Treatment modality and outcomes among early-stage non-small cell lung cancer patients with COPD: a cohort study

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Background: While there is an increasing number of early-stage non-small cell lung cancer (NSCLC) patients with chronic obstructive pulmonary disease (COPD), there are no specific clinical guidelines for treating them. This study aims to evaluate different treatment modalities and corresponding clinical outcomes among early-stage NSCLC patients with COPD.

Methods: We retrospectively reviewed 692 patients with stage I and II NSCLC and COPD from January 2012 to June 2014. Patients were categorized into four groups according to primary treatment modality: surgery only group (n=442), surgery with adjuvant treatment group (n=157), radiotherapy (RT) group (n=48), and supportive care (SC)-only group (n=45).

Results: Overall, mortality rate was the highest in the SC-only group (35.7 deaths per 100 person-years), followed by RT group (21.5 deaths per 100 person-years), surgery with adjuvant treatment group (8.9 deaths per 100 person-years) and surgery only group (7.2 deaths per 100 person-years). The adjusted hazard ratios (HR) for all-cause mortality compared to the surgery only group were 1.18 (95% CI, 0.84–1.67) in surgery with adjuvant treatment group, 1.61 (95% CI, 1.01–2.57) in RT group and 3.23 (95% CI, 1.99–5.23) in SC-only group.

Conclusions: Surgical resection should be considered as the first choice for early-stage NSCLC with COPD. Despite poor lung function or general patient condition, RT rather than SC can be an alternative option if surgery is not feasible. A multi-disciplinary approach and active communication between patients and physicians might be helpful for adequate decision-making regarding treatment for patients with early-stage NSCLC and COPD.

Keywords: Non-small cell lung cancer (NSCLC); chronic obstructive pulmonary disease (COPD); surgery; radiotherapy; supportive care

Introduction

Surgical resection is generally accepted as the optimal treatment for treating early-stage non-small cell lung cancer (NSCLC) (1,2) with 5-year survival rates of up to 73% and 50% for stage I and II NSCLC, respectively (3). However, not all patients with early-stage NSCLC are surgical candidates due to old age, poor pulmonary function, poor physical function, or comorbidities (4) and when untreated, the outcome of patients with routinely detected early stage NSCLC is a distinctly poor with median survival of 10 months (5).

Chronic obstructive pulmonary disease (COPD) is an established risk factor for the development of lung cancer (6-9). COPD is also the most frequent concomitant (15.3%) disease in early-stage NSCLC patients (10) and the prevalence of COPD in newly diagnosed lung cancer cases was six-fold greater than in people without lung cancer regardless of smoking exposure in ever-smokers (11). Moreover, patients with COPD have higher risk of pulmonary complications (PPCs) and poorer survival outcomes after surgical resection than those without COPD (12-15). Thus, pulmonary functions are evaluated to assess the feasibility for lung resection, and radiation therapy including stereotactic body radiotherapy (SBRT) is alternatively suggested for the treatment of the early-stage NSCLC, when patients are medically inoperable (16,17). Indeed, radiotherapy (RT) had shown better survival compared to those with supportive care alone (18,19). However, some COPD patients are reluctant to receive either surgery or RT due to cancer stigma, despite being diagnosed with early-stage, treatable lung cancer (20,21).

Recent guidelines from the American Society of Clinical Oncology and the American Society of Radiation Oncology emphasize the importance of timely treatment and shared decision-making in the management of early-stage NSCLC (22,23). While there are increasing number of early-stage NSCLC patients with COPD, there are no specific clinical treatment guidelines for them. Therefore, this real-world study aimed to investigate treatment modalities that early-stage NSCLC patients with COPD received and to evaluate the clinical outcomes based on treatment modalities.

Methods

Study population

This is a retrospective cohort study conducted with stage I and II NSCLC patients who were 40 years or older and who had spirometry tests at the time of cancer diagnosis in Samsung Medical Center, Seoul, Korea from January 2012 to June 2014. As our study objective was to evaluate treatment modalities among early stage NSCLC patients with COPD, we selected 703 subjects who had COPD [defined as pre-bronchodilator forced espiratory volue in 1 second (FEV1)/forced vital capacity (FVC) <0.70] at the time of cancer diagnosis. Patients who were diagnosed with interstitial lung disease (n=9), had history of lung cancer (n=1), and were transferred to other hospitals for further treatment (n=1) were excluded. The final study sample included 692 subjects. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board of Samsung Medical center approved this study (No. 2018-07-057) and waived the informed consent as we only used de-identified data retrieved from electronic medical records (EMR).

