



Current Status of Lung Cancer and Surgery Based on Studies Using a Nationwide Database

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Lung cancer is a fatal disease, highlighting the importance of research on related topics, including surgery for lung cancer. However, systematic research analyzing surgery on a national scale is limited. This study aimed to investigate the research on lung cancer using nationwide data in South Korea and to analyze trends in lung cancer surgery, including its clinical implications. Published articles and data from the Korean National Health Insurance database were used. Although the incidence and mortality of lung cancer have been improving, it is predicted to be the most common and fatal type of cancer in South Korea in 2021. The number of surgical procedures for lung cancer is increasing, especially among women, those ≥ 76 years of age, residents of non-metropolitan cities, and middle-income patients. Lobectomy and sublobectomy, including segmentectomy, are increasingly common. However, the proportion of pneumonectomy relative to other procedures is not increasing. Surgery has shown a reasonable survival rate, especially after lobectomy, but survival remains poor in patients ≥ 76 years of age who undergo pneumonectomy. The frequency of lung cancer surgery is increasing concomitantly with various socioeconomic changes. Lobectomy has become increasingly common, and the clinical results of surgery are satisfactory. Further research on the changing composition of surgical candidates is required.

Keywords: Neoplasms, Lung, Survival analysis, Statistics, Surgery

Introduction

Invasive lung and bronchus neoplasms are among the most common and fatal cancers worldwide. Lung cancer is the second most commonly diagnosed cancer and the leading cause of cancer-related deaths (18% of the total cancer deaths) in men in 93 countries [1]. In women, it ranks third in incidence (after breast and colorectal cancer) and second in mortality (after breast cancer) [1]. Fortunately, the mortality rate of lung cancer has decreased [2,3]. According to statistics from the United States, the 2-year relative survival of patients with non-small cell lung cancer increased from 34% to 42% for those diagnosed in 2009–2010 and 2015–2016, respectively [2]. In 2017, in South Korea, lung cancer was the second most common cancer in men and the fifth most common in women, and it is estimated to be the carcinoma with the highest incidence and

mortality in 2021 [4,5].

Various methods can help decrease lung cancer mortality. Smoking cessation [6], early diagnosis of lung cancer [7], new drugs [8], and surgery [9] have shown survival benefits in lung cancer. Of these, surgery is still the most effective treatment for early-stage lung cancer [10], and its clinical outcomes have improved with the wide use of video or robot-assisted thoracic surgery [11,12]. Moreover, the indications for surgery have increased with the adoption of segmentectomy, which might show comparable outcomes to lobectomy in small lung cancers [13]. Despite the importance of surgery, systematic or nationwide analyses of lung cancer surgery are limited in Korea. Meanwhile, researchers in other countries have investigated nationwide databases of lung cancer surgery [14,15] to analyze trends in cancer surgery and survival in their nations. Although the findings of those studies could be used to create effective



policies in the corresponding countries, they cannot be directly applied to Korea due to differences in insurance systems across countries. Instead, there is a need for a separate analysis of current trends in lung cancer surgery in Korea to inform the development of effective policies that could be useful for decreasing the social cost of lung cancer.

Therefore, this study aimed to investigate nationwide research on lung cancer in South Korea and to analyze trends in lung cancer surgery, including its clinical implications.

Methods

Data sources and subjects

Published articles and data from the Korean National Health Insurance (KNHI) database were used, which are available from the sharing service provided by the KNHI Corporation. The database provides detailed sociodemographic information, but not medical or pathologic records, so it was not possible to determine whether specific cases of lung cancer were small-cell or non-small-cell. Patients with the International Classification of Diseases (10th edition) Clinical Modification code C34 claims, indicating lung and bronchial carcinoma, were screened for eligibility. Patients without the application of exempted calculations were excluded to identify real cancer patients. The study protocol was approved by the Institutional Review Board of Chungbuk National University (2018-04-022). The requirement for informed consent to participate was waived by the Ethics Committee.

Statistical analyses

Trends in surgery were analyzed by patient sex, age, income category, and residential area. The annual p-trend was determined using the Wilcoxon test for trends across ordered groups. Survival was defined as the interval between the date of surgical resection and the date of death due to any cause. Survival curves were plotted using the Kaplan-Meier method and compared using the log-rank test. To determine the prognostic factors, multivariate analysis was performed using a Cox proportional hazards model. All statistical tests were 2-sided, with a significance level set at $p < 0.05$. Analyses were performed using Stata software ver. 12.1 (Stata Corp., College Station, TX, USA).

