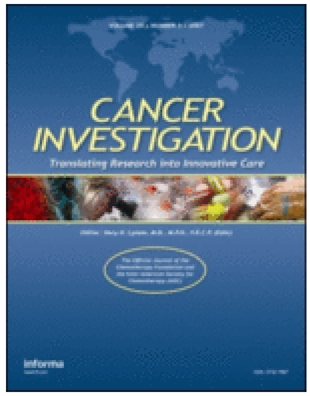

Trends in Survival based on Treatment Modality in Lung Cancer Patients: A Population-Based Study

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Trends in Survival based on Treatment Modality in Lung Cancer Patients: A Population-Based Study

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Conflict of Interest

The authors have no conflicts of interest to declare.

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ABSTRACT

Objectives: We compared the trends in survival based on treatment modality among lung cancer patients in the province of Ontario, Canada, from 2007 to 2015.

Methods: We compared the trends in survival based on treatment modality.

Results: Among 56,417 identified patients, the mean age at diagnosis was 70.1 years (SD=10.7). Treatment modalities varied significantly over time ($p < 0.001$). Overall, 23.0% of patients received surgical treatments. We observed more than 20% increase in five-year survival rates for all surgical groups over time.

Conclusions: Patients undergoing sublobar/lobar resections had the best survival.

Key words: Non-small cell lung cancer; Survival analysis; Treatment modality; Trends in survival

Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide (1). In 2017, lung cancer represented 17% of all new cancer diagnoses in Canada. It was also the leading cause of cancer death, with its mortality surpassing the combined mortalities of colorectal, breast, and prostate cancers (2). Similar figures have been reported in the United States, where lung cancer represented nearly 14% of all new cancer diagnoses, and 27% of all cancer-related deaths (3). The high mortality rate is partly attributable to the initial relatively asymptomatic nature of lung cancer patients. By the time symptoms manifest, the malignancy is often advanced and curative options are no longer available (4). Furthermore, there is still no screening test that can be implemented at a population-level, although provincial and national medical associations have proposed screening programs for high-risk patients (5).

For patients in whom the disease is identified early, there are several treatment modalities available. In those who are medically fit and able to tolerate an operation, surgical resection is the treatment of choice. Patients unfit for surgery can undergo a combination of radiation and chemotherapy (6). The decision-making process surrounding treatment modalities for patients with lung cancer is quite complex, and confounded by the existing co-morbidities, as the surgery places a tremendous physiologic demand on the cardiovascular and respiratory systems. In patients with early disease identification, the five-year survival can be as high as 73% compared to a five-year survival of 2-13% in patients with metastatic disease (7). Nevertheless, there is a paucity of literature comparing the associated effects of various treatment modalities for lung cancer on overall survival.

In this study, we investigated different treatment modalities, their potential covariates and effects on the survival of Canadian patients in the province of Ontario. To our best knowledge, this is the first population-based study in Canada to investigate trends in survival based on treatment modality among lung cancer patients. We explored the survival differences between varying treatment modalities as the main independent variable. The analysis was adjusted for demographics and tumor characteristics such as stage and histology of tumor at the time of diagnosis. This study was limited to patients with non-small cell lung cancer, as the natural history and prognosis of small cell lung cancer is drastically different from the non-small cell population.

Materials and methods

Data Source

The main dataset used in this analysis was the Ontario Cancer Registry (OCR) dataset, which includes diagnosis date, stage, and tumor characteristics for each cancer patient. The OCR includes all diagnosed cases of invasive neoplasia, except basal cell and squamous cell skin cancers, in Ontario (8). For this analysis we merged the OCR with several population-based or administrative datasets held at the Institute for Clinical Evaluative Sciences (ICES). These datasets include: Cancer Activity Level Reporting (chemotherapy and radiation), Discharge Abstracts Database (surgery, radiation, and chemotherapy), National Ambulatory Care Reporting System (chemotherapy and radiation), Ontario Health Insurance Plan Claims (chemotherapy and radiation), Same Day Surgery datasets (chemotherapy and radiation), and Registered Person Database (age, sex, date of death). These datasets were merged to include all Ontario residents diagnosed with primary invasive non-small cell lung cancer (NSCLC) with known disease stage from 2007 to 2015, with follow-up to the end of 2016.

Using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), we identified patients with NSCLC with the codes of C34.0

(malignant neoplasm of main bronchus), C34.1 (malignant neoplasm upper lobe, bronchus or lung), C34.2 (malignant neoplasm of middle lobe, bronchus or lung), C34.3 (malignant neoplasm of lower lobe, bronchus or lung), C34.8 (overlapping malignant lesion of bronchus or lung), and C34.9 (malignant neoplasm of bronchus or lung unspecified) in the OCR dataset. Then, using the International Classification of Diseases for Oncology (ICD-O-2 or ICD-O-3), we excluded all small cell carcinoma, carcinoid tumors, salivary gland tumors, mesenchymal tumors, lymphoproliferative tumors, and miscellaneous tumors (9). Patients were also excluded if the diagnosis was solely based on death certificate or autopsy as the survival time could not be identified for these patients. The analysis included patients who were 18 years and older at the time of diagnosis. Age at diagnosis was then classified as < 60, 60-69, 70-79, and ≥ 80 years. This analysis includes only patients with known disease stage, as staging and age are important factors that are taken into consideration when deciding on treatment modalities (6, 10).

