Original Article

Clinical and economic outcomes associated with lymph node examination status in early-stage non-small cell lung cancer: a real-world US study using the SEER-Medicare linked database

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Background: Clinical practice guidelines recommend adjuvant therapy for patients with early non-small cell lung cancer (eNSCLC), especially those with lymph node metastasis. This study evaluated the prevalence of lymph node examination and its association with adjuvant treatment rates, overall survival (OS), and healthcare costs among United States (US) Medicare patients with resected eNSCLC.

Methods: This retrospective observational cohort study used Surveillance, Epidemiology, and End Results cancer registry data linked with Medicare claims data. Eligible patients were aged ≥65 years with newly diagnosed non-small cell lung cancer (NSCLC) stages IA to IIIB [the *American Joint Committee on Cancer (AJCC) Cancer Staging Manual*, 7th edition] between January 2010 and December 2017 with surgery ≤1 month prior to or ≤12 months after diagnosis. Patients were grouped by lymph node examination status: no examination (pNX), examination and no metastasis (pN0), or metastasis staging in N1 (pN1) or N2 (pN2). OS and costs were evaluated by examination status and number of lymph node examined. OS was analyzed using extended Cox proportional hazards models for specific time periods and time interaction with examination status, and adjusted for patient characteristics. Adjusted post-surgical healthcare costs per patient per month (PPPM) were analyzed using gamma-log regression models.

Results: Among the 14,648 patients included in the study, approximately 11% were pNX, whereas most were pN0 (68%), followed by pN1 (11%) and pN2 (10%). Adjuvant treatment rates were higher for pNX (35%) than pN0 (18%), but lower than pN1 (68%) and pN2 (74%) patients (P<0.001). Unadjusted OS for pNX patients was nearly identical to pN2, and significantly worse compared to pN0 and pN1 (P<0.0001). After adjusting for patient characteristics, pNX patients had higher risk of death relative to pN0 patients (P<0.001). Marginal mean adjusted total costs were comparable across pNX ($15,827 PPPM), pN0 ($12,712 PPPM) and pN1 ($17,089 PPPM), but significantly less for pN0 compared to pN2 ($23,566 PPPM) (P=0.002).

Conclusions: Inadequate lymph node examination is associated with underutilization of adjuvant treatment and poor OS in resected NSCLC. In the current era of targeted and immunotherapies, lymph node examination is more important than ever, implicating the need for Quality Improvement practices and multidisciplinary coordination.

Keywords: Non-small cell lung cancer (NSCLC); lymph node examination; survival; healthcare costs; Medicare

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Introduction

Background

Surgery is the primary treatment approach for patients with early non-small cell lung cancer (eNSCLC), which includes stage I, stage II, or resectable stage III disease and accounts for approximately 50% of all non-small cell lung cancer (NSCLC) cases (1). Due to the risk of micrometastasis and recurrence after surgery (2,3), clinical practice guidelines recommend the use of adjuvant therapy, especially among patients with lymph node metastasis, who have been shown to benefit from adjuvant therapy post resection according to the location of the lymph node metastasis (4-6).

Rationale and knowledge gap

Missed lymph node metastasis can potentially lead to failure to provide appropriate adjuvant therapy (7-9). Therefore, lymph node examination is considered standard of care by the American College of Chest Physicians, the European Society of Thoracic Surgeons, and the National Comprehensive Cancer Network® (NCCN®) for appropriate disease staging and treatment determination for patients with eNSCLC (10,11). Additionally, the number of resected lymph nodes and lymph node ratio are predictive of survival in patients with NSCLC (7-9). As such, the American College of Surgeons Commission on Cancer recommends resection of 10 total lymph nodes regardless of station, and the Union for International Cancer Control recommends resection of 6 total lymph nodes (3 from N1 and 3 from N2 stations) (12).

Some work has been done to understand the prevalence and impact of lymph node examination in clinical practice. Data from the United States (US) Surveillance, Epidemiology, and End Results (SEER) database between 1998 and 2009 shows that approximately 13% of all resections did not include lymph node examination after resection (pNX) (13). The risk of death (all-cause) for pNX patients, after adjusting for potential confounders, was 36% higher than for patients with no lymph node metastasis after examination (pN0). These data suggest that lymph node metastasis may have been missed in a substantial proportion of pNX patients (13), and this was further supported by the similar survival rates among pNX patients compared with patients with lymph node metastasis (pN1) (13). Since these patients were not appropriately staged, they were not likely receiving appropriate adjuvant treatment. Krantz *et al.* [2018] reported that only 34% of resected patients had invasive mediastinal staging in the Society of Thoracic Surgeons General Thoracic Surgery Database, as well as considerable variability in invasive staging across participating treatment centers, and the overall trend did not change from 2012 to 2016 (14).

Historical standard of care for adjuvant treatment of patients with eNSCLC primarily comprised chemotherapy, which was associated with limited survival benefit and substantial safety considerations (6). Atezolizumab was the first immune checkpoint inhibitor approved in the US [2021] as adjuvant treatment following resection and platinum-based chemotherapy for adults with stage II–IIIA NSCLC based on findings from the IMpower010 clinical trial (15,16). Pembrolizumab was approved [2023] as adjuvant treatment

Highlight box

Key findings

- Lymph node examinations increased over time, but many resections lacked lymph node examination.
- Cancer stage distribution among no lymph node examination (pNX) was more similar to lymph node examination and no metastasis (pN0) than metastasis staging in N1 (pN1) or N2 (pN2) patients, but the pNX prognosis was similar to pN2 patients.
- Patients with more lymph nodes examined were more likely to receive adjuvant treatment and have better overall survival (OS) than those with fewer lymph nodes examined.

What is known and what is new?

- Lymph node examination is standard of care for patients with early non-small cell lung cancer; number of resected lymph node is predictive of survival.
- Using updated Surveillance, Epidemiology, and End Results-Medicare data, this study demonstrates that examination rates have increased but room for improvement remains, and also evaluates its impact on adjuvant treatment, OS, and costs.

What is the implication, and what should change now?

- Underperformance of lymph node examinations negatively impacts adjuvant treatment decisions and clinical outcomes, emphasizing the need for improved quality improvement practices.

following resection and platinum-based chemotherapy for patients with stage IB, II or IIIA NSCLC based on findings from the KEYNOTE-091 clinical trial (17). Additional therapies are under investigation in this setting. In light of the increased use of immunotherapy in the neoadjuvant and adjuvant settings, it is important to understand the current rate of lymph node examination status in the eNSCLC setting and to determine how lymph node examination status impacts adjuvant treatment patterns, survival, and subsequent outcomes such as healthcare resource use and costs.

Objective

This study evaluated the real-world prevalence of lymph node examination and the association of lymph node examination status with adjuvant treatment rates, overall survival (OS) and healthcare costs among US Medicare patients with resected eNSCLC. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1388/rc).