Results

Incidence and mortality of lung cancer

According to a study on nationwide cancer epidemiology using the Korea National Cancer Incidence Database from 1999 to 2017, the number of incident cases of lung cancer in 2017 was 26,985 [4], with 84,242 prevalent cases. Meanwhile, there were 17,980 deaths. Lung cancer was the most common cause of cancer-related mortality, with a crude mortality rate of 35.1 per 100,000 (51.9 in men and 18.4 in women) and age-standardized mortality of 16.7 per 100,000 (29.4 in men and 7.4 in women). The incidence and mortality of lung cancer decreased in the age-standardized analysis. The annual percentage change in lung cancer incidence was 0.2 (from 1999 to 2010) but decreased to -0.9 (from 2010 to 2017). Specifically, it decreased in both men (from 0.0 to -1.5) and women (from 1.9 to 0.2). Meanwhile, the annual percentage change in mortality decreased from 2.1 to -2.2, respectively (men: 2.0 to -2.6; women: -1.0 to -4.5). Therefore, the 5-year relative survival rates of localized lung cancer in 2017 were 61.1% in men and 81.7% in women.

In 2017, stomach, colon/rectum, and lung cancers were the most common, but the incidence of lung cancer was expected to increase [4]. For lung cancer, the crude and age-standardized incidence rates were 52.7 and 27.1 per 100,000, respectively, in 2017. However, lung cancer was estimated to be the most common cancer in 2021 because the decrease in the incidence of the other types of cancers was more pronounced, while the crude and age-standardized incidence rates of lung cancer were estimated to increase to 62.0 and 27.5 per 100,000, respectively [5]. A similar situation was expected in the mortality rates, with the crude and age-standardized mortality rates estimated at 35.5 and 14.0 per 100,000, respectively, in 2021 (35.1 and 16.7 in 2017). Although the overall mortality of lung cancer has decreased, it remains the leading cause of cancer-related death [5].

Lung cancer statistics by socioeconomic status

From 2003 to 2013, lung cancer was the most prevalent in the 60- to 79-year age group (approximately 64%), men (71%), suburban/rural residents (59%), and individuals in the highest (fourth) income quartile (31%) (Fig. 1A–D). Other noteworthy trends in lung cancer prevalence were that the number of female patients increased (from 27.5% to 31.6%) and the proportion of patients in the 60- to 69-

