Mediastinal Lymph Node Examination and Survival in Resected Early-Stage Non–Small-Cell Lung Cancer in the Surveillance, Epidemiology, and End Results Database

Raymond U. Osarogiagbon, MBBS, FACP, and Xinhua Yu, MD, PhD†*

Background: Pathologic nodal stage is the key prognostic factor in resectable non–small-cell lung cancer (NSCLC). Mediastinal lymph node (MLN) metastasis connotes a poor prognosis. Yet, some NSCLC resections exclude MLN examination.

Methods: We analyzed U.S. Surveillance, Epidemiology, and End Results program data from 1998 to 2002 to quantify the long-term survival impact of failure to examine MLN in resected NSCLC. We used Kaplan–Meier methods to compare the unadjusted survival difference between patients with, and without, MLN examination, and Cox proportional hazards and competing risk models to serially adjust for the impact of risk factors on survival differences.

Results: Sixty-two percent of patients with pathologic N0 or N1 NSCLC had no MLN examined. Overall 5-year survival rates were 52% for those with, versus 47% for those without, MLN examination; lung cancer-specific survival rates were 63% versus 58% respectively ($p < 0.001$); nonlung cancer mortality was identical between cohorts. Adjusting for potential confounders, MLN examination was associated with a 7% reduction in all-cause mortality (hazard ratio, 0.93; confidence interval, 0.88–0.97; $p = 0.002$), and 11% reduction in lung cancer-specific mortality (hazard ratio, 0.89; 95% confidence interval, 0.84–0.95; $p < 0.001$) rates. The excess risk in 1 year's cohort of U.S. lung resections was 3150 lives over 5 years.

Conclusions: Failure to examine MLN was a common practice in *MLN-negative* NSCLC resections, which significantly impaired long-term survival. Efforts to understand the etiology of this quality gap, and measures to eliminate it, are warranted.

Key Words: Non–small-cell lung cancer, Surgical resection, Mediastinal lymph nodes, Quality of care, Outcome of care, Staging.

(*J Thorac Oncol.* 2012;7: 1798–1806)

*The Multidisciplinary Thoracic Oncology Program, Boston Baskin Cancer Foundation, Baptist Cancer Center, Memphis, Tennessee; and †Department of Epidemiology and Biostatistics, School of Public Health, University of Memphis, Memphis, Tennessee.

Disclosure: Dr. Osarogiagbon has filed a U.S. patent application for a mediastinal lymph node specimen collection kit. The other author declares no conflict of interest.

Address for correspondence: Raymond U. Osarogiagbon, MBBS, FACP, 6027 Walnut Grove Road, Suite 201, Memphis, Tennessee 38120. E-mail: rosarogi@bmg.md

ISSN: 1556-0864/12/0712-1798

Lung cancer kills 160,000 individuals annually in the United States[1] and 1.4 million worldwide.[2] Non–small-cell lung cancer (NSCLC) represents approximately 85% of all lung cancer cases in the United States. Most long-term survivors of NSCLC have had surgical resection for early-stage disease. Yet, patients who undergo surgical resection remain at high risk for death, with 5-year mortality rates ranging from 27% for stage IA, to 76% for stage IIIA disease.[3]

Lymph node (LN) status is the paramount determinant of long-term postoperative survival. The 5-year survival rates are 56% in pathologic (p) N0, 38% in pN1, 26% in pN2, and 6% in pN3 disease.[4] Identifying LN metastasis is important for accurate prognostication and selection of postoperative adjuvant therapy.[5–8] Depending on the degree of thoroughness of application, preresection clinical staging underestimates pathologic stage in 10% to 40% of patients.[9–11] Therefore *clinically node-negative* patients need pathologic staging. All LNs within the resected lung[12] and certain mediastinal LNs (MLNs) should be examined.[13]

We hypothesized that failure to examine MLN leads to worse survival in patients who undergo resection for lung cancer, because of failure to identify MLN metastasis in a significant proportion, failure to accurately stratify risk, loss of putative benefits of surgical removal of LNs with metastasis, and (in recent times) failure to offer postoperative adjuvant therapy to high risk subsets. We examined the U.S. Surveillance, Epidemiology, and End Results database (SEER) to quantify the frequency and consequences of failure to examine MLN in patients with pN0 and pN1 disease (MLN-negative disease).

MATERIALS AND METHODS

With the approval of the University of Tennessee (Institutional Review Board no. 11-01649-XM), we queried the SEER lung cancer database in April 2012. SEER includes information on cancer incidence and survival from specific geographic areas, representing approximately 14% of the U.S. population during the time span included in our study.

Study Subjects

Study subjects had their first primary NSCLC diagnosed between 1998 and 2002 (because information on whether, or not, MLNs were examined is available in SEER only for resections performed during this period);

were 18 years or older; had received nonexploratory surgical resection to the primary site; had histologically confirmed diagnosis of NSCLC; and at least one LN examined after surgery. We excluded those with preoperative radiation therapy, no examined LN (so-called *pathologic NX*) or unknown number of examined LNs, distant metastasis at the time of lung resection, and unknown surgical laterality (Fig. 1). We also excluded patients with MLN metastasis for all analyses except the estimation of the relative impact of MLN metastasis on survival of patients with and without MLN examination. Finally, we excluded patients who died within 30 days postoperatively from the long-term survival analyses.

