Prognostic impact of lymphadenectomy on outcomes of sublobar resection for stage IA non–small cell lung cancer ≤ 2 cm

Jinlin Cao, MD, Jinming Xu, MD, Zehao He, MD, Ping Yuan, MD, Sha Huang, MD, Wang Lv, MD, and Jian Hu, MD, PhD

ABSTRACT

Objective: To investigate the prognostic impact of lymph node (LN) dissection on sublobar resection for stage IA non–small cell lung cancer (NSCLC) tumors ≤ 2 cm.

Methods: All patients who underwent sublobar resection for stage IA NSCLC tumors ≤ 2 cm were identified from the Surveillance, Epidemiology and End Results database. Patients were classified into no-LN dissection and LN dissection groups, and the latter was subclassified by the extent of LN dissection (1-3 regional LNs or ≥ 4 regional LNs). These groups were compared in terms of lung cancer–specific survival (LCSS) and overall survival (OS) rates. Propensity score–matched comparative analysis and a Cox regression model were used.

Results: A total of 3269 patients met our criteria, including 1459 (44.6%) who underwent no LN dissection, 891 (27.3%) who underwent dissection of 1 to 3 regional LNs, 919 (28.1%) who underwent dissection of ≥ 4 regional LNs. Compared with no LN dissection, LN dissection was associated with more favorable LCSS and OS rates in patients who underwent sublobar resection for stage IA tumors ≤ 2 cm. More extensive regional LN dissection (≥ 4 regional LNs) was associated with better LCSS and OS rates compared with less extensive regional LN dissection (1 to 3 regional LNs). A multivariable analysis of our patient population revealed independent associations of no LN dissection and less extensive regional LN dissection with poorer LCSS and OS rates compared with overall LN dissection and more extensive regional LN dissection, respectively.

Conclusions: This propensity score–matched analysis reveals an association of LN dissection, particularly more extensive regional LN dissection (≥ 4 regional LNs), with better survival rates in patients who undergo sublobar resection for stage IA NSCLC tumors ≤ 2 cm. (J Thorac Cardiovasc Surg 2018;156:796-805)

Kaplan–Meier curves of survival estimates for the propensity score–matched cohort.

Central Message

Lymph node dissection should be encouraged even for stage IA non–small cell lung cancer tumors ≤ 2 cm to improve prognostic accuracy.

Perspective

Our population-based, propensity score–matched analysis shows that when compared with no lymph nodes dissection, any lymph nodes dissection is associated with better survival outcomes in patients who undergo sublobar resection for stage IA non–small cell lung cancer tumors ≤ 2 cm. Furthermore, we found that a greater number of dissected regional lymph nodes were associated with longer survival duration.

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From the Department of Thoracic Surgery, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China.

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Address for reprints: Jian Hu, MD, PhD, Department of Thoracic Surgery, The First Affiliated Hospital, School of Medicine, Zhejiang University, 79 Qingchun Rd, Hangzhou 310003, China (E-mail: dr_hujian@zju.edu.cn).

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The widespread use of thin-section and low-dose computed tomography for lung cancer screening has led to an obvious increase in the detection of early-stage non–small cell lung cancer (NSCLC),¹ and the optimal extent of resection for these tumors has attracted increasing attention. Sublobar resection, which includes wedge resection or

Scanning this QR code will take you to the supplemental video, appendix, and tables for the article.

Abbreviations and Acronyms

CI	= confidence interval
HR	= hazard ratio
LCSS	= lung cancer–specific survival
LN	= lymph node
NSCLC	= non–small cell lung cancer
OS	= overall survival
SEER	= Surveillance, Epidemiology, and End Results

segmentectomy, has been reported by some to achieve oncologic results similar to those of lobectomy in patients with early-stage NSCLC, especially those with stage IA tumors ≤ 2 cm.^{2–4} In addition, sublobar resection has the advantages of improving patients' postoperative quality of life by preserving pulmonary function and reducing the rates of morbidity and disability.⁵ However, the importance of lymph node (LN) dissection during sublobar resection for early-stage NSCLC needs to be established.

Several previous studies have investigated whether the number of dissected LNs influences the postoperative survival rate in patients with NSCLC. Notably, these studies found that postoperative patient survival is associated with the number of dissected LNs, and that the number of LNs is correlated with more accurate node staging to reduce stage migration and long-term survival.^{6–11} However, these previous studies focused mainly on patients who underwent lobectomy, and few specifically evaluated the prognostic effect of the extent of LN dissection on sublobar resection for early-stage NSCLC.

In this study, we used the population-based Surveillance, Epidemiology, and End Results (SEER) database to investigate the outcomes of LN dissection on sublobar resection for stage IA NSCLC tumors ≤ 2 cm. Our analysis may provide a rationale and further support for LN dissection during sublobar resection for early-stage NSCLC.

PATIENTS AND METHODS**Patient Population**

All patients were selected from SEER 18 (covering 18 registries, 1973–2014), the latest version of the SEER database released in January 2018. The population-based cancer registries included in this database cover approximately 28% of the US population and were analyzed with SEER*-Stat, version 8.3.4.¹² We extracted eligible patients diagnosed with microscopically confirmed primary pathological stage IA NSCLC with tumors ≤ 2 cm between January 2004 and December 2014. Among these patients, we narrowed our focus to those who underwent sublobar resection (wedge resection or segmentectomy) without or with scope-assisted regional LN dissection (classified as none, 1–3 regional LNs removed, or ≥ 4 regional LNs removed) and subsequent pathological evaluation. The inclusion criteria were limited to active follow-up after surgery. Patients who had undergone chemotherapy or radiotherapy before, during, or after surgery or had an unknown radiation status were excluded. The selection codes for the SEER database queries are shown in [Appendix E1](#).

The outcomes of this study included lung cancer–specific survival (LCSS) and overall survival (OS). LCSS was calculated from the date of surgery to the date of lung cancer–related death. OS was calculated from the date of surgery to the date of death from any cause. The last follow-up included in this study was done on December 31, 2014.