Treatment modalities were investigated based on the Canadian Classification of Health Information (CCI) (11) and Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP) (12). Treatment modalities were classified as: 1) *no-treatment* for patients who received no treatment, or we could not find any record of treatment, 2) *radiation only* (RT) for patients that received only radiation therapy, 3) *chemotherapy only* (CT) for patients who received only chemotherapy, and 4) *chemoradiation* for patients who received both radiation and chemotherapy but no surgical resection. The surgical groups include: 5) *sublobar resection* or *lobectomy only* (Sub/Lob only) with no record of radiation or chemotherapy for this group, 6) *sublobar resection* or *lobectomy* with radiation or chemotherapy (Sub/Lob + RT/CT), 7) *pneumonectomy* with no record of radiation or chemotherapy (*pneumonectomy only*), and finally, 8) *pneumonectomy* with radiation or chemotherapy (pneumonectomy + RT/CT). To determine treatment classifications, a preliminary analysis was conducted to examine the Kaplan-Meier survival curves for all surgical and non-surgical groups. The Kaplan-Meier curves were adjusted for patient's age, stage of disease, and histology of tumor. Then, based on the similarity of the Kaplan-Meier curves (Figure A.1) sublobar-only and lobectomy-only resection groups were combined into one group (Sub/Lob only). Also, sublobar and lobectomy surgical groups with radiation or chemotherapy were combined into one group (Sub/Lob + RT/CT). For each patient, a treatment modality was accounted for and included in the analysis only if it was received up to one year after diagnosis.

Staging data has been made available in Ontario since 2007. Cancer Care Ontario uses a best stage grouping approach where stage is assigned to each case based on pathologic TNM when available, and clinical TNM otherwise (13). It collects stage data using the staging criteria of the American Joint Committee on Cancer or the Collaborative Stage initiative. If a case has more than one valid stage value, the "best stage" is derived based on a pre-specified algorithm; Otherwise in case of availability, the stage group provided by the treating regional cancer centre is used (14). This analysis only includes patients with known cancer stage.

Tumor histology was classified as: 1) carcinoma-NOS, 2) squamous cell carcinoma (SCC), 3) adenocarcinoma-NOS (AC), or 4) other.

Statistical Analysis

First, we conducted a logistic regression analysis to quantify the effects of demographics (sex and age groups) and tumor characteristics (stage and histology) on receiving any surgical resection. Treatment modalities were regrouped as *surgery* and *no-surgery* (reference group). The surgery group included all surgical resection groups with or without any adjuvant chemotherapy or radiation. The no-surgery group included all the non-surgical groups.

Second, the survival rate was estimated for patients diagnosed with NSCLC from 2007 and 2015 in Ontario with follow-up until the end of 2016. We used a flexible parametric (Royston-Parmar) model (15, 16) to estimate the trends in survival rate based on treatment modality, adjusted for sex, age, year of diagnosis, stage of tumor, and histology of tumor. This method uses a piecewise approach in modeling, which is more capable of mimicking the actual trends in mortality (hazard rate) and survival patterns compared to other traditional methods (17). We fitted the model by incorporating age, sex, year of diagnosis, histology of tumour, stage of disease, treatment modality, and the interaction term between each two variables into a multiple statistical model using a forward approach. The likelihood ratio test was used to compare different models, and to reach to a final model. All variables included in the final model were statistically significant ($p \leq 0.05$). Then, based on the final model, trends in one-, two-, and five-year survival rates for each treatment modality were estimated while adjusting for the other variables.

All the analyses were conducted using Stata/MP 15.1 (Stata Corporation, College Station, TX). The flexible parametric model was fitted using the freely available **stpm2** program (15) written for Stata package. The local ethics board at McMaster University, Hamilton, Canada, reviewed the research proposal and provided ethical approval for this retrospective study.

Results

Overall, 56,417 patients from the OCR dataset with invasive NSCLC were identified, of which 52.3% (n = 29,499) were male. The mean age at diagnosis was 70.1 years (SD=10.7); 70.5 (SD=10.3) years for males and 69.7 (SD=11.0) years for females. Approximately, 49.1% of patients were diagnosed with stage IV disease (50.4% of males and 47.7% of females). Adenocarcinoma was the most common subtype of NSCLC, accounting for 36.0% of cases.

Table 1 summarizes the distribution of sex, age group, histology of tumor, stage of disease, and year of diagnosis based on treatment modality. Overall, 23.0% of patients received surgical treatments, 26.3% radiation only, 7.2% chemotherapy only, and 21.0% chemoradiation; 22.5% did not receive any active treatment. We found a significant difference in the treatment modalities between males and females. About 21.0% of males underwent operative intervention, while 25.3% of females received surgical treatment ($p < 0.001$). The differences in treatment modalities were even more pronounced based on age group. The proportion of patients who underwent surgical resection was 26.1%, 28.3%, 24.7%, and 10.2% for age groups <60, 60-69, 70-79, and ≥80 years, respectively. Older patients were more likely to receive no treatment or radiation only, with the proportion of no-treatment or radiation only varying from 30.2% to 78.0% from the youngest to oldest age group (Table 1). However, the largest discrepancy in treatment modality was based on disease stage. While 62.8% of patients with stage I disease received surgical treatment, only 2.1% of patients with stage IV disease underwent operative intervention. Conversely, 62.0% of patients with stage IV disease received no treatment or radiation only, compared to 32.1% of patients with stage I disease. The proportion of patients receiving chemotherapy only varied from 1.35% to 11.0% for patients with stage I to stage IV disease. The proportion of patients who received chemoradiation varied from 3.8% in stage I disease to 33.8% among patients with stage III disease.

