# Lung Cancer in Korea

Sehhoon Park, MD, PhD,[a] Chang-Min Choi, MD, PhD,[b] Seung-Sik Hwang, MD, PhD,[c] Yoon-La Choi, MD, PhD,[d] Hyae Young Kim, MD,[e] Young-Chul Kim, MD, PhD,[f] Young Tae Kim, MD, PhD,[g] Ho Yun Lee, MD, PhD,[h] Si Yeol Song, MD, PhD,[i] Myung-Ju Ahn, MD, PhD[a,*]

## Epidemiology

South Korea is geographically located in East Asia, constituting the southern part of the Korean Peninsula (Fig. 1). The major administrative divisions in South Korea are nine provinces and seven metropolitan cities, with a current population of around 51.8 million and a density of 516 per km$^2$. In 2018, a total of 28,628 patients (accounting for 11.7% of all newly diagnosed cancers) was diagnosed with lung cancer in South Korea. Lung cancer is the second most common cancer in men and the fifth most common cancer in women.[1] According to the age-standardized incidence rates, whereas the incidence of lung cancer in men has decreased over time, the incidence of lung cancer in women has increased. Therefore, the overall incidence of lung cancer has remained steady since 1999 (Fig. 2*A*). Lung cancer remains the leading cause of cancer-related death both in men and women.[1] In 2018, the crude mortality rate per 100,000 population was 51.5 in men and 18.1 in women. However, age-standardized mortality rates have been decreasing continuously, especially in men (Fig. 2*B*). Although 36.4% of newly diagnosed patients with lung cancer in South Korea were never-smokers,[2] smoking is one of the most important risk factors of lung cancer. Fortunately, smoking prevalence in South Korea has decreased in both men (71.1% in 1992 to 39.7% in 2016) and women (6.5% in 1992 to 3.3% in 2016).[3] The Korean government has established several policies on tobacco control along with the WHO Framework Convention on Tobacco Control, including inflation of cigarette costs, the establishment of smoking-free public spaces, prohibition of tobacco advertisement in stores, and display of warnings on all cigarette packages.[4,5] However, the prevalence of electronic-cigarette users has increased, especially in adolescents, raising public health challenges.[6]

### *Lung Cancer Screening*

In 2016, the Korean Ministry of Health and Welfare announced the launch of the Korean Lung Cancer Screening Project (K-LUCAS) on the basis of the guidelines of lung cancer screening using low-dose computed tomography (LDCT) developed by the Korean National Cancer Center. K-LUCAS was conducted to evaluate the feasibility of implementing an organized national lung cancer screening program in South Korea.[7] This 2-year trial was performed in 14 general hospitals nationwide from February 2017 to December 2018. A high-risk population aged 55 to 74 years with a smoking history of at least 30 pack-years was enrolled, and 13,692 LDCTs were performed over 2 years. K-LUCAS reported the

*Corresponding author.

[a]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [b]Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea, [c]Division of Public Health Science, School of Public Health, Seoul National University, Seoul, South Korea, [d]Department of Pathology and Translational Genomics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [e]Department of Diagnostic Radiology, National Cancer Center, Goyang, South Korea, [f]Lung Cancer Clinic, Pulmonary Medicine, Chonnam National University Medical School, Chonnam National University Hwasun Hospital, Gwangju, South Korea, [g]Seoul National University Cancer Research Institute, Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital, Seoul, South Korea, [h]Department of Radiology and Center for Imaging, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, and [i]Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea.

*Disclosure: The authors declare no conflict of interest.*

Address for correspondence: Myung-Ju Ahn, MD, PhD, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, South Korea. E-mail: silkahn@skku.edu or silk.ahn@samsung.com



ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2021.09.007


**Figure 1.** The geographic location of South Korea.

LDCT screening results using the Lung Imaging Reporting and Data System version 1.0 suggested by the American College of Radiology and implemented a cloud-based system using computer-aided detection and volumetry software (A-view, Coreline Soft, Seoul, South Korea). The results revealed an increase in positive cancer findings but reduced variability among screening centers.[8]

On the basis of the results of K-LUCAS, a Korean population–based organized lung cancer screening program was created in 2019. Invitation letters were sent to eligible high-risk people selected from the electronically accumulated database already collected from the questionnaires of the national health screening program. Current smokers who received lung cancer screenings were offered mandatory smoking counseling through already established public smoking cessation programs and pharmacotherapy for free or at a very low cost. Approximately 23% among the approximately 690,000 eligible screening subjects underwent national lung cancer screening with LDCT in 2019 and 2020.