Methods

Study design and eligibility criteria

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective observational cohort study used SEER cancer registry data (which includes incident cancer cases from 2010-2017) linked with Medicare claims data through 2019.

Eligible patients were aged ≥65 years at time of diagnosis and were newly diagnosed with lung cancer (Table S1) and NSCLC (*International Classification of Diseases for Oncology* histology codes 8000-8040, 8046-9989) stages IA to IIIB [*the American Joint Committee on Cancer (AJCC) Cancer Staging Manual*, 7th edition] between January 2010 and December 2017. The date of diagnosis was considered the index date. Patients had to have a record of surgery ≤1 month prior to the date of diagnosis or ≤12 months after diagnosis (surgery identification period) (Figure S1).

For the assessment of lymph node examinations, eligible patients had to have continuous enrollment in Medicare Parts A and B for ≥6 months prior to diagnosis until the date of surgery (≤12 months after diagnosis). An 'outcome cohort' was created for the assessment of all other outcomes (adjuvant treatment, OS, healthcare costs). These patients had to have continuous enrollment in Medicare Parts A, B, and D for ≥6 months post-surgery or up to the date of death, whichever occurred first.

Patients were excluded if there was evidence of stage IV disease, small cell lung cancer (8041-8045), neuroendocrine/carcinoid tumors (8240-8246, 8249), large cell carcinoma (8012-8014), bronchioloalveolar carcinoma (8250-8254), certain histologies (complex mixed and stromal neoplasms, ductal and lobular neoplasms, mucoepidermoid neoplasms, transitional cell papillomas, and carcinomas), or lymph node metastasis with N3 status after examination. Patients with missing diagnosis/staging information, diagnosis information at death or autopsy in the SEER data, or enrollment in a health maintenance organization, Veterans Affairs, or military hospital were also excluded.

Study cohorts

Patients were grouped by lymph node examination status as follows: pNX; no lymph node metastasis after examination of ≥1 lymph node (pN0); lymph node metastasis staging in N1 after examination (pN1); or lymph node metastasis staging in N2 after examination (pN2). Patients in the outcome cohort who had a lymph node examination and a non-missing value for the number of lymph nodes examined were also grouped by the number of lymph nodes examined (<10 or ≥10, and <6 or ≥6 lymph nodes).

Outcomes

The prevalence of lymph node examination was evaluated as the proportion of the study population with (pN0–2) or without (pNX) lymph node examination overall and by year of diagnosis, as well as for trends by year of diagnosis.

Treatment patterns were evaluated within the outcome cohort. Utilization of adjuvant therapy, including chemotherapy, targeted therapy, immunotherapy, or radiation, was identified based on drug or procedure codes from the surgery date +1 day to 6 months after the surgery date or death, whichever occurred first (adjuvant treatment identification period) (Figure S1). Time to adjuvant treatment was calculated as the number of days between the surgery date and the adjuvant treatment start date.

For the analysis of lymph node examination status and OS, patients in the outcome cohort were followed from the NSCLC diagnosis date until death or until censored due to the end of continuous enrollment or end of the study period (December 31, 2019). The NSCLC diagnosis date was

considered the start of the survival period as patients were considered to typically have lymph node examination at time of diagnosis. If the patient died following the 6-month adjuvant treatment period, the continuous enrollment criterion after the 6-month identification period until death was not required.

Direct healthcare costs were evaluated in the outcome cohort on a per patient per month (PPPM) basis from the surgery date to the end of enrollment, end of the study period, or death, whichever occurred first. Costs were assessed overall and by lymph node examination group, including medical costs related to inpatient admissions, outpatient and physician services, use of durable medical equipment, hospice and home health services, and prescription drugs based on Medicare Part D claims. Costs included Medicare reimbursed amounts and beneficiary responsibility payments, all adjusted for inflation to 2021 US dollars using the medical care component of the US Consumer Price Index (www.bls.gov/cpi/factsheets/medical-care.htm).

Statistical analysis

Demographic and clinical characteristics at the time of NSCLC diagnosis included age, sex, race/ethnicity, US state, SEER registry region, urban/rural residence, socioeconomic status (aggregate area-level education and aggregate area-level median income), smoking status, lung cancer stage, grade and histology, and the type and extent of surgery. Smoking status was defined based on the International Classification of Diseases (ICD)-9 (305.1) and ICD-10 (F17.2) diagnosis codes identified during the 6-month baseline period. Given the low sensitivity of these diagnosis codes, it is well-established that smoking status is incompletely identified in the Medicare data set, leading to some misclassification (likely underestimation) of smoking status. Charlson Comorbidity Index (CCI) score, presence of interstitial lung disease, pneumonitis, and chronic obstructive pulmonary disease (COPD) were all estimated using claims data during the 6-month pre-index (baseline) period. Patient characteristics were assessed using descriptive statistics including mean (standard deviation) for continuous variables and frequencies and percentages for categorical variables. Characteristics were evaluated overall and by lymph node examination status. Differences in patient characteristics were tested using Kruskal-Wallis or Wilcoxon rank sum tests for continuous variables and chi-square tests for categorical variables.

The prevalence of lymph node examinations was analyzed overall and by year of diagnosis, including testing for trends by year of diagnosis. The median [interquartile range (IQR)] number of lymph nodes examined and the distribution of patients by number of lymph nodes examined were assessed descriptively.

Receipt of adjuvant treatment and time to adjuvant treatment (among those treated) were analyzed in the outcome cohort by lymph node examination status and by number of lymph nodes examined for non-pNX patients (<10 or ≥10, and <6 or ≥6). Differences in treatment patterns were tested using Wilcoxon rank sum tests for time to treatment and chi-square tests for categorical treatment variables.

Unadjusted OS was analyzed using the Kaplan-Meier method and differences in OS were tested using log-rank statistics by lymph node examination status and by number of lymph nodes examined (<10 or ≥10, and <6 or ≥6). The proportional hazards assumption was not met for the adjusted OS Cox models; therefore, the extended Cox models were used to estimate OS hazard ratios and 95% confidence intervals (CIs). The extended Cox models included specific time intervals and their interaction with lymph node examination status; they were adjusted for baseline measures of age, sex, race/ethnicity, urban/rural geography, CCI score, smoking history, presence of COPD, and histology, as well as time-varying surgery status (patients were allowed to be unexposed to surgery during follow-up until the surgery date).

Total post-surgical healthcare costs were analyzed descriptively and using gamma-log regression models to estimate adjusted costs for group comparisons. Gamma-log regressions were calculated among patients with cost data for each type of healthcare cost, and marginal costs at the means were calculated from these regression models (using the R emmeans package). Cost models were adjusted using the same covariates as those in the OS models, with the exception of time-varying surgery status. Instead of time-varying surgery status, dichotomized time to surgery was included in the covariate adjustment (≤1.15 *vs.* >1.15 months, where 1.15 months was the median time to surgery in the overall study population). Marginal mean costs for each group and differences in mean costs were estimated with 95% CIs. All analyses were performed using

R, version 4.1.2 (2021-11-01 release).

