

Chinese guidelines for diagnosis and treatment of primary lung cancer 2018 (English version)

National Health Commission of the People's Republic of China

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1. Overview

Primary lung cancer (PLC) is the most common malignant tumor in the world. PLC is generally divided into two major groups based on pathology and treatment: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for 80%–85% and the rest is SCLC. Because of the unique biological behavior of SCLC, the combination of chemotherapy and radiotherapy is mainly used, in addition to a few early cases. If not specified, lung cancer is always regarded as NSCLC.

Lung cancer is the fastest growing malignant tumor in China in recent 30 years. According to the data of the first death causes retrospective survey conducted in the mid-1970s, the mortality of lung cancer in China was 5.47/100,000, ranking fifth in cancer death, following gastric cancer, esophageal cancer, liver cancer and cervical cancer, accounting for 7.43% of all cancer deaths. The results of the second sampling survey of causes of death in China showed that in the 1990s, lung cancer was the third leading cause of death for cancer, only second to gastric cancer and esophageal cancer. The third retrospective survey of death causes conducted in this century shows that lung cancer has become the leading cause of cancer death. According to the latest statistics from the National Cancer Registry, there were about 650,000 new cases of lung cancer in China in 2011, and 520,000 patients died due to lung cancer, and both ranked first in malignant tumors. According to data released by the National Cancer Registry in 2016, there were 733,300 new cases of lung cancer in China (5,093,200 males and 224,000 females) in 2015, ranking first in malignant tumors (the first in males and the second in females), accounting for 17.09% of new cases in malignant tumors (20.27% for males and 12.59% for females). In the same period, the number of lung cancer deaths in China was 610,200 (43,224 males and 177,800 females), accounting for 21.68% of the causes of malignant tumors (23.89% for males and 17.70% for females). In terms of regional distribution, the mortality of lung cancer in urban areas in China is higher than that in rural areas. The mortality rate of lung cancer in urban and rural areas in east and central China was significantly higher than that in western China. The age of morbidity increased rapidly in the group of more than 40 years.

2. Screening and diagnosis

2.1 Risk factors for lung cancer

Due to the influence of the worsening air pollution caused

by the continual development of industrialization in China, and of the highest prevalence of tobacco use in the world, and of other factors like aging, the morbidity and mortality rates of lung cancer are increasing. In the next few decades, lung cancer will always be the top priority of cancer prevention and control in China. Plenty of epidemiological studies have shown the main risk factors for lung cancer as following.

2.1.1 Smoking and passive smoking

Smoking is currently recognized as the most important risk factor for lung cancer. During the ignition process, cigarettes will produce more than 60 kinds of carcinogens. Polycyclic aromatic, hydrocarbons and nicotine, produced during combustion of nitrosamines in tobacco, are the most carcinogenic substance to the respiratory system. In 1985, World Health Organization (WHO) International Cancer Research Institute (IARC) identified smoking as the cause of lung cancer. The relationship between smoking and the risk of lung cancer is related to the type of tobacco, the age at which one starts to smoke, the duration of smoking and the amount of smoking. In European and American countries, the mortality of lung cancer among smokers is about 10 times higher than that of non-smokers, which is relatively lower in Asia.

Passive smoking is also a risk factor for lung cancer, mainly in females. The association between passive smoking and lung cancer was first reported in the early 80s of last century. In 2007, Stayner *et al.* conducted a meta-analysis on a study of 22 workplaces on tobacco exposure and lung cancer risk in 2003, and it indicated that non-smoking workers increased their risk of lung cancer by 24% [relative ratio (RR)=1.24, 95% confidence interval (95% CI): 1.18–1.29] due to passive smoking in working environment, and the risk of lung cancer among workers highly exposed to environmental tobacco smoke is as high as 2.01 (95% CI: 1.33–2.60), moreover the exposure time of environmental tobacco smoke is strongly correlated with lung cancer.

2.1.2 Indoor pollution

Indoor pollution mainly includes indoor fuel and cooking oil fumes. Incomplete combustion of indoor coal fuels and cooking oil fumes can produce many carcinogens such as phenylpropylene pyrene, formaldehyde and polycyclic aromatic hydrocarbons. The relationship between indoor coal combustion and lung cancer is first discovered by research carried out in Xuanwei, Yunnan province of

China. Two case-control studies reported a positive association between coal consumption and lung cancer. Subsequent intervention studies showed that intervention with modified stove could significantly reduce the incidence of local lung cancer. Studies in Shanghai, Gansu and Hong Kong also show that cooking oil fumes (stir-fried and deep-fried) are associated with lung cancer.

2.1.3 Indoor radon exposure

Radon is a colorless, odorless, inert gas with radioactivity. When inhaled, radon-decaying radioactive particles can cause radiation damage to the respiratory system and cause lung cancer. Radon content is high in uranium mining area, and building materials are the main source of indoor radon, such as granite, brick sand, cement and gypsum, especially natural stones containing radioactive elements. The results of three pooled analyses in Europe, North America and China show that, the risk of lung cancer increases relatively by 8% (95% CI: 3%–16%), 11% (95% CI: 0%–8%) and 13% (95% CI: 1%–36%) per 100 Bq/m³ increase in radon concentration. In addition, there is interaction between radon and smoking.

2.1.4 Outdoor air pollution

Carcinogens in outdoor air pollutants include: benzoprene, benzene, some metals, particulate matter, ozone, etc. In a systematic review of 17 cohort studies and 20 case-control studies conducted between 1950 and 2007, Chen *et al.* found that the risk of lung cancer death increased by 15%–21% for every 10 µg/m³ increase in particulate matter (PM_{2.5}) in the air.

2.1.5 Occupational factors

Multiple kinds of specific occupational exposure can increase the risk of lung cancer, including asbestos, quartz dust, nickel, arsenic, chromium, dichloroethyl ether, mineral oil, dichloromethyl ether, etc. Results of the meta-analysis of a cohort of cancer deaths among asbestos-exposed people in China carried out by Sun *et al.* showed that asbestos was closely associated with lung cancer. Driscoll *et al.* estimated that occupational attribution ratio of lung cancer worldwide in males and females is 10% and 5%, respectively. Attribution ratio of occupational factors in China in male and female is 10.6% and 7.0%, respectively.

2.1.6 Family history of lung cancer and genetic susceptibility

Phenomenon of familial aggregation exists in patients with

lung cancer. These findings suggest that genetic factors may play an important role in populations and/or individuals susceptible to environmental carcinogens. Systematic review of Matakidou *et al.* showed that the RR of lung cancer and family history were 1.84 (95% CI: 1.64–2.05). After investigating 633 cases of lung cancer family, Lin Huan *et al.* reported that the adjusted odds ratio (OR) was 2.11 for one lung cancer patient in the family and 4.49 for two or more lung cancer patients. And that was 1.51 (95% CI: 1.11–2.06) in non-smokers. At present, it is believed that genetic polymorphisms involving carcinogen metabolism, genomic instability, DNA repair, cell proliferation and apoptosis regulation may be the genetic susceptibility factors of lung cancer. Metabolic enzyme gene and DNA damage repair gene polymorphisms are two aspects which are mostly studied.

2.1.7 Other factors

Other factors related to lung cancer include nutrition and diet, psychosocial factors, immune status, estrogen levels, infections [human immunodeficiency virus (HIV), human papillomavirus (HPV)], chronic inflammation of the lungs, economic and cultural levels, etc. However, the relationship between lung cancer and other factors is still controversial and needs further study and evaluation.

2.2 Screening for high-risk population

Screening for lung cancer among high-risk population is beneficial for early detection of early lung cancer and improving the cure rate. Low-dose computed tomography (LDCT) is 4–10 times more sensitive than conventional chest radiography in detecting early peripheral lung cancer. According to the International Early Lung Cancer Action Plan (I-ELCAP), 85% of stage I peripheral lung cancer can be detected by annual LDCT screening, and the post-operative expected 10-year survival rate is 92%.

The National Lung Cancer Screening Test in the United States has proved that LDCT screening can reduce lung cancer mortality by 20% in high-risk population, and is the most effective lung cancer screening tool at present. LDCT is recommended for lung cancer screening in high-risk population in the pilot technical guidelines for cancer screening and early diagnosis and treatment in a few areas in China.

The risk factors for lung cancer screening proposed in the National Comprehensive Cancer Network (NCCN) guidelines include smoking (present and past), radon

exposure, occupational exposure (arsenic, chromium, asbestos, nickel, cadmium, beryllium, silicon, diesel exhaust, smoke and soot), history of malignancy, family history of lung cancer in first degree relatives, history of chronic obstructive emphysema or pulmonary fibrosis, history of passive smoking.

Three groups are divided according to the risk states:

(1) High-risk group: 55–74 years old, smoking history ≥ 30 package years, time for smoking cessation <15 years; or ≥ 50 years old, smoking history ≥ 20 package years, and other risk factors besides passive smoking.

(2) Middle-risk group: age ≥ 50 years old, smoking history or passive smoking history ≥ 20 package years, no other risk factors.

(3) Low-risk group: age <50 years and smoking history <20 package years.

The NCCN guidelines recommend that lung cancer screening be performed in high-risk groups, and screening in low-risk and middle-risk groups is not recommended.

2.3 Clinical manifestations

The clinical manifestations of lung cancer are diverse but lack specificity, which often leads to delay in diagnosis of lung cancer. Peripheral lung cancer usually does not present any symptoms and is often found on a health check-up or chest imaging for other diseases. The clinical manifestations of lung cancer can be summarized as: symptoms arising from local growth of the primary tumor itself; symptoms of primary tumor invading the adjacent organs and structures; symptoms of distant metastasis and extrapulmonary manifestations of lung cancer (paraneoplastic syndrome), etc.

2.3.1 Symptoms arising from local growth of primary tumor itself

These symptoms and signs include: 1) Cough. Cough is the most common symptom of lung cancer patients, more than 50% of lung cancer patients present cough at the time of diagnosis; 2) Hemoptysis. Hemoptysis is found in about 25% to 40% of lung cancer patients, usually presenting as blood filaments in sputum, while massive hemoptysis is rarely seen. Hemoptysis is the most suggestive symptom of lung cancer; 3) Dyspnea. The mechanisms of dyspnea may include reduction of alveolar area caused by primary tumor expansion, obstruction of central lung cancer or compression of airway by metastatic lymph nodes, atelectasis and obstructive pneumonia, intrapulmonary

lymphatic dissemination, pleural effusion, pericardial effusion and pneumonia, etc; 4) Fever. Necrosis of tumor tissue can cause fever, and secondary pneumonia caused by tumor can also cause fever; and 5) Wheeze. If the tumor is located in the large airway, especially in the main bronchus, it can often cause localized wheezing symptoms.

2.3.2 Symptoms of primary tumor invading adjacent organs and structures

Primary tumors directly invade adjacent structures, such as the chest wall, diaphragm, pericardium, phrenic nerve, recurrent laryngeal nerve, superior vena cava or esophagus. Mechanical compression of the above structures by metastatic lymph nodes may lead to specific symptoms and signs, which include pleural effusion, hoarseness, phrenic paralysis, dysphagia, superior vena cava compression syndrome, pericardial effusion, Pancoast syndrome, etc.

2.3.3 Symptoms caused by distant metastasis of tumors

The most common symptoms are headache, nausea and vomiting caused by central nervous system metastasis. Bone metastases are usually accompanied by severe and progressive pain.

2.3.4 Extrapulmonary manifestations of lung cancer

Apart from the symptoms of local tumor progression and extra-thoracic metastasis, paraneoplastic syndrome can also occur in lung cancer patients. Lung cancer associated paraneoplastic syndrome can be seen in about 10%–20% of lung cancer patients, mostly in SCLC. Ectopic endocrine disorders, abnormal bone and joint metabolism and neuromuscular conduction disorders are common clinical manifestations. Paraneoplastic syndrome does not always positively correlate with the degree of tumorigenesis, and may sometimes precede the clinical diagnosis of lung cancer. For operable lung cancer with paraneoplastic syndrome, recurrence of symptoms has important implications for tumor recurrence.

2.4 Physical examination

(1) Most early lung cancer patients have no obvious related positive signs.

(2) Patients present extrapulmonary signs such as clubbing fingers (toes), non-wandering joint pain, male breast hyperplasia, skin darkness or dermatomyositis, ataxia and phlebitis.

(3) In patients with highly suspected lung cancer, vocal cord paralysis, superior vena cava obstruction syndrome,

Horner's syndrome and Pancoast syndrome were found by physical examination, suggesting the possibility of local invasion and metastasis.

(4) In patients with highly suspected lung cancer, physical examination revealed hepatomegaly with nodules, subcutaneous nodules, supraclavicular fossa lymph node enlargement and other indicators, suggesting the possibility of distant metastasis.

2.5 Accessory examination

2.5.1 Laboratory examination

2.5.1.1 General laboratory testing

Before treatment, routine laboratory tests are needed to know the general condition of the patient and whether he or she is suitable for corresponding treatment.

- (1) Routine blood test;
- (2) Liver and kidney function and other necessary biochemical and immunological tests;
- (3) Coagulation function test.

2.5.1.2 Serologic testing of tumor markers

The primary lung cancer markers currently recommended by the American Clinical Biochemical Commission and the European Group of Tumor Markers Experts are carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), cytokeratin fragment 21-1 (CYFRA21-1), pro-gastrin-releasing peptide (ProGRP), and squamous cell carcinoma antigen (SCC). Combined use of tumor markers above can improve their sensitivity and specificity in clinical application.