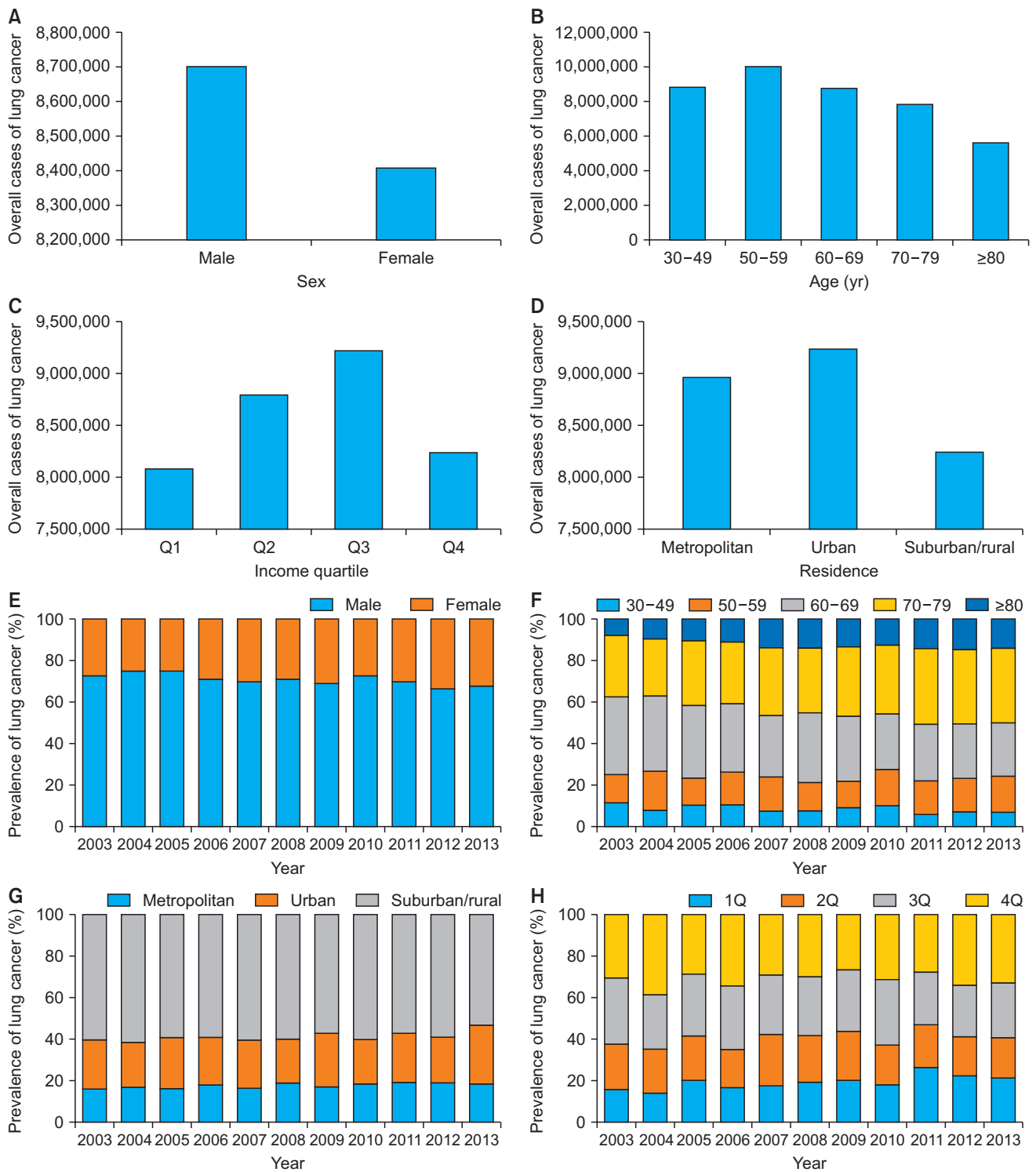


Fig. 1. Lung cancer statistics and trend analysis by sex, age, income, and residence. (A–D) Lung cancer was most prevalent in men (71%), the 60- to 79-year age group (64%), the highest income quartile (31%, fourth quartile of income), and suburban/rural residents (59%). (E–H) The prevalence of lung cancer increased among women (27.5% to 31.6%) and decreased in the 60- to 69-year age group (38.7% to 25.5%), but it increased in patients aged 70–79 years (28.3% to 37.7%) and over 80 years (7.6% to 13.9%). It also increased among residents of non-metropolitan urban areas (23.3% to 29.2%) and those with incomes belonging to the first or fourth quartile (16% to 21.8% in the first quartile and 29.6% to 33.3% in the fourth quartile).

year age group decreased (from 38.7% to 25.5%), which was counterbalanced by increasing proportions of patients in the 70- to 79-year age group (from 28.3% to 37.7%) and the over 80-year group (from 7.6% to 13.9%) (Fig. 1E–H) [16]. According to residence and income, the proportion of patients residing in urban areas (23.3% to 29.2%) and belonging to the first or fourth quartile of income also increased (from 16% to 21.8% in the first quartile and from 29.6% to 33.3% in the fourth quartile).

The pattern of primary treatment differed according to sex, income, residence area, and age group (Fig. 2A–D) [16]. More women received surgery as a primary treatment (21% versus 19%), but the proportion of patients who did not receive treatment was also higher (37% versus 30%). Patients with higher incomes were more likely to undergo surgery and were less likely to receive no treatment. Surgery was

performed in 14% of low-income patients (Q1), but 22% of high-income patients (Q4). Moreover, the proportion of patients who did not receive treatment was also higher in low-income patients (37%) than in those with high incomes (31%). Regarding area of residence, more patients in metropolitan areas received surgery, while patients residing in suburban/rural areas were more likely not to receive treatment. It was noticeable that as the patients got older, they received fewer treatments, including surgery; for instance, only 3% of patients aged over 80 years underwent surgery, while 74% received no treatment.

Trend analysis of surgery

The proportion of lung cancer patients who underwent surgery increased from 16% in 2003 to 21% in 2006 and

