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ORIGINAL SCIENTIFIC REPORT

Long-term Outcomes After Lung Cancer Resection in Smokers: Analysis of the National Lung Screening Trial

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Abstract

Background Smoking is a known risk factor for perioperative complications after lung resection; however, little data exists looking at the impact of smoking status (current versus former) on long-term oncologic outcomes after lung cancer surgery. We sought to compare overall survival (OS), progression-free survival (PFS), and cancer-specific mortality (CSM) in current and former smokers using data from the National Lung Screening Trial (NLST). Additionally, we performed subset analysis in current smokers in order to evaluate the effect of modern surgical techniques on long-term outcomes.

Methods Patients with clinical stage IA or IB NSCLC who underwent upfront resection within 180 days of diagnosis were identified in the NLST database. Cox proportional hazard regression models were used to assess differences in patient and treatment characteristics with respect to OS and PFS, with a cause-specific hazard model used for CSM.

Results A total of 593 patients were included in the study (269 former smokers, 324 current smokers). Lobar resection (LR) was performed more often than sublobar resection (SLR) (481 vs. 112), and thoracotomy was performed more often than thoracoscopy (482 vs. 86). Comparison of current versus former smokers showed no difference in OS or PFS after resection. Higher CSM was seen in current smokers ($p = 0.049$). Subset analysis of current smokers revealed no difference in OS or PFS between sub-lobar and lobar resection or thoracotomy and thoracoscopy. Although higher CSM was associated with thoracoscopy versus thoracotomy in this group, this finding was limited by a relatively small thoracoscopy sample size of 44 patients ($p = 0.026$).

Conclusion Our analysis of the NLST database shows no significant difference in OS and PFS when comparing current and former smokers undergoing resection for stage I NSCLC. Active smoking status was associated with higher CSM. Subset analysis of current smokers showed no difference in OS or PFS between sub-lobar and lobar resection or thoracotomy and thoracoscopy. Higher CSM was seen in current smokers who underwent thoracoscopy compared to thoracotomy; however, this finding was limited by a small sample size.

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Abbreviations

BMI	Body mass index
CSM	Cancer specific mortality
HR	Hazards ratio
OS	Overall survival
PFS	Progression free survival
LR	Lobar resection
NLST	National lung screening trial
NSCLC	Non-small cell lung cancer
SLR	Sublobar resection
VATS	Video-assisted thoracoscopic surgery

Introduction

Smoking is known to contribute to rates of morbidity and mortality after surgical resection for lung cancer [1–3]. This may contribute to an overall hesitancy by surgeons to consider active smokers for resection. While some studies looking at long-term outcomes after lung cancer resection have found an association between smoking and lower overall survival (OS) [4, 5], few have looked at the effects of modern, thoracic surgical techniques such as thoracoscopy and sub lobar resection on long-term outcomes in smokers.

The Lung Cancer Study Group established lobectomy as the standard of surgical care for stage I non-small cell lung cancer (NSCLC) in patients who are able to tolerate the procedure. Since that time, important advances in modalities for early lung cancer detection and clinical staging have led to a resurgence of sublobar resection (SLR) for early-stage NSCLC [6–14]. Advantages of SLR include preservation of lung parenchyma and pulmonary function, which may improve chances of future resections in the case of additional primary lung cancers. It is unclear if the oncologic value of a sub lobar resection is equally applicable to former versus current smokers, or if sub lobar resection exacerbates the previously noted differences in OS in current smokers undergoing resection.

While there are no randomized controlled trials comparing video-assisted thoracoscopy (VATS) and thoracotomy for resection of lung cancer, data from several large series provide strong evidence that patients who undergo VATS have less pain, fewer perioperative complications, shorter chest-tube duration, and decreased length of stay [15–17]. The impact of surgical approach on long-term outcomes after resection for lung cancer has also been explored, with some series favoring VATS and others favoring thoracotomy [18–21].