## Diagnosis

### *Initial Approach and Staging*

Patients with suspected lung cancer with chest radiograph or computed tomography (CT) scan are directed to referral hospitals, mostly affiliated with medical schools. Most referral centers are equipped with bronchoscopes, endobronchial ultrasound (EBUS), endoscopic ultrasound, multidetector CT scan, magnetic resonance imaging, and positron emission tomography (PET) CT scan instruments. The Korean Health Insurance Review and Assessment encourage chest CT including the upper abdomen, PET-CT, brain CT or magnetic resonance imaging (MRI), EBUS transbronchial needle aspiration or mediastinoscopy (currently infrequently used) of enlarged mediastinal lymph nodes, molecular tests for driver mutations, and subsequent multidisciplinary team (MDT) discussions for treatment planning. The staging guidelines for diagnosis and treatment are based on the clinical stage, using outcomes from CT, PET-CT, and brain MRI for advanced stages. One exception is lung adenocarcinoma manifesting as pure ground-glass opacity

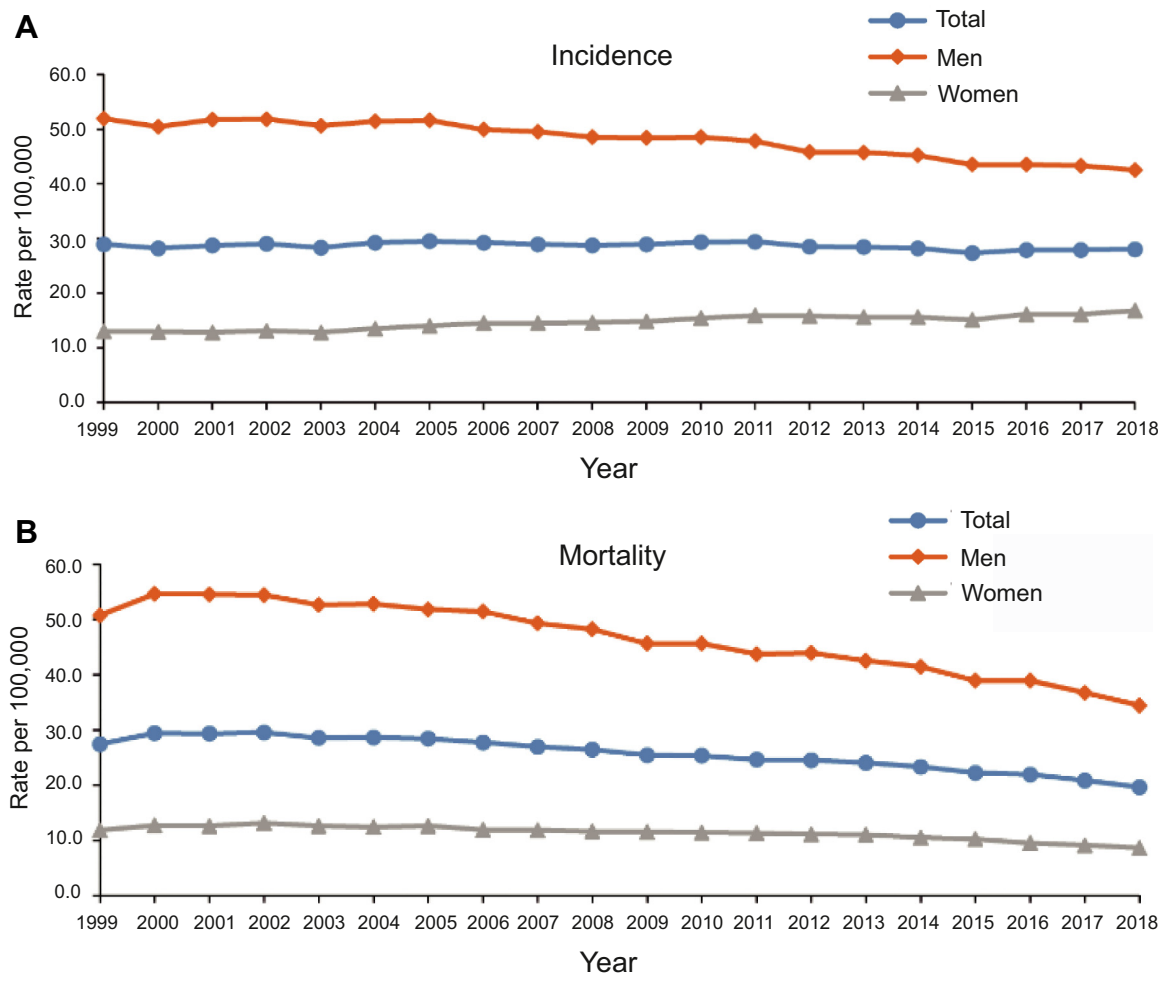


**Figure 2.** *(A)* Overall incidence and *(B)* mortality of lung cancer in South Korea.

nodule (GGN), in which PET-CT and brain MRI are not performed as a staging workup because they provide no additional information with regard to the management of pure GGN adenocarcinoma.[9]

### *Tissue Acquisition*

Tumor biopsy is performed by bronchoscopy or EBUS (47.1%), CT-guided lung biopsy (38.2%), image-guided lymph node biopsy (5.6%), or surgical biopsy (thoracoscopy or mediastinoscopy).[2] Recent advances in our understanding of cancer biology have yielded a new era of molecular-targeted therapy or immunotherapy. Therefore, in addition to comprehensive molecular profiling using sufficient tissue acquired at initial diagnosis, reassessment of tumor tissue at the time of treatment failure has been recommended as a mandatory procedure in a subgroup of patients.[10]

### *MDT Approach*

In many centers, the subsequent treatment planning process is performed through an MDT approach, with the participation of pulmonologists, medical oncologists, thoracic surgeons, radiation oncologists, radiologists, nuclear medicine specialists, and pathologists. Most of the MDTs follow the National Comprehensive Cancer Network and/or European Society for Medical Oncology guidelines according to the actual conditions of their centers.

