method [5] and compared with the log rank test [6].

MULTIVARIATE ANALYSES. Cox proportional hazards model [7] was used to estimate the joint effect of prognostic factors on survival. In the model fitting procedures, stepwise selection was used to determine more parsimonious models. Statistical significance was set at a significance level of 0.05, and all tests and p values reported are two tailed. Possible factors for inclusion in the model consisted of the stratification factors (nodal status, histology, weight loss, and lymph node staging), selected baseline patient characteristics (age group, gender, race, ECOG performance status), T stage (T1 vs not T1 and T3 vs not T3), skip metastases, primary tumor site (right vs left), and a term to account for any interaction between primary tumor site and dissection technique.

Subsequently, separate Cox models were fitted to the data for: (1) patients with complete node dissection, and (2) patients with sampling. Possible factors for inclusion were the same as in the overall model (except for lymph node staging).

Table 1. Patient Demographics

	SS (n = 187) (%)	Complete MLND (n = 186) (%)	*p* Value (Fischer's Exact Test)
Gender			
Male	117 (63)	99 (53)	
Female	70 (37)	87 (47)	0.08
Age			
< 60 years	94 (50)	93 (50)	
≥ 60 years	93 (50)	93 (50)	1.0
Race			
White	157 (84)	162 (87)	
Other	30 (16)	24 (13)	0.46
Performance status[a]			
0 (Fully active)	80 (43)	68 (37)	
1 (Ambulatory)	106 (57)	118 (63)	0.24
Histology			
Squamous	76 (41)	63 (34)	
Other	111 (59)	123 (66)	0.19
Weight loss in previous 6 months			
< 5%	139 (74)	146 (78)	
≥ 5%	48 (26)	40 (22)	0.39

[a] Data not available for 1 patient.

MLND = mediastinal lymph node dissection; SS = systematic sampling.

Table 2. Operative Data

	SS (n = 187) (%)	Complete MLND (n = 186) (%)	*p* Value (Fischer's Exact Test)
Tumor location			
Right	95 (51)	108 (58)	
Left	92 (49)	78 (42)	0.21
Surgery			
Lobectomy	120 (64)	126 (68)	
Pneumonectomy	65 (35)	60 (32)	0.81
Other	2 (1)		
Mediastinoscopy	65 (35)	57 (31)	0.38
Duration of operation (min)			
Median	229	240	
Range	42–460	34–925	0.62
Estimated blood loss (cc)			
Median	300	300	
Range	0–1700	0–1500	0.70
Transfusion (units)			
Mean	0.30	0.28	
Range	0–4	0–5	0.53

MLND = mediastinal lymph node dissection; SS = systematic sampling.

Results

Four hundred eighty-eight patients were registered during the study interval, 373 of whom fulfilled the eligibility criteria. The most common reason for ineligibility was lack of compliance with the lymph node sampling/dissection requirements (n = 103). For instance, the pathologist documented a lymph node metastases, but the nodal level was not identified. Similarly, patients were ineligible if neither the operative report nor the pathology report demonstrated sampling/dissection of the protocol specified lymph node levels. Twelve additional patients were ineligible due to the presence of extrathoracic metastatic disease (n = 7), absence of nodal involvement (n = 1), multiple primary tumors (n = 2), delayed randomization (n = 1), and decrease in performance status (n = 1).

Analysis of all registered patients by treatment arm failed to identify any significant difference in recurrence patterns or survival. Analogous results were obtained when the analysis was restricted to the eligible patients. Details have been reported elsewhere [1].

SS was performed in 187 patients, while complete MLND was accomplished in 186 patients. Seventy-eight (45%) of the 174 patients randomized to TRT alone and 109 (55%) of the 199 patients randomized to the combined treatment arm underwent SS. The remaining patients underwent complete MLND. Demographics of the eligible patients appear in Table 1. The median age was 60 years (range 35 to 78 years) in the complete MLND group and 61 years (range 34 to 81 years) in those patients who underwent SS. Adenocarcinoma was the most common histology, occurring in 101 of the patients who underwent complete MLND and 85 of the patients who had SS.