Our study aims to look at the effect of modern, thoracic surgical techniques on long-term outcomes among former and current smokers after resection of NSCLC, stratifying outcomes based on surgical approach, extent of resection, and smoking status. In order to provide a cross section of the current, contemporary treatment of lung cancer, we elected to use the NLST database.

Materials and methods

The National Lung Screening Trial was queried to identify patients with Stage IA and IB NSCLC (AJCC 7the edition) who underwent resection within 180 days of cancer diagnosis. ICD 9 codes used in this query can be found in Appendix Table 4. Queries of both the treatment and diagnostic procedure files were performed. Patients with a prior cancer diagnosis or with missing data regarding prior cancer diagnoses were excluded. In determining resection type, we included treatments within 1 week of the first noted resection, and coded patients with both sublobar and lobar resections in this period as lobar resection (n = 213) since this likely represents patients who had a diagnostic wedge resection followed by completion lobectomy. Similarly, patients with both thoracoscopy and thoracotomy were code as thoracotomy (n = 117). Two patients with unknown cause of death were excluded from analysis of cancer-specific mortality. (Fig. 1)

Differences in patient and treatment characteristics between former and current smokers were assessed using the Wilcoxon Rank-Sum test for continuous characteristics, and the Chi-Squared or Fisher's exact test for categorical characteristics as appropriate. Overall survival and progression-free survival were defined as the time from resection to death and progression or death, respectively. Cancer-specific mortality was defined as the time from resection to death due to cancer, with deaths of any other cause considered to be competing risks. Differences in OS, PFS, and CSM based on patient and treatment characteristics were assessed using Cox proportional hazard regression modeling, with a cause-specific hazard model used for CSM.

Results

A total of 593 patients with stage IA or IB NSCLCs were included in the study, 269 patients identified as former smokers and 324 as current smokers. Former smokers tended to be older (median age 64 vs. 62, $p = 0.001$), have a higher body mass index (median BMI 27 vs. 26, $p < 0.001$), and self-report as married or living as married (72.5% vs. 60.8%, $p = 0.004$) compared to current smokers. Black participants were more likely to be current smokers compared to white. Gender, education level, pack

years, and stage distribution were similar between the two groups.

Among the entire cohort of stage I lung cancer patients, lobar resection was more common than sub-lobar resection (LR = 481, SLR = 112) and thoracotomy was more common than thoracoscopy (OPEN = 482, VATS = 86). Data regarding surgical approach was missing in 25 patients. The distribution of resection type was not significantly different between current and former smokers, with lobectomy performed in 80.7% of former smokers and 81.5% of current smokers ($p = 0.884$). Similarly, surgical approach did not differ significantly between current and former smokers (16.3% vs. 14.2%, respectively, $p = 0.567$) Table 1.

Cox proportional hazard regression models revealed no difference in OS by resection type (HR 1.21 95% CI [0.78–1.89] $p = 0.400$), surgical approach (1.22 [0.72–2.08] $p = 0.467$), or smoking status (1.29 [0.88–1.87] $p = 0.187$). Additionally, no significant difference was noted in PFS by resection type (1.24 [0.84–1.83] $p = 0.273$), surgical approach (1.27 [0.81–2.01] $p = 0.301$), or smoking status (1.23 [0.89–1.7] $p = 0.221$). Finally, while no difference was seen in CSM by resection type (1.25 [0.74–2.12] $p = 0.401$) or surgical approach (1.68 [0.96–2.97] $p = 0.072$), current smokers had worse CSM compared to former smokers (1.58 [1–2.5] $p = 0.049$) Table 2.

When analyzing a subset that consisted only of current smokers, we did not find a significant difference in OS (1.05 [0.57–1.93] $p = 0.864$), PFS (0.86 [0.48–1.53] $p = 0.604$), or CSM (1.07 [0.54–2.15] $p = 0.840$) by extent of resection (Table 3). Similarly, among current smokers, no difference in OS (1.58 [0.8–3.12] $p = 0.189$) or PFS (1.58 [0.87–2.86] $p = 0.135$) was seen when comparing thoracotomy and thoracoscopy. We noted worse CSM (2.22 [1.1–4.51] $p = 0.026$) in current smokers who underwent thoracoscopy compared to thoracotomy; however, the sample size was small (thoracotomy 264 vs. thoracoscopy 44), which limits the validity of this finding.

