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2019

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Asian Journal of Surgery (2020) 43, 154–165

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-asianjournalsurgery.com

ORIGINAL ARTICLE

Outcomes of pulmonary resection in non-small cell lung cancer patients older than 70 years old

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Received 3 December 2018; received in revised form 23 January 2019; accepted 5 March 2019
Available online 18 March 2019

KEYWORDS
Old age;
Resectable NSCLC;
Lobectomy;
Prognostic factor;
Propensity score

Summary *Background:* An appropriate treatment of older lung cancer patients has become an important issue. The aim of this study is to evaluate the short and long-term surgical outcomes in lung cancer patients using 70 years as a cut-point, and to identify prognostic factors of cancer-specific mortality in patients older than 70 years.
Methods: Medical records of non-small cell lung cancer (NSCLC) patients who underwent pulmonary resection at Chiang Mai University Hospital from January 2002 through December 2016 were retrospectively reviewed. Patients were divided into age less than 70 years (control group) and 70 years or more (study group). Primary outcomes were major post-operative complications and in-hospital death (POM); secondary outcome was long-term survival.

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https://doi.org/10.1016/j.asjsur.2019.03.006
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Multivariable regression analysis was used.
Results: This study included 583 patients, 167 for study group, and 416 for control group. There were no differences in POM, both at univariable and multivariable analyses, however, for long-term cancer-specific mortality, the study group was more likely to die (HR_{adj} = 1.40, 95% CI = 1.03–1.89). Adverse prognostic factors for long-term mortality in study group were having universal coverage scheme (HR_{adj} = 1.70, 95%CI = 1.03–2.79), the presence of intratumoral lymphatic invasion (HR_{adj} = 2.83, 95%CI = 1.28–6.29), perineural invasion (HR_{adj} = 2.80, 95%CI = 1.13–6.94), underwent lymph node sampling (HR_{adj} = 2.23, 95% CI = 1.16–4.30) and higher stage of disease (HR_{adj} = 2.02, 95%CI = 1.06–3.85 for stage III, HR_{adj} = 3.40, 95%CI = 1.29–8.94 for stage IV).
Conclusions: In-hospital mortality and composite post-operative complications are acceptable in pulmonary resection for NSCLC patients older than 70 years. However, these patients had shorter long-term survival, especially who have some adverse prognostic factors. Further studies with larger sample size are warranted.
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1. Introduction

Surgical treatment is the standard of care with curative intent in early stage non-small cell lung cancer (NSCLC) patients, but also for symptomatic treatment in advanced disease. Nowadays, because of increasing in life span, and more than one-third of lung cancer patients being age >70 years old,[1,2] defining the appropriate treatment of elderly lung cancer patients has become an important issue in terms of perioperative morbidity, mortality and overall survival. Because of physiological changes in the cardiovascular and pulmonary function in elderly patients, morbidity and mortality after pulmonary resection should be a concern. Previous studies reported that there are approximately 30–50% postoperative complications in elderly NSCLC patients,[3–5] therefore alternative treatment strategies and surgical techniques were developed for avoiding postoperative complications such as stereotactic body radiotherapy, and minimally invasive approach.[6–8] Although previous studies demonstrated excellent outcomes with acceptable postoperative morbidity and mortality in elderly patients after either sublobar resection or lobectomy,[2,9,10] some studies report worse short-term and long-term outcomes in elderly patients (age≥70 years) in comparison to younger ones.[11] In this study, we retrospectively reviewed data on NSCLC patients who underwent curative pulmonary resection to analyze the short and long-term surgical outcomes comparing between patients age <70 years and age ≥70 years, to determine the impact of age on long-term survival and to identify prognostic factors of long-term cancer-specific mortality in patients age more than 70 years.

2. Patients and methods

This is a retrospective cohort study. Medical records of non-small cell lung cancer (NSCLC) patients who underwent pulmonary resection (either curative or palliative intent) with systematic mediastinal lymph node dissection or sampling in the general thoracic surgery unit, department of surgery, faculty of medicine, Chiang Mai university, Chiang Mai, Thailand between January 2002 to June 2015 were retrospectively reviewed. Clinical characteristics including age, gender, history of smoking, family history of cancer, comorbidities, patient physical status, laboratory findings, pre-operative cardiac and pulmonary function testing, surgery information, pathologic report and post-operative outcomes were extracted. The cut-of-point for age is debatable, however, according to previous studies,[12–15] we used the age of 70 years to divide all eligible patients into two groups; study group (age ≥ 70 years) and control group (age <70 years). The primary outcome was composite: major postoperative complication (POM) (including in-hospital mortality, pneumonia, acute respiratory distress syndrome (ARDS), intubation more than 24 h after surgery (delayed extubation), re-intubation, tracheostomy, atelectasis needing bronchoscopy and prolonged air leak more than 5 days according to STS GTDB guidelines.[16] The secondary outcomes were length of hospital stay, long-term cancer-specific mortality, and tumor recurrence. This study was reviewed and approved by the Institutional Review Board of Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand with Study Code: SUR-2558-033491/Research ID: 3349, and approval ID 434/2015.

All patients received preoperative cancer staging including computed tomography (CT) with contrast or whole-body positron emission tomography, bronchoscopy with biopsy, bronchial washing, brushing or bronchial lavage cytology. If mediastinal lymph nodes were larger than 1 cm, endobronchial ultrasound-guided (EBUS) fine needle aspiration, or mediastinoscope biopsy were performed. All patients had a biochemistry profile, a pulmonary function test, a room-air arterial blood gas, and an electrocardiography.

The pulmonary resections included wedge, segmentectomy, lobectomy and pneumonectomy, both for curative intent or palliative resection. The indication for sublobar resection (wedge resection or segmentectomy) included patients who had maximum tumor size less than 2 cm and

severe comorbid diseases or poor-pulmonary reserved function according to American College of Chest Physicians Evidence-Based Clinical Practice Guideline.[17] Surgical approaches included open thoracotomy and video-assisted thoracoscopic approach (VATS). Systematic mediastinal lymph node dissection (SLND) or sampling (SLNS) were performed in all cases. According to European Society of Thoracic Surgeons guidelines, systematic mediastinal lymph node dissection is to dissect and remove all mediastinal tissue containing the lymph nodes within anatomic landmark at least three mediastinal nodal stations, including the subcarinal node. Systematic mediastinal lymph node sampling means a lesser excision of certain nodal stations that seem to be representative or abnormal in preoperative evaluations or intraoperative.[18] Lymph node mapping was issued by International Association for the Study of Lung Cancer (IASLC), original by Naruke et al.[19] Lymph node ratio was calculated by the proportion of positive dissected lymph node over the total number of dissected lymph node. Tumor staging was reviewed according to the 8th edition of the TNM classification for lung cancer issued by (IASLC).[20]

After discharge, patients were followed up at 2 weeks and 1−2 months with CXR and physical examination, and then every 3 months for the first two years and then every 6 months with CT-scan. When tumor recurrence was suspected, diagnostic procedures were performed to confirm the diagnosis either with cytology or diagnostic radiology. Patients received chemotherapy and/or radiotherapy according to their performance status and tumor status. The regimens of chemotherapy included cisplatin, carboplatin, vinorelbine, vinorelbine, gemcitabine, docetaxel, pemetrexed and targeted therapy (erlotinib, gefitinib, crizotinib) depending on molecular testing and insurance coverage. Overall survival and recurrence-free survival were calculated from the date of surgery to the most recent follow-up contact or to the date of death, and from the date of first tumor diagnosis to either local recurrence or distant metastasis, respectively.