Changes in treatment modalities

As can be seen in Table 1, the changes in the treatment modalities were quite complex. Statistical analysis based on a Chi-square test indicated that the distribution of treatment modalities was not the same over the nine years of the study period ($p < 0.001$). Two obvious trends that can be found are: 1) the proportion of radiation only increased from 22.4% in 2007 to

28.7% in 2015 (p-for-trend < 0.001); and 2) the proportion of pneumonectomy, with or without radiation or chemotherapy, decreased from 2.4% in 2007 to 1.0% in 2015 (p-for-trend < 0.001). However, there has not been a steady increase in the resection rate over time. In general, the resection rate decreased from 24.8% in 2007 to 20.9% in 2010 and then increased to 25.7% in 2015. However, the linear trend indicated a significant increase from 2007 to 2015 (p-for-trend < 0.001).

Predictors of surgical resection

Table 2 presents the predictors of surgical resection as described earlier using a multiple logistic regression. It predicts the chance of surgical resection based on sex, age group, year of diagnosis, histology and stage of tumor. The results are presented as odds ratio (OR) with 95% confidence interval (95% CI). Female patients were 10% more likely to receive surgical resection compared to male patients (OR 1.10; 95% CI: 1.05- 1.17). The odds ratios for surgical resection for patients 70-79 years and 80 and over were 0.48 (95% CI: 0.44- 0.52) and 0.12 (95% CI: 0.11- 0.14), respectively, compared to patients < 60 years. The chance of surgical resection for patients with SCC and AC tumors was 3.26 (95% CI: 2.97- 3.58) and 3.40 (95% CI: 3.12- 3.73) times higher compared to patients with carcinoma NOS. Most importantly, those with a stage IV disease had merely a 1% chance of receiving a surgical resection compared to those with a stage I disease.

Trends in survival rate based on treatment modality

The final model from fitting a flexible parametric model included sex, age group, treatment modality, stage of disease, histology of tumor, and year of diagnosis. The following interaction terms were also included in the model: age group and stage, age group and histology, treatment modality and year of diagnosis, treatment modality and stage, and stage and year of diagnosis. In addition, age group, stage of tumor, treatment modality, histology of tumor, and year of diagnosis were included as time dependent variables. Then, based on the final model, trends in one-, two-, and five-year survival rates from 2007 to 2015 were estimated for each treatment modality. Results of fully the adjusted survival rates are shown in Figure 1. In general, we observed increasing trends in survival for all treatment modalities from 2007 to 2015, although it was more pronounced for the surgical resection groups. We observed an approximately 10% increase in two-year survival and an increase of more than 20% in five-year survival rates for all surgical groups.

We observed an increase of 10-15% in one-, two-, and five-year survival rate based on age group and sex from 2007 to 2015. Results of the fully adjusted survival model for five-year survival are shown in Figure 2. The trends were similar for all age groups, although a higher survival was evident for women across all age groups. Figure 3 depicts the trends in one-, two-, and five-year survival rates based on stage of disease. Although all one-, two-, and five-year survival rates improved for patients with stages I-III disease, they were less pronounced for patients with stage IV disease.

Overall five-year survival rate

The model-based average five-year survival rates based on histology, stage, and treatment modality are shown in Table 3. In general, the highest five-year survival rates were observed for the *Sub/Lob only* surgical resection group, followed by the *Sub/Lob + RT/CT* group. In comparison, the lowest survival rates were observed for the no-treatment group, the RT only group, and the CT only group. Chemoradiation seems to be more effective among patients with adenocarcinoma than carcinoma NOS and squamous cell carcinoma.

Discussion

In this large retrospective population-based study, we found that treatment modality was dependent on a patient's age, sex, and histology and stage of disease among lung cancer patients in Ontario. The overall survival of patients with lung cancer increased over the 9-year study period. The differences in survival rates highly varied based on treatment modality, with surgical resection offering the greatest survival advantage.

Surgery is the mainstay of treatment for non-small cell lung cancer, and offers the best chance of cure or longer survival (18). However, due to the physiologic burden associated with lung resection, not all patients are appropriate candidates for surgery (18). Furthermore, given the often advanced stage of disease at the time of diagnosis, curative resection may not be feasible (6). In our study, only 23.0% of patients received surgery. This is similar to a large study from the United States in which 29.1% of patients were treated surgically (19). Women were significantly more likely to undergo an operation, as were the youngest group of patients. In contrast, elderly patients were more likely to receive no treatment or receive radiation only. These findings are consistent with the existing body of literature. Women with lung cancer tend to be younger at the time of diagnosis, and are less likely to report significant comorbidities, which may account for differences in resection rates (20, 21). However, our analysis indicates a higher chance of surgical resection for women after adjusting for age, stage, and histology of tumor. Previous studies have also reported lower perioperative morbidity and mortality in women undergoing lung resections (21). In contrast, elderly patients with NSCLC are more likely to be offered radiation only, or best supportive care, despite existing evidence regarding the safety of surgery in selected elderly patients (22-24).

