

Lung Cancer in People's Republic of China



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Perspective

As of 2018, the People's Republic of China was the most populous country in the world, reaching a total population of approximately 1.39 billion people, of which about 831 million and 564 million people lived in urban and rural regions, respectively. The 2020 population is estimated to be 1.44 billion, remaining the largest in the world. Owing to the country's large population and rapid socioeconomic development, cancer represents a significant health, financial, and societal burden. Lung cancer is the leading cause of cancer-related morbidity and mortality in the People's Republic of China and has been increasing over the past decades. This creates a huge challenge for the Chinese government, health management department, and professional specialists in lung cancer. Many efforts have been undertaken to address this issue, including favorable policies for screening, effective measures, the People's Republic of China-specific programs on cancer prevention, screening, improvements in medical insurance, treatment advances, and creation of incentives for clinical research. This editorial will discuss the current scientific knowledge and diagnostic and treatment paradigms of lung cancer in the People's Republic of China.

The Chinese government has established a multilevel medical security system that includes the universal health care system (by the national agency), commercial

medical insurance (by commercial insurance organizations), and a medical charity aid (by charity institutions) to achieve the goals that "everyone will have access to health care" and "poor people can afford the medical costs." Chinese health care applies a universal system that comprises basic medical insurance, urban and rural medical assistance, serious illness aid, and critical illness insurance. Payment of health care costs is associated with the patients' medical insurance type.

Epidemiology

The People's Republic of China accounts for one-fifth of the world's population and is currently facing unprecedented challenges in cancer control and prevention with rapid socioeconomic development and an increasingly aging population. The government has recognized the importance of this problem and has implemented a series of strategies including developing a systematic cancer surveillance network and conducting cancer prevention and control programs. The National Cancer Registration and Follow-up Programme was launched by the Ministry of Health of the People's Republic of China in 2008, and the number of cancer registries increased from 95 in 2008 to 574 in 2019. The National Central Cancer Registry of the People's Republic of China is responsible for data collection, evaluation, and publishing of national cancer statistics.

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Table 1. Lung Cancer Incidence and Mortality in the People's Republic of China, 2015

Area	Sex	Incidence			Mortality				
		Cases	Prop. (%)	ASIR (1/10 ⁵)	Rank	Deaths	Prop. (%)	ASMR (1/10 ⁵)	Rank
All areas	Both sexes	787,000	20.0	35.92	1	630,500	27.0	28.02	1
	Male population	520,300	24.2	48.87	1	433,200	29.3	40.11	1
	Female population	266,700	15.0	23.52	2	197,300	23.0	16.54	1
Urban areas	Both sexes	460,200	19.6	36.07	1	365,900	27.5	27.82	1
	Male population	300,400	23.9	48.52	1	250,700	30.0	39.85	1
	Female population	159,800	14.6	24.17	2	115,200	23.3	16.40	1
Rural areas	Both sexes	326,800	20.7	35.68	1	264,600	26.3	28.25	1
	Male population	219,900	24.6	49.30	1	182,500	28.4	40.41	1
	Female population	106,900	15.6	22.61	1	82,100	22.6	16.73	1

ASIR, age-standardized incidence rate using Segi's population; ASMR, age-standardized mortality rate using Segi's population; prop., proportion.

Cancer statistics were updated by the National Central Cancer Registry on the basis of data from 368 qualified cancer registries. It was estimated that the total number of newly diagnosed cases of lung cancer in the People's Republic of China in 2015 was about 787,000, corresponding to over 2100 new lung cancer diagnoses each day. Lung cancer accounted for about 20% of all cancer diagnoses, and the age-standardized incidence rate by world standard population was estimated to be 35.92 per 100,000 in the country in 2015 (Table 1). The age-standardized incidence rates of lung cancer for male and female populations were 48.87 and 23.52 per 100,000, respectively, which represented 520,300 male and 266,700 female individuals diagnosed each year. The urban areas had a lower age-standardized incidence rate for lung cancer for the male population than the rural areas, whereas the opposite was true for the female population (24.17 and 22.61 per 100,000 in urban areas and in rural areas, respectively). The age-specific lung cancer incidence rate was relatively low below the age of 40 and increased dramatically after that, reaching a peak in the age group of 80 to 84 years, both in male and female populations. Before then, the incidence rates were significantly lower in female individuals than in male individuals (Fig. 1).

Regarding mortality, it was estimated that about 630,500 patients with lung cancer died in 2015, which is equivalent to an average of over 1700 deaths each day. Lung cancer accounted for 27% of the mortality of all sites combined, and the age-standardized mortality rate was estimated to be 28.02 per 100,000 in the People's Republic of China in 2015. The numbers of lung cancer deaths were 433,200 and 197,300, with age-standardized rates for lung cancer mortality of 40.11 and 16.54 per 100,000 for the male and female populations, respectively. The rural areas had relatively higher age-standardized rates of lung cancer mortality (40.41 per 100,000) for male individuals than the urban

areas (39.85 per 100,000). Age-specific mortality rates by sex and area are shown in Figure 2. The trend for lung cancer mortality in different age groups was similar to the trend for incidence.

