Prognostic and Functional Impact of Perioperative LA/A/LABA Inhaled Therapy In Patients With Lung Cancer and Chronic Obstructive Pulmonary Disease

Yoko Azuma
Toho University School of Medicine
https://orcid.org/0000-0003-3625-5729

Atsushi Sano
Toho University School of Medicine

Takashi Sakai
Toho University School of Medicine

Satoshi Koezuka
Toho University School of Medicine

Hajime Otsuka
Toho University School of Medicine

Naobumi Tochigi
Toho University School of Medicine

Kazutoshi Isobe
Toho University School of Medicine

Susumu Sakamoto
Toho University School of Medicine

Yujiro Takai
Toho University School of Medicine

Akira Iyoda (aiyoda@med.toho-u.ac.jp)
Toho University School of Medicine
https://orcid.org/0000-0002-0908-4840

Research article

Keywords: lung cancer, COPD, LAMA/LABA therapy, perioperative management

DOI: https://doi.org/10.21203/rs.3.rs-200524/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

Background: Chronic obstructive pulmonary disease (COPD) is an important risk factor for postoperative complications and mortality. The utility of several perioperative bronchodilators in patients with COPD requiring surgery for lung cancer has been reported, but the most suitable agent and its specific effect on postoperative long-term prognosis remain unclear. To determine the effects of perioperative combination therapy, using a long-acting muscarinic antagonist (LAMA) and a long-acting β₂ agonist (LABA), on preoperative lung function, postoperative morbidity and mortality, and long-term outcome in COPD patients.

Methods: Between January 2005 and October 2019, 130 consecutive patients with newly diagnosed COPD underwent surgery for lung cancer. We conducted a retrospective review of their medical records. Patients were divided into 3 groups according to perioperative management: LAMA/LABA (n=64), LAMA (n=23) and rehabilitation only (no bronchodilator) (n=43).

Results: Patients who received preoperative LAMA/LABA therapy showed significant improvement in lung function before surgery (p<0.001 for both forced expiratory volume in 1 second (FEV₁) and percentage of predicted forced expiratory volume in 1 second (FEV₁ %pred)). Compared with patients who received preoperative LAMA therapy, patients with LAMA/LABA therapy had significantly improved lung function (ΔFEV₁, 223.1 mL vs 130.0 mL, ΔFEV₁ %pred, 10.8% vs 6.8%; both p<0.05). There was a trend toward a lower incidence of postoperative complications in the LAMA/LABA group compared with the LAMA and rehabilitation-only groups. In patients with moderate to severe air flow limitation (n=61), those who received LAMA/LABA therapy had significantly longer overall survival and disease-free survival compared with patients in the other groups. Perioperative LAMA/LABA therapy was also associated with lower recurrence rates.

Conclusions: Patients who receive perioperative LAMA/LABA for moderate to severe COPD have improved prognosis and better pulmonary function with surgery for lung cancer. We believe this treatment combination is optimal for patients with lung cancer and COPD.

Background

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease of the airways characterized by persistent symptoms such as cough, sputum production, progressive breathlessness, and airflow obstruction [1]. Patients with lung cancer have a 6-fold greater risk of having COPD than do matched smokers [2]. Although eligible patients with lung cancer receive a survival benefit from surgical resection, COPD is an important patient-related risk factor for postoperative complications and mortality [3]. Patients with COPD often have nonspecific airway hyperactivity, suggesting the presence of bronchospasm or latent respiratory tract infection. It is important to alleviate peripheral airway obstruction and to reduce airway secretions to improve surgical outcomes [4]. The combination of
smoking cessation, physical therapy, and the use of bronchodilators reportedly reduces postoperative complications and improves surgical outcomes in patients with lung cancer and COPD [5, 6].

Long-acting muscarinic antagonists (LAMAs) prevent the neurotransmitter acetylcholine from binding to muscarinic receptors, leading to relaxation of the airway smooth muscle [7]. Long-acting β2 agonists (LABAs) act on β2-adrenergic receptors and cause relaxation of the smooth muscle [8]. Patients who receive combined LAMA/LABA therapy for COPD show superior improvement in lung function and clinical outcomes than those who receive bronchodilator monotherapy [9]. Combined LAMA/LABA therapy also leads to a lower incidence of pneumonia than the combination of inhaled corticosteroids (ICS) and a LABA [9].

Because the prognosis of patients with lung cancer complicated by COPD is reportedly poor [5], it is important to provide respiratory care for an extended duration, not just during the perioperative period. The aim of this study is to determinate the effects of perioperative LAMA/LABA therapy on preoperative lung function, postoperative morbidity and mortality, and long-term prognosis for patients with COPD and lung cancer. We hypothesize that perioperative LAMA/LABA therapy will improve surgical outcomes.