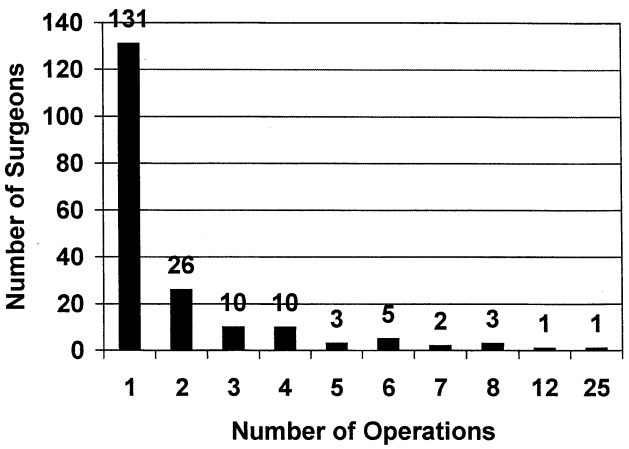

Fig 1. One hundred ninety-two surgeons accrued patients to the study. The majority entered only 1 patient.

Surgery

One hundred ninety-two surgeons entered patients in the study (Fig 1). Fifteen surgeons entered 5 or more patients. Two of these surgeons performed SS exclusively and two performed only complete MLND. Five of the remaining surgeons performed one procedure or the other in more than 75% of their patients. The remaining six surgeons were less consistent in their technique of lymph node dissection. Ninety percent of the surgeons

Table 3. Staging

	SS (n = 187) (%)	Complete MLND (n = 186) (%)	*p* Value (Fisher's Exact Test)
N1 only	75 (40)	76 (41)	0.92
N2 only (skip metastases)	39 (21)	38 (20)	1.0
N1 and N2	73 (39)	72 (39)	1.0
Multiple N2 Levels[a]	13 (12)	33 (30)	0.001

[a] Calculated as percent of patients with N2 disease.

MLND = mediastinal lymph node dissection; SS = systematic sampling.

were certified by the American Board of Thoracic Surgery or the Canadian equivalent. Details of the operative procedures are presented in Table 2.

One hundred twenty-two patients underwent mediastinoscopy. Mediastinal metastases limited to a single nodal level were identified in 8 patients before resection. Four of these patients underwent SS and 4 underwent complete MLND.

Staging

The percentage of patients with N1 or N2 disease was similar in both the SS and complete MLND groups, as were the number of patients found to have metastases to both N1 and N2 nodal levels. However, the patients with N2 disease who underwent complete MLND were found to have more positive N2 levels than those patients who underwent SS (Table 3).

Survival

Median follow-up was 44 months. Survival of the 186 patients who underwent complete MLND was significantly better than those patients who had undergone SS (Fig 2). The improved survival associated with complete MLND was present in patients with N1 (Fig 3) and N2 disease (Fig 4). However, this advantage was limited to patients with right lung tumors (Figs 5 and 6). Subgroup analysis demonstrated improved median survival after complete MLND in the 125 patients with right upper lobe tumors (median survival not reached vs 26.9 months, $p = 0.006$) as well as in the 66 patients with right lower lobe tumors (50.7 months vs 24.1 months, $p = 0.029$). Results of the multivariate analysis for those factors that proved statistically significant are presented in Table 4. Preoperative mediastinoscopy did not influence survival ($p = 0.11$).

Recurrence

Relapse data were available for 351 patients. Disease-free survival was not significantly different between the SS and complete MLND arms (median 33.2 months vs 21.4 months, $p = 0.086$). Recurrent disease developed in 92 (52%) of the patients who had undergone complete MLND and in 101 (58%) of the patients who had SS ($p = 0.28$). No significant difference in intrathoracic or extrathoracic recurrence patterns (eg, brain, bone, liver) was present between the two groups.

However, patients with right lung cancers who underwent complete MLND did have a significantly improved disease-free survival when compared with those patients who underwent SS (Fig 7). Recurrent disease developed in 52 (50%) patients with right lung cancers who had

