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Healthy Policy Analysis

Temporal Trend in an Initial Treatment, Survival, and Medical Costs Among Patients With Lung Cancer Between 2013 and 2018 in Kyoto City, Japan

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ABSTRACT

Objectives: This study aimed to identify the variation of treatment contents and outcomes and economic burden of lung cancer among the elderly population in Japan.

Methods: New-onset primary lung cancer from April 2013 to March 2019 were identified by using the Kyoto City administrative database for National Health Insurance and Advanced Elderly Medical Service System. Patient characteristics, initial treatment, medical costs, and deaths were analyzed. Continuous variables were calculated using standard descriptive statistical methods.

Results: A total of 4845 people who were diagnosed as having lung cancer and received any treatment between 2013 and 2018 were included in the study. The average age of patients was 73 to 74 years for a 6-year study period. The proportion of patients who received surgery, drug therapy, and radiation therapy as initial treatment was 31% to 42%, 36% to 44%, and 21% to 24%, respectively. Healthcare costs increased between fiscal year (FY) 2014 and FY 2018, with a particularly significant increase of 340 million for drug therapy, whereas the mortality rate in <2-year follow-up decreased from 42.7% in FY 2013 to 368% in FY 2016.

Conclusions: This cross-sectional study demonstrated that the improvement in the survival rate and proportion of surgery as an initial treatment was increased whereas drug therapy decreased and medical costs increased among patients with lung cancer over time. Based on these results, it is necessary to implement sustainable healthcare measures with a consideration of cost-effectiveness.

Keywords: administrative data, Japan, lung cancer, medical cost.

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Introduction

Lung cancer is the leading cause of cancer death. The World Health Organization reported that lung cancer was diagnosed in 2.2 million people and accounted for 1.8 million deaths worldwide in 2020.[1] It is also the most common cause of cancer death in Japan, with high prevalence and mortality rates in both men and women. It was reported that there were 138 532 new cases of lung cancer and 82 369 deaths because of lung cancer in 2018,[2] and both incidence and mortality will increase as the population ages. Although age-adjusted incidence rate and mortality rate of lung cancer are on a decreasing trend, it is important to identify the detailed trends.

The treatment landscape for lung cancer has changed in the last decade, especially in pharmacotherapy. Molecular targeted therapies and immune checkpoint inhibitors (ICIs) have been discovered to be effective in the treatment of advanced non–small cell lung cancer (NSCLC) and have been used in clinical practice.[3,4] Although these drugs have shown to be effective, they are more costly than conventional chemotherapy, and the per-unit cost of ICIs is particularly high. In terms of healthcare costs in Japan, the proportion of cancer treatment cost is particularly high, reaching 14.4% of total healthcare costs in 2018 and continuing to increase.[5] As Japan is facing a superaging society (the number of people at the age of 65 years and older is estimated as >35.0 million, which is 29% of the total population[6]) and healthcare costs became >43 trillion yen in 2018,[5] the current state of prevention and treatment, as well as costs, urgently need to be clarified and discussed.

Lung cancer survival is mostly determined by disease stage at the time of diagnosis. The 5-year survival rate for stage pT1N0M0 is >70%, whereas the 5-year survival rate for pT4 is only 22%.[7] Furthermore, various studies worldwide have shown that early detection of lung cancer can reduce the economic burden of the disease.[8,9] Given that healthcare systems vary from country to

country, their healthcare costs may differ as well. Taking into account that > 60% of the patients are diagnosed as having lung cancer after 65 years old or older,[10] assessment of data of Japan where the superaging society is proceeding and well-developed National Health Insurance (NHI) system covers high-priced medical care for everybody can give us important information; nevertheless, no studies have been conducted to look into this. There are also no reports comparing data before and after 2015, when ICIs were approved in Japan.

In Japanese NHI system, all citizens are required to participate in the insurance system, which is determined by age, residential area, and profession. All individuals including retirees who do not have company insurance coverage will be enrolled in either the NHI or the Advanced Elderly Medical Service System.[11] The NHI system covers self-employed and retirees and their family members. The Advanced Elderly Medical Service System covers 75-year-olds or older or 65- to 74-year-olds with certain disabilities. Data of these insurances usage are managed by local government, and Kyoto City creates a database for these insurances to evaluate the medical process and economics.