Discussion

Our analysis of the long-term outcomes after resection of stage I NSCLC in the NLST shows that resection type and surgical approach did not affect overall survival, progression-free survival, or cancer-specific mortality when comparing former and current smokers. Subset analysis of current smokers showed similar OS, PFS, and CSM between lobar and sublobar resections. When comparing thoracotomy and thoracoscopy in this subset, we found similar OS and PFS, but higher CSM in patients who underwent thoracoscopy.

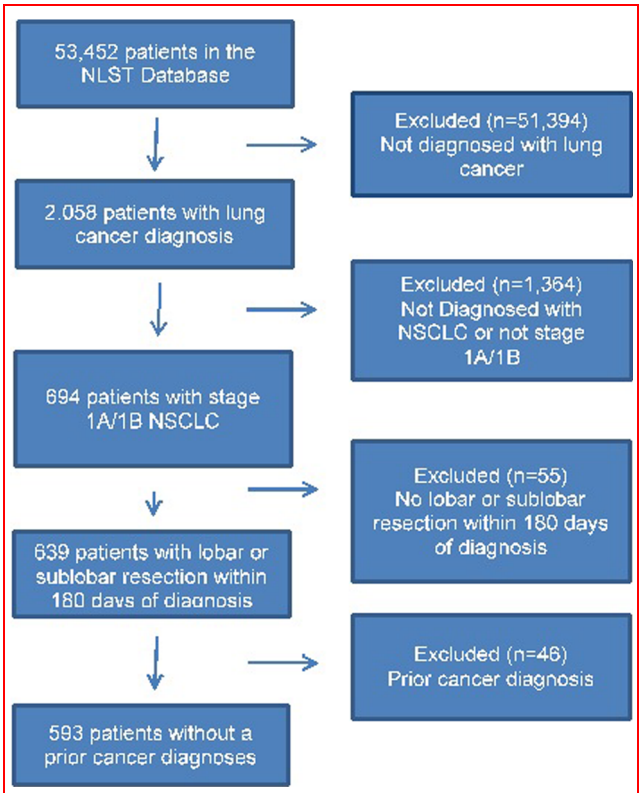

Fig. 1 Consort diagram

Limited data is available comparing long-term results of lung cancer surgery in current versus former smokers. Some studies have shown decreased survival and increased recurrence rates in current smokers [4, 5, 22]. These reports, however, included more advanced stages and did not factor the effect of modern thoracic surgical techniques. Our study of early-stage lung cancer failed to show any significant difference in OS, PFS, or CSM in current versus former smokers with stage I lung cancer undergoing resection.

The cumulative risk of developing a second primary lung cancer in smokers is up to 18% at 10 years [23]. This may lead some surgeons to forgo lobectomy in current smokers so as not to hinder their chance at lung resection for a second primary. Our data show similar OS, PFS, and CSM in patients treated with lobar and sublobar resection, regardless of smoking status. This suggests that even in patients who are active smokers opting for sub-lobar resection in an effort to preserve parenchyma can be done with acceptable oncologic results. Treatment of lung cancer in patients with decreased pulmonary reserve has improved in the last decade with advances in targeted radiation therapy, popularization of sublobar resection, and minimally invasive approaches. The improved ability to treat recurrence or new primaries may account for the

Table 1 Demographics of current and former smokers with stage IA or IB non-small cell lung cancer in the National Lung Screening Trial