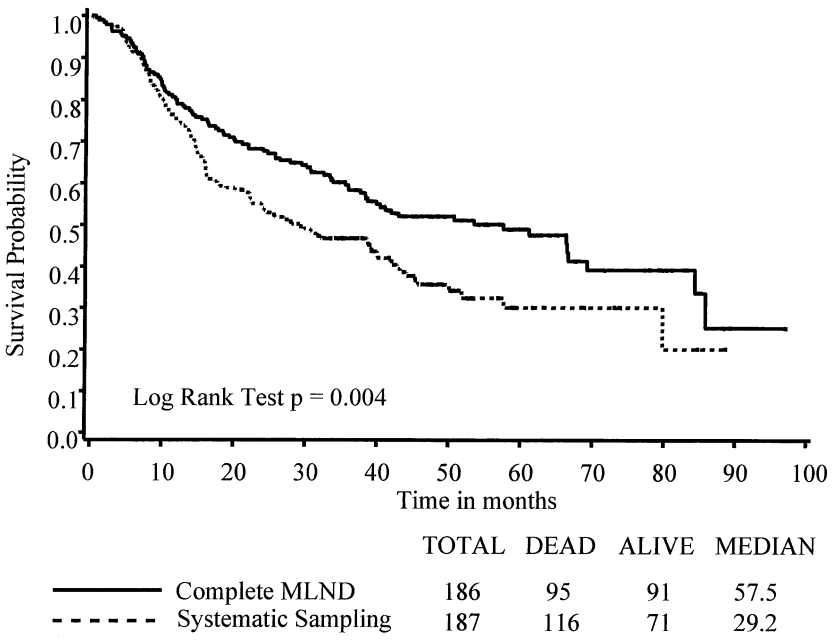

Fig 2. Survival. Patients who underwent complete MLND survived significantly longer than those patients who underwent SS.

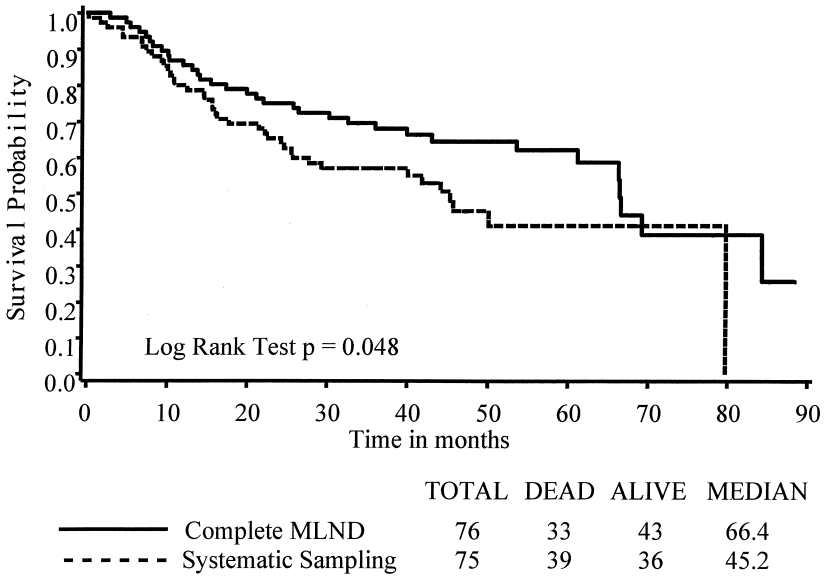

Fig 3. Survival with N1 disease. The median survival of patients with N1 disease was significantly prolonged if they had a complete MLND.

undergone complete MLND and in 52 (60%) patients who had SS ($p = 0.188$).

Comment

The importance of assessing the mediastinal lymph nodes was recognized early in the development of lung cancer surgery. The first detailed lymphadenectomy description was given in 1951 by Cahan and associates [8], who described en bloc resection of the mediastinal lymph nodes in continuity with a pneumonectomy. Though other authors subsequently documented variations of this technique, the extent of the lymphadenectomy necessary to accurately stage the patient and the therapeutic effect (if any) remained unclear. Recently, however, a number of investigators have addressed these issues.

The surgeon's inability to intraoperatively determine the presence or absence of tumor within the mediastinal lymph nodes without biopsy was demonstrated by Gaer and Goldstraw [9], who compared the intraoperative visual and tactile evaluation of resected mediastinal lymph nodes with pathologic examination in 95 consecutive patients with NSCLC. Palpation and visual inspec-

