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Preoperative cumulative smoking dose on lung cancer surgery in a Japanese nationwide database

Running head: Smoking status in lung cancer surgery

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Abstract

Background: Smoking is a known risk factor for postoperative mortality and morbidity. However, the significance of cumulative smoking dose in preoperative risk assessment has not been established. We examined the influence of preoperative cumulative smoking dose on surgical outcomes after lobectomy for primary lung cancer.

Methods: A total of 80,989 patients with primary lung cancer undergoing lobectomy from 2014 to 2016 were enrolled. Preoperative cumulative smoking dose was categorized by pack-years (PY): Non-smokers, PY = 0; Light smokers, 0 < PY < 10; Moderate smokers, 10 ≤ PY < 30; and Heavy smokers, 30 ≤ PY. The risk of short-term outcomes was assessed according to PY by multivariable analysis adjusted for other covariates.

Results: Postoperative 30-day mortality, as well as pulmonary, cardiovascular, and infectious complications, increased with preoperative PY. Multivariable analysis revealed the odds ratios (ORs) for postoperative mortality compared with non-smokers were 1.76 for light smokers (p=0.044), 1.60 for moderate smokers (p=0.026), and 1.73 for heavy smokers (p=0.003). The ORs for pulmonary complications compared with non-smokers were 1.20 for light smokers (p= 0.022), 1.40 for moderate smokers (p<0.001), and 1.72 for heavy smokers (p<0.001). Heavy smokers had a significantly increased risk of postoperative cardiovascular (OR, 1.26; p=0.002) and infectious complications (OR, 1.39; p=0.007) compared with non-smokers.

***Conclusions*:** The risk of mortality and morbidity after lung resection could be predicted according to preoperative cumulative smoking dose. These findings contribute to the development of strategies in perioperative management of lung resection patients.

Keywords: smoking, lung resection, lobectomy, pack-year, complication

Introduction

Smokers are at a high risk of more frequent postoperative complications compared with individuals who have never smoked. This is primarily due to smoking-related comorbidities and the adverse effects of smoking on the cardiovascular and pulmonary systems and wound healing function.(1-3) In addition, lung resection in patients with a smoking history requires delicate surgical procedures because of emphysematous lung parenchyma, which is a risk factor for postoperative pulmonary complications such as prolonged air leakage.(4) To decrease smoking-related complications after lung resection, the risk of preoperative smoking status on surgical outcomes should be adequately evaluated. However, the significance of cumulative smoking dose in preoperative risk assessment has not been established.

To evaluate the prevailing state of surgical treatment in Japan and perform a nationwide survey of surgical outcomes, the National Clinical Database (NCD) was established with the cooperation of major Japanese surgical associations in 2010. With respect to general thoracic surgery, patient surgical information was recorded into NCD since 2014, and these data have been used for various purposes including establishment of risk model for mortality and morbidity after lung cancer surgery since 2017(5-7). This system also enabled us to perform large-scale analysis on the influence of the preoperative smoking status on lung resection.

We aimed to examine the effects of preoperative cumulative smoking dose on surgical mortality and postoperative pulmonary, cardiovascular, and infectious complications after lung resection using this nationwide database to help improve strategies in the perioperative management of lung surgery patients.

Patients and Methods

The nationwide database

More than 1,500,000 surgical cases from 5,619 institutions were registered in the NCD in 2018. Almost all surgical institutions support this data entry system, which covers more than 95% of surgeries performed in Japan. Information on general thoracic surgery patients has been collected since 2014, and more than 100,000 cases were registered on NCD in 2017. With regards lung cancer surgery, 95% of cases in Japan have been registered.(5) The system is thus a large-scale, nationwide database that reflects the current state of lung cancer surgery in Japan with reliable accuracy.

Patient population

We analyzed data from 80,989 patients with primary lung cancer who underwent lobectomy from January 2014 to December 2016. Bilobectomy and sleeve lobectomy were assessed in this study. Data on thoracotomy, mini-thoracotomy, and complete video-assisted thoracic surgery were also assessed.

Patients in c-T0 or TX, c-N3 or NX and c-M1 or MX were excluded from the study because curative intent could not be assured. Procedures involving combined resection with neighboring organs, robotic-assisted thoracic surgery and emergency surgery were also excluded to standardize the study population. Patients with unknown smoking history and incomplete analysis data were also excluded from the study (Fig.1).

The protocol was implemented in accordance with the principles of the Declaration of Helsinki with approval from the Clinical Research Area Ethics Committee of Kobe University Graduate School of Medicine (#180217). Clinical information was collected, and postoperative risk factors were retrospectively assessed.

