Lung Cancer in Republic of China

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Introduction

Located in the west Pacific between Japan and the Philippines, the Republic of China has a population of more than 23 million people. Malignant tumors are the leading cause of death in the Republic of China, and lung cancer is the main cause of death for male and female individuals with cancers.[1] In 2018, the five-year survival rate of lung cancer was approximately 26.5%. Between 1998 and 2018, the number of lung cancer deaths increased from 5749 to 9388. Approximately 70% of the 14,282 individuals diagnosed as having cancers of the lung, bronchus, or trachea in 2017 had stage III or IV lung cancer. These statistics reveal the severe threat of lung cancer to the health and well-being of the Taiwanese people.[2]

In 1995, the Taiwanese government implemented the National Health Insurance (NHI) program to improve the efficiency, accessibility, and coverage of health care. The program is compulsory for all citizens, regardless of age, sex, or employment status.[3] In 2019, the satisfaction rate of the general public toward the NHI was 89.7%.[4] The program provides comprehensive medical services for individuals with lung cancer, including those who are economically disadvantaged.

Epidemiology

Of all malignancies in the Republic of China, 12.8% were in the lung, bronchus, or trachea, accounting for 19.2% of all cancer deaths in 2017. From 1986 to 2017,[2,5] the overall age-standardized incidence of lung cancer in the Republic of China increased from 16.5 to 37 cases per 100,000. The incidence in men and women increased from 22.5 to 43.5 and from 9.5 to 31.6 cases per 100,000, respectively. The age-standardized mortality rate increased from 21 to 23.1 deaths per 100,000. In men and women, this rate increased from 28 to 31.6 and from 13.5 to 15.9 deaths per 100,000, respectively (Fig. 1). The incidence of lung cancer has not decreased with time, indicating that much remains to be done to prevent and treat this disease. The age-standardized incidence of lung cancer by regions in the Republic of China is found in Figure 2,[6] ranging from 16.5 to 42.4 per 100,000 in 2017. The increase in mortality rate over time underscores the severity of its threat to public health and reveals the unmet needs for its effective long-term treatment. Furthermore, trends in the survival rate of patients with lung cancer shed light on this problem. Of the 10 most common cancers in the Republic of China, lung cancer has the lowest overall 5-year survival rate;

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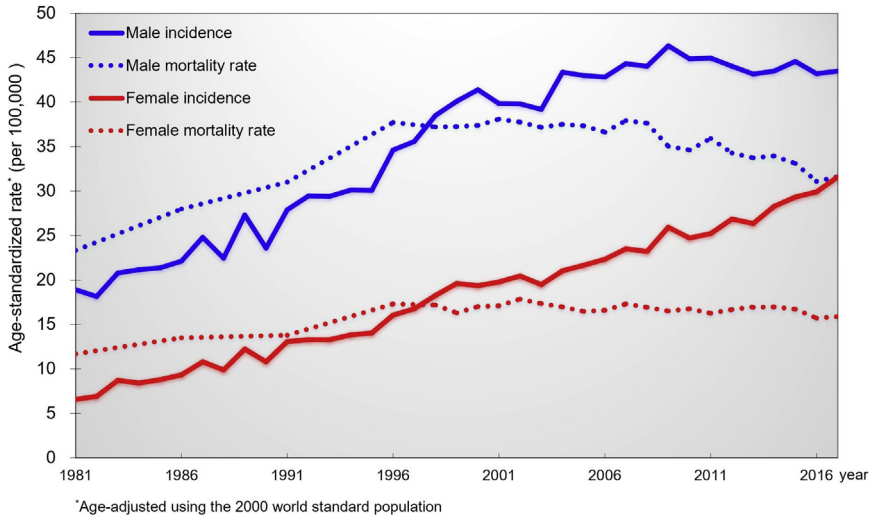

Figure 1. Age-standardized incidence and mortality of lung cancer in the Republic of China (1981–2017).

from 2012 to 2016, this rate (among patients with stages I to IV lung cancer) was 75.2%, 45.2%, 24%, and 8% respectively,[7,8] indicating that only a relatively small proportion of approximately 10% to 30% of patients achieve remission. In other words, approximately 70% to 90% of the patients with lung cancer will die within 5 years. Thus, early detection (e.g., through effective screening) and surgical treatment are essential to reduce the rate of mortality. Moreover, these would help improve the overall survival rate.

