

# Lung Cancer in Japan



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## Introduction

Japan is located in East Asia and consists of five large islands and numerous smaller islands, with a total of 6852 islands (Fig. 1). Mountainous areas cover 75% of the country, and the population is concentrated in the plains along the coast. Because it is an island nation and because of the policy of seclusion that lasted for more than 300 years during the Edo period, it is almost ethnically homogeneous. The total population is 125.36 million, ranking 11th in the world. The average life expectancy of men is 81 years, and that of women is 87 years, making Japan a country with one of the highest life expectancies in the world.

## Epidemiology

In 2019, lung cancer accounted for the highest number of deaths for all cancers, followed by colorectal cancer and stomach cancer.<sup>1</sup> Lung cancer-related deaths among men ranked first with 53,200 deaths, and those among women ranked second with 22,300 deaths. Aging also plays a role in this situation, with age-adjusted death rates showing a downward trend after peaking in the 1990s (Fig. 2). In 2017, lung cancer was the fourth most common cancer among men (86,800 cases) and the third most common cancer among women (43,100 cases), ranking third among all cancer types. Among all cancers, colorectal cancer ranked first in the number of cases, followed by stomach cancer. Among patients with lung cancer diagnosed in 2013, 38.6% were stage I, 8.7% were stage II, 17.7% were stage III, and 33.0% were stage IV according to the Union for International Cancer Control stage at diagnosis. The 3-year relative survival rates were 89%, 64.4%, 38.2%, 12.3%, and 51.7% for stage I, II, III, IV, and overall lung cancer, respectively. Although there are various background factors, it has been pointed out that, when compared with other countries, Japan has a higher percentage of early-stage diagnoses, mainly stage I, and a better survival rate of lung cancer.<sup>2</sup>

Smoking rates among men have been declining since 1995 and among women since 2004. As of 2018, the smoking rates among men and women were reported to be 29% and 8.1%, respectively. Of these, 12.1% of men and 2.8% of women smoked more than 21 cigarettes per day.

Associated with declining smoking rates, adenocarcinoma accounts for more than 80% of cases, and about 50% of advanced adenocarcinomas are EGFR mutation positive.

Although the Health Promotion Law promulgated in 2002 stated that passive smoking should be prevented, it was only an effort obligation and there were no penal regulations. In 2020, the Health Promotion Law was revised to strengthen efforts to prevent passive smoking, and penalties (fines) were added. This amendment stipulates that smoking is not allowed indoors, with some exceptions, in public facilities, public transportation, and restaurants used by a large number of citizens. In addition, schools, hospitals, children's facilities, and government agencies now prohibit smoking on their premises.

## Screening

The rate of lung cancer screening has improved in recent years. In 2010, a total of 26.4% of men and 23.0% of women were reported to have been screened, and 53.4% and 45.6%, respectively, were screened in 2019.<sup>1</sup>

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**Figure 1.** Map of Japan and neighboring countries.

Chest radiography is now nationally available with public assistance for people aged more than 40 years, and sputum cytologic testing is available for high-risk patients. The significance of lung cancer screening by chest radiography has been negatively evaluated in randomized controlled trials in the United States and Europe. In contrast, multiple case-control studies conducted in Japan have shown that lung cancer screening with chest radiography and sputum cytologic testing reduced lung cancer mortality. Considering this evidence, Japanese screening guidelines focusing on chest radiography have been developed.

Low-dose computed tomography (CT) screening, which has been recently highlighted, has not yet been added to the list of lung cancer screening items covered by public funds. In addition to public screening programs, there are a significant number of incidental lung cancer diagnoses on the basis of the world's leading number of CT.<sup>3</sup> In terms of the number of CT scanners owned, Japan ranks first among Organisation for Economic Co-operation and Development countries with 111.49 scanners per 1 million persons, which far exceeds Australia, which ranks second with 64.34 scanners per 1 million persons. In terms of the number of magnetic resonance imaging (MRI) machines owned, Japan has