Categorization of preoperative smoking status

Patients were categorized into four groups according to cumulative smoking dose: patients who had never smoked, light smokers, moderate smokers, and heavy smokers. Pack-years (PY) was used as a measure of cumulative smoking dose in this study. A light smoker was defined as a patient with smoking of PY <10, a moderate smoker with $10 \leq$ PY <30, and a heavy smoker with PY ≥ 30.

Study outcomes

The outcomes measured in this study were surgical morbidity, surgical mortality, surgical duration, blood loss, and hospital length of stay. Surgical mortality was defined as the number of patients who died during hospitalization or within 30 days regardless of hospitalization status. The deaths of patients who were transferred to another hospital were also included in surgical mortality. Pulmonary, cardiovascular, and infectious complications were defined as postoperative complications. Pulmonary complications included prolonged air leakage, bronchopleural fistula, pneumonia, interstitial pneumonia, atelectasis, and respiratory insufficiency. Cardiovascular complications included cardiac infarction, cerebral stroke, arrhythmia, and pulmonary embolism. Infectious complications included wound infection and empyema. Prolonged air leakage was defined as postoperative air leakage that continued for >7 days or that required an additional postoperative procedure, such as surgery or adhesion therapy, within 7 days. Pneumonia was defined as the development of infection and lung consolidation on chest X-ray or computed tomography. Comorbidity of interstitial pneumonia was defined by characteristic appearance on chest computed tomography such as honeycombing or reticular pattern, and postoperative complications of interstitial pneumonia was defined as its acute exacerbation. Respiratory insufficiency was defined as a need for reintubation, tracheostomy, or ventilatory assistance >48 hours after surgery. Arrhythmia was defined as which developed after surgery and needed treatment.

Statistical analysis

Categorical variables were compared using the Pearson's chi-squared test or Fisher's exact test, and continuous variables were compared using the Kruskal–Wallis test. Multivariable logistic regression analysis was used to evaluate the association between preoperative smoking status and postoperative outcomes with odds ratios and 95% confidence intervals (CI). As with previous reports, we also selected sex; age; smoking status; surgical procedure; Eastern Cooperative Oncology Group performance status (PS); respiratory function; body mass index (BMI); preoperative comorbidities (interstitial pneumonia, hemodialysis, diabetes mellitus, ischemic heart disease, cerebral stroke, autoimmune disease, arrhythmia, hepatic dysfunction); preoperative treatment (chemotherapy, radiotherapy); histology; and clinical T and clinical N factors as covariates for multivariable analysis. The forced expiratory volume in 1 second (FEV1)% predicted was excluded in this multivariable analysis because there is a strong causal relationship showing that FEV1% predicted decreases with an increase in the cumulative smoking dose. Therefore, the influence of preoperative smoking in this multivariable analysis was evaluated including its past effect on the lung parenchyma. A p value <0.05 was considered statistically significant. About model performance, discrimination and calibration were checked. Statistical analyses were performed using STATA 16 (STATA Corp., TX, USA).

Results

The clinical characteristics of 80,989 patients with primary lung cancer who underwent pulmonary lobectomy are listed in Table 1. Of the total number of patients enrolled, 27,680 (34.2%) had never smoked, 4,136 patients (5.1%) were light smokers, 10,143 patients (12.5%) were moderate smokers, and 39,030 patients (48.2%) were heavy smokers. The proportion of male and PS 2 patients increased with preoperative PY. In contrast, percent vital capacity (%VC) and FEV1% predicted decreased with higher preoperative PY.

Detailed information on lung cancer and surgical procedures is shown in Table 2. The clinical

T and N factors increased with higher preoperative PY. The proportion of patients with adenocarcinoma decreased as preoperative PY increased. Preoperative chemotherapy and radiotherapy were often performed on patients in the heavy smoker group. Thoracotomy was also more frequently performed on patients in the heavy smoker group. Meanwhile, complete video-assisted thoracic surgery was often performed on patients who had never smoked or who had a minimal smoking status.

Preoperative comorbidities were more frequently observed in patients with a higher cumulative smoking dose. In particular, patients were more likely to exhibit interstitial pneumonia, diabetes mellitus, ischemic heart disease, and cerebral stroke. Preoperative comorbidities are listed in Table 3.

Intraoperative and postoperative outcomes in accordance with preoperative smoking status are shown in Table 4. The surgical mortality, the incidence rates of pulmonary complications, cardiovascular complications and infectious complications were clearly positively associated with preoperative PY (Supplemental Fig.1). Surgical duration, blood loss, and hospital length of stay were likewise directly correlated with PY. Detailed information about postoperative complications is shown on Table 5. In addition, surgical mortality according to age and PY was shown in supplemental Table 1 and the surgical mortality according to PY increased similarly in each age group.