Results

Study population

A total of 14,648 patients were included in the overall cohort (Figure S2). The mean age at diagnosis was 74 years, 52% were women, and 88% were White (*Table 1*). For the extent of lung cancer resection, most patients had lobectomy (61%, n=8,985). Among those with known surgery type, thoracotomy was most prevalent (90%, n=6,022/6,708).

Approximately 11% (n=1,596) of patients had no lymph node examination (pNX); most patients were pN0 (68%), followed by pN1 (11%) and pN2 (10%). Patients in the pNX group were slightly older than those in all other groups (mean age, 75 years; P<0.001) and had a lower aggregate median income (mean US Census tract median income, $61,839; P<0.001). Patients in the pNX group also had a higher mean CCI score (2.42; P<0.001) than all other groups and had the highest proportion of patients with baseline smoking history (18%; P<0.001) and baseline COPD diagnosis (45%; P<0.001) (*Table 1*).

Stage distribution among pNX patients was more similar to pN0 patients than to pN1 or pN2 patients, with more patients in earlier stages. Significantly fewer grade 3 and 4 tumors were observed among pNX and pN0 patients (both ~31%) compared with pN1 and pN2 patients (~47% and ~43%, respectively; P<0.001). pNX patients were most likely to have received wedge resection (48%) and more likely than pN0 or pN1 patients to have received neoadjuvant treatment (14% *vs.* 5% and 8%, respectively; pN2, 25%) (*Table 1*).

Lymph node examination

The proportion of pNX patients decreased from 14% in 2010 to 8% in 2017, which was a statistically significant trend (P<0.001) (*Figure 1*). Among the 12,123 (83%) patients with a lymph node examination and known number of lymph nodes examined, the median number of lymph nodes examined was 9 (IQR, 5–15), which increased over time from a median of 8 in 2010 to 11 in 2017 (*Figure 2*). Distribution of the number of lymph nodes examined is shown in Figure S3.

Table 1 Patient characteristics in the overall cohort and by lymph node examination status

Characteristic	Overall (N=14,648)	pNX (n=1,596)	pN0 (n=9,916)	pN1 (n=1,607)	pN2 (n=1,529)	P value
Age at diagnosis, years	74.06±5.72	75.26±6.27	74.01±5.66	73.71±5.57	73.48±5.49	<0.001
Sex, female	7,682 [52]	794 [50]	5,376 [54]	746 [46]	766 [50]	<0.001
Race						0.04
Black	856 [6]	111 [7]	563 [6]	84 [5]	98 [6]	
White	12,951 [88]	1,417 [89]	8,770 [88]	1,427 [89]	1,337 [87]	
Other	841 [6]	68 [4]	583 [6]	96 [6]	94 [6]	
Median income, USD[†]	65,944±31,559	61,839±29,951	66,848±32,315	64,884±29,730	65,484±29,693	<0.001
Unknown	16	0	15	0	**	
College education completed, %[†]	31±19	28±18	31±19	30±18	31±18	<0.001
Unknown	15	0	14	0	**	
Baseline CCI score (excluding cancer)	2.03±1.86	2.42±2.05	2.02±1.84	1.84±1.72	1.84±1.80	<0.001
Baseline interstitial lung disease	24 [0.2]	**	14 [0.1]	**	**	0.12
Baseline pneumonitis	94 [1]	24 [2]	57 [1]	**	**	<0.001
Baseline COPD	5,487 [37]	720 [45]	3,720 [38]	551 [34]	496 [32]	<0.001
Baseline smoking history	2,216 [15]	287 [18]	1,510 [15]	242 [15]	177 [12]	<0.001

Table 1 (*continued*)

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Characteristic	Overall (N=14,648)	pNX (n=1,596)	pN0 (n=9,916)	pN1 (n=1,607)	pN2 (n=1,529)	P value
Cancer stage (AJCC 7th edition derived)						<0.001
Stage IA	5,587 [38]	711 [45]	4,876 [49]	0	0	
Stage IB	3,470 [24]	297 [19]	3,173 [32]	0	0	
Stage II	2,964 [20]	204 [13]	1,600 [16]	1,160 [72]	0	
Stage IIIA	2,383 [16]	275 [17]	267 [3]	447 [28]	1,394 [91]	
Stage IIIB	244 [2]	109 [7]	0	0	135 [9]	
Tumor grade						<0.001
1	2,010 [14]	208 [13]	1,653 [17]	77 [5]	72 [5]	
2	6,416 [44]	566 [35]	4,605 [46]	666 [41]	579 [38]	
3	4,818 [33]	474 [30]	2,963 [30]	735 [46]	646 [42]	
4	125 [1]	**	83 [1]	20 [1]	13 [1]	
Missing	1,279 [9]	**	612 [6]	109 [7]	219 [14]	
Histology						<0.001
Adenoma and adenocarcinoma‡	7,650 [52]	769 [48]	5,183 [52]	799 [50]	899 [59]	
Squamous cell carcinoma	4,726 [32]	566 [35]	3,157 [32]	580 [36]	423 [28]	
Other	2,272 [16]	261 [16]	1,576 [16]	228 [14]	207 [14]	
Extent of lung cancer resection						<0.001
Lobectomy	8,985 [61]	275 [17]	6,564 [66]	1,110 [69]	1,036 [68]	
Wedge resection	3,086 [21]	773 [48]	1,936 [20]	163 [10]	214 [14]	
Bilobectomy	195 [1]	**	111 [1]	53 [3]	25 [2]	
Pneumonectomy	402 [3]	**	153 [2]	155 [10]	75 [5]	
Segmentectomy	1,236 [8]	152 [10]	933 [9]	77 [5]	74 [5]	
Other surgery	478 [3]	244 [15]	156 [2]	37 [2]	41 [3]	
Unknown/unreported	266 [2]	127 [8]	63 [1]	12 [1]	64 [4]	
Surgery						<0.001
Robotic-assisted thoracic surgery	522 [4]	39 [2]	374 [4]	54 [3]	55 [4]	
Video-assisted thoracic surgery	49 [0.3]	23 [1]	17 [0.2]	**	**	
Thoracotomy	6,022 [41]	482 [30]	4,004 [40]	785 [49]	751 [49]	
Sternotomy	115 [1]	21 [1]	53 [1]	**	**	
Unknown	7,940 [54]	1,031 [65]	5,468 [55]	754 [47]	687 [45]	
Neoadjuvant treatment						<0.001
Yes	1,207 [8]	231 [14]	465 [5]	134 [8]	377 [25]	
No	13,441 [92]	1,365 [86]	9,451 [95]	1,473 [92]	1,152 [75]	

Data are presented as mean ± SD or n [%] or n. †, based on US Census tract aggregate data, not individual patient data; ‡, adenoma is included in the data source histology field and could not be separated for this analysis; **, suppressed cell values according to the Centers for Medicare & Medicaid Services Cell Size Suppression Policy (n<11) (https://resdac.org/articles/cms-cell-size-suppression-policy). AJCC, American Joint Committee on Cancer; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; pNX, no examination; pN0, examination and no metastasis; pN1, metastasis staging in N1; pN2, metastatic staging in N2; SD, standard deviation; USD, US dollars.