The survival of patients with NSCLC increased over the study period. The difference in survival was most pronounced for the younger age groups, patients with stages I to III disease, and those undergoing operative intervention. As outlined above, numerous studies have shown the safety of surgery in carefully selected elderly patients (22-24). The improvement in survival of patients over the age of 80 from 2007 to 2015 (Figure 2) suggests that these patients are actually receiving treatment with curative intent, as opposed to best supportive care. This hypothesis is supported by further analysis that more elderly patients were treated with radiation-only towards the latter portion of the study period (see Table A.1). The observed differences in survival based on disease stage are not surprising, and in keeping with the poor prognosis of advanced stages of lung cancer (6). This study highlights the differences in survival based on treatment modality, while controlling for disease stage, information that is invaluable to patients and clinicians. The improved survival of patients with stages I to III from 2007 to 2015 is likely attributable to the improved medical care of these patients, including advances in radiation and peri-operative care. These results are similar to a recent American study, which examined the survival of lung cancer patients within the Surveillance, Epidemiology, and End Results (SEER) database (25). Another large study from Singapore also reported improvement in the survival of lung cancer patients over time, and attributed this to the increasing incidence of never-smokers in patients with NSCLC (26). Never-smokers represent an increasing proportion of patients with non-small cell lung cancer (27); however, the smoking status of patients was outside the scope of this study. Since the introduction of screening recommendations by the Canadian Medical Association in 2016, it can be hypothesized that the survival of lung cancer in Canada may continue to improve due to early detection. In contrast to the patients with local or regional disease, the overall survival of patients with stage IV lung cancer continues to be poor, despite advances in targeted therapies (28).

Patients undergoing surgical resection via a sublobar/lobar resection had the best survival rates. Patients undergoing a pneumonectomy, with or without radiation or chemotherapy, had improved survival compared to those undergoing no treatment, radiation only, chemotherapy only, or chemoradiation but poorer survival than the lobar/sublobar resection patients. This is likely attributable to the increased morbidity associated with a pneumonectomy (29). As per guidelines put forth by the National Comprehensive Cancer Network (NCCN), radiation therapy currently plays a role in all stages of NSCLC (30). For patients with early disease, radiation therapy is offered to patients medically unfit for surgery, or those who decline surgery. In patients with advanced or metastatic disease, radiation therapy can help achieve palliation and symptom control. In comparison, chemotherapy plays a role in the multimodal treatment of locally advanced disease, in adjuvant therapy of resected disease, or as palliative therapy for metastatic disease (30). However, the platinum-based chemotherapy regimens, used as part of the NCCN guidelines, are often poorly tolerated and have significant toxic side effects (31). Examining specific chemotherapy regimens was beyond the scope of this study, and a stage-based analysis of the utility of chemotherapy is necessary to determine which patients should be offered systemic therapies.

This study has several limitations. First, incomplete submission of cancer staging data for all patients diagnosed with NSCLC in Ontario limited our ability to analyze the entire cohort between 2007 and 2015. Second, besides sex, age, stage, histology of tumor, various other factors could be involved in treatment decisions (e.g. comorbidity and patient preferance) that could not be captured using administrative datasets. Third, this study is susceptible to coding and recording error, a limitation inherent to most studies conducted with administrative datasets. Finally, this study was conducted within a single-payer healthcare system in Ontario and its findings may not be generalizable to private healthcare systems. The treatment effects of radiation, chemotherapy, and surgery in patients with lung cancer can be hypothesized to differ in multi-payer systems, and the results of this study should therefore be taken in context of a universal healthcare system.

The strengths of this study include the use of a high-quality population-based dataset and long follow-up over an extended period. The ability to report one- and two-, and five-year survival rates provides more insight into the mortality and survival of lung cancer patients. Also, the use of a flexible parametric model for analysis allows for a more flexible and powerful approach in mimicking the actual trends in mortality and survival patterns (17, 32).

Conclusions

In summary, the present study found that the survival of lung cancer patients in Ontario has improved from 2007 to 2015. We observed more than 20% increase in five-year survival rates for all surgical groups. This study also indicates that radiation therapy offers significant long-term survival advantage over no treatment in elderly patients with lung cancer. Thus, radiation therapy plays an important role in both the treatment of patients with unresectable disease, and the palliation of patients with lung cancer.