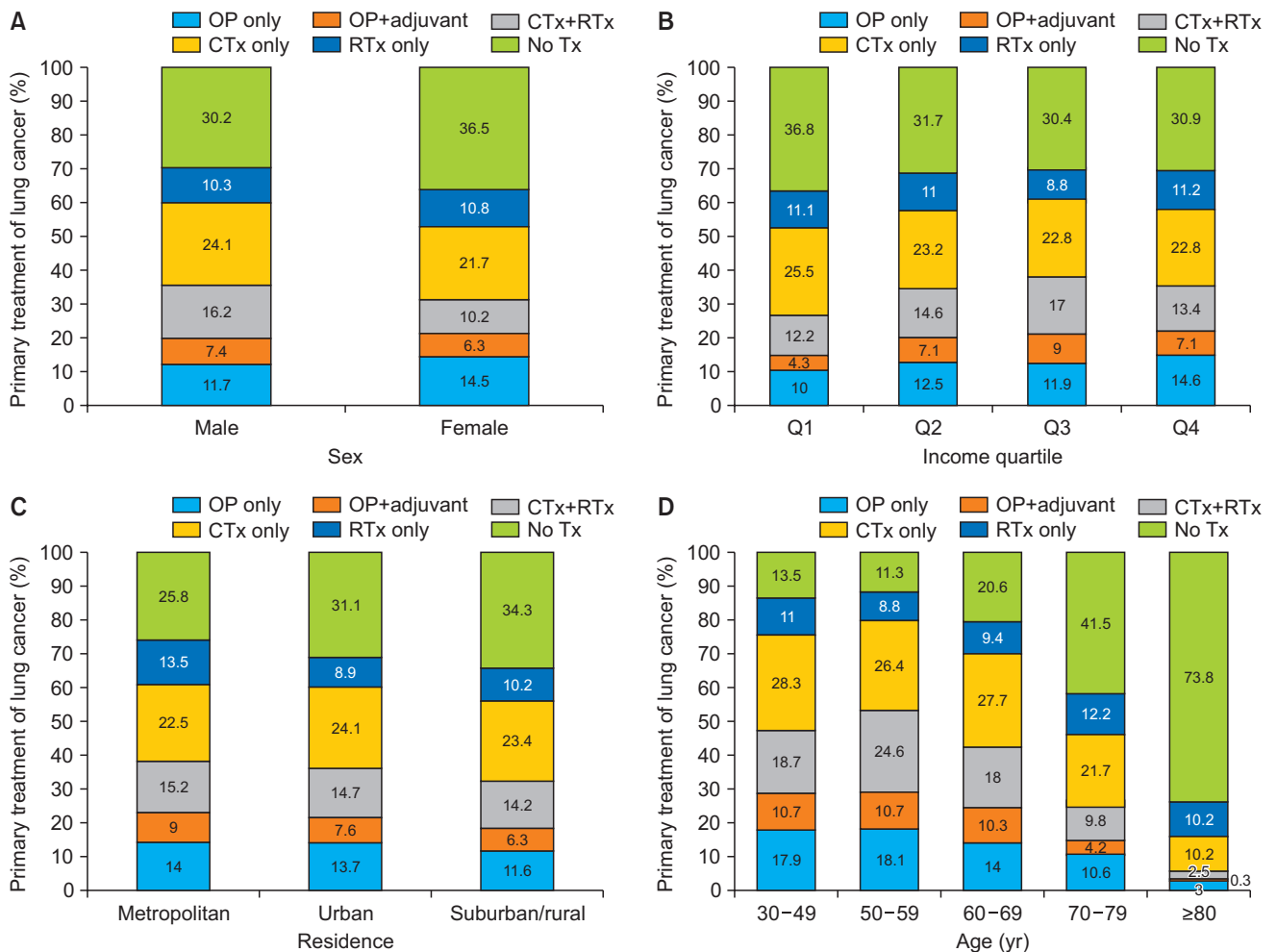


Fig. 2. Trends in the primary treatment of lung cancer in Korea, 2003–2013. Trends in the primary treatment of lung cancer are shown based on the proportion of newly diagnosed cases for each year. The trends are presented by sex (A), income (B), residential area (C), and age (D). OP, surgical treatment; CTx, chemotherapy; RTx, radiation therapy; OP+adjuvant, OP+CTx or OP+RTx or OP+CTx+RTx; Tx, treatment; MLND, mediastinal lymph node dissection.

25% in 2012 (Fig. 3A) [16]. The frequency of surgery alone and surgery with adjuvant treatment both increased simultaneously. However, radiotherapy alone or no treatment steadily became less common (from 12% or 34%, respectively, in 2003 to 7% or 30%, respectively, in 2011) (Fig. 3B).

Specifically, the frequency of surgery with curative intent, including segmentectomy and lobectomy, increased [16,17]. Lobectomy, the standard operation for lung cancer, increased in frequency (from 60% in 2003 to 81% in 2008), but this was not the case for pneumonectomy (from 19% in