Lymph Node Evaluation

Since 1988, SEER has routinely collected LN information including the number examined, the number with metastasis, and the pN-category. However, the identification of anatomical locations from which LNs were collected during surgery is only available between 1998 and 2002. This information is categorized as whether, or not, MLN were examined (yes or no). The number of MLN examined, number with metastasis, extent of MLN dissection, and information about invasive preoperative MLN examination are not reported in SEER.

Patient Demographic and Clinical Characteristics

SEER includes demographic information such as age at cancer diagnosis, sex, race/ethnicity, and marital status. Available clinical information includes the year of diagnosis, tumor characteristics (size, grade, histology, and extension) and the first course, and timing, of radiation and surgery. Classification of histology was based on the third edition of the International Classification of Diseases for Oncology. SEER does not provide information about chemotherapy.

SURVIVAL

In 2012, the public release of SEER reported deaths up to December 31, 2009, including cause-specific mortality data obtained from death certificates. We determined overall survival from the date of diagnosis to the date of death (irrespective of cause) or end of follow-up, and cause-specific survival from date of diagnosis to date of death from the cause or end of follow-up.

Statistical Analysis

We compared demographic and clinical characteristics between those with and without MLN examination using the Pearson χ^2 test for categorical variables, the *t* test for continuous variables, trend test for ordered variables, log-rank test for mortality comparison, and the nonparametric rank-sum test for

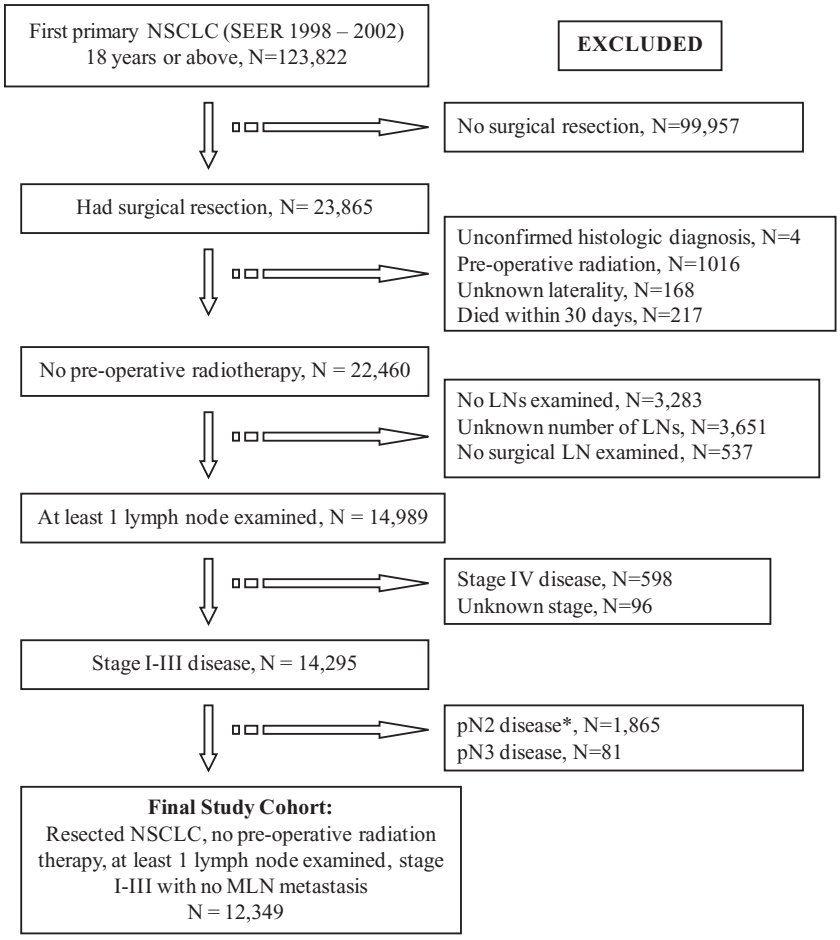

FIGURE 1. Cohort selection. *These patients were included in a specific analysis to estimate the impact of MLN metastasis on the population without MLN examination. NSCLC, non–small-cell lung cancer; SEER, Surveillance, Epidemiology, and End Results database; MLN, mediastinal lymph nodes; LN, Lymph nodes.

the number of LNs examined. We used Kaplan–Meier methods to visually compare the unadjusted survival difference between MLN examination cohorts. In the multivariate analysis, we used Cox proportional hazards model to examine overall survival, adjusted for the above-mentioned confounders. Because death by causes other than lung cancer was common among the lung cancer survivors, we used a competing risk model[14] to examine the association between MLN examination and lung cancer–specific mortality. Death caused by lung cancer was the event of interest, death by other causes was the competing event, and those who survived were censored at December 31, 2009. We also compared the non–lung-cancer deaths between MLN examination cohorts by treating the other causes of death as the outcome and death by lung cancer as the competing risk.

No variable selection procedure was attempted because all these confounders were chosen based on prior clinical knowledge and literature. We conducted sequential modeling in which these confounders were serially entered as groups. We also performed separated analyses for those with and without hilar/intrapulmonary (N1) LN metastasis. Different categorization of variables and interaction analysis were explored. We conducted additional sensitivity analysis by restricting data to 5-year survival, and also by excluding those who died within 60 days, to account for possible differences in operative risk between those with and without MLN examination. Results from these models were similar to those reported (data not shown). Finally, we assessed the impact of MLN metastasis on survival by reintegrating patients with pN2 (who were excluded for all the preceding analyses and who, by definition, had received MLN examination) back into the data analysis.

We used Stata 12 (Stata Corp, College Station, TX) for all statistical analysis. All tests were two-sided, with a statistical significance level set at p values of 0.05 or lower. We also reported hazard ratios (HR) and 95% confidence intervals (CIs).