Methods

This study was approved by the Ethics Committee of Faculty of Medicine, Toho University (A19039_27128_25095_25047) and written informed consent or opt-out consent was obtained from all patients.

Study design and population

We performed a retrospective review of the medical records of patients who underwent surgical resection of lung cancer at Toho University Hospital between January 2005 and October 2019. We included patients with both airflow limitation (AFL) and a smoking history of greater than 10 pack-years. We defined AFL as a ratio of expiratory volume in 1 second (FEV₁) to forced vital capacity (FVC) less than 70%, as determined by spirometry at the patient's initial visit. We excluded patients with a history of asthma or a history of inhaled therapy, and those who were missing data.

All patients with newly defined COPD received perioperative rehabilitation. The patients were divided into 3 groups according to their perioperative management: a LAMA/LABA group, a LAMA group, and a group that did not receive bronchodilators (No-BD group). The severity of AFL was classified according to the spirometric grades outlined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [10].

Postoperative complications

Pneumonia was defined as the presence of at least 3 of the following: a persistent lung infiltrate on chest radiography, chest computed tomography or both; a temperature of > 37.5°C; and a leukocyte count > 10 000 /mm³. Prolonged air leakage was defined as the continuation of air leakage for more than 7 days.
after surgery. Atrial brillation was diagnosed by electrocardiography and required to persist for at least 1 hour.

**Statistical analysis**

The data were presented as the mean ± standard deviation (SD) or as the median value with interquartile ranges. Categorical variables were shown as the percentage of the sample. Comparisons between 2 groups were assessed using Student's t-test for normally distributed variables or using the Mann-Whitney U test for nonnormally distributed variables. Differences were considered statistically significant when the \( p \) value was less than 0.05. Survival curves were prepared using the Kaplan-Meier method, and univariate comparison was performed using the log-rank test. To determine which factors were significantly associated with survival, we performed multivariate analysis using the Cox proportional hazards model. All statistical analyses were performed using JMP software, version 14.0 (SAS Institute Inc., Cary, NC, USA).

**Results**

**Patient characteristics**

Between January 2005 and October 2019, a total of 1330 patients with lung cancer underwent surgical resection at our institution. Of these, 192 patients (14.4%) met the inclusion criteria. A total of 62 patients had at least 1 exclusion criterion (Supplementary Fig. 1).

A total of 130 patients with COPD who underwent surgical resection of lung cancer and who received perioperative rehabilitation were enrolled in this study. The patients were divided into 3 subgroups according to their perioperative management: the LAMA/LABA group (\( n = 64 \)), the LAMA group (\( n = 23 \)), and the No-BD group (rehabilitation only; \( n = 43 \)). The main patient characteristics are summarized in Table 1. Patients who received LAMA/LABA therapy were significantly older than patients in the LAMA group \( (p = 0.045) \) and those in the No-BD group \( (p = 0.014) \). There was no significant difference between patients in the LAMA/LABA group and the other groups with regard to sex, smoking status or pack-years of smoking.
### Table 1
**Patient characteristics**

| Patients with COPD (n = 130) | LABA/LAMA | LAMA | p value* | No-BD | p value** |
|-----------------------------|-----------|------|----------|-------|----------|
|                             | n = 64    | n = 23 |          | n = 43 |          |
| **Age**                     | 73.4 ± 6.7| 70.6 ± 6.5| 0.045    | 70.5 ± 6.2 | 0.014    |
| **Sex**                     |           |       |          |       |          |
| Male                        | 50 (78.1)| 19 (82.6)| 0.644    | 39 (90.7)| 0.088    |
| Female                      | 14 (21.9)| 4 (17.4)|          | 4 (9.3) | -        |
| **Smoking status**          |           |       |          |       |          |
| Current smoker              | 25 (39.0)| 11 (47.8)| 0.466    | 18 (41.9)| 0.772    |
| Ex-smoker                   | 39 (61.0)| 12 (52.2)|          | 25 (58.1)|          |
| **Tobacco, pack-years**     | 53.2 ± 27.3| 60.6 ± 29.4| 0.86    | 63.8 ± 40.2 | 0.976    |
| **Pulmonary function**      |           |       |          |       |          |
| FEV₁ (mL)                   | 1787.5 ± 558.8| 1429.5 ± 412.5| 0.003 | 2168.8 ± 535.2 | 0.999 |
| FEV₁/FVC (%)                | 58.3 ± 9.6| 53.4 ± 11.4| 0.027    | 61.4 ± 10.2| 0.947    |
| FEV₁ %pred (%)              | 85.3 ± 22.6| 64.3 ± 12.4| < 0.001  | 94.6 ± 2.9 | 0.991    |
| **Severity of AFL**         |           |       |          |       |          |
| Mild                        | 32 (50.0)| 1 (4.4) | < 0.001  | 36 (83.7)| 0.002    |
| Moderate to Severe          | 32 (50.0)| 22 (95.6)|          | 7 (16.3)|          |
| **Surgical procedure**      |           |       |          |       |          |
| Pneumonectomy               | 1 (1.6)  | 0      | 0.367    | 0      | 0.844    |
| Lobectomy                   | 56 (87.5)| 23 (100.0)| 40 (93.0)|          |          |
| Segmentectomy               | 2 (3.1)  | 0      | 1 (2.3)  |          |          |
| Partial resection           | 5 (7.8)  | 0      | 2 (4.7)  |          |          |
| **Histology**               |           |       |          |       |          |
| Adenocarcinoma              | 31 (48.4)| 6 (26.1)| 0.172    | 26 (60.5)| 0.412    |
Patients with COPD (n = 130)