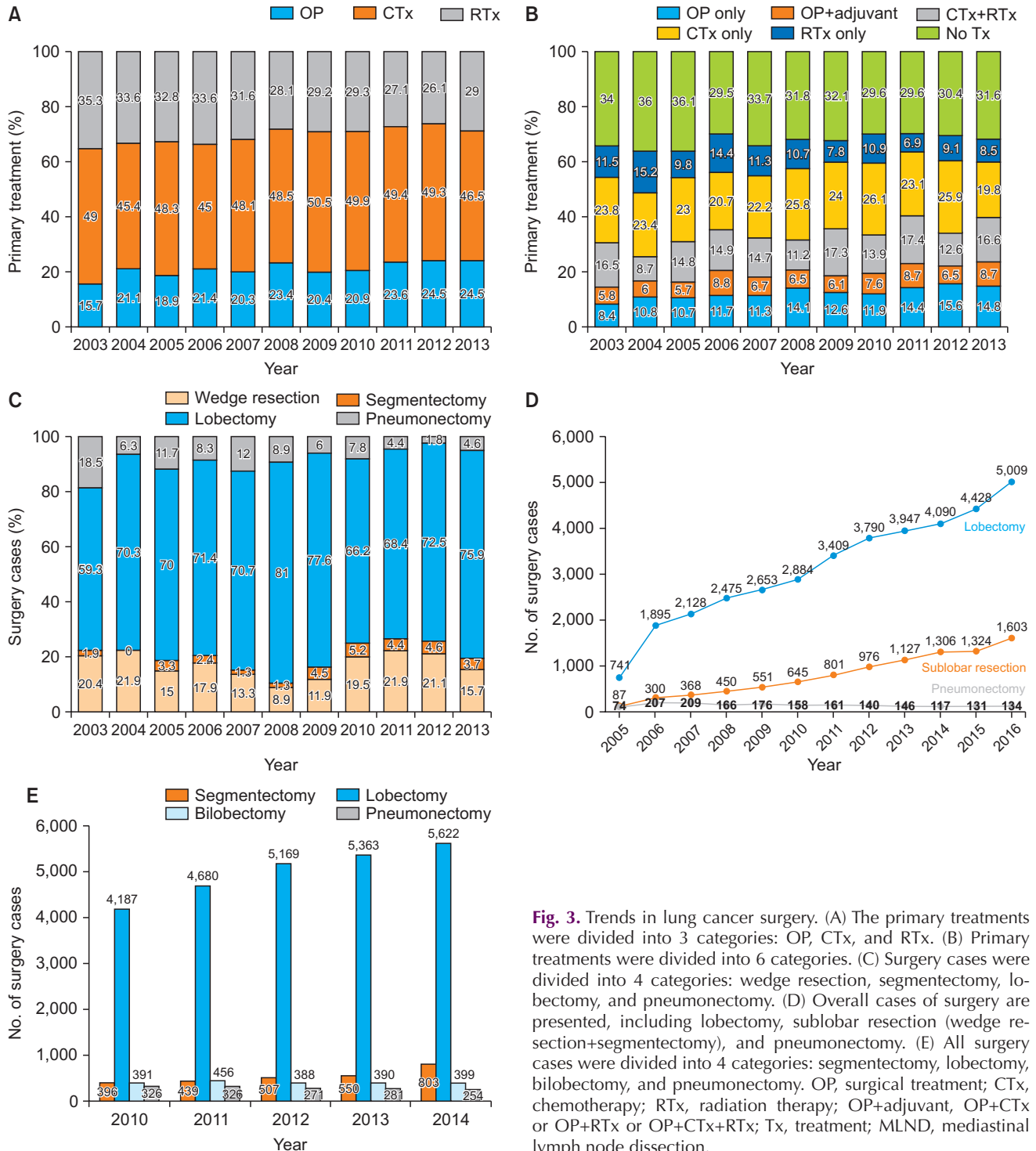


Fig. 3. Trends in lung cancer surgery. (A) The primary treatments were divided into 3 categories: OP, CTx, and RTx. (B) Primary treatments were divided into 6 categories. (C) Surgery cases were divided into 4 categories: wedge resection, segmentectomy, lobectomy, and pneumonectomy. (D) Overall cases of surgery are presented, including lobectomy, sublobar resection (wedge resection+segmentectomy), and pneumonectomy. (E) All surgery cases were divided into 4 categories: segmentectomy, lobectomy, bilobectomy, and pneumonectomy. OP, surgical treatment; CTx, chemotherapy; RTx, radiation therapy; OP+adjuvant, OP+CTx or OP+RTx or OP+CTx+RTx; Tx, treatment; MLND, mediastinal lymph node dissection.

2003 to 2% in 2012), which was associated with high mortality and morbidity (Fig. 3C) [18]. In the analysis of upfront surgery for lung cancer, to which an exempted calculation was applied, there were increases in the frequency of lobectomy and sublobar resection, as well as a decrease in the frequency of pneumonectomy (Fig. 3D). In another study analyzing all cases of lung cancer surgery from 2010 to 2014, the frequency of segmentectomy increased from 396 cases in 2010 to 803 cases in 2014, while that of lobectomy increased from 4,187 cases in 2010 to 5,622 in 2014. Meanwhile, the frequency of pneumonectomy, a curative treatment associated with a high complication rate, decreased from 326 to 254 cases during the same period (Fig. 3E) [17].