The risk factors associated with surgical mortality and postoperative complications as determined by multivariable analysis are listed in Table 6 and Supplemental Table 2. Preoperative smoking was significant risk factor for surgical mortality, but the risk did not depend on cumulative smoking dose (Supplemental Fig. 2A). For postoperative pulmonary complications, preoperative smoking was also a significant risk factor and the risk had a dose-response relationship (Supplemental Fig. 2B). For cardiovascular and infectious complications, only heavy smoking was a significant risk factor compared with never smoking (Supplemental Fig. 2C and D).

Comment

Pulmonary complications after lung resection have been discussed in previous reports, with preoperative smoking history repeatedly identified as a risk factor.(8-14) However, few studies have discussed the association between preoperative cumulative smoking dose and postoperative pulmonary complications, and those that have present controversial results.(15-17) We infer that insufficient statistical power due to a relatively small sample size and limited clinical information from the database influenced the results of those studies. In terms of cardiovascular and infectious complications, many reports have demonstrated preoperative smoking history as a risk factor. However, those reports were not conducted exclusively on lung resection.(18-22)

In general, smoking causes adverse effects on alveolar tissue, the arterial endothelium, the coagulation fibrinolytic system, and the immune system due to excessive proteolysis, cell apoptosis, and oxidative damage. (23-27) Some literature reviews on major surgeries other than lung surgery found preoperative PY as a risk factor for postoperative pulmonary, cardiovascular, and infectious complications. However, the risk varied with the type of surgery used in each study. (1, 2) In contrast to previous reports, the present study included only cases of lobectomy for primary lung cancer and focused on the risk of postoperative complications associated with preoperative PY. Our results demonstrated that PY before lung resection is most strongly associated with postoperative pulmonary complications, given that a dose–response relationship with PY was observed only in pulmonary complications. Thus, the risk of pulmonary complications by preoperative PY is higher in lung resection compared with other types of surgery. (28-30)

Given that postoperative mortality increased with a higher preoperative PY and was significantly associated with an increased risk of postoperative complications, we expected to find a dose–response relationship between postoperative mortality and preoperative PY. Although a significantly increased risk was observed even in patients with preoperative smoking of <10 PY, no dose–response relationship was established by multivariable analysis. The reason for this may be that even light smoking, irrespective of preoperative comorbidities, can trigger physiological changes in cardiopulmonary function and can influence postoperative mortality. We also considered that surgeons tend to perform lobectomies, as a standard treatment for lung cancer, primarily to improve long-term prognosis and avoid postoperative death. To reduce the incidence of postoperative death, either segmentectomy or wedge resection is performed on patients who are ineligible for lobectomy. (31) In addition, advancements have been made in treatments for postoperative complications, including those that require intensive care. We postulate that these advancements also contributed to the lack of significant increased risk for postoperative mortality in moderate and heavy smokers, as compared with light smokers.

Our results show that most preoperative comorbidities, tumor size, and lymph node metastasis increased with a higher preoperative PY. These conditions can increase the difficulty of the surgical procedure and contribute to a longer surgical duration, as well as to a greater degree of blood loss in patients with a higher cumulative smoking dose. Furthermore, the present study found a higher surgical mortality and a higher incidence of various postoperative complications in patients with a higher cumulative smoking dose. However, we do not advocate non-surgical treatment modalities for heavy smokers with oncologically resectable primary lung cancer, considering that the postoperative complications and mortality were within the acceptable limit even in heavy smokers in this study. It is crucial to fully understand the risk of postoperative complications for heavy smokers and prepare for them preoperatively via the enforcement of preoperative smoking cessation and respiratory rehabilitation.

There are some limitations to our present study. First, PY could have been underestimated because it was obtained from the patients' self-reported data.(32) However, in this study, the preoperative FEV1% predicted decreased with the increase in preoperative PY. There is a strong causal relationship as per which FEV1% predicted decreases with an increase in the cumulative smoking dose; therefore, we believe that the preoperative PY data in this study were unlikely to be underestimated. Second, we were unable to collect information on long-term prognosis and postoperative smoking status. In the future, the analysis including those information is needed. Third, the influence of preoperative smoking cessation period for postoperative outcomes was not analyzed in this study. For patients who were at a high risk of postoperative complications, the surgeons tend to perform surgery after a certain period of smoking cessation. However, they may not emphasize the necessity of preoperative smoking cessation period to low-risk patients. We were concerned that the analysis of preoperative smoking cessation could be susceptible to the surgeon's selection bias in this retrospective database study.

In conclusion, even a minimal preoperative cumulative smoking dose (i.e., <10 PY) already increases the risk of surgical mortality and pulmonary complications after lobectomy for primary lung cancer. Furthermore, a more extensive preoperative cumulative smoking dose (PY > 30) increases the risk of postoperative cardiovascular and infectious complications. These findings help us to predict the type and rate of postoperative complications and surgical mortality based on preoperative cumulative smoking dose. Furthermore, our results contribute to further the development of perioperative management strategies.