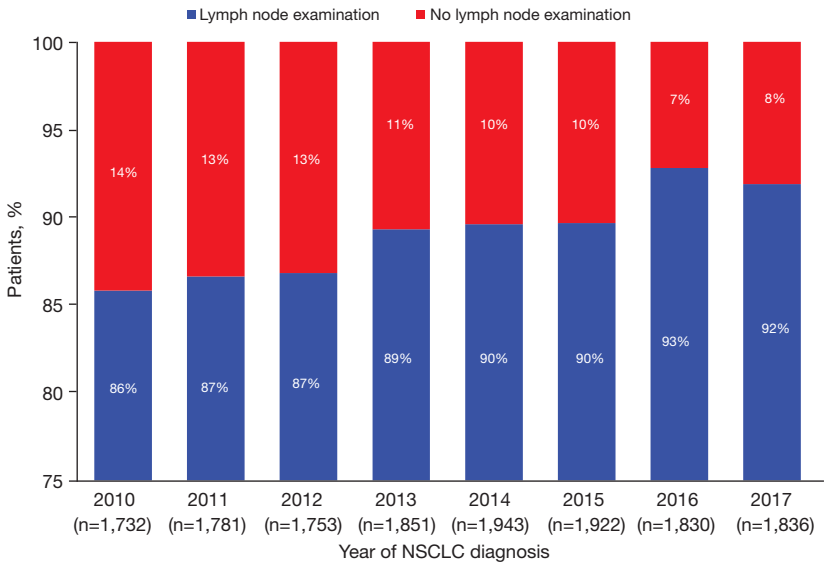

Figure 1 Prevalence of lymph node examination by year of NSCLC diagnosis. NSCLC, non-small cell lung cancer.

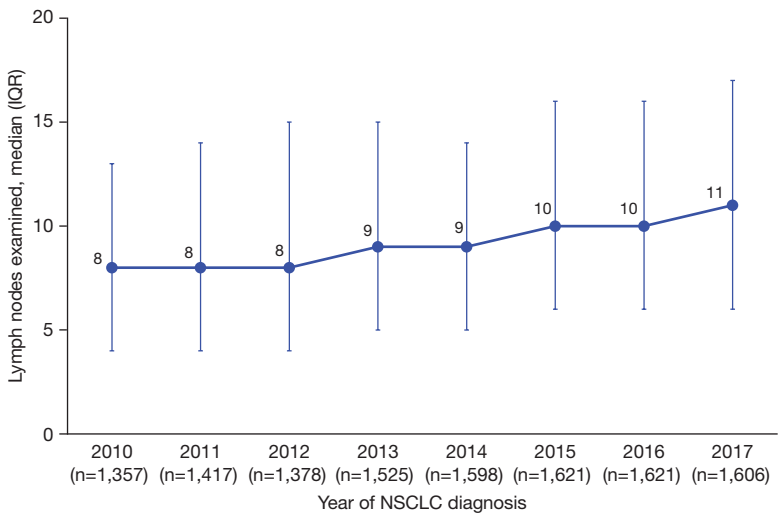

Figure 2 Lymph nodes examined by year of NSCLC diagnosis (n=12,123). IQR, interquartile range; NSCLC, non-small cell lung cancer.

Outcome cohort

More than half of the overall study population (n=9,448; 65%) was eligible for inclusion in the outcome cohort (Figure S2). Compared with patients in the other lymph node examination groups, patients in the pNX group in the outcome cohort were older with lower median income and greater baseline smoking history (Table S2).

Of the 9,448 patients included in the outcome cohort, 8,452 had a lymph node examination; nearly all (7,876/8,452; 93%) had a non-missing number of lymph nodes examined and were eligible for grouping by number of lymph nodes examined. Most of these patients had ≥6 (n=5,634; 72%) lymph nodes examined [n=2,242 (28%) had <6 lymph nodes examined]. Using different thresholds, approximately half of these patients had ≥10 (n=3,844; 49%) or <10 (n=4,032; 51%) lymph nodes examined.

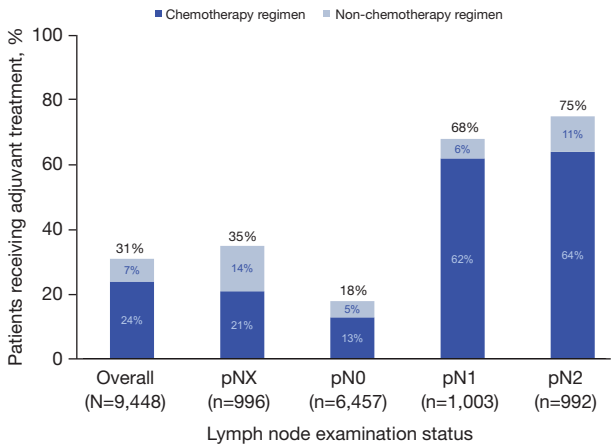

Figure 3 Prevalence of adjuvant treatment in the outcome cohort by type of regimen and lymph node examination status (N=9,448)[†]. [†], non-chemotherapy regimens included targeted therapy, immunotherapy, or radiation. pNX, no examination; pN0, examination and no metastasis; pN1, metastasis staging in N1; pN2, metastatic staging in N2.

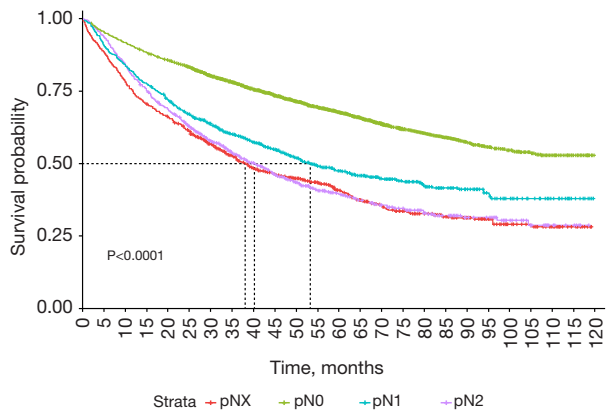

Figure 4 Unadjusted OS by lymph node examination status. OS, overall survival; pNX, no examination; pN0, examination and no metastasis; pN1, metastasis staging in N1; pN2, metastatic staging in N2.