By sex and age

The frequency of surgery increased, especially in female and elderly patients (Fig. 4) [16,17]. Men and patients aged

61–75 years comprised the majority of surgical patients, but the number of females and patients ≥ 76 years continuously increased in the analysis of upfront surgery (Fig. 4A, B). In a combined analysis of surgery by sex and age, the highest proportion was found in the 60- to 69-year age group, increasing in those aged over 70 years [17]. The proportion of patients undergoing surgery in 2010 was 67% in men, but it decreased to 61.6% in 2014, while it increased by about 5.7% in women during the same period. Considering both age and sex, the proportion of female patients older than 65 years increased ($p < 0.05$), while that of male patients younger than 65 years decreased significantly ($p < 0.05$) [17].

By income and residence

The trend analysis of lung cancer from 2003 to 2013, showed 2 characteristic features [16]. First, high-income and metropolitan patients underwent surgery more fre-

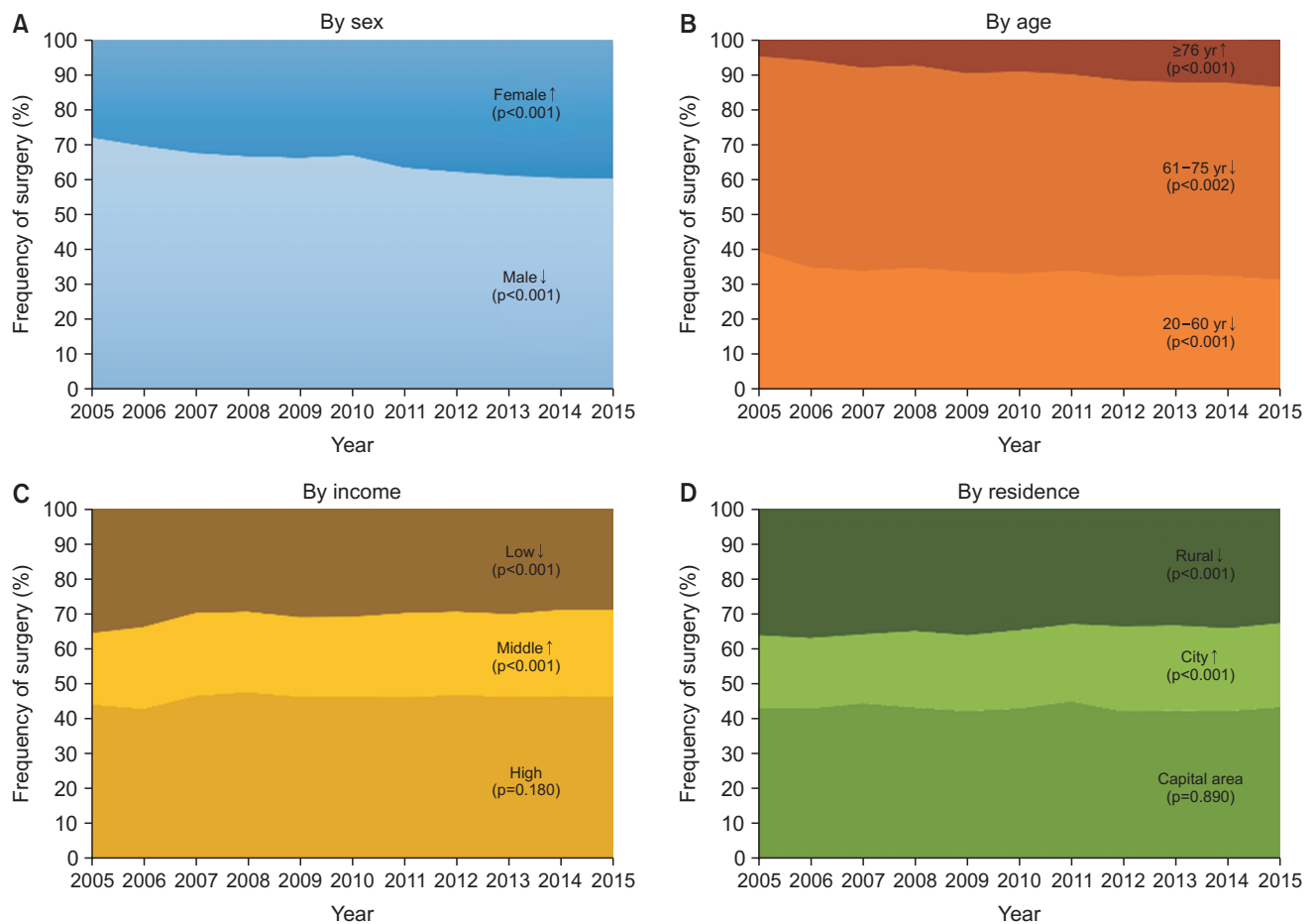


Fig. 4. Trends in surgery by socioeconomic factors. The trends in surgery are presented according to patients' socioeconomic characteristics: (A) sex, (B) age, (C) income, and (D) residence.