Smoking Status			
	Former (n = 269)	Current (n = 324)	*p* value
Screening Modality			0.362
Spiral CT	184 (68.4)	209 (64.5)	
X-ray	85 (31.6)	115 (35.5)	
Age (years)	64 (55,74)	62 (55,74)	0.001
Gender			0.122
Female	105 (39.0)	148 (45.7)	
Male	164 (61.0)	176 (54.3)	
Race			0.006
White	257 (95.9)	284 (89.0)	
Black	**	25 (7.8)	
Other	**	**	
Missing	**	**	
Body Mass Index	27 (18,42)	26 (17,65)	< 0.001
College Education			0.116
No	187 (69.5)	245 (75.6)	
Yes	82 (30.5)	79 (24.4)	
Married or living as married			0.004
No	74 (27.5)	127 (39.2)	
Yes	195 (72.5)	197 (60.8)	
Pack years	57 (30,200)	55 (30,224)	0.961
Stage			> 0.999
IA	212 (78.8)	256 (79)	
IB	57 (21.2)	68 (21.0)	
Resection type			0.884
Lobar	217 (80.7)	264 (81.5)	
Sublobar	52 (19.3)	60 (18.5)	
Surgical approach			0.567
Thoracotomy	216 (83.7)	266 (85.8)	
Thoracoscopy	42 (16.3)	44 (14.2)	
Missing	11	14	

Values are median (range) or n (%) CT: computer aided tomography

**Variables with less than 11 patients

oncologic outcomes seen in our analysis among current smokers.

The oncologic equivalence of thoracoscopy and thoracotomy has been reported previously. Several population-based analyses have shown no difference in OS or PFS between the two approaches [20, 21, 24–26]. Our study confirms similar OS, PFS, and CSM between thoracoscopy and thoracotomy; however, we did see worse CSM in the small subset of current smokers. The overall rate of thoracoscopic resection in the NLST was only 29.6%, which is similar to our series [27]. One limitation of this analysis is the small number of patients in our study who were current smokers and also underwent thoracoscopy (N = 44). This fact makes it difficult to argue for the superiority of thoracotomy over thoracoscopy in this particular case. Furthermore, previous analysis of short-term outcomes on this group suggests decreased rates of complications/death with thoracoscopy. [27]

Our analysis did not include perioperative outcomes as these have been previously reported and our intent was to highlight the association of smoking with long-term outcomes. One of the limitations of our study is the designation as current or former smoker was recorded at the time of randomization. It is not possible to know if patients were current smokers at the time of resection or beyond, which

Table 2 Long-term outcomes in patients with stage IA or IB non-small cell lung cancer treated with resection in the National Lung Screening Trial

	Overall Survival		Progression Free Survival		Cancer Specific Mortality	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Resection Type						
Lobar resection	Reference	0.400	Reference	0.273	Reference	0.401
Sublobar Resection	1.21 (0.78–1.89)		1.24 (0.84–1.83)		1.25 (0.74–2.12)	
Surgical Approach						
Thoracotomy	Reference	0.467	Reference	0.301	Reference	0.072
Thoracoscopy	1.22 (0.72–2.08)		1.27 (0.81–2.01)		1.68 (0.96–2.97)	
Smoking Status						
Former	Reference	0.187	Reference	0.221	Reference	0.049
Current	1.29 (0.88–1.87)		1.23 (0.89–1.7)		1.58 (1–2.5)	

HR Hazard Ratio, *CI* Confidence Interval

Table 3 Subset analysis of long-term outcomes in current smokers with stage IA or IB non-small cell lung cancer treated with resection in the National Lung Screening Trial

	Overall Survival		Progression Free Survival		Cancer Specific Mortality	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Resection type						
Lobar resection	Reference	0.864	Reference	0.604	Reference	0.84
Sublobar Resection	1.05 (0.57–1.93)		0.86 (0.48–1.53)		1.07 (0.54–2.15)	
Surgical approach						
Thoracotomy	Reference	0.189	Reference	0.135	Reference	0.026
Thoracoscopy	1.58 (0.8–3.12)		1.58 (0.87–2.86)		2.22 (1.1–4.51)	

HR: Hazard Ratio, CI: Confidence Interval

could impact rates of new primary lung cancers and recurrence.