Adjuvant treatment

A total of 2,947 (31%) patients in the outcome cohort received adjuvant treatment during the adjuvant treatment identification period. Adjuvant treatment rates for pNX (35%) patients were higher than those for pN0 (18%) patients, but lower than those for pN1 (68%) and pN2 (74%) patients (*Figure 3*) (P<0.001).

Among those with lymph node examinations and non-missing number of lymph nodes examined (n=7,876), a significantly greater proportion of those with more lymph nodes examined received adjuvant treatment (≥6 *vs.* <6: 32% *vs.* 25%; ≥10 *vs.* <10: 34% *vs.* 27%, respectively, P<0.001) (Figure S4).

Among the 2,947 patients who received adjuvant treatment during the identification period, the median time from surgery to adjuvant treatment was lowest for pNX patients (36 days) compared with pN2 (44 days), pN1 (49 days), and pN0 (50 days) patients. Mean and median times from surgery to adjuvant treatment are provided in Table S3.

Among those grouped by number of lymph nodes examined (n=2,389), patients with more lymph nodes examined had longer times from surgery to adjuvant treatment, both for those with ≥6 *vs.* <6 lymph nodes examined (median 49 *vs.* 46 days, respectively; P=0.02) and for those with ≥10 *vs.* <10 lymph nodes examined (median 49 *vs.* 47 days, respectively; P=0.01).

OS

Of the 9448 patients included in the outcome cohort, unadjusted OS was worse for pNX, pN1 and pN2 patients compared with pN0 patients; the unadjusted OS for pNX was similar to pN2 patients (*Figure 4*). Unadjusted OS was also significantly worse for patients with <6 *vs.* ≥6 lymph nodes examined (Figure S5A), but similar for those with <10 *vs.* ≥10 lymph nodes examined (Figure S5B).

Adjusted OS models showed a continued higher risk of death for pNX, pN1 and pN2 patients compared with pN0 patients, and the risk decreased over time (*Table 2*). Adjusted OS models also showed a continued higher risk of death for patients with fewer lymph nodes examined, with the exception of the ≥10 *vs.* <10 group comparison within 2 years of follow-up (Table S4).

Total post-surgical healthcare costs

Marginal mean adjusted total costs for pNX patients ($15,827 PPPM) were comparable to those of pN0 ($12,712 PPPM) and pN1 ($17,089 PPPM) patients, but pN0 was significantly less compared to those of pN2 patients ($23,566 PPPM) (P=0.002). Total costs were driven primarily by inpatient costs, followed by physician services (*Table 3*).

Total healthcare costs were similar among patients with more *vs* fewer lymph nodes examined, both for those with ≥10 *vs.* <10 (P=0.42) and those with ≥6 *vs.* <6 (P=0.65) (Table S5). Medical costs by components were also similar

Table 2 Adjusted OS hazard ratio (95% CI) by lymph node examination status[†]

Time from diagnosis	Hazard ratio (95% CI)			P value
	pNX *vs.* pN0	pN1 *vs.* pN0	pN2 *vs.* pN0	
0–2 years	2.50 (2.13–2.93)	2.23 (1.89–2.63)	2.78 (2.38–3.26)	<0.001 for all cells
2–3 years	2.19 (1.63–2.96)	1.64 (1.18–2.28)	2.73 (2.03–3.66)	<0.001 for all cells
3–5 years	1.65 (1.19–2.27)	1.73 (1.27–2.37)	2.48 (1.81–3.38)	<0.001 for all cells

[†], all comparisons *vs.* pN0 reference group. Extended Cox proportional hazard models adjusted for time and time interaction with lymph node examination status, as well as age, sex, race, urban/rural geography, CCI score, smoking history, presence of COPD, and histology. CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; OS, overall survival; pNX, no examination; pN0, examination and no metastasis; pN1, metastasis staging in N1; pN2, metastatic staging in N2.

Table 3 Adjusted healthcare costs by lymph node examination status

Healthcare costs	Marginal mean costs PPPM [95% CI], $			
	pN0	pNX	pN1	pN2
Overall	12,712 [3,770–42,859]	15,827 [4,541–55,166]	17,089 [4,876–59,888]	23,566 [6,719–82,650]
Inpatient services	8,325 [1,793–38,646]	9,879 [2,033–48,011]	10,512 [2,154–51,294]	14,602 [2,988–71,365]
Outpatient services	633 [363–1,105]	1,002 [565–1,778]	1,276 [718–2,268]	1,782 [1,002–3,169]
Physician services	1,957 [863–4,436]	3,087 [1,332–7,157]	2,921 [1,256–6,798]	4,023 [1,728–9,366]
Other services	458 [268–783]	961 [553–1,671]	685 [393–1,196]	719 [412–1,254]
Medications	286 [163–500]	384 [216–684]	387 [217–691]	410 [230–731]

PPPM, per patient per month; CI, confidence interval; pN0, examination and no metastasis; pNX, no examination; pN1, metastasis staging in N1; pN2, metastatic staging in N2.

for those with more *vs* fewer lymph nodes examined, with the exception that patients with <10 lymph nodes examined had higher outpatient service costs (P=0.02) and higher other services costs (P=0.01) than those with ≥10 lymph nodes examined (Table S5).

Discussion

Key findings

This retrospective observational study evaluated the prevalence and impact of lymph node examination on clinical and economic outcomes in the US Medicare population with eNSCLC. The prevalence of lymph node examination increased from 2010 to 2017, but despite an adequate number of lymph nodes excised at resection, many resections continued to lack follow-up examination of the excised lymph nodes. Since pNX patients are less likely to receive adjuvant chemotherapy, the failure to examine excised lymph nodes could contribute to worse survival outcomes (7-9). This study confirmed that pNX patients were less likely than pN1 or pN2 patients to receive adjuvant treatment, and after adjusting for potential confounders, pNX patients were at significantly higher risk of death compared with pN0 patients. This study also showed that stage distribution in pNX patients was more similar to that of pN0 than that of pN1 or pN2 patients. However, the prognosis for pNX patients was quite similar to the prognosis for pN2 patients, suggesting that a potentially substantial proportion of pNX patients may have a missed diagnosis of mediastinal (N2 or N3) lymph node metastasis, and implicates pathologic understaging.

Explanation of findings and contextual considerations

Number of lymph nodes examined is associated with more accurate staging and better OS for patients with early-stage NSCLC (18), and the quality of lymph node staging is associated with perioperative outcomes and survival in this setting (19-21). This study showed that a greater proportion of patients with more lymph nodes examined

received adjuvant treatment and had generally better OS compared with those with fewer lymph nodes examined. Outcomes were most distinct between those with ≥6 *vs.* <6 lymph nodes examined (as opposed to those with ≥10 *vs.* <10). Although patients with more lymph nodes examined were more likely to receive adjuvant treatment and to live longer, total healthcare costs were similar between those with more *vs.* fewer lymph nodes examined, suggesting that the increased adjuvant treatment costs may be offset by decreased healthcare utilization. In fact, significantly higher outpatient and other service costs were observed for those with fewer (<10 *vs.* ≥10) lymph nodes examined.