Statistical Analysis

The optimal cutoff values for the extent of LN dissection were determined using X-Tile software (<http://www.tissuearray.org/rimmlab>) and the minimal *P* value approach ([Figure E1](#)).¹³ A propensity score–matched comparative analysis is used to simultaneously balance clinical variables and reduce selection bias caused by an existing dataset for a nonrandom controlled assignment analysis.^{14–16} We used a propensity score–matching analysis to adjust for potential differences in the patients' baseline characteristics between the no-LN dissection and LN dissection groups (1:1 match) and between the groups with 1 to 3 and ≥ 4 dissected regional LNs (1:1 match). In each analysis, we generated a propensity score for matched groups using logistic regression based on the patients' potential confounding baseline characteristics, including age, sex, race, marital status, location, SEER registry region, histological type, surgical procedure, and tumor site, size and grade. We next created a balanced cohort using an optimized performance-matching algorithm with a caliper setting of 0.01. Year of procedure was not included in the propensity score and was handled with model adjustment. We used the standardized differences to assess balance.

We used the *t* test and χ^2 test to compare differences between continuous and categorical variables, respectively. We used the Kaplan–Meier method to estimate LCSS and OS curves separately for the various LNs dissection categories of patients who underwent sublobar resection for stage IA NSCLC tumors ≤ 2 cm and evaluated statistical differences using the log-rank test. Survival functions were also compared by univariable Cox regression analysis. Predictors (*P* < .10) identified in univariable analyses were entered into a multivariable analysis. Surgery type and histology are huge confounders that were also adjusted. For all analyses, a 2-sided *P* value of < .05 was considered to indicate statistical significance. Hazard ratios (HRs), 95% confidence intervals (CIs), and *P* values for each variable were conducted using SPSS 24.0 (IBM, Armonk, NY), and survival curves were drawn using Prism 7.0 (GraphPad Software, La Jolla, Calif).

RESULTS

We identified 3269 eligible patients with stage IA NSCLC with tumors ≤ 2 cm, including 1459 (44.6%) with no dissected regional LNs, 891 (27.3%) with 1 to 3 dissected regional LNs, and 919 (28.1%) with ≥ 4 dissected regional LNs. The 30-day mortality rate was 1.1% (35 of 3269), including 15 deaths (0.8%) in the LN resection group and 20 (1.4%) in the no LN resection group (*P* = .185). The patients' baseline characteristics are summarized in [Tables 1–3](#). Patients who underwent sublobar resection with regional LN dissection were more likely to be younger and female, to reside in the northeastern and southern regions, to have larger tumors, to have undergone segmentectomy, and to have been treated more recently ([Table 1](#)). Compared with patients who underwent dissection of ≥ 4 LNs, those with 1 to 3 dissected regional LNs were more likely to be older, to reside in the northeastern and southern regions, and to have undergone wedge resection ([Table 2](#)). Patients with no LN dissection had a higher rate of death due to lung cancer and heart disease

TABLE 1. Baseline characteristics of patients who underwent sublobar resection for stage IA non–small cell lung cancer (≤ 2 cm) with or without lymph node dissection before and after propensity score matching

Variables	Full cohort			Matched cohort		
	LN dissection (n = 1810)	None (n = 1459)	Standardized difference, %	LN dissection (n = 1235)	None (n = 1235)	Standardized difference, %
Age, y, mean (SD)	67.6 (9.8)	69.4 (10.2)	18.0	68.5 (9.5)	68.9 (10.2)	4.1
Sex, n (%)						
Female	1141 (63.0)	862 (59.1)	8.1	765 (61.9)	745 (60.3)	3.3
Male	669 (37.0)	597 (40.9)	8.1	470 (38.1)	490 (39.7)	3.3
Race, n (%)						
White	1560 (86.2)	1289 (88.3)	6.5	1080 (87.4)	1079 (87.4)	0.2
Black/other	250 (13.8)	170 (11.7)	6.5	155 (12.6)	156 (12.6)	0.2
Marital status, n (%)						
Married	1016 (56.1)	759 (52.0)	8.3	662 (53.6)	663 (53.7)	0.2
Single	190 (10.5)	151 (10.3)	0.5	120 (9.7)	133 (10.8)	3.5
Other	604 (33.4)	549 (37.6)	8.9	453 (36.7)	439 (35.5)	2.4
Location, n (%)						
Metropolitan	1607 (88.8)	1278 (87.7)	3.7	1092 (88.4)	1089 (88.2)	0.8
Nonmetropolitan	203 (11.2)	180 (12.3)	3.5	143 (11.6)	146 (11.8)	0.8
SEER registry region, n (%)						
Northeast	510 (28.2)	351 (24.1)	9.4	315 (25.5)	312 (25.3)	0.6
Midwest	176 (9.7)	144 (9.9)	0.5	134 (10.9)	131 (10.6)	0.8
South	445 (24.6)	305 (20.9)	8.8	275 (22.3)	275 (22.3)	0
West	679 (37.5)	659 (45.2)	15.6	511 (41.4)	517 (41.9)	1.0
Year of procedure, n (%)						
2004–2006	276 (15.2)	297 (20.4)	13.4	236 (19.1)	244 (19.8)	1.6
2007–2008	295 (16.3)	236 (16.2)	0.3	260 (21.1)	198 (16.0)	12.9
2009–2010	308 (17.0)	285 (19.5)	6.5	251 (20.3)	245 (19.8)	1.2
2011–2012	404 (22.3)	311 (21.3)	2.4	279 (22.6)	260 (21.1)	3.7
2013–2014	527 (29.1)	330 (22.6)	14.9	209 (16.9)	288 (23.3)	16.0
Histology, n (%)						
Adenocarcinoma	1195 (66.0)	936 (64.2)	3.9	819 (66.3)	802 (64.9)	2.9
Squamous cell carcinoma	369 (20.4)	350 (24.0)	8.7	271 (21.9)	283 (22.9)	2.3
Other	246 (13.6)	173 (11.9)	5.2	145 (11.7)	150 (12.1)	1.2
Tumor site, n (%)						
Upper	1132 (62.5)	889 (60.9)	3.3	780 (63.2)	775 (62.8)	0.8
Middle	91 (5.0)	104 (7.1)	8.8	76 (6.2)	75 (6.1)	0.3
Lower	587 (32.4)	466 (31.9)	1.1	379 (30.7)	385 (31.2)	1.1
Tumor size, mm, mean (SD)	14.0 (4.1)	13.3 (4.4)	16.5	13.7 (4.1)	13.6 (4.1)	2.4
Grade, n (%)						
Grade I	534 (29.5)	366 (25.1)	9.9	333 (27.0)	338 (27.4)	0.9
Grade II	715 (39.5)	562 (38.5)	2.0	484 (39.2)	495 (40.1)	1.8
Grade III–IV	407 (22.5)	323 (22.1)	0.8	282 (22.8)	280 (22.7)	0.4
Not determined	154 (8.5)	208 (14.3)	18.2	136 (11.0)	122 (9.9)	3.7
Surgical procedure, n (%)						
Wedge resection	1314 (72.6)	1300 (89.1)	42.9	1077 (87.2)	1077 (87.2)	0
Segmentectomy	496 (27.4)	159 (10.9)	42.9	158 (12.8)	158 (12.8)	0