## Pathology and Molecular Study

Most hospitals in South Korea have pathologists who have specialized in pulmonary pathology in at least one hospital with major provisions. Various samples such as those of biopsy, aspiration, resection, EBUS, and needle aspiration, among others, are used for pathologic diagnosis. Immunohistochemistry is conducted to determine the type of tumor whenever possible. In most institutes, subsequent testing for drug targets is performed after pathologic diagnosis in patients with advanced non-squamous NSCLC.

To apply lung cancer precision medicine, various molecular diagnoses and accompanying diagnoses are

applied in South Korea. Currently, the Korean Cardiopulmonary Pathology Study Group guidelines[11] recommend that *EGFR*, *ALK*, *ROS1*, and *BRAF* tests be performed, whereas *NTRK, MET, RET, HER2*, and *KRAS* tests are recommended when the results of the original four markers are negative or as part of broad testing panels. Currently, *EGFR* (PANAMutyper R EGFR, Cobas EGFR Mutation Test V2, GenesWell ddEGFR Mutation Test), *ALK* (Vysis ALK Break Apart FISH, ALK D5F3 CDx Assay), *ROS1* (AmoyDx ROS1 Gene Fusions Detection Kit), and programmed death-ligand 1 (22C3 PharmDx, SP263 Ventana, SP142 Ventana) are covered by government reimbursement. Moreover, plasma DNA testing for the detection of EGFR mutations has been covered in South Korea since 2018. More importantly, 50% of insurance coverage for next-generation sequencing (NGS) by the government began in 2018, resulting in large institutions implementing a variety of platforms of NGS, such as Illumina, Thermo Fisher Scientific, and self-developed panels. Quality control programs with annual proficiency testing for *EGFR, ALK*, programmed death-ligand 1, and NGS tests are performed by the Korean Society of Pathologists and the Korean Institute of Genetic Testing Evaluations.

## Surgical Approach

Most lung cancer surgeries are performed by dedicated general thoracic surgeons working in academic centers. According to the Korean Association for Thoracic Surgical Oncology, approximately 190 active general thoracic surgeons currently work in 35 hospitals treating patients with lung cancer.