2.1. Statistical analysis

categorical variables were presented as frequency and proportion (%); continuous variables were presented as mean ± standard deviation (SD) or median ± interquartile range (IQR) depending on the data distribution. When the two groups were compared, Fisher exact test was used for categorical data and unpaired student t-test or Wilcoxon rank sum test for continuous variables. Univariable and multivariable logistic regression analysis were used to identify risk factors of POM and presented with odd ratios and 95% confidence intervals; matching propensity score was also performed and showed in the supplement data. Multiple imputations with multivariate normal equation were performed for any variables with at least 10% missing values.[21] We then compared the results from a complete-case analysis with the results of multiple imputations (MI) analysis. Cox proportional hazard model was used to assess prognostic factors of recurrence of disease and long-term survival, which were presented as hazard ratios with 95% confidence interval. Any risk factors or prognostic factors with p value < 0.1 in the univariable analyses and other potential clinical confounders associated with POM, tumor recurrence, and long-term survival were included in the multivariable analysis model. Multicollinearity of independent factors was tested before performing multivariable analysis. Patients with stage IV disease were excluded when analyzing for prognostic factors for tumor recurrence. The statistical analysis was completed in STATA statistical package (Release 15.1,2018; StataCorp, CS, TX, USA), with $p < 0.05$ indicating a statistically significant difference.

3. Results

There were 583 patients diagnosed with NSCLC who underwent curative or palliative pulmonary resection enrolled in this study, 167 in study group and 416 in control group. The mean age was 62.4 ± 10.4 years (range from 18 to 86 years), 74.5 ± 4.0 years in the study group and 57.5 ± 8.0 years in the control group. Their demographics, preoperative characteristics, and pathologic results are shown in Table 1. There were 36 patients diagnosed stage IVA who underwent pulmonary resection; 20 patients presented with single brain metastasis and received whole brain radiation or excision and 16 patients had single lung to lung metastasis. Patients in the study group were more likely to have the civil servant medical benefit scheme, be active smoker, have a higher number of pack-year of smoking, COPD, HT, dyslipidemia, abnormal preoperative ECG than patients in the control group. There were no statistically significant differences in gender, body mass index, preoperative pulmonary function test, ejection fraction, tumor stage and pathologic findings between the two groups. Patients in the study group were more likely to undergo sublobar resection (wedge resection or segmentectomy), SLNS, and to die in hospital, whereas less likely to receive chemotherapy (either adjuvant or neoadjuvant regimen), and to be immediately extubated after surgery than those in the control group (Table 2). There were no statistically significant differences in term of approach (VATS or open thoracotomy), lymph node ratio, operative time, estimated blood loss, and length of intensive care unit stay between the two groups. Postoperative complications, major complications, and overall mortality were not different between the two groups. However, in-hospital mortality, postoperative arrythmia, air leak, acute renal failure and other minor complications were documented more often among patients in the study group than the control group. The most common postoperative complication in both groups was postoperative air leak; these patients only had forced expiratory air leak and success for conservative treatment. The incidence of postoperative acute renal failure in the study group was higher than in the control group (2.5% versus 0.5%, $p = 0.059$). Patients in the study group had shorter follow-up time than the control group. In a subgroup analysis according to stage, patients in the study group were more likely to undergo sublobar resection than those in the control group; however, only stage IA3 patients showed a statistically significant difference between the two groups (Supplement A).

POM was not statistically different between the two groups. The adjusted Odds Ratio for study group compared to the control group was 0.89 (95% confidence interval (CI) = 0.43−1.84) (Table 3).

Table 1 Patient characteristics according to age groups.

Variables	Study group N = 167	Control group N = 416	p-value
Gender, n (%)			0.192
Female	61 (36.5)	178 (42.8)	
Male	106 (63.5)	238 (57.2)	
BMI (kg/m^2), Mean ± SD	21.2 ± 3.7	21.5 ± 3.9	0.387
Insurance type, n (%)			<0.001
UCS	77 (46.1)	234 (56.3)	
CSMBS	87 (52.1)	148 (35.6)	
SSS	2 (1.2)	31 (7.5)	
PI/cash	1 (0.6)	3 (0.7)	
Smoking status, n (%)			0.038
Non-smokers	34 (20.4)	100 (24.0)	
Active smoker or ex-smokers	119 (71.4)	274 (65.9)	
Passive smokers	0	14 (3.4)	
Unknown	14 (8.4)	28 (6.7)	
Pack-year, Median (IQR)	30 (18—47)	20 (10—40)	0.004
Comorbid disease, n (%)			
COPD	38 (22.8)	49 (11.8)	0.001
Diabetes mellitus	26 (15.6)	42 (10.1)	0.086
Hypertension	97 (58.1)	129 (31.0)	<0.001
Dyslipidemia	45 (27.0)	68 (16.4)	0.005
History of other malignancy	13 (7.8)	23 (5.5)	0.342
Pulmonary function test			
Precent predicted FEV1, Mean ± SD	82.5 ± 25.0	78.1 ± 21.0	0.199
Preoperative PaO_2, Mean ± SD	125.5 ± 55.4	124.9 ± 49.5	0.970
Preoperative $PaCO_2$, Mean ± SD	43.4 ± 11.0	47.6 ± 31.2	0.562
Preoperative ECG, n (%)			<0.001
Normal	94 (56.3)	315 (75.7)	
ST-T segment abnormality	24 (14.4)	21 (5.1)	
Bundle branch block	10 (6.0)	14 (3.4)	
Arrhythmias	9 (5.3)	5 (1.2)	
Non-specific abnormality	30 (18.0)	61 (14.7)	
Ejection fraction (%), Mean ± SD	65.5 ± 9.1	65.5 ± 9.5	0.990
Histology, n (%)			0.072
Adenocarcinoma	102 (61.1)	280 (67.3)	
Squamous cell carcinoma	49 (29.3)	83 (20.0)	
Large cell carcinoma	5 (3.0)	11 (2.6)	
Others	11 (6.6)	42 (10.1)	
Tumor staging			0.401
IA1	3 (1.8)	11 (2.6)	
IA2	14 (8.4)	33 (7.9)	
IA3	22 (13.2)	45 (10.8)	
IB	29 (17.4)	45 (10.8)	
IIA	10 (6.0)	26 (6.3)	
IIB	30 (18.0)	80 (19.2)	
IIIA	34 (20.4)	119 (28.6)	
IIIB	11 (6.6)	32 (7.7)	
IIIC	1 (0.6)	2 (0.5)	
IVA	13 (7.8)	23 (5.5)	
Cell differentiation, n (%)			0.543
Well differentiation	57 (40.4)	116 (33.5)	
Moderately differentiation	52 (36.9)	146 (42.2)	
Poorly differentiation	28 (19.9)	73 (21.1)	
Undifferentiation	4 (2.8)	11 (3.2)	
Intratumoral lymphatic invasion, n (%)	125 (74.9)	297 (71.4)	0.414
Intratumoral vascular invasion, n (%)	64 (38.3)	160 (38.5)	1.000
Visceral pleural invasion, n (%)	27 (16.2)	79 (19.0)	0.477