LN, Lymph node; SD, standard deviation; SEER, Surveillance, Epidemiology, and End Results.

compared with those who underwent any LN dissection (Table 3); however, there was no statistical difference in deaths from chronic pulmonary disease between the 2 groups ($P = .090$; Table 3).

After propensity score matching, 1235 pairs were formed in the no-LN dissection and LN dissection groups, and 762

pairs were formed in the subgroups with 1 to 3 and ≥ 4 regional LN dissections (Tables 1 and 2). A Kaplan–Meier survival analysis and log-rank comparison revealed that compared with no LN dissection, LN dissection was significantly associated with better LCSS (HR, 2.236; 95% CI, 1.805–2.770; $P < .001$) and OS (HR, 2.074; 95%

TABLE 2. Baseline characteristics of patients who underwent sublobar resection for stage IA non–small cell lung cancer (≤ 2 cm) with the dissection of 1 to 3 regional lymph nodes or ≥ 4 regional lymph nodes before and after propensity score matching

Variables	Full cohort			Matched cohort		
	1-3 regional LNs (n = 891)	≥ 4 regional LNs (n = 919)	Standardized difference, %	1-3 regional LNs (n = 762)	≥ 4 regional LNs (n = 762)	Standardized difference, %
Age, y, mean (SD)	68.2 (9.6)	66.9 (9.9)	13.3	67.7 (9.6)	67.8 (9.6)	1.0
Sex, n (%)						
Female	547 (61.4)	594 (64.6)	6.7	482 (63.3)	477 (62.6)	1.4
Male	344 (38.6)	325 (35.4)	6.7	280 (36.7)	285 (37.4)	1.4
Race, n (%)						
White	773 (86.8)	787 (85.6)	3.2	667 (87.5)	662 (86.9)	2.0
Black/other	118 (13.2)	132 (14.4)	3.2	95 (12.5)	100 (13.1)	2.0
Marital status, n (%)						
Married	507 (56.9)	509 (55.4)	3.1	429 (56.3)	415 (54.5)	3.7
Single	80 (9.0)	110 (12.0)	9.8	76 (10.0)	77 (10.1)	0.4
Other	304 (34.1)	300 (32.6)	3.1	257 (33.7)	270 (35.4)	3.6
Location, n (%)						
Metropolitan	776 (87.1)	831 (90.4)	10.6	672 (88.2)	679 (89.1)	2.9
Nonmetropolitan	115 (12.9)	88 (9.6)	10.6	90 (11.8)	83 (10.9)	2.9
SEER registry region, n (%)						
Northeast	278 (31.2)	232 (25.2)	13.3	223 (29.3)	219 (28.7)	1.2
Midwest	92 (10.3)	84 (9.1)	4.0	74 (9.7)	78 (10.2)	1.8
South	234 (26.3)	211 (23.0)	7.7	190 (24.9)	190 (24.9)	0
West	287 (32.2)	392 (42.7)	21.7	275 (36.1)	275 (36.1)	0
Year of procedure, n (%)						
2004-2006	139 (15.6)	137 (14.9)	1.9	122 (16.0)	134 (17.6)	4.2
2007-2008	145 (16.3)	150 (16.3)	0.1	126 (16.5)	145 (19.0)	6.5
2009-2010	169 (19.0)	139 (15.1)	10.2	141 (18.5)	129 (16.9)	4.1
2011-2012	198 (22.2)	206 (22.4)	0.5	170 (22.3)	181 (23.8)	3.4
2013-2014	240 (26.9)	287 (31.2)	9.5	203 (26.6)	173 (22.7)	9.1
Histology, n (%)						
Adenocarcinoma	567 (63.6)	628 (68.3)	9.9	500 (65.6)	507 (66.5)	1.9
Squamous cell carcinoma	199 (22.3)	170 (18.5)	9.5	159 (20.9)	155 (20.3)	1.3
Other	125 (14.0)	121 (13.2)	2.5	103 (13.5)	100 (13.1)	1.2
Tumor site, n (%)						
Upper	556 (62.4)	576 (62.7)	0.6	480 (63.0)	475 (62.3)	1.4
Middle	49 (5.5)	42 (4.6)	4.3	42 (5.5)	40 (5.2)	1.2
Lower	286 (32.1)	301 (32.8)	1.4	240 (31.5)	247 (32.4)	2.0
Tumor size, mm, mean (SD)	14.0 (4.3)	13.9 (3.9)	2.4	14.0 (4.1)	14.0 (4.0)	0.2
Grade, n (%)						
Grade I	258 (29.0)	276 (30.0)	2.4	225 (29.5)	219 (28.7)	1.7
Grade II	344 (38.6)	371 (40.4)	3.6	308 (40.4)	296 (38.8)	3.2
Grade III-IV	211 (23.7)	196 (21.3)	5.6	167 (21.9)	181 (23.8)	4.4
Not determined	78 (8.8)	76 (8.3)	1.7	62 (8.1)	66 (8.7)	1.9
Surgical procedure, n (%)						
Wedge resection	681 (76.4)	633 (68.9)	17.0	567 (74.4)	566 (74.3)	0.3
Segmentectomy	210 (23.6)	286 (31.1)	17.0	195 (25.6)	196 (25.7)	0.3

LN, Lymph node; SD, standard deviation; SEER, Surveillance, Epidemiology, and End Results.