quently than others. Second, the incidence of lung cancer increased in low-income patients and those residing in non-metropolitan cities. Similarly, patients with high income and those residing in the capital area comprised larger proportions of those who underwent upfront surgery, but these proportions remained stable; meanwhile, patients in the middle-income categories and those residing in non-metropolitan cities showed a prominent increase (Fig. 4C, D).

Survival in various age groups

The 5- and 10-year survival rates of upfront surgery without adjuvant treatment were 71% and 53%, respectively (Fig. 5A, B). These rates were higher in younger patients

(20–60 years old: 83% and 69%, respectively) and lower in the older groups (61–75 years old: 65% and 48%, respectively; ≥ 76 years old: 52% and 25%, respectively). Lobectomy showed better survival than pneumonectomy (Fig. 5C, D), and the survival difference was the highest at 5 years (26%) and the lowest at 14 years (18%). Similarly, the survival differences between lobectomy and pneumonectomy were highest at 5 years in all age groups. In addition, patients’ survival rate decreased markedly with age. The difference in the survival rates between these 2 types of surgery was largest in patients aged ≥ 76 , with a 31% difference in the 5-year survival rate. In addition, the 5-year survival rate of pneumonectomy for patients aged ≥ 76 years was 20%, while their 10-year survival rate was 6%.