The economic growth and the increasingly urbanized and westernized lifestyle experienced in the country have resulted in increased environmental pollution. Outdoor air pollution, considered to be among the worst in the world, and indoor air pollution, through heating and cooking using coal and other biomass fuels, mean that the Chinese population is exposed to many environmental carcinogens. Nevertheless, the measured attributable risk for environmental pollution is low, and most lung cancer incidence and deaths can be attributed to smoking. The leading preventable cause of cancer death was active smoking in men.¹ According to the Global Adult Tobacco survey in the People's Republic of China, the current smoking rate is about 26.6% of adults

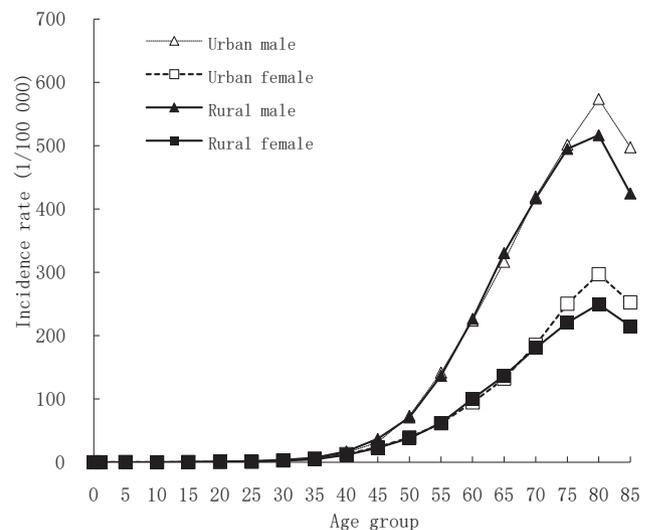


Figure 1. Age-specific incidence rates per 100,000 population, 2014.

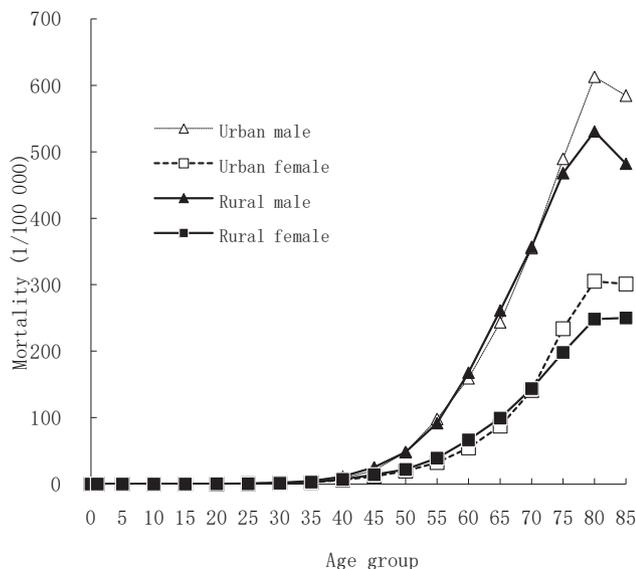


Figure 2. Age-specific mortality rates per 100,000 population, 2014.

(about 50.5% of men and 2.1% of women smoke). Though the difference was not statistically significant (28.1% in 2010 and 26.6% in 2018), the overall current rate of tobacco smoking revealed a trend toward decrease from 2010 to 2018. Only 16.1% of current smokers plan to or are thinking about quitting in the next 12 months; however, over 90% of smokers who tried to quit in the past 12 months did not use any quitting assistance for at least one quit attempt. Tobacco control is one of the most important issues in lung cancer prevention and control in the People's Republic of China (Fig. 3).

Screening

Screening is conceptually a reliable strategy for reducing mortality in lung cancer. According to the findings from the National Lung Screening Trial, screening for lung cancer with low-dose computed tomography (LDCT) is the most effective way to reduce mortality in lung cancer.² During the past few decades, great efforts, regarding both organized and opportunistic lung cancer screening, have been made in the country.

Two large-scale, population-based, organized lung cancer screening programs have been conducted across the country in recent decades in the context of the National Cancer Screening Programs funded by the National Health Commission. One is the Rural People's Republic of China Screening Program (RuraCSP) initiated in 2010 among the rural population that is at high risk of developing cancer. Through the RuraCSP, lung cancer screening has been conducted in six provinces and about 13,000 high-risk individuals have been assessed by LDCT scan with a lung cancer detection rate of 1%.³ For