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Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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Table 1. Distribution of lung cancer patients based on demographics, tumor stage, year of diagnosis and treatment

	No treatment	Radiation only	Chemo. only	Chemorad.	Sub/Lob only	Sub/Lob + RT/CT	Pneum. only	Pneum. + RT/CT	Total
Sex									
Male	6,795 (23.0)	7,995 (27.1)	2,190 (7.4)	6,342 (21.5)	3,292 (11.2)	2,338 (7.9)	163 (0.6)	384 (1.3)	29,499
Female	5,899 (21.9)	6,822 (25.3)	1,858 (6.9)	5,529 (20.5)	3,971 (14.8)	2,474 (9.2)	109 (0.4)	256 (1.0)	26,918
Age group									
< 60 years	1,034 (10.9)	1,837 (19.3)	796 (8.4)	3,355 (35.3)	1,116 (11.7)	1,110 (11.7)	48 (0.5)	207 (2.2)	9,503
60 – 69 years	2,395 (14.6)	3,621 (22.1)	1,285 (7.9)	4,428 (27.1)	2,427 (14.8)	1,869 (11.4)	87 (0.5)	248 (1.5)	16,360
70 – 79 years	4,230 (22.2)	5,419 (28.5)	1,369 (7.2)	3,326 (17.5)	2,838 (14.9)	1,581 (8.3)	113 (0.6)	168 (0.9)	19,044
≥ 80 years	5,035 (43.7)	3,940 (34.2)	598 (5.2)	762 (6.6)	882 (7.7)	252 (2.2)	24 (0.2)	17 (0.2)	11,510
Age: Mean (SD)	75.4 (10.3)	72.2 (10.2)	68.5 (10.5)	65.1 (9.9)	69.1 (9.1)	66.1 (9.0)	68.5 (8.9)	63.5 (9.4)	70.1 (10.7)
Histology									
Carc.[1]	2,536 (20.8)	4,462 (36.5)	882 (7.2)	3,366 (27.5)	387 (3.2)	465 (3.8)	34 (0.3)	92 (0.8)	12,224
SCC[2]	1,611 (13.9)	3,464 (29.9)	508 (4.4)	2,646 (22.8)	1,736 (15.0)	1,182 (10.2)	134 (1.2)	302 (2.6)	11,583
AC[3]	3,292 (16.2)	5,436 (26.8)	1,992 (9.8)	5,119 (25.2)	2,603 (12.8)	1,687 (8.3)	51 (0.3)	140 (0.7)	20,320
Other	5,255 (42.8)	1,455 (11.8)	666 (5.4)	740 (6.0)	2,537 (20.6)	1,478 (12.0)	53 (0.4)	106 (0.9)	12,290
Stage									
I	1,172 (9.8)	2,652 (22.3)	161 (1.4)	447 (3.8)	5,918 (49.7)	1,451 (12.2)	71 (0.6)	38 (0.3)	11,910
II	512 (11.1)	763 (16.6)	82 (1.8)	410 (8.9)	893 (19.4)	1,609 (35.0)	113 (2.5)	217 (4.7)	4,599
III	2,385 (19.6)	2,838 (23.3)	754 (6.2)	4,128 (33.8)	318 (2.6)	1,364 (11.2)	74 (0.6)	337 (2.8)	12,198
IV	8,625 (31.1)	8,564 (30.9)	3,051 (11.0)	6,886 (24.9)	134 (0.5)	388 (1.4)	14 (0.1)	48 (0.2)	27,710

Table 1. (Continued)

	No treatment	Radiation only	Chemo. only	Chemorad.	Sub/Lob only	Sub/Lob + RT/CT	Pneum. only	Pneum. + RT/CT	Total
Year									
2007	986 (19.5)	1,133 (22.4)	456 (9.0)	1,230 (24.3)	660 (13.0)	474 (9.4)	39 (0.8)	85 (1.7)	5,063
2008	1,129 (20.9)	1,369 (25.3)	438 (8.1)	1,213 (22.4)	690 (12.7)	454 (8.4)	44 (0.8)	77 (1.4)	5,414
2009	1,357 (23.4)	1,474 (25.4)	433 (7.5)	1,239 (21.3)	687 (11.8)	515 (8.9)	30 (0.5)	72 (1.2)	5,807
2010	1,668 (25.2)	1,723 (26.0)	465 (7.0)	1,391 (21.0)	794 (12.0)	485 (7.3)	28 (0.4)	78 (1.2)	6,632
2011	1,557 (24.2)	1,798 (27.9)	399 (6.2)	1,335 (20.7)	741 (11.5)	520 (8.1)	27 (0.4)	67 (1.0)	6,444
2012	1,763 (26.2)	1,684 (25.0)	396 (5.9)	1,314 (19.5)	857 (12.7)	601 (8.9)	32 (0.5)	78 (1.2)	6,725
2013	1,762 (25.1)	1,873 (26.7)	468 (6.7)	1,365 (19.4)	876 (12.5)	583 (8.3)	29 (0.4)	66 (0.9)	7,022
2014	1,433 (20.7)	1,930 (27.9)	498 (7.2)	1,410 (20.3)	997 (14.8)	569 (8.2)	26 (0.4)	68 (1.0)	6,931
2015	1,039 (16.3)	1,833 (28.7)	495 (7.8)	1,374 (21.5)	961 (15.1)	611 (9.6)	17 (0.3)	49 (0.8)	6,379
Total	**12,694 (22.5)**	**14,817 (26.3)**	**4,048 (7.2)**	**11,871 (21.0)**	**7,263 (12.9)**	**4,812 (8.5)**	**272 (0.5)**	**640 (1.1)**	**56,417**

1- Carcinoma, NOS 2- Squamous cell carcinoma 3- Adenocarcinoma

Table 2. Predictors of surgical resection among patients diagnosed with non-small cell lung cancer