RESULTS

SEER included 12,349 patients who met our selection criteria (Fig. 1). The overall cohort characteristics are typical of a U.S. lung cancer surgical resection cohort (Table 1), with a median age of 66 years, a white predominance (86%), majority (69%) with stage I disease, and lobectomy as the

TABLE 1. Patient Demographic and Clinical Characteristics by Mediastinal Lymph Node Examination Status

Characteristics	Overall[a] n = 12,349	Mediastinal lymph nodes examined[b] Yes n = 4638 (38%)	No n = 7711 (62%)	*p*
Demographic factors				
Age, years, mean (SD)	66.2 (10.3)	66.3 (10.3)	66.2 (10.3)	0.45
Age group, years				
<50	793 (6)	299 (38)	494 (62)	0.86
50–64	4108 (33)	1522 (37)	2586 (63)	
65–74	4630 (38)	1769 (38)	2861 (62)	
≥75	2818 (23)	1048 (37)	1770 (62)	
Race				
White	10,557 (86)	4033 (38)	6524 (62)	<0.001
Black	1033 (8)	324 (31)	709 (69)	
Other	759 (6)	281 (37)	478 (63)	
Sex				
Male	6539 (53)	2371 (36)	4168 (64)	0.002
Female	5810 (47)	2267 (39)	3543 (61)	
Marital status				
Married	7364 (60)	2777 (38)	4587 (62)	0.67
Living alone	4985 (40)	1861 (37)	3124 (63)	
Clinical factors				
Tumor location				
Upper lobe	7320 (59)	2821 (39)	4499 (62)	0.012
Middle lobe	581 (5)	199 (34)	382 (66)	
Lower lobe	3822 (31)	1372 (36)	2450 (64)	
Multiple lobe or unspecified	626 (5)	246 (39)	380 (61)	
Stage				
I	8550 (69)	3245 (38)	5305 (62)	<0.001
II	2168 (18)	734 (34)	1434 (66)	
III	1631 (13)	659 (40)	972 (60)	

(*Continued*)

TABLE 1. (Continued)

Characteristics	Overall[a] n = 12,349	Mediastinal lymph nodes examined[b] Yes n = 4638 (38%)	No n = 7711 (62%)	*p*
Histology				
Adenocarcinoma	5224 (42)	1946 (37)	3278 (63)	0.637
Squamous cell carcinoma	3648 (30)	1368 (38)	2280 (63)	
Large-cell carcinoma	681 (6)	244 (36)	437 (64)	
Bronchioalveolar cell carcinoma	1481 (12)	568 (38)	913 (62)	
Other	1315 (11)	512 (39)	803 (61)	
Tumor grade (differentiation)				
Well	1273 (10)	454 (36)	819 (64)	0.001
Moderate	4535 (37)	1679 (37)	2856 (63)	
Poor	4943 (40)	1938 (39)	3005 (61)	
Undifferentiated	556 (5)	222 (40)	334 (61)	
Other	1042 (8)	345 (33)	697 (67)	
Tumor size (cm)				
<3	5510 (45)	2065 (38)	3445 (63)	0.014
3–4.9	3972 (32)	1481 (37)	2491 (63)	
≥5	2614 (21)	1019 (39)	1595 (61)	
Unknown	253 (2)	73 (29)	180 (71)	
Tumor extension				
Confined to one lung	6885 (56)	2685 (39)	4200 (61)	<0.001
Involving main stem bronchus	3833 (31)	1294 (34)	2539 (66)	
Extended to pleura	1049 (9)	393 (38)	656 (63)	
Extended to chest wall, carina, and farther	582 (5)	266 (46)	316 (54)	
Treatment factors				
Extent of resection				
Lobectomy	9956 (81)	3663 (37)	6293 (63)	0.001
Pneumonectomy	1528 (12)	617 (40)	911 (60)	
Other	865 (7)	358 (41)	507 (59)	
Postsurgery radiation				
No	10450 (85)	3953 (38)	6497 (62)	0.146
Yes	1899 (15)	685 (36)	1214 (64)	
Number of LN examined, median (IQR)	6 (3–11)	9 (5–14)	5 (3–9)	<0.001
LN metastasis detected				
No (pN0)	9652 (78)	3717 (39)	5935 (62)	<0.001
Yes (pN1)	2697 (22)	921 (34)	1776 (66)	
Survival outcomes				
Death in a year				
No	10323 (84)	3947 (38)	6376 (62)	<0.001
Yes	2026 (16)	691 (34)	1335 (66)	
Overall death status				
Alive	4268 (35)	1743 (41)	2525 (59)	<0.001
Dead	8081 (65)	2895 (36)	5186 (64)	
Cause specific death				
Alive	4268 (35)	1743 (41)	2525 (59)	<0.001
Lung cancer	5268 (43)	1838 (35)	3430 (65)	
Other, not lung cancer	2813 (23)	1057 (38)	1756 (62)	

[a]Shows counts and column percent.
[b]Shows counts and row percent.
LN, lymph node; IQR, interquartile range; pN0, pathologic N0; pN1, pathologic N1.

most common resection procedure (81%). Postoperative radiation therapy was administered to 15% of the patients. In 4638 patients (38%), at least one MLN was examined; 7711 patients (62%) had no MLN examined.