Interestingly, this study showed that although pNX patients have worse OS relative to pN0 patients, their average healthcare costs were not significantly higher and were more similar to those for pN1 patients. This finding may reflect underutilization of health care in general, including systemic therapy, among resected pNX NSCLC patients. Systemic treatment in the overall resected stage II–III NSCLC patient population is known to be less than ideal, as demonstrated by previous real-world studies using the SEER-Medicare database (22) and the National Cancer Database (23).

Findings from this study are consistent with those of Osarogiagbon *et al.* [2013] which also emphasized the importance of lymph node examination for clinical treatment decisions and outcomes (13). This study extends previous research by using more recent data to evaluate the prevalence of lymph node examinations. Inadequate lymph node evaluation essentially defaults clinical decision-making to be based largely on clinical (radiographic) staging. Clinical staging may fail to detect tumor [T]4 disease in about 10% of cases and is associated with misclassified nodal disease in about 38%; as a result, 10% to 38% of patients may receive different treatments with the use of clinical staging only compared with if lymph node evaluation is used as well (24).

Despite guideline-directed recommendations for adequate lymph node dissection and stage-based recommendations for adjuvant chemotherapy in resected NSCLC, rates of adherence to adequate lymph node dissection and administration of adjuvant chemotherapy are inadequately understood in the real-world setting. Recently, in the ongoing ALCHEMIST trial among patients enrolled in a nationwide US screening protocol for adjuvant treatment trials for resected NSCLC, only 53% of patients had adequate lymph node dissection (defined as ≥1 N1 nodal station and ≥3 N2 nodal stations), and receipt of adjuvant chemotherapy was 57% (25). Given the US approval of adjuvant atezolizumab (IMpower010) (15,16), osimertinib (ADAURA) (26), and pembrolizumab (KEYNOTE-091) (17,27) following complete resection in eNSCLC based on the disease-free survival advantage compared with standard of care, it is more important than ever to adequately stage lymph nodes to prevent omission of targeted or immunotherapies.

Strengths and limitations

This study used the SEER-Medicare linked data; the SEER database is a large, linked database representative of the US Medicare fee-for-service population (adults aged ≥65 years). Findings from this study may not be generalizable beyond the US Medicare population due to population and health system factors that are inherent or influential to clinical treatment decisions and outcomes, whether to patients who are insured commercially or through a Health Maintenance Organization in the US or to patient populations outside of the US. Given the time period of this study, the results reflect real-world practice before approval and use of immune checkpoint inhibitors in the adjuvant setting. With the advent of immune checkpoint inhibitors, which have been shown to improve outcomes relative to previous standards of care (15-17), it is even more imperative that lymph nodes are properly examined so that patients are able to receive the most appropriate available treatments.

It should be noted that pNX patients are more likely to have characteristics that may impact their OS outcomes, such as older age and lower income. Multivariate analyses were performed to address the potential selection bias issue, to control for confounders including age, sex, race/ethnicity, urban/rural geography, CCI score, smoking history, presence of COPD, histology, and surgery status. While the pNX cohort may appear to have been a biased sample, patients who undergo lung cancer resection with no lymph node assessment are a clinically relevant group who are subject to ambiguity in clinical decision-making related to adjuvant systemic therapy. This is supported by our findings that show underutilization of systemic therapy in the pNX cohort compared to the pN1 or pN2 cohorts. We expect that the pNX cohort is inherently under-staged due to nonexamination of lymph nodes. It was our intent to provide observations from real-world data analysis that inadequate lymph node examination is associated with underutilization of adjuvant treatment and poor OS in resected NSCLC. In the current era of targeted

and immunotherapies, lymph node examination is more important than ever. Furthermore, current clinical trial designs focused on targeted or immunotherapy for high-risk lymph node-negative patients include the pNX cohort as a poor risk "lymph node-negative" group along with other risk factors such as margin positivity at resection, lymphovascular invasion, visceral pleural invasion, and satellite tumors. As such, it is important for clinicians treating patients with lung cancer to appreciate lymph node staging and to have greater awareness of the pNX cohort as being a poor-risk population and a highly clinically relevant scenario in real-world practice.

Conclusions

Overall, these findings suggest that underperformance of lymph node examinations may negatively impact adjuvant treatment decisions and clinical outcomes, emphasizing the need for continued education of the clinical community and for broader implementation of quality improvement practices and multidisciplinary coordination.

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Portions of these data have been presented previously as a poster by Lee JM, *et al.* at ESMO 2022.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Supplementary

Table S1 Lung cancer diagnosis codes

Code type	Codes
ICD-O	C33.9, C34.0-34.3, C34.8, C34.9
ICD-9	1622-1625, 1628, 1629, 1658, 1970, 20921, 2357, V1011
ICD-10	C3400-3402, C3410-3412, C342, C3430-3432, C3480-3482, C3490-3492, C7A090, C7800, Z85118, D381, C399

ICD, International Classification of Diseases.

