9-30-2022

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General Thoracic and Cardiovascular Surgery
https://doi.org/10.1007/s11748-022-01876-6

ORIGINAL ARTICLE

Lymph node dissections and survival in sublobar resection of non-small cell lung cancer ≤ 20 mm

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Received: 1 January 2022 / Accepted: 19 September 2022

Abstract

Background A randomized trial of lobectomy versus segmentectomy for small-sized (≤ 20 mm) non-small cell lung cancer (NSCLC) showed that patients who had undergone segmentectomy had a significantly longer overall survival (OS) than those who had lobectomy. More attention is needed regarding the required extent of thoracic lymphadenectomy in patients with small-sized NSCLC who undergo sublobar resection.

Methods The National Cancer Database was queried for patients with clinically node-negative NSCLC ≤ 20 mm who had undergone sublobar resection between 2004 and 2017. OS of NSCLC patients by the number of lymph node dissections (LNDs) was analyzed using log-rank tests and Cox proportional hazards model. The cutoff value of the LNDs was set to 10 according to the Commission on Cancer's recommendation.

Results This study included 4379 segmentectomy and 23,138 wedge resection cases. The sequential improvement in the HRs by the number of LNDs was evident, and the HR was the lowest if the number of LNDs exceeded 10. Patients with ≤ 9 LNDs had a significantly shorter OS than those with ≥ 10 LNDs (hazard ratio [HR] 1.50, 95% confidence interval [CI] 1.40–1.61, $P < 0.0001$). Multivariable analysis revealed that performing ≤ 9 LNDs was an independent factor for predicting OS (HR for death: 1.34, 95% CI 1.24–1.44, $P < 0.0001$). These results remained significant in subgroup analyses by the type of sublobar resection (segmentectomy, wedge resection).

Conclusions Performing ≥ 10 LNDs has a prognostic role in patients with small-sized NSCLC even if the resection is sublobar.

Keywords Lung cancer · Surgery · Prognosis · Lung · Lymph node dissection

Introduction

Lung cancer is the leading cause of cancer death [1]. The majority of lung cancers are classified as non-small cell lung cancer (NSCLC). Lobectomy has been the historical standard therapy for NSCLC patients with clinical IA disease. For NSCLC patients who do not tolerate lobectomy, however, sublobar resection is one of the treatment options [2]. A recent Japanese phase III randomized trial of lobectomy versus segmentectomy for small-sized (≤ 20 mm) peripheral NSCLC showed that patients who had undergone segmentectomy had a significantly longer overall survival (OS) in comparison with those who had lobectomy [3]. The number of early-stage NSCLC patients who are indicated for sublobar resection is expected to increase, and thus more attention is warranted regarding the required extent of thoracic lymphadenectomy in this population.

This study was presented at the 74th Annual Scientific Meeting of The Japanese Association for Thoracic Surgery (LOP4-2) and recommended for submission.

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Published online: 30 September 2022

In patients with early-stage NSCLC who undergo curative lung resection, the required extent of thoracic lymphadenectomy has been debated [4–8]. The American College of Surgery Oncology Group (ACOSOG) Z0030 randomized trial of complete systemic lymph node (LN) dissection vs. mediastinal LN sampling revealed that complete removal of the LNs via systemic LN dissection did not improve OS in patients with early-stage NSCLC if systemic sampling of the mediastinal and hilar LN was negative [4]. In contrast, several previous studies reported that systemic LN dissection provided a longer disease-free survival and OS than mediastinal LN sampling in patients with early-stage NSCLC [5, 6]. Based on the data of these previous studies, the Commission on Cancer (CoC) recommends that at least ten LNs (hilar and mediastinal LNs) should be pathologically examined for resected early-stage NSCLC [9]. However, with regard to patients with small-sized NSCLC who undergo sublobar resection, the necessary extent of thoracic lymphadenectomy has not been comprehensively investigated. The CoC and National Comprehensive Cancer Network (NCCN) have no recommendations for this. Thus, the aim of the current study is to examine the prognostic significance of the number of LN dissections (LNDs) in patients with small-sized (≤ 20 mm) NSCLC who undergo sublobar resection using data from National Cancer Database (NCDB).

Materials and methods

NCDB

The NCDB is a joint project between the CoC of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC NCDB are the source of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors. The data are considered as hospital based rather than population based. Based on the use of only de-identified data, the study was exempted by the Parkview institutional review board. The study flow diagram of case eligibility is shown in Supplemental Fig. 1.