Factors Associated with MLN Examination

Women were slightly more likely than men to have MLNs examined, as were whites compared with African Americans. There was no association between other demographic factors and MLN examination (Table 1). Multiple tumor characteristics were associated with differences in MLN examination rate. It was highest in patients with upper lobe tumors, American Joint Committee on Cancer stage I disease, pN0 disease, poorly differentiated tumors, tumors larger than 5 cm, and tumors confined within the lung. There was no association with tumor histology. Pneumonectomy recipients were more likely to have MLN examination than those with a lesser resection. A higher total number of LNs was examined in those with MLN examination (median, 9; interquartile range, 5–14) than in those without (median, 5; interquartile range, 3–9; $p < 0.001$).

MLN Examination and Survival.

The 30-day mortality rate was similar: 0.64% for those with, versus 0.96% for those without, MLN examination ($p = 0.07$). Survival was significantly associated with examination of MLN. Death within 1 year of surgery was more frequent in those without MLN examination (17%) than in those with examination (15%), p value less than 0.001. There were significantly more deaths and deaths from lung cancer in those with no MLN (67% and 45%) than in those with MLN (62% and 40%), p value less than 0.001 (Table 1).

The unadjusted survival analysis shows that MLN examination was associated with better overall, and lung cancer-specific, survival (Fig. 2*A* and *B*). The overall 5-year survival rate was 49% for the whole cohort, 52% in the MLN

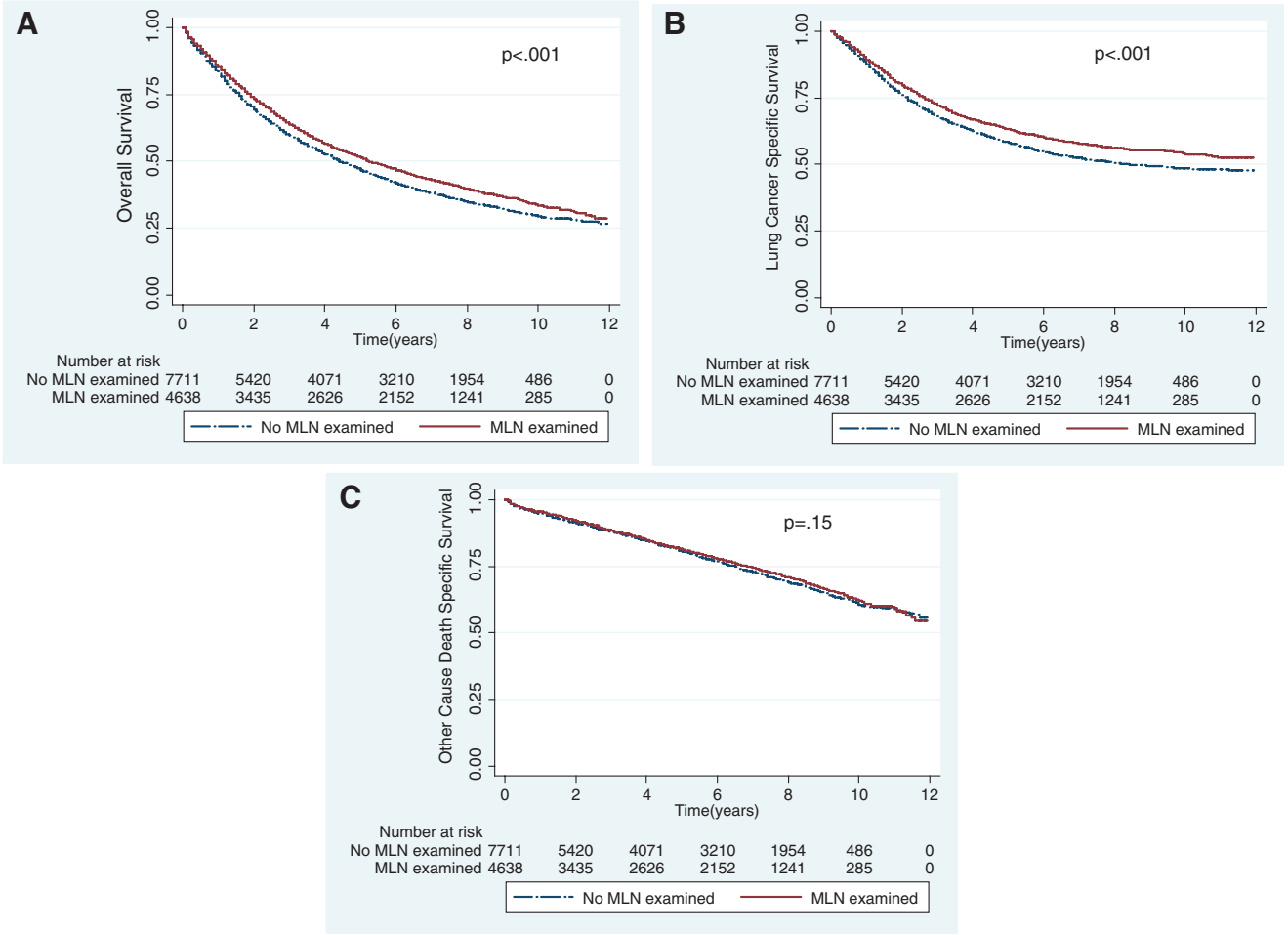

FIGURE 2. *A,* Overall survival curves of patients with and without examination of mediastinal lymph nodes after surgical resection for non–small-cell lung cancer: SEER database from 1998 to 2002. *B,* Lung cancer-specific survival curves of patients with and without examination of mediastinal lymph nodes after surgical resection for non–small-cell lung cancer: SEER database from 1998 to 2002. *C,* Survival curves for other causes of patients with and without examination of mediastinal lymph nodes after surgical resection for non–small-cell lung cancer: SEER database from 1998 to 2002. MLN, mediastinal lymph nodes; SEER, Surveillance, Epidemiology, and End Results database.