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Disclosures:

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Table 1. Patient characteristics

Factor		Total (80,989)	PY=0 (27,680)	0<PY<10 (4,136)	10≦PY<30 (10,143)	30<PY (39,030)	p-value
Sex	Male	49,700 (61.4%)	4,901 (17.7%)	2,304 (55.7%)	7,346 (72.4%)	35,149 (90.1%)	<0.001
	Female	31,289 (38.6%)	22,779 (82.3%)	1,832 (44.3%)	2,797 (27.6%)	3,881 (9.9%)	
Age	-59	10,336 (12.8%)	3,759 (13.6%)	891 (21.5%)	2,103 (20.7%)	3,583 (9.2%)	<0.001
	60-64	10,002 (12.3%)	3,050 (11.0%)	600 (14.5%)	1,225 (12.1%)	5,127 (13.1%)	
	65-69	17,887 (22.1%)	5,747 (20.8%)	823 (19.9%)	2,063 (20.3%)	9,254 (23.7%)	
	70-74	19,103 (23.6%)	6,349 (22.9%)	740 (17.9%)	2,043 (20.1%)	9,971 (25.5%)	
	75-79	15,034 (18.6%)	5,483 (19.8%)	665 (16.1%)	1,691 (16.7%)	7,195 (18.4%)	
	80-	8,627 (10.7%)	3,292 (11.9%)	417 (10.1%)	1,018 (10.0%)	3,900 (10.0%)	
PS	0-1	78,494 (96.9%)	26,958 (97.4%)	4,031 (97.5%)	9,840 (97.0%)	37,665 (96.5%)	<0.001
	2	2,495 (3.1%)	722 (2.6%)	105 (2.5%)	303 (3.0%)	1,365 (3.5%)	
%VC	100-	39,979 (49.4%)	15,674 (56.6%)	2,290 (55.4%)	5,188 (51.1%)	16,827 (43.1%)	<0.001
	90-99	20,245 (25.0%)	6,502 (23.5%)	969 (23.4%)	2,522 (24.9%)	10,252 (26.3%)	
	80-89	13,248 (16.4%)	3,744 (13.5%)	595 (14.4%)	1,612 (15.9%)	7,297 (18.7%)	
	70-79	5,335 (6.6%)	1,267 (4.6%)	202 (4.9%)	601 (5.9%)	3,265 (8.4%)	
	60-69	1,665 (2.1%)	393 (1.4%)	59 (1.4%)	166 (1.6%)	1,047 (2.7%)	
	50-59	408 (0.5%)	75 (0.3%)	17 (0.4%)	41 (0.4%)	275 (0.7%)	
	-49	109 (0.1%)	25 (0.1%)	4 (0.1%)	13 (0.1%)	67 (0.2%)	
FEV1% predicted	100-	29,522 (36.5%)	16,451 (59.4%)	1,933 (46.7%)	3,554 (35.0%)	7,584 (19.4%)	<0.001
	90-99	17,276 (21.3%)	5,603 (20.2%)	972 (23.5%)	2,457 (24.2%)	8,244 (21.1%)	
	80-89	15,511 (19.2%)	3,363 (12.1%)	693 (16.8%)	2,099 (20.7%)	9,356 (24.0%)	
	70-79	10,308 (12.7%)	1,487 (5.4%)	345 (8.3%)	1,198 (11.8%)	7,278 (18.6%)	
	60-69	5,216 (6.4%)	519 (1.9%)	130 (3.1%)	567 (5.6%)	4,000 (10.2%)	
	50-59	2,195 (2.7%)	191 (0.7%)	40 (1.0%)	188 (1.9%)	1,776 (4.6%)	

	-49	961 (1.2%)	66 (0.2%)	23 (0.6%)	80 (0.8%)	792 (2.0%)	
BMI	<18.5	6,890 (8.5%)	2,666 (9.6%)	338 (8.2%)	856 (8.4%)	3,030 (7.8%)	<0.001
	>30	2,084 (2.6%)	814 (2.9%)	118 (2.9%)	230 (2.3%)	922 (2.4%)	<0.001

Values are presented as n (%). Pearson's chi-squared test was used for comparison.