Measurements

Spirometry and diffusing capacity of the lungs for carbon monoxide (DLco) were performed using the Vmax 22 system (SensorMedics, Yorba Linda, CA, USA) according to criteria established by the American Thoracic Society/European Respiratory Society (24,25). Absolute values of FVC, FEV_1, and DLco were obtained, and the percentage of the predicted values (% pred) were calculated using data obtained with a representative Korean sample (26,27). The severity of COPD was staged by the Global Initiative for Chronic Obstructive Lung Disease (GOLD); mild (FEV_1 ≥80% pred), moderate (50%≤ FEV_1 <80% pred), severe (30%≤ FEV_1 <50% pred), or very severe (FEV_1 <30% pred) (25). Low DLco was defined as DLco <80% pred (28).

Stage of NSCLC

Stage of NSCLC was determined according to the seventh edition of TNM classification (29). NSCLC included adenocarcinoma, squamous cell carcinoma, and other types such as large cell carcinoma, neuroendocrine carcinoma, poorly- or undifferentiated carcinoma, and pleomorphic sarcomatoid carcinoma. Some patients who could not undergo histologic confirmation were included, when the diagnosis of lung cancer was unequivocal based on clinical and image findings.

Treatment modality and outcome

Patients were primarily grouped into 'surgery group' or

'no surgery (NS) group' according to whether patients received curative surgery or not. The surgery group was further categorized as 'surgery only group' for patients who received surgery only and 'surgery with adjuvant treatment group' for patients who received adjuvant chemotherapy and/or RT after surgical resection. The NS group included patients who received definitive RT (RT group) and patients who did not receive any definitive treatment for lung cancer including surgery or definitive RT (supportive care only group, SC-only group). Two investigators (NK and SS) reviewed patient medical records to determine the decision-making process behind treatment decisions for the NS group. When there was any discordance between the reviewers, the study team reviewed those cases and made the final decision. The primary outcome was all-cause mortality, calculated by total number of deaths divided by the person-year (summation of follow-up periods of each person). Person-time was calculated from the first date of treatment (surgery group and RT group) or the date of diagnosis (SC-only group) to the date of death, last date known to be alive, or the end of the study period (April 23, 2018), whichever comes first. All dates of patient deaths were ascertained from the medical records or the death records from Statistics Korea. In addition, we obtained the following data from the EMR: demographic, behavioral, and other clinical information including age at diagnosis, sex, smoking status, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) performance status at diagnosis, comorbid conditions, tumor histology, and hemoglobin level that would be associated with either exposure or outcome.

Statistical analysis

Survival curves were generated by the Kaplan-Meier product-limit method and compared by log-rank tests. We calculated hazard ratios (HR) with 95% confidence intervals (CI) for all-cause mortality using the Cox proportional hazards regression models. We adjusted for age (continuous), sex (male or female), smoking status (never, or ever), BMI (continuous), performance status (ECOG ≤ 1, or ≥ 2), comorbidity (none, or any), tumor stage (clinical stage I or II), hemoglobin level (continuous), FEV1 % predicted and DLco % pred (continuous) to account for potential confounding factors at the time of NSCLC diagnosis. To improve comparability of the patients in different treatment modality, additional analyses were performed limiting to patients with age <70 or ≥ 70 and patients with clinical stage I. We examined the proportional hazards assumption using

plots of the log (-log) survival function and Schoenfeld residuals. All tests were two-sided, and P values <0.05 were considered significant. All analyses were performed using Stata software (ver. 14.0; Stata Corporation, College Station, TX, USA).

Results

Patient characteristics

The mean (SD) age of the total study population was 67.9 (7.7) years and 87.7% of patients were male. Of the total, 63.9%, 22.7%, 6.9%, and 6.5% patients received surgery only, surgery with adjuvant treatment, RT, or SC-only, respectively (*Table 1*). The mean (SD) age of surgery only, surgery with adjuvant treatment, RT, and SC-only was 68.0 (7.4) years, 64.9 (6.7) years, 72.8 (9.5) years and 73.1 (6.8) years, respectively. Compared with patients who received surgery regardless of adjuvant therapy, patients in RT and SC-only group were older (P<0.001) and more likely to be ever-smokers (P=0.007), and have lower BMI (P<0.001). The surgery group had better ECOG performance than RT or SC-only group (ECOG performance status of 0-1, 99.3% in surgery only group, and 98.1% in surgery with adjuvant treatment group *vs.* 68.8% in RT group and 77.8% in SC-only group, P<0.001). Previous history of other cancer was mostly found in RT group (25.0%, P=0.002). Adenocarcinoma was common in surgery only group (56.6%) while other groups were mostly consisted of squamous cell carcinoma (60.5% in surgery with adjuvant treatment group, 54.2% in RT group and 57.8% in SC-only group, P<0.001). Surgery with adjuvant treatment group had more clinical stage II (62.4%) than other groups (23.8% in surgery only, 33.3% in RT group and 40.0% in SC-only group, P<0.001). Among the RT group, 15 patients received SBRT. The clinical characteristics of the SC-only group were not different from those of the RT group (*Table S1*). Compared to the surgery group, the NS group had significantly poor lung function in terms of FVC, FEV$_1$, FEV$_1$/FVC, and DLco (*Table 2*). In terms of COPD severity, while only 3.8% of the surgery group had severe-to-very severe COPD, 33.3% of the RT and 28.9% of the SC-only group had severe-to-very severe COPD, respectively (*Figure 1*). Prevalence of reduced DLco (<80% pred) was 51.8%, 55.5%, 76.7%, and 63.4% in the surgery only, surgery with adjuvant treatment, RT, or SC-only group, respectively (*Figure 2*).