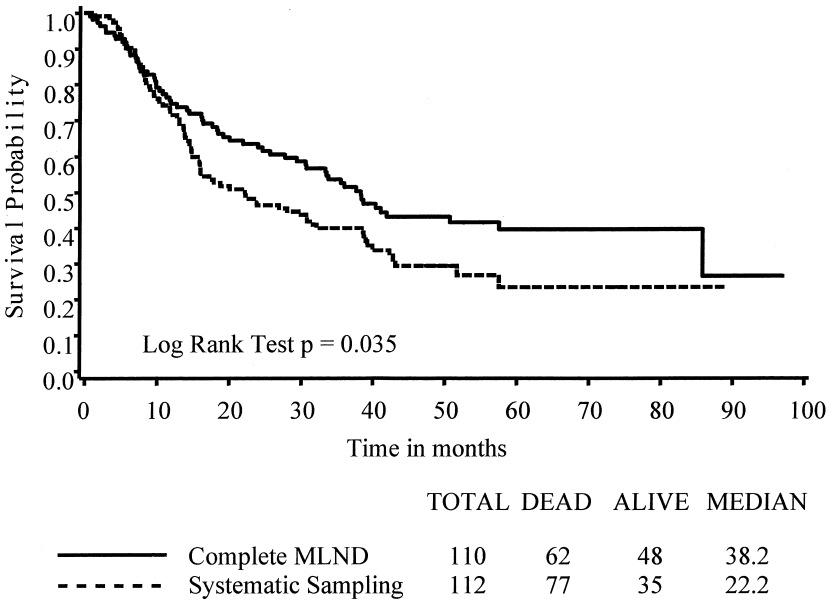

Fig 4. Survival with N2 disease. The survival advantage for patients who had undergone complete MLND was also present for those patients with N2 disease.

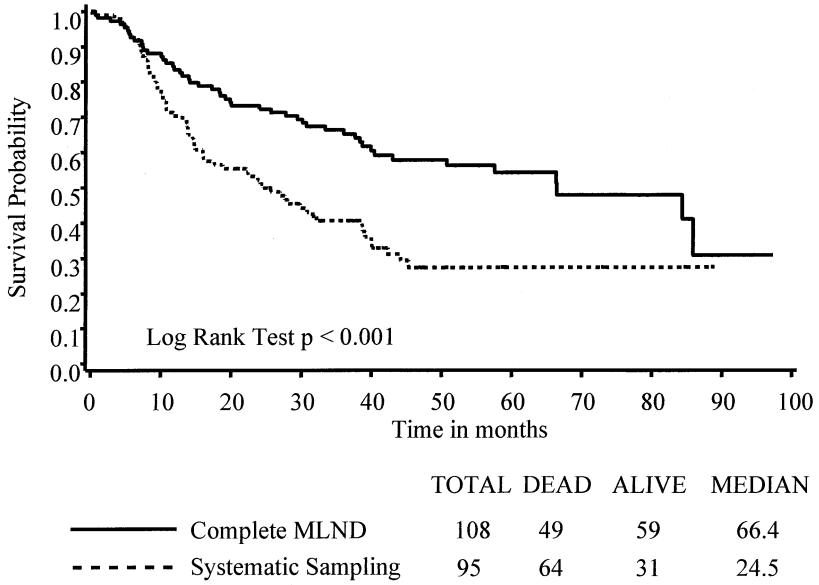

Fig 5. Right lung tumors. The improved survival with complete MLND was limited to right lung cancers and was present for both upper and lower lobe tumors.

tion of 287 lymph node levels produced a sensitivity of 71% and a positive predictive value of 64%. Evaluation of the nodal levels through an unopened mediastinal pleura would presumably have produced even less accurate results.

Bollen and associates [10] retrospectively evaluated the staging of 155 patients with resected NSCLC who had undergone sampling (n = 70), SS (n = 20), or complete MLND (n = 65). Thirty-two patients were found to have N2 disease: 9 (13%) in the sampling group, 7 (35%) in the SS group, and 16 (25%) in the complete MLND group. The discovery ratio of N2 disease in patients with NSCLC who underwent complete MLND or SS was 2.7 (95% confidence interval, 1.2 to 6.3) when compared with those patients who underwent sampling alone. They concluded that sampling was not sufficient for the accurate staging of NSCLC.

Izbicki and associates [11] compared SS with complete MLND in a randomized prospective trial containing 182 patients (N0, 103; N1, 29; N2, 45; N3, 5). The percentage of patients found to have N1 or N2 disease was not significantly different between the two study arms. However,