(1) Auxiliary diagnosis

Lung cancer related tumor markers can be detected according to needs in clinical diagnosis, to be used as auxiliary diagnosis and differential diagnosis, and to predict the possible pathological types of lung cancer.

- 1) SCLC: NSE and ProGRP are ideal markers for auxiliary diagnosis of SCLC.
- 2) NSCLC: Elevated serum levels of CEA, SCC and CYFRA21-1 contribute to the diagnosis of NSCLC. SCC and CYFRA21-1 are generally considered to be highly specific for lung squamous cell carcinoma. Combined detecting of NSE, CYFRA21-1, ProGRP, CEA and SCC could improve the accuracy of differentiating SCLC and NSCLC.

(2) Notes

- 1) The detection results of tumor markers are closely related to the detection methods used, and the results obtained by different detection methods should not be

directly compared. In the process of treatment observation, if the detection method is changed, the original detection method must be used simultaneously for parallel detection, so as to avoid wrong medical interpretation.

- 2) Each laboratory should study the detection methods to establish appropriate reference intervals.

3) Unqualified specimens such as hemolysis, coagulation and insufficient blood volume can affect the detection results of coagulation function, NSE and other tumor markers and even liver and kidney indicators.

- 4) The specimens should be sent to the laboratory as soon as possible after collection, and the test results of tumor markers such as pro-gastrin-releasing peptide (ProGRP) and other laboratory indicators can be affected after being placed for too long.

2.5.2 Imaging examination

Imaging examination methods of lung cancer mainly include X-ray chest, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, radionuclide imaging, positron emission tomography-CT (PET-CT) and other methods. It is mainly used for the diagnosis and differential diagnosis of lung cancer, staging and re-staging, evaluation of resectability, therapeutic effect monitoring and pre-evaluation, etc. Imaging examination is the best method for non-invasive detection and evaluation of tumors. The imaging information makes clinicians more confident in the judgment of tumor prognosis and the formulation of treatment decisions. In the diagnosis and treatment of lung cancer, one or more imaging examination methods should be selected reasonably and effectively according to different examination purposes.

2.5.2.1 X-ray chest

In China, positive and lateral chest radiography is often the basic image examination method for the discovery of lung diseases in primary hospitals, which has limited value in the diagnosis of early lung cancer. Once lung cancer was suspected in the chest radiography, CT scan should be timely executed.

2.5.2.2 Chest CT scanning

Chest CT is the most important and commonly used imaging method in the diagnosis, staging, therapeutic evaluation and follow-up after treatment of lung cancer. CT scan can display the image information which cannot be clearly identified on chest X-ray, which can effectively detect early-stage lung cancer, and further verify the location and extent of involvement of lesions. The chest CT scan should cover both adrenal glands in patients with

primary lung cancer. For chest lesions that are difficult to be diagnosed qualitatively, the cytological or histological diagnosis can be obtained by means of CT-guided percutaneous lung puncture biopsy.

The traditional imaging type of lung cancer is divided into central, peripheral and specific sites according to the location of lung cancer. Central lung cancer occurs in the main bronchus, lobes and segments, often causing secondary obstructive changes. Peripheral lung cancer occurs in distal segment of bronchus. The specific sites of lung cancer include superior pulmonary sulcus tumor (Pancoast tumor), etc.

(1) Central lung cancer

Central lung cancer is mostly squamous cell carcinoma and small cell carcinoma, and adenocarcinoma of the central lung cancer has increased in recent years. Early central lung cancer is characterized by localized thickening of the bronchial wall, irregular internal wall, stenosis of the lumen, and increased density in the bronchi with pulmonary artery (axial view), usually without obstructive changes. The imaging findings can sometimes be dominated by obstructive pneumonia, and the inflammation may dissipate after receiving anti-inflammatory treatment, but it is still necessary to consider whether the proximal bronchial wall is thickened. The main manifestations of middle and late central lung cancer were central tumors and obstructive changes, and the earliest obstructive changes were obstructive emphysema, which further developed into obstructive pneumonia and atelectasis. Due to the convex tumor, obstruction of the proximal lung usually forms the opposite "S" sign. The "bronchial ventilation sign" can be seen in CT if there were incomplete bronchial obstruction existing. Enhanced CT can often see dilated and mucus-filled bronchi. A few cases of central lung cancer may show branching changes along segment and sub-segment bronchus. CT thin slice (reconstruction thickness of 1–1.25 mm) enhanced scanning and multi-planar reconstruction (MPR) are of great value in preoperative evaluation of central lung cancer and should be routinely applied. If there is no contraindication, an enhanced scan should be performed. When central lung cancer is accompanied by atelectasis, MRI can help to distinguish the difference between tumor and atelectasis, the signal of atelectasis on T2WI is higher than that of tumor, and the intensity of atelectasis on T1WI enhanced scan is higher than that of tumor.

(2) Peripheral lung cancer

In general, the limited lesions within the lung no more

than 1 cm are called small nodules, no more than 3 cm are called nodules, and those with >3 cm are called masses. The size, morphology, density, internal structure, tumor-lung interface, and volume-doubling time of the node or mass are the most important diagnostic indications in the process of analyzing the image presentation. When observing the characteristics of nodules/masses, thin CT (layer thickness of 1.00–1.25 mm) should be routinely applied. MPR can observe the morphology of nodules in all directions, which is helpful for qualitative diagnosis. As for solid nodules, enhanced, biphasic and dynamic enhanced scans can be selected for differential diagnosis. Intrapulmonary sub-solid nodules, especially pure ground glass nodules, are recommended to be used only in a thin layer.

1) Size and shape

The typical peripheral lung cancer is mostly round, oval or irregular, and mostly lobulated. With the gradual popularity of physical examination, the imaging manifestations of lung nodules and lung nodules in the early stage of lung cancer are increasing. At this point, the diagnosis was relatively easy according to the contour and marginal features of the tumor.

2) Density

CT plain scan: the nodules can be divided into solid nodules, partial solid nodules and pure ground glass nodules according to whether the nodules cover the lung parenchyma (the latter two are collectively referred to as ground glass nodules with nodes or sub-solid nodules). The pure ground glass nodules show simple ground glass density, which means the tumor is creeping along the alveolar framework without covering the lung parenchyma. Peripheral pulmonary vessels can be seen in the lesions. Solid nodules completely cover the lung parenchyma without ground-glass density. Both components are partially solid nodules. Persistent frost-glass nodules, depending on their size and density, are mostly associated with atypical adenomatoid hyperplasia, *in situ* adenocarcinoma, micro-infiltrated adenocarcinoma, and infiltrated adenocarcinoma. The manifestations of lung cancer with ground-glass nodules tend to be multiple. Preoperative careful observation of the thin layer of the whole lung is beneficial to the determination of treatment program.

Enhanced scanning: compared with plain scanning, enhanced CT scan was used to increase 15–20 HU as the threshold to identify benign and malignant lesions. When peripheral nodules are difficult to diagnose, double-phase enhanced scanning and dynamic enhanced scanning can be

selected for further diagnosis.

3) Internal construction

Bronchial gas phase and vacuoles: These can be seen in lung cancer, pneumonia or lymphoma, but lung cancer is more common. Thin-slice CT showed better, and usually existed simultaneously with vacuolar sign. Image reprocessing techniques such as MPR are helpful in showing the oblique bronchial gas phase. Vacuoles generally refer to small cavities of about 1 mm, which are common in adenocarcinoma, accounting for about 20%–25%. They are often multiple, and some of them may be axial phases of the air bronchus, but they are also residual air alveoli that are not filled by tumor.

Calcification: The incidence of intra-nodule calcification was much higher than that of conventional CT, and calcification was found in about 6%–10% of lung cancer. The calcification in the center of nodules/tumors was mostly malignant, and the diffuse small “pepper” shape and indefinite shape were mostly malignant, while the diffuse dense calcification, stratified or popcorn calcification were almost all benign. High spatial resolution algorithm (HRCT) produces edge enhanced artifacts, which are easy to sketch the “high density” of the nodules edge, and easy to mistake for calcification. Standard algorithm or soft tissue reconstruction algorithm can avoid such artifacts.

Vacuole and vesicle: The vacuole is generally believed to be formed by removal of necrotic material through bronchi, which can reach 1–10 cm, and can be central or eccentric. The vacuole wall was mostly 0.5–3 cm, and the thick-walled vacuole and lumpy inner wall supported the diagnosis of lung cancer. The cyst vacuole is generally considered to be a part of lung bullae or lung cyst wall cancer, and a part is caused by the active valve effect formed inside the tumor. The lesions can be located on one side of the cyst vacuole, or can grow around the cyst vacuole. The cyst wall is often uneven, and the main components of the tumor can be solid or glass grinding.

Lung consolidation: The growth and infiltration of the tumor along the alveolar wall have not completely destroyed the inter-alveolar septum, but make the alveolar wall thickened or have secretions in the adjacent alveoli, and some alveoli still contain gas, forming pulmonary consolidation, also known as pneumonia type change. The enhancement scanning can be seen through the enhanced vessels in the parenchyma of solid lung tissue. This can be seen in lung mucinous adenocarcinoma, as well as in obstructive and infectious pneumonia, lymphoma,

pulmonary infarction and pulmonary edema.

4) Tumor-lung interface

Linear shadows extending from the margin of the nodules to the periphery and slightly coarser burr like changes in the proximal nodules are more common in lung cancer. Usually the thickness <2 mm is called fine burr, while the thickness >2 mm is called rough burr. The pathological basis for the formation of burrs is the invasion of adjacent interlobular septa, peritoneal pulmonary parenchymal fibrosis or/and accompanied by inflammatory cell infiltration.

5) Nearby structures

Pleural changes: Pleural tail sign or warping from the fine line of the nodule or mass to the pleura or strip density increase, sometimes a bell mouth peripheral vein, gross lesions is focally as pleural indentation, mainly by the mass endo-genetic fiber caused by scar contraction force caused by local pleural reaction, which can be liquid or fat outside the pleura, pulmonary adenocarcinoma is the most common. The possibility of tumor infiltration along the pleura should be considered in those with thick or irregular linear changes.

Satellite lesions: It is common in lung adenocarcinoma, the shape may be performed as nodules or small flaps. The satellite tumors and the main lesions are located in the same lobes in T3 stage and in the same side of the lung in T4 stage. Benign lesions, especially tuberculosis, can also be seen as satellite lesions.

6) Tumor volume doubling time

Tumor volume doubling time refers to the time required for the doubling of tumor volume (about 26% in diameter), which is an important indicator for judging benign and malignant tumors. The growth rate of lung cancer of different disease types is significantly different, and the doubling time changes greatly, generally the time last more than 30 days, less than 400 days, squamous cell carcinoma < adenocarcinoma < infiltrated adenocarcinoma or orthotopic adenocarcinoma < atypical adenomatoid hyperplasia, the volume doubling time of ground glass nodules in the lung often exceeds 800 days. Three-dimensional volume measurements are easier to accurately compare the changes in nodal volume and determine the doubling time.

(3) Pancoast tumor

CT can show the lesion of apex pulmonis, distinguish the tumor or pleural thickening, and show the extent of bone destruction, chest wall invasion and whether the tumor is invading to the root of the neck. The application of

enhanced CT-MPR and maximum density projection (MIP) is very important, and the latter is mainly used to show whether large vessels, such as subclavian artery, are invaded. MRI has a good soft tissue resolution, showing the anatomical details of the thoracic entrance and brachial plexus, and is superior to CT in determining the extent of tumor invasion and bone marrow invasion. CT is superior to MRI in determining the invasion of cortical bone.

(4) Differential diagnosis of lung cancer in imaging examination

a. Differential diagnosis of bronchial obstructive lesions

Reasons of bronchial obstructive lesions:

Oncogenicity: including central lung cancer, endobronchial benign tumors such as hamartoma and papilloma, and inflammatory myofibroblastoma. Metastatic tumors and lymphoma in a few cases can also cause bronchial obstructive changes.

Infectious: tuberculosis, sarcoidosis, right lobe syndrome, etc.

Other: foreign body, broncholithiasis, pulmonary amyloidosis, etc.

a1. Central lung cancer: As mentioned above.

a2. Tuberculosis: Lung involvement is more in one or more segments than in the whole lobe. Sometimes diffuse lesions can be seen in different lobes or opposite sides. If the whole lobes are cheesy, the lobes can be enlarged in volume, interlobular fissure dilated, and there can be cavities within. Most obstructive changes caused by lung cancer are obstruction of distal whole or leaf or atelectasis (or inflammation).

Tuberculous bronchial lesions may cause bronchial distortion and stenosis, or may be the expansion of the irregular bronchi, and there is no tumor in the proximal end of the lesion, which is an important differentiator from lung cancer. Sometimes, calcification can be seen in the bronchial wall, which supports the diagnosis of tuberculosis. It is difficult to differentiate lung cancer from bronchial stenosis.

There was no significant correlation between the location of the lymph node and the lymphatic drainage area, and there was calcification or edge ring enhancement. Metastatic lymph nodes of lung cancer are related to the distribution of drainage area. Peripheral ring enhancement of lymph nodes can be seen in the metastasis of squamous cell carcinoma, but rarely in adenocarcinoma and small cell carcinoma.

a3. Intraluminal neoplasms: Endobronchial neoplasms are rare, and pathognomias, papilloma, and neurogenic

neoplasms can all lead to different degrees of obstructive alteration. It is difficult to differentiate benign and malignant tumors by imaging when there is no mediastinal or hilar lymph node enlargement in patients with intraluminal soft tissue density masses or nodules with atelectasis in the bronchial cavity. However, benign tumor is very rare. Preoperative diagnosis of central lung cancer is usually very rare. The thin layer CT of hamartoma in the bronchial cavity can detect the fat density and calcification, and the differentiation is relatively easy.