4654

Kang et al. Treatment outcomes of NSCLC patients with COPD

Table 1 Baseline characteristics of 692 patients with early-stage NSCLC and COPD

	Surgery only (n=442)	Surgery with adjuvant treatment (n=157)	RT (n=48)	SC-only (n=45)	P values
Age, yr	68.0 (7.4)	64.9 (6.7)	72.8 (9.5)	73.1 (6.8)	<0.001
Male sex	380 (86.0)	141 (89.8)	43 (89.6)	43 (95.6)	0.203
Smoking status[†]					0.007
Current smoker	162 (36.7)	77 (49.0)	15 (31.3)	19 (42.2)	
Former smoker	203 (45.9)	65 (41.4)	28 (58.3)	23 (51.1)	
Never smoker	77 (17.4)	15 (9.6)	4 (8.3)	2 (4.4)	
BMI (kg/m^2)[†]	23.7 (2.7)	24.0 (2.9)	22.3 (3.4)	21.7 (3.1)	<0.001
ECOG Performance Status[‡]					<0.001
0–1	439 (99.3)	154 (98.1)	33 (68.8)	35 (77.8)	
2–3	3 (0.7)	3 (1.9)	11 (22.9)	2 (4.4)	
Unknown	0	0	4 (8.3)	8 (17.8)	
History of other cancer	83 (18.8)	11 (7.0)	12 (25.0)	6 (13.3)	0.002
Double primary cancer	40 (9.1)	8 (5.1)	4 (8.3)	4 (8.9)	0.451
Comorbidities					
Tuberculosis	62 (14.0)	25 (15.9)	13 (27.1)	9 (20.0)	0.100
Heart disease	52 (11.8)	17 (10.8)	8 (16.7)	9 (20.0)	0.294
Hypertension	199 (45.0)	63 (40.1)	20 (41.7)	20 (44.4)	0.748
Diabetes	104 (23.5)	24 (15.3)	11 (22.9)	6 (13.3)	0.090
Hemoglobin (g/dL)[†]	12.9 (1.4)	12.8 (1.5)	12.8 (1.4)	13.0 (1.6)	0.701
Tumor histology					<0.001
Adenocarcinoma	250 (56.6)	47 (29.9)	13 (27.1)	9 (20.0)	
Squamous cell carcinoma	164 (37.1)	95 (60.5)	26 (54.2)	26 (57.8)	
Other NSCLC	28 (6.3)	15 (9.6)	2 (4.2)	5 (11.1)	
Unknown	0	0	7 (14.6)	5 (11.1)	
Clinical stage					<0.001
I	337 (76.2)	59 (37.6)	32 (66.7)	27 (60.0)	
II	105 (23.8)	98 (62.4)	16 (33.3)	18 (40.0)	

Values are in mean (standard deviation) or number (%). [†]The number of patients with missing value was smoking status (n=2), BMI (n=4), and hemoglobin (n=3). [‡]Performance status was based on Eastern Cooperative Oncology Group (ECOG) scale. BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NSCLC, non-small cell lung cancer; RT, radiotherapy; SC, supportive care.

### All-cause mortality according to the treatment modality

During the median follow up of 4.3 year (interquartile range 2.7–5.1 years; 2,714 person-years), 257 patients died. During the first 90 days, 16 patients (16/692, 2.31%) died and all of them were patients in the surgery group.