CI, 1.785-2.410; $P < .001$) rates in patients with stage IA NSCLC tumors ≤ 2 cm who underwent sublobar resection (Figure 1, A and B). When the patients who underwent LN dissection were divided into those with 1 to 3 dissected

regional LNs and those with ≥ 4 dissected regional LNs, the latter group had better LCSS (HR, 1.382; 95% CI, 1.024-1.866; $P = .034$) and OS (HR, 1.356; 95% CI, 1.095-1.679; $P = .005$) rates (Figure 2, A and B).

TABLE 3. Baseline characteristics of causes of death from death certificates

Cause of death	Lymph node dissection			P value
	None (n = 1459)	1-3 regional (n = 891)	≥4 regional (n = 919)	
Lung cancer	250 (17.1)	114 (12.8)	80 (8.7)	<.001
Chronic pulmonary disease	81 (5.6)	38 (4.3)	34 (3.7)	.090
Diseases of heart	74 (5.1)	27 (3.0)	21 (2.3)	.001
Other	132 (9.0)	55 (6.2)	37 (4.0)	<.001

A multivariable Cox regression analysis revealed independent associations of no LN dissection with lower LCSS (HR, 2.014; 95% CI, 1.617-2.508; $P < .001$) and OS (HR, 1.892; 95% CI, 1.626-2.203; $P < .001$) rates compared with any LN dissection (Table 4). Furthermore, a lower number of dissected regional LNs (1-3 regional LNs) was found to be independently associated with poorer LCSS (HR, 1.396; 95% CI, 1.034-1.885; $P = .029$) and OS (HR, 1.319; 95% CI, 1.065-1.634; $P = .011$), compared with a higher number of dissected regional LNs (≥ 4 regional LNs) among patients who underwent sublobar resection for stage IA NSCLC tumors ≤ 2 cm (Table 5). The results were similar to those from the entire data analysis (Tables E1 and E2).

DISCUSSION

The extent of LN dissection is a vital component of a surgical treatment for early-stage NSCLC.^{6,17,18} Several studies have demonstrated an association between an increased number of dissected LNs following resection for NSCLC and better long-term survival rates. Using the SEER database, Ludwig and colleagues⁷ found that in those studies, the survival benefit peaked at approximately 13 to 16 dissected LNs. Ou and Zell⁸ found that removal of 11

to 15 lymph nodes conferred the lowest HR for death. Gulack and colleagues⁹ noted at least 4 LNs should be removed for tumors ≤ 2 cm, whereas the removal of at least 14 LNs was required for larger tumors. Samayoa and colleagues¹⁰ suggested that surgical treatment of early-stage NSCLC should include the dissection of at least 10 nodes. A more recent analysis of the US SEER database and a Chinese multi-institutional registry reported by Liang and colleagues¹¹ identified a significant reduction in the mortality rate among patients with at least 16 dissected LNs and declared node-negative NSCLC; however, those findings focused mainly on patients who underwent lobectomy. In contrast, no previous studies had evaluated the prognostic effect of the extent of LN dissection specifically in patients who underwent sublobar resection.

Sublobar resection, which includes wedge resection or segmentectomy, has been reported to yield survival outcomes similar to those of lobectomy in patients with early-stage NSCLC, especially for patients with smaller stage IA tumors.²⁻⁴ However, the value of LNs dissection remains unclear in this setting, and decisions regarding whether to perform LN dissection with sublobar resection and to what extent remain important. A study based on the National Cancer Data Base from 2003 to 2011 found

FIGURE 1. Kaplan-Meier curves of survival estimates for our propensity score-matched cohort with or without lymph node dissection. A, Lung cancer-specific survival data from patients who underwent sublobar resection for stage IA non-small cell lung cancer (≤ 2 cm). B, Overall survival data from patients who underwent sublobar resection for stage IA non-small cell lung cancer (≤ 2 cm). NSCLC, Non-small cell lung cancer; HR, hazard ratio; CI, confidence interval.

FIGURE 2. Kaplan–Meier curves of survival estimates for our propensity score–matched cohort with the dissection of 1 to 3 regional lymph nodes or ≥ 4 regional lymph nodes. A, Lung cancer–specific survival data from patients who underwent sublobar resection for stage IA non–small cell lung cancer (≤ 2 cm). B, Overall survival data from patients who underwent sublobar resection for stage IA non–small cell lung cancer (≤ 2 cm). NSCLC, Non–small cell lung cancer; HR, hazard ratio; CI, confidence interval.

that LN evaluation was not performed in 28.8% of patients who underwent sublobar resection for clinical stage IA NSCLC.¹⁹ In our study, which used the population-based SEER database, 44.6% of patients who underwent sublobar resection for stage IA NSCLC tumors ≤ 2 cm had not undergone LN dissection. Thus, many thoracic surgeons clearly do not believe LN dissection to be an important part of the surgical procedure during sublobar resection for NSCLC, especially smaller early-stage tumors. Stiles and colleagues²⁰ demonstrated that LN dissection with wedge resection for lung cancer does not increase the morbidity rate or the length of stay and appears to decrease the regional recurrence rate while improving the survival rate. The results of our propensity score matched–based analysis of LCSS and OS after sublobar resection for small stage IA NSCLC tumors suggests that any LN dissection is associated with better survival compared with no LN dissection, and that a larger number of dissected regional LNs (≥ 4) is correlated with an additional survival benefit.

These findings may be attributed to several plausible underlying reasons. First, a greater number of dissected LNs can be interpreted as associated with a lower risk of undiscovered positive lymph nodes, which increases the staging accuracy.^{11,21} Some patients with no or only a few dissected nodes actually might have underdiagnosed stage N1 or N2 disease. This phenomenon may explain the more favorable outcomes observed among patients with a large number of dissected LNs and declared node-negative disease. Second, more extensive LN dissection may reflect better technical skill of the surgeon and the adequacy of surgical, pathological, and specialized care provided by the treatment team, and thus would affect treatment outcomes.^{8,22} Previous studies have identified that better organization of the care given by high-volume providers might improve outcomes for patients with early-

stage lung cancer.²³ Although we used a propensity score–matching analysis to simultaneously balance clinical variables (eg, patient location, SEER registry region, surgical procedure) and control for potential confounder bias, it is likely that differences in center volume influence the effects of the extent of dissection on survival. Third, LNs, which filter foreign particles, play an important role in the immune system. The number of negative LNs would reflect the host’s immune response to tumor cells, which also might affect survival.²²