On the basis of the Korean Association for Lung Cancer Registry 2014 data set,[2] the proportion of patients by clinical stage was 29.8%, 8.4%, 18.1%, and 43.3% for clinical stages I, II, III, and IV, respectively. The treatment of stage I NSCLC is surgical resection if tolerated by patients. For stage II, surgery followed by adjuvant chemotherapy is recommended. The treatment strategies of stage III vary among the major hospitals and typically are decided by MDTs. For locally advanced cases in which adjacent organs need to be resected, en bloc surgical resection is performed in centers of excellence. With the recent development of targeted agents and immune checkpoint inhibitors, salvage surgeries are not infrequently performed by experienced surgeons after an in-depth discussion by MDT. Lobectomy remains the most frequently performed resection (75%–80%).[12] With the popularity of LDCT scan screening, small lung cancers are increasingly found, and the number of sublobar resections is increasing. Video-assisted thoracic surgery is adopted in most centers, and on average, 70% (80%–85% in major academic centers) of lung cancer surgeries are performed by video-assisted thoracic surgery. Open thoracotomy is reserved only for locally advanced cases. Robotic-assisted thoracic surgery has begun to be used for lung cancer surgeries and is increasing in popularity.

Surgical resection is advised for small GGNs if they remain persistent or grow in solid portions. Resection often is required to use various localization methods such as hook wires, radio-opaque materials, dye- or indocyanine green-guided CT, or electromagnetic bronchoscopy. Because there is no clear evidence, the extent of surgical resection of these GGN lesions depends on the surgeons' experience and institutional policies.

## Radiation Oncology

Radiotherapy is accessible in 95 radiotherapy centers across the country. Two proton centers are currently available, and two carbon-ion facilities are under construction. Most hospitals have up-to-date linear accelerators for intensity-modulated radiotherapy (IMRT), respiratory-gating, and image-guided radiotherapy. IMRT is the mainstay of radiotherapy techniques in most cancers, and stereotactic ablative radiotherapy is a popular treatment for early or metastatic tumors in various sites. Some centers operate specified machines like tomotherapy, cyberknife, and magnetic resonance imaging guided-linear accelerators. Surface-guided radiotherapy systems are available in several institutions. Quality assurance for radiotherapy instruments and procedures is well-controlled according to strict standard protocols and schedules.

In 2016, approximately 45% of patients with lung cancer received radiotherapy. Lung cancer was the second most frequently treated disease with radiotherapy after breast cancer. IMRT was often applied for lung cancer and stereotactic ablative radiotherapy was most often performed in the lung[13] The Korean Society for Radiation Oncology was associated with 321 radiation oncologists in 2019, and the Korean Radiation Oncology Group has been operating cooperative clinical research in the field of radiotherapy since 2002.

## Systemic Therapy

Approved chemotherapy, targeted agents, and immune checkpoint inhibitors as first- or second-line therapy are detailed in Figure 3, and the reimbursement status for these agents is depicted separately with red dot boxes.