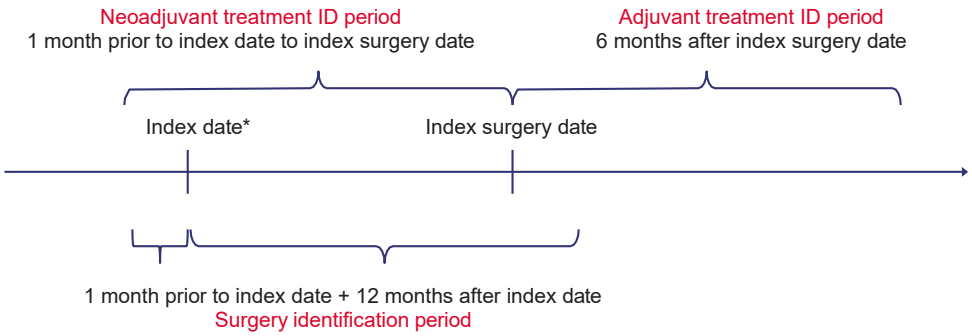
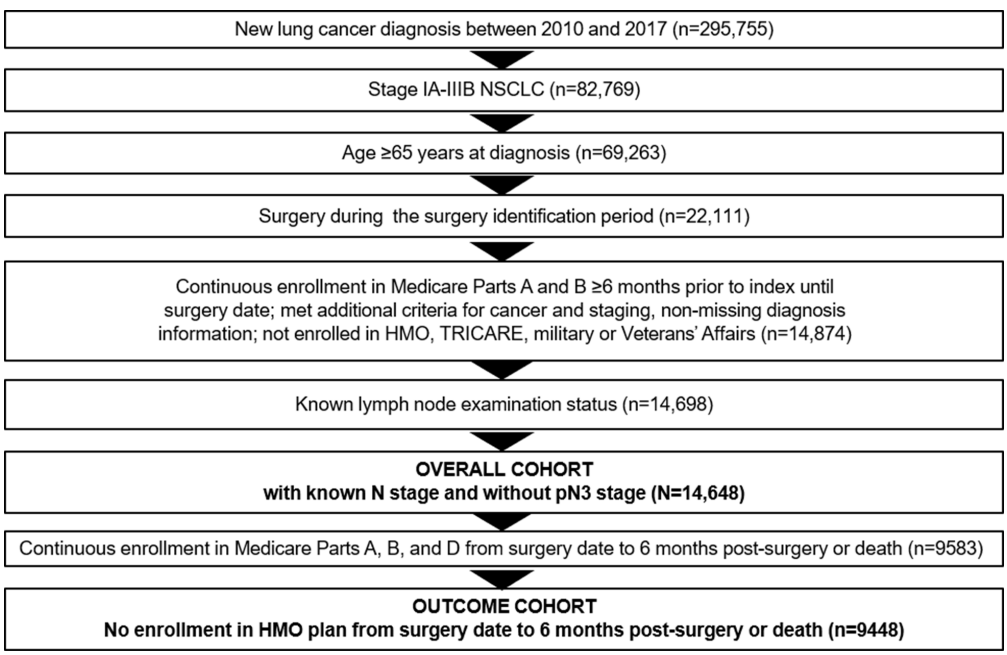


Figure S1 Study identification periods. *, index date was defined as the earliest Medicare lung cancer claim that occurred in the same year/month as the SEER diagnosis. If no Medicare claim existed, the SEER diagnosis date was used, set to the 15th of the month. SEER, Surveillance, Epidemiology, and End Results.



HMO, health maintenance organization; NSCLC, non-small cell lung cancer; pN2, metastatic staging in N2.

Figure S2 Patient attrition.

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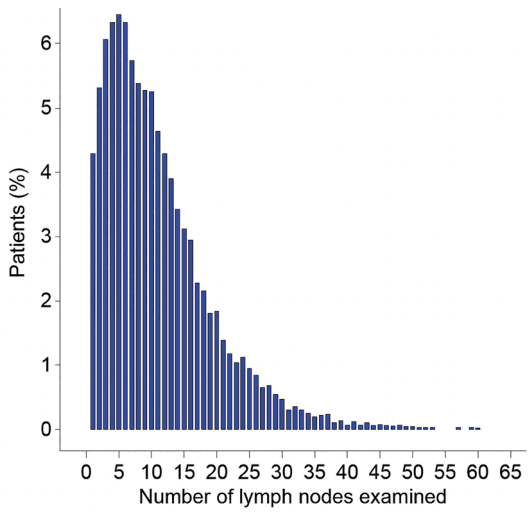

Figure S3 Distribution of number of lymph nodes examined (n=12,123).

Table S2 Characteristics of patients in the outcome cohort (N=9,448)

Characteristic	Overall (N=9,448)	pNX (n=996)	pN0 (n=6,457)	pN1 (n=1,003)	pN2 (n=992)	P value
Age at diagnosis, mean ± SD, years	73.92±5.59	74.95±6.14	73.87±5.54	73.70±5.46	73.41±5.31	<0.001
Sex, female, n [%]	5,211 [55]	529 [53]	3,658 [57]	499 [50]	525 [53]	<0.001
Race, n [%]						0.2
Black	556 [6]	67 [7]	375 [6]	52 [5]	62 [6]	
White	8,265 [87]	879 [88]	5,639 [87]	892 [89]	855 [86]	
Other	627 [7]	50 [5]	443 [7]	59 [6]	75 [8]	
Median income, mean ± SD, USD[a]	66,038±32,425	61,398±30,554	67,113±33,257	64,895±30,395	64,869±30,240	<0.001
Unknown, n	13	0	12	0	**	
Baseline CCI score (excluding cancer), mean ± SD	2.14±1.88	2.52±2.08	2.13±1.87	1.93±1.74	1.96±1.84	<0.001
Baseline interstitial lung disease, n [%]	11 [<1]	**	**	**	**	0.3
Baseline pneumonitis, n [%]	67 [1]	14 [1]	43 [1]	**	**	0.036
Baseline COPD, n [%]	3,797 [40]	478 [48]	2,581 [40]	382 [38]	356 [36]	<0.001
Baseline smoking history, n [%]	1,495 [16]	194 [19]	1,022 [16]	158 [16]	121 [12]	<0.001
Cancer stage (AJCC 7th edition derived), n [%]						<0.001
Stage IA	3,691 [39]	450 [45]	3,242 [50]	0	0	
Stage IB	2,233 [24]	195 [20]	2,038 [32]	0	0	
Stage II	1,852 [20]	126 [13]	1,010 [16]	716 [71]	0	
Stage IIIA	1,517 [16]	159 [16]	167 [3]	287 [29]	904 [91]	
Stage IIIB	154 [2]	66 [7]	0	0	88 [9]	
Tumor grade, n [%]						<0.001
1	1,333 [14]	132 [13]	1,104 [17]	45 [5]	52 [5]	
2	4,169 [44]	358 [36]	3,027 [47]	410 [41]	374 [38]	
3	3,059 [32]	293 [29]	1,884 [29]	468 [47]	414 [42]	
4	82 [1]	**	50 [1]	14 [1]	**	
Missing	805 [9]	**	392 [6]	66 [7]	**	
Histology, n [%]						<0.001
Adenomas and adenocarcinomas[a]	4,964 [53]	485 [49]	3,391 [53]	498 [50]	590 [59]	
Squamous cell carcinoma	3,006 [32]	357 [36]	2,026 [31]	355 [35]	268 [27]	
Other	1,478 [16]	154 [15]	1,040 [16]	150 [15]	134 [14]	
Extent of lung cancer resection, n [%]						<0.001
Lobectomy	5,843 [62]	172 [17]	4,286 [66]	698 [70]	687 [69]	
Wedge resection	1,952 [21]	490 [49]	1,237 [19]	96 [10]	129 [13]	
Bilobectomy	136 [1]	**	76 [1]	36 [4]	20 [2]	
Pneumonectomy	227 [2]	**	81 [1]	98 [10]	38 [4]	
Segmentectomy	829 [9]	97 [10]	637 [10]	45 [5]	50 [5]	
Other surgery	290 [3]	141 [14]	100 [2]	**	28 [3]	
Unknown/unreported	171 [2]	82 [8]	40 [1]	**	40 [4]	
Surgery, n [%]						<0.001
Robotic-assisted thoracic surgery	321 [3]	26 [3]	223 [4]	**	33 [3]	
Video-assisted thoracic surgery	28 [<1]	13 [1]	**	**	**	
Thoracotomy	3,898 [41]	319 [32]	2,586 [40]	500 [50]	493 [50]	
Sternotomy	79 [1]	11 [1]	**	**	**	
Unknown	5,122 [54]	627 [63]	3,603 [56]	454 [45]	438 [44]	
Neoadjuvant treatment, n [%]						<0.001
Yes	778 [8]	139 [14]	308 [5]	83 [8]	248 [25]	
No	8,670 [92]	857 [86]	6,149 [95]	920 [92]	744 [75]	