TABLE 2. Adjusted Association between Mediastinal Lymph Nodes Examined and Mortality in Sequentially Adjusted Model

Models	All-Cause Mortality HR (95%CI)	*p*	Lung Cancer Specific Mortality HR (95%CI)	*p*
Overall				
Model 1: demographic characteristics	0.89 (0.85–0.93)	<0.001	0.87 (0.82–0.92)	<0.001
Model 2: demographic + clinical characteristics	0.88 (0.84–0.92)	<0.001	0.85 (0.80–0.90)	<0.001
Model 3: model 2 + number of LNs examined	0.93 (0.88–0.97)	<0.001	0.89 (0.84–0.95)	<0.001
Model 4: model 3 + number of LN metastasis detected	0.93 (0.89–0.98)	0.008	0.91 (0.86–0.97)	0.003
Among those without detected LN metastasis (pN0), *n* = 9652				
Model 1: demographic characteristics	0.93 (0.88–0.98)	0.006	0.92 (0.86–0.99)	0.019
Model 2: demographic + clinical characteristics	0.90 (0.86–0.95)	<0.001	0.89 (0.83–0.95)	0.001
Model 3: model 2 + number of LNs examined	0.95 (0.90–1.01)	0.086	0.93 (0.87–1.01)	0.072
Among those with detected LN metastasis (pN1), *n* = 2697				
Model 1: demographic characteristics	0.82 (0.75–0.90)	<0.001	0.79 (0.71–0.87)	<0.001
Model 2: demographic + clinical characteristics	0.81 (0.74–0.88)	<0.001	0.79 (0.71–0.87)	<0.001
Model 3: model 2 + number of LNs examined	0.86 (0.78–0.95)	<0.001	0.83 (0.75–0.93)	0.001
Model 4: model 3 + number of LN metastasis detected	0.88 (0.80–0.97)	0.013	0.86 (0.77–0.96)	0.006

LN, Lymph node; pN0, pathologic N0; pN1, pathologic N1.

examination cohort, compared with 47% in the group without examination ($p < 0.001$). The median overall survival was 5.3 years in the group with, versus 4.4 years in the group without, MLN ($p < 0.001$). The 5-year lung-cancer–specific survival rate was 60% for the whole group, 63% in those with MLNs versus 58% in those without ($p < 0.001$). There was no difference in the non–lung-cancer specific survival rates between the MLN examination cohorts (Fig. 2*C*).

To adjust for the potential impact of risk factor heterogeneity, we compared the survival of patients in both cohorts using different risk-factor models by sequentially entering different groups of confounders (Table 2). With more confounders entering the models, the beneficial effect of MLN examination remained across all models, although it decreased from 11% to 7% for overall survival (all $p < 0.05$), and from 14% to 9% for lung-cancer–specific survival (all $p < 0.05$). This difference persisted even in an overadjusted model (model 4, Table 2) that included both the number of LNs with metastasis and American Joint Committee on Cancer stage.

The separated analysis for those with and without N1 LN metastasis yielded similar results. In patients with pN0, the benefit of MLN examination ranged from 7% improvement in overall survival in the least stringent model, to 5% in the most stringent. The improvement in lung-cancer–specific survival ranged from 8% to 7%. In those with pN1 disease, MLN examination improved overall survival by 18% to 12% in the various models. The improvement in lung-cancer–specific survival ranged from 21% to 14% (Table 2). In the model including patient demographics, clinical characteristics, and the number of LNs examined, MLN examination was associated with 7% lower all-cause mortality risk (HR, 0.93; 95%CI, 0.88–0.97; $p = 0.002$) (Table 3). The lung-cancer–specific mortality risk reduction was 11% (HR, 0.89; 95% CI, 0.84–0.95; $p < 0.001$). Furthermore, after incorporating patients with MLN metastasis back into the data, MLN examination was still associated with improved overall (HR, 0.94; 95%CI, 0.90–0.98; $p = 0.008$), and lung-cancer–specific (HR, 0.94; 95%CI, 0.89–0.99; $p = 0.024$), survival. The number of LNs examined (irrespective of location) was one of several other factors independently associated with survival (Table 3).

Assuming a 7% overall survival benefit of MLN examination, an annual case-volume of 45,000 lung resections for pN0 or pN1 NSCLC, and 22% of those with MLN examination having MLN metastasis, we estimate that failure to examine MLN is associated with an excess mortality risk, in 1 year's cohort of U.S. lung resections, of 3150 lives over 5 years.

DISCUSSION

An *oncologically sound* lung cancer resection requires negative surgical margins and examination of sufficient hilar, intrapulmonary, and mediastinal LNs to accurately determine pathologic stage. MLNs must be provided by the surgeon, otherwise the pathologist has no access to them. Most experts recommend a systematic nodal dissection that includes a minimum of three MLN stations.[15–17] Prior studies have compared the outcomes of patients who underwent surgical MLN staging of varying degrees of extensiveness.[18–20] In this study, we quantified the incidence and survival impact of nonexamination of MLNs in a population-based series. Failure to examine MLNs was common and impactful. The greater impact on lung-cancer–specific survival, the greater effect size in patients with more advanced disease, and the absence of difference in non–lung-cancer mortality between cohorts, suggests that failure to identify subsets of patients with MLN metastasis is the etiology of the survival difference. Because patients with larger tumors[21,22] and those with N1 nodal metastases[23,24] are more likely to have MLN metastasis, failure to examine MLN in these patients is more likely to be associated with missed MLN disease, hence higher risk of understaging, with negative consequences for postoperative decision making and long-term survival.