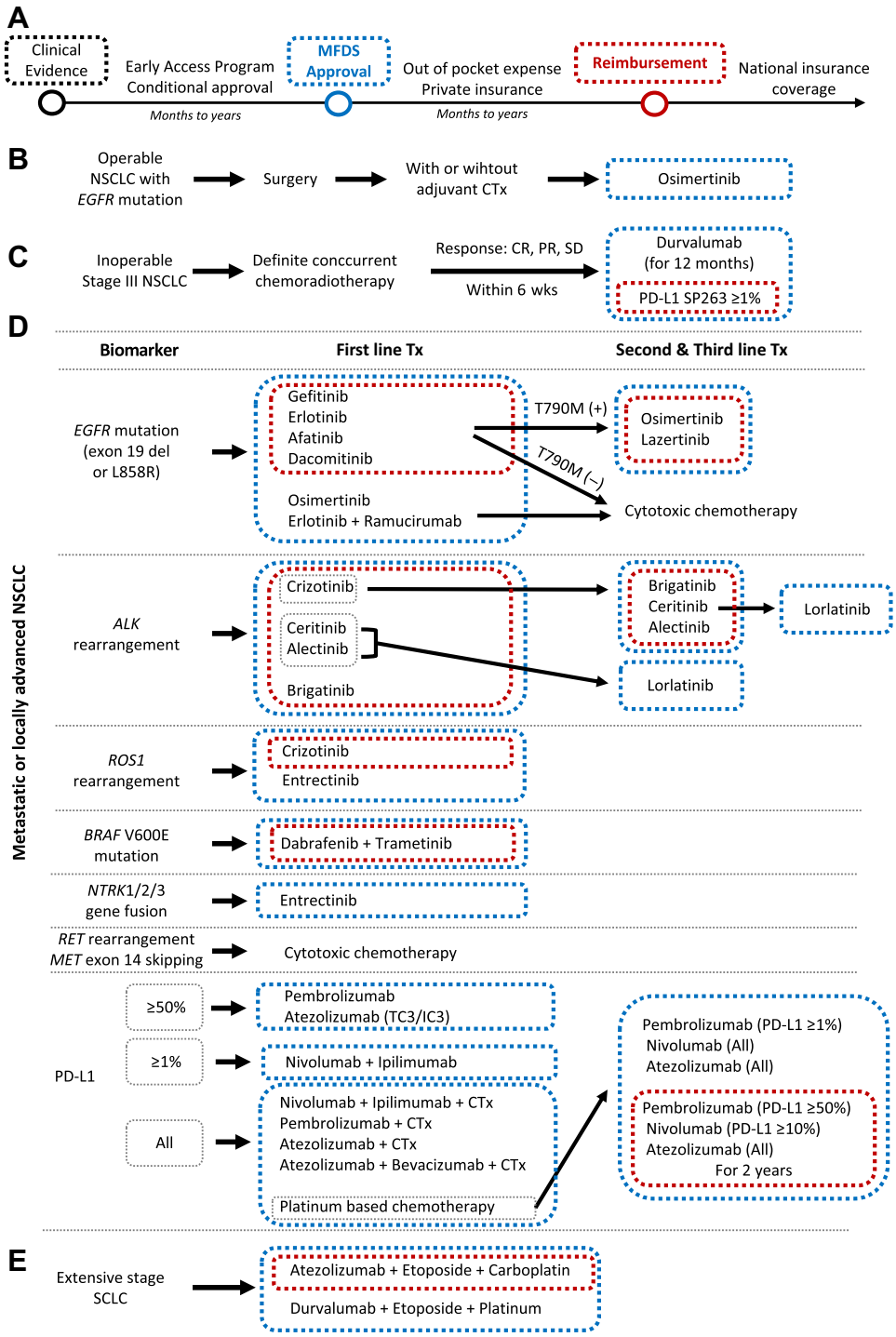


**Figure 3.** Approved and reimbursed status of systemic target therapy and immunotherapy as either the first or the second line of treatment in South Korea. CR, complete response; CTx, chemotherapy; Del, deletion; IC, immune cell; MFDS, Ministry of Food and Drug Safety; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease; TC, tumor cell; Tx, therapy; wks, weeks.

## Challenges and Unique Features of Reimbursement Policies in South Korea

In South Korea, under the single-payer health care system, the systemic treatment option is dependent mainly on drug approval (by the Ministry of Food and Drug Safety [MFDS]) and the national insurance reimbursement status. Once a new drug is approved, pricing and reimbursement (P&R) guidelines for the specific indications are reviewed and determined by the Korean Health Insurance Review and Assessment, National Health Insurance Service, and Korean Ministry of Health

and Welfare for final endorsement on the basis of clinical usefulness, pharmacoeconomic data, the reimbursement status of other countries, global treatment guidelines, and budget impacts. After notification, the drug is accessible to most Koreans and is covered up to 95% of the price by the National Health Insurance Service for patients with lung cancer.

In the clinic, the availability of the drug is limited on the basis of the current status of MFDS approval and the P&R process, which takes several months to years after approval. For drugs under the review process or not approved by MFDS, off-label use is prohibited despite any clinical evidence. To address the gap in clinical benefits and regulation for off-label use, bridging pharmaceutical early-access programs or conditional approval on specific indications is allowed. After MFDS approval (but before reimbursement), the drug has to be paid either as an out-of-pocket expense from the patients or by private insurance. However, once reimbursement is endorsed, universal access to the treatment is available.