Statistical analysis

Kaplan–Meier curves by the number of LNDs were compared using the log-rank test. The number of LNDs was analyzed according to two schemata. In the first schema, they were classified into two groups (≥ 10, ≤ 9) according to the CoC's recommendation [9]. In the second schema, they were classified into six groups (0, 1–2, 3–4, 5–6, 7–9, ≥ 10). The associations between the number of LNDs and clinical demographics were assessed by Chi-square Fisher's two-sided exact test. OS was defined as the time (months) from diagnosis to death from any cause. Univariate and multivariable Cox proportional hazards analyses were performed using JMP® 14.0 (SAS Institute Inc., Cary, NC, USA). A two tailed, $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Patient characteristics ($n = 27{,}517$) are summarized in Supplemental Table 1. In total, 4379 (16%) and 23,138 (84%) patients received segmentectomy and wedge resection, respectively. Of the patients who had segmentectomy, 3557 (81%) and 822 (19%) of 4379 patients had ≤ 9 and ≥ 10 LNDs, respectively. In patients who underwent wedge resection, 21,567 (93%) and 1571 (7%) of 23,138 patients had ≤ 9 and ≥ 10 LNDs, respectively. Patients who had segmentectomy were significantly associated with female sex ($P < 0.0001$), academic institution ($P < 0.0001$), and late years of diagnosis ($P < 0.0001$), tumor-bearing lobe other than upper lobe ($P < 0.0001$), laterality other than right ($P < 0.0001$), tumor size ≥ 10 mm ($P < 0.0001$), early pathologic T stage ($P < 0.0001$), pathologic N1–2 stage ($P = 0.0003$), negative resected margin status ($P < 0.0001$), without or unknown status of adjuvant chemotherapy ($P = 0.0003$), without or unknown status of adjuvant chest radiation therapy ($P < 0.0001$), and ≤ 9 LNDs ($P < 0.0001$). Regarding tumor size and pathologic T stage, the fact that segmentectomy was associated with larger tumor size and earlier pathologic T stage appears to be contradictory. This may be because patients who had peripheral small tumors tended to have wedge resection, and peripheral tumors can more frequently have pleural invasion (T2) than center-located tumors. In addition, adjuvant chemotherapy or chest radiation therapy was significantly more frequently performed in patients who underwent wedge resection than in those who underwent segmentectomy. This may be because wedge resection is associated with less number of patients with negative resected margin status than those who had segmentectomy, and those who had positive resected margin status need adjuvant chemotherapy or chest radiation.

Relationship between clinical factors of patients with small-sized NSCLC and the number of the LNDs by surgical procedures

The associations between clinical factors of patients with small-sized NSCLC and the number of the LNDs (≤ 9 vs. ≥ 10) according to the surgical procedures (segmentectomy vs. wedge resection) are shown in Table 1. In patients who underwent sublobar resection, patients