With the passage of the Tobacco Hazards Prevention Act in 1997 and the promotion of smoking cessation, the adult smoking rate in the Republic of China dropped from 21.9% in 2008 to 13.0% in 2018, a substantial

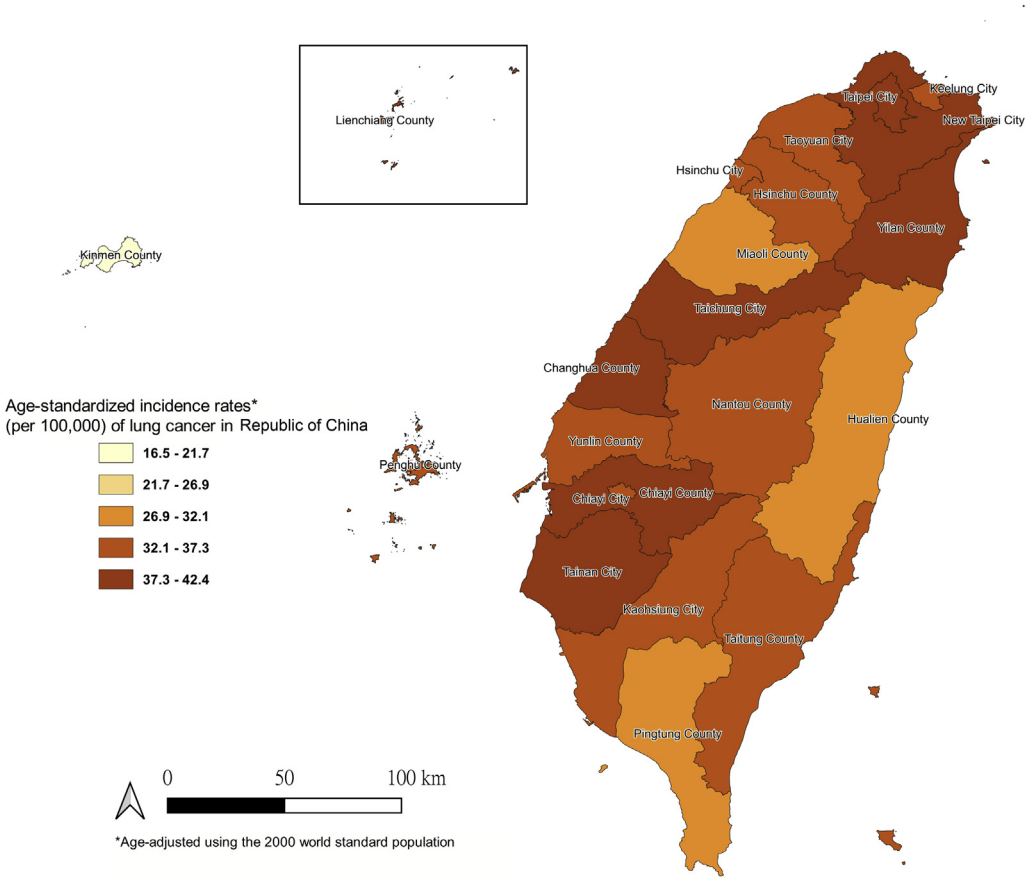

Figure 2. Age-standardized incidence rates of lung cancer by regions in the Republic of China, 2017.

reduction of 40.6%. More than half of the patients with lung cancer are nonsmokers.[9] Nevertheless, nearly 3 million individuals remain exposed to tobacco smoke.[10] In general, smokers have a higher risk of lung cancer than nonsmokers, and women have a higher risk than men. The risk of pulmonary squamous cell carcinoma is up to 5 to 10 times higher in smokers than in nonsmokers and that of pulmonary adenocarcinoma is up to 1.5 to 3 times higher.[11,12] Therefore, efforts to reduce the smoking rate and secondhand smoke exposure rate must continue.

Screening

Screening is one of the most effective ways to control cancer. No screening tool for lung cancer had been proven effective until 2011, when the National Lung Screening Trial (NLST) reported that annual screening through low-dose computed tomography (LDCT) of the chest resulted in significantly reduced lung cancer mortality.[13] Its effectiveness was confirmed in the Nederlands-Leuvens Longkanker Screenings Onderzoek trial.[14]

To the best of our knowledge, the first large lung cancer screening program in the Republic of China was conducted between 1979 and 1986. It was a collaborative program, initially conducted by the Taipei Veterans General Hospital and the S.Y. Dao Cancer Prevention Foundation and later joined by the Lung Cancer Foundation in Memory of Kwang-Shun Lu and the Republic of China Anti-Tuberculosis Association in 1982. Eligible participants were aged 40 years or over, had a smoking history, and had no history of suspected or known lung cancer. The screening procedures comprised chest radiography and sputum cytology performed every 4 months. In the first 3 years, the program was hospital based. It was later changed to a community-based screening program performed by medical professionals operating diagnostic equipment in mobile radiograph vehicles. In the first round, 47 diagnoses of lung cancer were made among 19,694 participants.[15] In the 8-year study period, 94 diagnoses of lung cancer were made among 111,153 participants.[16]