Variable	**OR (95% CI)**
Sex	
Male	Referent
Female	1.10 (1.05, 1.17) ++
Age group	
< 60 years	Referent
60 – 69 years	0.81 (0.75, 0.88) ++
70 – 79 years	0.48 (0.44, 0.52) ++
≥ 80 years	0.12 (0.11, 0.14) ++
Year of diagnosis	0.95 (0.94, 0.96) ++
Histology	
Carcinoma, NOS	Referent
SCC[1]	3.26 (2.97, 3.58) ++
AC[2]	3.40 (3.12, 3.73) ++
Other	5.88 (5.35, 6.47) ++
Stage	
I	Referent
II	0.97 (0.90, 1.05)
III	0.11 (0.10, 0.11) ++
IV	0.01 (0.01, 0.01) ++

+ p <0.05, ++ p <0.001, 1- Squamous cell carcinoma, 2- Adenocarcinoma

Table 3. Five-year survival rate (95% CI) based on histology, stage, and treatment modality

Histology	Stage	No treatment	RT only	CT only	Chemorad.	Sub/Lob only	Sub/Lob + RT/CT	Pneum. only	Pneum. + RT/CT
Carc.[1]	I	.17 (.16, .19)	.35 (.34, .37)	.07 (.05, .10)	.19 (.16, .21)	.75 (.74, .76)	.58 (.56, .60)	.55 (.43, .68)	.44 (.27, .61)
	II	.09 (.07, .10)	.16 (.15, .17)	.05 (.02, .08)	.18 (.16, .20)	.53 (.50, .57)	.57 (.56, .59)	.29 (.24, .34)	.54 (.50, .58)
	III	.04 (.04, .04)	.07 (.07, .07)	.04 (.03, .05)	.16 (.15, .16)	.40 (.34, .46)	.43 (.42, .44)	.18 (.11, .25)	.35 (.32, .37)
	IV	.02 (.02, .02)	.01 (.01, .01)	.04 (.04, .04)	.03 (.03, .04)	.25 (.20, .30)	.19 (.18, .21)	**	.16 (.12, .19)
SCC[2]	I	.19 (.18, .21)	.38 (.37, .39)	.09 (.06, .12)	.17 (.15, .19)	.73 (.73, .74)	.55 (.54, .56)	.50 (.46, .55)	.32 (.24, .40)
	II	.08 (.08, .09)	.16 (.15, .17)	.06 (.04, .09)	.19 (.18, .21)	.53 (.51, .54)	.54 (.53, .54)	.31 (.27, .34)	.51 (.49, .52)
	III	.05 (.04, .05)	.07 (.07, .07)	.05 (.04, .05)	.16 (.15, .16)	.36 (.34, .39)	.40 (.40, .41)	.23 (.20, .26)	.35 (.33, .36)
	IV	.02 (.02, .02)	.01 (.01, .01)	.04 (.04, .05)	.03 (.03, .03)	.28 (.24, .32)	.15 (.14, .16)	**	.13 (.11, .15)
AC[3]	I	.27 (.25, .28)	.44 (.43, .45)	.17 (.14, .20)	.28 (.26, .30)	.79 (.79, .79)	.63 (.62, .64)	.57 (.51, .63)	.53 (.45, .62)
	II	.13 (.12, .15)	.24 (.22, .25)	.10 (.07, .14)	.26 (.24, .28)	.59 (.58, .61)	.60 (.60, .61)	.36 (.29, .44)	.59 (.56, .63)
	III	.07 (.07, .07)	.11 (.11, .12)	.07 (.06, .07)	.23 (.23, .24)	.43 (.41, .46)	.49 (.48, .50)	.27 (.19, .36)	.41 (.39, .44)
	IV	.04 (.04, .04)	.02 (.02, .02)	.08 (.07, .08)	.06 (.06, .06)	.33 (.31, .35)	.21 (.20, .23)	.08 (.00, .17)	.22 (.20, .26)
Other	I	.22 (.21, .23)	.45 (.44, .47)	.11 (.07, .14)	.24 (.20, .29)	.81 (.80, .81)	.64 (.63, .65)	.62 (.54, .69)	.50 (.38, .62)
	II	.10 (.09, .11)	.20 (.17, .22)	.08 (.05, .10)	.27 (.22, .32)	.59 (.57, .60)	.62 (.61, .63)	.42 (.35, .48)	.64 (.60, .68)
	III	.05 (.05, .05)	.10 (.09, .11)	.05 (.04, .06)	.23 (.21, .24)	.46 (.44, .49)	.51 (.50, .52)	.28 (.23, .34)	.43 (.41, .46)
	IV	.03 (.03, .03)	.02 (.02, .02)	.06 (.06, .06)	.06 (.06, .07)	.31 (.27, .34)	.24 (.23, .25)	.10 (.03, .16)	.23 (.20, .26)

1- Carcinoma, NOS, 2-Squamous cell carcinoma, 3- Adenocarcinoma

Table A.1 Trends of radiation in eldery patients (80+) over the study period (p-for-trend < 0.001)