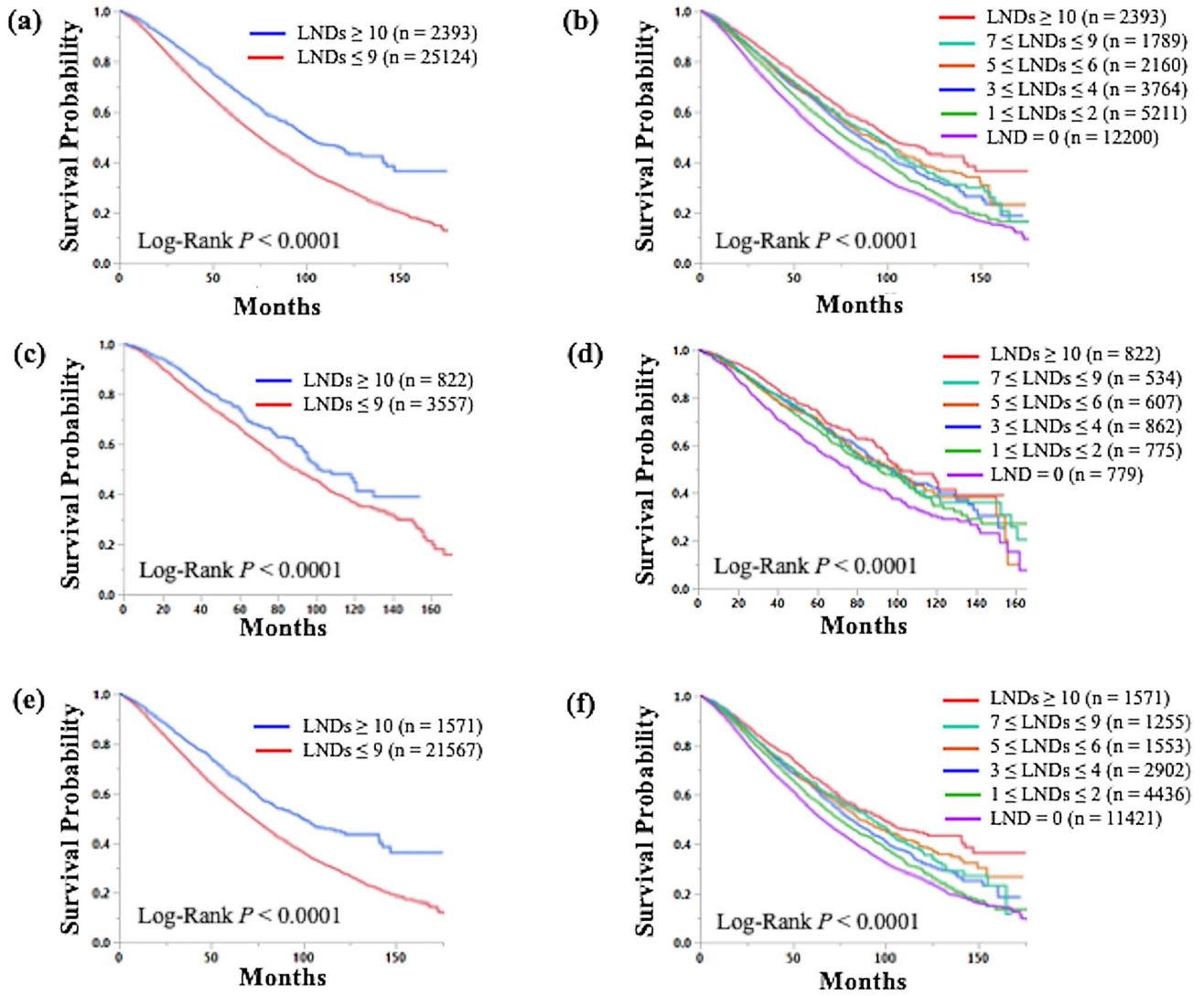

Fig. 1 The Kaplan–Meier curves of overall survival in patients with small-sized (≤20 mm) non-small cell lung cancer who underwent **a**, **b** sublobar resection, **c**, **d** segmentectomy, **e**, **f** wedge resection by the number of lymph node dissections (**a**, **c**, **e**: ≥10 vs. ≤9, **b**, **d**, **f**: ≥10 vs. 7–9 vs. 5–6 vs. 3–4 vs. 1–2 vs. 0) are shown. LND; lymph node dissection

with ≥10 LNDs were significantly associated with younger age ($P < 0.0001$), other races ($P = 0.0046$), academic institution ($P < 0.0001$), low Charlson–Deyo score ($P = 0.0006$), late years of diagnosis ($P < 0.0001$), larger tumor size ($P < 0.0001$), early pathologic T stage ($P < 0.0001$), advanced pathologic N stage ($P < 0.0001$), negative resected margin status ($P < 0.0001$), and without or unknown status of adjuvant chest radiation therapy ($P < 0.0001$). In patients who underwent segmentectomy, patients with ≥10 LNDs were significantly associated with male sex ($P = 0.0148$), institution other than academic ($P < 0.0001$), low Charlson–Deyo score ($P = 0.0366$), late years of diagnosis ($P < 0.0001$), early pathologic T stage ($P = 0.0014$), advanced pathologic N stage ($P = 0.0060$), and negative resected margin status ($P = 0.0437$). In patients who underwent wedge resection, patients with ≥10 LNDs were significantly associated with younger age ($P < 0.0001$), other races ($P = 0.0011$), academic institution ($P < 0.0001$), low Charlson–Deyo score ($P = 0.0127$), late years of diagnosis ($P < 0.0001$), right laterality ($P < 0.0001$), larger tumor size ($P < 0.0001$), early pathologic T stage ($P < 0.0001$), advanced pathologic N stage ($P < 0.0001$), negative resected margin status ($P < 0.0001$), adjuvant chemotherapy ($P = 0.0143$), and without or unknown status of adjuvant chest radiation therapy ($P < 0.0001$). The reasons why the LN dissection with ten or more LNs was performed may be mainly because such patients were young and the their Charlson–Deyo score was low, indicating a promising long-term prognosis.