On the basis of the NLST findings, several U.S. medical societies recommended LDCT lung cancer screening in high-risk populations between 2011 and 2013. In the Republic of China, a task force for this purpose was organized with collaboration among three medical societies (i.e., the Taiwan Society of Pulmonary and Critical Care Medicine, the Radiological Society of the Republic of China, and the Taiwan Lung Cancer Society) in 2013. The consensus they reached, which was based on evidence from the NLST, recommends annual LDCT screening in heavy smokers. Furthermore, the task force acknowledges that with approximately 50% of patients newly diagnosed as having lung cancer being nonsmokers in the Republic of China, lung cancer in nonsmokers is a major public health problem. An LDCT study on nonsmokers is suggested. The prospective, single-arm Taiwan Lung Cancer Screening in Never Smoker Trial (TALENT), sponsored by the Ministry of Health and Welfare (MOHW), was launched in 2014. This project aims to develop a model of lung cancer risk in nonsmokers, establish the protocol for future LDCT screening programs, and provide evidence of cost-effectiveness. It plans to enroll 12,000 nonsmokers with at least one of the following lung cancer risk factors: a family history of lung cancer (less than or equal to third-degree relatives), a history of secondhand smoke exposure, chronic lung disease (e.g., tuberculosis and chronic obstructive pulmonary disease), exposure to cooking smoke (cooking index $\geq$ 110), and cooking without using a ventilation hood. The final patient was enrolled in July 2019. The first-round results are expected to be available before the end of 2020. It is hoped that its results can inform not only public health policy makers in the Republic of China but also medical societies or health authorities worldwide.

Diagnosis and Staging

As is done in other countries, diagnosis and staging of lung cancer in the Republic of China involve various invasive and noninvasive modalities, including computed tomography (CT), 18F-fluoro-2-deoxy-D-glucose positron emission tomography, magnetic resonance imaging, and transthoracic or transbronchial tissue biopsy.

In the Republic of China, biopsy method is typically based on the availability and accessibility of the modality. Radial-probe endobronchial ultrasound-guided biopsy with or without fluoroscopy assistance is widely practiced for peripheral lung lesions.[17,18] In addition, convex-probe endobronchial ultrasound, used for the diagnosis and staging of central thoracic or lymph node lesions, is available in most of the top 10 hospitals that specialize in lung cancer treatment. This technique is unique in that it narrows the differential diagnosis between lymph node metastasis and tuberculosis lymphadenopathy in tuberculosis-prevalent regions, such as the Republic of China.[19] In a few medical centers in northern Republic of China, transbronchial cryoprobe biopsy is also performed in cases of tumors with central airway invasion.[20] Notably, these transbronchial biopsy procedures are mostly conducted under conscious sedation by pulmonologists rather than under general anesthesia by surgeons.[21] CT- or ultrasound-guided core needle biopsy is the widely available transthoracic

approach. Physicians may choose such methods in cases in which the lesions are close to the chest wall. Furthermore, they are used when transbronchial approaches are not available. In cases in which the sole lesion is pleural effusion, thoracoscope-assisted pleural biopsy (pleuroscopy) may be used.[22]

Contrast-enhanced CT for thoracic and abdominal regions are a routine, including a whole-body 18F-fluoro-2-deoxy-D-glucose positron emission tomography scans. Lung cancer diagnosis typically involves assessment of brain metastasis, for which the technique used depends on the availability of equipment at a hospital. In general, magnetic resonance imaging is standard practice. CT scan may also be used. In most of the top 10 hospitals, when clinical staging for particular cases is challenging or controversial, a multidisciplinary meeting of oncologists, pulmonologists, radiologists, pathologists, and surgeons is held to reach a consensus.

Pathology

The pathologic diagnosis of lung cancer in the Republic of China follows the recommendations in the 2015 *WHO Classification of Tumors of the Lung, Pleura, Thymus, and Heart*.[23] In more than 96% of the cases, tumor classification is confirmed through either or both histologic and cytologic examination.[2] For small biopsy specimens, a limited initial panel of immunohistochemical markers comprising one squamous marker and one glandular differentiation marker (e.g., p40 and TTF-1, respectively) is recommended for NSCLC. For resection specimens, a report template or checklist is issued by the Taiwan Society of Pathology to guide pathologists.[24]