In addition, inflammatory myofibroblastoma located in the bronchial cavity may be associated with obstructive pneumonia and atelectasis, belonging to low-grade interlobar tumors.

a4. Intrabronchial foreign body: A history of foreign body inhalation, repeated immobilization of infection at the site supports the diagnosis of foreign body with obstructive changes. CT examination can easily diagnose when fat density lesions (lipid inhalation) or high-density lesions (bone inhalation) are found in the bronchial cavity.

b. Differential diagnosis of isolated pulmonary nodules/tumors

Etiology of isolated pulmonary nodules/tumors:

Neoplastic: malignant tumors include peripheral lung cancer, single lung metastatic tumor, malignant lymphoma, lung malignant interlobular tissue tumor; benign tumor includes hamartoma, sclerosing hemangioma and so on.

Infectious inflammatory diseases: tuberculosis, spherical pneumonia, pulmonary abscess, mechanical pneumonia and fungal infection.

Dysplasia: bronchial/pulmonary cyst, pulmonary sequestration and arteriovenous fistula.

Others: spherical atelectasis.

b1. Peripheral lung cancer: As mentioned above.

b2. Tuberculous bulb: Tuberculous bulb is usually located in the posterior segment of the upper lobe or the dorsal segment of the lower lobe, but it is not frequently occurring in atypical sites. The image is usually in a circular, quasi-circular shape, regular or irregular, and the contour is often straight into Angle. Based on the characteristics of inflammation, the edge may have long antenna shape or cable shape shadow, and there is often pleural thickening and adhesion in the vicinity, which is different from the burr and pleural entrapment caused by fibro-genic reaction or infiltration of tumor cells along the interlobular septa. Calcification and cavities are quite common, and the nodular thickening of the wall of the tuberculous cavity caused by the necrosis of lung cancer is

more thin and light, and liquid level is rare in the cavity. The nodule hole can also be crescent shaped or a “ring” of oddities. Patchy satellite lesions are often seen around tubercular nodules (masses). In some cases, drainage bronchi can be seen. Enhanced scanning is characterized by no enhancement or circular enhancement, and the thickness of circular enhancement depends on the amount of granulation tissue surrounding the nodule.

b3. Pulmonary hamartoma: Round nodules smooth or with shallow lobes, calcified, typically “popcorn”. Thin-slice CT examination of the fat content in the tumor is helpful for diagnosis. There was no obvious enhancement in enhanced scanning. Chondromatous hamartoma may be lobulated, not calcified or fatty, and may sometimes be differentiated from peripheral lung cancer.

b4. Sclerosing alveolar cell tumor: On chest radiograph, a mass or nodule with a circular, ovoid border, as outlined with a pen. CT scanning has uniform density, sometimes with small and low-density areas and massive punctate calcification, with cystic changing occasionally. Moderate to significant enhancement after CT enhancement. Delayed scanning should be performed for tumors or nodules with a circular, ovoid border with obvious uneven enhancement at the early stage of enhancement. Slight obstructive changes may sometimes occur in the distal portion of the lesion. Pulmonary hilar and mediastinal lymph nodes were rarely involved, and the prognosis was not affected.

b5. Spherical pneumonia, pulmonary abscess and organizing pneumonia: Most of them occur in the dorsal and basal segments of the lower lobe of both lungs, which are located at the periphery of the lung near the pleura, and can be square, flat or triangular. The MPR shows that the lesion is irregular, while the lung cancer is mostly spherical in all directions. In acute inflammation, when the central density is high, the surrounding density is low, the margins are blurred, and an abscess is formed, the center of the lesion may have a regular area of low-density necrosis, and the wall of the cavity is relatively regular when a small cavity is formed. Adjacent to the pleural reactivity thickened, the range is wider. After effective anti-infective treatment, the lesions are usually significantly reduced.

b6. Fungal infection: Aspergilloma: typically, there is a thick wall or thin wall cavity where the nodules with clear edge can be seen inside, with air crescent sign, changing body position to scan, the aspergilloma ball can move. Angio-invasive aspergillosis is characterized by blurred margins or focal lung consolidation with ground glass

density in the early stage, and by vacuolar nodules, or aspergillus, in the late stage. Chronic necrotic aspergillosis can be manifested as consolidation, large cavities, and irregular internal walls. It can be accompanied by lymph node enlargement in pulmonary hilum, mediastinal, pleural effusion and pleural thickening.

b7. Pulmonary sequestration: Imaging examination is very important in the diagnosis of pulmonary sequestration, and the diagnosis can be confirmed in most cases. Most of them are located in posterior inferior lobe or inner basal segment, more on the left side than on the right side. Intra-lobe pulmonary sequestration mainly manifests as uniform density lump, which is circular, ovoid, few can be triangular or polygonal, the boundary is clear, some with uniform density have similar CT value to muscles, and bronchial mutually is characterized by uneven density, cystic change, within the cyst density close to the water, clear boundary, gas sometimes can be seen in the cyst, if any infection, the liquid level is visible, which can change in the short term. The appearance of the extra-lobe pulmonary sequestration is characterized by an increasing density shadow near the posterior mediastinum or on the diaphragm, with clear margins and uniform density and few cystic changes. Multi-slice CT angiography has greater advantages in displaying abnormal arteries and internal structures, and can be used to observe the source of abnormal blood supply arteries from thoracic aorta, abdominal aorta or other rare arteries and drainage veins from multiple perspectives.

b8. Bronchial/pulmonary cysts: It is not difficult to diagnose the patient who is located near the trachea of mediastinum or the hilum of lung. In peripheral lung, most of them are round or nearly round, with clear contour, smooth and few lobes. Water density is typical, and high density is not uncommon. A few people with calcium in milk have higher density than that of soft tissues, but no enhancement was found in enhanced scanning. The cyst wall may be calcified. The occurrence of cysts with bronchioles which can be lobulated, with not only rounded edges, but even small vacuoles which can be seen inside. It is difficult to distinguish from lung cancer, and no changes in density before and after enhancement can be helpful for diagnosis.

b9. Pulmonary arteriovenous fistula: Pulmonary arteriovenous fistula is congenital vascular dysplasia, which is common in young females. CT presented as one or more round or oval nodules, with circular or arcuate calcification, and enhanced scans usually showed thickened blood supply arteries and draining veins.

b10. Spherical atelectasis: Spherical atelectasis is commonly seen after pleurisy and effusion absorption due to local pleural adhesion limiting the expansion of the lung caused by a special type of atelectasis. Most of them are located at the bottom of the lung or the back of the lung, showing round or nearly circular margin clear masses. The CT scan can show that the vascular and bronchial shadow is curved and twisted in the center of the tumor, like a snail or comet tail, adjacent to pleural thickening. The lung volume of the diseased part shrinks, and compensatory emphysema occurred in the surrounding lung.

b11. Single lung metastatic tumor: Most images show circular or slightly lobed nodules with distinct edges, uniform or uneven density, but a few may show irregular edges with burrs. The patients with clear edge and photocoagulation need to be identified with granuloma, hamartoma and other lung benign diseases, while the patients with irregular edge need to be identified with the second primary lung cancer.

2.5.2.3 MRI testing

MRI can be used selectively in the chest to determine whether the chest wall or mediastinum is invaded: to show the relationship between the Pancoast tumor and the brachial plexus and blood vessels; to identify the boundary between pulmonary mass and atelectasis and obstructive pneumonia. For patients are contraindicated in injection of iodine-forming agent, MRI is the first choice for observation of mediastinal, pulmonary large vessels invasion and lymph node enlargement. It is also valuable for differentiating fibrosis and the recurrence of tumors after radiotherapy. MRI is especially suitable to confirm whether there is brain or spinal cords metastasis, and brain enhanced MRI should be used as the preoperative routine examination for staging of lung cancer. MRI's high sensitivity and specificity in metastasis of bone marrow can be selected according to clinical requirements.

2.5.2.4 PET/CT testing

PET-CT is now the best test for the diagnosis, stage and re-stage, evolution of the effects and assessment of prognosis of lung cancer, according to the clinical practice manual of NCCN and The American College of Chest Physicians (ACCP) and the consensus of domestic experts, PET-CT was recommended in such conditions: 1) diagnosis and differential diagnosis of the isolated nodule in lung (solid nodules diameter ≥ 8 mm, partial solid nodules diameter ≥ 6 mm persist and the solid components diameter ≥ 6 mm); 2) preoperative stage of lung cancer, PET-CT has great efficiency in diagnosis of the lymph nodes and extra-chest (except brain metastasis) metastasis; 3) localization of radiotherapy for lung cancer and delineation of target area; 4) adjuvant testing method for the identification of the postoperative scarring of tumor or the recurrence of the tumors that CT cannot help, if the lesions uptake in PET-CT, biopsy is needed for the further diagnosis; 5) adjuvant testing method for diagnosis for the fibrosis of tumor after radiotherapy or postoperative tumor recurrence, if PET-CT uptake, biopsy is needed to confirm; and 6) adjuvant testing method to evaluate the therapy efficiency of the lung cancer (especially the molecule targeting therapy), PET Response Criteria in Solid Tumors (PERCIST) is recommended (*Table 1*).

2.5.2.5 Ultrasound testing

Due to the obstruction of the air in lung and ribs and sternum, ultrasound usually cannot show the lesion in the lung. Ultrasound is always used in the supraclavicular lymph nodules, liver, adrenal glands, kidneys and other viscera where tumor metastasis to support the information of the stage of the tumors. Ultrasound can help to detect the pleural and pericardial effusion and locate the fluid before pumping. Ultrasound-guided puncture can be used to perform biopsy for metastatic tumor of sub-pleural lung tumor, supraclavicular lymph nodes and parenchymal

Table 1 PET Response Criteria in Solid Tumors (PERCIST) (2009)

Category	Definition
Complete metabolic remission (CMR)	The uptake of ^{18}F -FDG in the lesions can be completely disappeared, which is lower than the average radiation activity of liver, and cannot be distinguished from the background area of surrounding blood pool
Partial metabolic remission (PMR)	The uptake of target lesion ^{18}F -FDG decreased more than 30% and the absolute value decreased more than 0.8
Stable disease metabolic (SMD)	Not CMR, PMR, PMD
Progressed disease metabolic (PMD)	The uptake of target lesion ^{18}F -FDG increased more than 30% and the absolute value increased more than 0.8; Or the new lesion come out.

It is recommended to adopt lean body weight (LBW) calibration standard uptake value (standardized uptake value) to reduce the influence of patients' weight change on parameters during treatment.

viscera. The diagnosis of lung cancer is mainly based on the clinical manifestations and the various auxiliary examinations. Lung cancer, especially peripheral lung cancer, is difficult to differentiate in image from some tuberculosis lesions, as well as some chronic inflammatory lesions. Therefore, the diagnosis of lung cancer requires various biopsy or puncture techniques to obtain pathological or cytological evidence.

2.5.2.6 Bone scintigraphy

Bone scintigraphy becomes the routine examination of bone metastasis of lung cancer. When the bone scintigraphy revealed suspicious bone metastasis, MRI, CT and PET/CT examination were performed to verify the suspicious site. Preoperative PET-CT examination can replace bone scintigraphy.

2.5.3 Endoscopy and other examinations

2.5.3.1 Bronchoscopy and ultrasound trans-bronchial needle aspiration biopsy

Bronchoscopy is of great value in localization and histologic diagnosis of tumors. For central lung carcinoma, bronchoscopy can directly observe the lesion, and more than 95% of the lesions can be confirmed by cytological brush and histological biopsy. Biopsy can also be performed in lung hilum and mediastinal lymph nodes adjacent to the bronchus by ultrasound bronchoscopy for the qualitative diagnosis of lung cancer and diagnosis for the stage of mediastinal draining. A variety of navigation techniques have been used to perform biopsy for peripheral lung cancer.

2.5.3.2 Mediastinoscopy

By standard and expanded mediastinoscopy, 2R, 2L, 4R, 4L, 5, 6, 7, and 10 lymph nodes can be obtained for qualitative diagnosis of lung cancer and regional lymph node staging. Previously, it was used as the gold standard for the assessment of mediastinal lymph node metastasis. Due to the need of general anesthesia for mediastinoscopy and the maturity of ultrasound bronchoscopy and esophagoscopic biopsy, mediastinoscopy has a decreasing trend in the diagnosis and staging of lung cancer.

2.5.3.3 Thoracoscopy or open lung biopsy

For lung lesions found in the imaging examination, sputum cytology examination, bronchoscopy and puncture for biopsy examination failed to obtain histological and cytological evidence in the diagnosis of lung cancer, or lung cancer cannot be excepted after clinically short-term observation, thoracoscope and even open-surgery lung biopsy can be one of the methods of qualitative diagnosis of

lung cancer.

2.5.3.4 Sputum exfoliation cytology examination

Sputum exfoliation cytology is simple, non-invasive and can be accepted by patients easily. It is one of the simple and effective methods for qualitative diagnosis of lung cancer and can also be used as a screening method for high-risk groups of lung cancer. The positive rate of sputum exfoliation cytology was related to the collection of sputum specimens, the preparation of cytology smear, the diagnostic level of cytologists, the location of tumors and the pathological type.