|                        | LAMA/LABA | LAMA | COPD | LAMA/LABA | LAMA | COPD |
|------------------------|-----------|------|------|-----------|------|------|
| Squamous cell carcinoma| 28 (43.8) | 14 (60.9) | 15 (34.9) |
| Other                  | 5 (7.8)   | 3 (13.0) | 2 (4.6)   |

**Pathologic staging**

|      | LAMA/LABA | LAMA | COPD | LAMA/LABA | LAMA | COPD |
|------|-----------|------|------|-----------|------|------|
| I    | 50 (78.1) | 11 (47.8) | 0.063 | 33 (76.7) | 0.706 |
| II   | 8 (12.5) | 9 (39.0) | 3 (7.0) |
| III  | 6 (9.4) | 3 (13.0) | 7 (16.3) |

**Recurrence (present)**

|      | LAMA/LABA | LAMA | COPD | LAMA/LABA | LAMA | COPD |
|------|-----------|------|------|-----------|------|------|
|      | 7 (10.9) | 11 (47.8) | <0.001 | 15 (34.9) | 0.008 |

Data are presented as n (%) or as mean ± SD; *Significance of LAMA/LABA vs LAMA; **Significance of LAMA/LABA vs No-BD; COPD: chronic obstructive pulmonary disease; LAMA: long-acting muscarinic antagonists; LABA: long-acting \( \beta \)-agonists; BD: bronchodilator; FEV1: forced expiratory volume in 1 second; FEV1%pred: percentage of predicted forced expiratory volume in 1 second; FVC: forced vital capacity; AFL: airflow limitation;

Pulmonary function at the initial visit was significantly worse in the LAMA group than in the LAMA/LABA group, as measured by FEV1, FEV1/FVC, and the percentage of predicted FEV1 (FEV1% pred) \( p < 0.05 \) for all. The LAMA group had a higher proportion of patients with moderate to severe AFL than the LAMA/LABA group \( p < 0.001 \), while the No-BD group included a higher proportion of patients with mild AFL \( p = 0.002 \).

**Perioperative inhaled therapy**

The components of perioperative inhaled therapy are provided in Supplementary Table 1. In the LAMA/LABA group, patients received a LAMA plus a LABA \( n = 11 \) or a combined LAMA/LABA agent \( n = 53 \). All patients in the LAMA group received inhaled tiotropium bromide hydrate. The average duration of preoperative inhalation therapy in the LAMA/LABA group and the LAMA group was 27.7 days and 24.5 days, respectively. The postoperative inhalation period was 396.6 days and 827.2 days, respectively.

**Improvement in lung function with preoperative inhaled LAMA/LABA therapy**

We reassessed lung function 1 or 2 days before surgery. The values for FEV1 and FEV1 %pred were significantly improved in the LAMA/LABA group (both \( p < 0.001 \); Fig. 1A, B). In the LAMA/LABA group, the treatment response tended to correlate with the severity of AFL. The patients with severe AFL showed an excellent response compared with patients with mild or moderate AFL (both \( p < 0.05 \); Fig. 1C). We also compared the improvement in lung function between the LAMA/LABA group and the LAMA group. The increases in FEV1 and FEV1 %pred were significantly higher for LAMA/LABA therapy than for LAMA therapy \( \Delta \text{FEV}_1, 223.1 \text{ mL \ vs \ } 130.0 \text{ mL}; \Delta \text{FEV}_1 \ %\text{pred, } 10.8\% \ \text{vs \ } 6.8\%; \ \text{both \ } p < 0.05; \ \text{Fig. 2A, B}. \)
proportion of excellent treatment response was also higher in the LAMA/LABA group (ΔFEV₁ > 200 mL, 59.4% vs 17.4%; ΔFEV₁ > 300 mL, 34.4% vs 4.4%; both \( p < 0.05 \); Fig. 2C)