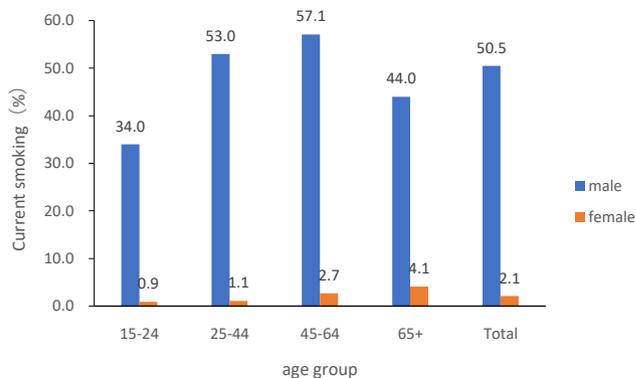


Figure 3. Current tobacco smoking by age and sex, 2018.

the general community population in the country, the Cancer Screening Program in the Urban People's Republic of China (CanSPUC) was initiated since 2012.⁴ By the end of 2017, a total of 521,302 eligible participants were identified as being at high risk of lung cancer, of which 163,752 participants underwent LDCT screening. Follow-up of the CanSPUC is ongoing. To optimize the use of the limited health care resources, the following two-step process has been adopted in both RuraCSP and CanSPUC: screening that involves a relative risk assessment for lung cancer and subsequent LDCT scan for high-risk individuals. In addition to the national programs, several population-based, organized lung cancer screening programs were funded by the local governments, such as in Tianjin⁵ and Shanghai.⁶

Hospital-based opportunistic lung cancer screening with LDCT in the country has also been conducted. The main findings of the collaboration between the Cancer Hospital Chinese Academy of Medical Sciences and the International Early Lung Cancer Action Program revealed a lung cancer detection rate of 0.6% in 4690 asymptomatic participants aged 40 years or older, of which 76% of the cases were in the early stage (I and II).⁷ Meanwhile, a series of opportunistic LDCT lung cancer screening studies conducted in Guangdong,⁸ Beijing,⁹ Hebei,¹⁰ Shanxi,¹¹ and Shanghai¹² are consistent in the conclusion that opportunistic lung cancer screening could increase the early detection rate of lung cancer.

Nevertheless, identification of the high-risk population of lung cancer and the high false-positive rate of LDCT detection still pose challenges to the success and cost-effectiveness of lung cancer screening. Several studies have been supported by the Ministry of Science and Technology to address key issues in lung cancer screening. The study of the National Cohort of Lung Cancer was initiated in 2017 and aims to collect bio-samples from a population at risk of lung cancer and patients with lung cancer for further research. The

People's Republic of China National Cancer Early Screening trial: lung and colorectal cancer began in 2019 and is the first population-based cancer screening randomized controlled trial in the country. It seeks to determine whether screening with LDCT could reduce lung cancer-specific mortality in Chinese urban residents who are at high risk of developing lung cancer. If there is a significant lung cancer-specific mortality reduction in screening groups, lung cancer-specific mortality between high-risk population receiving annual LDCT screening versus biennial LDCT screening will be compared. Currently, more than 10,000 people have been recruited in the People's Republic of China National Cancer Early Screening trial. On the basis of the evidence of the above-mentioned programs, the People's Republic of China National Cancer Center is currently preparing the national lung cancer screening guidelines for the country.

Diagnosis

There are many types of imaging that can be used for diagnosing lung cancer. The most important technology for the diagnosis of lung cancer is high-resolution computed tomography. For early stage lung cancer or "ground-glass" nodules, a series of very clear images of the tumor can be obtained, thanks to the tiny intervals between scan slices (1 mm or even lower up to 0.5 mm), which are much thinner than those of normal computed tomography (usually 5 mm). This type of CT gives surgeons the ability to observe slight changes in the nodules over time. Another advantage of high-resolution computed tomography is its ability to reconstruct a three-dimensional image of the target lung, which is crucial for complicated segmentectomy. Other technologies have specific advantages for different types of evaluations. Contrast CT is recommended for most central lung cancers, cancers with enlarged mediastinal lymph nodes, and three-dimensional reconstructions. Positron emission tomography-computed tomography (PET-CT) is being applied with rapidly increasing frequency. As outlined here, there are many methods of diagnosing and staging lung cancer that can be customized to the patient's health and financial needs. PET-CT is valuable not only for the evaluation of the whole body, and especially for possible distal metastasis, but also for the discovery of some lesions that are difficult to diagnose with CT, because it reveals the active glucose metabolism (standard uptake value) of the lesions. In addition, bone emission CT is often performed to evaluate bone metastatic status for people with financial constraints. Ultrasonography is generally used to detect supraclavicular lymph nodes. Chest radiograph is not usually applied now because it can only reveal large

tumors and is not helpful for operation. Magnetic resonance imaging is rarely used except in some special tumors invading the chest wall and mediastinum.