Year of diagnosis	No treatment	Radiation only	Chemotherapy only	Chemoradiation	Surgery groups	Total
2007	333 (38.9)	278 (32.5)	68 (7.9)	64 (7.5)	113 (13.2)	856
2008	426 (43.3)	314 (31.9)	60 (6.1)	74 (7.5)	110 (11.2)	984
2009	480 (45.3)	363 (34.3)	58 (5.5)	60 (5.7)	99 (9.3)	1,060
2010	629 (48.3)	405 (31.1)	53 (4.1)	86 (6.6)	129 (9.9)	1,302
2011	622 (45.8)	475 (35.0)	63 (4.6)	82 (6.0)	117 (8.6)	1,359
2012	767 (50.9)	448 (29.8)	60 (4.0)	88 (5.8)	143 (9.5)	1,506
2013	762 (47.1)	547 (33.8)	80 (4.9)	94 (5.8)	135 (8.3)	1,618
2014	617 (40.8)	567 (37.5)	82 (5.4)	98 (6.5)	149 (9.9)	1,513
2015	399 (30.4)	543 (41.4)	74 (5.6)	116 (8.8)	180 (13.7)	1,312
Total	**5,035 (43.7)**	**3,940 (34.2)**	**598 (5.2)**	**762 (6.6)**	**1,175 (10.2)**	**11,510**

Figure Legends

Figure 1. Trends in one-year, two-year, and five-year survival rates based on treatment modality

The graph is based on the final model which included sex, age group, treatment modality, stage of disease, histology of tumor, and year of diagnosis. The model also included interaction terms between age group and stage, age group and histology, treatment modality and year of diagnosis, treatment modality and stage, and stage and year of diagnosis. In addition, age group, stage of tumor, treatment modality, histology of tumor, and year of diagnosis were included as time dependent variables.

Figure 2. Trends in five-year survival rate based on sex and age group

The graph is based on the final model which included sex, age group, treatment modality, stage of disease, histology of tumor, and year of diagnosis. The model also included interaction terms between age group and stage, age group and histology, treatment modality and year of diagnosis, treatment modality and stage, and stage and year of diagnosis. In addition, age group, stage of tumor, treatment modality, histology of tumor, and year of diagnosis were included as time dependent variables.

Figure 3. Trends in one-year, two-year, and five-year survival rates based on stage of tumor

The graph is based on the final model which included sex, age group, treatment modality, stage of disease, histology of tumor, and year of diagnosis. The model also included interaction terms between age group and stage, age group and histology, treatment modality and year of diagnosis, treatment modality and stage, and stage and year of diagnosis. In addition, age group, stage of tumor, treatment modality, histology of tumor, and year of diagnosis were included as time dependent variables.

Figure A.1. Adjusted Kaplan-Meier survival curves based on the preliminary treatment classification

This graph was adjusted based on age group, stage of disease, and histology. This was used to combine sublobar only and lobectomy only groups into one group (Sub/Lob only). Also, we combined sublobar with radiation or chemotherapy and lobectomy with radiation or chemotherapy into one group (Sub/Lob + RT/CT).

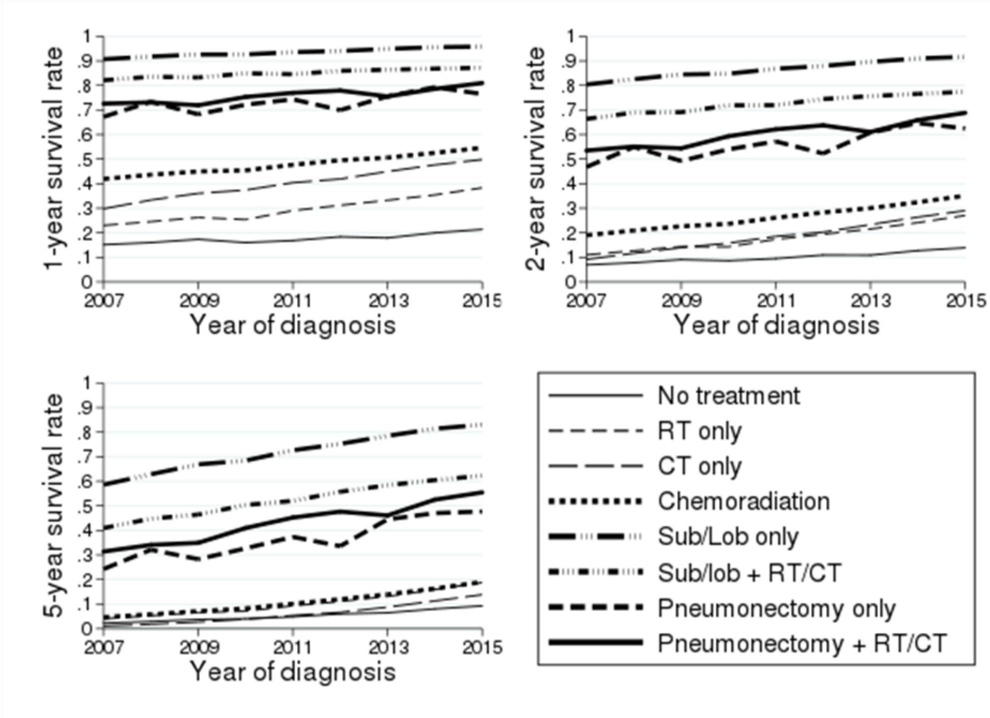

Figure 1. Trends in one-year, two-year, and five-year survival rates based on treatment modality