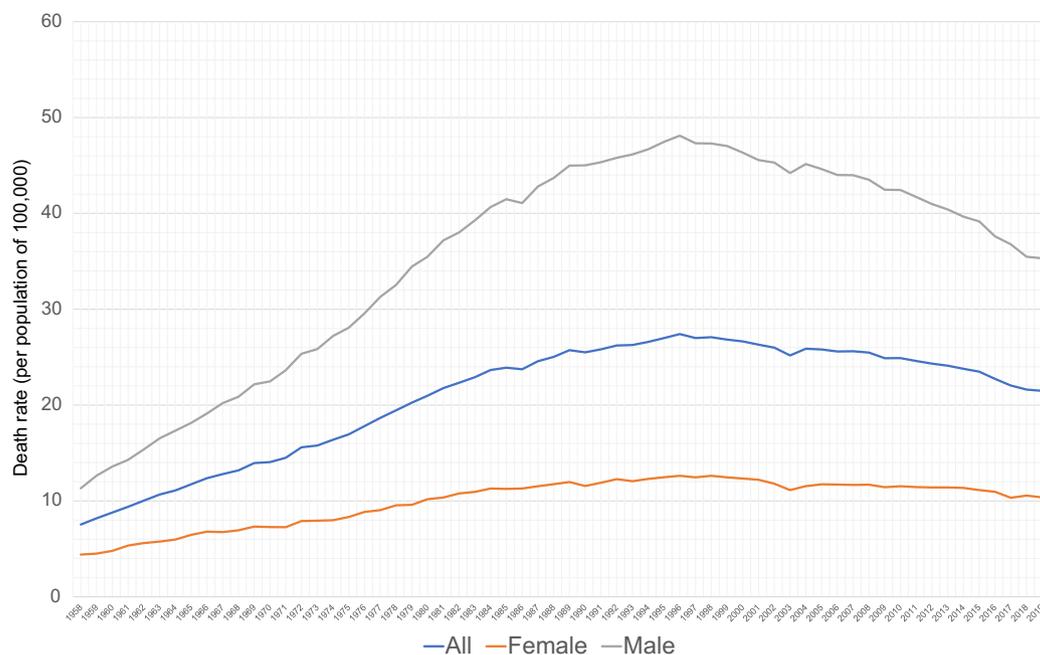


Figure 2. Trends in age-adjusted mortality rate by lung cancer (1958-2019).

55.21 machines per 1 million persons, which is significantly higher than the 37.65 machines per 1 million persons in the United States (which ranks second). Although Denmark ranks first in the number of positron emission tomography (PET) scanners owned, Japan is still in the second place with 4.62 scanners per 1 million persons. Following the United States with 255.1 CT scans per 1000 people, Japan remained in the second place with 230.8 CT scans per 1000 people. Similarly, Japan ranks second among Organisation for Economic Co-operation and Development countries in the number of MRI and PET examinations performed, following the United States. In particular, even small- and medium-sized family clinics generally own CT equipment, and scans are provided at low cost, even for minor complaints covered by public health insurance.

## Diagnosis

As mentioned in the previous chapter, the availability of diagnostic imaging equipment such as CT, MRI, and PET in Japan is one of the highest in the world, and many of these tools are covered by national health insurance, making diagnostic imaging highly accessible.

Bronchoscopy is the standard for definitive histologic diagnoses. In 1966, Dr. Shigeto Ikeda developed a flexible bronchoscope at the National Cancer Center Hospital in Japan. This tool is now widely used not only for diagnostic purposes but also for intervention purposes. According to the 2016 national survey, a total of 98,497 bronchoscopies were performed, and 55,335 forceps biopsies (of which, 23,916 were performed using a guide

sheath) and 9713 endobronchial ultrasound-guided transbronchial needle aspirations were performed.<sup>4</sup> Considering the 125,806 new diagnoses of lung cancer in Japan in 2016, it would be prudent to state that bronchoscopy is a major diagnostic tool in Japan.