PY: pack-years, PS: Eastern Cooperative Oncology Group performance status, VC: vital capacity, FEV1: forced expiratory volume in 1 second, BMI: body mass index

Table 2. Detailed information of lung cancer and treatment

Factor		Total (80,989)	PY=0 (27,680)	0<PY<10 (4,136)	10≦PY<30 (10,143)	30<PY (39,030)	p-value
cT factor	Tis-1	48,663 (60.1%)	18,574 (67.1%)	2,647 (64.0%)	6,121 (60.3%)	21,321 (54.6%)	<0.001
	T2	27,381 (33.8%)	8,252 (29.8%)	1,299 (31.4%)	3,389 (33.4%)	14,441 (37.0%)	
	T3-4	4,945 (6.1%)	854 (3.1%)	190 (4.6%)	633 (6.2%)	3,268 (8.4%)	
cN factor	N0	70,291 (86.8%)	25,734 (93.0%)	3,762 (91.0%)	8,854 (87.3%)	31,941 (81.8%)	<0.001
	N1	6,787 (8.4%)	1,239 (4.5%)	223 (5.4%)	809 (8.0%)	4,516 (11.6%)	
	N2	3,911 (4.8%)	707 (2.6%)	151 (3.7%)	480 (4.7%)	2,573 (6.6%)	
Histology	AD	57,124 (70.5%)	25,142 (90.8%)	3,545 (85.7%)	7,472 (73.7%)	20,965 (53.7%)	<0.001
Preoperative treatment	CT	1,725 (2.1%)	292 (1.1%)	62 (1.5%)	211 (2.1%)	1,160 (3.0%)	<0.001
	RT	853 (1.1%)	130 (0.5%)	36 (0.9%)	94 (0.9%)	593 (1.5%)	<0.001
Procedure	Thoracotomy	10,400 (12.8%)	2,565 (9.3%)	421 (10.2%)	1,290 (12.7%)	6,124 (15.7%)	<0.001
	Mini-thoracotomy	37,604 (46.4%)	12,602 (45.5%)	1,851 (44.8%)	4,712 (46.5%)	18,439 (47.2%)	
	cVATS	32,985 (40.7%)	12,513 (45.2%)	1,864 (45.1%)	4,141 (40.8%)	14,467 (37.1%)	
Bronchoplasty		1,411 (1.7%)	240 (0.9%)	43 (1.0%)	158 (1.6%)	970 (2.5%)	<0.001

Values are presented as n (%).

Pearson's chi-squared test was used for comparison.

PY: pack-years, cT: clinical T, cN: clinical N, AD: adenocarcinoma, CT: chemotherapy,

RT: radiation therapy, cVATS: complete video assisted thoracic surgery

Table 3. Preoperative comorbidities

Comorbidity	Total (80,989)	PY=0 (27,680)	0<PY<10 (4,136)	10≦PY<30 (10,143)	30<PY (39,030)	p-value
Interstitial pneumonia	3,480 (4.3%)	212 (0.8%)	70 (1.7%)	403 (4.0%)	2,795 (7.2%)	<0.001
Hemodialysis	498 (0.6%)	118 (0.4%)	24 (0.6%)	78 (0.8%)	278 (0.7%)	<0.001
Diabetes mellitus	12,414 (15.3%)	2,760 (10.0%)	437 (10.6%)	1,399 (13.8%)	7,818 (20.0%)	<0.001
Ischemic heart disease	4,490 (5.5%)	691 (2.5%)	150 (3.6%)	518 (5.1%)	3,131 (8.0%)	<0.001
Cerebral stroke	4,944 (6.1%)	1,105 (4.0%)	201 (4.9%)	589 (5.8%)	3,049 (7.8%)	<0.001
Autoimmune disease	1,705 (2.1%)	619 (2.2%)	80 (1.9%)	244 (2.4%)	762 (2.0%)	0.008
Arrhythmia	3,120 (3.9%)	795 (2.9%)	158 (3.8%)	445 (4.4%)	1,722 (4.4%)	<0.001
Hepatic dysfunction	349 (0.4%)	65 (0.2%)	15 (0.4%)	53 (0.5%)	216 (0.6%)	<0.001

Values are presented as n (%).

Pearson's chi-squared test was used for comparison.

PY: pack-years

Table 4. Postoperative outcomes

Outcome	Total (80,989)	PY=0 (27,680)	0<PY<10 (4,136)	10≦PY<30 (10,143)	30<PY (39,030)	p-value
Mortality (30 day)	600 (0.7%)	45 (0.2%)	20 (0.5%)	69 (0.7%)	466 (1.2%)	<0.001
Complication (Lung)	6,420 (7.9%)	947 (3.4%)	223 (5.4%)	767 (7.6%)	4,483 (11.5%)	<0.001
Complication (CVD)	2,013 (2.5%)	500 (1.8%)	92 (2.2%)	234 (2.3%)	1,187 (3.0%)	<0.001
Complication (Infection)	848 (1.0%)	144 (0.5%)	33 (0.8%)	95 (0.9%)	576 (1.5%)	<0.001
Operation time	200 (158-253)	185 (147-233)	195 (153-243)	200 (158-252)	213 (168-269)	<0.001
Blood loss	52 (18-130)	42 (10-100)	50 (12.5-110)	50 (19-128)	75 (25-165)	<0.001
Hospital LOS	9 (7-13)	8 (7-11)	8 (7-12)	9 (7-12)	10 (7-14)	<0.001

Values are presented as median (25th–75th percentile interval) or n (%).