Hence, the purpose of this study was to identify the variation of treatment contents and outcomes and economic burden of lung cancer among the elderly population in Japan, by describing the changes in treatment and medical expenses over time using the Kyoto City administrative database for NHI and Advanced Elderly Medical Service System.

Methods

Study Design, Population, and Setting

The study is a cross-sectional study using data from the "Kyoto City Integrated Database" managed by the Kyoto City government. Kyoto, with an area of 827 km^2, is a major city in Japan with a population of approximately 1.5 million.[12]

The Kyoto City Integrated Database consists of some administrative database and contains data from April 2013 to March 2019. Considering the number of persons belonging to NHI and Advanced Elderly Medical Service System among Kyoto residents,[13-15] this database covers approximately 35% of Kyoto residents from fiscal year (FY) 2013 to FY 2018. This database includes usage records of medical insurance and long-term care insurance, results of specific health check-ups and health check-ups for the elderly, and information from basic resident register (information on deaths, move-ins, and move-outs). All information is anonymized and given a unique identification that identifies a specific individual, making it possible to link individual information between each data.

The subjects of this study were patients with new-onset primary lung cancer. One of the limitations of the database is that the status of lung cancer incidence before April 2013 is unknown, and the validity of disease status is limited in medical administrative data.[16-18] Therefore, in our study, individuals who had no record of lung cancer in the first 6 month in FY 2013 (between April 1, 2013, and September 30, 2013); had a disease name of lung cancer between October 1, 2013, and the end of FY 2018 (March 31, 2019); and had a record of receiving any treatment for lung cancer were included. For disease names, cases with International Classification of Diseases, Tenth Revision (ICD-10), codes C33 and C34 were extracted, and then individual disease names were reviewed, and cases other than lung cancer were excluded. The treatment of lung cancer was defined as surgical resection (see Appendix Table 1 in Supplemental Materials found https://doi.org/10.1016/j.vhri.2022.05.004), drug therapy (see Appendix Table 2 in Supplemental Materials found https://doi.org/10.1016/j.vhri.2022.05.004), and radiation therapy (see Appendix Table 3 in Supplemental Materials found https://doi.org/10.1016/j.vhri.2022.05.004), each of which was identified by medical practice billing codes and recorded in accordance with the disease name of lung cancer, as a result of discussion between D.K. (pulmonologist) and Y.T. (pharmacist) (see Appendix in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2022.05.004).

This study was reviewed and approved by the Kyoto University Graduate School and Faculty of Medicine, Ethics Committee (R3107-1). Given that data were obtained from an anonymized existing database, an informed consent was not necessary.

Data Collection and Quality Control

The date of the first record of treatment for lung cancer was set as the index date, and sex and age of patients at that time were extracted. For cases where information is available only for the month, the first day of the month is used. The comorbidities were extracted by ICD-10 codes (see Appendix Table 4 in Supplemental Materials found https://doi.org/10.1016/j.vhri.2022.05.004) from the disease names in the medical insurance claims data for the previous 6 months including the index date. The extraction of disease name related to comorbidities was agreed upon by physicians T.I. and D.K. (see Appendix in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2022.05.004). Comorbidities in cases disease name with "suspected" were excluded from the definition. The long-term care certification information within 6 months before the index date is used. The criteria for the certification of long-term care are classified from Need Support to level 5 (daily time required for caregiving is <30 minutes, <50 minutes, <70 minutes, <90 minutes, <110 minutes, and >110 minutes).[19] Confirmations of survival, death, and move-outs were based on the Basic Resident Registers as of the end of FY 2018. Given that information in the Basic Resident Registers exists only in monthly units, the survival period was calculated on a per-month basis.