EGFR mutations are frequent in those of Asian ethnicity, and molecular testing is performed in more than 80% of patients with advanced lung cancer before first-line treatment. Multiple single gene tests for EGFR, ALK, and other mutations have been applied in a sequential manner, and the OncoPrint Dx Target Test was approved in 2019 with a cost of approximately \$1000, 70% to 100% of which is covered by national health insurance. This test indicates the genetic and fusion status of 46 and 13 genes, respectively, which is a function of companion diagnostics of drugs including gefitinib, erlotinib, afatinib, osimertinib, crizotinib, alectinib, entrectinib, dabrafenib, and trametinib. Comprehensive genomic panel testing (OncoPrint, Foundation One, Foundation ONE Liquid), which costs approximately \$5000, was also approved for all types of solid cancer, but only for patients who have completed standard treatment, in the 404 designated hospitals under the national cancer genome network. In addition, the LC-SCRUM, a large ongoing study in collaboration with industry, government, and academia, is currently being conducted under the leadership of the National Cancer Center East, in which the participants can undergo the cancer gene panel test free of charge. Recently, the National Cancer Center has established the Center for Cancer Genomics and Advanced Therapeutics (C-CAT,

[https://www.ncc.go.jp/en/c\\_cat/](https://www.ncc.go.jp/en/c_cat/)). The C-CAT was established on the basis of the report of the Expert Meeting for Cancer Genomic Medicine Promotion Consortium of the Ministry of Health, Labour and Welfare. The report indicated that the C-CAT would consolidate cancer genome information in Japan and build a repository of cancer genomics information. The results of various gene panel tests conducted in Japan (OncoGuide, Foundation ONE, Foundation ONE Liquid, etc.) are required to be registered in the C-CAT repository. As of September 2021, more than 20,000 cases of genetic abnormalities and clinical processes have been accumulated. A portal site for the utilization of the accumulated data has been established, and its application to research and clinical practice is planned to be promoted.

## Surgical Approaches

The Japanese Joint Committee of Lung Cancer Registry periodically conducts nationwide surveys of lung cancer surgery. Previous surveys were conducted in 1994, 1999, and 2004, with the most recent report published in 2010. The information obtained from this survey has also contributed substantially to the TNM staging project being led by the International Association for the Study of Lung Cancer. In a 2010 survey, 18,973 patients underwent lung cancer surgery at 297 institutions (Table 1).<sup>5</sup> Along with the aging of the Japanese population as a whole, the average age of patients undergoing lung cancer surgery is also increasing. In this survey, the percentage of patients aged more than 70 years was 49%, whereas that of those aged more than 80 years was 10.5%. The proportion of patients aged more than 80 years has tripled from 3.1% in the 1994 survey. The number of small-sized lung cancers is also increasing as a result of advances in diagnostic technology, mainly the widespread use of CT, and the increase in the proportion of adenocarcinomas owing to the decline in smoking rates. Indeed, the frequency of small lung cancers of less than 2 cm in diameter increased from 23.4% in 1994 to 39.0% in 2010. Related to this trend, the frequency of limited resections, including wedge resections and segmentectomies, increased from 6.4% in 1994 to 22.7% in 2010 (Table 2). Using data from the 2004 national survey, the outcomes of 436 patients with cN2/pN2 NSCLC have been reported. Adjuvant chemotherapy was administered to 151 patients (34.6%), neoadjuvant chemotherapy or chemoradiotherapy was administered to 108 patients (24.8%), and surgical treatment alone was administered to 137 patients (31.4%).

## Radiation Approaches

According to the Japanese Structure Survey of Radiation Oncology in 2017 by the Japanese Society for

Radiation Oncology, a total of 185,523 patients, including 30,870 patients (16.6%) with lung cancer, were treated by radiation therapy (RT).<sup>6</sup> Over 800 radiation oncology institutions were included, with approximately 50% of these institutions treating fewer than 200 patients, and 13% treating at least 500 patients in 1 year. Stereotactic RT (SRT) was applied in 18,484 patients with brain tumors and in 7072 patients with extracranial tumors, including 5046 patients with lung tumors. Intensity-modulated RT (IMRT) was employed in 12,373 patients with prostate cancer, 6892 patients with head and neck cancer, 1767 patients with brain tumors, and 9797 patients with other cancers, including lung cancer. As of 2021, a total of 1322 board-certified radiation oncologists and 1337 board-certified medical physicists are employed in Japan, but there is still a significant shortage of these professionals, particularly in small-scale institutions.