Overall, mortality rate was the highest in the SC-only group (35.7 deaths per 100 person-years), followed by RT group (21.5 deaths per 100 person-years), surgery with adjuvant treatment group (8.9 deaths per 100 person-years) and surgery only group (7.2 deaths per 100 person-years) (*Table 3* and *Figure 3*). After adjusting for age, sex,

Table 2 Lung function of study participants at the time of NSCLC diagnosis

	Surgery only (n=442)	Surgery with adjuvant treatment (n=157)	RT (n=48)	SC-only (n=45)	P values
FVC (L)	3.67 (0.8)	3.80 (0.7)	3.07 (0.7)	3.14 (0.7)	<0.001
FVC (%predicted)	89.5 (13.1)	90.7 (13.6)	78.8 (15.3)	79.3 (15.7)	<0.001
FEV_1 (L)	2.23 (0.6)	2.31 (0.5)	1.68 (0.5)	1.69 (0.6)	<0.001
FEV_1 (%predicted)	75.9 (15.0)	75.4 (14.3)	65.1 (22.6)	62.5 (21.9)	<0.001
FEV_1/FVC	60.7 (8.0)	60.8 (6.9)	55.1 (11.5)	53.0 (12.7)	<0.001
DLco (mL/min/mmHg)[†]	16.0 (4.4)	16.2 (3.8)	11.7 (3.0)	13.0 (4.3)	<0.001
DLco (% predicted)[†]	79.7 (18.4)	77.9 (16.4)	62.9 (16.7)	70.4 (20.9)	<0.001

Values are in mean (standard deviation). [†]Data regarding DLco (L) and DLco % predicted were available in 675 patients. COPD, chronic obstructive pulmonary disease; DLco, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; NSCLC, non-small cell lung cancer; RT, radiotherapy; SC, supportive care.
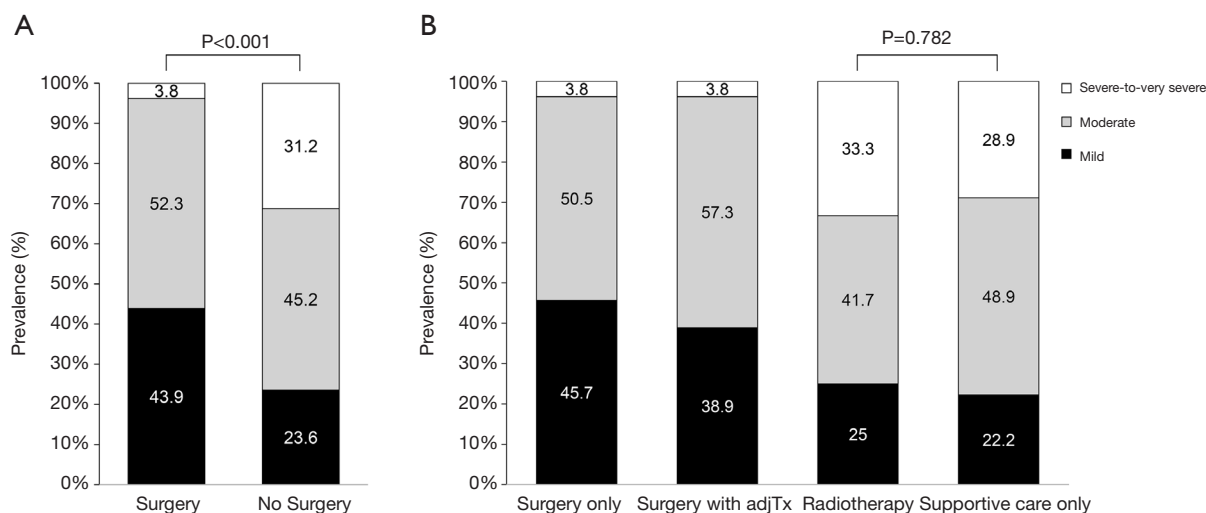
Figure 1 The distribution of COPD severity between (A) surgery *vs*. no surgery groups and (B) by treatment modalities. COPD, chronic obstructive pulmonary disease.

smoking status, BMI, performance status, comorbidity, hemoglobin level, tumor stage, FEV_1 (% pred), and DLco (% pred), the adjusted hazard ratios (aHR) for all-cause mortality compared to the surgery only group were 1.18 (95% CI, 0.84–1.67) in surgery with adjuvant treatment group, 1.61 (95% CI, 1.01–2.57) in RT group and 3.23 (95% CI, 1.99–5.23) in SC-only group. Compared to surgery group, adjusted HR of NS group was 2.04 (95% CI, 1.41–2.96). Among NS group, when outcomes between RT and SC-only group were compared, the SC-only group had significantly higher risk of death compared to RT (aHR, 2.99; 95% CI, 1.51–5.94).