2.6 Histopathological examination

2.6.1 Diagnostic criteria

The pathological diagnosis of lung cancer in biopsy specimens mainly detects the presence and type of tumor. The pathological diagnosis should be classified into subtypes as far as possible for patients with advanced inoperability, and immunohistochemical staining is necessary for morphological atypical cases. The diagnosis of non-specific types (NSCLC-NOS) should be avoided. Histologic type of large lung cancer specimen resected by surgery should be based on the 2015 WHO classification standard version of lung cancer. The pathological diagnosis of adenocarcinoma *in situ*, minimally invasive adenocarcinoma and large cell carcinoma cannot be completed in small biopsy specimens and intraoperative freezing, and the diagnosis can only be made after surgical removal of all specimens or sampling.

2.6.2 Specifications for diagnosis

The pathological diagnosis of lung cancer is composed of specimen processing, specimen collection, pathological examination and pathological report.

2.6.2.1 Specimen processing essentials

It is recommended that 10% neutral buffer formalin fixative solution should be used to avoid the use of fixed liquid containing heavy metals. The amount of fixed liquid should be more than 10 times than the volume of the fixed specimen and fixed at constant temperature. Specimens should not be left *in vitro* for more than 30 min. Biopsy specimens can be inserted directly into the fixative fluid, lung lobes or total pneumonectomy specimens can be injected with sufficient fixative fluid from the bronchi, or the probes can be inserted along the bronchial wall and cut into lung tissue for fixation. Fixed time: the biopsy specimen of bronchoscope should be 6–24 h; Surgical

specimens resected should be stored for 12–48 h.

Cytological smear (sputum, pleural fluid) should be fixed with 95% alcohol solution, which should not be less than 15 min, or non-gynecological liquid-based cytological fixative solution (fixation time and method can be operated according to the instructions). When the exfoliated cell wax block was needed, the cell mass after centrifugation was the same as the tissue fixation procedure, and was fixed with 10% neutral buffer formalin fixative solution for a duration of more than 2 h.

2.6.2.2 General description and requirements for sampling

- (1) All biopsy specimens will be taken after check.
- (2) Specimens for local pneumonectomy.
 - 1) Remove surgical sutures or metal pins;
 - 2) Record the size of the specimen and the appearance of the pleural surface;
 - 3) The lung parenchyma was excised from the vertical incisional margin to describe the size of the mass, the cut surface (with no bleeding, necrosis, cavitation) and its relationship with the pleura and lung parenchyma, as well as the distance between the edge of the mass and the incisional margin;
 - 4) Tumor, tumor and pleura, tumor and lung parenchyma were cut according to the lesion location and size, and the tumor body should be collected when the tumor <3 cm;
 - 5) Excise lung tissues from non-tumor sites.
- (3) Lobectomy specimen.
 - 1) Five basic structures of the lung: airways, lung parenchyma, pleura, blood vessels, and lymph nodes. Measurements were taken to locate the specimen in the hilum of the lung;
 - 2) The bronchial incisional edge, the vascular incisional edge, and the proximal part of the tumor to the pleura, or the adhesion to other pulmonary lobes were taken;
 - 3) Looking for lymph nodes of lung hilum;
 - 4) According to the location and stage of the tumors, there are two choices: First, the specimens of lung tissue (by means of a probe inserted into the trachea) can be incised along the bronchial wall and tumor, by which the bronchi and their branches can be exposed greatly, and so is the relationship of the lesion and the surrounding lung tissues. Second, for those samples with main bronchus filled with formaldehyde should be cut every 0.5–1.0 cm, and the section should be in the frontal plane, perpendicular to the hilum of the lung;
 - 5) Describing the tumor size, cross-section (with no bleeding, necrosis, caviation), position in lobes and lung segments and relationship with bronchi, range of lesions

(focal or metastasis), and distal and local secondary changes. The number of the samples relies on the size of the lesion (tumors should be taken if diameter <3 cm), the site, accompanying symptoms (related to clinical stage), and it should contain tumor and pleura, tumor and lobe or segment bronchus (different from specimens), tumor and peripheral lung tissues or secondary lesions, tumor and pulmonary or bronchial broken residual. Cross-lobes specimens should also include the part of the tumor and the crossed lobes. All lymph nodes should be collected from N2 or other sites. It is recommended that the volume of tissue blocks obtained should not be greater than 2.5 cm × 1.5 cm × 0.3 cm.

2.6.2.3 Key pathological features

General descriptions contained type of specimen, size of tumor, relationship with bronchial (different specimens) or with the pleural, other accompanying lesions and multiple lesions, incisional margins.

Diagnosis contents contained tumor location, histological subtypes, range of involvement (bronchi, pleural, vascular, nerves, types of accompanying lesions, intra-pulmonary spread and metastasis of lymph nodes), incisional margin and necessary special dyeing, immunohistochemical results or molecular pathological results. And the included information should satisfy the need of clinical stage, offering the pTNM stage. Multiple lung cancers should be identified as clearly as possible according to the morphological features of each lesion, namely intra-pulmonary metastasis or multiple primary cancers.

2.6.2.4 Immunohistochemical, special dyeing and molecular pathological examination

Immunohistochemical biomarkers (namely TTF-1, Napsin-A, p63, P40, and CK5/6) should be chosen to differentiate adenocarcinoma and lung squamous-cell cancer. TTF-1 and P40 can be firstly chose if the tissue was not enough. CD56, Syn, CgA, Ki-67 and TTF-1 should be selected as the markers of neuroendocrine tumor. Based on the morphological features of neuroendocrine, at least one neuroendocrine marker is definitely positive, and the number of positive cells should be more than 10% of the tumor cells before the diagnosis of neuroendocrine tumor. The identification of intracellular mucous substances should be carried out by special staining of mucicarmine staining and AB-PAS. Special staining of elastic fibers should be performed for suspected involvement of pleura.

It is recommended that epidermal growth factor receptor (EGFR) mutation should be examined for II–IIIa non-squamous-cell lung cancer with positive N1/N2 and small

specimen squamous-cell lung cancer patients. For patients with advanced NSCLC, EGFR, anaplastic lymphoma kinase (ALK) fusion gene and ROS1 detection should be routinely performed at the time of diagnosis. If condition permitted, Braf, Cmet, Her-2, Ret and PD-L1 immunohistochemistry can also be performed. The detection of EGFR mutation can adopt ARMS method. The detection of ALK fusion gene can be performed by Ventana immunohistochemistry, fluorescence *in situ* hybridization (FISH) or RT-PCR. The detection of ROS1 fusion gene can be done by RT-PCR or FISH. For some patients, the tissues cannot be offered, blood can replace tissues for the EGFR examination, detection methods can be selected by technologies such as highly sensitive ARMS high-throughput sequencing or digital PCR. Liquid biopsy was not recommended in ALK and ROS1 fusion genetic detection. Detection of EGFR T790M was recommended in patients with EGFR TKIs resistance. Histological examination was the gold standard, if tissues cannot be offered, detection of ctDNA, EGFR, T790M of blood can be the effective supplement. High-throughput sequencing can be used as a supplementary method for genetic testing, but the NGS quality control and industry standards are lacking currently, as well as high cost and prices, which limits the application of this technology in clinical practice.

2.6.3 Pathological diagnosis report

2.6.3.1 Tumor

- (1) Histological type
- (2) Range of involvement
- (3) Pleural invasion
- (4) Vascular invasion
- (5) Neuro invasion

2.6.3.2 Incisal margin

- (1) Bronchi incisal margin
- (2) Vascular incisal margin
- (3) Pulmonary incisal margin (regional lung incisal margin)

2.6.3.3 Other pathological stuff (such as obstructive pneumonia, changes related to the treatment)

2.6.3.4 Regional lymph nodes (including peripheral bronchi, hilar and isolate lymph nodes)

- (1) Total number
- (2) Number of involvement

2.6.3.5 Metastasis

2.6.3.6 Other tissues/organs

2.6.3.7 For cases with difficulty, submit to a superior hospital for consultation (provide original pathology report to check

the submitted biopsy information to reduce errors, provide adequate pathological sections or wax blocks, intraoperative condition, etc.)

3. Pathological type and stage of lung cancer

3.1 WHO's 2015 standard (Table 2)

The main tissue types of lung cancer are squamous cell carcinoma and adenocarcinoma, accounting for about 80% of all PLC. Other rare types include: adeno-squamous carcinoma, large cell carcinoma, neuroendocrine carcinoma (carcinoid, atypical carcinoid and small cell carcinoma) and small parotid-derived cancer (adeno-cystic cystic carcinoma, mucoepidermoid cancer and malignant pleomorphic adenoma).

3.1.1 Squamous cell carcinoma

The incidence of lung squamous cell carcinoma has declined in recent years, accounting for 30%–40% of lung cancer, of which 2/3 is central type, 1/3 is peripheral type, and can be formed with cavities. Polyps can be located at the center. The spurs protrude toward the bronchial lumen. This type of cancer is generally thought originating from squamous metaplasia of bronchial epithelium after smoking stimulation, and is classified into high, medium, and poor differentiated according to the degree of differentiation of cancerous keratinocytes. Squamous cell carcinoma is frequently metastasized by lymphoid and blood vessels, and may directly invade mediastinal lymph nodes, bronchus and mediastinal soft tissues. Postoperative local recurrence was more common than other types of lung cancer. Extensive, multifocal molecular pathology exists in bronchial and respiratory epithelium of smokers and lung cancer patients. Abnormal, regional carcinogenic effects can result in multi-center lung tumors caused by smoking.

3.1.2 Adenocarcinoma

Adenocarcinoma, which accounts for 40%–55% of lung cancer, has surpassed squamous cell carcinoma as the most common type of lung cancer in many countries. Adenocarcinoma is more common in clinic with peripheral type, and the formation of cavities is rare. In recent years, the most important change in the pathology of lung adenocarcinoma is the concept of “*in situ* adenocarcinoma”. It is suggested that the term “bronchioloalveolar carcinoma” should not be used any more. For invasive

Table 2 Histological type of lung cancer (WHO 2015)

Histological type	ICDO	Histological type and subtype	ICDO
Epithelial tumor		Neuroendocrine tumor	
Adenocarcinoma	8140/3	Small cell lung cancer	8041/3
Embryonic adenocarcinoma	8250/3	Mixed small cell carcinoma	8045/3
Acinar adenocarcinoma	8551/3	Large cell neuroendocrine carcinoma	8013/3
Papillary adenocarcinoma	8265/3	Mixed large cell nerve	8013/3
Solid adenocarcinoma	8230/3	Carcinoid	
Infiltrating mucous gland	8253/3	Typical carcinoid	8240/3
Mucus/non-mucus mixing	8254/0	Atypical carcinoid	8249/3
Globular adenocarcinoma	8480/3	Preinvasive lesion	
Fetal adenocarcinoma	8333/3	Diffuse idiopathic pulmonary nerve	8040/0
Intestinal adenocarcinoma	8144/3	Large cell carcinoma	8012/3
Microinvasive adenocarcinoma		Adenosquamous carcinoma	8560/3
Non-mucinous	8256/3	Sarcomatoid carcinoma	
Mucinous	8257/3	Polymorphic cell carcinoma	8022/3
Preinvasive lesion		Spindle cell carcinoma	8032/3
Atypical adenomatoid	8250/0d	Giant cell carcinoma	8031/3
Adenocarcinoma <i>in situ</i>		Sarcoma	8980/3
Non-mucinous	8250/2	Pulmonary cell tumor	8972/3
Mucinous	8253/2	Other unclassified carcinoid	
Squamous cell carcinoma	8070/3	Lymphoid epithelial carcinoma	8082/3
Keratinized squamous	8071/3	NUT cancer	8023/3
Non-keratinized scaly	8072/3	Salivary gland tumor	
Basal squamous	8083/3	Mucin epidermoid carcinoma	8430/3
Preinvasive lesion		Adenoid cystic carcinoma	8200/3
Squamous cell carcinoma <i>in situ</i>	8070/2	Epithelial-myoepithelial carcinoma	8562/3
		Pleomorphic adenoma	8940/0

adenocarcinoma, it should be named by it preponderant components while indicating the proportion of other components, and the type of “mixed adenocarcinoma” should no longer be used. Briefly as follows: 1) Atypical adenomatous hyperplasia (AAH). AAH is at least a precancerous lesion of lung adenocarcinoma. AAH is usually within 0.5 cm, and the “ground glass” is the characteristic of CT scanning. Microscopic histology show that the alveolar structures are intact, alveolar epithelial hyperplasia is uniformly cuboid or short column, with mildly atypical, and nucleoli are absent or vague; 2) Adenocarcinoma *in situ* (AIS). AIS is a new concept proposed in 2011. Solitary adenocarcinoma defined as no more than 3 cm, which is confined to normal alveolar structures (adherent growth) and consists of type II alveolar epithelium and/or Clara cells. AIS nuclear heteromorphism is not obvious, and the widening of alveolar septum with

fibrosis is common. The disease-free survival rate after surgical resection is 100%; 3) Micro-invasive adenocarcinoma (MIA). MIA is defined as a single adenocarcinoma of ≤ 3 cm, with clear boundaries and adherent growth. The invasive carcinoma should be in a form other than adherence. The maximum diameter of the invasive interstitial is less than 5 mm, except for vascular invasion and pleural invasion, and risk factors such as dissemination of tumor cells in the airway. Adenocarcinoma that occurs in multiple lungs can also be used for the diagnosis of MIA, except for the possibility of dissemination in the lungs. If the MIA is completely excised, the overall 5-year survival rate is 100%; and 4) Invasive adenocarcinoma. Adenocarcinoma can be single, multiple, or diffuse. The morphology of invasive adenocarcinoma mainly includes adherent, acinar (glandular), papillary, micropapillary and solid mucus secretion.