(*continued on next page*)

Table 1 (*continued*)

Variables	Study group N = 167	Control group N = 416	p-value
Perineural invasion, n (%)	13 (3.1)	11 (6.6)	0.066
Tumor necrosis, n (%)	44 (26.4)	123 (29.6)	0.479

BMI = body mass index, UCS = Universal coverage scheme, CSMBS = Civil servant medical benefit scheme, SSS = Social security scheme, PI = Private insurance, COPD = chronic obstructive pulmonary disease, FEV_1 = forced expiratory volume in 1 s, PaO_2 = partial pressure of oxygen in arterial blood, $PaCO_2$ = partial pressure of carbon dioxide in arterial blood, ECG = electrocardiogram.

Table 2 Treatment and postoperative outcomes according to age groups.

Variables	Study group N = 167	Control group N = 416	p-value
Procedures			0.003
Wedge resection	38 (22.8)	58 (14.1)	
Segmentectomy	9 (5.4)	7 (1.7)	
Lobectomy	118 (70.7)	337 (81.8)	
Pneumonectomy	2 (1.2)	10 (2.4)	
Approach			0.230
Open thoracotomy	132 (79.0)	345 (83.5)	
Video-assisted thoracoscopic surgery	35 (21.0)	68 (16.5)	
Mediastinal lymph node evaluation			0.013
Lymph node sampling	31 (22.8)	48 (13.2)	
Systematic lymph node dissection	105 (77.2)	315 (86.8)	
Lymph node ratio, Median (IQR)	0.20 (0.06–0.48)	0.15 (0.07–0.36)	0.155
Chemotherapy			<0.001
No	115 (68.8)	171 (41.1)	
Adjuvant therapy	44 (26.4)	208 (50.0)	
Neoadjuvant therapy or induction therapy	8 (4.8)	37 (8.9)	
Operative time (minutes), Mean ± SD	138.6 ± 3.7	148.0 ± 54.5	0.055
Estimated blood loss (mL), Median (IQR)	150 (100–300)	200 (100–300)	0.673
ICU stay (hours), Median (IQR)	35.3 (18.8–70.2)	36.5 (18.1–67.4)	0.741
Immediate extubation after surgery	134 (80.2)	364 (87.5)	0.028
In-hospital mortality	7 (4.2)	4 (1.0)	0.016
Postoperative complications			
Pneumonia	5 (3.0)	14 (3.4)	1.000
Re-intubation	3 (1.8)	12 (2.9)	0.572
Atelectasis with bronchoscopy needed	5 (3.0)	9 (2.2)	0.556
Arrhythmias	3 (3.2)	3 (1.0)	0.137
Air leakage	15 (9.0)	31 (7.5)	0.610
Acute renal failure	4 (2.4)	2 (0.5)	0.059
Acute pulmonary embolism	0	1 (0.2)	1.000
Chylothorax	2 (1.2)	4 (1.0)	1.000
Other minor complications	16 (9.6)	30 (7.2)	0.395
Composite major postoperative complications (POM)	20 (12.0)	48 (11.5)	0.887
Length of hospital stay (day), Median (IQR)	7 (6–10)	7 (5–10)	0.205
Long-term cancer-specific mortality	100 (62.5)	229 (55.7)	0.157
Median survival time, month (IQR)	40.98 (28.68–70.38)	56.17 (39.16–88.97)	0.006[a]
Tumor recurrence, n (%)	70 (41.92)	190 (45.67)	0.839
Median (IQR)	10.98 (5.23–18.77)	11.97 (6.13–23.60)	0.469[a]
Mean ± SD	17.22 ± 17.92	18.86 ± 19.29	
Follow-up time (month)			0.006
Median (IQR)	24.0 (9.3–50.4)	34.1 (13.0–61.5)	
Mean ± SD	33.9 ± 31.0	42.9 ± 36.5	

[a] Analyzed by log-rank test.

Tumor recurrence was not statistically significant different between groups, while long-term cancer-specific mortality was: patients in the study group had shorter long-term survival than those in the control group (Fig. 1). In multivariable analysis, the adjusted hazard ratio (HR_{adj}) for tumor recurrence in the study group compared to the

Table 3 Univariable and multivariable analysis to identify risk factors for composite major complications and in-hospital mortality (POM).