[a], adenoma is included in the data source histology field and could not be separated for this analysis; **, suppressed cell values according to the Centers for Medicare & Medicaid Services Cell Size Suppression Policy (n<11) (https://resdac.org/articles/cms-cell-size-suppression-policy). AJCC, American Joint Committee on Cancer; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; pNX, no examination; pN0, examination and no metastasis; pN1, metastasis staging in N1; pN2, metastatic staging in N2; SD, standard deviation; USD, US dollars.

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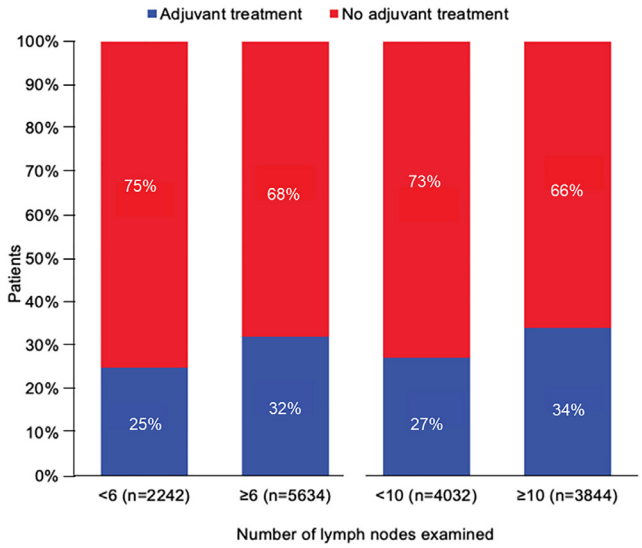

Figure S4 Receipt of adjuvant treatment by number of lymph nodes examined (n=7,876).

Table S3 Time from surgery to adjuvant treatment (n=2,947)

Time to adjuvant treatment, days	Overall (n=2,947)	pNX (n=346)	pN0 (n=1,181)	pN1 (n=682)	pN2 (n=738)	P value
Mean [SD]	55 [36]	49 [43]	61 [41]	55 [28]	50 [28]	<0.001
Median [IQR]	48 [33–68]	36 [19–61]	50 [34–77]	49 [37–65]	44 [33–61]	

IQR, interquartile range; pNX, no examination; pN0, examination and no metastasis; pN1, metastasis staging in N1; pN2, metastatic staging in N2; SD, standard deviation.

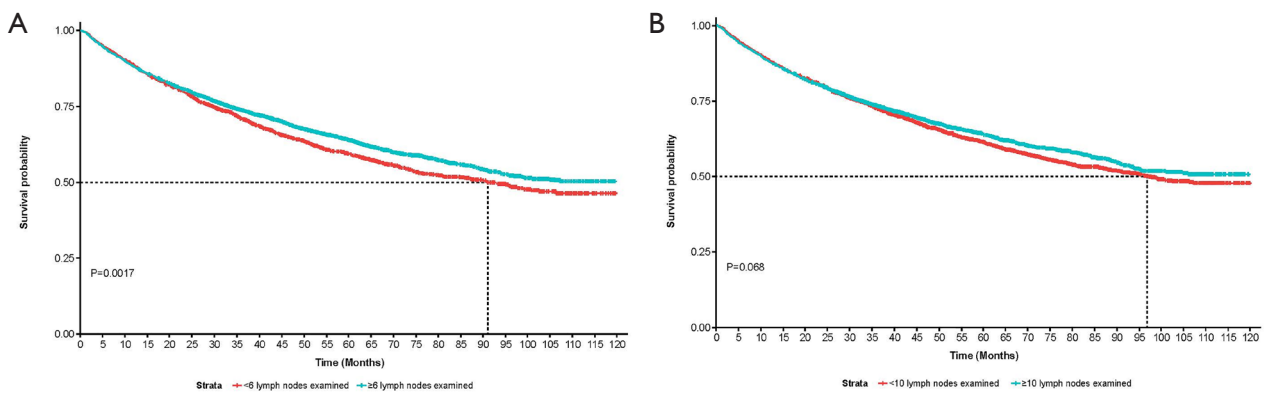

Figure S5 Unadjusted OS by number of lymph nodes examined. (A) Patients with ≥6 *vs.* <6 lymph nodes examined; (B) patients with ≥10 *vs.* <10 lymph nodes examined. OS, overall survival.

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Table S4 Adjusted OS hazard ratio (95% CI) by number of lymph nodes examined

Time from diagnosis	LNs examined, <6 *vs.* ≥6		LNs examined, <10 *vs.* ≥10	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
0–2 years	1.17 (1.05–1.31)	0.005	1.07 (0.97–1.19)	0.168
2–3 years	1.49 (1.23–1.79)	<0.001	1.38 (1.16–1.65)	<0.001
3–5 years	1.44 (1.20–1.73)	<0.001	1.34 (1.13–1.59)	<0.001

Extended Cox proportional hazard models adjusted for time and time interaction with lymph node examination status, as well as age, sex, race, urban/rural geography, CCI score, smoking history, presence of COPD, and histology. CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; LN, lymph node; OS, overall survival.

Table S5 Adjusted healthcare costs by number of lymph nodes examined

Healthcare costs, USD	Marginal mean costs PPPM (95% CI) by number of lymph nodes examined			
	<10	≥10	<6	≥6
Overall	15,245 (4,249–54,703)	16,771 (4,654–60,435)	16,720 (4,613–60,608)	15,769 (4,373–56,854)
Inpatient services	9864 (1,999–48,669)	11,228 (2,265–55,668)	11,164 (2,234–55,791)	10,514 (2,119–52,164)
Outpatient services	907 (536–1,534)	810 (478–1,374)	924 (540–1,582)	835 (489–1,427)
Physician services	2,375 (998–5,654)	2,460 (1,030–5,873)	2,548 (1,065–6,095)	2,357 (989–5,619)
Other services	577 (345–966)	508 (303–852)	633 (383–1,046)	500 (303–824)
Medications	338 (187–610)	329 (182–594)	344 (190–621)	329 (183–594)

CI, confidence interval; PPPM, per patient per month; USD, US dollars.

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