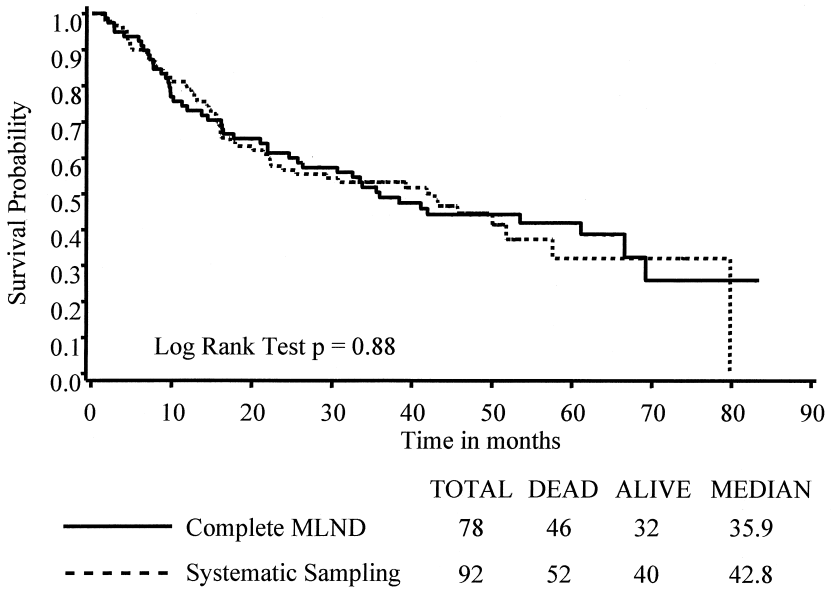

Fig 6. Left lung tumors. The type of lymph node dissection did not influence the survival of patients with left lung cancers regardless of whether the tumor originated in the upper (log rank test, p = 0.90) or lower lobes (log rank test, p = 0.89).

Table 4. Multivariate Analysis of Prognostic Factors

	Relative Risk	95% CI for Relative Risk	*p* Value (Wald Test)
N2 vs N1	1.988	1.466, 2.695	0.0001
SS vs complete MLND	1.502	1.139, 1.980	0.0034
Age	1.019	1.005, 1.034	0.0080
Skip metastases (yes vs no)	1.704	1.168, 2.481	0.0079
T2 and T3 vs T1	1.608	1.111, 2.331	0.0159

MLND = mediastinal lymph node dissection; SS = systematic sampling.

the number of N2-positive levels was greater in the patients who had complete MLND (59% vs 17%, $p = 0.007$). No difference in tumor recurrence patterns was noted between the two groups, nor was any survival difference apparent (median follow-up 28 months). However, survival of patients with multiple positive N2 levels was significantly poorer than those patients with only one positive N2 nodal level. The authors recommended complete MLND in order to obtain the additional staging information for the subgroup of patients with N2 disease.

Sugi and associates [12] conducted a randomized prospective trial comparing SS with complete MLND in 115 patients with clinical T1N0 tumors that were less than 2 cm in diameter. Mediastinal metastases were found in 13% of each study group. Once again, no difference in recurrence patterns or survival was found. The investigators concluded that SS is sufficient for patients with T1 NSCLC less than 2 cm in diameter.

The current study represents the largest comparison of node dissection techniques in patients with documented lymph node metastases. Our results confirm that SS is as efficacious as complete MLND for accurately staging patients with stages II and IIIa NSCLC. In addition, we demonstrate improved survival for those patients with right lung cancers who underwent complete MLND.

Restriction of improved survival to patients with right lung cancers may be explained by the lymph node drainage patterns and the ready intraoperative access to the right mediastinal lymph nodes. Right lung cancers typically metastasize to the ipsilateral mediastinal lymph nodes, while left lower lobe tumors are known to spread via the subcarinal lymph nodes to the contralateral mediastinum. Though the paratracheal, perivascular, subcarinal, and paraesophageal mediastinal lymph nodes are easily removed during a right thoracotomy, access to some of these levels is limited from the left chest.

Should a more aggressive approach to lymphadenectomy in the left chest be undertaken? Some authors have described mobilization of the aortic arch to approach the left paratracheal lymph nodes [13]. Others have advocated mediansternotomy for resection of the primary tumor and dissection of both ipsilateral and contralateral paratracheal lymph nodes [14, 15]. Though these investigators claim improved survival, the numbers of patients in these studies are small. In view of the results of the current study, these more complete procedures deserve further investigation.

Potential complications of SS and complete MLND may arise from interruption of the blood supply to the bronchial stump, injury to the recurrent laryngeal nerve, and removal of a large portion of the intrathoracic lymphatics. Data regarding the morbidity of these two procedures were not collected in the present trial. However, prospective data regarding operating time, blood loss, or transfusion requirements were accumulated. No difference between SS and complete MLND was found (Table 2).