3.1.3 Neuroendocrine carcinoma

Neuroendocrine cancers are classified into carcinoid, atypical carcinoid, SCLC, and some large cell neuroendocrine carcinomas. SCLC accounts for 15%–18% of all lung cancers, and is a poorly differentiated neuroendocrine carcinoma with necrosis and a high mitotic index. SCLC has neuroendocrine granules in at least two-thirds of cases under electron microscopy. Combined SCLC refers to SCLC combined with other non-small cell types, found in less than 10% of SCLC cases. According to the clinical behavior and pathological features, the carcinoid is divided into carcinoid and atypical carcinoid, the former is low malignant and the latter is slightly more malignant. The difference between the two is that every 10 high-power fields have two mitotic figures as boundaries. In addition, the presence or absence of small necrosis is a kind of the differences. Compared with carcinoid, atypical carcinoids often occurs in the periphery, the metastasis rate increases, and the prognosis is relatively poor. Carcinoids differ from other lung cancers in that they are not associated with smoking, but have many similarities in molecular pathology to other types of lung cancer. Large cell lung cancer is a poorly differentiated adenocarcinoma with no differentiation feature of adenocarcinoma, squamous cell carcinoma or SCLC, accounting for about 9% of lung cancer, and is an exclusive diagnosis. Subtypes include large cell neuroendocrine carcinoma, lymphoid epithelial carcinoma, basal cell type, clear cell-like carcinoma, and large cell carcinoma with striated muscle phenotype components. Large cell carcinoma is usually large in size and located in the periphery, often invading the visceral pleura, chest wall or adjacent organs. Basal cell types can be central and grow along the bronchial wall. Tumor spreads like other types of non-small cell carcinoma. Large cell neuroendocrine carcinoma is a large cell carcinoma characterized by immunohistochemistry and morphological neuroendocrine differentiation. Usually, the peripheral nodules are accompanied by necrosis, and the prognosis is similar to that of SCLC. Combined large cell lung cancer refers to the combination of other differentiated non-small cell carcinoma components, and most of the composite components are adenocarcinoma.

3.1.4 Other types of lung cancer

(1) Adeno-squamous carcinoma. It only accounts for 0.6%–2.3% of all lung cancers. According to the new WHO classification, tumors must contain at least 10% adenocarcinoma or squamous cell carcinoma to diagnose adeno-squamous carcinoma, often located in the periphery

with central scar formation. Metastatic characteristics and molecular biology are indistinguishable from other NSCLCs. (2) Sarcomatoid cancer. A poorly differentiated non-small cell carcinoma containing sarcoma or sarcomatoid components (fusiform or/and giant cell-like), divided into 5 subtypes: pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma and pulmonary blastoma. (3) Small parotid-derived cancers. Including adenoid cystic carcinoma, mucoepidermoid carcinoma and malignant pleomorphic adenoma. Sometimes mucinous epidermoid carcinoma and solid lung adenocarcinoma secreted by mucus are differentially diagnosed. The key difference is that the latter belongs to the poorly differentiated adenocarcinoma category, and the atypical shape is obvious.

3.1.5 Immunohistochemistry and special staining

Reasonable and appropriate selection of immunohistochemistry projects can effectively retain enough tissue specimens for molecular diagnosis. When tumor differentiation is poor and there is no clear morphological features of adenocarcinoma or squamous cell carcinoma, it is necessary to use immunohistochemistry or mucin staining to confirm the diagnosis.

Immunohistochemical markers for the differentiation of adenocarcinoma and squamous cell carcinoma should be selected from TTF-1, Napsin-A, P63, P40 and CK5/6. Among them, P40 and TTF-1 can solve the problem of differential diagnosis of most adenocarcinoma and squamous cell carcinoma. For patients with further progression of the disease, in order to preserve the tissue as much as possible for molecular pathology, it is recommended to use the restriction immunohistochemistry to detect histological classification. For example, to detect the protein P63/P40 expressed in squamous cell carcinoma, single expression in the protein TTF-A/Napsin-1 on adenocarcinoma cells can classify most NSCLC. The identification of mucous material in solid adenocarcinoma cells should be carried out by sticking and AB-PAS special staining; if the pleura is suspected, special staining of elastic fiber should be confirmed. Neuroendocrine tumor markers can be selected from CD56, Syn, CgA, Ki-67 and TTF-1. On the basis of neuroendocrine morphological features, at least one neuroendocrine marker is clearly positive, and the number of positive cells should be >10% of tumor cells to diagnose neuroendocrine tumors; endocrine markers only need to be closely combined with pathological morphology when CD56 performs positive.

3.2 Stage of lung cancer

TNM staging (pTNM staging UICC version 8) standard:

T stage (primary tumor)

pTX: no primary tumor was found, or cancer cells were found through sputum cytology or bronchial lavage, but imaging and bronchoscopy were not available.

PT0: no evidence of primary tumors.

pTis: carcinoma *in situ*.

pT1: the maximum diameter of the tumor was ≤ 3 cm, surrounding lung tissues and the visceral pleura, and the tumor invaded the lobe bronchus by bronchoscopy, but not the main bronchus.

pT1mi: small invasive adenocarcinoma.

PT1a: the maximum diameter of tumor is less than or equals to 1 cm.

PT1b: the maximum diameter of tumor is less than or equals to 2 cm but more than 1 cm.

PT1c: the maximum diameter of tumor is less than or equals to 3 cm but more than 2 cm.

PT2: the maximum diameter of tumor is less than or equals to 5 cm but more than 3 cm; or the tumor has invaded the main bronchus (uncommon surficial extension tumor, no matter how much the volume is, if the tumor invaded the wall of bronchus, it should be classified as T1, although the tumor may invade main bronchus), without invading carina of trachea; the visceral pleura was invaded; obstructive pneumonia or partial/total atelectasis. Any of the above condition will be classified as T2.

pT2a: the maximum diameter of tumor is less than or equals to 4 cm but more than 3 cm.

pT2b: the maximum diameter of tumor is less than or equals to 5 cm but more than 4 cm.

pT3: the maximum diameter of tumor is less than or equals to 7 cm but more than 5 cm. Or any tumor invades the following organs: wall of chest (including Pancost tumor), phrenic nerve, the pericardium; or sole tumor nodule occurs in the same lobe. Any of above will be classified as T3.

pT4: the maximum diameter of tumor is more than 7 cm; or any diameter with any of following organs invaded, including mediastinal, cardiac, large vessels, carina, laryngeal recurrent nerve, main bronchus, esophageal, vertebral, diaphragm; sole tumor nodules occur in ipsilateral different lobes.

N-regional lymph nodules

pNX: regional lymph nodes cannot be evaluated.

pN0: no regional lymph nodes metastasis.

pN1: ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and pneumonia inner lymph nodes metastasis, including direct invasion.

pN2: ipsilateral mediastinal and/or subcarinal lymph node metastasis.

pN3: contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalenus anterior and super clavicular lymph nodes.

M-distant metastasis

MX: distant metastasis cannot be defined.

pM1a: located in thoracic cavity, contralateral pneumonia tumor nodules; pleura or nodules of pericardium; or malignant pleural (pericardium) effusion.

pM1b: distant single organ single focal metastasis/multiorgan metastasis beyond the thoracic.

pM1c: distant single organ multifocal metastasis/multiorgan metastasis beyond the thoracic.

Clinical stage

Occult carcinoma: TisN0M0

IA1: T1a (mis) N0M0, T1aN0M0

IA2: T1bN0M0

IA3: T1cN0M0

IB: T2aN0M0

IIA: T2bN0M0

IIB: T1a-cN1M0, T2aN1M0, T2bN1M0, T3N0M0

IIIA: T1a-cN2M0, T2a-bN2M0, T3N1M0, T4N0M0, T4N1M0

IIIB: T1a-cN3M0, T2a-bN3M0, T3N2M0, T4N2M0

IIIC: T3N3M0, T4N3M0

IVA: any T, any N, M1a; any T, any N, M1b

IVB: any T, any N, M1c

4. Lung cancer treatment

The treatment of lung cancer should follow the principle that combines the multidisciplinary team and personalized treatment together, according to the patient's performance status (PS), histologic type, molecular profiling, tumor involvement and prognosis. Multiple modalities are commonly used properly either alone or in combination, including surgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy, with an aim to maximize tumor control, improve survival results and minimize treatment toxicity.

4.1 Surgery

In general, anatomic lung resection is the essential

approach for stage I or II disease. The resections are defined as complete, incomplete and uncertain resection. Complete resection is preferred to reduce the incidence of tumor recurrence and metastasis, and secure the accurate pathologic staging and molecular types, thus determining the postoperative treatment.

4.1.1 Surgical anatomy of bronchi and lung system

The trachea is a ventilation pipe connecting the throat and bronchoalveolar system. The length of the trachea is about 10–13 cm. From the inferior margin of the cricoid cartilage (about the level of lower margin of the 6th cervical vertebra) to the carina (about the level of the 4th thoracic vertebra), there are usually 18–22 cartilage rings. The blood supply of the trachea is segmental: the upper part of the trachea mainly comes from the branches of the inferior thyroid artery and the lower part from the branches of the bronchial artery. Therefore, isolating trachea too long would affect the blood supply and healing of the reserved trachea.

The trachea is divided into the left and right main bronchi at the carina level. The angle between the main bronchus and the trachea is more straight on the right side than on the left side, so the foreign body inhaled into the trachea by mistake is more likely to enter the right main bronchus. The right main bronchus bifurcates into the right upper lobe bronchus and the intermediate bronchus, and the latter further bifurcates into the middle lobe and the lower lobe bronchus. The right upper lobe bronchus is further divided into 3 segments of bronchus: apex, posterior and anterior. The middle lobe bronchus is further divided into 2 segments of bronchus: medial and lateral. The lower lobe bronchus consists of 1 superior and 4 basal bronchi: internal, anterior, posterior and posterior. The length of the left main bronchus is about 4.5–5 cm, which bifurcates into the upper lobe and the lower lobe bronchus. The left upper lobe bronchus is further divided into the intrinsic upper lobar bronchus and the lingual lobar bronchus. The former is usually divided into anterior bronchus and posterior apical bronchus, while the latter is divided into upper lingual bronchus and lower lingual bronchus. The lower lobe bronchus also consists of superior bronchus and basal bronchi: internal anterior, posterior and posterior. The right lung is divided into 3 lobes by horizontal and oblique fissure and 10 segments, accounting for 55% of the respiratory function. The left lung is divided into 2 lobes by oblique fissure and 8 segments, accounting for 45% of the respiratory function.

The blood supply of the lung includes the pulmonary circulation system in pulmonary arteriovenous pattern and body circulation system in bronchial vessels pattern. The bronchial artery is mainly emanated from the descending aorta or intercostal artery, accompanied by the bronchi, and eventually forms a network of capillaries supplying the bronchi in the adventitia and submucosa. Venous blood mainly flows into the pulmonary vein, a small part into the bronchial vein, and then into the azygos vein and the semiazygos vein. The main trunk of pulmonary artery originates from the right ventricle, ascending to the left, and divided into left and right pulmonary trunk under the aortic arch. The right pulmonary trunk is longer than the left pulmonary artery, but its branches begin earlier than the left ones. The pulmonary artery is usually accompanied with the corresponding bronchi. Both left and right pulmonary veins consist of superior and inferior pulmonary veins, which go into the left atrium respectively. The right pulmonary middle lobe veins usually join together with the right superior lobe veins to form the superior pulmonary veins.

4.1.2 Indications for lung cancer surgery

From the perspective of lung cancer alone, the absolute indication of lung cancer surgery is the T1–3N0–1M0 disease, the relative indication of the surgery is part of T4N0–1M0 disease, and the controversial indication is the T1–3N2M0 disease. Exploratory surgical indications for lung cancer include part of stage T1–3N0–1M1 with solitary metastases.

4.1.3 Contraindications of lung cancer surgery

The contraindications recognized for lung cancer surgery include: 1) the stage of lung cancer beyond the scope of surgical indications; 2) poor PS, with a Karnofsky score below 60%; 3) acute myocardial infarction within 6 weeks; 4) severe ventricular arrhythmia or uncontrollable heart failure; 5) cardiopulmonary failure to meet the intended operation; 6) more than 50% of carotid artery stenosis for patients over 75 years old, or patients under 75 with more than 70% of carotid artery stenosis; 7) patients over 80 years old requiring pneumonectomy; 8) serious, uncontrollable accompanying disease continues to impair the patient's physiological and psychological function; and 9) patients refused surgery.

4.1.4 Complete resection of lung cancer

At present, surgical resection of lung cancer should include

anatomical lobectomy (including combined lobectomy), lobectomy with bronchoangioplasty, pneumonectomy, and systematic mediastinal lymph node dissection. The NCCN guidelines defined criteria for complete resection of lung cancer. Complete resection: 1) all incisional margins including bronchi, arteries, veins, peribronchial tissues and tissues adjacent to tumors are negative; 2) systemic lymph node dissection must include 6 stations of lymph nodes, 3 of which come from intrapulmonary (lobar, interlobar or segmental) and hilar lymph nodes, and the other 3 stations are from mediastinal lymph nodes, including subcarinal lymph nodes; 3) no extracapsular nodal extension of the tumor; and 4) the highest mediastinal node removed must be negative. Complete resection requires all the criteria above, otherwise the resection would be defined as incomplete.