Statistical Analysis

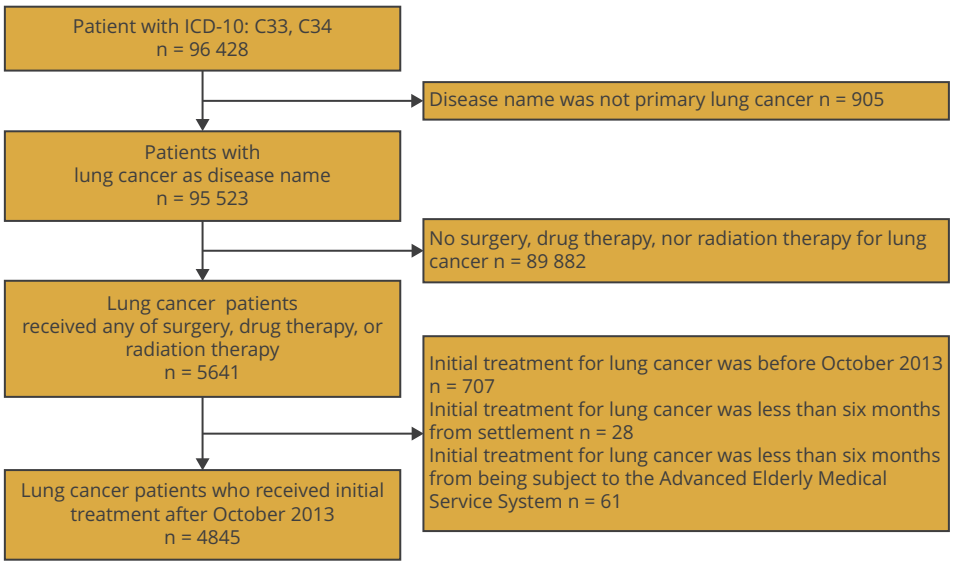
To understand the changes in the incidence of lung cancer and its treatment in each year, patient characteristics, initial treatment, medical costs, and deaths in each year were summarized. The numerical scale was described as mean and SD, and the categorical scale was described as percent.

Patient characteristics included age, sex, and comorbidities. The certification status of long-term care was indicated on a 6-point scale from Need Support to level 5.

The initial treatment was divided into 3 categories (surgery, drug therapy, and radiation therapy), and surgery was also categorized into thoracotomy and video-assisted thoracic surgery. Drug therapy was classified into 3 categories: chemotherapy, molecular targeted therapy, and ICIs. In addition, molecular targeted therapy was also categorized and described into epidermal growth factor receptor inhibitors (afatinib, erlotinib, gefitinib and osimertinib), anaplastic lymphoma kinase inhibitors (alectinib, ceritinib, and crizotinib), and v-Raf murine sarcoma viral oncogene homolog B inhibitors (dabrafenib and trametinib). To evaluate the change in the proportion of surgery, drug therapy, and radiation therapy in the initial treatment over time, the Cochran-Armitage trend test was performed to assess each treatment option.

The sum of the cost of medical treatments is defined as the total medical cost, assuming a fee-for-service payment system associated with each treatment. The total medical costs were calculated for each year in cases who received their first treatment in that year. The patients who received their initial treatment in FY

Figure 1. Patient flow.



ICD-10 indicates International Classification of Diseases, Tenth Revision.

2013 were excluded from the calculation of medical costs because of the shorter period of inclusion than other years, and thus, the comparison was not appropriate.

The survival time from the index date to death and the number and proportion of deaths in each survival period are described for each year. The duration of follow-up is dependent on the timing of enrollment in the cohort: 5 years for those enrolled in 2013, and after that, the follow-up period will decrease by 1 year depending on the year of participation. FY 2018 was the last year of the cohort, and cases that occurred in FY 2018 were excluded from the description of survival and deaths because of insufficient observation period. Cochran-Armitage trend test was performed to evaluate the annual change in the mortality rate for each survival period.

Analysis was performed with SQL server management studio version 15.0 (Microsoft Corporation). Cochran-Armitage trend test was conducted with R version 4.04 (R Core Team), with $\alpha = 0.05$, 2-tailed test.

Results

The database included claims data for 724 928 patients and 96 428 cases with ICD-10 codes C33 or C34 at least once during the study period. From these, the disease names associated with ICD-10 codes were confirmed, and 905 patients with disease names other than lung cancer were excluded. Patients who did not receive any treatment for lung cancer were also excluded from the study; 5641 people remained. The following patients whose index

Table 1. Temporal trends in patient characteristics.