**Postoperative morbidity and mortality**

Patient characteristics are given in Table 1. There was no significant difference between patients in the LAMA/LABA group and the other groups with regard to the type of surgical procedure performed. Most patients underwent lobectomy (LAMA/LABA, 87.5%; LAMA, 100%; No-BD, 93.9%). Postoperative complications and mortality are summarized in Table 2. Postoperative complications were more frequent in the LAMA group than in the LAMA/LABA group (\( p = 0.007 \)). The proportion of patients who required home oxygen therapy was higher in the LAMA group than in the LAMA/LABA group (\( p = 0.008 \)). Prolonged air leakage was more frequent in the No-BD group than in the LAMA/LABA group (\( p = 0.012 \)). The incidence of all postoperative complications was lower in the LAMA/LABA group than in the other groups. Only the LAMA/LABA group had no mortality at 90 days.

| Complications                  | LABA/LAMA (n = 64) | LAMA (n = 23) | \( p \)   | No-BD (n = 43) | \( p \) value** |
|--------------------------------|--------------------|--------------|----------|---------------|----------------|
| Any                           | 14 (21.9)          | 12 (52.2)    | 0.007    | 16 (37.2)     | 0.083          |
| Pneumonia                     | 7 (11.0)           | 6 (26.1)     | 0.081    | 7 (16.3)      | 0.422          |
| Prolonged air leakage         | 6 (9.4)            | 5 (21.7)     | 0.126    | 11 (25.6)     | 0.012          |
| Atrial fibrillation           | 4 (6.3)            | 2 (8.7)      | 0.776    | 4 (10.5)      | 0.557          |
| Introduction of HOT           | 3 (4.7)            | 3 (13.0)     | 0.008    | 0             | 0.176          |
| 30-day mortality              | 0                  | 0            | -        | 0             | -              |
| 90-day mortality              | 0                  | 1 (4.4)      | 0.093    | 1 (2.3)       | 0.246          |

Data are presented as n (%)

COPD: chronic obstructive pulmonary disease; LAMA: long-acting muscarinic antagonists; LABA: long-acting \( \beta_2 \)-agonists; BD: bronchodilator; HOT: home oxygen therapy

*Significance of LAMA/LABA vs LAMA

**Significance of LAMA/LABA vs No-BD

**Survival analysis of all patients**
Patient characteristics are presented in Table 1. There was no significant difference between patients in the LAMA/LABA group and the other groups in regard to tumor histology, pathologic staging. Although a comparable proportion of patients received adjuvant chemotherapy or treatment for recurrence in all groups (data not shown), the recurrence rate was significantly lower in the LAMA/LABA group compared with both the LAMA group ($p < 0.001$) and the No-BD group ($p = 0.008$).

Five patients (7.8%) in the LAMA/LABA group, 14 patients (60.8%) in the LAMA group, and 20 patients (46.5%) in the No-BD group died during the study period. The causes of death for these 39 patients are given in Supplementary Table 2. Lung-cancer related death was the most frequent cause in all groups. No patients in the LAMA/LABA group died of pneumonia. The cumulative OS at 5 years was 79.8% in the LAMA/LABA group, 53.2% in the LAMA group, and 51.7% in the No-BD group (Fig. 3A). The DFS at 5 years was 70.8%, 39.2%, and 39.9%, respectively (Fig. 3B). The patients in the LAMA/LABA group had significantly longer OS and DFS than patients in the LAMA group ($p = 0.021$; $p = 0.017$), and longer DFS than patients in the No-BD group ($p = 0.044$).