After pathologic diagnosis, molecular testing for targetable mutations is routinely performed in patients with advanced nonsquamous NSCLC. The most prevalent targetable mutation, *EGFR* mutation can be identified in approximately 55% of patients with lung adenocarcinoma in the Republic of China.[25] The NHI reimburses testing for *EGFR* mutations in patients with advanced nonsquamous NSCLC. According to a 2019 survey by the Taiwan Society of Pathology, commercial real-time polymerase chain reaction assays are the principal testing methods for such mutations in pathology laboratories (Taiwan Society of Pathology, unpublished data, 2019). In patients with *EGFR* wild-type lung cancer, testing for *ALK* rearrangement is also routinely performed. Approximately 10% of patients with *EGFR* wild-type lung adenocarcinoma are positive for *EML4-ALK* rearrangements in the Republic of China.[25] Most pathology laboratories use immunohistochemistry (IHC) with the VENTANA ALK (D5F3) CDx Assay (VENTANA Medical Systems, Oro Valley, AZ). Fluorescence in situ hybridization for *ALK* rearrangement is performed in only a few laboratories (Taiwan Society of Pathology, unpublished data, 2019). For *ROS1* rearrangement, IHC is most often used as a screening tool, followed by confirmatory fluorescence in situ hybridization or next-generation sequencing (NGS). Testing for other less common targetable mutations, such as *BRAF*, *NTRK*, *RET*, and *MET* alterations, is usually performed using targeted gene NGS panels. Academic institutions, medical centers, and local or international biotechnology companies alike offer numerous clinically oriented in-house or commercial NGS panels. However, they are not reimbursed by the NHI or supported by pharmaceutical industry funds.

For patients with *EGFR*, *ALK*, and *ROS1* wild-type NSCLCs, programmed death-ligand 1 (PD-L1) IHC testing is reimbursed by the NHI (one test per lifetime). Most pathology laboratories use PD-L1 assays approved by the Food and Drug Administration (FDA) in the United States. A 2019 survey by the Taiwan Society of Pathology revealed that the PD-L1 IHC 22C3 pharmDx (Dako, Carpinteria, CA) is the most common assay provided by participating pathology laboratories and that 40% of pathology laboratories offer more than one type of FDA-approved PD-L1 assays (Taiwan Society of Pathology, unpublished data, 2019).

Most molecular testing laboratories are accredited by the Taiwan Accreditation Foundation ISO 15189 or the College of American Pathologists and actively participate in external quality assurance programs. The Taiwan Society of Pathology offers annual molecular proficiency testing for *EGFR* mutation, *ALK* IHC, and PD-L1 IHC for lung cancer.

Surgical Approaches

With the rapid development of technology, minimally invasive surgery has become possible and beneficial in all fields of surgery.[2,26] In the Republic of China, almost 90% of patients with thoracic diseases receive video-assisted thoracoscopic surgery as a primary treatment.[27] In a study by Chen et al.,[28] nonintubated thoracoscopic lobectomy was found to be technically feasible and equally safe as lobectomy performed with intubation in selected patients. In 2011, the NLST Research Group reported that LDCT screening can reduce lung cancer mortality by approximately 20%.[13] Recent years have found a rise in the rate of this approach and subsequently a substantial increase in cases with pulmonary ground-glass opacity (GGO). To remove these small pulmonary lesions, precise localization is mandatory. Techniques include chest CT-guided localization with dye, hook wire, micro coil, and indocyanine green; electromagnetic navigation bronchoscopy localization; or localization in a hybrid operation theater.[29,30] Results from

a propensity score-matched analysis comparing electromagnetic navigation- and CT-guided methods of percutaneous transthoracic localization revealed similar results.[31] The authors concluded that the two methods were comparable for the preoperative localization of small lung nodules before uniportal video-assisted thoracoscopic surgery.

Because patients with small pulmonary GGO lesions have a favorable prognosis, sublobar resection with or without mediastinal lymph node dissection may be appropriate to preserve pulmonary function and avoid complications. In a 2020 study by Lin et al.,[32] the consolidation-to-tumor ratio (CTR) was found to be a satisfactory preoperative predictor of lymphatic metastasis in patients with lung cancer with GGO lesions. For patients in whom the GGO lesions present CTR greater than or equal to 50%, radical resection is mandatory to avoid local recurrence. By contrast, for patients in whom their GGO lesions present CTR less than 50%, lymphadenectomy may not be necessary because lymph node metastasis is unlikely.[32]

Radiation Approaches

Radiotherapy is highly accessible in the Republic of China, offered by 333 board-certified radiation oncologists at 81 hospitals. The health care system is equipped with more than 143 medical linear accelerators, six CyberKnifes, nine GammaKnifes, 20 TomoTherapy, and 37 remote-afterloading brachytherapy systems in the Republic of China.

Particle therapy, which has long been available at two proton centers, has rapid, widespread embracement in recent years. A number of proton centers are under construction, all equipped with the latest image-guiding and pencil-beam systems. A carbon ion particle therapy system is also under construction, with a planned launch date in 2022. Reactor-based boron neutron capture therapy is available for compassionate use.[33]

Intensity modulated radiotherapy, including volumetric-modulated arc therapy, is covered by the NHI and has become standard of care for thoracic radiotherapy. Stereotactic body radiation therapy or stereotactic ablative radiotherapy is also covered for medically inoperable early stage lung cancer.