This study has several limitations of note. First, the SEER database was not generated from a randomized controlled trial, and thus inherent bias can be adjusted for but might never be completely eliminated. Although we used rigorous selection procedures, propensity score matching, and a multivariate analysis to balance the covariates among the arms, some potential biases, such as the experiences of surgeons and institutions, remain unknown. The date of procedure was handled with model adjustment and was not included in the propensity score. Second, the SEER database did not provide information about the presence or absence of a ground glass opacity (GGO) component in pulmonary nodules. GGOs are frequently encountered in the lungs, and their presence might correlate with survival outcomes in patients with early-stage NSCLC.^{24,25} According to the eighth TNM classification system, the solid component size, rather than the whole tumor size, is considered a better measure for T staging and prognostic predictions.^{25,26} Third, information regarding surgical technique (video-assisted or open procedures), comorbidities, and pulmonary function is not available from the SEER database, and thus this information could not be included in the propensity score matching. Patients who did not undergo LN dissection tended to have worse comorbidities at

TABLE 4. Univariable and multivariable Cox regression analysis for patients who underwent sublobar resection for stage IA non–small cell lung cancer (≤ 2 cm) with or without lymph node dissection on the propensity score–matched cohort

Variables	Lung cancer–specific survival				Overall survival			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.041 (1.029-1.054)	<.001	1.036 (1.023-1.049)	<.001	1.049 (1.041-1.058)	<.001	1.041 (1.032-1.050)	<.001
Sex		<.001		.001		<.001		<.001
Female	Reference		Reference		Reference		Reference	
Male	1.585 (1.285-1.954)		1.449 (1.172-1.793)		1.571 (1.357-1.818)		1.525 (1.303-1.784)	
Race		.462				.059		.055
White	Reference				Reference		Reference	
Black/other	0.885 (0.639-1.226)				0.796 (0.628-1.008)		0.788 (0.618-1.005)	
Marital status		.103				.007		.097
Married	Reference				Reference		Reference	
Single	0.983 (0.677-1.427)	.929			0.807 (0.612-1.064)	.129	0.837 (0.633-1.108)	.214
Other	1.257 (1.007-1.568)	.043			1.198 (1.027-1.397)	.021	1.127 (0.957-1.326)	.152
Location		.236				.069		.481
Metropolitan	Reference				Reference		Reference	
Nonmetropolitan	1.204 (0.886-1.638)				1.219 (0.985-1.508)		1.081 (0.871-1.340)	
SEER registry region		.154				.610		
Northeast	Reference				Reference			
Midwest	1.468 (1.030-2.091)	.034			1.132 (0.874-1.466)	.347		
South	1.233 (0.912-1.666)	.173			1.127 (0.917-1.385)	.255		
West	1.095 (0.831-1.443)	.521			1.034 (0.857-1.247)	.726		
Year of procedure		.002		.072		<.001		.003
2004-2006	Reference		Reference		Reference		Reference	
2007-2008	0.739 (0.567-0.963)	.025	0.843 (0.646-1.102)	.211	0.764 (0.635-0.920)	.005	0.851 (0.706-1.027)	.093
2009-2010	0.588 (0.432-0.801)	.001	0.679 (0.497-0.926)	.015	0.601 (0.483-0.749)	<.001	0.677 (0.541-0.846)	.001
2011-2012	0.561 (0.387-0.814)	.002	0.667 (0.458-0.972)	.035	0.592 (0.452-0.774)	<.001	0.668 (0.509-0.876)	.004
2013-2014	0.523 (0.267-1.024)	.059	0.617 (0.315-1.209)	.159	0.586 (0.366-0.937)	.026	0.681 (0.425-1.091)	.110
Histology		.001		.359		<.001		.082
Adenocarcinoma	Reference		Reference		Reference		Reference	
Squamous cell carcinoma	1.414 (1.103-1.814)	.006	0.882 (0.679-1.145)	.344	1.862 (1.580-2.194)	<.001	1.222 (1.025-1.458)	.026
Other	1.598 (1.196-2.137)	.002	1.121 (0.826-1.522)	.463	1.481 (1.195-1.836)	<.001	1.070 (0.854-1.342)	.555
Tumor site		.585				.053		.347
Upper	Reference				Reference		Reference	
Middle	0.856 (0.523-1.402)	.536			0.673 (0.466-0.973)	.035	0.761 (0.524-1.105)	.151
Lower	1.088 (0.866-1.366)	.469			0.884 (0.750-1.043)	.143	1.003 (0.846-1.189)	.972
Tumor size	1.064 (1.036-1.093)	<.001	1.045 (1.017-1.074)	.002	1.057 (1.038-1.077)	<.001	1.036 (1.016-1.056)	<.001
Grade		<.001		<.001		<.001		<.001
Grade I	Reference		Reference		Reference		Reference	
Grade II	2.956 (2.095-4.172)	<.001	2.675 (1.881-3.805)	<.001	2.225 (1.783-2.776)	<.001	1.863 (1.480-2.345)	<.001
Grade III-IV	3.198 (2.228-4.591)	<.001	2.773 (1.895-4.056)	<.001	2.451 (1.940-3.097)	<.001	1.951 (1.518-2.507)	<.001
Not determined	1.977 (1.225-3.188)	.005	2.262 (1.394-3.668)	.001	1.768 (1.300-2.405)	<.001	2.022 (1.478-2.766)	<.001
Surgical procedure		.001		.001		<.001		<.001
Wedge resection	Reference		Reference		Reference		Reference	
Segmentectomy	0.568 (0.404-0.800)		0.570 (0.404-0.805)		0.613 (0.488-0.772)		0.609 (0.483-0.768)	
Lymph node dissection		<.001		<.001		<.001		<.001
Yes	Reference		Reference		Reference		Reference	
None	2.239 (1.801-2.783)		2.014 (1.617-2.508)		2.096 (1.803-2.437)		1.892 (1.626-2.203)	

HR, Hazard ratio; CI, confidence interval; SEER, Surveillance, Epidemiology, and End Results.