4.1.5 Lymph node dissection for lung cancer

Mediastinal and hilar lymph node dissection is indispensable for lung cancer surgery. Lobectomy or pneumonectomy with systemic mediastinal lymph node dissection is considered the standard surgical procedure for lung cancer.

So far, the lymph node atlas in 2009 from International Association for the Study of Lung Cancer (IASLC) is used worldwide. In this atlas, the mediastinal lymph nodes consist of 9 stations. Standard mediastinal lymph node dissection, also known as complete mediastinal lymph node dissection, requires *en bloc* resection of the mediastinal lymph node and its surrounding adipose tissue.

4.1.6 Surgical procedures for lung cancer

Lung cancer surgery can be divided into complete resection (radical resection), incomplete resection (palliative resection) and biopsy for diagnostic purposes, according to the degree of resection completeness. It also can be defined by the removed lung as wedge resection, lobectomy, combined lobectomy (removal of more than one lobe), pneumonectomy, lobectomy with bronchoangioplasty, and extended resection of organs and tissues involved; According to the size of the incision, lung cancer surgery can be defined as conventional thoracotomy, small-incision thoracotomy, video-assisted thoracic surgery (VATS), and other minimally invasive surgery. Generally, resection of lung cancer specifically refers to complete resection. Lobectomy with systematic lymphadenectomy is the standard procedure for lung cancer surgery.

The standard procedure of anesthesia for lung cancer resection is double lumen endotracheal intubation, while the operative side is not ventilated. The patient lies on the contra-operative side. Surgical incision is usually performed by the posterolateral incision through the 5th or 6th intercostal spaces. The key to lobectomy is to dissect the fissures between the lobes, ligate the branches of pulmonary arteries and pulmonary veins of the lobe, and cut off all these blood vessels and the bronchus of the lobe, so as to removed the lobe. For lobectomy, the procedure is commonly started with the dissection of fissure. Sleeve lobectomy is usually considered when a central disease invades the opening the lobar bronchus, which results in the tumor residual at the margin of bronchus, or the margin that is too close to the tumor. If sleeve lobectomy is not enough for a free margin, pneumonectomy should be considered. The most common reason for pneumonectomy is not the unsafe margin of the bronchus, but the involvement of the pulmonary artery. Basically, the left pneumonectomy is usually performed. Right pneumonectomy is not commonly used in our clinical practice because of the pulmonary function loss, poor quality of life and poor tolerance to adjuvant treatment consequently. Bilobectomy mainly refers to middle and lower lobe resection and upper and middle lobectomy. The common reason for the former is to secure a safe margin when the tumor involves the root of middle lobe bronchus or the root of the superior bronchus in lower lobe. Since the right middle lobe pulmonary veins usually converge into the superior lobe pulmonary veins to form the superior pulmonary veins, the upper and middle lobectomy may be necessary if the junction of superior lobe veins and the middle lobe veins are invaded.

4.1.7 Surgical complications of lung cancer

The incidence of postoperative complications of lung cancer is about 8%–35%. The most common complications are related to respiratory and cardiovascular system, whereas air leakage and bronchopleural fistula are particular for lung surgery.

4.1.7.1 Respiratory complications

It usually happens in patients with chronic bronchitis preoperatively. The common problems are atelectasis and obstructive emphysema, resulting from the sputum blocking the airway. The reasons for the formation of sputum thrombus vary, such as intubation by anesthesia, intraoperative manipulation, which caused increased

mucous secretion, together with the postoperative pain, bronchial branch of vagus injury, as well as insufficient ventilation, which compromises the effectiveness of cough postoperatively. The clinical symptoms are low breathing, hypopnea, low oxygen saturation and infection with fever. The patients need to be helped to expel sputum, and some patients undergo bronchoscopic aspiration of sputum, while very few patients need tracheotomy.

4.1.7.2 Air leakage of the lung

Because the dissecting pulmonary fissure may cause air leakage on the surface of fissure, this complication usually happens in patients with emphysematous bulla. The diagnosis is persistent bubbles escaping from the thoracic drainage tube, which should also be differentiated with bronchopleural fistula. The key of the treatment is adequate drainage to ensure the recovery of the reserved lungs and prevent infection. By the postoperative adhesions on the surface of the lung, the volume of air leakage reduced gradually in most of the patients.

4.1.7.3 Bronchopleural fistula

Bronchopleural fistula is a series of clinical symptoms and signs caused by poor healing of bronchial stump that gets the airway into pleural cavity. Vest *et al.* has reported that the incidence of bronchopleural fistula was 1.6%, based on 2,243 cases of lung surgery in 1991, whereas the incidence in China was about 1% in a large group of cases reported. Most cases occurred about one week after operation. Clinical symptom includes cough, producing sputum, hard breath and fever. Chest X-ray shows encapsulated hydro-pneumothorax and empyema, while some have the sign of aspiration pneumonia. The early symptom is markedly increased sputum volume, thinner, reddish pleural effusion, and purulent sputum would be noted in the following days, especially when there is empyema. To confirm the diagnosis, a bronchoscopy examination is necessary. Pleural drainage is the essential treatment for this complication and drainage tube is often placed near the fistula. For postoperative patients in early stage, surgical repair can be tried, otherwise the repair would be very difficult, and the drainage would be the only approach. It has been reported that tracheal stent could be placed to temporarily close the fistula. Some studies also reported that for the cases with limited inflammation, medical biological protein glue could be another method to solve the problem.

4.1.8 Advances in surgical treatment of lung cancer

(1) The role of VATS in the surgical treatment of lung cancer. VATS is one of the greatest advances and

developments in techniques of thoracic surgery over the past twenty years. We attached more and more importance to video-assisted thoracoscopic lung cancer surgery, which is one of directions of lung cancer surgery development in the future. There are still many different opinions about the indication of VATS, which is associated with the time when the techniques started, the preference of the surgeon, and the proficiency of the surgeon. However, as what has been written in NCCN guidelines, VATS should also follow the principles of lung cancer surgery, that is, the completeness of the resection, as well as the safety of surgery.

(2) Options of surgery for early stage lung cancer. It has been accepted for a long time that lobectomy is the standard surgical procedure for stage I NSCLC. Recent studies proved that segmentectomy or wedge resection might be the best procedure for less than 2 cm peripheral stage I NSCLC, especially for those ground-glass nodules. However, most of the studies were retrospective analysis, and the number of cases was not large. There are a number of ongoing randomized clinical trials in China and foreign countries. We expect the results would make it clear the extent of surgical resection for stage I NSCLC.

4.2 Radiotherapy

Radiotherapy for lung cancer includes radical radiotherapy, palliative radiotherapy, adjuvant radiotherapy and preventive radiotherapy.

4.2.1 Principles of radiotherapy

(1) Radical radiotherapy is suitable for patients with Karnofsky score >70, including those unresectable early stage NSCLC, locally advanced NSCLC, and limited stage SCLC who are inoperable due to objective or subjective reasons.

(2) Palliative radiotherapy is suitable for the treatment of primary lung cancer and metastatic lesions from advanced lung cancer. Postoperative whole brain radiotherapy can be performed on patients with single brain metastases, and chest radiotherapy can be performed on extensive stage SCLC patients.

(3) Adjuvant radiotherapy is suitable for patients with positive margins (R1 and R2) postoperatively; patients with uncertain surgical exploration or unsafe surgical margins; and the patients with positive pN2 after surgery are encouraged to participate in clinical trials on postoperative radiotherapy.

(4) The plan of postoperative radiotherapy should refer to patient's postoperative pathology report and operation record.

(5) Preventive radiotherapy of whole brain is suitable for SCLC patients who performed complete response after chemotherapy and radical radiotherapy.

(6) Indication of concurrent chemoradiation: For patients with inoperable stage III A or stage III B, concurrent chemoradiation is recommended by EP regimen (etoposide + cisplatin). If the patient cannot tolerate the complications, sequential or concurrent chemo-radiation (pemetrexed + cisplatin/carboplatin) can be performed.

(7) Patients with chemoradiation will have more potential side effects and should be informed before treatment. We should lay more emphasis on the protection of lung, heart, esophagus and spinal cord when designing and implementing radiotherapy. During the treatment, we should avoid the unplanned interruption of radiotherapy due to improper treatment of toxic side effects.

(8) It is suggested that stereotactic body radiation therapy (SBRT) should be carried out under the condition of excellent radiophysical techniques by using advanced radiotherapy techniques such as three-dimensional conformal radiotherapy, intensity modulated radiotherapy (IMRT) or image-guided radiotherapy.

(9) Enhanced CT localization or PET-CT localization is recommended for radiotherapy target area delineation. We can refer to the tumor biological image of PET-CT and delineate tumor radiotherapy target in enhanced CT imaging.

(10) Patients undergoing radiotherapy or chemoradiation should be given adequate monitoring and supportive treatment during rest.

4.2.2 Indications for NSCLC radiotherapy

Radiotherapy can be used for radical therapy of early NSCLC patients who are not medically inoperable, adjuvant therapy before and after surgery for operable patients, local treatment for patients with locally advanced lesions that cannot be excised, and palliative therapy for patients with advanced incurable diseases.

For stage I NSCLC patients with contraindications for surgery or refuse surgery due to medical conditions, large fractionation radiotherapy is an effective radical therapy, and SBRT is recommended. The principle should be high dose, less fractionation and short course of treatment. The segmentation scheme can be considered comprehensively

according to the location of the lesion, distance from the chest wall and other factors, and the total dose is usually given ≥ 100 Gy. Radiotherapy tolerance doses of organs and tissues should be fully considered and carefully assessed in SBRT planning, such as spinal cord, esophagus, trachea, heart, chest wall and brachial plexus.

For NSCLC patients who undergo surgery, if the pathology of surgical margin is negative and the mediastinal lymph node is positive (pN2 stage), besides routine postoperative adjuvant chemotherapy, adjuvant radiotherapy can be used, and chemotherapy followed by sequential radiotherapy is recommended. For pN2 patients with positive margin, postoperative concurrent chemoradiation is recommended, if patients are physically permitted. For patients with positive margins, radiotherapy should start as early as possible.

If the physical conditions permit, conformal radiotherapy combined with concurrent chemotherapy should be used in patients with stage II–III NSCLC who are unable to undergo surgery for physical reasons. For patients expected to cure, more conformal radiotherapy plans and more active supportive care should be recommended to avoid interruptions or dosage reductions during radiotherapy or concurrent chemo-radiation. For stage IV NSCLC patients with extensive metastasis, some patients can receive radiotherapy on primary and metastatic lesions to achieve palliative reduction. When the benefit from systemic therapy is apparent, SBRT technique can be used on the residual primary and/or oligo-metastatic lesions, so as to obtain potential curative effect.

4.2.3 Indications for SCLC radiotherapy

Combined chemo-radiation is the standard treatment for limited stage SCLC. Patients with limited disease are recommended to receive concurrent chemoradiation at the initial treatment or two cycles of induction chemotherapy followed by concurrent chemo-radiation. If patients are intolerant, sequential chemo-radiation is also feasible. Radiotherapy for limited stage SCLC should begin as early as possible if the condition permits, and concurrent with chemotherapy in the first or second cycle. If the lesion is large and the risk of radiation-induced lung injury is too high, concurrent radiotherapy during the third cycle of chemotherapy may also be considered.

For patients with SCLC in extensive stage, if the distant metastases have been controlled by chemotherapy, chest radiotherapy can also increase tumor control and prolong survival.

4.2.4 Prophylactic cranial irradiation (PCI)

PCI is recommended for limited stage SCLC patients after complete remission in primary lesions, and is also recommended for patients with partial response. PCI can also reduce the risk of brain metastasis in extensive stage SCLC when chemotherapy is effective. The recommended time for PCI is about 3 weeks after the end of all chemoradiation. Enhanced magnetic resonance imaging should be performed before PCI to rule out brain metastasis, and a dose of 25 Gy in 10 fractions within 2 weeks is recommended.

An adequate and effective communication between the doctor and the patient is necessary before making the decision of PCI, weighing the pros and cons of each patient's situation.

4.2.5 Palliative radiotherapy for patients with advanced lung cancer

The main purpose of palliative radiotherapy for advanced lung cancer patients is to relieve the local compression symptoms caused by primary or metastatic lesions, the pain caused by bone metastasis, and the neurological symptoms caused by brain metastasis. For such patients, low-fractionation irradiation can be considered, so that it would be more convenient for treatment and more rapid for symptoms relief.

4.2.6 Treatment effect evaluation

The short-term efficacy of radiotherapy is evaluated according to WHO response evaluation criteria in solid tumors (RECIST).

4.2.7 Radiation protection

Advanced techniques of radiotherapy should be used as much as possible to protect the lungs, heart, esophagus and spinal cord from serious radiation damage. Acute radiation lung injury refers to the international radiation therapy cooperation group acute radiation injury classification standard.

4.3 Medication

The systemic therapy for lung cancer includes chemotherapy, molecular targeted therapy and immunotherapy. Chemotherapy can be defined as neoadjuvant chemotherapy, adjuvant chemotherapy and palliative chemotherapy. Clinical indications should be strictly controlled and carried out under the guidance of oncologists.

Chemotherapy should give full consideration to the stage of the disease, physical condition, adverse effect, quality of life and the patient's desire, so as to avoid overtreatment or inadequate treatment. After evaluating clinical response and monitoring adverse effect, the administration and/or dose should be adjusted in time. Molecular targeted therapy should be used after identifying the gene mutation status. In recent years, immunotherapy represented by immuncheckpoint inhibitors (such as PD-1 or PD-L1 monoclonal antibody) has made great progress. Based on the evidence of confirmed survival benefits of immune check-point inhibitor, and Chinese are also be proven benefit in survival, the first PD-1 inhibitor (Nivolumab) was approved for advanced lung cancers' treatment.