Table 1 Clinical characteristics of patients with small-sized non-small cell lung cancer patients with ≥ 10 and those with ≤ 9 lymph nodes dissected according to the surgical procedures ($n = 27,517$)

Factors	Sublobar resection ($n = 27,517$)			Segmentectomy ($n = 4379$)			Wedge resection ($n = 23,138$)		
	Number of lymph nodes dissected		*P* value	Number of lymph nodes dissected		*P* value	Number of lymph nodes dissected		*P* value
	≤ 9 ($n = 25,124$)	≥ 10 ($n = 2393$)		≤ 9 ($n = 3557$)	≥ 10 ($n = 822$)		≤ 9 ($n = 21,567$)	≥ 10 ($n = 1571$)	
Age									
≥ 70	13,090 (52%)	1124 (47%)	< 0.0001	1717 (48%)	405 (49%)	0.6149	11,373 (53%)	719 (46%)	< 0.0001
< 70	12,034 (48%)	1269 (53%)		1840 (52%)	417 (51%)		10,194 (47%)	852 (54%)	
Sex									
Male	10,210 (41%)	1002 (42%)	0.2486	1304 (39%)	339 (41%)	0.0148	8906 (38%)	663 (42%)	0.4903
Female	14,914 (59%)	1391 (58%)		2253 (61%)	483 (59%)		12,661 (62%)	908 (58%)	
Race									
Whites	22,544 (90%)	2102 (88%)	0.0046	3189 (90%)	734 (89%)	0.7516	19,355 (90%)	1368 (87%)	0.0011
Others	2580 (10%)	291 (12%)		368 (10%)	88 (11%)		2212 (10%)	203 (13%)	
Institution									
Others	15036 (60%)	1305 (55%)	< 0.0001	2058 (61%)	551 (67%)	< 0.0001	12,978 (60%)	754 (48%)	< 0.0001
Academic	10088 (40%)	1088 (45%)		1499 (39%)	271 (33%)		8589 (40%)	817 (52%)	
Charlson–Deyo score									
≥ 2	4657 (19%)	376 (16%)	0.0006	642 (18%)	123 (15%)	0.0366	4015 (19%)	253 (16%)	0.0127
0–1	20467 (81%)	2017 (84%)		2915 (82%)	699 (85%)		17,552 (81%)	1318 (84%)	
Year of diagnosis									
2004–2010	8431 (34%)	578 (24%)	< 0.0001	1057 (30%)	155 (19%)	< 0.0001	7374 (34%)	423 (27%)	< 0.0001
2011–2017	16,693 (66%)	1815 (76%)		2500 (70%)	667 (81%)		14,193 (66%)	1148 (73%)	
Tumor-bearing lobe									
Upper	15,967 (64%)	1495 (62%)	0.2965	2040 (57%)	455 (55%)	0.3096	13,927 (65%)	1040 (66%)	0.1989
Others	9157 (36%)	898 (38%)		1517 (43%)	367 (45%)		7640 (35%)	531 (34%)	
Laterality									
Right	13,261 (53%)	1313 (55%)	0.0512	1665 (47%)	366 (45%)	0.2445	11,596 (54%)	947 (60%)	< 0.0001
Others	11,863 (47%)	1080 (45%)		1892 (53%)	456 (55%)		9971 (46%)	624 (40%)	
Tumor size									
≥ 10 mm	21,276 (85%)	2122 (89%)	< 0.0001	3157 (89%)	732 (89%)	0.8540	18,119 (84%)	1390 (88%)	< 0.0001
< 10 mm	3848 (15%)	271 (11%)		400 (11%)	90 (11%)		3448 (16%)	181 (12%)	
Histology									
Others	9605 (38%)	881 (37%)	0.1791	1334 (38%)	312 (38%)	0.8107	8271 (38%)	569 (36%)	0.0955
Adenocarcinoma	15,519 (62%)	1512 (63%)		2223 (62%)	510 (62%)		13,296 (62%)	1002 (64%)	
Pathologic T stage									
T2–4	7202 (29%)	529 (22%)	< 0.0001	840 (24%)	152 (18%)	0.0014	6362 (29%)	377 (24%)	< 0.0001
T1	17,922 (71%)	1864 (78%)		2717 (76%)	670 (82%)		15,205 (71%)	1194 (76%)	
Pathologic N stage									
N1–2	399 (2%)	127 (5%)	< 0.0001	85 (2%)	35 (4%)	0.0060	314 (1%)	92 (6%)	< 0.0001
N0	24,698 (98%)	2266 (95%)		3472 (98%)	787 (96%)		21,226 (99%)	1479 (94%)	
Resected margin status									
Other	1374 (5%)	69 (3%)	< 0.0001	106 (3%)	14 (2%)	0.0437	1268 (6%)	55 (4%)	< 0.0001
Negative	23,750 (95%)	2324 (97%)		3451 (97%)	808 (98%)		20,299 (94%)	1516 (96%)	
Adjuvant chemotherapy									
Yes	1618 (6%)	176 (7%)	0.0909	186 (5%)	46 (6%)	0.0592	1432 (7%)	130 (8%)	0.0143
No/unknown	23,506 (94%)	2217 (93%)		3371 (95%)	776 (94%)		20,135 (93%)	1441 (92%)	