**Survival analysis of patients with moderate to severe AFL**

We assessed the effects of perioperative inhaled LAMA/LABA therapy on the prognosis of patients with moderate to severe AFL. A total of 51 patients with moderate to severe AFL were included in the study. Of these, 32 were in the LAMA/LABA group, 12 were in the LAMA group, and 7 were in the No-BD group. Patient characteristics are given in Table 3. There was no significant difference between patients in the LAMA/LABA group and the other groups in regard to age, sex, smoking status, severity of AFL, surgical procedure, pathologic staging, or treatment for recurrence. A comparable proportion of patients received adjuvant chemotherapy in all groups. As seen in the analysis of COPD patients of all severities, the recurrence rate was significantly lower in the LAMA/LABA group compared with the LAMA group ($p = 0.006$) and the No-BD group ($p = 0.008$; Table 3).
### Table 3
Characteristics of patients with moderate to severe airflow limitation

| Patients with moderate to severe AFL (n = 61) | LABA/LAMA (n = 32) | LAMA (n = 22) | p value* | No-BD (n = 7) | p value** |
|---------------------------------------------|--------------------|---------------|----------|---------------|----------|
| **Age**                                     | 72.2 ± 6.7         | 70.8 ± 6.6    | 0.236    | 69.9 ± 5.6    | 0.203    |
| **Sex**                                     | 0.804              | 0.929         |          |               |          |
| Male                                        | 27 (84.4)          | 18 (81.8)     |          | 6 (85.7)      |          |
| Female                                      | 5 (15.6)           | 4 (18.2)      | -        | 1 (14.3)      | -        |
| **Smoking status**                          | 0.412              | 0.262         |          |               |          |
| Current smoker                              | 11 (34.4)          | 10 (45.5)     | 4 (57.1) |              |          |
| Ex-smoker                                   | 21 (65.6)          | 12 (54.5)     | 3 (42.9) | -             |          |
| **Severity of AFL**                         | 0.344              | 0.399         |          |               |          |
| Moderate                                    | 29 (90.6)          | 18 (81.8)     | 7 (100)  |              |          |
| Severe                                      | 3 (9.4)            | 4 (18.2)      | 0        |               |          |
| **Surgical procedure**                      | 0.098              | 0.887         |          |               |          |
| Lobectomy                                   | 26 (81.3)          | 22 (100)      | 6 (85.7) |              |          |
| Segmentectomy                               | 1 (3.1)            | 0             | 0        |               |          |
| Partial resection                           | 5 (15.6)           | 0             | 1 (14.3) |              |          |
| **Pathologic staging**                      | 0.063              | 0.228         |          |               |          |
| I                                           | 16 (81.3)          | 11 (50.0)     | 4 (57.1) |              |          |
| II                                          | 2 (6.2)            | 8 (36.4)      | 0        |               |          |
| III                                         | 4 (12.5)           | 3 (13.6)      | 3 (42.9) |              |          |
| **Adjuvant chemotherapy**                   | 4 (12.5)           | 5 (22.7)      | 0.322    | 2 (28.6)      | 0.286    |
| **Recurrence (present)**                    | 4 (12.5)           | 10 (45.5)     | 0.006    | 4 (57.1)      | 0.008    |
| Treatment for recurrence                    |                    |               |          |               |          |
| Anticancer drug                             | 2                  | 6             | 3        |               |          |
| Molecular targeted drug                     | 0                  | 1             | 1        |               |          |
| ICI                                          | 0                  | 0             | 0        |               |          |
The OS in the LAMA/LABA, LAMA, and No-BD groups at 5 years was 82.7%, 55.8%, and 28.6%, respectively (Fig. 4A). The DFS at 5 years was 75.3%, 41.1%, and 14.3% (Fig. 4B). The patients in the LAMA/LABA group had significantly longer OS and DFS compared with the LAMA group \( (p = 0.043; p = 0.026) \) and with the No-BD group \( (p = 0.002; p < 0.001) \).

### Univariate and multivariate analyses of beneficial factors for long-term mortality

On univariate analysis, a low pathologic stage and perioperative LAMA/LABA therapy were beneficial factors for long-term mortality. On multivariate analysis, perioperative LAMA/LABA therapy remained a beneficial factor (Table 4A). Only perioperative LAMA/LABA therapy was identified as a beneficial factor for recurrence on both univariate and multivariate analyses (Table 4B).

Table 4. Univariate and multivariate analysis of favorable factors for postoperative prognosis in patients with moderate to severe AFL

| A. Analysis of favorable factors for overall survival |  |  |  |
|---|---|---|---|
| None | 2 | 2 | 0 |

Data are presented as n (%) or as mean ± SD; COPD: chronic obstructive pulmonary disease; LAMA: long-acting muscarinic antagonists; LABA: long-acting β2-agonists; BD: bronchodilator; AFL: airflow limitation;