Regulated by the Cancer Control Act,[34] radiotherapy administration is mostly dependent on treatment guidelines. According to the 2017 Cancer Registry Annual Report of the Health Promotion Administration of the MOHW,[2] 47.7% of the patients with stage IIIB NSCLC received radiotherapy as part of their first-course treatment, with 29.1% receiving concurrent chemoradiotherapy. Although evidence of locally aggressive treatment for oligometastatic lung cancer is increasing, the NHI has also started to reimburse high-precision radiotherapy for oligometastatic tumors.

Systemic Therapy (Targeted Therapy)

The Republic of China has participated or played leading roles in early phase and late-phase development of most molecular-targeted agents, such as gefitinib, afatinib, osimertinib, alectinib, ceritinib, brigatinib, lorlatinib, crizotinib, capmatinib, and tepotinib.[35–44] The treatment of advanced or metastatic NSCLC is in line with many international guidelines, such as the Pan-Asian–adapted European Society for Medical Oncology Clinical Practice Guidelines, which are endorsed by oncology societies in many Asian countries, including the Taiwan Oncology Society.[45] The reimbursement guidance or scope of benefits for anticancer drugs is defined by the Republic of China's single-payer NHI system.[3] EGFR tyrosine kinase inhibitors (e.g., gefitinib, erlotinib, and afatinib) are reimbursed as first-line therapy for advanced or metastatic *EGFR* mutation-positive NSCLC (stages IIIB, IIIC, and IV; Table 1). Dacomitinib is reimbursed for only advanced or metastatic *EGFR* exon 21 L858R or exon 19 deletion-positive NSCLC without central nervous system metastasis (stages IIIB, IIIC, and IV). Osimertinib is reimbursed as first-line treatment for only metastatic *EGFR* exon 19 deletion-positive NSCLC (stage IV) without central nervous system metastasis or as a second-line treatment after failure of EGFR tyrosine kinase inhibitors therapy, with proven presence of *EGFR* T790M mutation through rebiopsy. The diagnosis of *EGFR* mutation must be made using NHI-reimbursed tissue-based companion in vitro diagnostics. Osimertinib reimbursement requires preapproval and renewal every 3 months through the submission of imaging evidence of nonprogression. Bevacizumab plus erlotinib and ramucirumab plus erlotinib both received regulatory approval as first-line treatments for advanced *EGFR* mutation-positive NSCLC. However, they are not covered under the NHI system. Afatinib is reimbursed as a second-line treatment for platinum-pretreated advanced or metastatic lung squamous cell carcinoma.

ALK fusion is usually detected early through IHC. ALK inhibitors, crizotinib, alectinib, and ceritinib, are reimbursed as first-line treatments for advanced or metastatic *ALK*-positive NSCLC. However, alectinib and ceritinib have been approved but are not reimbursed as second-line treatments for crizotinib-pretreated, *ALK*-positive NSCLC, for which the only reimbursed drug is brigatinib. Lorlatinib has been approved for the treatment of alectinib or ceritinib-pretreated, *ALK*-positive NSCLC but is reimbursed only in patients with brain metastasis. Notably, the reimbursement of ALK inhibitors requires preapproval and renewal every 3

Table 1. Availability (Reimbursement) of Systemic-Targeted Therapies in the Republic of China

Targeted therapies	Availability
Indication	
Gefitinib, erlotinib, or afatinib, first line, *EGFR* mutation-positive	Available
Dacomitinib, first line, *EGFR* mutation-positive (*EGFR* exon 21 L858R mutation and exon 19 deletion)	Available with restriction
Osimertinib, second line, post-EGFR TKI, *EGFR* T790M-positive	Available
Osimertinib, first line, *EGFR* mutation-positive (*EGFR* exon 21 L858R mutation and exon 19 deletion)	Available with restriction
Crizotinib, first line, *ALK*-positive	Available
Crizotinib, any line, *ROS1*-positive	Available
Alectinib or ceritinib, first line, *ALK*-positive	Available
Alectinib or ceritinib, second line, *ALK*-positive, postcrizotinib	N/A
Brigatinib, second line, *ALK*-positive, postcrizotinib	Available
Lorlatinib, second line, *ALK*-positive, postalectinib, or ceritinib	Available with restriction
Dabrafenib plus trametinib, *BRAF* V600E–positive	N/A
Entrectinib or larotrectinib, *NTRK* fusion–positive	N/A
Molecular testing	
EGFR mutation, first line	Available
EGFR T790M mutation, second line	N/A
ALK rearrangement	Available (IHC only)
ROS1 rearrangement	N/A
BRAF V600E mutation	N/A
NTRK fusion	N/A