Variables	Univariable analysis			Multivariable analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age ≥70 years vs age <70 years	1.04	0.60–1.82	0.882	0.89	0.43–1.84	0.763
Male vs female	1.52	0.89–2.61	0.125	1.27	0.62–2.61	0.517
BMI (kg/m2)	0.91	0.84–0.98	0.010	0.95	0.86–1.04	0.267
UCS or SSS versus CSMBS or PI	1.22	0.72–2.06	0.451	1.09	0.56–2.12	0.793
Active smoker vs non-smoker	2.31	1.11–4.80	0.006	1.61	0.64–4.03	0.313
Pack-year[a]	2.49	1.28–4.83	0.007	–	–	
COPD	2.79	1.56–4.98	0.001	2.64	1.29–5.41	0.008
Diabetes mellitus	1.01	0.46–2.22	0.978	–	–	
Hypertension	0.79	0.46–1.34	0.374	–	–	
Dyslipidemia	0.78	0.40–1.54	0.478	–	–	
History of other malignancy	0.43	0.11–1.93	0.252	–	–	
Percent predicted FEV1	0.98	0.96–0.99	0.012	0.98	0.96–1.01	0.153
Preoperative PaO_2	0.99	0.98–1.01	0.184	–	–	
Preoperative $PaCO_2$	1.00	0.98–1.02	0.941	–	–	
Preoperative ECG, n (%)						
Normal	1.00	Reference		–	–	
ST-T segment abnormality	1.57	0.66–3.73	0.309	0.89	0.27–2.95	0.853
Bundle branch block	1.70	0.56–5.21	0.351	1.45	0.39–5.46	0.583
Arrhythmias	1.42	0.31–6.55	0.654	1.32	0.24–7.44	0.751
Non-specific abnormality	1.29	0.65–2.56	0.462	1.04	0.45–2.38	0.926
Ejection fraction (%), Mean ± SD	0.99	0.93–1.06	0.785	–	–	
Histology						
Adenocarcinoma	1.00	Reference		1.00	Reference	
Squamous cell carcinoma	2.20	1.26–3.87	0.006	1.51	0.75–3.06	0.247
Large cell carcinoma	3.30	1.01–10.80	0.048	1.77	0.41–4.61	0.440
Others	1.03	0.38–2.76	0.949	0.82	0.25–2.69	0.745
Tumor staging (8th IASLC edition)						
Stage I	1.00	Reference		1.00	Reference	
Stage II	1.43	0.71–2.91	0.319	1.12	0.57–2.83	0.788
Stage III	1.93	1.03–3.63	0.041	1.28	0.65–2.96	0.527
Stage IV	1.36	0.43–4.30	0.601	1.65	0.33–5.69	0.518
Surgical Procedure						
Lobectomy	1.00	Reference		1.00	Reference	
Sublobar resection	0.64	0.30–1.33	0.228	1.03	0.31–3.43	0.960
Pneumonectomy	3.64	1.06–22.75	0.040	2.97	0.59–14.78	0.183
VATS vs Open thoracotomy	0.50	0.22–1.12	0.092	0.59	0.16–2.15	0.429
SLNS vs SLND	1.30	0.66–2.56	0.418	0.83	0.36–1.90	0.661
Neoadjuvant therapy or induction therapy	1.18	0.48–2.90	0.717	1.30	0.47–3.59	0.617
Operative time (minutes)	1.01	1.01–1.02	0.002	1.00	0.99–1.01	0.652
Estimated blood loss (mL)	1.01	1.01–1.02	<0.001	1.00	0.99–1.01	0.732

BMI = Body mass index, UCS = Universal coverage scheme, CSMBS = Civil servant medical benefit scheme, SSS = Social security scheme, PI = Private insurance, COPD = chronic obstructive pulmonary disease, FEV1 = Force expiratory volume in 1 min, SLND = Systematic lymph node dissection, SLNS = Systematic lymph node sampling, OR = Odd ratio, CI = Confidence interval.

[a] Not include in multivariable analysis due to multicollinearity with smoking status.

control group was 0.93 (95% CI = 0.61–1.44, p-value = 0.821). Median time to progression in the two groups was comparable (10.98 months for the study group and 11.97 months for the control group, Table 2). For long-term cancer-specific mortality, patients in the study group were more likely to die (HR_{adj} = 1.40, 95%CI = 1.03–1.89, p-value = 0.030) than those in the control group; the median overall survival in the study group was 40.98 months while in the control group was 56.17 months (p = 0.006) (Tables 2 and 4). The 2-year and 5-year survival rate in the study group and the control group were 58.24% and 36.43%, and 64.60% and 46.17%, respectively.

In additional analysis, we perform matching (1:1) propensity score (PS) which was calculated by logistic regression. The variables included in the model for PS were gender, insurance status, number of pack year of smoking, COPD, DM, hypertension, dyslipidemia, preoperative ECG finding, histology, tumor stage, intratumoral lymphatic invasion, intratumoral vessel invasion, perineural invasion, tumor necrosis, surgical approach, surgical procedures,

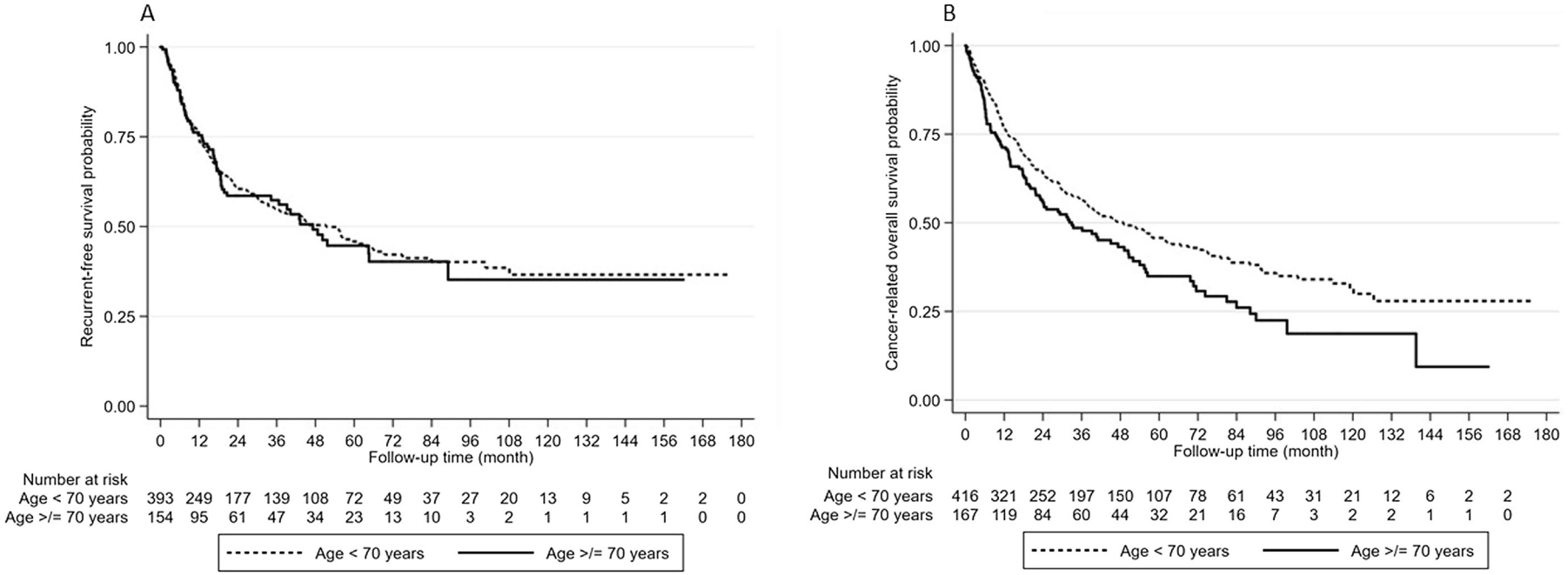

Figure 1 Kaplan—Meier curve demonstrated recurrent-free survival (A) and overall survival (B) probability between elderly and non-elderly group ($p = 0.469$ and $p = 0.006$, respectively, analyzed by log-rank test.

Table 4 Univariable and multivariable analysis to identify prognostic factors of long-term cancer-specific mortality.