Table 1 (continued)

Factors	Sublobar resection ($n=27,517$)			Segmentectomy ($n=4379$)			Wedge resection ($n=23,138$)		
	Number of lymph nodes dissected		*P* value	Number of lymph nodes dissected		*P* value	Number of lymph nodes dissected		*P* value
	≤9 ($n=25,124$)	≥10 ($n=2393$)		≤9 ($n=3557$)	≥10 ($n=822$)		≤9 ($n=21,567$)	≥10 ($n=1571$)	
Adjuvant chest radiation									
Yes	1713 (7%)	93 (4%)	<0.0001	132 (4%)	32 (4%)	0.8384	1581 (7%)	61 (4%)	<0.0001
No/unknown	23,411 (93%)	2300 (96%)		3425 (96%)	790 (96%)		19,986 (93%)	1510 (96%)	

Univariate survival analyses in patients with small-sized NSCLC who underwent sublobar resection according to the number of LNDs

The Kaplan–Meier curves comparing OS according to the number of LNDs in patients with small-sized NSCLC who underwent sublobar resection are shown in Fig. 1. As shown in Fig. 1a, patients with ≤9 LNDs had a significantly shorter OS than those with ≥10 LNDs (median OS: 89.4 vs. 120.2 months, hazard ratios [HR] for death: 1.50, 95% confidence interval [CI] 1.40–1.61, $P<0.0001$). The OS was significantly influenced by the number of LNDs (Fig. 1b, $P<0.0001$). The subgroup analyses according to surgical procedure (segmentectomy vs. wedge resection) were performed. In patients with small-sized NSCLC who underwent segmentectomy, patients with ≤9 LNDs had a significantly shorter OS than those with ≥10 LNDs (Fig. 1c, median OS: 90.0 vs. 102.8 months, HR for death 1.32, 95% CI 1.15–1.52, $P<0.0001$). The OS was significantly affected by the number of LNDs (Fig. 1d, $P<0.0001$). Similarly, as shown in Fig. 1e, patients with small-sized NSCLC who had wedge resection and ≤9 LNDs had a significantly shorter OS than those with ≥10 LNDs (median OS: 72.6 vs. 99.3 months, HR for death: 1.47, 95% CI 1.35–1.60, $P<0.0001$). The OS was significant by the number of LNDs (Fig. 1f, $P<0.0001$).

Figure 2a. summarizes the HRs for death by the number of LNDs who underwent sublobar resection of small-sized NSCLC. Sequential improvement in the HRs was observed, and the HR was the lowest if the number of LNDs exceeded 10. These findings were similar in subgroup analyses according to the surgical procedures (segmentectomy; Fig. 2b, wedge resection; Fig. 2c).

Univariate and multivariable analyses of OS in small-sized NSCLC patients who underwent sublobar resection

The results of univariate and multivariable analyses for OS in small-sized NSCLC patients who underwent sublobar resection are shown in Table 2. Univariate analysis showed that older age ($P<0.0001$), male sex ($P<0.0001$), white race ($P<0.0001$), non-academic institution ($P<0.0001$), high Charlson–Deyo score ($P<0.0001$), early year of diagnosis ($P<0.0001$), tumor-bearing lobe in upper lobe ($P=0.0451$), larger tumor size ($P<0.0001$), wedge resection ($P<0.0001$), non-adenocarcinoma histology ($P<0.0001$), pathologic T2–4 stage ($P<0.0001$), pathologic N1–2 stage ($P<0.0001$), positive/unknown status of resected margin ($P<0.0001$), adjuvant chemotherapy ($P<0.0001$), and nine or fewer number LNDs (HR for death: 1.50, 95% CI 1.40–1.61, $P=0.0115$) were significantly associated with worse OS. In multivariable analysis, older age ($P<0.0001$), male sex ($P<0.0001$), white race ($P=0.0002$), non-academic institution ($P<0.0001$), high Charlson–Deyo score ($P<0.0001$), early year of diagnosis ($P=0.0002$), tumor size in upper lobe ($P<0.0001$), wedge resection ($P<0.0001$), non-adenocarcinoma histology ($P<0.0001$), pathologic T2–4 stage ($P<0.0001$), pathologic N1–2 stage ($P<0.0001$), positive/unknown status of resected margin ($P<0.0001$), adjuvant chemotherapy ($P=0.0010$), adjuvant chest radiation ($P<0.0001$), and nine or fewer number LNDs (HR for death: 1.34, 95% CI 1.24–1.44, $P<0.0001$) were independent factors for predicting OS. In subgroup analyses of the patients who had segmentectomy and wedge resection, nine or fewer number LNDs was an independent factor for predicting worse OS (HR for death 1.27, 95% CI 1.10–1.46, $P=0.0010$ and HR for death 1.36, 95% CI 1.25–1.49, $P<0.0001$; Supplemental Tables 2 and 3, respectively).