Almost two thirds of patients had no MLNs examined, similar to other reports. Little et al.[25] found that 42% of

TABLE 3. Multivariate Adjusted Association Between Mediastinal Lymph Node Examination Status and Mortality

	All-Cause Mortality		Lung Cancer Specific Mortality	
Variables	**HR (95%CI)**	***p***	**HR (95%CI)**	***p***
Mediastinal LN examined (reference: no examination)				
Yes	0.93 (0.88–0.97)	0.002	0.89 (0.84–0.95)	<0.001
Age, years	1.03 (1.03–1.04)	<0.001	1.01 (1.00–1.02)	<0.001
Race (reference: white)				
Black	1.18 (1.09–1.28)	<0.001	1.16 (1.05–1.27)	0.004
Other	0.90 (0.82–0.99)	0.025	0.92 (0.82–1.03)	0.140
Sex (reference: male)				
Female	0.72 (0.69–0.76)	<0.001	0.85 (0.81-0.91)	<0.001
Marital status (reference: married)				
living alone	1.19 (1.14–1.25)	<0.001	1.05 (0.99–1.11)	0.099
Tumor location (reference: upper lobe)				
Middle lobe	1.18 (1.06–1.31)	0.002	1.23 (1.08–1.40)	0.002
Lower lobe	1.10 (1.05–1.16)	<0.001	1.17 (1.11–1.25)	<0.001
Multiple lobe or unspecified	1.14 (1.03–1.26)	0.009	1.21 (1.07–1.37)	0.002
AJCC Stage, 3rd version (reference: stage I)				
II	1.68 (1.58–1.78)	<0.001	1.96 (1.83–2.11)	<0.001
III	1.94 (1.76–2.15)	<0.001	2.23 (1.96–2.53)	<0.001
Histology (reference: adenocarcinoma)				
Squamous cell carcinoma	1.01 (0.96–1.06)	0.748	0.85 (0.80–0.91)	<0.001
Large cell carcinoma	0.99 (0.88–1.12)	0.902	0.92 (0.79–1.07)	0.279
Bronchioalveolar cell carcinoma	0.82 (0.76–0.90)	<0.001	0.88 (0.79–0.97)	0.007
Other	0.99 (0.92–1.07)	0.865	0.93 (0.84–1.02)	0.224
Tumor grade (reference: well differentiation)				
Moderate	1.35 (1.23–1.48)	<0.001	1.32 (1.18–1.47)	<0.001
Poor	1.45 (1.32–1.58)	<0.001	1.43 (1.28–1.60)	<0.001
Undifferentiated	1.56 (1.35–1.81)	<0.001	1.53 (1.27–1.85)	<0.001
Other	1.34 (1.20–1.50)	<0.001	1.33 (1.16–1.53)	<0.001
Tumor size (cm) (reference: <3cm)				
3–4.9	1.22 (1.16–1.29)	<0.001	1.26 (1.18–1.35)	<0.001
≥5	1.45 (1.36–1.54)	<0.001	1.63 (1.51–1.76)	<0.001
Unknown	1.34 (1.20–1.50)	<0.001	1.33 (1.10–1.64)	0.004
Tumor extension (reference: confined to one lung)				
Involving main stem bronchus	1.10 (1.04–1.15)	<0.001	1.17 (1.10–1.24)	0.053
Extended to pleura, visceral or NOS	0.91 (0.81–1.02)	<0.001	0.87 (0.75–1.01)	0.065
Postsurgery radiation (reference: no radiation)				
Yes	1.27 (1.20–1.35)	<0.001	1.34 (1.24–1.44)	<0.001
Extent of resection (reference: lobectomy)				
Pneumonectomy	1.16 (1.08–1.25)	<0.001	1.14 (1.05–1.25)	0.003
Other	1.27 (1.17–1.38)	<0.001	1.24 (1.12–1.38)	<0.001
No. of LNs examined (reference: 1–3)				
4–5	0.95 (0.88–1.01)	0.108	0.92 (0.85–1.01)	0.073
6–8	0.85 (0.80–0.91)	<0.001	0.84 (0.77–0.91)	<0.001
9–12	0.87 (0.81–0.94)	<0.001	0.87 (0.79–0.95)	0.002
≥13	0.75 (0.70–0.81)	<0.001	0.76 (0.69–0.84)	<0.001

LN, lymph node; AJCC, American Joint Committee on Cancer; HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified.

resections in a 2001 National Cancer Database cohort had no MLN, Varlotto et al.[26] found that 49% of patients with stage I NSCLC in the SEER database from 1992 to 2002 had either no LN dissection or dissection of only N1 LNs. We found that 42% of a Memphis cohort had no MLN.[27] Including patients with pN2 and N3 disease, 48% of patients in the current analysis had no MLN. We excluded patients without examination of any LN (pNX), who constitute approximately 17% of the

SEER database[26] because some may have been marginally fit for surgery as evidenced by their relatively high wedge resection rate, and so an unknown proportion may have competing reasons for a higher mortality rate.[28] However, if fit patients who undergo a pNX resection are considered, the problem may be worse than we report.