Drug approval and reimbursement status largely impact clinical practice. Despite most drugs being approved and reimbursed in a timely manner, there is an inevitable gap between global guidelines and clinical practice in South Korea. For patients with NSCLC, molecular testing is prioritized on indications available for approved and reimbursed drugs such as *EGFR* mutations, *ALK/ROS1* rearrangements, and *BRAF* mutations. Other biomarkers are tested subsequentially after the reimbursed indications for early-access programs, clinical trial enrollments, or conditional approval use. For immunotherapy, although immune checkpoint inhibitors apply to patients with NSCLC for the first or second line of treatment, most patients are treated in a second-line setting after first-line platinum-based chemotherapy on the basis of the reimbursement guidelines.

However, despite the rapid changes of practice guidelines in lung cancers, most of the targeted therapy and immunotherapy are applicable to Korean patients with lung cancer. In addition, the P&R system and regulation in South Korea are evolving to enable early access to drugs.

## CRediT Authorship Contribution Statement

**Sehhoon Park, Chang-Min Choi, Seung-Sik Hwang, Yoon-La Choi, Hyae Young Kim, Young-Chul Kim, Young Tae Kim, Ho Yun Lee, Si Yeol Song:** Resources, Writing - original draft, Writing - review & editing, Visualization.

**Myung-Ju Ahn:** Resources, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration.

## References


1. Jung KW, Won YJ, Hong S, Kong HJ, Im JS, Seo HG. Prediction of cancer incidence and mortality in Korea, 2021. *Cancer Res Treat*. 2021;53:316-322.
2. Choi CM, Kim HC, Jung CY, et al. Report of the Korean Association of Lung Cancer registry (KALC-R), 2014. *Cancer Res Treat*. 2019;51:1400-1410.
3. Chang Y, Kang HY, Lim D, Cho HJ, Khang YH. Long-term trends in smoking prevalence and its socioeconomic inequalities in Korea, 1992-2016. *Int J Equity Health*. 2019;18:148.
4. Gunter R, Szeto E, Jeong SH, Suh S, Waters AJ. Cigarette smoking in South Korea: a narrative review. *Korean J Fam Med*. 2020;41:3-13.
5. Lee SG. Assessing impacts of the WHO FCTC on national legislations: a case study of the Republic of Korea. *Health Policy*. 2017;121:604-612.
6. Hyeon JH, Shelley C, Lee CM. Prevalence and correlates of prior experimentation with e-cigarettes over conventional cigarettes among adolescents: findings from the 2015 Korea Youth Risk Behaviour Web-based Survey. *Tob Prev Cessat*. 2019;5:33.
7. Lee J, Kim Y, Kim HY, et al. Feasibility of implementing a national lung cancer screening program: interim results from the Korean Lung Cancer Screening Project (K-LUCAS). *Transl Lung Cancer Res*. 2021;10:723-736.
8. Hwang EJ, Goo JM, Kim HY, Yi J, Yoon SH, Kim Y. Implementation of the cloud-based computerized interpretation system in a nationwide lung cancer screening with low-dose CT: comparison with the conventional reading system. *Eur Radiol*. 2021;31:475-485.
9. Cho H, Lee HY, Kim J, et al. Pure ground glass nodular adenocarcinomas: are preoperative positron emission tomography/computed tomography and brain magnetic resonance imaging useful or necessary? *J Thorac Cardiovasc Surg*. 2015;150:514-520.
10. Yoon HJ, Lee HY, Lee KS, et al. Repeat biopsy for mutational analysis of non-small cell lung cancers resistant to previous chemotherapy: adequacy and complications. *Radiology*. 2012;265:939-948.
11. Chang S, Shim HS, Kim TJ, et al. Molecular biomarker testing for non-small cell lung cancer: consensus statement of the Korean Cardiopulmonary Pathology Study Group. *J Pathol Transl Med*. 2021;55:181-191.
12. Yoo JE, Han K, Shin DW, et al. Conditional relative survival and competing mortality in patients who underwent surgery for lung cancer: a nationwide cohort study. *Int J Cancer*. 2021;148:626-636.
13. Kim E, Jang WI, Kim MS, et al. Clinical utilization of radiation therapy in Korea, 2016. *J Radiat Res*. 2020;61:249-256.