Discussion

The standard therapy for early-stage lung cancer is lobectomy and thoracic lymphadenectomy [10], and the CoC recommends that at least ten LNs should be pathologically examined for resected early-stage NSCLC [9]. However, whether the recommendations can be applied to patients with small-sized NSCLC who undergo sublobar resection had been unclear. Given that a Japanese phase III randomized trial of lobectomy versus segmentectomy for small-sized (≤20 mm) peripheral NSCLC revealed that patients who

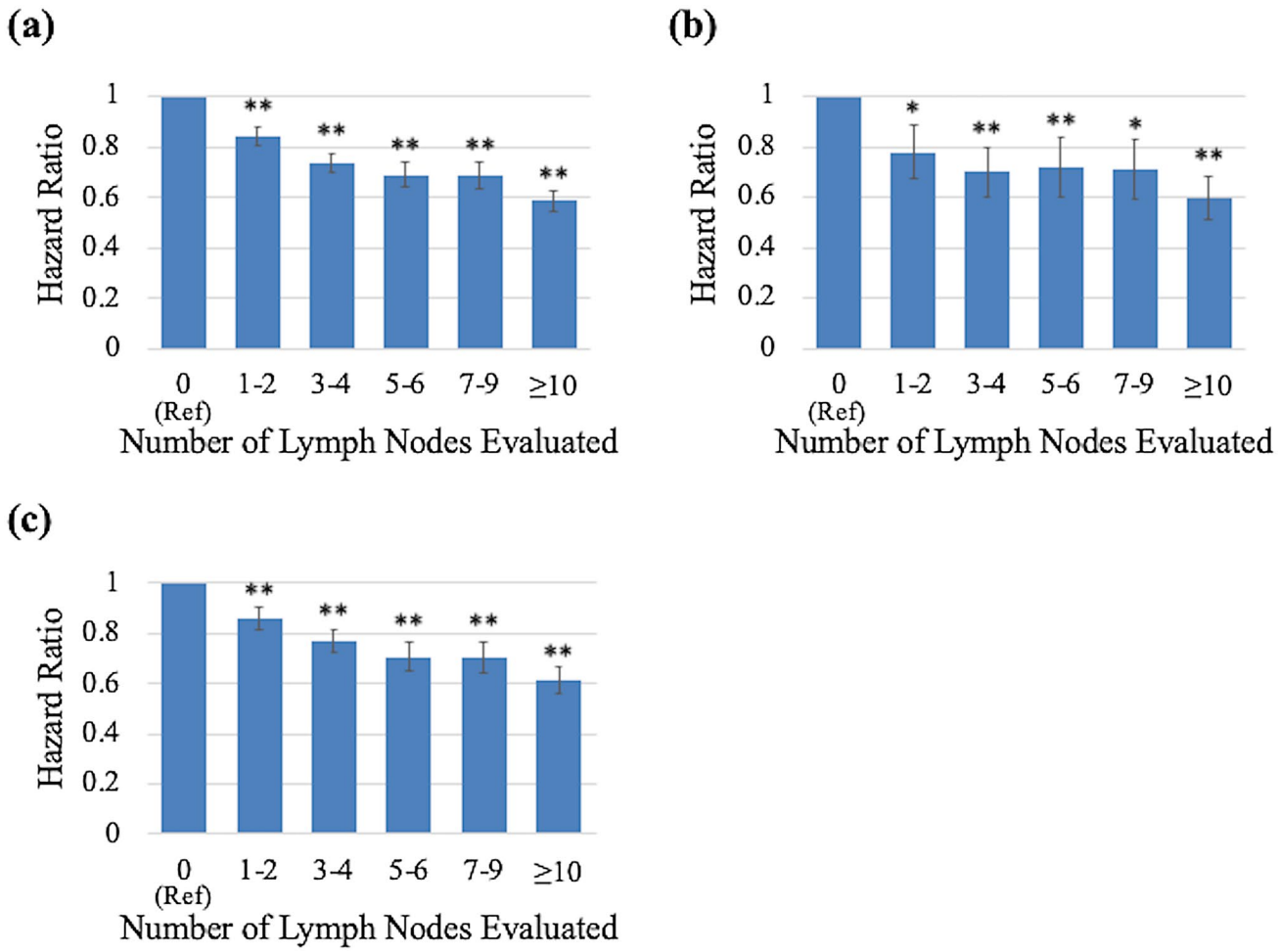

Fig. 2 Hazard ratios for death by the number of lymph nodes evaluated who undergo **a** sublobar resection, **b** segmentectomy, and **c** wedge resection are shown. *$P < 0.05$; **$P < 0.001$