This study suggests that patients enrolled in screening programs can derive significant benefit in long-term survival with resection for early-stage lung cancer whether they are current or former smokers. Smoking status should not in and of itself be considered a deterrent to resection or influence extent of resection beyond objective values of cardiopulmonary reserve. While minimally invasive approaches may offer benefits in the perioperative period in smokers, further research is needed to determine oncologic equivalency in current smokers.

Conclusion

In the setting of a lung cancer screening program, resection of early-stage lung cancer can result in similar oncologic benefits in current and former smokers. In current smokers undergoing surgery, lobar and sub-lobar resections result in similar long-term outcomes, with no difference in OS, PFS, or CSM. Further research is needed to determine if thoracoscopy and thoracotomy have equivalent oncologic effectiveness in current smokers.

Appendix

See Table 4.

Table 4 Codes Used for cohort identification and procedure types

Aspect	Source	Code
Diagnosis		
Site	ICD-10-CM	C34.1, C34.2, C34.3, C34.8, C34.9
Histologic Type	ICD-O-3	8012, 8046, 8070, 8071, 8072, 8140, 8250, 8560, 8251, 8252, 8253, 8254, 8255
Extent of Resection	NLST	
Lobar		203 (Lobectomy), 204 (Bilobectomy), 205 (Pneumonectomy)
Sublobar		206 (Wedge Resection), 207 (Segmental Resection), 212 (Multiple Wedge Resections), 213 (Multiple Segmental Resections)
Approach	NLST	
Thoracoscopy (VATS)		Diagnostic Procedures: 49 (Thoracoscopy) 50 (Biopsy – Thoracoscopic) Treatment: 215 (Thoracoscopy VATS)
Thoracotomy		Diagnostic Procedures: 46 (Thoractomy) Treatment: 202 (Median Sternotomy) 214 (Thoracotomy) 216 (Thoracoscopy (VATS) with conversion to Thoracotomy)

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Declarations

Conflict of interest There are no conflicts of interest reported by any author.

Ethical approval This study was approved by our institutional review board, IRB protocol No. 17–67.

References

1. Fukui M, Suzuki K, Matsunaga T, Oh S, Takamochi K (2019) Importance of smoking cessation on surgical outcome in primary lung cancer. Ann Thorac Surg 107:1005–1009
2. Lugg ST, Tikka T, Agostini PJ et al (2017) Smoking and timing of cessation on postoperative pulmonary complications after curative-intent lung cancer surgery. J Cardiothorac Surg 12:52
3. Mason DP, Subramanian S, Nowicki ER et al (2009) Impact of smoking cessation before resection of lung cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database study. Ann Thorac Surg 88:362–371
4. Sawabata N, Miyoshi S, Matsumura A et al (2007) Prognosis of smokers following resection of pathological stage I non-small-cell lung carcinoma. Gen Thorac Cardiovasc Surg 55:420–424
5. Poullis M, McShane J, Shaw M et al (2013) Smoking status at diagnosis and histology type as determinants of long-term outcomes of lung cancer patients. Eur J Cardiothorac Surg 43:919–924
6. Koike T, Yamato Y, Yoshiya K et al (2003) Intentional limited pulmonary resection for peripheral T1 N0 M0 small-sized lung cancer. J Thorac Cardiovasc Surg 125:924–928
7. Keenan RJ, Landreneau RJ, Maley RH Jr et al (2004) Segmental resection spares pulmonary function in patients with stage I lung cancer. Ann Thorac Surg 78:228–233
8. Harada H, Okada M, Sakamoto T, Matsuoka H, Tsubota N (2005) Functional advantage after radical segmentectomy versus lobectomy for lung cancer. Ann Thorac Surg 80:2041–2045
9. Okada M, Nishio W, Sakamoto T et al (2005) Effect of tumor size on prognosis in patients with non-small cell lung cancer: the role of segmentectomy as a type of lesser resection. J Thorac Cardiovasc Surg 129:87–93
10. Yoshida J, Nagai K, Yokose T et al (2005) Limited resection trial for pulmonary ground-glass opacity nodules: fifty-case experience. J Thorac Cardiovasc Surg 129:991–996
11. Altorki NK, Yip R, Hanaoka T et al (2014) Sublobar resection is equivalent to lobectomy for clinical stage 1A lung cancer in solid nodules. J Thorac Cardiovasc Surg 147:754–764
12. Dziedzic R, Żurek W, Marjański T et al (2017) Stage I non-small-cell lung cancer: long-term results of lobectomy versus sublobar resection from the Polish National Lung Cancer Registry. Eur J Cardiothorac Surg 52:363–369
13. Kates M, Swanson S, Wisnivesky JP (2011) Survival following lobectomy and limited resection for the treatment of stage I non-small cell lung cancer<=1 cm in size: a review of SEER data. Chest 139:491–496
14. Wisnivesky JP, Henschke CI, Swanson S et al (2010) Limited resection for the treatment of patients with stage IA lung cancer. Ann Surg 251:550–554
15. Paul S, Altorki NK, Sheng S et al (2010) Thoracoscopic lobectomy is associated with lower morbidity than open lobectomy: a propensity-matched analysis from the STS database. J Thorac Cardiovasc Surg 139:366–378
16. Flores RM, Park BJ, Dycoco J et al (2009) Lobectomy by video-assisted thoracic surgery (VATS) versus thoracotomy for lung cancer. J Thorac Cardiovasc Surg 138:11–18
17. Falcoz PE, Puyraveau M, Thomas PA et al (2016) Video-assisted thoracoscopic surgery versus open lobectomy for primary non-small-cell lung cancer: a propensity-matched analysis of outcome from the European Society of Thoracic Surgeon database. Eur J Cardiothorac Surg 49:602–609
18. Al-Ameri M, Bergman P, Franco-Cereceda A, Sartipy U (2018) Video-assisted thoracoscopic versus open thoracotomy lobectomy: a Swedish nationwide cohort study. J Thorac Dis 10:3499–3506
19. Long H, Tan Q, Luo Q et al (2018) Thoracoscopic surgery versus thoracotomy for lung cancer: short-term outcomes of a randomized trial. Ann Thorac Surg 105:386–392