Considering that there is significant difference of age among patients with different treatment modalities, we performed a subgroup analysis with age <70 and ≥70 years (*Table S2*). However, there was no interaction with age and the results remained as same. When we restricted the analysis with clinical stage I patients, RT group had worse survival compared to the surgery only group (HR, 2.40; 95% CI, 1.31–4.42), but had better survival than SC-only group (HR in SC-only group compared to RT group, 3.15; 95% CI, 1.13–8.80) (*Table S3*).

Discussion

In this large cohort study of early stage NSCLC patients with COPD, most patients underwent surgical resection only (63.9%) or surgical resection with adjuvant treatment

4656

Kang et al. Treatment outcomes of NSCLC patients with COPD
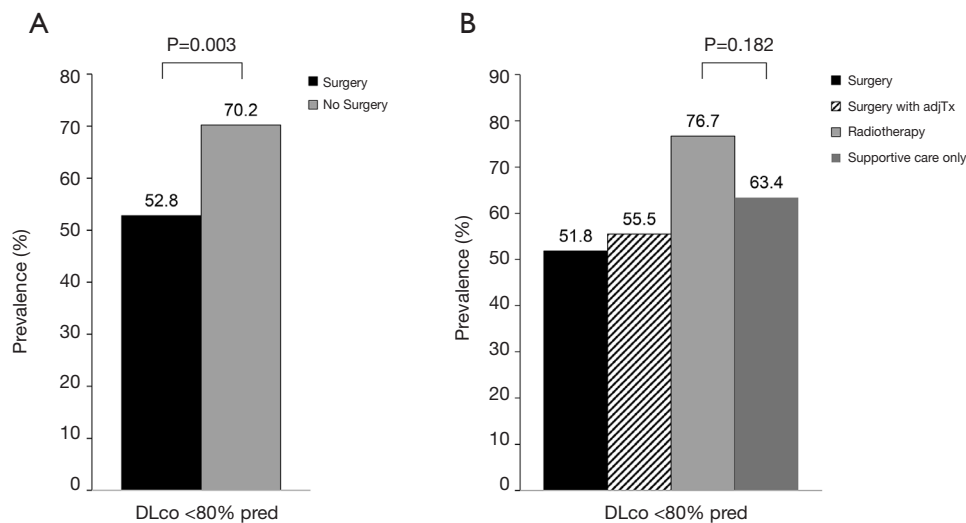
Figure 2 Prevalence of reduced DLco (<80% predicted) between (A) surgery *vs.* no surgery groups and (B) by treatment modalities. DLco, diffusing capacity for carbon monoxide.

Table 3 Hazard ratios (95% confidence intervals) for all-cause mortality according to the treatment modality

	No. of death	Incidence rate per 100-person year	Crude, HR (95% CI)	Adjusted[†], HR (95% CI)
Surgery				
Surgery (n=599)	189	7.7	Reference	Reference
No surgery (n=93)	68	27.2	3.52 (2.66, 4.66)	2.04 (1.41, 2.96)
Specific treatment modality				
Surgery only (n=442)	132	7.2	Reference	Reference
Surgery with adjuvant treatment (n=157)	57	8.9	1.23 (0.90, 1.67)	1.18 (0.84, 1.67)
RT (n=48)	32	21.5	2.95 (2.00, 4.35)	1.61 (1.01, 2.57)
SC only (n=45)	36	35.7	4.90 (3.37, 7.12)	3.23 (1.99, 5.23)

[†]Adjusted for age, sex, smoking status. BMI, performance status, any comorbidity, hemoglobin level, tumor stage, FEV$_1$ % pred and DLco % pred. CI, confidence interval; HR, hazard ratio; RT, radiotherapy; SC, supportive care; FEV$_1$, forced expiratory volume in 1 s; DLco, diffusing capacity for carbon monoxide.

(22.7%) while relatively few received RT (6.9%) or SC-only (6.5%). After adjusting for confounders, patients without surgery had two times higher risk of death compared to patients with surgery, and among patients without surgery, patients who only received SC had about three times higher risk of death compared to patients with RT. These outcomes were consistently observed in clinically relevant subgroups by age and clinical stage. As early curative surgical treatment affects the subsequent treatment, we separated surgery patients with adjuvant treatment from patients with surgery only, and the risk of death were not

significantly different between two groups.