had undergone segmentectomy had a significantly longer OS than those who had lobectomy [3], the required extent of thoracic lymphadenectomy in this population would be of interest to thoracic surgeons. In the current study, we showed the prognostic and therapeutic significance for performing ≥ 10 LNDs in patients with small-sized (≤ 20 mm) NSCLC who undergo sublobar resection. Regarding methodology of the lymph node examination, the NCDB distinguishes lymph node sampling from LNDs by code numbers. In this study, LNDs data was used instead of lymph node sampling. Therefore, we recommend performing ≥ 10 LNDs. Moreover, the subgroup analyses confirmed the survival benefit from ≥ 10 LNDs in both patients who had segmentectomy and those who had wedge resection. The cutoff value of the number of LNDs was determined with reference to CoC recommendations [9]. In addition, our analyses of the HRs for death by the number of LNDs who underwent sublobar resection also showed that the HR was the lowest when the number of LNDs exceeded ten.

The reason why patients with ≥ 10 LNDs had a significantly longer OS than those with fewer LNDs could be explained by their therapeutic and diagnostic roles. Regarding the therapeutic role, more LNDs might contribute to the removal of the potential metastatic LNs. In patients with NSCLC ≤ 20 mm, the frequency of hilar and/or mediastinal lymph node metastases has been reported to be 10–15% [11]. In addition, the ACOSOG Z0030 randomized trial showed that "unexpected" LN metastases were observed in 4% of patients who underwent systemic LN dissection [5]. As shown in Table 1, our analyses of the clinical characteristics showed a significantly higher rate of pathological nodal involvement in patients with ≥ 10 LNDs compared with those with ≤ 9 LNDs, regardless of the surgical procedures (segmentectomy, wedge resection). Sufficient dissecting of LNs may eliminate microscopic nodal metastases, resulting in higher rate of remission. With regard to the diagnostic role, checking LNs in the middle of surgery may reveal microscopic nodal involvement, leading to more accurate

Table 2 Univariate and multivariable analyses of overall survival in patients with small-sized non-small cell lung cancer ≤ 20 mm who underwent sublobar resection ($n = 27,517$)

Factors	Univariate HR (95% CI) *P* value	Multivariable HR (95% CI) *P* value
Age		
≥ 70	1.62 (1.57–1.68)	1.53 (1.48–1.59)
< 70 (Ref)	< 0.0001	< 0.0001
Sex		
Male	1.45 (1.40–1.50)	1.38 (1.33–1.42)
Female (Ref)	< 0.0001	< 0.0001
Race		
Whites	1.22 (1.15–1.29)	1.12 (1.05–1.19)
Others (Ref)	< 0.0001	0.0002
Institution		
Others	1.23 (1.19–1.28)	1.11 (1.07–1.15)
Academic (Ref)	< 0.0001	< 0.0001
Charlson–Deyo score		
≥ 2	1.43 (1.38–1.49)	1.31 (1.26–1.37)
0–1 (Ref)	< 0.0001	< 0.0001
Year of diagnosis		
2004–2010	1.24 (1.19–1.29)	1.07 (1.03–1.12)
2011–2017 (Ref)	< 0.0001	0.0002
Tumor-bearing lobe		
Upper	1.04 (1.00–1.08)	1.00 (0.96–1.04)
Other (Ref)	0.0451	0.9709
Laterality		
Others	1.03 (0.99–1.07)	1.04 (0.99–1.07)
Right (Ref)	0.1006	0.0502
Tumor size		
≥ 10 mm	1.30 (1.24–1.37)	1.16 (1.10–1.23)
< 10 mm (Ref)	< 0.0001	< 0.0001
Surgical procedure		
Wedge	1.34 (1.28–1.41)	1.23 (1.17–1.30)
Segmentectomy (Ref)	< 0.0001	< 0.0001
Histology		
Others	1.30 (1.26–1.35)	1.20 (1.16–1.25)
Adenocarcinoma (Ref)	< 0.0001	< 0.0001
Pathologic T stage		
T2–4	1.64 (1.58–1.70)	1.50 (1.44–1.55)
T1 (Ref)	< 0.0001	< 0.0001
Pathologic N stage		
N1–2	1.36 (1.21–1.53)	1.38 (1.21–1.56)
N0 (Ref)	< 0.0001	< 0.0001
Resected margin status		
Other	1.67 (1.56–1.79)	1.36 (1.27–1.46)
Negative (Ref)	< 0.0001	< 0.0001
Adjuvant chemotherapy		
Yes	1.29 (1.21–1.37)	1.13 (1.05–1.21)
No/unknown (Ref)	< 0.0001	0.0010
Adjuvant chest radiation		
Yes	1.46 (1.37–1.55)	1.22 (1.15–1.30)
No/unknown (Ref)	0.8022	< 0.0001
Number of lymph nodes dissected		
≤ 9	1.50 (1.40–1.61)	1.34 (1.24–1.44)
≥ 10 (Ref)	0.0115	< 0.0001