Our study is limited by the limitations of the SEER database, such as its retrospective design, the absence of certain clinical information such as patients' performance status, preoperative staging details, the status of surgical resection margins, and the use of chemotherapy. For example, we were constrained to restrict analysis to the 1998–2002 resection population because of the absence of information from other eras. It is possible that current surgical practice has improved since 2002. However, this seems unlikely, given the results of our analysis of surgical practice in a U.S. metropolitan area from 2004 to 2007.[29,30]

Our retrospective study design precludes determination of the etiology of failure to examine MLN. We can only speculate. A high rate of failure to examine MLN may be a sign of poor overall program quality which leads, via multiple avenues (not only stage misattribution) to poor outcomes. We speculate that multiple factors contribute to the quality gap we demonstrated in this report, for example, surgeon factors (specialty training,[31–33] case-volume),[34] institutional factors (case-volumes,[35,36] teaching status),[37] and heterogeneity in pathology practice.[38,39] Solutions to the problem will require elucidation of the relative impact of processes in each of these areas. Irrespective of etiology, the effect of failing to examine MLNs is large, the problem is highly prevalent,[25–27,30] and the impact of corrective action is potentially huge, as we have demonstrated in our pilot studies of corrective interventions within the operating room[40] and in the pathology laboratory.[39]

Other limitations arise from our combination of all types of MLN examination, despite the likely survival differences between those with varying degrees of thoroughness of examination.[41] For example, patients who undergo random MLN sampling have a worse survival than those who undergo systematic nodal dissection.[19,42] We were constrained to compare the binary cohorts of patients with and without MLN examination, irrespective of the number or location of the stations because SEER does not report the number of N1, N2, and N3 LNs examined (or positive), nor does it identify the type of MLN collection procedure performed. Even if it did, the information is unlikely to be accurate, as we have demonstrated in a close review of surgeons' operation notes and pathology reports from all lung resection cases performed from 2004 to 2007 in a metropolitan U.S. area.[30,43] Therefore, it seems likely that our report significantly underestimates the negative survival impact of failing to properly examine the MLNs, because the MLN examination group in our study probably included a large number of cases in which systematic nodal dissection was not performed.

Finally, we are unable to analyze the impact of chemotherapy on the survival differences in this data set. Differences in the use of pre- or postoperative chemotherapy may account for the differences we report. This is unlikely because the use of adjuvant chemotherapy was uncommon in the 1998–2002 time span covered by our analysis. However, it is possible that routine use of postoperative adjuvant chemotherapy in patients with stage II and III NSCLC can reduce the survival difference that we report because the survival benefit of postoperative adjuvant chemotherapy is approximately 5% (HR for death, 0.89),[7] which is similar to the survival deficit in those without MLN examination (Table 2). However, most patients with *pN0* and undetected MLN skip metastasis would have been deprived the benefit of postoperative adjuvant chemotherapy and the magnitude of the survival difference in the pN1 patients exceeds the expected benefit of current postoperative adjuvant chemotherapy.

In conclusion, nonexamination of MLNs is associated with impaired survival in a large population in the United States. This is especially important now that improving upon the results of recent adjuvant therapy trials is the objective of intense ongoing research activity. Studies to localize the etiology of this quality gap in surgical oncology practice are much needed. Logically conceived, and carefully implemented, interventions to eliminate the gap must be promoted.

REFERENCES

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009;59:225–249.
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011;61:69–90.
3. Goldstraw P, Crowley J, Chansky K, et al. International Association for the Study of Lung Cancer International Staging Committee; Participating Institutions. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol* 2007;2:706–714.
4. Rusch VW, Crowley J, Giroux DJ, et al. International Staging Committee; Cancer Research and Biostatistics; Observers to the Committee; Participating Institutions. The IASLC Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 2007;2:603–612.
5. The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 2004;350:351–60.
6. Winton T, Livingston R, Johnson D, et al. National Cancer Institute of Canada Clinical Trials Group; National Cancer Institute of the United States Intergroup JBR.10 Trial Investigators. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med* 2005;352:2589–2597.
7. Pignon JP, Tribodet H, Scagliotti GV, et al.; LACE Collaborative Group. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol* 2008;26:3552–3559.
8. Lally BE, Zelterman D, Colasanto JM, Haffty BG, Detterbeck FC, Wilson LD. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. *J Clin Oncol* 2006;24:2998–3006.
9. Fernando HC, Goldstraw P. The accuracy of clinical evaluative intrathoracic staging in lung cancer as assessed by postsurgical pathologic staging. *Cancer* 1990;65:2503–2506.
10. D'Cunha J, Herndon JE, II Herzan DL, et al.; Cancer and Leukemia Group B. Poor correspondence between clinical and pathologic staging in stage 1 non-small cell lung cancer: results from CALGB 9761, a prospective trial. *Lung Cancer* 2005;48:241–246.
11. Annema JT, van Meerbeeck JP, Rintoul RC, et al. Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: a randomized trial. *JAMA* 2010;304:2245–2252.
12. Association of Directors of Anatomic and Surgical Pathology. Recommendations for processing and reporting of lymph node