Recently, the use of IMRT has been increasing for patients with locally advanced lung cancer, with the aim of reducing the risk of radiation pneumonitis. Particle therapy is available in 24 institutions (protons in 17, carbon ions in six, and both in one), and the efficacy of this therapy relative to IMRT is under active investigation to determine whether it should be covered by medical insurance.

Quality assurance is crucial to maximize the efficacy and safety of RT. Poorer treatment outcomes were reported to be caused by deviation from RT guidelines.<sup>7-9</sup> A prospective radiotherapy trials quality assurance program was initiated in the Japan Clinical Oncology Group (JCOG) clinical trial 20 years ago, which became mandatory in all subsequent JCOG studies involving RT. All registered cases have been reviewed with feedback provided to participating institutions if needed, and the compliance of RT has increased to greater than 90%, ensuring the scientific and statistical power of these studies.<sup>10</sup> The JCOG has also been a steering committee member of the radiotherapy trials quality assurance global harmonization group to facilitate international collaboration since its foundation.<sup>11</sup> These efforts will also lead to high quality daily practice by flow-on effects and the safe use of advanced technologies such as IMRT and SRT.

## Systemic Therapy

Japan is one of the few countries in the world where a wide range of citizens, regardless of income or residential region, have the opportunity to receive systemic cancer therapy. There are two main reasons for this situation. First, the cost of medical care remains relatively low owing to the universal health insurance system. Second, owing to the regulation reform by the Pharmaceuticals and Medical Devices Agency and the

Table 1. Demographic Characteristics, OS, and Disease-Free Survival

Characteristics	N	%	5-y OS, %
<b>Sex</b>			
Male	11,771	62	67.9
Female	7202	38	85.7
<b>Age, y</b>			
≤19	9	0.9	90.3
20-29	21		
30-39	148		
40-49	604	3.2	83
50-59	2221	11.7	83.2
60-69	6685	35.2	78.9
70-79	7301	38.5	70.6
80-89	1963	10.5	60.1
90-99	21		
<b>Performance status</b>			
0	15,456	81.5	78.2
1	2589	13.6	56.6
2	364	1.9	62.6
3	79	0.5	45.7
4	8		
Unknown	477	2.5	NA
<b>Smoking history</b>			
No	6714	35.4	86.8
Yes	11,622	61.3	67.9
Pack-years, median	11,223	46 (30-65) <sup>a</sup>	NA
Unknown	637	3.4	NA
<b>Surgery</b>			
Wedge resection	2456	12.9	73.8
Segmentectomy	1855	9.8	84.2
Lobectomy	13,654	72	75.3
Bilobectomy	427	2.3	56.8
Pneumonectomy	337	1.8	51.1
Others	52	0.3	63.8
Exploration	192	1	27.6
<b>Tumor histologic type</b>			
Preinvasive tumor	95	0.5	96.5
Adenocarcinoma	13,175	70.1	81.7
SCC	3776	20.1	59.7
Large cell carcinoma	573	3	59.3
Adenosquamous cell carcinoma	373	2	53.2
Small cell carcinoma	321	1.7	45.4
Others	493	2.6	62.4
<b>5-y OS rate by stage</b>			
Clinical stage in the eighth edition			
0	1100	5.8	97
IA1	2199	11.6	91.6
IA2	3857	20.4	81.4
IA3	2704	14.3	74.8
IB	2309	12.1	71.5
IIA	641	7.6	60.2
IIB	1561	4.1	58.1
IIIA	1176	6.2	50.6
IIIB	326	1.7	40.5
IIIC	17	0.1	37.5
IVA/IVB	189	0.5	36
Pathologic stage in the seventh edition			
IA	7316	44.5	88.9
IB	3772	23	76.7