After diagnostic imaging, preoperative pathology is important for subsequent treatment plans. Bronchoscopy is of good value for taking biopsy or brush cytology specimens in central lung cancers, through which more than 95% of lesions can be pathologically confirmed.¹³ CT-guided percutaneous tumor puncture is suitable for peripheral lesions or for people who cannot tolerate bronchoscopy. There are three main ways for nodal staging, which are the following: Endobronchial ultrasound-guided transbronchial needle aspiration is very helpful in the diagnosis of N2 or N3 disease and for the judgment of surgical or systemic therapy-based multimodal treatments. Ultrasound-guided lymph node aspiration is performed for suspicious supraclavicular or cervical node metastasis. Mediastinoscopy, a classic approach for node staging, is now mostly performed in a minimally invasive way (video-assisted mediastinoscopic lymphadenectomy). Some regional medical centers in Guangdong do it very well, whereas most other hospitals tend to treat patients directly by video-assisted thoracoscopic surgery (VATS). The basic examination for lung cancer diagnosis is a chest CT scan. If ground-glass nodules or subsolid nodules are detected and there is suspicion of malignancy, patients should be referred for follow-up procedures. At least one-time follow-up of 3 months is recommended if the surgeon thinks the nodule is "highly suspected for malignancy." If a peripheral lesion is big enough (>1 cm) and properly located for puncture, CT-guided percutaneous biopsy is recommended. After all evaluation, patients eligible and able to tolerate surgery should be introduced to surgery-based multimodal treatment (Fig. 4). It should be noted that there is no universal treatment plan for all patients suspected of lung cancer; however, imaging, pathology, and follow-up are all very important.

Surgical Approaches

All clinical staging in the People's Republic of China is based on the latest TNM staging system of the Union for International Cancer Control, which is currently in its eighth edition. There is little controversy that surgery is the key player in the treatment of stages I to II lung cancer for eligible patients. Although lobectomy is the standard management in many cases, sublobular resections have been found to have remarkable potential in selected patients with stage I for similar overall survival (OS) and more preserved pulmonary function. Anatomical partial lobectomy is a recently developed surgical technique, which is defined as lesion-centered resection of anatomical sublobular parts, such as