IHC, immunohistochemistry; N/A, not available; TKI, tyrosine kinase inhibitor.

months through the submission of imaging evidence of nonprogression. Both crizotinib and entrectinib have been approved for advanced or metastatic *ROS1*-positive NSCLC, but only crizotinib is reimbursed. Combination therapy of dabrafenib plus trametinib has been approved but is not reimbursed for the treatment of advanced or metastatic *BRAF* V600E-positive NSCLC. Larotrectinib and entrectinib have received approval for treating metastatic *NTRK* fusion-positive NSCLC but are not reimbursed. As of September 28, 2020, no drug has received approval for the treatment of *MET* exon 14 skipping-, *HER2* mutation-positive, or *RET* fusion-positive NSCLC.

As mentioned previously, the diagnostics for *ROS1* rearrangement, *NTRK* fusion, *BRAF* V600E mutation, *MET* exon 14 skipping, *HER2* mutation, and *RET* fusion, such as tissue NGS, are not reimbursed in the Republic of China. We encourage patients with wild-type *EGFR* and *ALK*-negative tumors to participate in clinical research programs or clinical trials that provide tissue or plasma NGS tests to detect potentially targetable genetic alterations. The Taiwan Lung Cancer Consortium is a platform conducting tissue tests and clinical trials, especially investigator-initiated trials.[46] It has close connections with domestic lung cancer care experts and engages in international collaboration with consortiums in other countries such as Singapore and Australia.

Systemic Therapy (Chemotherapy and Immunotherapy)

In the Republic of China, molecular diagnosis is routinely performed for every patient newly diagnosed as having advanced adenocarcinoma and is conditionally implemented in those with squamous cell carcinoma. Patients with tumors lacking driver mutations typically receive chemotherapy and occasionally immunotherapy according to the guidelines for approval and reimbursement of the FDA and NHI Administration of the MOHW.[3] Platinum-based doublet chemotherapy is a

Table 2. Chemotherapy Availability for Patients With Different Types of Pan-Negative Advanced Lung Cancer (Covered Under the NHI Program)

Nonsquamous NSCLC	Squamous cell carcinoma	Small cell carcinoma
Platinum	Platinum	Platinum
Pemetrexed	Gemcitabine	Etoposide
Gemcitabine	Taxane	Topotecan
Taxane	Vinorelbine	
Vinorelbine	TS-1	
TS-1		

NHI, National Health Insurance.

Table 3. Immunotherapy Availability for Patients With Pan-Negative Advanced Lung Cancer Whose PD-L1 TPS Are Greater Than or Equal to 50% (Covered Under the NHI Program)

NSCLC	SCLC
Pembrolizumab (first line and later line)	
Nivolumab (second line or later line)	N/A
Atezolizumab (second line or later line)	

N/A, not available; NHI, National Health Insurance; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

standard first-line treatment for pan-negative NSCLC. In patients with nonsquamous NSCLC, four to six cycles of platinum-pemetrexed treatment followed by pemetrexed maintenance is preferred. Currently used chemotherapeutics comprise platinum, pemetrexed, gemcitabine, vinorelbine, taxane, and TS-1. The combination of chemotherapy with either or both anti-angiogenetic agents and immunotherapy as first-line treatment is approved by the FDA of the MOHW but not reimbursed by the NHI. Thus, such treatments are infrequently administered. In April 2019, reimbursement for pembrolizumab was granted as a standard first-line treatment for patients with *EGFR/ALK/ROS1* wild-type advanced NSCLC whose PD-L1 tumor proportion scores are greater than or equal to 50% according to the Dako 22C3 (Dako) or SP263 (VENTANA Medical Systems) IHC test results.[3] For the other patients with nonresectable advanced or metastatic NSCLC whose PD-L1 expression is greater than or equal to 50% and for whom platinum-based chemotherapy has failed, immunotherapy (e.g., with programmed cell death protein-1/PD-L1 inhibitors, nivolumab, pembrolizumab, and atezolizumab) can be used as second-line or third-line treatment according to PD-L1 test results. Durvalumab is approved for consolidation therapy in patients with advanced-stage III NSCLC and for combination therapy in patients with advanced SCLC but is not reimbursed. Tables 2 and 3 present the treatment options for patients with *EGFR/ALK/ROS1* wild-type advanced lung cancer under the NHI benefit package.

Conclusions

Both the incidence and mortality rate of lung cancer in the Republic of China are high. Exposure to tobacco smoke is an important risk factor for this disease. Therefore, continual efforts for reducing both smoking rate and secondhand smoke exposure rate are imperative. An ongoing screening trial for lung cancer in nonsmokers, a major public health problem, will be used to develop protocols for future lung cancer screening programs. Under the NHI system, comprehensive medical services, including precision pathology diagnosis, modern thoracic surgery, advanced systemic treatments, and contemporary radiotherapy can be efficiently provided to the entire population, with constant consideration of new, cost-effective treatments. The Republic of China has actively participated or played key roles in numerous clinical trials of systemic therapies. Through close connections between domestic lung cancer care providers and international collaboration, more efforts and resources can be implemented to prevent lung cancer and improve the outcome of this fatal disease.