Ref reference

staging. NCCN recommends chemotherapy for NSCLC patients with pathological hilar LN metastasis (N1) and chemotherapy for those with mediastinal LN metastasis (N2) [2, 12]. Consistently, our analyses showed that patients with ≥ 10 LNDs had a higher rate of adjuvant chemotherapy than those with ≤ 9 LNDs. Thus, NSCLC patients with more LNDs may be more accurately diagnosed and appropriately assigned to receive adjuvant therapy or follow-up alone, resulting in improved survival.

The multivariate analysis of OS showed that administration of adjuvant chemotherapy and/or chest radiation therapy was associated with shorter OS. This may be because the analyzed cohort included not only patients who were indicated for adjuvant therapy, but also those who were not. This may also be because patients who were eligible for adjuvant therapy but did not receive it were associated with higher risks, such as interstitial pneumonia and older age.

Although clinical significance of lymph node dissection in patients with resectable NSCLC has been well investigated, previous studies have analyzed NSCLC patients with various sized tumors and those who had undergone lobectomy or sublobar resection [4–8]. Based on the results from the controlled randomized trial of lobectomy versus segmentectomy for small-sized NSCLC, the patients with NSCLC within 20 mm should be recognized as a distinct population who would benefit from segmentectomy [13, 14]. In that population specifically, survival benefit from lymph node dissection has not been well clarified. A previous study investigating survival of patients with stage I NSCLC (< 20 mm) who undergo sublobar resection using the Surveillance, Epidemiology, and End Results database showed the similar results with our findings [15]. In that study, the number of LNDs was significantly associated with survival after adjusting for several covariables, although the authors did not analyze the comorbidity, which is important in deciding the extent of LND, and the sample size investigated (715 segmentectomy and 3201 wedge resection cases) was much smaller than ours (4379 segmentectomy and 23,138 wedge resection cases) [15]. The authors did not set the cutoff value of LNDs, but we adopted ten LNDs as the

cutoff value according to the CoC's recommendation. Thus, our study elucidated that the CoC's recommendation is applicable to patients with small-sized NSCLC even if the surgical procedure is sublobar.

There are several limitations in association with our study. First, this was a retrospective study in association with biases from surgeon's decision and/or patients' statuses, including age, comorbidities, and performance status. Our findings should be validated in future studies with well-designed randomized trials. A Japanese randomized trial of lobe-specific vs. systemic nodal dissection for clinical stage I-II NSCLC (JCOG1413) may reveal whether the difference in the area of LNDs influences the OS in patients with resected early-stage NSCLC [7]. Second, the quality of data about the number of LNDs is subject to the pathologists' and surgeons' assessment of LNDs [16–19]. If pathologists fail to adequately investigate LNs within the specimen, or surgeons removed some LNs in fragments during lung cancer resections, NCDB can end up identifying a lesser or greater number of total LNDs. These factors influence the final available information regarding the extent of LNs involvement, and these issues should be investigated in further studies with clearly-defined protocol parameters. Third, the stations of the LNDs were not available in the NCDB databases. Not only the number of the LNDs, but also their stations are associated with OS in patients with resected NSCLC [20–22], which should be analyzed in future studies. Fourth, since the study analysis is based on the NCDB, it is not possible to comprehensively collect several important data including recurrence or cause of death for explaining the oncologic effect regarding the number of LNDs.

In conclusion, our retrospective analysis investigating a large sample size of patients with small-sized ($\leq$20 mm) NSCLC who underwent sublobar resection showed that $\geq$10 LNDs was an independent predictor of longer OS, suggesting the prognostic and therapeutic roles for performing $\geq$10 LNDs. Appropriate lymph node dissection is an important issue in patients with small-sized NSCLC even if the resection is sublobar. Further research is warranted to validate these findings.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11748-022-01876-6.

Acknowledgements We thank Mindy Flannagan for statistical assistance.

Funding There are no sources of funding to report.

Declarations

Conflict of interest Takefumi Komiya received travel fee from Merck and honoraria from Boehringer Ingelheim. All the authors declare no conflicts of interest in association with this study.

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