In our observational study, however, patients who received surgery and those who did not are a different population with a distinct entity. This is the reflection of the real-world practice of early-staged NSCLC patients with COPD. The surgery group had relatively mild COPD and better general condition, leading to a favorable outcome, compared with NS group. Whereas, the NS group were older, and had more advanced COPD with poor performance status, indicating that those were deemed medically inoperable. Among the patients who did
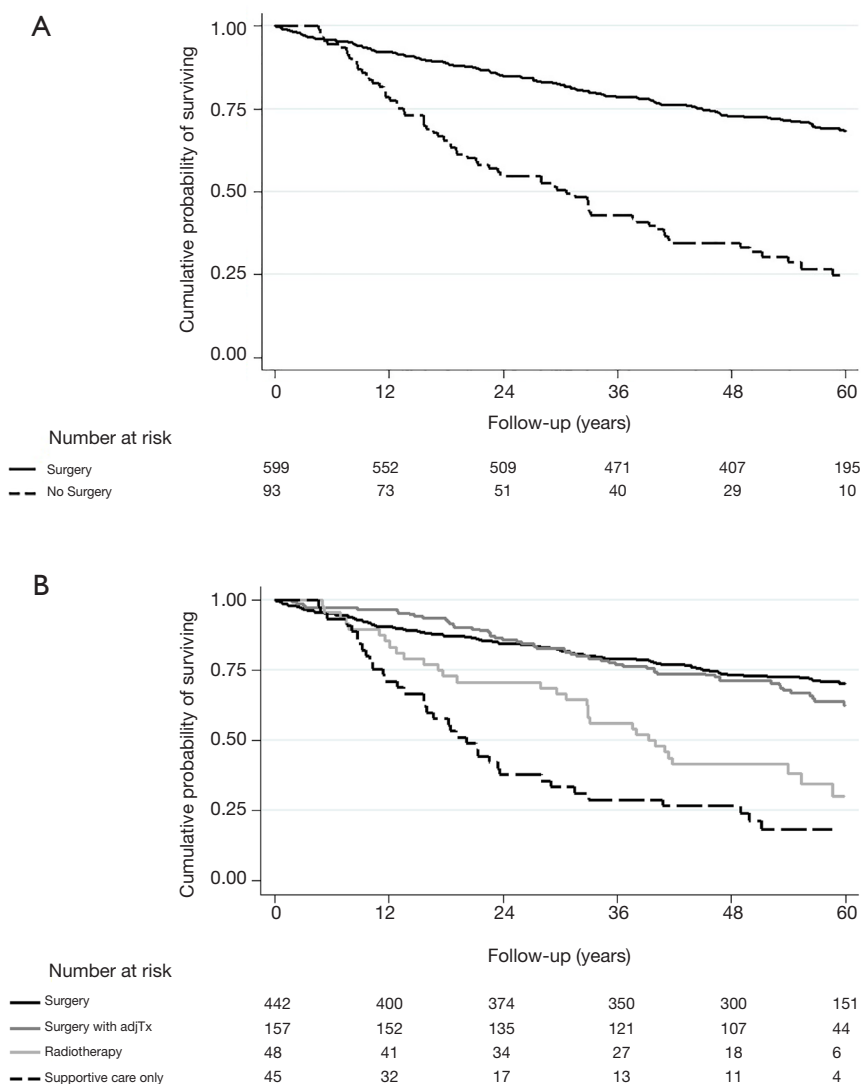
Figure 3 Cumulative probability of surviving between (A) surgery *vs*. no surgery groups and (B) by treatment modalities.

not undergo surgery, only half of them received RT as an alternative option and the other half of them did not receive curative treatment. The RT group showed significantly better survival than the SC group despite similar age, smoking status, BMI, comorbidities, and lung function between the RT group and SC group. Indeed, previous study demonstrated that definitive radiotherapy was well tolerated in early-stage NSCLC patients with COPD (30). Thus, RT should be taken into account than supportive care only for better survival outcomes in COPD patients who are not feasible to undergo surgical resection.

Our study confirmed that surgical resection is the primary and preferred treatment option for early-stage NSCLC patients with COPD when the COPD patients are feasible to undergo surgical resection, which was consistent with the general guidelines for treating early-stage NSCLC (1). In our study, however, the surgery group had higher postoperative mortality than the NS group during the first 90 days (*Figure 3A*), which is in accordance with existing literature documenting the risks of surgery (31,32). Thus, clinicians should be aware of postoperative mortality risk and evaluate patient lung function and overall profiles carefully when considering lung resection surgery for early-stage NSCLC patients with COPD.