Variables	Total		2013		2014		2015		2016		2017		2018	
	N = 4845		n = 426		n = 857		n = 864		n = 865		n = 899		n = 934	
Age, average (SD)	73	(7.9)	73	(7.9)	73	(7.9)	73	(8.5)	74	(8.0)	73	(7.4)	74	(7.8)
75 years and over, n (%)	2408	(49.7)	219	(51.4)	426	(49.7)	394	(45.6)	434	(50.2)	434	(48.3)	501	(53.6)
Male, n (%)	3102	(64.0)	265	(62.2)	564	(65.8)	542	(62.7)	560	(64.7)	567	(63.1)	604	(64.7)
Comorbidity, n (%)														
Chronic lung disease	1961	(40.5)	155	(36.4)	311	(36.3)	338	(39.1)	379	(43.8)	378	(42.0)	400	(42.8)
Congestive heart failure	1098	(22.7)	85	(20.0)	201	(23.5)	194	(22.5)	196	(22.7)	179	(19.9)	243	(26.0)
Cerebrovascular disease	762	(15.7)	68	(16.0)	129	(15.1)	135	(15.6)	138	(16.0)	142	(15.8)	150	(16.1)
Renal dysfunction	243	(5.0)	28	(6.6)	47	(5.5)	43	(5.0)	45	(5.2)	33	(3.7)	47	(5.0)
Liver dysfunction	371	(7.7)	38	(8.9)	51	(6.0)	65	(7.5)	67	(7.7)	71	(7.9)	79	(8.5)
Dementia	65	(1.3)	5	(1.2)	9	(1.1)	12	(1.4)	16	(1.8)	10	(1.1)	13	(1.4)
Needing long-term care, n (%)														
Need support	310	(6.4)	24	(5.6)	55	(6.5)	59	(6.8)	53	(6.1)	48	(5.3)	71	(7.6)
Level 1	144	(3.0)	8	(1.9)	28	(3.3)	22	(2.5)	21	(2.4)	37	(4.1)	28	(3.0)
Level 2	145	(3.0)	5	(1.2)	24	(2.8)	36	(4.2)	30	(3.5)	33	(3.7)	17	(1.8)
Level 3	59	(1.2)	5	(1.2)	15	(1.8)	7	(0.8)	12	(1.4)	11	(1.2)	9	(1.0)
Level 4	37	(0.8)	3	(0.7)	12	(1.4)	6	(0.7)	5	(0.6)	2	(0.2)	9	(1.0)
Level 5	17	(0.4)	2	(0.5)	3	(0.4)	1	(0.1)	6	(0.7)	1	(0.1)	4	(0.4)

Table 2. Temporal trends in an initial treatment for lung cancer.

Variables, n (%)	Total		2013		2014		2015		2016		2017		2018		*P* for trend
	N = 4845		n = 426		n = 857		n = 864		n = 865		n = 899		n = 934		
Surgery	1820	(37.6)	150	(35.2)	272	(31.7)	301	(34.8)	347	(40.1)	380	(42.3)	370	(39.6)	<.001*
Thoracotomy	143	(3.0)	14	(3.3)	15	(1.8)	23	(2.7)	34	(3.9)	24	(2.7)	33	(3.5)	
Video-assisted thoracic surgery	1677	(34.6)	136	(31.9)	257	(30.0)	278	(32.2)	313	(36.2)	356	(39.6)	337	(36.1)	
Drug therapy	1917	(39.6)	188	(44.1)	379	(44.2)	352	(40.7)	318	(36.8)	329	(36.6)	351	(37.6)	<.001*
Chemotherapy	1534	(31.7)	158	(37.1)	320	(37.3)	309	(35.8)	257	(29.7)	237	(26.4)	253	(27.1)	
Molecular targeted therapy	274	(5.7)	30	(7.0)	58	(6.8)	42	(4.9)	49	(5.7)	44	(4.9)	51	(5.5)	
EGFR inhibitors	260	(5.3)	28	(6.0)	57	(7.2)	42	(5.0)	48	(5.5)	38	(4.2)	47	(5.0)	
ALK inhibitors	14	(0.3)	2	(0.5)	1	(0.1)	0	(0)	1	(0.1)	6	(0.7)	4	(0.4)	
BRAF inhibitors	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	
Immune checkpoint inhibitors	109	(2.2)	0	(0)	1	(0.1)	1	(0.1)	12	(1.4)	48	(5.3)	47	(5.0)	
Radiation therapy	1108	(22.9)	88	(20.7)	206	(24.0)	211	(24.4)	200	(23.1)	190	(21.1)	213	(22.8)	.64

ALK indicates anaplastic lymphoma kinase; BRAF, v-Raf murine sarcoma viral oncogene homolog B; EGFR, epidermal growth factor receptor.
*Indicates statistical significance.

date could not be identified as initial treatment were also excluded from the study: 707 patients received initial treatment for lung cancer before October 2013, 28 patients received initial treatment for lung cancer within 6 months of moving into Kyoto City, 61 patients had no medical claims data before the age 75 years and index date within 6 months of age 75. After the exclusions, 4845 people were included in the study (Fig. 1).