Variables	Univariable analysis			Multivariable analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age ≥70 years vs Age <70 years	1.35	1.07–1.70	0.010	1.40	1.03–1.89	0.030
Male vs female	1.61	1.29–2.01	<0.001	1.22	0.91–1.63	0.181
UCS or SSS versus CSMBS or PI	1.43	1.15–1.79	0.001	1.82	1.37–2.42	<0.001
Active smoker vs non-smoker	1.67	1.27–2.20	<0.001	1.20	0.86–1.67	0.303
Pack-year[a]	1.01	1.01–1.02	0.011	–	–	
COPD	1.37	1.03–1.81	0.028	1.46	1.03–2.07	0.038
Diabetic mellitus	1.16	0.84–1.60	0.378	–	–	
Hypertension	0.84	0.67–1.05	0.126	–	–	
Dyslipidemia	0.84	0.63–1.12	0.229	–	–	
History of other malignancy	0.54	0.32–0.93	0.025	–	–	
Histology						
Adenocarcinoma	1.00	Reference		1.00	Reference	
Squamous cell carcinoma	1.02	0.79–1.32	0.881	0.67	0.48–0.94	0.020
Large cell carcinoma	2.22	1.24–3.97	0.007	1.29	0.49–3.37	0.658
Others	1.10	0.76–1.59	0.607	0.85	0.37–1.94	0.851
Cell differentiation						
Well differentiation	1.00	Reference		1.00	Reference	
Moderately differentiation	1.19	0.91–1.56	0.204	1.06	0.76–1.48	0.769
Poorly differentiation	1.57	1.15–2.13	0.004	1.29	0.89–1.50	0.162
Undifferentiation	1.88	1.03–3.43	0.040	2.52	0.89–7.17	0.084
Intratumoral lymphatic invasion	1.58	1.21–2.05	0.001	1.56	1.02–2.39	0.031
Intratumoral vascular invasion	1.54	1.24–1.91	<0.001	1.13	0.85–1.50	0.282
Visceral pleural invasion	1.23	1.08–1.41	0.003	1.58	1.14–2.19	0.007
Perineural invasion	1.29	0.76–2.20	0.351	–	–	
Tumor necrosis	1.44	1.15–1.80	0.002	1.20	0.89–1.63	0.227
Tumor staging (8th IASLC edition)						
Stage I	1.00	Reference		1.00	Reference	
Stage II	1.55	1.15–2.10	0.005	1.84	1.25–2.70	0.002
Stage III	2.30	1.75–3.03	<0.001	2.48	1.67–3.67	<0.001
Surgical Procedure						
Lobectomy	1.00	Reference		1.00	Reference	
Sublobar resection	1.02	0.77–1.36	0.879	1.02	0.61–1.68	0.849
Pneumonectomy	2.47	1.26–4.85	0.006	2.62	1.07–6.37	0.028
VATS vs Open thoracotomy	0.86	0.63–1.19	0.367	–	–	
SLNS vs SLND	1.52	1.13–2.05	0.006	1.37	0.91–2.07	0.160
Lymph node ratio	2.94	1.87–4.64	<0.001	1.48	0.80–2.72	0.190
Chemotherapy[b]						
No	1.00	Reference		1.00	Reference	
Adjuvant therapy	0.73	0.57–0.95	0.019	0.52	0.38–0.71	<0.001
Neoadjuvant therapy or induction therapy	0.94	0.55–1.62	0.740	0.68	0.38–1.19	0.136

UCS = Universal coverage scheme, CSMBS = Civil servant medical benefit scheme, SSS = Social security scheme, PI = Private insurance, COPD = Chronic obstructive pulmonary disease, SLND = Systematic lymph node dissection, SLNS = Systematic lymph node sampling, HR = Hazard ratio, CI = Confidence interval.

[a] Not include in multivariable analysis due to multicollinearity with smoking status.

[b] Stage I patients were not included in this analysis.

type of lymph node dissection, and chemotherapy. After matching, 153 patients were included in both groups. There were no statistically significant differences in term of patient characteristics, pulmonary function test, histologic findings, tumor staging, pathologic findings, surgical procedures, surgical approaches, lymphatic dissection, and induction chemotherapy between the two groups. Hypertension was significant higher in the study group (Appendix B). There were 6 patients died after surgery in the study group; caused by multiple postoperative complications such as pneumonia, septicemia, or acute respiratory distress syndrome. ICU stay was significantly longer in the study group. Long-term cancer-specific mortality was significant higher in the study group (Appendix C). In multivariable analysis, there were no significant difference in term of ICU stay, composite major postoperative complications, and tumor recurrence between the two groups. However, patients in the study group were more likely to die (long-term cancer-specific mortality) than the control group (Appendix D). In summary, the

results from matching propensity score analysis were not different from regression analysis in both short-term and long-term outcomes.

In subgroup analysis in patients age ≥70 years, adverse prognostic factors for long-term cancer specific mortality were having universal coverage scheme, presence of intratumoral lymphatic invasion, presence of perineural invasion, undergoing pneumonectomy (compared to lobectomy), not undergo systematic lymph node dissection, not receiving adjuvant chemotherapy (in stage II and III disease after surgery) and higher stage of disease (Table 5).

4. Discussion

Pulmonary resection with or without mediastinal lymph node sampling or dissection is commonly accepted as the standard treatment of choice for early or local NSCLC patients;

Table 5 Univariable and multivariable analysis to identify prognostic factors of long-term cancer-specific mortality in patients age more than 70 years (N = 167).