Pearson's chi-squared test for mortality and complications.

Kruskal-Wallis test for operation time, blood loss and hospital LOS.

PY: pack-years, CVD: cardiovascular disease, LOS: length of stay

Table 5. Postoperative complications

Complication		Total (80,989)	PY=0 (27,680)	0<PY<10 (4,136)	10≦PY<30 (10,143)	30<PY (39,030)	p-value
Lung	Prolonged air leakage	3,927 (4.8%)	638 (2.3%)	160 (3.9%)	471 (4.6%)	2,658 (6.8%)	<0.001
	Bronchopleural fistula	282 (0.3%)	25 (0.1%)	12 (0.3%)	32 (0.3%)	213 (0.5%)	<0.001
	Pneumonia	1,621 (2.0%)	184 (0.7%)	41 (1.0%)	179 (1.8%)	1,217 (3.1%)	<0.001
	Interstitial pneumonia	504 (0.6%)	22 (0.1%)	5 (0.1%)	56 (0.6%)	421 (1.1%)	<0.001
	Atelectasis	557 (0.7%)	90 (0.3%)	10 (0.2%)	58 (0.6%)	399 (1.0%)	<0.001
	Respiratory insufficiency	408 (0.5%)	35 (0.1%)	8 (0.2%)	39 (0.4%)	326 (0.8%)	<0.001
Cardiovascular	Cardiac infarction	37 (0.0%)	1 (0.0%)	1 (0.0%)	4 (0.0%)	31 (0.1%)	<0.001
	Cerebral stroke	296 (0.4%)	66 (0.2%)	17 (0.4%)	39 (0.4%)	174 (0.4%)	<0.001
	Pulmonary embolism	111 (0.1%)	31 (0.1%)	6 (0.1%)	8 (0.1%)	66 (0.2%)	0.080
	Arrhythmia	1,601 (2.0%)	408 (1.5%)	68 (1.6%)	186 (1.8%)	939 (2.4%)	<0.001
Infection	Wound infection	233 (0.3%)	48 (0.2%)	9 (0.2%)	26 (0.3%)	150 (0.4%)	<0.001
	Empyema	648 (0.8%)	104 (0.4%)	27 (0.7%)	75 (0.7%)	442 (1.1%)	<0.001

Values are presented as n (%).

Pearson's chi-squared test for prolonged air leakage, pneumonia, empyema and arrhythmia.

Fisher's exact test for other complications.

PY: pack-years

Table 6. Multivariable analysis for postoperative mortality and complications (Cumulative smoking dose)

Variable		Mortality			Complication (Lung)			Complication (CVD)			Complication (Infection)		
		OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
Cumulative smoking dose	PY=0	Ref.			Ref.			Ref.			Ref.		
	0<PY<10	1.76	1.02-3.04	0.044	1.20	1.03-1.40	0.022	1.15	0.91-1.45	0.232	1.16	0.79-1.72	0.446
	10≤PY<30	1.60	1.06-2.43	0.026	1.40	1.25-1.56	<0.001	1.09	0.91-1.30	0.334	1.12	0.84-1.49	0.458
	30≤PY	1.73	1.20-2.50	0.003	1.72	1.57-1.89	<0.001	1.26	1.09-1.46	0.002	1.39	1.09-1.77	0.007

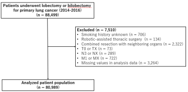
This result was assessed after adjusting for the following covariates: sex; age; smoking status; surgical procedure; Eastern Cooperative Oncology Group performance status; respiratory function; body mass index; preoperative comorbidities (interstitial pneumonia, hemodialysis, diabetes mellitus, ischemic heart disease, cerebral stroke, autoimmune disease, arrhythmia, hepatic dysfunction); preoperative treatment (chemotherapy, radiotherapy); histology, and clinical T and clinical N factor.

Ref: reference, CVD: cardiovascular disease, OR: odds ratio, CI: confidence interval, PY: pack-years

Figure legends

Figure 1

Flowchart of inclusion criteria in this study.