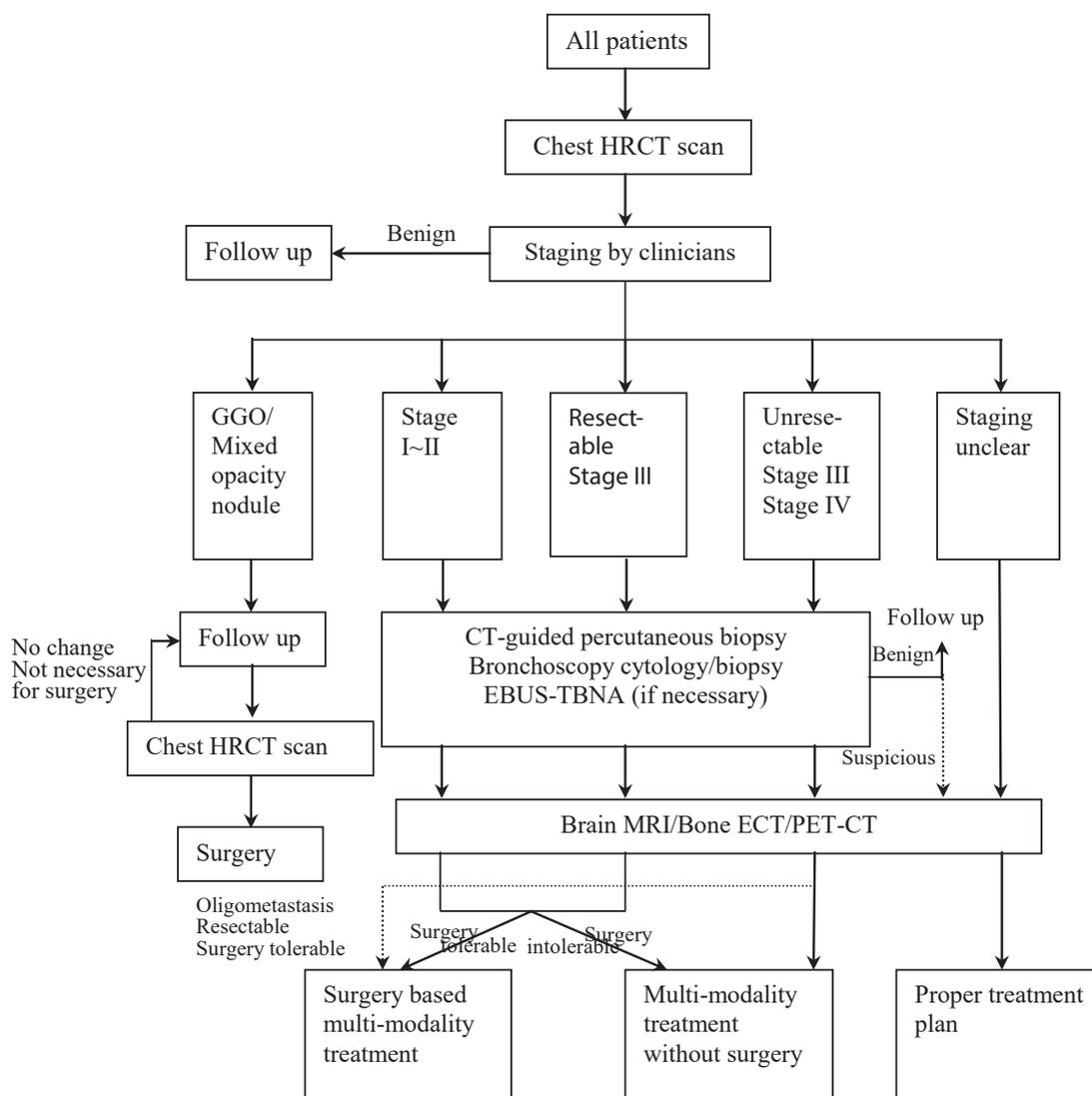


Figure 4. Diagnostic flowchart for suspicious patients with lung cancer. The most crucial examination is the chest HRCT scan. CT, computed tomography; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; ECT, emission computed tomography; GGO, ground-glass opacity; HRCT, high-resolution computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

segmentectomy, combined segmentectomy, and segmentectomy plus adjacent subsegmentectomy.¹⁴ For resectable stage IIIA cases, the timing of surgery differs because either neoadjuvant or adjuvant systemic therapy can elevate the 5-year survival rate by 5%.¹⁵ Nodal status, age, and performance status (PS) are important factors that affect survival benefit. Every case is discussed by a multidisciplinary team consisting of surgeons, medical oncologists, and radiation oncologists. Some surgeons prefer to remove the tumor and the affected lymph nodes first if possible. The common interval between systemic therapy and surgery is 4 to 6 weeks and 2 weeks longer if radiotherapy is included in the systemic therapy. In recent years, new therapeutic combinations of surgery with tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors have been

attracting wide attention and have been found to have encouraging results in (neo)adjuvant applications.^{16,17} Surgery is not routinely used in the management of stage IV cancer, although it can be considered in patients who present with resectable oligometastatic lesions and well-controlled primary tumors. The proportion of surgery of metastatic lesions to total surgery volume is not high (less than 10%) in big hospitals but brings substantial survival benefit for eligible patients with advanced-stage disease.

Surgery for lung cancer has been evolving very rapidly in the country in the past two decades. In most provincial or regional medical centers, minimally invasive approaches, such as VATS, are widely applied in routine cases. For example, the percentage of VATS in all thoracic surgeries rose over 30% from 2008 to 2014 in

the National Cancer Center¹⁸ and even higher (up to 80%) between 2014 and 2019. Surgical incisions became “fewer and smaller,” whereas resection procedures went up to becoming “more complicated and faster.” More surgeons are challenging uniportal VATS on the basis of three portal techniques and practical improvements of surgical instruments to minimize the surgical damage to patients, both physically and psychologically. In contrast, skillful surgeons are trying to accomplish more complicated surgeries, such as sleeve or double-sleeve resection, by VATS. Robotic-assisted thoracic surgery (RATS) is a newly emerging technique used in various lung cancer cases since 2010, mainly for its improved viewing ability and operation at arbitrary angles and is not as technically challenging as it was originally thought to be. In the People’s Republic of China, most experienced surgeons think that VATS can satisfy major clinical requirements of thoracic surgery whereas RATS only has a role in some difficult reconstruction procedures, such as carinoplasty or artery anastomosis. An obvious obstacle for the popularization of RATS is high expense (up to \$4 million for the new-generation Da Vinci Xi machine, which is not covered by the National Medical Care Insurance). Thoracotomy is performed in some complex resections (e.g., Pancoast tumor, bulky tumor with enlarged lymph nodes, or large fibrosarcoma). Nevertheless, the advantages of VATS and RATS are gradually becoming indispensable in some scenarios, such as separation of extensive thorax adhesion and surgical experience sharing, which are critical for improvement of surgical movements.

Radiation Oncology

There are 1413 radiotherapy centers in the People’s Republic of China. Three-dimensional conformal radiation therapy and intensity-modulated radiation therapy (IMRT) are available in 86.2% and 67.4% centers, respectively, and most are academic cancer centers or with university affiliation.¹⁹ Advanced technologies, including four-dimensional CT or PET-CT simulation, IMRT/volumetric-modulated arc therapy, image-guided radiation therapy, and motion management, are widely used for lung cancer across the country, and the IMRT technique has been reported to have a significantly improved locoregional recurrence-free survival and comparable OS than three-dimensional conformal radiation therapy in locally advanced NSCLC, along with reduction of pulmonary toxicity.²⁰