Patient characteristics and their changes over years are presented in Table 1. The average age of patients was 73 to 74 years for a 6-year study period, and the proportion of patients older than 70 years was 45.6% to 53.6%. The proportion of males was consistently at 62% to 65%. Regarding comorbidities, the proportion of chronic lung disease increased from 36.4% to 42.8% over a 6-year study period. The proportions of congestive heart failure, cerebrovascular disease, renal failure, hepatic failure, and dementia were 22.7%, 15.7%, 5.0%, 7.7%, and 1.3%, respectively. In total, 15.7% of the patients were identified as needing long-term care before the index date, and the proportion has remained at 15% to 17% since 2014.

Annual proportions of initial treatment are presented in Table 2. From 2013 to 2015, the proportion of patients who received surgery was 31% to 36%; nevertheless, since 2016, the percent increased to >39%. The proportion of patients who received drug therapy reached its highest proportion in 6 years at 44.1% in 2013 and declined to 36.1% in 2018. The proportion of patients who received radiation therapy remained between 20.7% and 23.1%. In terms of details of surgical cases, video-assisted thoracic surgery represent >90% of all cases, and the proportion has not changed over time. Regarding drug therapy, the use of ICIs as initial treatment has increased since 2014. The results of the trend test showed an increasing trend of surgery and a decreasing trend of drug therapy between FY 2013 and FY 2018 (surgery, *P* for trend <.001; drug therapy, *P* for trend <.001).There was no trend in proportion of radiation therapy.

The total cost of surgery, drug therapy, and radiation therapy for lung cancer patients who received initial treatment in each year are presented in Table 3. For all treatments, healthcare costs increased between FY 2014 and FY 2018, with a particularly significant increase of 340 million for drug therapy. In addition, the usage of ICIs has gradually increased since FY 2014, and in FY 2018, it has accounted for >60% of drug costs.

The overall survival and mortality rates for each year are presented in Table 4. The mortality rate in <6-month follow-up from initial treatment was the lowest in FY 2013 (10.6%) and remained between 14.9% and 13.1% from FY 2014 to FY 2017. The highest mortality rate in <1-year follow-up was 26.7% in FY 2014 and has

Table 3. Total cost in each year.

Variables	2014		2015		2016		2017		2018	
Total cost, ¥1000 (n)	n = 814		n = 836		n = 838		n = 881		n = 898	
Surgery	235 067	(280)	249 893	(304)	296 930	(359)	327 195	(392)	314 883	(378)
Drug therapy	320 580	(446)	386 133	(432)	416 602	(405)	524 574	(413)	606 397	(462)
Chemotherapy	299 230	(387)	308 213	(385)	241 786	(344)	202 073	(321)	206 263	(356)
Molecular targeted therapy	20 749	(75)	26 191	(64)	17 655	(64)	21 719	(57)	33 316	(68)
EGFR inhibitors	20 172	(74)	24 964	(62)	15 841	(61)	11 366	(49)	30 299	(62)
ALK inhibitors	577	(1)	1227	(2)	1814	(3)	10 353	(8)	3016	(7)
BRAF inhibitors	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Immune checkpoint inhibitors	601	(1)	51 728	(15)	157 161	(42)	300 782	(99)	366 818	(135)
Radiation therapy	115 919	(287)	127 930	(314)	116 766	(284)	102 937	(263)	142 486	(296)

ALK indicates anaplastic lymphoma kinase; BRAF, v-Raf murine sarcoma viral oncogene homolog B; EGFR, epidermal growth factor receptor.

Table 4. Temporal trends in survival.