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References

1. Ministry of Health and Welfare, Taiwan. Cause of death statistics. https://www.mohw.gov.tw/lp-4650-2.html. Accessed October 1, 2020.
2. Health Promotion Administration. Ministry of Health and Welfare, Taiwan. 2017 Cancer Registry Annual Report. https://www.hpa.gov.tw/Pages/ashx/File.ashx?FilePath=~/File/Attach/12235/File_13854.pdf. Accessed October 1, 2020.
3. National Health Insurance Administration. Ministry of Health and Welfare, Taiwan. National Health Insurance. https://www.nhi.gov.tw/English/Default.aspx. Accessed October 1, 2020.
4. National Health Insurance Administration, Ministry of Health and Welfare. Public satisfaction with National Health Insurance System in 2019. https://www.nhi.gov.tw/English/News_Content.aspx?n=996D1B4B5DC48343&sms=F0EAFEB716DE7FFA&s=B8D5EE50036E8B4D. Accessed October 1, 2020.
5. Chen CJ, Chen KY, Li YJ. *Epidemiological characteristics and preventive strategies of cancers in Taiwan*. S.Y. Dao Cancer Prevention Foundation; 2011.
6. Health Promotion Administration, Ministry of Health and Welfare, Taiwan. Cancer Registry Online Interactive Query system. https://cris.hpa.gov.tw/pagepub/Home.aspx. Accessed October 1, 2020.
7. Taiwan Caner Registry. Five-year relative survival rate for cancer. http://tcr.cph.ntu.edu.tw/main.php?Page=A5B3. Accessed October 1, 2020.
8. Health Promotion Administration, Ministry of Health and Welfare, Taiwan. Cancer quality information management systems. https://pfp.hpa.gov.tw/security/login.aspx?target=/. Accessed October 1, 2020.
9. Yang P. National lung screening program in Taiwan. *J Thorac Oncol*. 2018;13(suppl):S274-S275.
10. Health Promotion Administration, Ministry of Health and Welfare, Taiwan. Survey of smoking behavior in Taiwan. https://www.hpa.gov.tw/Pages/Detail.aspx?nodeid=1718&pid=9913. Accessed October 1, 2020; 2018.
11. Health Promotion Administration, Ministry of Health and Welfare, Taiwan; 2016 Cancer Registry Annual