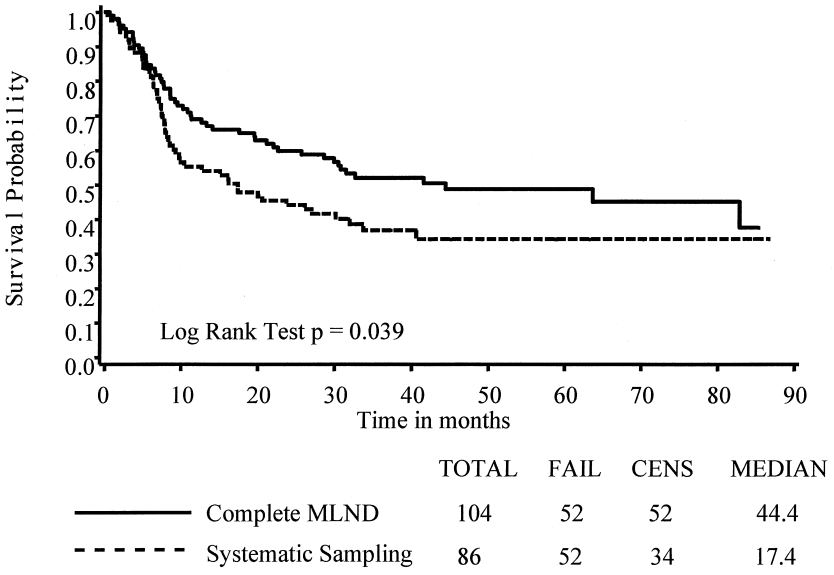

Fig 7. Disease-free survival, right lung tumors. Median disease-free survival was significantly prolonged in patients with right lung tumors who underwent complete MLND compared with those who underwent SS.

Bollen and associates found no significant difference in intraoperative blood loss or the need for transfusion among the three patient cohorts contained in his study [10]. However, 3 patients (5%) who underwent complete MLND suffered unintentional left recurrent laryngeal nerve injury, and 2 additional patients developed chylothoraces. No bronchopleural fistulas occurred in the group of patients who underwent complete MLND. Hata and associates reported two left recurrent laryngeal nerve injuries and one phrenic nerve paralysis in 50 patients who underwent extensive mediastinal dissection. No patient developed a bronchopleural fistula or required reoperation [14].

Izbicki and associates prospectively compared the morbidity and mortality associated with SS and complete MLND and found no increase in blood loss, mortality, or need for reoperation [11]. One chylothorax occurred in each group. Six patients who underwent SS and 5 patients who underwent complete MLND sustained recurrent laryngeal nerve injury. The duration of chest tube drainage and hospitalization were similar in both groups.

Though the data in the current study were collected in a prospective fashion from multiple institutions, the patients were not randomized to a specific lymph node dissection technique. Rather, they were stratified by the type of nodal dissection before randomization to one of two adjuvant therapy regimens. Thus, our results are open to the important criticisms of a nonrandomized trial.

The patients in the two groups were well matched by age, gender, performance status, and weight loss. They underwent similar operative procedures and were found to have comparable TNM staging. Where then might bias have entered the study? The obvious suggestion is that the surgeon somehow selected those patients destined to survive longer to undergo complete MLND. In fact, some variation in the operative routine was present. In addition, the type of adjuvant treatment was not equally distributed between the two lymph node dissection groups. However, as no difference in survival was demonstrated between the two adjuvant therapy arms, it is unlikely that this imbalance influenced the current analysis. Therefore, though the results of this study do not have the strength of a randomized prospective trial, they represent substantial observations that should guide clinical practice and serve as a catalyst for the development of future trials.

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DISCUSSION

DR DOUGLAS E. WOOD (Seattle, WA): Doctor Kouchoukos and Dr Pairolero, thank you for allowing me the privilege of discussing this year's J. Maxwell Chamberlain Memorial Paper. This work by Dr Keller and his colleagues stands out as exceptional and truly deserving of the J. Maxwell Chamberlain Award. I would like to offer my congratulations to Dr Keller for an elegant, straightforward, and insightful presentation.

The optimum lymph node dissection during lung cancer surgery remains controversial among thoracic surgical oncologists. Those in favor of lymphadenectomy argue that the procedure improves the accuracy of lung cancer staging and improves results by directing more accurate adjuvant therapy and decreasing locoregional recurrence.

Those opposed feel that lymphadenectomy increases operative time, blood loss, incidence of recurrent laryngeal nerve injury, chylothorax, and bronchopleural fistula, with no evidence of improved oncologic staging or survival. The strengths and weaknesses of the current analysis have been well pre-

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