Variables	Univariable analysis			Multivariable analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Male vs female	1.42	0.95–2.12	0.092	1.01	0.57–1.79	0.985
UCS versus CSMBS	1.33	0.91–1.94	0.141	1.70	1.03–2.79	0.037
Active smoker vs non-smoker	1.73	1.01–2.96	0.046	1.38	0.66–2.86	0.394
Pack-year[a]	1.01	0.99–1.01	0.147	–	–	
COPD	1.10	0.71–1.72	0.674	–	–	
Diabetic mellitus	1.25	0.76–2.05	0.387	–	–	
Hypertension	0.62	0.42–0.90	0.013	0.60	0.35–1.01	0.054
Dyslipidemia	0.64	0.40–1.02	0.061	1.14	0.59–2.19	0.700
History of other malignancy	0.43	0.17–1.06	0.066	0.69	0.22–2.12	0.515
Histology						
Adenocarcinoma	1.00	Reference		1.00	Reference	
Squamous cell carcinoma	1.15	0.75–1.76	0.523	0.75	0.44–1.30	0.308
Large cell carcinoma	1.62	0.59–4.47	0.351	1.57	0.51–4.84	0.434
Others	1.81	0.92–3.55	0.084	1.88	0.75–4.71	0.178
Cell differentiation						
Well differentiation	1.00	Reference		–	–	–
Moderately differentiation	0.88	0.54–1.42	0.598	–	–	–
Poorly differentiation	1.60	0.95–2.70	0.078	–	–	–
Undifferentiation	0.97	0.30–3.14	0.954	–	–	–
Intratumoral lymphatic invasion	1.88	1.13–3.13	0.015	2.83	1.28–6.29	0.010
Intratumoral vascular invasion	1.47	1.01–2.15	0.050	1.20	0.70–2.05	0.516
Visceral pleural invasion	1.35	0.81–1.05	0.067	0.84	0.60–1.18	0.313
Perineural invasion	2.22	1.07–4.61	0.032	2.80	1.13–6.94	0.026
Tumor necrosis	1.28	0.84–1.96	0.248	–	–	–
Tumor staging (8th IASLC edition)						
Stage I	1.00	Reference		1.00	Reference	
Stage II	1.42	0.87–2.31	0.161	1.13	0.61–2.09	0.692
Stage III	1.53	0.94–2.49	0.086	2.02	1.06–3.85	0.033
Stage IV	2.55	1.32–4.93	0.005	3.40	1.29–8.94	0.013
Procedures						
Lobectomy	1.00	Reference		1.00	Reference	
Sublobar resection	0.81	0.52–1.27	0.357	1.08	0.54–2.14	0.847
Pneumonectomy	14.29	3.15–64.87	0.001	72.58	5.34–986.21	0.001
VATS vs Open thoracotomy	0.85	0.50–1.43	0.534	–	–	
SLNS vs SLND	1.96	1.22–3.15	0.005	2.23	1.16–4.30	0.017
Lymph node ratio	2.64	1.21–5.74	0.014	1.30	0.49–3.48	0.598
Chemotherapy[b]						
No chemotherapy	1.00	Reference		1.00	Reference	
Adjuvant therapy	0.71	0.43–1.17	0.179	0.51	0.29–0.89	0.013
Neoadjuvant therapy or induction therapy	0.82	0.30–2.29	0.709	0.52	0.17–1.54	0.227

UCS = Universal Coverage Scheme, CSMBS = the Civil Servant Medical Benefit Scheme, SSS = Social security scheme, PI = Private insurance, COPD = chronic obstructive pulmonary disease, SLND = Systematic lymph node dissection, SLNS = Systematic lymph node sampling, HR = Hazard ratio, CI = Confidence interval.

[a] Not include in multivariable analysis due to multicollinearity with smoking status.

[b] Stage I patients were not included in data analysis.

however, previous studies demonstrated that surgery rate in elderly patients is lower than in younger ages (4.9% versus 17.7%).[4] This may be due to a combination of poor medical and physiological status in elderly patients, which could be responsible for the higher postoperative morbidity and mortality.[22] Moreover, impairment of immune response in elderly patients may lead to postoperative complications such as respiratory tract infections.[23]

The present study found that some clinical characteristics were different between patient age ≥70 years and age <70 years such as the incidence of COPD, hypertension, dyslipidemia, abnormal ECG, and number of pack-years of smoking. This difference may explain by age-related difference occurs in the general population,[24] not only in the analyzed groups operated for NSCLC. For postoperative outcomes in NSCLC patients between the study group and the control group patients, shows no statistically significant differences in term of POM between the two groups. Therefore, patients age ≥70 years seem to have no increased risk of postoperative complications compared to patients age <70 years, except for the incidence of postoperative acute renal failure. This difference may be explained by the decline in glomerular filtrate rate in elderly patients.[25] The incidence of in-hospital mortality in our cohort was 1.9% (11 in 583): 4.2% for study group and 1.0% for control group, which was comparable to the result of a recent study by Detillon et al.[26] The operative mortality in their cohort was 2.1%: 2.6% for patients aged 70–79 years and 1.0% for patients aged 60–69 years. Similar to our study, they also found that there was no statistically significant difference in the incidence of postoperative complications between the two groups. Ogawa et al[27] reported that lung cancer elderly patients (cut-off age of 75 years) were not at a significant higher risk for postoperative complications (OR = 1.13, 95% CI = 0.70–1.83). On the contrary, Liu et al[4] found that the postoperative hospital stay, comorbidities and mortality rates, and length in intensive care unit in elderly patients were significantly greater than in non-elderly patients. Unfortunately, this publication only present univariable analyses without any multivariable analysis results. In matching propensity score analysis of this study, ICU stay and in-hospital mortality in the study group were significantly greater than in the control group. However, there was no statistically significant differences in term of POM between the two groups, like showed in the regression method.

We found that sublobar resection was more frequent performed in study group with stage I disease, especially in stage IA3, however, in other stages, the proportion of patients who underwent sublobar and lobar resection was not statistically different between the two groups. The multivariable analysis showed that there was no significant difference in POM. This suggests that lobectomy is safe even in patients older than 70 years. Previous studies stated that sublobar resection might achieve similar long-term survival compared to lobectomy in elderly patients, especially those with low %FEV1 and tumor less than 2 cm.[28–31] However, Zhang et al stated that elder age alone could not be used to select patients for sublobar resection in early stage NSCLC because older patients tend to have worse overall survival and lung cancer-specific survival.[32] Recently, Yang et al[33] have developed a prospective randomized controlled multicenter non-inferiority trial to compare disease-free survival, peri-operative complications and mortality and overall survival between sublobar resection and lobectomy. The trial is still ongoing.

COPD was one of the risk factors included in the major complications and in-hospital mortality in the present study, similar to the study by Detillon et al.[26] However other studies[26,27] found that other factors associated with operative morbidities and mortality are gender, being a smoker, FEV1% or DLCO % per 10% decrease, coronary artery bypass graft, congestive heart failure, high ECOG score (eastern cooperative oncology group) and resection more extensive than limited. We found that smoking status, % predicted FEV1, and pneumonectomy were significant risk factors for composite postoperative complications and in-hospital mortality at the univariable analysis only. We attribute the results of previous studies to the small sample size causing lower statistical power.

There was no statistically significant difference in tumor recurrence between the two groups both in the univariable and multivariable analysis. However, this result is not conclusive because the median follow-up time in the study group was significantly shorter than in the control group (24 versus 34.1 months); therefore, a longer follow-up time is needed.