20. Lee PC, Nasar A, Port JL et al (2013) Long-term survival after lobectomy for non-small cell lung cancer by video-assisted thoracic surgery versus thoracotomy. Ann Thorac Surg 96:951–961
21. Paul S, Isaacs AJ, Treasure T et al (2014) Long term survival with thoracoscopic versus open lobectomy: propensity matched comparative analysis using SEER-Medicare database. BMJ. 349:g5575
22. Fujisawa T, Iizasa T, Saitoh Y et al (1999) Smoking before surgery predicts poor long-term survival in patients with stage I non-small-cell lung carcinomas. J Clin Oncol 17:2086–2091
23. Ripley RT, McMillan RR, Sima CS et al (2014) Second primary lung cancers: smokers versus nonsmokers after resection of stage I lung adenocarcinoma. Ann Thorac Surg 98:968–974
24. Higuchi M, Yaginuma H, Yonechi A et al (2014) Long-term outcomes after video-assisted thoracic surgery (VATS) lobectomy versus lobectomy via open thoracotomy for clinical stage IA non-small cell lung cancer. J Cardiothorac Surg 9:88
25. Yang HX, Woo KM, Sima CS et al (2017) Long-term survival based on the surgical approach to lobectomy for clinical stage i nonsmall cell lung cancer: comparison of robotic, video-assisted thoracic surgery, and thoracotomy lobectomy. Ann Surg 265:431–437
26. Kneuertz PJ, D'Souza DM, Richardson M, Abdel-Rasoul M, Moffatt-Bruce SD, Merritt RE (2020) Long-term oncologic outcomes after robotic lobectomy for early-stage non-small-cell lung cancer versus video-assisted thoracoscopic and open thoracotomy approach. Clin Lung Cancer 21(214–224):e2
27. Kamel MK, Lee B, Harrison S et al (2019) Do the surgical results in the National Lung Screening Trial reflect modern thoracic surgical practice? J Thorac Cardiovasc Surg. 157(2038–2046):e1