ICI: Immune checkpoint inhibitor
| Clinicopathologic variable                  | Univariate analysis |                       | Multivariate analysis |                       |
|--------------------------------------------|---------------------|-----------------------|-----------------------|-----------------------|
|                                            | RR      | 95%CI    | p value  | RR      | 95%CI    | p value  |
| **Sex (male)**                             | 1.24    | 0.35–3.38| 0.703    | -       | -       | -       |
| **Age (< 75 y)**                           | 0.88    | 0.44–3.50| 0.797    | -       | -       | -       |
| **Histology**                              | 0.083   | -       | -       | -       | -       | -       |
| Squamous cell carcinoma                    | 1.00    | reference| -       | -       | -       | -       |
| Adenocarcinoma                             | 0.46    | 0.17–1.13| 0.094    | -       | -       | -       |
| Other                                      | 0.17    | 0.01–1.08| 0.051    | -       | -       | -       |
| **Lymph node metastasis (absent)**         | 0.61    | 0.25–1.55| 0.289    | -       | -       | -       |
| **Pathologic stage:**                      | 0.027   | 0.154    | 0.027    | 1.00    | reference| 0.027    | 1.00    | reference| 0.154    |
| I                                          | 1.00    | reference| 1.00    | reference| 1.00    | reference| 1.00    | reference| 1.00    |
| II                                         | 2.96    | 0.11–0.94| 0.052    | 2.25    | 0.65–7.36| 0.190    |
| III                                        | 3.65    | 0.08–0.77| 0.024    | 2.58    | 0.80–8.07| 0.107    |
| **Bronchodilator**                         | 0.011   | 0.062    | 0.011    | 1.00    | reference| 0.062    | 1.00    | reference| 0.062    |
| LAMA/LABA                                  | 1.00    | reference| 1.00    | reference| 1.00    | reference| 1.00    | reference| 1.00    |
| LAMA                                       | 3.26    | 0.99–14.1| 0.049    | 2.43    | 0.66–11.2| 0.186    |
| No-BD                                      | 7.54    | 1.97–35.4| 0.003    | 5.59    | 1.31–21.5| 0.019    |

COPD: chronic obstructive pulmonary disease; LAMA: long-acting muscarinic antagonists; LABA: long-acting β2-agonists; BD: bronchodilator; RR: relative risk; CI: confidence interval

B. Analysis of favorable factors for disease-free survival
| Clinicopathologic variable | Univariate analysis | Multivariate analysis |
|-----------------------------|---------------------|----------------------|
|                             | RR | 95%CI    | p value | RR | 95%CI    | p value |
| Sex (male)                  | 1.18  | 0.44–4.07 | 0.757  | - | - | - |
| Age (< 75 y)                | 0.58  | 0.19–1.45 | 0.265  | - | - | - |
| **Histology:**              |     |           |       |     |           |       |
| Squamous cell carcinoma     | 1.00  | reference | 1.00   | reference | 0.038  | 0.362 |
| Adenocarcinoma              | 0.42  | 0.17–0.96 | 0.039  | 0.56 | 0.18–1.73 | 0.311 |
| Other                       | 0.16  | 0.08–0.90 | 0.035  | 0.22 | 0.01–1.56 | 0.142 |
| **Lymph node metastasis (absent)** | 0.48  | 0.22–1.12 | 0.091  | - | - | - |
| **Pathologic stage**        |     |           |       |     |           |       |
| I                           | 1.00  | reference | 1.00   | reference | 0.007  | 0.065 |
| II                          | 3.21  | 1.17–8.16 | 0.024  | 1.48 | 0.41–5.55 | 0.541 |
| III                         | 4.13  | 1.47–10.9 | 0.008  | 2.01 | 0.55–6.77 | 0.278 |
| **Bronchodilator**          |     |           |       |     |           |       |
| LAMA/LABA                   | 1.00  | reference | 1.00   | reference | 0.003  | 0.025 |
| LAMA                        | 3.14  | 1.16–9.91 | 0.023  | 2.47 | 0.78–8.45 | 0.120 |
| No-BD                       | 7.29  | 2.17–25.5 | 0.001  | 6.04 | 1.63–23.6 | 0.007 |

COPD: chronic obstructive pulmonary disease; LAMA: long-acting muscarinic antagonists; LABA: long-acting β2-agonists; BD: bronchodilator; RR: relative risk; CI: confidence interval

**Discussion**

In patients with lung cancer, COPD is an independent risk factor for morbidity and mortality. In the present study, we clarified the efficacy of perioperative LAMA/LABA therapy for pulmonary function, postoperative complications, and long-term prognosis in patients with newly diagnosed COPD requiring surgery for lung cancer.