TABLE 5. Univariable and multivariable Cox regression analysis for patients who underwent sublobar resection for stage IA non–small cell lung cancer (≤ 2 cm) with the dissection of 1 to 3 regional lymph nodes or ≥ 4 regional lymph nodes on the propensity score–matched cohort

Variables	Lung cancer–specific survival				Overall survival			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.024 (1.007-1.040)	.004	1.029 (1.011-1.046)	.001	1.038 (1.026-1.051)	<.001	1.039 (1.026-1.053)	<.001
Sex		<.001		.001		<.001		<.001
Female	Reference		Reference		Reference		Reference	
Male	1.844 (1.372-2.479)		1.652 (1.223-2.232)		1.884 (1.526-2.326)		1.694 (1.367-2.099)	
Race		.748				.448		
White	Reference				Reference			
Black/other	0.928 (0.588-1.464)				0.879 (0.630-1.227)			
Marital status		.661				.101		
Married	Reference				Reference			
Single	0.828 (0.480-1.427)	.479			0.776 (0.518-1.163)	.219		
Other	1.071 (0.782-1.468)	.668			1.174 (0.940-1.465)	.156		
Location		.852				.504		
Metropolitan	Reference				Reference			
Nonmetropolitan	1.046 (0.650-1.685)				1.119 (0.805-1.556)			
SEER registry region		.037		.072		.016		.020
Northeast	Reference		Reference		Reference		Reference	
Midwest	1.230 (0.717-2.112)	.452	1.221 (0.706-2.112)	.475	1.205 (0.824-1.764)	.336	1.159 (0.787-1.705)	.455
South	1.611 (1.085-2.391)	.018	1.535 (1.022-2.304)	.039	1.470 (1.108-1.949)	.007	1.404 (1.050-1.878)	.022
West	0.991 (0.666-1.475)	.964	0.958 (0.640-1.433)	.835	1.003 (0.759-1.324)	.985	0.926 (0.699-1.227)	.593
Year of procedure		.028		.116		<.001		.010
2004-2006	Reference		Reference		Reference		Reference	
2007-2008	0.677 (0.464-0.988)	.043	0.740 (0.505-1.085)	.123	0.648 (0.496-0.846)	.001	0.731 (0.558-0.959)	.024
2009-2010	0.662 (0.434-1.009)	.055	0.754 (0.492-1.157)	.196	0.548 (0.397-0.756)	<.001	0.637 (0.460-0.881)	.006
2011-2012	0.516 (0.313-0.850)	.009	0.589 (0.356-0.974)	.039	0.544 (0.377-0.783)	.001	0.627 (0.434-0.906)	.013
2013-2014	0.345 (0.121-0.988)	.047	0.359 (0.125-1.030)	.057	0.446 (0.226-0.882)	.020	0.483 (0.244-0.956)	.037
Histology		.127		.296		<.001		.308
Adenocarcinoma	Reference		Reference		Reference		Reference	
Squamous cell carcinoma	1.400 (0.983-1.996)	.063	0.738 (0.504-1.082)	.119	2.035 (1.611-2.570)	<.001	1.123 (0.866-1.455)	.381
Other	1.305 (0.855-1.992)	.217	0.885 (0.569-1.375)	.586	1.176 (0.847-1.632)	.333	0.853 (0.606-1.200)	.360
Tumor site		.784				.758		
Upper	Reference				Reference			
Middle	0.763 (0.336-1.733)	.518			0.812 (0.464-1.419)	.464		
Lower	1.029 (0.747-1.417)	.862			0.974 (0.773-1.227)	.823		
Tumor size	1.047 (1.008-1.088)	.018	1.032 (0.992-1.074)	.113	1.065 (1.036-1.095)	<.001	1.042 (1.013-1.072)	.004
Grade		<.001		<.001		<.001		<.001
Grade I	Reference		Reference		Reference		Reference	
Grade II	2.910 (1.821-4.650)	<.001	2.863 (1.770-4.629)	<.001	2.310 (1.694-3.149)	<.001	2.050 (1.484-2.832)	<.001
Grade III-IV	3.328 (2.042-5.425)	<.001	3.192 (1.907-5.344)	<.001	2.534 (1.826-3.515)	<.001	2.128 (1.495-3.028)	<.001
Not determined	1.338 (0.616-2.906)	.462	1.609 (0.733-3.532)	.236	1.210 (0.723-2.025)	.467	1.480 (0.876-2.500)	.143
Surgical procedure		.498		.633		.553		.616
Wedge resection	Reference		Reference		Reference		Reference	
Segmentectomy	0.888 (0.630-1.252)		0.918 (0.647-1.303)		0.929 (0.729-1.184)		0.939 (0.733-1.202)	
Lymph node dissection		.021		.029		.002		.011
≥ 4 regional	Reference		Reference		Reference		Reference	
1-3 regional	1.419 (1.053-1.911)		1.396 (1.034-1.885)		1.386 (1.122-1.713)		1.319 (1.065-1.634)	

HR, Hazard ratio; CI, confidence interval; SEER, Surveillance, Epidemiology, and End Results.

VIDEO 1. Prognostic impact of lymphadenectomy on outcomes of sublobar resection for stage IA non-small cell lung cancer ≤ 2 cm. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)30905-X/fulltext](https://www.jtcvs.org/article/S0022-5223(18)30905-X/fulltext).

baseline, which might have affected the results of our analyses. However, the 30-day mortality rates and deaths from chronic pulmonary disease were not statistically significantly different between the groups. Fourth, although the SEER database records the number of dissected regional LNs, it does not include information about the locations of retrieved LNs, and thus it is impossible to determine the number of dissected nodal stations. As a result, we could not use uniform counting methods to investigate the effects on nodal station. Other limitations included a lack of information on clinical stage in SEER (only pathological stage), variability in pathologist counting of LNs, and inability to discriminate between LN sampling and systematic LN dissection.