Patients underwent lobectomy or bilobectomy for primary lung cancer (2014-2016)
(n = 88,499)
Excluded (n = 7,510)
Smoking history unknown (n = 706)
Robotic-assisted thoracic surgery (n = 134)
Combined resection with neighboring organs (n = 2,322)
T0 or TX (n = 73)
N3 or NX (n = 289)
M1 or MX (n = 722)
Missing values in analysis data (n = 3,264)
Analyzed patient population
(n = 80,989)

Supplemental Table 1. Surgical mortality according to age and PY

Age, range (n)	Total (80,989)	PY=0 (27,680)	0<PY<10 (4,136)	10≦PY<30 (10,143)	30<PY (39,030)
-59 (10,336)	19/10,366 (0.18%)	3/3,759 (0.08%)	0/891 (0.00%)	3/2,103 (0.14%)	13/3,583 (0.36%)
60-64 (10,002)	32/10,002 (0.32%)	1/3,050 (0.03%)	1/600 (0.17%)	5/1,225 (0.41%)	25/5,127 (0.49%)
65-69 (17,887)	79/17,887 (0.44%)	2/5,747 (0.03%)	2/823 (0.24%)	4/2,063 (0.19%)	71/9,254 (0.77%)
70-74 (19,103)	154/19,103 (0.81%)	8/6,349 (0.13%)	4/740 (0.54%)	15/2,043 (0.73%)	127/9,971 (1.27%)
75-79 (15,034)	178/15,034 (1.18%)	15/5,483 (0.27%)	6/665 (0.90%)	18/1,691 (1.06%)	139/7,195 (1.93%)
80- (8,627)	138/8,627 (1.60%)	16/3,292 (0.49%)	7/417 (1.68%)	24/1,018 (2.36%)	91/3,900 (2.33%)
Total (80,989)	600/80,989 (0.74%)	45/27,680 (0.16%)	20/4,136 (0.48%)	69/10,143 (0.68%)	466/39,030 (1.19%)

PY: pack-years

Supplemental Table 2 Multivariable analysis for postoperative mortality and complications (Other covariates)

		Mortality			Complication (Lung)			Complication (CVD)			Complication (Infection)		
		OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
Gender	Male	2.84	2.02-3.99	<0.001	2.14	1.97-2.34	<0.001	1.22	1.07-1.39	0.004	1.91	1.53-2.39	<0.001
	Female	Ref.			Ref.			Ref.			Ref.		
Age	< 60 years	Ref.			Ref.			Ref.			Ref.		
	5 year increase (60-80 years)	1.48	1.38-1.58	<0.001	1.14	1.12-1.16	<0.001	1.21	1.17-1.25	<0.001	1.07	1.02-1.12	0.005
Procedure	Thoracotomy	Ref.			Ref.			Ref.			Ref.		
	Mini-thoracotomy	0.86	0.70-1.06	0.168	0.92	0.85-0.99	0.036	0.92	0.81-1.05	0.231	0.88	0.73-1.06	0.188
	Complete VATS	0.61	0.47-0.78	<0.001	0.90	0.83-0.98	0.012	0.85	0.74-0.98	0.024	0.71	0.58-0.87	<0.001
PS	0-1	Ref.			Ref.			Ref.			Ref.		
	>2	1.87	1.39-2.51	<0.001	1.11	0.97-1.27	0.119	0.74	0.56-0.96	0.025	1.27	0.92-1.76	0.144
%VC	> 100%	Ref.			Ref.			Ref.			Ref.		
	10% decrease (50-100%)	1.44	1.35-1.52	<0.001	1.09	1.06-1.11	<0.001	1.03	0.99-1.07	0.118	1.06	1.00-1.13	0.033
BMI	<18.5	1.55	1.20-1.99	0.001	1.94	1.79-2.11	<0.001	1.08	0.92-1.27	0.351	1.39	1.11-1.73	0.004
	≥18.5	Ref.			Ref.			Ref.			Ref.		
BMI	≤30	Ref.			Ref.			Ref.			Ref.		
	>30	0.86	0.47-1.58	0.618	0.90	0.75-1.09	0.281	0.88	0.64-1.20	0.414	1.63	1.13-2.34	0.008
Interstitial pneumonia	+	4.57	3.76-5.54	<0.001	1.96	1.79-2.15	<0.001	1.16	0.96-1.40	0.122	1.14	0.87-1.49	0.33
	-	Ref.			Ref.			Ref.			Ref.		
Hemodialysis	+	2.90	1.63-5.14	<0.001	1.19	0.89-1.59	0.237	1.59	1.02-2.48	0.04	1.16	0.55-2.47	0.696
	-	Ref.			Ref.			Ref.			Ref.		
Diabetes mellitus	+	0.86	0.70-1.05	0.139	0.97	0.90-1.04	0.34	0.97	0.86-1.10	0.656	1.20	1.02-1.42	0.032
	-	Ref.			Ref.			Ref.			Ref.		