The utility of perioperative bronchodilator therapy has been validated in several previous reports, but the most suitable agent has not been clarified. Combined LAMA/LABA therapy achieves bronchodilation through different mechanisms: the muscarinic antagonist blocks acetylcholine-mediated bronchoconstriction by binding to M3 receptors in the smooth muscle of the airway [9], and the β2 agonist induces relaxation of the smooth muscle by stimulating β2-adrenergic receptors [9]. We previously analyzed the data of 32 patients with moderate to severe COPD and lung cancer and reported that perioperative LAMA/LABA therapy improves lung function and reduces postoperative complications to a
greater degree than LAMA therapy [11]. In the present study, we assessed 130 patients with COPD of all severity levels, with similar results.

Some previous studies reported that preoperative LAMA monotherapy improves lung function or prevents postoperative respiratory complications, but other reports do not [12, 13]. Bolukbas et al reported that adding ICS to LAMA and LABA led to improvement in lung function and fewer respiratory complications [6]. However, the use of ICS is associated with severe pneumonia [14], and steroid use is a significant risk factor for bronchopleural fistula formation [15]. Therefore, the use of perioperative ICS is controversial. Combined LAMA/LABA therapy during the perioperative period provides a rapid and powerful bronchodilating effect, by the dual action of LAMA and LABA without adverse events such as pneumonia.

The effect of perioperative bronchodilator use on postoperative long-term prognosis in COPD patients with lung cancer has not been reported. We found that perioperative LAMA/LABA therapy is associated with a favorable prognosis compared with LAMA therapy or rehabilitation alone, especially in patients with moderate to severe COPD. The use of LAMA/LABA therapy enable effective management of COPD by significant improvement in lung function, dyspnea, use of rescue medication, and exacerbations compared with the monotherapies [9].

COPD is a strong promoting factor for lung cancer, and patients with COPD have poorer postoperative long-term survival due to a higher recurrence rate [16]. Chronic inflammation of the bronchial and alveolar mucosa [17], direct effects to DNA restoration by oxidative stress [18] and genetic mutation or variation [19] are associated with COPD and with the development of lung cancer. Recent reports propose that bronchodilators are able to inhibit inflammation and oxidative stress [20]. Muscarinic receptors expressed on lung cancer cells can reportedly stimulate tumor growth via acetylcholine [21]. The M₃ muscarinic receptor subtype, in particular, is associated with cell proliferation. As M₃ receptor antagonists, LAMAs have the potential to inhibit the growth of lung cancer cells [21]. Li et al reported that indacaterol induces apoptosis in lung cancer cells harboring the epidermal growth factor receptor T790M mutation and may be a novel candidate for treatment of gefitinib-resistant lung cancer [22]. Our results are consistent with these previous reports and suggest that the dual anticancer effects of LAMA/LABA—prevention of cancer development and inhibition of proliferation signals of lung cancer—may contribute to a favorable prognosis and inhibition of recurrence.

This retrospective study has limitations and biases. The duration of bronchodilator use and the individual bronchodilators employed was inconsistent. Finally, changes in surgical technique over time, including the use of different surgical tools and different anesthetic agents over the years of the study period, may have affected the incidence of postoperative complications.

**Conclusions**

Our data demonstrate that LAMA/LABA therapy improves not only short-term outcomes such as respiratory function and postoperative complications, but also long-term prognosis in patients with lung
cancer and COPD. Perioperative combined LAMA/LABA therapy is the optimal bronchodilator for patients with COPD who require surgery for lung cancer.

**Abbreviations**

COPD  
chronic obstructive pulmonary disease  
LAMA  
long-acting muscarinic antagonist  
LABA  
long-acting β2 agonist  
ICS  
inhaled corticosteroid  
AFL  
airflow limitation  
FEV₁  
forced expiratory volume in 1 second  
FVC  
forced vital capacity  
GOLD  
Global Initiative for Chronic Obstructive Lung Disease  
SD  
standard deviation  
OS  
overall survival  
BD  
bronchodilator  
FEV₁ %pred  
percentage of predicted expiratory volume in 1 second  
DFS  
disease-free survival

**Declarations**

**Ethics approval and consent to participate**

This study was approved by the Ethics Committee of Faculty of Medicine, Toho University (A19039_27128_25095_25047).

**Consent for publication**
Informed consent or opt-out consent was obtained from all patients.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

AY, SA and IA contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. AY, SA, ST, KS, OH, TN, IK, SS and TY had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgments

Not applicable.