specimens submitted for evaluation of metastatic disease. *Am J Clin Pathol* 2001;115:799–801.
13. Rami-Porta R, Wittekind C, Goldstraw P. International Association for the Study of Lung Cancer (IASLC) Staging Committee. Complete resection in lung cancer surgery: proposed definition. *Lung Cancer* 2005;49:25–33.
14. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509.
15. Lardinois D, De Leyn P, Van Schil P, et al. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. *Eur J Cardiothorac Surg* 2006;30:787–792.
16. Part IV, Thorax. In Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (Eds.), *AJCC Cancer Staging Handbook*, 7th Ed. New York, NY: Springer;2010:297–323.
17. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed December 16, 2011.
18. Izbicki JR, Passlick B, Pantel K, et al. Effectiveness of radical systematic mediastinal lymphadenectomy in patients with resectable non-small cell lung cancer: results of a prospective randomized trial. *Ann Surg* 1998;227:138–144.
19. Wu Y, Huang ZF, Wang SY, Yang XN, Ou W. A randomized trial of systematic nodal dissection in resectable non-small cell lung cancer. *Lung Cancer* 2002;36:1–6.
20. Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. *J Thorac Cardiovasc Surg* 2011;141:662–670.
21. Graham ANJ, Chan KJM, Pastorino U, Goldstraw P. Systematic nodal dissection in the intrathoracic staging of patients with non-small cell lung cancer. *J Thorac Cardiovasc Surg* 1999;11:246–251.
22. Veeramachaneni NK, Battafarano RJ, Meyers BF, Zoole JB, Patterson GA. Risk factors for occult nodal metastasis in clinical T1N0 lung cancer: a negative impact on survival. *Eur J Cardiothorac Surg* 2008;33:466–469.
23. Fukui T, Mori S, Yokoi K, Mitsudomi T. Significance of the number of positive lymph nodes in resected non-small cell lung cancer. *J Thorac Oncol* 2006;1:120–125.
24. Lee JG, Lee CY, Park IK, et al. Number of metastatic lymph nodes in resected non-small cell lung cancer predicts patient survival. *Ann Thorac Surg* 2008;85:211–215.
25. Little AG, Rusch VW, Bonner JA, et al. Patterns of surgical care of lung cancer patients. *Ann Thorac Surg* 2005;80:2051–2056.
26. Varlotto JM, Recht A, Nikolov M, Flickinger JC, Decamp MM. Extent of lymphadenectomy and outcome for patients with stage I nonsmall cell lung cancer. *Cancer* 2009;115:851–858.
27. Allen JW, Farooq A, O'Brien TF, Osarogiagbon RU. Quality of surgical resection for nonsmall cell lung cancer in a US metropolitan area. *Cancer* 2011;117:134–142.
28. Osarogiagbon RU, Allen JW, Farooq A, Berry A, Spencer D, O'Brien T. Outcome of surgical resection for pathologic N0 and Nx non-small cell lung cancer. *J Thorac Oncol* 2010;5:191–196.
29. Osarogiagbon RU, Allen JW, Farooq A, Berry A, O'Brien T. Pathologic lymph node staging practice and stage-predicted survival after resection of lung cancer. *Ann Thorac Surg* 2011;91:1486–1492.
30. Osarogiagbon RU, Allen JW, Farooq A, Wu JT. Objective review of mediastinal lymph node examination in a lung cancer resection cohort. *J Thorac Oncol* 2012;7:390–396.
31. Silvestri GA, Handy J, Lackland D, Corley E, Reed CE. Specialists achieve better outcomes than generalists for lung cancer surgery. *Chest* 1998;114:675–680.
32. Schipper PH, Diggs BS, Ungerleider RM, Welke KF. The influence of surgeon specialty on outcomes in general thoracic surgery: a national sample 1996 to 2005. *Ann Thorac Surg* 2009;88:1566–1572.
33. Farjah F, Flum DR, Varghese TK Jr, Symons RG, Wood DE. Surgeon specialty and long-term survival after pulmonary resection for lung cancer. *Ann Thorac Surg* 2009;87:995–1004; discussion 1005.
34. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. *N Engl J Med* 2003;349:2117–2127.
35. Bach PB, Cramer LD, Schrag D, Downey RJ, Gelfand SE, Begg CB. The influence of hospital volume on survival after resection for lung cancer. *N Engl J Med* 2001;345:181–188.
36. Bilimoria KY, Bentrem DJ, Feinglass JM, et al. Directing surgical quality improvement initiatives: comparison of perioperative mortality and long-term survival for cancer surgery. *J Clin Oncol* 2008;26:4626–4633.
37. Meguid RA, Brooke BS, Chang DC, Sherwood JT, Brock MV, Yang SC. Are surgical outcomes for lung cancer resections improved at teaching hospitals? *Ann Thorac Surg* 2008;85:1015–1024.
38. Gephardt GN, Baker PB. Lung carcinoma surgical pathology report adequacy: a College of American Pathologists Q-Probes study of over 8300 cases from 464 institutions. *Arch Pathol Lab Med* 1996;120:922–927.
39. Ramirez RA, Wang CG, Miller LE, et al. Incomplete intrapulmonary lymph node retrieval after routine pathologic examination of resected lung cancer. *J Clin Oncol* 2012;30:2823–2828.
40. Osarogiagbon RU, Miller LE, Ramirez RA, et al. Use of a surgical specimen-collection kit to improve mediastinal lymph-node examination of resectable lung cancer. *J Thorac Oncol* 2012;7:1276–1282.
41. Detterbeck F, Puchalski J, Rubinowitz A, Cheng D. Classification of the thoroughness of mediastinal staging of lung cancer. *Chest* 2010;137:436–442.
42. Gajra A, Newman N, Gamble GP, Kohman LJ, Graziano SL. Effect of number of lymph nodes sampled on outcome in patients with stage I non-small-cell lung cancer. *J Clin Oncol* 2003;21:1029–1034.
43. Detterbeck FC. The fable of Babel and building a foundation for quality. *J Thorac Oncol* 2012;7:267–268.