(continued)

Table 1. Continued

Characteristics	N	%	5-y OS, %
IIA	1704	10.4	64.1
IIB	1024	6.2	56.1
IIIA	2110	12.8	47.9
IIIB	89	0.5	30.2
IV	415	2.5	36.1
5-y disease-free survival rate after R0 surgery by stage			
Clinical stage in the eighth edition			
0	1082	7.3	95.9
IA1	2154	14.6	88.2
IA2	3693	25	73.6
IA3	2541	17.2	64.5
IB	2123	14.4	60.1
IIA	576	3.9	48.9
IIB	1367	9.3	45.1
IIIA	960	6.5	39.8
IIIB	249	1.7	34.2
Pathologic stage in the seventh edition			
IA	7217	47.6	84.3
IB	3623	23.9	65.8
IIA	1598	10.5	49.7
IIB	902	5.9	46.3
IIIA	1777	11.7	27.8

Adapted and modified from Okami et al., *Journal of Thoracic Oncology* 2018. <https://doi.org/10.1016/j.jtho.2018.10.002>

<sup>a</sup>From the 25th to 75th percentile.

NA, not applicable; OS, overall survival; SCC, squamous cell carcinoma.

Ministry of Health, Labour and Welfare, systemic cancer therapies that have been approved overseas will be available and reimbursed (approval is linked to insurance reimbursement) within an average period of 6

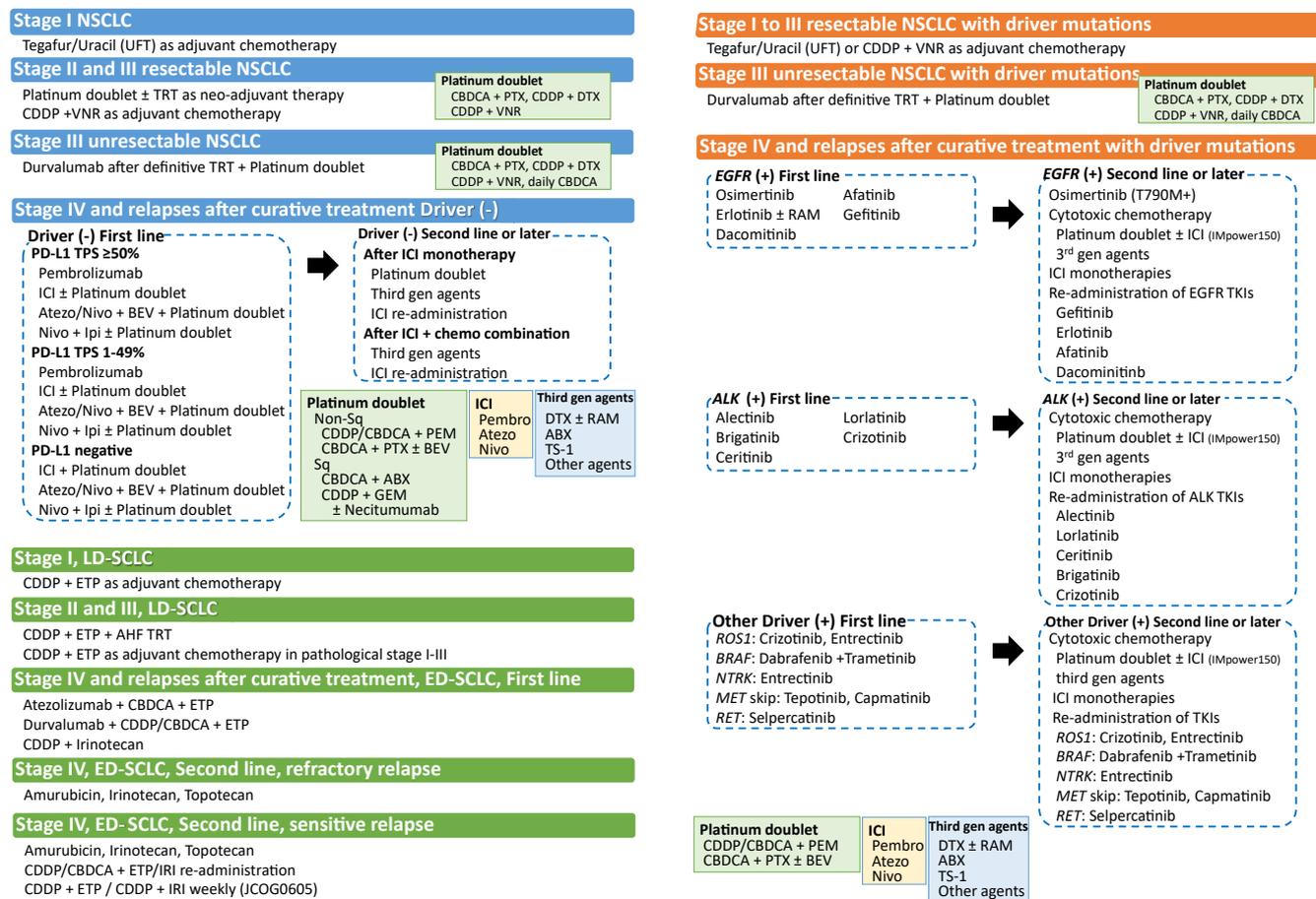
months, even after accounting for drug development and reviewing processes. There are many cases in which the domestic development of a drug precedes that overseas, and the drug is first approved in Japan. The National