Report. https://www.hpa.gov.tw/Pages/ashx/File.ashx?FilePath=~/File/Attach/10227/File_11644.pdf. Accessed October 1, 2020.
12. Health Promotion Administration, Ministry of Health and Welfare, Taiwan. Survey of smoking behavior in Taiwan. https://www.hpa.gov.tw/Pages/Detail.aspx?nodeid=1718&pid=9913. Accessed October 1, 2020; 2016.
13. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365:395–409.
14. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N Engl J Med*. 2020;382:503–513.
15. Hsing CT. *Bull S.Y. Dao Mem Fund*. 1982;18:20–22.
16. SY, DAO Cancer Prevention Foundation. Lung cancer screening from 1979 to 1986. http://www.sydao.org.tw/intro/intro.asp. Accessed October 1, 2020.
17. Kuo CH, Lin SM, Chen HC, Chou CL, Yu CT, Kuo HP. Diagnosis of peripheral lung cancer with three echoic features via endobronchial ultrasound. *Chest*. 2007;132:922–929.
18. Huang CT, Tsai YJ, Ho CC, Yu CJ. Radial endobronchial ultrasound-guided transbronchial biopsy for peripheral pulmonary malignancy: biopsy- or brushing-first? *BMC Pulm Med*. 2019;19:193.
19. Kuo CH, Chen HC, Chung FT, et al. Diagnostic value of EBUS-TBNA for lung cancer with non-enlarged lymph nodes: a study in a tuberculosis-endemic country. *PLoS One*. 2011;6:e16877.
20. Chou CL, Wang CW, Lin SM, et al. Role of flexible bronchoscopic cryotechnology in diagnosing endobronchial masses. *Ann Thorac Surg*. 2013;95:982–986.
21. Hsieh CH, Lin TY, Wang TY, et al. The safety and efficacy of alfentanil-based induction in bronchoscopy sedation: a randomized, double-blind, controlled trial. *Medicine (Baltimore)*. 2016;95:e5101.
22. Chen CH, Cheng WC, Wu BR, et al. Feasibility and safety of pleuroscopic cryobiopsy of the pleura: a prospective study. *Can Respir J*. 2018;2018:6746470.
23. Travis WD, BE BAP, Marx A, Nicholson AG. *WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart*. Lyon, France: International Agency for Research on Cancer; 2015.
24. Taiwan Society of Pathology. Lung cancer checklist. http://www.twiap.org.tw/data/content.asp?ID=1214&FDType=11. Accessed October 1, 2020.
25. Hsu KH, Ho CC, Hsia TC, et al. Identification of five driver gene mutations in patients with treatment-naive lung adenocarcinoma in Taiwan. *PLoS One*. 2015;10:e0120852.
26. Barta JA, Powell CA, Wisnivesky JP. Global epidemiology of lung cancer. *Ann Glob Health*. 2019;85:8.
27. Liu CY, Hsu PK, Chien HC, Hsieh C, Ting C, Tsou M. Tubeless single-port thoracoscopic sublobar resection: indication and safety. *J Thorac Dis*. 2018;10:3729–3737.
28. Chen JS, Cheng YJ, Hung MH, Tseng YD, Chen KC, Lee YC. Nonintubated thoracoscopic lobectomy for lung cancer. *Ann Surg*. 2011;254:1038–1043.
29. Hsu PK, Wu YC. The feasibility of electromagnetic navigation-guided percutaneous microcoil localization for thoracoscopic resection of small pulmonary nodules. *J Thorac Cardiovasc Surg*. 2019;157:e211–e214.
30. Lin CW, Ko HJ, Yang SM, et al. Computed tomography-guided dual localization with microcoil and patent blue vital dye for deep-seated pulmonary nodules in thoracoscopic surgery. *J Formos Med Assoc*. 2019;118:979–985.
31. Hung CT, Chen CK, Chang YY, et al. Electromagnetic navigation-guided versus computed tomography-guided percutaneous localization of small lung nodules before uniportal video-assisted thoracoscopic surgery: a propensity score-matched analysis. *Eur J Cardiothorac Surg*. 2020;58(suppl 1):i85–i91.
32. Lin YH, Chen CK, Hsieh CC, et al. Lymphadenectomy is unnecessary for pure ground-glass opacity pulmonary nodules. *J Clin Med*. 2020;9:672.
33. Jiang SH, Hsueh Liu YW, Chou FI, et al. The overview and prospects of BNCT facility at Tsing Hua Open-pool reactor. *Appl Radiat Isot*. 2020;161:109143.
34. Ministry of Health and Welfare. Cancer control act. https://law.moj.gov.tw/ENG/LawClass/LawAll.aspx?pcode=L0070008. Accessed October 1, 2020.
35. Yang JC, Shih JY, Su WC, et al. Afatinib for patients with lung adenocarcinoma and epidermal growth factor receptor mutations (LUX-Lung 2): a phase 2 trial. *Lancet Oncol*. 2012;13:539–548.
36. Jänne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor–resistant non-small-cell lung cancer. *N Engl J Med*. 2015;372:1689–1699.
37. Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study [published correction appears in Lancet Oncol. 2019;20:e10]. *Lancet Oncol*. 2018;19:1654–1667.
38. Paik PK, Felip E, Veillon R, et al. Tepotinib in non-small-cell lung cancer with MET Exon 14 skipping mutations. *N Engl J Med*. 2020;383:931–943.
39. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361:947–957.
40. Yang JC, Ou SI, De Petris L, et al. Pooled systemic efficacy and safety data from the pivotal phase II studies (NP28673 and NP28761) of alectinib in ALK-positive non-small cell lung cancer. *J Thorac Oncol*. 2017;12:1552–1560.
41. Soria JC, Tan DSW, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study [published correction appears in *Lancet*. 2017;389:908]. *Lancet*. 2017;389:917–929.
42. Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2018;379:2027–2039.
43. Wu YL, Yang JC, Kim DW, et al. Phase II study of crizotinib in East Asian patients with ROS1-positive advanced non-small-cell lung cancer. *J Clin Oncol*. 2018;36:1405–1411.

44. Bang YJ, Su WC, Schuler M, et al. Phase 1 study of capmatinib in MET-positive solid tumor patients: dose escalation and expansion of selected cohorts. *Cancer Sci*. 2020;111:536–547.
45. Wu YL, Planchard D, Lu S, et al. Pan-Asian adapted Clinical Practice Guidelines for the management of patients with metastatic non-small-cell lung cancer: a CSCO-ESMO initiative endorsed by JSMO, KSMO, MOS, SSO and TOS. *Ann Oncol*. 2019;30:171–210.
46. Taiwan ClinicalTrials. Consortium Member. Lung Cancer Consortium. https://www.taiwanclinicaltrials.tw/tctc/member/4. Accessed October 1, 2020.