4.3.1 Medication for advanced NSCLC

4.3.1.1 First-line of systemic therapy

The platinum-based regimen is the standard first-line chemotherapy regimen, which can be used in combination with endostatin; Bevacizumab combined with chemotherapy is another option in advanced non-squamous NSCLC patients without known driver gene. Patients with EGFR mutation (including exon 19 deletion, exon 21 L858R and L861Q, exon 18 G719X, and exon 20 S768I) can receive epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), including gefitinib, erlotinib, icotinib or afatinib. Patients with ALK or ROS1 fusion genes positive can receive crizotinib. The choice of medication is shown in *Table 3, 4*.

Maintenance therapy is optional for patients who have achieved disease control (complete remission, partial response and stable disease) with first-line treatment. So far, pemetrexed (non-squamous cell carcinoma), bevacizumab (non-squamous cell carcinoma) and gemcitabine have been proved by medical evidence as options for continuation maintenance therapy, and pemetrexed (non-squamous cell carcinoma) has been proved effective as switch maintenance therapy. EGFR-TKI can be selected for maintenance therapy in patients with sensitive EGFR gene mutation.

4.3.1.2 Second-line systemic therapy

Alternative drugs for second-line treatment include docetaxel, pemetrexed, nivolumab, EGFR-TKI and crizotinib. In patients with positive mutations in lung cancer-driving genes, if no corresponding molecular targeting drugs are used for first-line and maintenance therapy, molecular targeting drugs should be given priority in second-line treatment. In patients with first-line EGFR-

TKIs resistance and harboring EGFR T790M mutation, Osimertinib should be given priority in second-line treatment. For ALK mutation patients who develop drug resistance after first-line crizotinib, seretinib can be used sequentially during second-line treatment. For patients with resistance to EGFR-TKI or xazotinib in the first-line treatment and chemotherapy in the second-line treatment, double-drug or single-drug treatment regimens containing platinum can be selected according to the Eastern Cooperative Oncology Group (ECOG) PS score of patients.

Chemotherapy should be given priority in patients with negative driver genes, and afatinib may be used in patients without driver genes and with histologic type of squamous cell carcinoma (Table 5).

Nivolumab, a PD-1 inhibitor, can be considered for NSCLC patients who fail to respond to platinum-based combination chemotherapy and targeted therapy.

4.3.1.3 Third-line systemic therapy

Clinical trials are optional. Oral monotherapy of VEGFR-TKI can be used in third-line treatment. As for the evidence-based VEGFR-TKI drugs that for third-line treatment, there is anlotinib at present.

4.3.2 Systemic therapy for unresectable NSCLC

Combination of radiotherapy and chemotherapy is recommended. Synchronous or sequential chemo-radiotherapy can be chosen according to specific circumstances. Recommended regimens for synchronous chemotherapy include etoposide combined with cisplatin (EP) or carboplatin (EC) and paclitaxel or docetaxel combined with platinum. Sequential chemotherapy regimens include cisplatin + etoposide, cisplatin + paclitaxel, cisplatin + docetaxel, cisplatin or carboplatin + pemetrexed (non-squamous NSCLC). The multi-disciplinary team should discuss and evaluate the possibility of surgery for downstaging patients after induction therapy. Surgical treatment should be considered if complete resection could be achieved.

4.3.3 Perioperative chemotherapy for NSCLC

Postoperative adjuvant chemotherapy: Completely resected stage II–III NSCLC is recommended for 4 cycles of adjuvant chemotherapy with platinum based dual drug regimen. Adjuvant chemotherapy begins with the patient's postoperative physical condition returning to normal, generally starting at 4–6 weeks and not exceeding 3 months

Table 3 First-line chemotherapy regimen for NSCLC

Regimen	Dose	Time	Cycle
NP			
Vinorelbine	25 mg/m ²	d1, d8	21 d/cycle, 4–6 cycles
Cisplatin	75 mg/m ²	d1	
TP			
Paclitaxel	135–175 mg/m ²	d1	21 d/cycle, 4–6 cycles
Cisplatin	75 mg/m ²	d1	
or Carboplatin	AUC=5–6	d1	
GP			
Gemcitabine	1,000–1,250 mg/m ²	d1, d8	21 d/cycle, 4–6 cycles
Cisplatin	75 mg/m ²	d1	
or Carboplatin	AUC=5–6	d1	
DP			
Docetaxel	75 mg/m ²	d1	21 d/cycle, 4–6 cycles
Cisplatin	75 mg/m ²	d1	
or Carboplatin	AUC=5–6	d1	
or Nedaplatin (SCC)	100 mg/m ²	d1	
PP			
Pemetrexed (non-SCC)	500 mg/m ²	d1	21 d/cycle, 4–6 cycles
Cisplatin	75 mg/m ²	d1	
or Carboplatin	AUC=5–6	d1	

Table 4 Anti-angiogenic drugs and targeted therapies for NSCLC

Regimen	Dose	Time
Anti-angiogenic drugs		
Endostatin	7.5 mg/m ²	d1–d14, 21 d/cycle
Bevacizumab	7.5–15 mg/kg	d1, 21 d/cycle
Targeted therapies		
Gefitinib	250 mg	Qd
Erlotinib	150 mg	Qd
Icotinib	125 mg	Tid
Alfatinib	40 mg	Qd
Crizotinib	250 mg	Bid

Table 5 Commonly used second-line chemotherapy regimens for NSCLC

Regimen	Dose	Medication time	Cycle length
Docetaxel	75 mg/m ²	d 1	21 d
Pemetrexed (non-squamous)	500 mg/m ²	d 1	21 d
Afatinib (squamous)	40 mg	Qd	Qd
Osimertinib (T790M)	80 mg	Qd	Qd

after surgery. According to AJCC the eighth edition, adjuvant chemotherapy for stage III patients is generally not recommended after radical resection due to lack of high-level evidence support.

Neoadjuvant chemotherapy: For resectable stage III NSCLC, 2 cycles of preoperative neoadjuvant chemotherapy can be carried out with platinum-based dual drugs. The responses should be evaluated in time, and adverse reactions should be monitored and treated to avoid the increase of surgical complications. Surgery is usually performed 2–4 weeks after chemotherapy. Postoperative adjuvant chemotherapy should be adjusted according to the preoperative staging and the efficacy of neoadjuvant chemotherapy. The effective ones should continue the original regimen or adjust according to the patient's tolerance. The ineffective ones should adjust the treatment regimen. The overall perioperative chemotherapy is recommended for 4 cycles.

4.3.4 Systemic therapy for SCLC

4.3.4.1 First-line treatment

Limited stage (T1–2, N0) SCLC is recommended for lobectomy + hilar and mediastinal lymph node dissection, and postoperative adjuvant chemotherapy. Limited stage (more than T1–2, N0) SCLC is recommended for

radiation and chemotherapy based comprehensive treatment. The recommended regimens include EP or EC. Extensive stage SCLC is recommended for chemotherapy based comprehensive treatment. Those with local symptoms or brain metastases are recommended to combine radiotherapy or other treatments based on chemotherapy. The recommended regimens include EP, EC, irinotecan combined with cisplatin (IP), irinotecan combined with carboplatin (IC), or etoposide combined with luoplatinum (EL).

4.3.4.2 Second-line treatment

Topotecan, irinotecan, gemcitabine, temozolamine, or taxane is recommended for patients with recurrence or progression within 3 months after first-line chemotherapy. Topotecan, irinotecan, gemcitabine, docetaxel, temozolamide, or vinorelbine is recommended for patients with recurrence or progression at 3–6 months. Patients who relapse or progress after 6 months can choose the initial treatment plan. Patients are encouraged to participate in clinical trials of new drugs.

4.3.5 Principles of lung cancer chemotherapy

(1) Lung cancer patients with KPS <60 or ECOG >2 are not suitable for chemotherapy.

(2) Lung cancer patients with leukocytes less than $3.0 \times 10^9/L$, neutrophils less than $1.5 \times 10^9/L$, platelets less than $6 \times 10^{10}/L$, red blood cells less than $2 \times 10^{12}/L$, and hemoglobin lower than 80 g/L should not be treated with chemotherapy in principle.

(3) Lung cancer patients with abnormal liver and kidney function, laboratory indicators more than twice the normal value, or with serious complications and infections, fever, bleeding tendency should not be treated with chemotherapy.

(4) Discontinuation or replacement regimens should be considered: If the disease progresses after 2 cycles of treatment or deteriorates again during the interval of the chemotherapy cycle, the original regimen should be discontinued and alternative regimens should be chosen in the following treatment. If the adverse reaction of chemotherapy reaches grade 3–4, and the patient's life is obviously threatened, the drug should be discontinued, and alternative regimens should be used in the following treatment. If serious complication occurs, the drug should be discontinued and alternative regimens should be used in the following treatment.

(5) Emphasis must be placed on the standardization and individualization of treatment protocols. The basic requirements of chemotherapy should be mastered. Besides

the routine use of antiemetic drugs, hydration and diuresis are required during the use of platinum drugs other than carboplatin. Routine blood tests should be performed two times a week after chemotherapy.

(6) The efficacy of chemotherapy was assessed according to WHO solid tumor efficacy evaluation criteria or RECIST criteria.

4.4 Endobronchoscopic interventional therapy

With the increasing popularity of bronchoscopy in clinical applications, the following local treatments are optional for patients unable to undergo surgery or radiotherapy: bronchoscope-mediated laser, high-frequency electrotome, radiofrequency ablation, argon plasma coagulation (APC), microwave, laser, photodynamic therapy, cryotherapy, airway stent, balloon dilatation, submucosal or intratumoral drug injection, etc. Endobronchial interventional therapy should be based on strict indications, with accurate treatment purpose and objective assessment of whether a certain treatment technology can achieve a desired goal. The treatment should be carried out in qualified hospitals.

(1) For intracavitary polypoid tumors, trap removal or carbon dioxide cryosurgery is feasible, and APC is performed at the root of tumor.

(2) For wall-infiltrated tumors, photodynamic therapy can be performed after the resection of intraluminal tumor, and then radiation and chemotherapy particles can be considered in patients contraindicated of external radiation.

(3) Endoscopic endoscopic interventional therapy may be considered for patients with central airway stenosis who cannot be or refuse to be operated on. The technologies include thermal ablation (high frequency electrotome, radiofrequency ablation, APC, microwave, laser, etc.), photodynamic therapy, cryotherapy, airway stent, submucosal or intratumoral drug injection, etc.

(4) For airway stenosis and airway fistula that cannot be relieved by conventional treatment, internal stent implantation should be considered as the main treatment. The endotracheal stent can be divided into metal stent and non-metallic stent. The metal stent can be divided into the membrane stent and the non-membrane stent (bare stent). Non-metallic stent can be divided into silicone stent, plastic stent, etc.

(5) Endoscopic interventional therapy should be carefully chosen if distal lung function is lost or small airway obstruction occurs simultaneously.

Selection of individualized endobronchoscopic inter-

ventional therapy is very important. It needs to be discussed in multidisciplinary treatment (MDT) and to combine with the equipment performance of the proposed technology and personnel conditions at the same time. The ideal treatment is a combination of several methods, such as thermocoagulation or cryosurgery to remove large lesions in the lumen, and freeze-thaw treatment to remove basal lesions.

4.5 Staged treatment mode of NSCLC

4.5.1 Comprehensive treatment for patients with stage I NSCLC

(1) Surgical treatment is preferred, including lobectomy plus systemic pulmonary hilus and mediastinal lymph node dissection. Minimally invasive operations such as VATS or thoracotomy can be used.

(2) For partial stage IA NSCLC patients with advanced age or low lung function, anatomical segmental or wedge resection plus systemic hilar or mediastinal lymph node dissection or sampling should be considered.

(3) Postoperative adjuvant chemotherapy, radiotherapy and targeted therapy are not recommended for completed resected stage IA, IB NSCLC patients.

(4) Reoperation is recommended for stage I lung cancer with positive margin. Postoperative radiotherapy is recommended for patients who are unable to reoperation for any reason.

(5) SBRT is available for patients with severe medical complication, advanced age and those who refuse surgery.

4.5.2 Comprehensive treatment for patients with stage II NSCLC

(1) Surgical treatment is preferred, including lobectomy plus systemic pulmonary hilus and mediastinal lymph node dissection.

(2) For patients with advanced age or low lung function, anatomical segmental or wedge resection plus systemic hilar or mediastinal lymph node dissection or sampling should be considered.

(3) Postoperative adjuvant chemotherapy is recommended for completed resected stage II NSCLC patients.

(4) *En bloc* of chest wall should be carried out when the tumor invades the parietal pleura or chest wall. The resection range should be at least 2 cm from the upper and lower edges of the ribs nearest to the lesion, and the resection length of the invaded ribs should be at least 5 cm from the tumor.

(5) Reoperation is recommended for stage II lung cancer with positive margin. If physically permitted, postoperative concurrent chemoradiotherapy is recommended for patients who are unable to receive reoperation for any reason. Radiotherapy should start as soon as possible.

4.5.3 Comprehensive treatment for patients with stage III NSCLC

Locally advanced NSCLC refers to patients with TNM stage III. Multidisciplinary treatment is the best choice for stage III NSCLC. Locally advanced NSCLC can be divided by resectable and non-resectable.