Survival time	2013		2014		2015		2016		2017		*P* for trend
	n = 426		n = 857		n = 864		n = 865		n = 899		
Less than 6-months, n (%)	45	(10.6)	128	(14.9)	115	(13.3)	116	(13.4)	118	(13.1)	.81
< 1 year	109	(25.6)	229	(26.7)	214	(24.8)	204	(23.6)	209	(23.2)	.09
< 2 years	182	(42.7)	352	(41.1)	335	(38.8)	318	(36.8)	NA	NA	.02*
< 3 years	221	(51.9)	437	(51.0)	417	(48.3)	NA	NA	NA	NA	.18
< 4 years	243	(57.0)	485	(56.6)	NA	NA	NA	NA	NA	NA	NA
< 5 years	248	(58.2)	NA	NA	NA	NA	NA	NA	NA	NA	NA

NA indicates not applicable.
*Indicates statistical significance.

subsequently decreased over time to 23.2% in FY 2017. The mortality rate in <2-year follow-up decreased from 42.7% in FY 2013 to 36.8% in FY 2016. The decreasing trend of mortality rates was shown by trend test in <2 years.

Discussion

This study revealed recent trends in patients' characteristics, treatment, survival, and medical costs of new lung cancer using a large database of NHI and Advanced Elderly Medical Service System, which covers most of the elderly people in Kyoto City with a population of approximately 1.5 million. Our study demonstrated that treatment contents have changed, medical costs related to drug therapy have increased, and the mortality rate has improved during the study period. The trends related to treatment, clinical outcomes, and costs shown in this study would be useful as a reference for future medical policies, given that Japan is ahead of the rest of the world in terms of superaging population and has a well-established NHI system that allows most Japanese to receive the best available medical care.

In this study, the proportion of surgery as the initial treatment increased over time, whereas the proportion of drug therapy decreased accordingly. Japanese guidelines for the clinical practice of lung cancer recommend surgical resection in stage I and II and selected stage III patients with NSCLC, and surgical operation has been recommended for selected patients with small cell lung cancer.[20] Among patients with small cell lung cancer, only a limited number of patients are eligible for surgical treatment.[21] The increase in the proportion of surgery as initial treatment would reflect an increase in the number of cases of early detection in patients with NSCLC. In Japan, there is a lung cancer screening program promoted by the local government, and further detailed study is needed to investigate whether this program leads to early detection of lung cancer.

Importantly, this study demonstrates a trend of mortality reduction over time. It is reported that the mortality rate of cancer is decreasing in developed countries such as the United States, Denmark, France, Germany, Sweden, and Australia.[22] Smoking cessation and early diagnosis of lung cancer at a stage when surgery is applicable might be possible explanations of improvement in survival as previously reported.[23-25] It also showed that ICIs were approved for lung cancer in Japan in September 2014, and the number of patients receiving these drugs has been increasing since 2015. These changes in treatment may have influenced the improvement in survival.

From 2014 to 2018, the total healthcare costs have shown an increasing trend over time. In surgical cases, the increase in healthcare costs is associated with an increase in the number of patients. For drug therapy, there was no significant change in the number of patients, but there was a large increase in healthcare costs. Considering the change in the type of medications used, it can be seen that ICIs were increasingly used and their costs resulted in the increase in drug costs. The prices of ICIs, nivolumab (NHI listed since 2014) and pembrolizumab (NHI listed in 2017), were gradually discounted until August 2021. Although overall drug costs for ICIs have increased during the period of this study, increase in individual units has been limited in light of the increase in users since 2016. In addition, the NHI prices of atezolizumab, listed since April 2018, and durvalumab, listed since August 2018, have been discounted after the end of the study period.

There are several limitations in this study. There are a small number of patients who cannot be traced because of them entering or leaving the NHI system. The database did not include the data before FY 2013. Therefore, the validity of initial treatment for lung cancer is limited, but excluded patients who received initial treatment in first 6 month in FY 2013. The risk of the miss classification is minimal. The database covers only the elderly, self-employed, unemployed, and their family members, so we need to be careful when extrapolating our results to other settings. The validity of disease name from administrative data is usually very limited.[16-18] As a countermeasure, not only disease name but also the insurance claim of the treatment was used as inclusion criteria. Given that this was a descriptive study, the causal relationship among the variables that changed over time is unclear. In addition, this database has no information on cancer type or stage. For a more detailed study, it is necessary to conduct a comprehensive comparative survey by adding information on cancer statistics.

Conclusion

This study demonstrated that the improvement in the survival rate and proportion of surgery as an initial treatment was increased whereas drug therapy decreased and medical costs increased among patients with lung cancer over time by analyzing a database consisting of subjects covered by the NHI and the Advanced Elderly Medical Service System in Kyoto, Japan. Based on these results, it is necessary to implement sustainable healthcare measures with a consideration of cost-effectiveness.

Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.vhri.2022.05.004.

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