Patients in the study group were more likely to experience long-term cancer-specific mortality than those in the control group, similarly to what reported by previous studies.[27,34] In study group, we found 7 adverse prognostic factors associated with long-term cancer-specific mortality: universal coverage scheme, presence of intratumoral lymphatic invasion, perineural invasion, undergoing pneumonectomy (compared with lobectomy), undergoing systematic lymph node sampling (compared with systematic lymph node dissection), not receiving adjuvant chemotherapy (in stage II and III disease after surgery) and higher stage of disease. In Thailand, targeted therapy (Epidermal growth factor receptor-Tyrosine kinase inhibitor) been approved for use as first-line therapy but patients must pay out of pocket. For second-line or third-line therapy, the reimbursement has been approved since 2012 but limited to the Civil Servant Medical Benefits Scheme under restricted criteria. The reimbursement did not cover in the universal coverage scheme or social security scheme. This may be the reason for shorter survival in patients with universal coverage scheme or social security insurance scheme. Intratumoral lymphatic invasion and perineural invasion were reported as adverse prognostic factors for long-term cancer-specific mortality in previous studies,[35–37] however, these factors were not studied as we did in the present study. Although patients in the study group undergoing pneumonectomy showed worse long-term survival than those undergoing lobectomy, the outcomes in the study group were similar to the control group in terms of POM. This suggests that patients should not be denied pneumonectomy based on age alone. Very careful selection of elderly patients is essential in order to optimize survival and quality of life, as reported by previous studies.[38,39] Because there were only 2 patients (1.87%) in the study group who underwent pneumonectomy and both of them died, the adjusted hazard ratio was overestimated with

very wide 95% confidence interval. Therefore, the association between pneumonectomy and overall survival could not be assessed in this study. However, pneumonectomy would have poorer survival because tumor stage was more advance and quality of life was certainly worse.[40]

Previous studies demonstrated that systematic lymph node dissection (radical dissection) in patients age ≥ 70 years resulted in increased postoperative pulmonary complications, shorter survival, and increase overall mortality.[41,42] However, our study found that systematic lymph node dissection was associated with longer survival in comparison to lymph node sampling in study group. Further studies are needed to clarify this aspect. VATS approach is acceptable for non-elderly NSCLC patients; however, in elderly patients it is still controversial. Recent studies demonstrated that VATS approach was less invasive, had lower postoperative morbidity, shorter length of hospital stay than open thoracotomy,[43] however some studies stated that this approach is associated with higher postoperative complication rates.[44] Our result showed that VATS approach was associated with longer survival but not in a statistically significant manner, similar to previous studies.[45] Previous studies demonstrated that stage of disease was not significantly associated with overall survival in elderly patients, and that half of the elderly NSCLC patients (especially octogenarians) died of non-cancer related disease.[45,46] However, our result showed that stage of disease was associated with long-term cancer-specific mortality in the multivariable analysis model. Although this study did not add anything new in the fields of lung cancer or VATS, the result of this study ensures that surgery in selected older patients is safe and the results comparable to what observed in younger patients. Furthermore, we can reassure or convince our patients who have indication or fit for adjuvant therapy which still have benefits on long-term survival in patients age >70 years, especially in patients who have adverse prognostic factors. Some patients and their relatives believe that they cannot tolerate the side effects of the drug because of old age.

This study has some limitations: it is retrospective in nature and single center. There are some selection biases for surgical procedures in elderly patients. Although there was no difference of pulmonary function between the two groups, sublobar resection was more likely to undergo in patients age ≥70 years. The reason may from other unrecorded comorbid diseases that may influence the decision of surgical procedures. However, this single-center data set is built in a systematic way with a good data recording system, therefore, the missing data in each variable of this study is less than 5%, except for pulmonary function test (15% of missing data). In addition, we used multiple imputations to address missing data, and presented multivariable analyses to analyze the data in a more comprehensive way in comparison to previous papers on this topic.[4]

5. Conclusion

Postoperative morbidity and in-hospital mortality for pulmonary resection in NSCLC patients age ≥70 years were acceptable and comparable to what observed in patients age <70 years. Disease-free survival was not different between groups, however, patients age ≥70 years had shorter long-term survival than patients age <70 years. In the subgroup of patients age ≥70 years, there were 7 adverse prognostic factors for long-term cancer-specific mortality; UCS coverage, presence of intratumoral lymphatic invasion, perineural invasion, higher stage of disease, underwent pneumonectomy, underwent systematic lymph node sampling, and not receiving adjuvant chemotherapy. Therefore, systematic lymph node dissection should be performed rather than lymph node sampling. Patients age ≥70 years presenting with intratumoral lymphatic invasion or perineural invasion should be further considered for possible adjuvant chemotherapy. Effect of insurance coverage on lung cancer survival should be explored in future studies. Further studies with larger sample size are warranted.

Conflict of interest

The authors have no conflicts of interest to declare.

Acknowledgements

This work was supported by Faculty of Medicine Research Fund, Chiang Mai University (Grant number 070/2559), Chiang Mai, Thailand.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.asjsur.2019.03.006.

References

1. Gridelli C, Maione P, Colantuoni G, et al. Chemotherapy of non-small cell lung cancer in elderly patients. *Curr Med Chem*. 2002;9(16):1487–1495.
2. Pei G, Zhou S, Han Y, et al. Risk factors for postoperative complications after lung resection for non-small cell lung cancer in elderly patients at a single institution in China. *J Thorac Dis*. 2014;6(9):1230–1238.
3. Shiono S, Abiko M, Sato T. Postoperative complications in elderly patients after lung cancer surgery. *Interact Cardiovasc Thorac Surg*. 2013;16(6):819–823.
4. Liu HC, Huang WC, Wu CL, et al. Surgery for elderly lung cancer. *Ann Thorac Cardiovasc Surg*. 2013;19(6):416–422.
5. Srisomboon C, Koizumi K, Haraguchi S, et al. Thoracoscopic surgery for non-small-cell lung cancer: elderly vs. octogenarians. *Asian Cardiovasc Thorac Ann*. 2013;21(1):56–60.
6. Nakagawa T, Negoro Y, Matsuoka T, et al. Comparison of the outcomes of stereotactic body radiotherapy and surgery in elderly patients with cT1-2N0M0 non-small cell lung cancer. *Respir Invest*. 2014;52(4):221–226.
7. Rusthoven CG, Kavanagh BD, Karam SD. Improved survival with stereotactic ablative radiotherapy (SABR) over lobectomy for early stage non-small cell lung cancer (NSCLC): addressing the fallout of disruptive randomized data. *Ann Transl Med*. 2015;3(11):149.
8. Davis JN, Medbery 3rd C, Sharma S, et al. Stereotactic body radiotherapy for early-stage non-small cell lung cancer: clinical outcomes from a National Patient Registry. *J Radiat Oncol*. 2015;4(1):55–63.