References

1. Lopez-Campos JL, Tan W, Soriano JB. Global burden of COPD. Respirology. 2016;21:14–23.
2. Young RP, Hopkins RJ, Christmas T, Black PN, Metcalf P, Gamble GD. COPD prevalence is increased in lung cancer, independent of age, sex and smoking history. Eur Respir J. 2009;34:380–6.
3. Win T, Jackson A, Sharples L, Groves AM, Wells FC, Ritchie AJ, et al. Relationship between pulmonary function and lung cancer surgical outcome. Eur Respir J. 2005;25:594–9.
4. Zhai R, Yu X, Shafer A, Wain JC, Christiani DC. The impact of coexisting COPD on survival of patients with early-stage non-small cell lung cancer undergoing surgical resection. Chest. 2014;145:346–53.
5. Yoshida Y, Kage H, Murakawa T, Sato Y, Ota S, Fukayama M, et al. Worse Prognosis for Stage IA Lung Cancer Patients with Smoking History and More Severe Chronic Obstructive Pulmonary Disease. Ann Thorac Cardiovasc Surg. 2015;21:194–200.
6. Bolukbas S, Eberlein M, Eckhoff J, Schirren J. Short-term effects of inhalative tiotropium/formoterol/budenoside versus tiotropium/formoterol in patients with newly diagnosed
chronic obstructive pulmonary disease requiring surgery for lung cancer: a prospective randomized trial. Eur J Cardiothorac Surg. 2011;39:995–1000.

7. Roux E, Molimard M, Savineau JP, Marthan R. Muscarinic stimulation of airway smooth muscle cells. Gen Pharmacol. 1998;31:349–56.

8. Cazzola M, Molimard M. The scientific rationale for combining long-acting beta2-agonists and muscarinic antagonists in COPD. Pulm Pharmacol Ther. 2010;23:257–67.

9. Ficker JH, Rabe KF, Welte T. Role of dual bronchodilators in COPD: A review of the current evidence for indacaterol/glycopyrronium. Pulm Pharmacol Ther. 2017;45:19–33.

10. Singh D, Agusti A, Anzueto A, Barnes JP, Bourbeau J, Celli RB, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: the GOLD science committee report 2019. Eur Respir J. 2019;53:1900164.

11. Makino T, Otsuka H, Hata Y, Koezuka S, Azuma Y, Isobe K, et al. Long-acting muscarinic antagonist and long-acting beta2-agonist therapy to optimize chronic obstructive pulmonary disease prior to lung cancer surgery. Mol Clin Oncol. 2018;8:647–52.

12. Ueda K, Tanaka T, Hayashi M, Hamano K. Role of inhaled tiotropium on the perioperative outcomes of patients with lung cancer and chronic obstructive pulmonary disease. Thorac Cardiovasc Surg. 2010;58:38–42.

13. Kobayashi S, Suzuki S, Niikawa H, Sugawara T, Yanai M. Preoperative use of inhaled tiotropium in lung cancer patients with untreated COPD. Respirology. 2009;14:675–9.

14. Suissa S, Dell’Aniello S, Ernst P. Comparative Effects of LAMA-LABA-ICS vs LAMA-LABA for COPD: Cohort Study in Real-World Clinical Practice. Chest. 2020;157:846–55.

15. Shekar K, Foot C, Fraser J, Ziegenfuss M, Hopkins P, Windsor M. Bronchopleural fistula: an update for intensivists. J Crit Care. 2010;25:47–55.

16. Sekine Y, Yamada Y, Chiyo M, Iwata T, Nakajima T, Yasuhuku K, et al. Association of chronic obstructive pulmonary disease and tumor recurrence in patients with stage IA lung cancer after complete resection. Ann Thorac Surg. 2007;84:946–50.

17. Lourenço RV, Klimek MF, Borowski CJ. Deposition and clearance of 2 micron particles in the tracheobronchial tree of normal subjects—smokers and nonsmokers. J Clin Invest. 1971;50:1411–20.

18. Galaris D, Evangelou A. The role of oxidative stress in mechanisms of metal-induced carcinogenesis. Crit Rev Oncol Hematol. 2002;42:93–103.

19. Schwartz AG, Ruckdeschel JC. Familial lung cancer: genetic susceptibility and relationship to chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2006;173:16–22.

20. Wollin L, Pieper MP. Tiotropium bromide exerts anti-inflammatory activity in a cigarette smoke mouse model of COPD. Pulm Pharmacol Ther. 2010;23:345–54.

21. Song P, Sekhon HS, Fu XW, Maier M, Jia Ye, Duan J, et al. Activated cholinergic signaling provides a target in squamous cell lung carcinoma. Cancer Res. 2008;68:4693–700.
22. Li H, Tong CW, Leung Y, Wong MH, To KK, Leung KS. Identification of Clinically Approved Drugs Indacaterol and Canagliflozin for Repurposing to Treat Epidermal Growth Factor Tyrosine Kinase Inhibitor-Resistant Lung Cancer. Front Oncol. 2017;7:288.