In the multidisciplinary treatment of lung cancer, radiotherapy is mainly used for early and middle-stage NSCLC. Stereostatic body radiotherapy is the standard treatment for inoperative patients with early disease. Definitive radiotherapy, combined with chemotherapy, is

mainly used for those with locally advanced disease, with the standard dose of 60 Gy. Compared with the European and American countries, less Chinese patients might receive concurrent chemoradiation therapy (CCRT). Nevertheless, the percentage of patients receiving CCRT has not been adequately reported. One possible reason is the susceptibility of the Chinese population to radiation pneumonitis according to the early evidence, which has been validated recently in the PACIFIC (Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer) study (57.6% [34 of 59] in the CCRT control arm for Asian patients).²¹ Different genetic backgrounds between whites and Chinese might be a possible explanation.²² Therefore, the recommended dose limits of normal lungs are lower in the People’s Republic of China. The mean dose to the lungs should optimally be 17 Gy; the lung volumes, minus gross tumor volume receiving more than 20 Gy (V20) and 30 Gy (V30), were limited to less than 30% and less than 20%, respectively.²³ By these limits, similar incidence of radiation pneumonitis could be gained between Chinese and white populations.²⁴ For patients with completely resected pIIIA-N2 NSCLC, the role of post-operative radiotherapy still remains debated. A phase III multicenter trial (NCT 00880917) from the People’s Republic of China indicated that PORT (An Update of the Phase III Trial Comparing Whole Pelvic to Prostate Only Radiotherapy and Neoadjuvant to Adjuvant Total Androgen Suppression: Updated Analysis of RTOG 94-13, With Emphasis on Unexpected Hormone/Radiation Interactions) failed to achieve improved disease-free survival or OS for patients, though it improved locoregional recurrence-free survival.²⁵ For patients with advanced NSCLC, radiotherapy mainly plays a palliative role to improve their quality of life. For limited-stage SCLC, 60 Gy in 30 daily fractions is often used, which is found to have a similar outcome to the 45-Gy 3-week twice-daily regimen but is more convenient for patients and centers.

The use of radiation therapy for lung cancer has been significantly increasing in the People’s Republic of China in the past decades. Nevertheless, there is still a gap between availability and demand of radiation therapy. On the basis of the 2017 survey of the People’s Republic of China Society for Radiation Oncology, less than 50% of patients in need of radiotherapy actually received the treatment. This is mainly owing to insufficient number of both equipment and health care providers per million people. For example, the available facility ratio was 1.49 in 2015. In addition, access to radiation therapy varies across the country.¹⁹ The government is planning to increase medical linear accelerators to 1500 and proton accelerators to 10 in the next few years.

Systematic Therapy

Given that more than one-third of patients with lung cancer are initially diagnosed as having advanced/metastatic disease, systemic therapy is the main treatment strategy, including chemotherapy, targeted therapy, and immunotherapy. The selection of therapeutic strategies is based on the histology and molecular pathology of the tumor and age, PS, and the patient's preferences.²⁶ Multidisciplinary teams are encouraged to participate in the discussion of the treatment decisions. After initial morphologic diagnosis, it is strongly recommended to test for treatment-driven strategies. There are distinct testing strategies between squamous cell carcinoma (SCC) and non-SCC. Molecular testing involving *EGFR* mutations, rearrangements in *ALK* or *ROS1*, and *BRAF V600E* mutation is recommended for non-SCC, especially for adenocarcinoma; for SCC, however, it is only recommended for never-smokers, patients with mixed adenosquamous components, or those with diagnosis based on small biopsies. Although single-gene testing is by far the most common technology used in clinical practice, next-generation sequencing-based multigene testing has become increasingly popular.

EGFR mutations represent the most frequent aberrations in lung adenocarcinoma, with a prevalence of around 50% in Chinese patients,²⁷ much higher than the approximately 10% found in the white population. For non-SCCs harboring activating *EGFR* mutations (exon 19 DEL and exon 21 *L858R*, which account for about 85%) except for exon 20 insertion, EGFR TKIs are the preferred treatment in the first-line setting, such as gefitinib, erlotinib, icotinib, afatinib, dacomitinib, and osimertinib. Although osimertinib illustrated superior progression-free survival and OS than gefitinib in the FLAURA (Osimertinib in Untreated *EGFR*-Mutated Advanced Non-Small-Cell Lung Cancer List of authors) study, a non-negligible number of patients are still unsuitable for osimertinib as first-line treatment, considering that it is not reimbursed by medical insurance and there is no evidence of OS benefit in the subset of patients with an *EGFR exon 21 L858R* mutation. The combination of bevacizumab, an antivascular endothelial growth factor antibody, with erlotinib has been identified as being superior to erlotinib alone regardless of exon 19 DEL or *exon 21 L858R* in terms of progression-free survival. In addition, both bevacizumab and erlotinib are covered by medical insurance, pushing bevacizumab plus erlotinib delivered in first-line therapy as an optional treatment. Platinum-doublet chemotherapy combined with EGFR TKI is seldom adopted owing to the elevated toxicity and unprolonged OS in the past. It is typically only employed when a patient needs rapid tumor debulking for symptom management. Nevertheless,

with deeper understanding of tumor heterogeneity, accumulating evidences have revealed better clinical outcome of combination therapy than monotherapy for certain subgroup of patients, for example, patients with *EGFR 21 L858R* or with concurrent mutations in addition to *EGFR* mutations; however, this requires further validation. Once a patient experiences disease progression, rebiopsy and testing for *T790M* mutation and other potential targets are recommended. Osimertinib will be delivered to patients with *T790M* mutation and extensive progression. For progression in an oligo-lesion or central nervous system metastasis, continuous delivery of the former EGFR TKI and definitive local therapy (e.g., radiation or surgery) for limited lesions should be usually considered. For patients without *T790M* mutation and experiencing disease progression with multiple lesions, platinum-doublet plus or minus bevacizumab is the leading available strategy.