9. Baldvinsson K, Oskarsdottir GN, Orrason AW, et al. Resection rate and operability of elderly patients with non-small cell lung cancer: Nationwide study from 1991 to 2014. *Interact Cardiovasc Thorac Surg*. 2017;24(5):733—739.
10. Bolukbas S, Beqiri S, Bergmann T, et al. Pulmonary resection of non-small cell lung cancer: is survival in the elderly not affected by tumor stage after complete resection? *Thorac Cardiovasc Surg*. 2008;56(8):476—481.
11. Park B, Lee G, Kim HK, et al. A retrospective comparative analysis of elderly and younger patients undergoing pulmonary resection for stage I non-small cell lung cancer. *World J Surg Oncol*. 2016;14(1):13.
12. Cerfolio RJ, Bryant AS. Survival and outcomes of pulmonary resection for non-small cell lung cancer in the elderly: a nested case-control study. *Ann Thorac Surg*. 2006;82(2):424—429. discussion 9-30.
13. Owonikoko TK, Ragin CC, Belani CP, et al. Lung cancer in elderly patients: an analysis of the surveillance, epidemiology, and end results database. *J Clin Oncol*. 2007;25(35):5570—5577.
14. Burfeind Jr WR, Tong BC, O'Branski E, et al. Quality of life outcomes are equivalent after lobectomy in the elderly. *J Thorac Cardiovasc Surg*. 2008;136(3):597—604.
15. Schulte T, Schniewind B, Walter J, et al. Age-related impairment of quality of life after lung resection for non-small cell lung cancer. *Lung Cancer*. 2010;68(1):115—120.
16. SoTS. http://sts.org/sections/stsnationaldatabae_2010; 2010.
17. Howington JA, Blum MG, Chang AC, et al. Treatment of stage I and II non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 Suppl):e278S—e313S.
18. Lardinois D, De Leyn P, Van Schil P, et al. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. *Eur J Cardiothorac Surg*. 2006;30(5):787—792.
19. Naruke T, Suemasu K, Ishikawa S. Lymph node mapping and curability at various levels of metastasis in resected lung cancer. *J Thorac Cardiovasc Surg*. 1978;76(6):832—839.
20. Goldstraw P, Chansky K, Crowley J, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2016;11(1):39—51.
21. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Stat Med*. 1991;10(4):585—598.
22. Balduyck B, Hendriks J, Lauwers P, et al. Quality of life evolution after lung cancer surgery in septuagenarians: a prospective study. *Eur J Cardiothorac Surg*. 2009;35(6):1070—1075. discussion 5.
23. Meyer KC. Lung infections and aging. *Ageing Res Rev*. 2004;3(1):55—67.
24. Santoni G, Angleman S, Welmer AK, et al. Correction: age-related variation in health status after age 60. *PLoS One*. 2015;10(6), e0130024.
25. Venuta F, Diso D, Onorati I, et al. Lung cancer in elderly patients. *J Thorac Dis*. 2016;8(Suppl 11):S908—S914.
26. Detillon D, Veen EJ. Postoperative outcome after pulmonary surgery for non-small cell lung cancer in elderly patients. *Ann Thorac Surg*. 2018;105(1):287—293.
27. Ogawa F, Wang G, Matsui Y, et al. Risk factors for postoperative complications in the elderly with lung cancer. *Asian Cardiovasc Thorac Ann*. 2013;21(3):313—318.
28. Qiu C, Wang G, Xu J, et al. Sublobectomy versus lobectomy for stage I non-small cell lung cancer in the elderly. *Int J Surg*. 2017;37:1—7.
29. Razi SS, John MM, Sainathan S, et al. Sublobar resection is equivalent to lobectomy for T1a non-small cell lung cancer in the elderly: a surveillance, epidemiology, and end results database analysis. *J Surg Res*. 2016;200(2):683—689.
30. Fiorelli A, Caronia FP, Daddi N, et al. Sublobar resection versus lobectomy for stage I non-small cell lung cancer: an appropriate choice in elderly patients? *Surg Today*. 2016;46(12):1370—1382.
31. Liu T, Liu H, Li Y. Early lung cancer in the elderly: sublobar resection provides equivalent long-term survival in comparison with lobectomy. *Contemp Oncol (Pozn)*. 2014;18(2):111—115.
32. Zhang Y, Yuan C, Zhang Y, et al. Survival following segmentectomy or lobectomy in elderly patients with early-stage lung cancer. *Oncotarget*. 2016;7(14):19081—19086.
33. Yang F, Sui X, Chen X, et al. Sublobar resection versus lobectomy in Surgical Treatment of Elderly Patients with early-stage non-small cell lung cancer (STEPS): study protocol for a randomized controlled trial. *Trials*. 2016;17:191.
34. Onaitis MW, Furnary AP, Kosinski AS, et al. Prediction of long-term survival after lung cancer surgery for elderly patients in the society of thoracic Surgeons general thoracic surgery database. *Ann Thorac Surg*. 2018;105(1):309—316.
35. Ma KF, Chu XY, Liu Y. Clinical significance of lymphatic vessel invasion in stage I non-small cell lung cancer patients. *Genet Mol Res*. 2015;14(1):1819—1827.
36. Nentwich MF, Bohn BA, Uzunoglu FG, et al. Lymphatic invasion predicts survival in patients with early node-negative non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2013;146(4):781—787.
37. Kilicgun A, Turna A, Sayar A, et al. Very important histopathological factors in patients with resected non-small cell lung cancer: necrosis and perineural invasion. *Thorac Cardiovasc Surg*. 2010;58(2):93—97.
38. Kim TH, Park B, Cho JH, et al. Pneumonectomy for clinical stage I non-small cell lung cancer in elderly patients over 70 Years of age. *Kor J Thorac Cardiovasc Surg*. 2015;48(4):252—257.
39. Speicher PJ, Ganapathi AM, Englum BR, et al. Survival in the elderly after pneumonectomy for early-stage non-small cell lung cancer: a comparison with nonoperative management. *J Am Coll Surg*. 2014;218(3):439—449.
40. Leo F, Scanagatta P, Vannucci F, et al. Impaired quality of life after pneumonectomy: who is at risk? *J Thorac Cardiovasc Surg*. 2010;139(1):49—52.
41. Okami J, Higashiyama M, Asamura H, et al. Pulmonary resection in patients aged 80 years or over with clinical stage I non-small cell lung cancer: prognostic factors for overall survival and risk factors for postoperative complications. *J Thorac Oncol*. 2009;4(10):1247—1253.
42. Chida M, Minowa M, Karube Y, et al. Worsened long-term outcomes and postoperative complications in octogenarians with lung cancer following mediastinal lymph-node dissection. *Interact Cardiovasc Thorac Surg*. 2009;8(1):89—92.
43. Saha SP, Bender M, Ferraris VA, et al. Surgical treatment of lung cancer in octogenarians. *South Med J*. 2013;106(6):356—361.
44. Sui X, Zhao H, Wang J, et al. Outcome of VATS lobectomy for elderly non-small cell lung cancer: a propensity score-matched study. *Ann Thorac Cardiovasc Surg*. 2015;21(6):529—535.
45. Hino H, Murakawa T, Ichinose J, et al. Results of lung cancer surgery for octogenarians. *Ann Thorac Cardiovasc Surg*. 2015;21(3):209—216.
46. Fanucchi O, Ambrogi MC, Dini P, et al. Surgical treatment of non-small cell lung cancer in octogenarians. *Interact Cardiovasc Thorac Surg*. 2011;12(5):749—753.