Table 2. Time Trends of the Principal Data in the JJCLCR Studies

Characteristics	Y			
	2010	2004	1999	1994
Total patients, n	18,973	11,663	13,344	7238
Sex, %				
Male	62	63.2	67.1	70.1
Female	38	36.8	32.9	29.9
Age, y				
Mean	68.3	66.7	65.8	64.5
≥80, %	10.5	6	4.6	3.1
Surgery, %				
Limited resection	22.7	17	12.2	6.4
Pneumonectomy	1.8	3.4	5.3	8.7
Tumor size, cm				
≤2.0, clinical	39	37.5	30.1	23.4
≤2.0, solid component	49.2	NA	NA	NA
≤2.0, pathologic	41.9	36.9	NA	NA
Tumor histologic type, %				
Adenocarcinoma	69.4	67.9	61.7	55.7
Squamous cell carcinoma	19.9	22.3	27.7	33
5-y OS, %	74.7	69.6	61.6	51.9

Adapted and modified from Okami et al., *Journal of Thoracic Oncology* 2018. <https://doi.org/10.1016/j.jtho.2018.10.002>

JJCLCR, Japanese Joint Committee of Lung Cancer Registry; NA, not applicable; OS, overall survival.



**Figure 3.** Current standard medical treatment for NSCLC. ABX, albumin-bound nanoparticle formulation of paclitaxel; Atezo, atezolizumab; Bev, bevacizumab; CBDCA, carboplatin; CDDP, cisplatin; Chemo, chemotherapy; DTX, docetaxel; ED-SCLC, extensive disease-SCLC; ETP, etoposide; GEM, gemcitabine; gen, generation; ICI, immune checkpoint inhibitor; Ipi, ipilimumab; IRI, irinotecan; Nivo, nivolumab; PD-L1, programmed death-ligand 1; Pembro, pembrolizumab; PTX, paclitaxel; RAM, ramucirumab; TKI, tyrosine kinase inhibitor; TPS, tumor proportion score; TRT, thoracic radiotherapy; TS-1, Tegafur/Gimeracil/Oteracil; UFT, tegafur and uracil; VNR, vinorelbine.