TKIs targeting rearrangements of *ALK* (crizotinib and alectinib) or *ROS1* (crizotinib) are the optimal first-line therapy for patients with the corresponding genetic aberration. Crizotinib was used more extensively than alectinib considering the cost-effectiveness and insurance coverage. Ceritinib and alectinib have been approved by the National Medical Products Administration (NMPA) as second-line therapy after the failure of crizotinib. Subsequent delivery of platinum-doublet plus or minus bevacizumab or TKI plus definitive local therapy was decided usually according to progression modes with limited or multiple lesions. Different from western countries, anlotinib is recommended and has been approved as third-line therapy after the failure of upfront TKIs and chemotherapies. Owing to uncertain efficacy, inferior accessibility, and unsatisfactory cost-effectiveness, drugs targeting uncommon molecular driver mutations, such as *BRAF V600E* mutation, amplifications of *HER2* and *MET*, *MET exon 14* mutations, and fusion genes involving *RET* and *NTRK1*, are seldom used as front-line therapy by Chinese physicians, who usually prefer platinum-doublet chemotherapy-based regimens.

A considerable fraction of patients cannot provide sufficient and high-quality tumor tissues for molecular testing. In particular, re-biopsies for acquired resistant mutations are often unavailable. This situation has led to the development of liquid biopsy as a complementary approach, which provides an elevated opportunity for patients, whose tumors do not have targetable/actionable mutations during initial tissue-based molecular genotyping, to receive target therapies.

For patients without molecular drivers or SCC, platinum-doublet plus programmed cell death-protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) antibodies are the preferred regimens, and platinum-doublet plus

bevacizumab is optional in non-SCC. To date, the NMPA has approved four anti-PD-1/PD-L1 monoclonal antibodies for lung cancer, including two anti-PD-1 antibodies (nivolumab and pembrolizumab) and two anti-PD-L1 antibodies (atezolizumab and durvalumab). Only pembrolizumab has an indication in the first-line setting, where it has been approved as a single agent for patients with positive PD-L1 expression ($\geq 1\%$) or in combination

with chemotherapy regardless of PD-L1 expression. Nevertheless, most physicians prefer to deliver single-agent pembrolizumab, or even combined with platinum doublet, in patients with PD-L1 greater than or equal to 50% simultaneously under the consideration of tumor burden, PS score, liver metastasis, and morbidity. Single-agent use of nivolumab was approved as second-line therapy regardless of PD-L1 expression or *EGFR/ALK*

Table 2. Systematic Therapy for Advanced NSCLC

Advanced NSCLC With Driver Oncogenic Aberrations					
Treatment Status	Stratification	EGFR Mutation	ALK Rearrangement	ROS1 Rearrangement	BRAF V600E
First line		Preferred: osimertinib, gefitinib, erlotinib, icotinib, afatinib, or dacomitinib Optional: erlotinib + bevacizumab, platinum-doublet ^a ± bevacizumab/EGFR TKI	Preferred: alectinib, crizotinib Optional: platinum-doublet ^a ± bevacizumab	Preferred: crizotinib Optional: platinum-doublet ^a ± bevacizumab	Platinum-doublet ^a ± bevacizumab Optional: dabrafenib ± trametinib, vemurafenib
Resistance to TKI	PD of oligo-lesion or CNS	Continuous TKI + definitive local therapy (e.g., radiation or surgery) Rebiopsy for molecular testing ^b	Continuous TKI + definitive local therapy (e.g., radiation or surgery); ceritinib or alectinib (PD after crizotinib)	Continuous TKI + definitive local therapy (e.g., radiation or surgery)	
	Extensive PD	Rebiopsy for molecular testing ^b ; osimertinib for T790M positive (PD after first- or second-generation TKIs); platinum-doublet ^a ± bevacizumab	Ceritinib or alectinib (PD after crizotinib); platinum-doublet ^a ± bevacizumab	Platinum-doublet ^a ± bevacizumab	
PD after TKIs and platinum-doublet	PS = 0-2	Single chemo-drug ^c ± bevacizumab; anlotinib			
Advanced NSCLC Without Driver Oncogenic Aberrations					
Treatment Status	Stratification	Non-SCC		SCC	
First line	PS = 0-1	Platinum-doublet ^d + pembrolizumab; platinum-doublet ^a ± bevacizumab; pembrolizumab (PD-L1 $\geq 1\%$, preference to $\geq 50\%$)		Platinum-doublet ^e + pembrolizumab; platinum-doublet; pembrolizumab (PD-L1 $\geq 1\%$, preference to $\geq 50\%$)	
	PS = 2	Single chemodrug ^f ± bevacizumab		Single chemodrug ^f	
Second line	PS = 0-2	Nivolumab, docetaxel, or pemetrexed (if not received before)		Nivolumab or docetaxel (if not received before)	
	PS = 3-4	BSC		BSC	
Third line	PS = 0-2	Nivolumab, docetaxel, or pemetrexed (if not received before); anlotinib		Nivolumab or docetaxel (if not received before); anlotinib (limited to peripheral lung lesions)	

^aIncludes cisplatin/carboplatin + pemetrexed/gemcitabine/paclitaxel/docetaxel/novelbline.