In conclusion, our population-based, propensity score-matched analysis shows that when compared with no LN dissection, any LN dissection is associated with better survival outcomes in patients who undergo sublobar resection for stage IA NSCLC tumors ≤ 2 cm. Furthermore, the dissection of a greater number of regional LNs was associated with longer duration of survival. Based on these results, we recommend that increased LN dissection be widely encouraged even for stage IA NSCLC tumors ≤ 2 cm to improve the prognoses of patients who undergo sublobar

resection (Video 1). Despite the use of some advanced statistical methods and strategies, our study has some inherent limitations; more evidence from continuous large-scale registry analyses is needed to verify our results.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: non-small cell lung cancer, sublobar resection, lymphadenectomy, prognosis, survival

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APPENDIX E1. PROGRAM SELECTION CODES FOR SEER DATABASE QUERIES

{Race, Sex, Year Dx, Registry, County.Year of diagnosis}
=

'2004','2005','2006','2007','2008','2009','2010','2011',
'2012','2013','2014'

AND {Site and Morphology.Primary Site} = 341-343

AND {Site and Morphology.Histologic Type ICD-O-
3} = 8000-8576,8940-8950,8980-8981

AND Not{Site and Morphology.Histologic Type ICD-O-
3} = 8041,8045

AND {Multiple Primary Fields.Sequence number} = 'One
primary only'

AND ({Stage - AJCC.Derived AJCC Stage Group, 6th ed
(2004+)} = 'IA'

OR {Stage - AJCC.Derived AJCC Stage Group, 7th ed
(2010+)} = 'IA')

AND {Extent of Disease - CS.CS tumor size (2004+)} =
0-20

AND {Therapy.RX Summ-Surg Prim Site (1998+)} =
21-22

AND {Therapy.Radiation sequence with surgery} = 'No
radiation and/or cancer-directed surgery'

AND {Therapy.RX Summ-Scope Reg LN Sur
(2003+)} = 'None','1 to 3 regional lymph nodes
removed','4 or more regional lymph nodes removed'

AND Not{Therapy.Chemotherapy recode (yes, no/unk)} =
'Yes'

AND {Site and Morphology.Diagnostic Confirmation} =
'Microscopically confirmed'

AND {Cause of Death (COD) and Follow-up.Type of
follow-up expected} = 'Active follow-up'

AND {Cause of Death (COD) and Follow-up.Survival
months} = 0-132

FIGURE E1. X-Tile analysis of survival based on lymph nodes examined from the entire lymph node dissection cohort. A, Lung cancer-specific survival data from patients who underwent sublobar resection for stage IA non-small cell lung cancer (≤ 2 cm). B, Overall survival data from patients who underwent sublobar resection for stage IA non-small cell lung cancer (≤ 2 cm).

TABLE E1. Univariable and multivariable Cox regression analysis for patients who underwent sublobar resection for stage IA non-small cell lung cancer (≤ 2 cm) with or without lymph node dissection on the entire cohort

Variables	Lung cancer-specific survival				Overall survival			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.035 (1.025-1.046)	<.001	1.031 (1.020-1.041)	<.001	1.046 (1.038-1.053)	<.001	1.038 (1.030-1.046)	<.001
Sex		<.001		<.001		<.001		<.001
Female	Reference		Reference		Reference		Reference	
Male	1.624 (1.355-1.947)		1.461 (1.216-1.754)		1.604 (1.412-1.823)		1.518 (1.324-1.740)	
Race		.534				.191		
White	Reference				Reference			
Black/other	0.915 (0.690-1.212)				0.874 (0.715-1.069)			
Marital status		.323				.004		.325
Married	Reference				Reference		Reference	
Single	0.955 (0.692-1.317)	.779			0.867 (0.684-1.099)	.237	0.928 (0.731-1.177)	.536
Other	1.142 (0.942-1.384)	.176			1.203 (1.051-1.375)	.007	1.090 (0.945-1.259)	.237
Location		.379				.062		.430
Metropolitan	Reference				Reference		Reference	
Non-metropolitan	1.130 (0.860-1.485)				1.196 (0.991-1.443)		1.079 (0.893-1.304)	
SEER registry region		.065		.121		.226		
Northeast	Reference		Reference		Reference			
Midwest	1.309 (0.954-1.798)	.096	1.226 (0.891-1.687)	.211	1.087 (0.858-1.376)	.491		
South	1.261 (0.979-1.624)	.073	1.158 (0.895-1.500)	.264	1.196 (1.000-1.431)	.050		
West	0.982 (0.776-1.244)	.882	0.914 (0.720-1.160)	.460	1.042 (0.885-1.227)	.623		
Year of procedure		<.001		.022		<.001		<.001
2004-2006	Reference		Reference		Reference		Reference	
2007-2008	0.802 (0.635-1.012)	.063	0.900 (0.712-1.138)	.379	0.784 (0.666-0.924)	.004	0.871 (0.738-1.028)	.102
2009-2010	0.631 (0.485-0.819)	.001	0.756 (0.580-0.984)	.037	0.571 (0.471-0.691)	<.001	0.676 (0.557-0.820)	<.001
2011-2012	0.527 (0.386-0.718)	<.001	0.677 (0.495-0.926)	.015	0.531 (0.424-0.665)	<.001	0.661 (0.526-0.830)	<.004
2013-2014	0.379 (0.218-0.658)	.001	0.501 (0.288-0.871)	.014	0.451 (0.314-0.649)	<.001	0.603 (0.418-0.869)	.007
Histology		<.001		.423		<.001		.044
Adenocarcinoma	Reference		Reference		Reference		Reference	
Squamous cell carcinoma	1.470 (1.189-1.817)	<.001	0.885 (0.707-1.108)	.287	1.851 (1.604-2.135)	<.001	1.217 (1.043-1.420)	.012
Other	1.483 (1.146-1.918)	.003	1.055 (0.805-1.384)	.696	1.443 (1.195-1.743)	<.001	1.100 (0.903-1.341)	.345
Tumor site		.885				.073		.232
Upper	Reference				Reference		Reference	
Middle	0.902 (0.600-1.357)	.621			0.698 (0.509-0.958)	.026	0.778 (0.566-1.070)	.122
Lower	0.993 (0.814-1.211)	.944			0.942 (0.818-1.084)	.403	1.037 (0.897-1.198)	.623
Tumor size	1.059 (1.036-1.084)	<.001	1.041 (1.017-1.066)	.001	1.051 (1.035-1.068)	<.001	1.031 (1.015-1.048)	<.001
Grade		<.001		<.001		<.001		<.001
Grade I	Reference		Reference		Reference		Reference	
Grade II	3.233 (2.367-4.417)	<.001	2.877 (2.093-3.955)	<.001	2.206 (1.814-2.683)	<.001	1.819 (1.486-2.228)	<.001
Grade III-IV	3.705 (2.680-5.123)	<.001	3.204 (2.280-4.503)	<.001	2.558 (2.083-3.141)	<.001	2.022 (1.622-2.521)	<.001
Not determined	2.111 (1.399-3.186)	<.001	2.163 (1.426-3.281)	<.001	1.783 (1.375-2.312)	<.001	1.816 (1.394-2.366)	<.001
Surgical procedure		.023		.159		.003		.088
Wedge resection	Reference		Reference		Reference		Reference	
Segmentectomy	0.751 (0.586-0.961)		0.834 (0.648-1.074)		0.768 (0.647-0.913)		0.858 (0.719-1.023)	
Lymph node dissection		<.001		<.001		<.001		<.001
Yes	Reference		Reference		Reference		Reference	
None	1.623 (1.352-1.948)		1.432 (1.185-1.730)		1.686 (1.482-1.918)		1.438 (1.258-1.644)	