Cancer Center periodically conducts surveys of cancer drugs approved in the United States or the European Union but not in Japan. As of April 30, 2021, the unapproved or off-label drugs in the field of thoracic cancers in Japan are cemiplimab, adjuvant osimertinib, pralsetinib, selpercatinib, pembrolizumab, and nivolumab for SCLC; afatinib for squamous NSCLC; and nintedanib, many of which are currently being prepared for filing in Japan.<sup>12</sup>

The figure summarizes the cancer systemic therapies often used in Japan (Fig. 3). As mentioned earlier, Oncomine DxTT and various genetic tests are reimbursed before first-line treatment. Therefore, in patients who are positive for driver gene alterations, including rare driver oncogenes, molecularly targeted agents are generally used as first-line treatment. For patients without driver gene alterations, a combination of immune checkpoint inhibitors and platinum-based

chemotherapy, regardless of the programmed death-ligand 1 status, is widely used and is reimbursed. For second-line therapy and thereafter, docetaxel plus ramucirumab, abraxane, S-1, and other third-generation monotherapies are reimbursed. In particular, there is no restriction on the re-administration of anticancer drugs. With the exception of second-line and later osimertinib, which is restricted to use in EGFR T790M-positive patients, many drugs are available for re-administration. Therefore, for a wide range of drugs, such as molecular-targeted drugs for driver gene alterations and immune checkpoint inhibitors, re-administration of a different drug of the same class that has already been used is common. This re-administration is also performed as a subsequent treatment in clinical trials and has been highlighted as one of the reasons for the better postprogression survival in the Japanese subgroup.

## What Are Specific Challenges in the Country or Unique Features

There are two issues that Japan needs to address in the future: the universal health insurance system in terms of medical care as a whole and lung cancer in nonsmokers in terms of thoracic oncology.

Japan's universal health insurance system ensures that all citizens are covered by public medical insurance, that patients can almost freely choose hospitals including cancer centers, that the cost of medical care is low, and that the government provides funds from the national budget to cover medical expenses.<sup>13</sup> As a result, medical care is available at 30% of the cost for patients aged less than 70 years, 20% for those aged 70 to 75 years, and 10% for those aged more than 75 years. Furthermore, with the ceiling-amount application for medical expenses, a patient with an average annual income will be able to keep their monthly medical expenses capped at approximately \$850. In addition to the cost of receiving medical care, citizens pay insurance fees on the basis of their income. In 2018, of approximately \$400 billion in total health care spending, \$200 billion was financed by insurance fees, \$50 billion was paid by patients, and the remaining \$150 billion was covered by government funds. The proportion of elderly persons aged 65 years or more is 29.1% in Japan, which is the highest in the world, far ahead of second-ranked Italy (23.6%). This population is increasingly dependent on medical care not only for malignant tumors but also for a variety of other diseases and bears a low percentage of medical costs. Owing to the universal health insurance system, Japan has been able to maintain the highest access to lung cancer treatment in the world, but there are concerns surrounding how long this situation can be sustained.

The issue specific to thoracic oncology in Japan is lung cancer in nonsmokers. It is well known that the frequency of lung cancer characterized by nonsmoking, such as EGFR mutation-positive lung cancer, is high in Japan. In Japan, where smoking rates are declining, the prevalence of lung cancer among nonsmokers has reached one of the highest levels in the world. This is not only an epidemiologic event but also has an impact on lung cancer screening and treatment. In lung cancer screening, there is controversy as to whether the evidence for low-dose CT screening for high-risk populations with a history of smoking, which has been established overseas, should be extrapolated to Japan. In lung cancer surgery, the number of small peripheral lung cancers has been steadily increasing, which has led us to consider the importance of limited surgery and radiotherapy, such as stereotactic body RT. In the medical treatment of lung cancer, the frequency of driver

mutation-positive lung cancer is expected to increase further. In the area of perioperative treatment, Japan is expected to lead the world in improving the curative rate among patients with driver gene alterations such as *EGFR* and *ALK*.

## CRedit Authorship Contribution Statement

**Hidehito Horinouchi:** Conceptualization, Data curation, Writing - original draft preparation.

**Masahiko Kusumoto, Yasushi Yatabe, Keiju Aokage, Shun-ichi Watanabe:** Writing - review & editing.

**Satoshi Ishikura:** Conceptualization, Writing - review & editing, Supervision.

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