^bT790M mutation and optimal multiple gene alterations.

^cIncludes pemetrexed/gemcitabine/paclitaxel/docetaxel/novelbline.

^dRefers to cisplatin/carboplatin + pemetrexed.

^eRefers to cisplatin/carboplatin + paclitaxel/albumin-bound paclitaxel.

^fIncludes gemcitabine/paclitaxel/docetaxel/novelbline.

BSC, best supportive care; CNS, central nervous system; PD, progressive disease; PD-L1, programmed death-ligand 1; PS, performance status; SCC, squamous cell carcinoma; TKI, tyrosine kinase inhibitor.

status. Generally, anti-PD-1/PD-L1 antibodies are not used as frequently as expected or completely following indications, mainly owing to the high cost. As to the selection of chemodrugs, pemetrexed and paclitaxel/albumin-paclitaxel are usually selected for non-SCC and SCC, respectively. Systematic therapy for advanced NSCLC was summarized in [Table 2](#).

For extensive-stage SCLC, etoposide plus platinum has been the most popular regimen for decades. Atezolizumab, recently approved by the NMPA, will be added to chemotherapy as standard therapy in the first-line setting. Subsequent therapy is determined according to the interval between last delivery of front etoposide and cisplatin chemotherapy and the date of disease progression.

Specific Challenges and Unique Features

Lung cancer is the leading cause of cancer-related morbidity and mortality in the People's Republic of China. The country's large population, changing living environment, and sometimes unique treatment modalities present a distinct situation with specific challenges. In this last section, we will discuss some of these factors.

The high burden of lung cancer and the high proportion of late-stage lung cancer in the country make cancer prevention, surveillance, and development of novel treatment strategies an urgent need, which already draws great attention from the government but is still insufficient. In addition, the causative factors underlying the increasing incidence of lung cancer need to be investigated. In particular, the incidence of ground-glass opacity-dominant lung cancer is rising in the country. Although relatively less invasive procedures, such as VATS segmentectomy and robot-assisted VATS, are widely applied, Chinese physicians should be cautious of overtreatment by surgery because a considerable portion of ground-glass opacities is benign.

Regarding treatment strategies, considering that long-term survival is still the goal of all treatments, standardized follow-up and active surveillance after curative treatment should be emphasized, to identify early recurrence and evaluate prognosis appropriately. Mediastinoscopy before surgery is not widely used across the People's Republic of China yet, which should be encouraged to improve precise staging and to facilitate decision making of perioperative medication.

Surgery, radiotherapy, and systemic therapy have been fully and efficiently developed in the past decade, and the concept of multidisciplinary treatment of lung cancer has been popular even in second- or third-class cities for a long time, which has helped push forward the standardized treatment and improved patients' outcome. More and more high-cost drugs, such as

gefitinib, erlotinib, osimertinib, crizotinib, alectinib, and sintilimab, are now covered by medical insurance from the national agency. Nevertheless, limitations of available novel drugs are still a challenge for medical oncologists, which further illustrates the importance of promoting well-designed high-quality clinical trials to accelerate the approval of effective novel drugs in the country.

An intriguing feature of lung cancer in the People's Republic of China is that the genomic profiles are distinct: as we already know that *EGFR* mutations present as the most frequent genetic aberration in Chinese patients with NSCLC and are found at a much higher frequency than in the white population. Based on this, liquid biopsy of *EGFR* mutations and dynamic surveillance of resistance gene aberrations are relatively common in the country, which stimulates the advancement of genomic testing techniques and favors investigational research for next-generation EGFR TKIs.

Favorable policies from the government and quick enrollment based on the large patient population are two features in the field of clinical trials that boost the nationwide novel drug investigation.²⁸ The NMPA has approved four PD-1 inhibitors developed by local companies for cancer treatment, including troparia, sintilimab, camrelizumab, and tislelizumab in 2018 to 2019. We believe that this will bring more benefit to Chinese patients at least by decreasing the economic burden of cancer treatment. Finally, the fact that most patients with lung cancer concentrated in large hospitals of first-class cities because of highly specialized doctors and better available treatment is a unique feature of the country, which needs rational distribution of medical resources and development of remote consultation to help patients get better medical care throughout the country.

These challenges would not be challenges in the near future, based on the joint efforts and contributions from experts of every single segment on prevention, screening, diagnosis, treatment, and novel strategy investigation, after recognizing the clinical and genetic features of lung cancer in the People's Republic of China, and we are on the way to conquering lung cancer.

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