157x114mm (150 x 150 DPI)

Figure 2. Trends in five-year survival rate based on sex and age group

157x114mm (150 x 150 DPI)

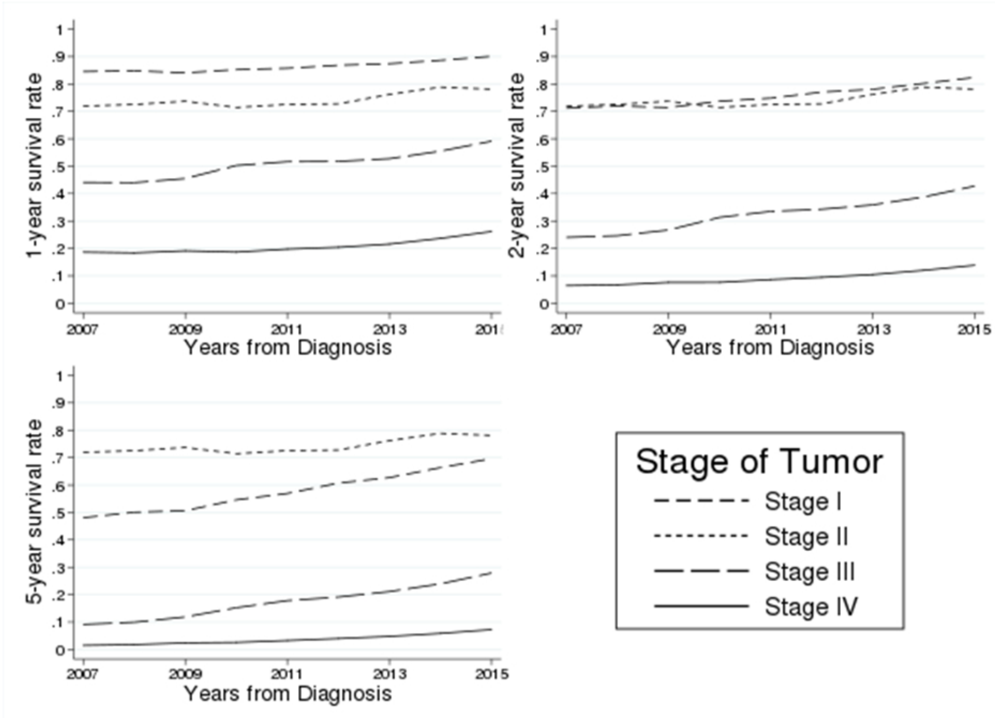

Figure 3. Trends in one-year, two-year, and five-year survival rates based on stage of tumor

157x114mm (150 x 150 DPI)

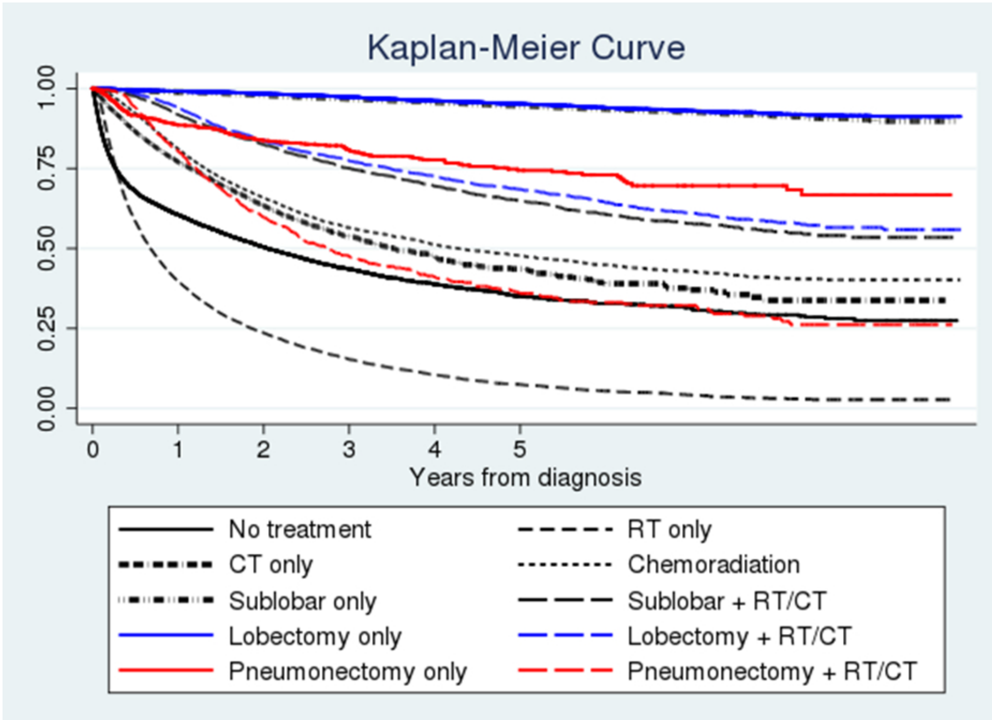

Figure A.1. Adjusted Kaplan-Meier survival curves based on the preliminary treatment classification

157x114mm (150 x 150 DPI)