4658

Kang et al. Treatment outcomes of NSCLC patients with COPD

In terms of treatment decision, RT was mostly decided by physicians (concerned primarily with poor lung function) whereas SC-only was mostly decided by patients and family in accordance with their preference not to have active treatment (*Table S4*). We reviewed medical records to identify key factors used to support the decision to pursue surgical or non-surgical interventions. Some factors that lead to non-surgical intervention were old age, poor lung function, comorbid disease, performance status, and patient will. These factors are in line with the findings from the prospective cohort study of early-stage NSCLC patients (33). In our study, the decision to rely exclusively on SC was typically made by the patient or family with the main reason for not receiving any other definitive treatment including RT being 'patient and family will.' One reason patients and families might decide against treatment is the stigma associated with cancer (20). Despite increasing survival rates, many still consider cancer to be a death sentence and are unwilling to consider any treatment options (34). Furthermore, patients might not have enough information about alternative treatment options such as RT or they might worry too much about treatment complications. Considering that patients in the SC-only group had similar lung function and performance status, more tailored education would be necessary for early-stage NSCLC patients with advanced COPD at diagnosis. In addition, clinicians need to encourage shared decision-making by providing accurate therapeutic information.

There are several limitations of this study. First, since COPD was based on a pre-bronchodilator spirometry (35), the diagnosis of COPD might be overestimated. Second, this study was conducted with patients at a tertiary hospital and the results of the study might not be generalizable to patients at different settings. Thirdly, because this is a retrospective cohort study, we were not able to include all influencing factors which affect the outcomes. Further studies are necessary to confirm our finding. In addition, there might be some information we missed regarding treatment decisions because we only included information available on the EMR and there might be other reasons physicians or patients decide on specific treatments.

Conclusions

While there are many epidemiologic studies showing the high prevalence of COPD in patients with NSCLC patients, there is limited evidence in terms of treatment modalities and its associated clinical outcomes for lung cancer patients with COPD. The results of our study suggest that surgical resection should be considered as the first choice for early-stage NSCLC with COPD. RT can be an alternative option if surgery is not feasible due to poor lung function or general patient condition. A multi-disciplinary approach for treating early lung cancer patients with COPD is necessary. In addition, more active communication between patients and physicians might be helpful for adequate decision-making regarding treatment for patients with early-stage NSCLC and COPD.

Footnote

Data Sharing Statement: Available at http://dx.doi.org/10.21037/jtd-20-667

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-667). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board of Samsung Medical center approved this study (No. 2018-07-057) and waived the informed consent as we only used de-identified data retrieved from electronic medical records (EMR).

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4660

Kang et al. Treatment outcomes of NSCLC patients with COPD

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Table S1 Baseline characteristics of patients with early-stage NSCLC and COPD

	RT (n=48)	SC-only (n=45)	P values
Age, yr	72.8 (9.5)	73.1 (6.8)	0.853
Male sex	43 (89.6)	43 (95.6)	0.437
Smoking status[†]			0.675
Current smoker	15 (31.3)	19 (42.2)	
Former smoker	28 (58.3)	23 (51.1)	
Never smoker	4 (8.3)	2 (4.4)	
BMI (kg/m^2)[†]	22.3 (3.4)	21.7(3.1)	0.346
ECOG Performance Status[‡]			0.023
0–1	33 (68.8)	35 (77.8)	
2–3	11 (22.9)	2 (4.4)	
Unknown	4 (8.3)	8 (17.8)	
History of other cancer	12 (25.0)	6 (13.3)	0.155
Double primary cancer	4 (8.3)	4 (8.9)	0.999
Comorbidities			
Tuberculosis	13 (27.1)	9 (20.0)	0.422
Heart disease	8 (16.7)	9 (20.0)	0.678
Hypertension	20 (41.7)	20 (44.4)	0.787
Diabetes	11 (22.9)	6 (13.3)	0.232
Hemoglobin (g/dL)[†]	12.8 (1.4)	13.0 (1.6)	0.485
Tumor histology			0.530
Adenocarcinoma	13 (27.1)	9 (20.0)	
Squamous cell carcinoma	26 (54.2)	26 (57.8)	
Other NSCLC	2 (4.2)	5 (11.1)	
Unknown	7 (14.6)	5 (11.1)	
Clinical stage			0.505
I	32 (66.7)	27 (60.0)	
II	16 (33.3)	18 (40.0)	
Lung function			
FVC (L)	3.07 (0.7)	3.14 (0.7)	0.621
FVC (%predicted)	78.8 (15.3)	79.3 (15.7)	0.877
FEV$_1$ (L)	1.68 (0.5)	1.69 (0.6)	0.972
FEV$_1$ (%predicted)	65.1 (22.6)	62.5 (21.9)	0.573
FEV$_1$/FVC	55.1 (11.5)	53.0 (12.7)	0.409
DLco (mL/min/mmHg)[†]	11.7 (3.0)	13.0 (4.3)	0.115
DLco (% predicted)[†]	62.9 (16.7)	70.4 (20.9)	0.074

Values are in mean (standard deviation) or number (%). [†]The number of patients with missing value was smoking status (n=2), BMI (n=3), hemoglobin (n=3) and DLco (n=9). [‡]Performance status was based on Eastern Cooperative Oncology Group (ECOG) scale. BMI, body mass index; COPD, chronic obstructive pulmonary disease; DLco, diffusing capacity for carbon monoxide; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; NSCLC, non-small cell lung cancer; RT, radiotherapy; SC, supportive care.