HR, Hazard ratio; CI, confidence interval; SEER, Surveillance, Epidemiology, and End Results.

TABLE E2. Univariable and multivariable Cox regression analysis for patients who underwent sublobar resection for stage IA non–small cell lung cancer (≤ 2 cm) with the dissection of 1 to 3 regional lymph nodes or ≥ 4 regional lymph nodes on the entire cohort

Variables	Lung cancer–specific survival				Overall survival			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.028 (1.013-1.044)	<.001	1.029 (1.014-1.045)	<.001	1.040 (1.029-1.052)	<.001	1.037 (1.026-1.049)	<.001
Sex		<.001		.001		<.001		<.001
Female	Reference		Reference		Reference		Reference	
Male	1.888 (1.436-2.483)		1.639 (1.240-2.165)		1.930 (1.588-2.345)		1.748 (1.422-2.147)	
Race		.501				.398		
White	Reference				Reference			
Black/other	0.864 (0.564-1.323)				0.878 (0.650-1.187)			
Marital status		.359				.051		.310
Married	Reference				Reference		Reference	
Single	0.829 (0.497-1.382)	.472			0.798 (0.550-1.157)	.234	0.989 (0.677-1.444)	.953
Other	1.164 (0.872-1.556)	.303			1.206 (0.982-1.480)	.074	1.178 (0.948-1.462)	.139
Location		.547				.129		
Metropolitan	Reference				Reference			
Nonmetropolitan	1.140 (0.745-1.745)				1.253 (0.936-1.676)			
SEER registry region		.024		.088		.006		.022
Northeast	Reference		Reference		Reference		Reference	
Midwest	1.156 (0.704-1.899)	.566	1.061 (0.642-1.753)	.818	1.133 (0.795-1.613)	.490	1.031 (0.721-1.476)	.866
South	1.501 (1.048-2.148)	.027	1.386 (0.958-2.006)	.084	1.425 (1.102-1.844)	.007	1.331 (1.021-1.737)	.035
West	0.898 (0.623-1.293)	.563	0.884 (0.611-1.279)	.513	0.948 (0.734-1.224)	.680	0.900 (0.694-1.166)	.424
Year of procedure		.029		.169		<.001		.006
2004-2006	Reference		Reference		Reference		Reference	
2007-2008	0.692 (0.484-0.991)	.044	0.759 (0.529-1.091)	.136	0.681 (0.531-0.875)	.003	0.773 (0.600-0.997)	.048
2009-2010	0.688 (0.466-1.015)	.060	0.804 (0.542-1.191)	.276	0.559 (0.416-0.750)	<.001	0.664 (0.493-0.894)	.007
2011-2012	0.547 (0.347-0.862)	.009	0.635 (0.402-1.004)	.052	0.512 (0.365-0.717)	.001	0.601 (0.428-0.844)	.003
2013-2014	0.402 (0.177-0.914)	.030	0.460 (0.202-1.047)	.064	0.434 (0.250-0.754)	.003	0.518 (0.298-0.902)	.020
Histology		.014		.562		<.001		.256
Adenocarcinoma	Reference		Reference		Reference		Reference	
Squamous cell carcinoma	1.589 (1.156-2.183)	.004	0.835 (0.593-1.177)	.304	1.984 (1.599-2.463)	<.001	1.121 (0.883-1.425)	.348
Other	1.321 (0.889-1.962)	.168	0.877 (0.579-1.328)	.534	1.193 (0.884-1.610)	.249	0.856 (0.624-1.174)	.334
Tumor site		.517				.340		
Upper	Reference				Reference			
Middle	0.622 (0.274-1.409)	.255			0.659 (0.378-1.150)	.142		
Lower	1.003 (0.746-1.349)	.984			0.988 (0.799-1.221)	.909		
Tumor size	1.058 (1.022-1.097)	.002	1.039 (1.002-1.077)	.039	1.071 (1.044-1.098)	<.001	1.044 (1.017-1.072)	.001
Grade		<.001		<.001		<.001		<.001
Grade I	Reference		Reference		Reference		Reference	
Grade II	2.857 (1.839-4.439)	<.001	2.688 (1.711-4.222)	<.001	2.090 (1.574-2.775)	<.001	1.784 (1.326-2.400)	<.001
Grade III-IV	3.595 (2.284-5.657)	<.001	3.288 (2.034-5.316)	<.001	2.491 (1.852-3.351)	<.001	2.054 (1.489-2.834)	<.001
Not determined	1.427 (0.702-2.901)	.325	1.709 (0.833-3.508)	.144	1.275 (0.809-2.010)	.295	1.573 (0.988-2.502)	.056
Surgical procedure		.230		.407		.459		.721
Wedge resection	Reference		Reference		Reference		Reference	
Segmentectomy	0.819 (0.591-1.135)		0.869 (0.624-1.211)		0.918 (0.733-1.150)		0.959 (0.763-1.206)	
Lymph node dissection		.005		.033		<.001		.018
≥ 4 more regional	Reference		Reference		Reference		Reference	
1-3 regional	1.494 (1.131-1.974)		1.359 (1.024-1.803)		1.432 (1.176-1.744)		1.275 (1.043-1.558)	

HR, Hazard ratio; CI, confidence interval; SEER, Surveillance, Epidemiology, and End Results.