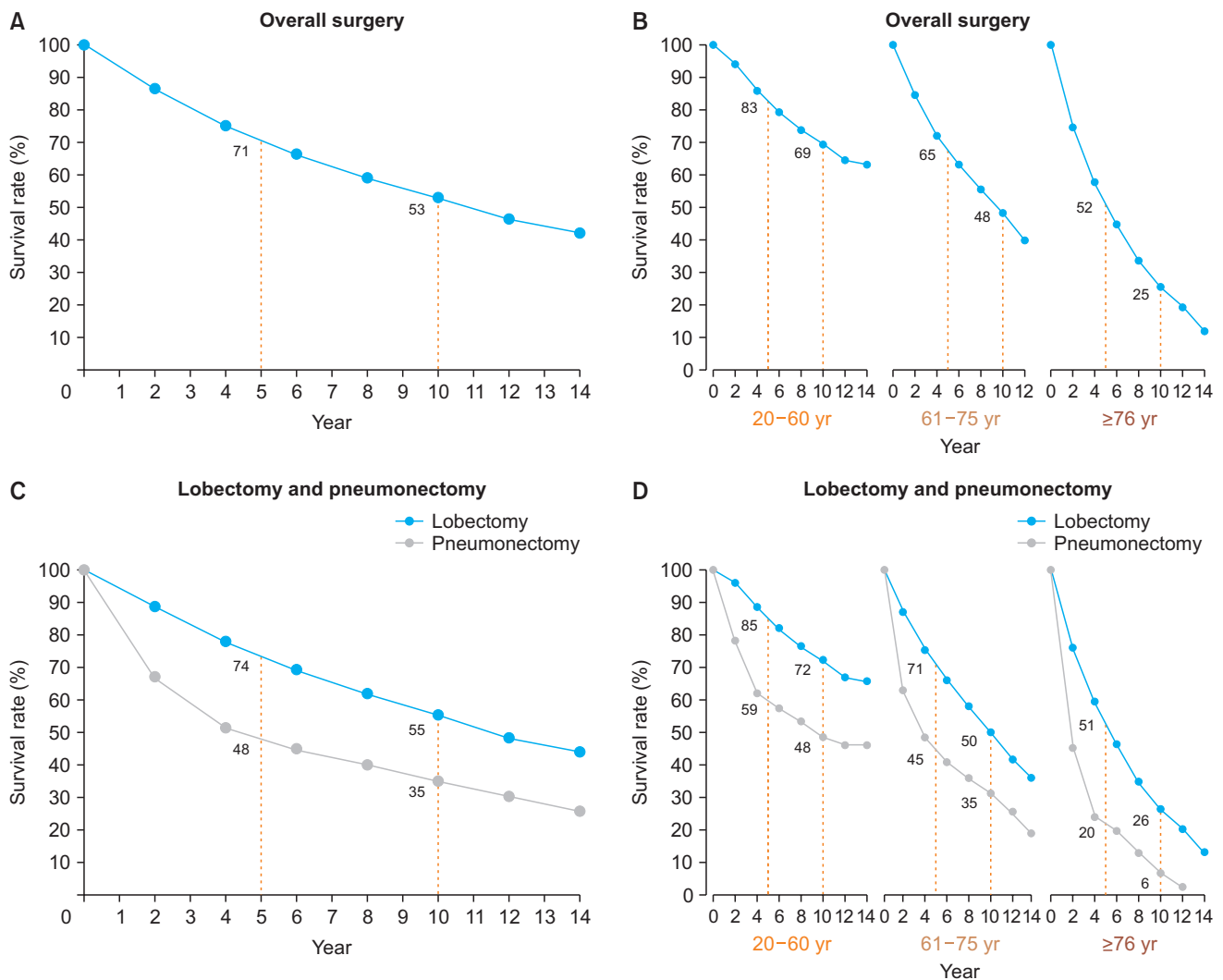


Fig. 5. Survival analysis of surgery. (A, B) Survival graph of overall surgery, divided into 3 age groups: 20–60, 61–75, and ≥ 76 years. (C, D) Survival graph of lobectomy and pneumonectomy, divided into 3 age groups: 20–60, 61–75, and ≥ 76 years.

Discussion

Surgery remains an essential treatment option for lung cancer. Based on the information from the KNHI database, the prevalence of lung cancer and the frequency of surgery for lung cancer have steadily increased [4,5,16,17]. As the population of lung cancer patients has evolved, the composition of surgical candidates has also changed [16,17]. Regardless of these changes, the frequency of surgery for lung cancer increased in both studies. Moreover, in the era of lung cancer screening, the incidence of early lung cancer, which is an indication for surgery, is expected to increase, leading to an increase in the number of surgical procedures for lung cancer [7,19]. In addition, as shown in the lung cancer survival curve of this study, surgical treatment—even with pneumonectomy in the 20- to 60-year age group—could achieve reasonable survival. Various efforts to improve clinical outcomes and expand surgical indications may have produced these results [11-13,20-25].

Lobectomy and sublobar resection, but not pneumonectomy, became increasingly common. Lobectomy is considered to be the standard procedure [10], while segmentectomy is recognized as a feasible technique for small lung cancers and can be applied in patients with poor lung function [13,20,23]. The 5-year survival rate of lobectomy was 71% in all age groups and 52% even in patients ≥ 76 years of age. Therefore, the indications for lobectomy in lung cancer patients are expected to expand. Pneumonectomy could be risky because it can result in fatal complications [18]. In particular, for elderly patients (≥ 76 years of age), it is important to select an appropriate treatment method suitable for the patient's condition because the difference in the survival rate between pneumonectomy and lobectomy is larger than in younger age groups (31% versus 26% at 5 years), as shown in this report. However, this does not mean that pneumonectomy should always be avoided. Invasive surgery, including pneumonectomy, can be recommended for younger patients (20–60 years old) because their survival rates are relatively reasonable (5- and 10-year survival rates of 59% and 48%, respectively) and better than those of other age groups.

The candidates for lung cancer surgery have changed. It is well known that the majority of patients over the past decade are men, aged 61–75 years, in the highest income quartile, and residents of the capital area [16,17]. However, the number of women, patients aged ≥ 76 years, middle and low-income patients, and patients living in cities has continued to increase. Changes in patient composition require changes in the response of the medical system. Elderly pa-

tients (≥ 76 years of age) are vulnerable to complications, requiring additional efforts to reduce the risk of unexpected problems postoperatively [26]. Although many large hospitals are located in the capital area, the number of patients in other areas is also steadily increasing [16,17]. Patients who leave their areas of residence to visit hospitals in the capital area inevitably have other associated needs and expenditures [27]. Because these social disparities and their resulting inequalities are particularly harsh for low-income patients, a reasonable policy is required for this patient category.

Because large-scale data from the KNHI were used, it was possible to overcome the selection bias of individual hospitals and recognize trends in lung cancer surgery in Korea at a glance. However, care must be taken in interpreting these findings because pathological data and medical records were not included. If the operational definitions are inappropriate and the study design does not reflect clinical practice, the results may not necessarily reflect the real situation.

Conclusion

The frequency of lung cancer surgery, especially lobectomy and segmentectomy, is continuing to increase. Although pneumonectomy is becoming less common, it can be selectively applied to young patients because of their feasible survival rates. Surgery for lung cancer showed an increasing trend among women, elderly patients aged ≥ 76 years, non-metropolitan city residents, and middle-income patients. Further research on these social phenomena and related problems is required.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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