Ischemic heart disease	+	1.29	0.99-1.66	0.056	1.17	1.06-1.29	0.002	1.26	1.07-1.48	0.005	0.88	0.66-1.16	0.349
	-	Ref.			Ref.			Ref.			Ref.		
Cerebral stroke	+	1.28	0.99-1.66	0.058	1.20	1.09-1.32	<0.001	1.37	1.18-1.59	<0.001	1.21	0.95-1.54	0.13
	-	Ref.			Ref.			Ref.			Ref.		
Autoimmune disease	+	1.10	0.67-1.82	0.698	1.39	1.18-1.64	<0.001	0.98	0.71-1.35	0.89	1.73	1.18-2.55	0.005
	-	Ref.			Ref.			Ref.			Ref.		
Arrhythmia	+	1.51	1.12-2.04	0.007	1.26	1.12-1.42	<0.001	2.75	2.38-3.18	<0.001	1.33	0.99-1.78	0.057
	-	Ref.			Ref.			Ref.			Ref.		
Hepatic dysfunction	+	4.76	2.65-8.54	<0.001	1.37	0.99-1.91	0.057	0.95	0.49-1.84	0.87	2.84	1.58-5.10	<0.001
	-	Ref.			Ref.			Ref.			Ref.		
Preoperative CT	+	1.38	0.79-2.42	0.256	1.14	0.92-1.40	0.222	0.49	0.30-0.78	0.003	1.20	0.75-1.93	0.439
	-	Ref.			Ref.			Ref.			Ref.		
Preoperative RT	+	1.04	0.48-2.26	0.926	1.12	0.84-1.48	0.439	2.19	1.27-3.78	0.005	1.05	0.56-1.96	0.884
	-	Ref.			Ref.			Ref.			Ref.		
T factor	Tis-1	Ref.			Ref.			Ref.			Ref.		
	T2	1.07	0.89-1.29	0.453	1.12	1.06-1.19	<0.001	1.16	1.05-1.28	0.003	1.19	1.02-1.38	0.023
	T3-4	1.41	1.08-1.84	0.012	1.23	1.11-1.36	<0.001	1.20	1.01-1.43	0.043	1.37	1.08-1.74	0.01
N factor	N0	Ref.			Ref.			Ref.			Ref.		
	N1	1.44	1.15-1.81	0.002	1.21	1.11-1.31	<0.001	1.11	0.96-1.30	0.159	1.5	1.23-1.83	<0.001
	N2	1.39	1.03-1.87	0.029	1.03	0.92-1.16	0.620	1.5	1.25-1.80	<0.001	1.5	1.16-1.94	0.002
Histology	AD	0.55	0.45-0.66	<0.001	0.78	0.73-0.82	<0.001	0.93	0.84-1.03	0.148	0.81	0.70-0.94	0.006
	Non AD	Ref.			Ref.			Ref.			Ref.		
Bronchoplasty	+	1.77	1.22-2.58	0.003	1.33	1.13-1.56	<0.001	1.68	1.30-2.18	<0.001	1.66	1.19-2.31	0.003
	-	Ref.			Ref.			Ref.			Ref.		

Ref: reference, CVD: cardiovascular disease, OR: odds ratio, CI: confidence interval, VATS: video assisted thoracic surgery, PS: Eastern Cooperative Oncology Group performance status, VC: vital capacity, BMI: body mass index, AD: adenocarcinoma, CT: chemotherapy, RT: radiation therapy

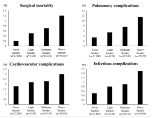
Figure legends

Supplemental Figure 1

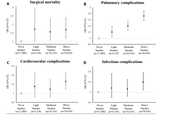
Relationship between postoperative outcomes and preoperative cumulative smoking dose. Preoperative cumulative smoking dose was categorized by pack-years (PY): Non-smokers, PY = 0; light smokers, 0 < PY < 10; moderate smokers, 10 ≤ PY < 30; and heavy smokers, 30 ≤ PY. A) Surgical mortality; B) Postoperative pulmonary complications; C) Postoperative cardiovascular complications; and D) Postoperative infectious complications.

Supplemental Figure 2

Risk of short-term outcomes was assessed according to cumulative smoking dose using multivariable analysis. The odds were adjusted for covariates. Preoperative cumulative smoking dose was categorized by pack-years (PY): Non-smokers, PY = 0; light smokers, 0 < PY < 10; moderate smokers, 10 ≤ PY < 30; and heavy smokers, 30 ≤ PY. A) Surgical mortality; B) Postoperative pulmonary complications; C) Postoperative cardiovascular complications; and D) Postoperative infectious complications.



Surgical mortality
Pulmonary complications
Cardiovascular complications
Infectious complications
(%)
Never Smoker (n=27,680)
Light Smoker (n=4,136)
Moderate Smoker (n=10,143)
Heavy Smoker (n=39,030)



A
Surgical mortality
OR (95% CI)
Never Smoker (n=27,680)
Light Smoker (n=4,136)
Moderate Smoker (n=10,143)
Heavy Smoker (n=39,030)
B
Pulmonary complications
C
Cardiovascular complications
D
Infectious complications