Table S2 Hazard ratios (95% confidence intervals) for all-cause mortality according to the treatment modality by age group

	No. of death	Incidence rate per 100-person year	Crude, HR (95% CI)	Adjusted[†], HR (95% CI)	P for interaction
Surgery					0.385
Age <70 years (N=377)					
Surgery (n=353)	87	5.7	Reference	Reference	
No surgery (n=24)	19	31.6	5.38 (3.26, 8.91)	2.44 (1.26, 4.71)	
Age ≥70 years (N=315)					
Surgery (n=246)	102	10.8	Reference	Reference	
No surgery (n=69)	49	25.8	2.37 (1.68, 3.34)	2.20 (1.41, 3.42)	
Specific treatment modality					0.084
Age <70 years (N=377)					
Surgery only (n=237)	49	4.7	Reference	Reference	
Surgery with adjuvant treatment (n=116)	38	8.0	1.70 (1.11, 2.60)	1.19 (0.75, 1.91)	
RT (n=13)	9	21.9	4.55 (2.23, 9.29)	1.72 (0.76, 3.93)	
SC only (n=11)	10	52.8	11.3 (5.62, 22.66)	9.36 (3.60, 24.4)	
Age ≥70 years (N=315)					
Surgery only (n=205)	83	10.7	Reference	Reference	
Surgery with adjuvant treatment (n=41)	19	11.4	1.07 (0.65, 1.77)	1.11 (0.64, 1.90)	
RT (n=35)	23	21.4	1.98 (0.24, 3.14)	1.77 (1.00, 3.14)	
SC only (n=34)	26	31.7	2.97 (1.90, 4.64)	2.92 (1.67, 5.12)	

[†]Adjusted for sex, smoking status. BMI, performance status, any comorbidity, hemoglobin level, tumor stage, FEV_1 % pred and DLco % pred. CI, confidence interval; HR, hazard ratio; RT, radiotherapy; SC, supportive care; FEV_1, forced expiratory volume in 1 s; DLco, diffusing capacity for carbon monoxide.

Table S3 Hazard ratios (95% confidence intervals) for all-cause mortality according to the treatment modality among patients with clinical stage I (N=455)

	No. of death	Incidence rate per 100 person-year	Crude, HR (95% CI)	Adjusted[†], HR (95% CI)
Surgery				
Surgery (n=396)	99	5.8	Reference	Reference
No surgery (n=59)	42	26.4	4.63 (3.21, 6.67)	2.91 (1.81, 4.67)
Specific treatment modality				
Surgery only (n=337)	77	5.2	Reference	Reference
Surgery with adjuvant treatment (n=59)	22	9.3	1.83 (1.14, 2.94)	2.04 (1.24, 3.33)
RT (n=32)	20	19.6	3.84 (2.35, 6.30)	2.40 (1.31, 4.42)
SC only (n=27)	22	38.4	7.67 (4.71, 12.49)	4.69 (2.46, 8.92)

[†]Adjusted for age, sex, smoking status. BMI, performance status, any comorbidity, hemoglobin level, FEV_1 % pred and DLco % pred. CI, confidence interval; HR, hazard ratio; RT, radiotherapy; SC, supportive care; FEV_1, forced expiratory volume in 1 s; DLco, diffusing capacity for carbon monoxide.

Table S4 Decision making process for NSCLC patients with COPD who did not receive surgical resection

	RT (n=48)	SC-only (n=45)	P value
Major decision maker			<0.001
Patient or families	13 (27.1)	32 (71.1)	
Doctor	35 (72.9)	13 (28.9)	
Main reason(s) for treatment decision[†]			
Old age	12 (25.0)	3 (6.7)	0.016
Comorbid disease	12 (25.0)	2 (4.4)	0.006
Poor performance state	2 (4.2)	7 (15.6)	0.084
Poor lung function	27 (56.3)	7 (15.6)	<0.001
Patient and family will	13 (27.1)	33 (73.3)	<0.001

The values are in n (%). [†]Multiple choice questionnaire. NSCLC, non-small cell lung cancer; COPD, chronic obstructive pulmonary disease; RT, radiotherapy; SC, supportive care.