4.5.3.1 Resectable locally advanced NSCLC

(1) Surgical treatment + adjuvant chemotherapy or radical chemotherapy are recommended in T3–4N1 or T4N0 patients, and neoadjuvant treatment is worth considering.

(2) For stage N2 NSCLC patients with imaging findings of a single group of mediastinal lymph nodes with diameter less than 3 cm, or two groups of mediastinal lymph nodes enlarged but not fused which means a complete resection could be achieved, and MDT is recommended, neoadjuvant chemotherapy +/- radiotherapy + surgery, or surgery + chemotherapy +/- radiotherapy are also recommended. For patients with EGFR mutation, surgery + adjuvant EGFR-TKI treatment +/- postoperative radiotherapy. Preoperative mediastinoscope examination, EBUS-TBNA or EUS guided fine needle aspiration (EUS-FNA), after N2 staging, preoperative neoadjuvant chemotherapy or neoadjuvant chemo-radiotherapy was performed, followed by surgical treatment. As for lung cancer with N2 lymph metastasis, and predictable completely excision, concurrent chemo-radiotherapy was recommended for the risk of recurrence higher than mono-lymph metastasis. Simultaneously, the neoadjuvant chemotherapy +/- radiotherapy + surgery +/- adjuvant chemotherapy +/- postoperative radiotherapy should also be considered as the combined treatment. Some patients have the lung cancer with EGFR mutation, the treatment of surgery + combined adjuvant EGFR-TKI treatment +/- postoperative radiotherapy should also be recommended.

(3) NSCLC in stage II–IIIA, according to the benefit treatment data of ADJUVANT and EVAN trials, EGFR mutation test was recommended for patients with non-squamous NSCLC in stage II–IIIA (N1–2).

4.5.3.2 Unresectable locally advanced NSCLC includes:

(1) Part of IIIa (N2) NSCLC patients with enlarged and

fused mediastinal lymph nodes, which were confirmed positive by mediastinoscopy, EBUS-TBNA or EUS-FNA and should be identified as unresectable after discussion of the chest tumor MDT.

(2) Stage IIIB/IIIC patients.

(3) The preferred treatment for unresectable locally advanced NSCLC is synchronous radiotherapy.

4.5.4 Comprehensive treatment for patients with stage IV NSCLC

Patients with stage IV NSCLC should first obtain tumor tissues for *EGFR*, *ALK* and *ROS1* gene detection before treatment, and then decide the appropriate treatment strategy according to the above gene status. Stage IV NSCLC is mainly treated by systemic therapy with the aim of improving the quality of life and prolonging the survival of patients.

4.5.4.1 Treatment of IV stage NSCLC patients with solitary brain metastases

(1) In NSCLC patients with solitary brain metastases and resectable lung lesions, brain lesions can be resected surgically or treated with stereotactic radiotherapy and the primary pulmonary lesions should be performed according to the principle of staged treatment.

(2) In NSCLC patients with solitary adrenal metastases and resectable lung lesions, adrenal lesions can be considered surgical removal and the primary pulmonary lesions should be performed according to the principle of staged treatment.

(3) Solitary nodules in contralateral lung or different lobes of the ipsilateral lung can be treated according to the respective stages of the two primary tumors.

4.5.4.2 Systemic treatment for stage IV NSCLC treatment

(1) First-line EGFR-TKI treatment is recommended for stage IV NSCLC patients with EGFR-sensitive mutation. Patients with positive ALK fusion gene are recommend first-line treatment with Crizotinib. Patients with positive ROS1 fusion gene are recommend first-line treatment with Crizotinib.

(2) Stage IV NSCLC patients whose EGFR, ALK and ROS1 fusion genes are negative or whose mutation status is unknown should begin systemic chemotherapy with platinum as soon as possible if the ECOG PS score is 0–1. For patients who are not suitable for platinum treatment, non-platinum dual drug regimen may be considered.

(3) Patients with advanced NSCLC with ECOG PS score of 2 should be given single-drug chemotherapy, but

those with ECOG PS score >2 are not recommended to use cytotoxic drugs.

(4) For elderly patients, the evidence does not support age as the sole criterion for choosing chemotherapy regimens, and a comprehensive assessment of organ function and ECOG PS status is required. If organ function indicators meet the requirements of chemotherapy, patients with ECOG PS 0–1 can still consider platinum-based dual drug regimens. Patients with ECOG PS score 2 can consider single-drug chemotherapy. Patients with severe organ dysfunction or ECOG PS score >2 should not be recommended systemic chemotherapy.

(5) Second-line treatment options include docetaxel, pemetrexed, immuncheckpoint inhibitors, and EGFR-TKI. EGFR-TKI should be given priority in second-line treatment if EGFR-TKI is not used in first-line and maintenance therapy in patients with EGFR-sensitive mutations. It is recommended to treat NSCLC patients with EGFR-TKI resistance and positive EGFR T790M mutation with osimertinib monotherapy. For patients with EGFR mutation negative/ALK fusion negative (including non-squamous cell carcinoma and squamous cell carcinoma), based on the fact that PD-1 inhibitor nivolumab is significantly superior to chemotherapy in efficacy and safety, the use of nivolumab for second-line treatment should be given priority.

(6) Patients with stage IV NSCLC with an ECOG PS score >2 do not benefit from chemotherapy generally, and the best supportive treatment is recommended. On the basis of systemic treatment, appropriate local treatment can be selected to improve symptoms and the quality of life.

(7) Second-generation sequencing technology (NGS) has been widely used in clinical practice. It is recommended for conditioned patients with progressive disease after first-line treatment to help determining the resistance mechanism of molecular targeted drugs and guiding the following treatment.

4.6 Staged treatment mode of SCLC

The staging of SCLC has been followed by the two-stage method of The Veterans Administration Lung Study Group (VALG), mainly based on the importance of radiotherapy in the treatment of SCLC. The AJCC TNM staging system is suitable for selecting T1–2N0 patients who are suitable for surgery. TNM staging system should be given priority in clinical research, because it can assess prognosis more accurately and guide treatment.

4.6.1 T1–2N0 limited stage SCLC

For T1–2N0 SCLC after systematic staging examination showing no mediastinal lymph node metastasis, surgery + adjuvant chemotherapy (EP or EC regimen, 4–6 cycles) is recommended. If the diagnosis of mediastinal lymph node metastasis is still uncertain after systematic staging examination, mediastinoscopy, endoscopic ultrasonography or pathological examination may be used to exclude potential mediastinal lymph node metastasis. Postoperative adjuvant radiotherapy is recommended for patients with N1 and N2. PCI is recommended after surgery.

4.6.2 Limited stage (more than T1–2, N0) SCLC

Combined chemotherapy and radiotherapy should be used. PCI is recommended if disease (complete remission or partial remission) is controlled.

4.6.2.1 ECOG PS 0–2

Concurrent radiotherapy is preferred. Sequential chemoradiotherapy is also an option if patients can not tolerate concurrent chemoradiotherapy.

4.6.2.2 ECOG PS score 3–4 caused by SCLC

All factors should be considered comprehensively, and the therapeutic regimen should be carefully chosen. The single-drug regimen or combined regimen with dose reduction should be considered. If the ECOG PS score of the patients reaches 2 points or less after treatment, sequential radiotherapy can be considered. If the ECOG PS score remains more than 2 points, thoracic radiotherapy should be considered according to the specific circumstances.

4.6.2.3 ECOG PS 3–4 score not induced by tumor

The best supportive treatment is given in principle.

4.6.3 Extensive stage SCLC

Patients with ECOG PS score 0–2 or ECOG PS score 3–4 caused by SCLC should receive comprehensive therapy including chemotherapy. First-line recommendations are EP or EC regimen, IP or IC regimen for 4–6 cycles chemotherapy. Patients with ECOG PS 3–4 score that are not induced by tumor should be given the best supportive treatment.

4.6.3.1 Patients without local symptoms and no brain metastases

For patients with first-line chemotherapy reaching CR/PR, thoracic radiotherapy is feasible. Patients with no brain metastasis after effective initial treatment should receive PCI.

4.6.3.2 Patients with local symptoms

Selective local treatment should be carried out on

symptomatic conditions based on first-line chemotherapy. Patients with superior vena cava syndrome or obstructive atelectasis or spinal cord compression can be given selective local radiotherapy. In addition to selective palliative external irradiation, patients with bone metastases can also perform local orthopaedic fixation on sites at high risk of fracture if necessary. Patients with no brain metastasis after effective initial treatment should receive PCI.

4.6.3.3 Patients with brain metastases

Besides first-line systemic chemotherapy, whole brain radiotherapy is recommended. For patients with first-line chemotherapy reaching CR/PR, thoracic radiotherapy is feasible. Stereotactic radiotherapy (SRT/SRS) is recommended for patients with small tumor size, less than 4 cm in diameter, or oligometastasis, or recurrent metastasis after whole brain radiotherapy, if the patient has poor physical condition and is not able to tolerate conventional radiotherapy or surgery.

4.6.3.4 Follow-up treatment for relapsed/drug-resistant SCLC patients

Patients with relapse or progression after first-line chemotherapy are recommended to enter clinical trials. Topotecan, irinotecan, gemcitabine, paclitaxel monotherapy or nivolumab monotherapy or combined ipilimumab immunotherapy are recommended for patients with recurrence or progression at 3–6 months. Patients who relapse or progress after 6 months can choose the initial treatment plan.

4.7 Palliative treatment

Palliative care, as a special way of treatment, aims to improve the quality of life of patients and their families who are suffering from disease and facing death threats by controlling pain, relieving symptoms and providing spiritual and social support. In our country, with the expected progress of population aging and increased cancer incidence and mortality, the number of patients requiring palliative care also increased significantly. Therefore, to provide palliative treatment within the criteria of WHO and NCCN has become more and more important.

Palliative treatment includes treatment on the body, mental, psychological and social needs of the cancer patients. Palliative care can be initiated as soon as cancer is diagnosed and in early stage, and can be adjusted to meet the changing needs of patients. Studies have shown that early introduction of palliative care can not only improve the quality of life of patients with advanced cancer, but also

improve their survival rate. It can reduce the depression and stress score of nurses. There is ample evidence that palliative care combined with standard anticancer therapies, or as a focus of treatment, can lead to better outcomes for patients and caregivers. Therefore, for patients with any metastatic cancer, and/or with a high burden of symptoms, the combination of standard anticancer therapy and palliative care should be considered at an early stage of treatment. Palliative care for lung cancer patients includes palliative surgery, chemotherapy, radiotherapy, endocrine therapy, targeted therapy, immunotherapy, and/or other means of relieving symptoms such as pain and dyspnea. Patient comfort is a priority problem at all stages of treatment. Hospice care may be considered if physicians and patients both believe that treatment can no longer delay or prevent cancer progression.

The aim of palliative care is to relieve symptoms, relieve pain and improve the quality of life. All lung cancer patients should receive palliative screening, evaluation and treatment. Screening symptoms include not only pain, dyspnea, fatigue, anorexia and nausea, nausea and vomiting, constipation, diarrhea and other common physical symptoms, but also sleep disorders, anxiety and depression, delirium and other psychological problems.

Evaluation of quality of life should be included in the overall evaluation system of lung cancer patients and palliative treatment evaluation. The European Organization for Research and Treatment of Cancer quality of life-C30 (EORTC QLQ-C30) is recommended for overall assessment. EORTC QLQ-LC13 can also be used to screen and assess the common symptoms of lung cancer patients.

5. Prognosis

The prognosis of patients with lung cancer (including NSCLC and SCLC) is based on the comprehensive clinical pathological features of patients. According to the existing research results, the clinical pathological stage of the tumor, the patient's physical condition, age and gender are important prognostic factors; in addition, some biochemical indicators (such as white blood cell count and hypercalcemia), and blood tumor marker levels (such as CEA) have also shown to be significantly associated with the prognosis of lung cancer patients. At present, clinical pathological staging, TNM staging, is still the most important and stable indicator for predicting the survival time of patients with lung cancer. The prognosis of patients

with lung cancer largely depends on the TNM stage of the tumor at the time of disease discovery. There is a significant difference in the prognosis of patients with different clinical stages. According to the seventh edition of the Tumor Staging Manual of American Joint Committee on Cancer (AJCC) reported in 2010 on the meta-analysis of 26,859 patients with NSCLC and 2,664 patients with SCLC. For NSCLC, the 5-year survival rate of stage I patients is approximately 70%, of which, the 5-year survival rate of patients with stage IA is over 80%, the median survival time is close to 10 years; the 5-year survival rate of stage II patients is about 40%; for stage III patients, the 5-year survival rate is reduced to about 15%. The 5-year survival rate for patients with stage IV was less than 5%, and the median survival time was only 7 months. The malignancy of SCLC is higher than that of NSCLC, and recurrence and metastasis are more likely to occur. Therefore, the survival of patients with SCLC is significantly shorter than that of NSCLC. The 5-year survival rate of patients with stage I SCLC is about 50%;

stage II is about 25%; stage III is about 10%; and stage IV is less than 3%. The prognostic data of each TNM staged lung cancer patient reported in China are similar to the AJCC statistics. A comprehensive analysis of several large-scale statistical results from 2000 to 2009 shows that the 5-year survival rate of stage I in NSCLC patients in China is about 70%; stage II is about 50%, stage III is about 15%, and IV is about 5%. For patients with SCLC in China, the above data are 45%, 25%, 8% and 3%, respectively.

6. Follow-up

Regular review of lung cancer is required after treatment. The purpose of the review is to monitor the efficacy and discover early recurrence and metastasis. The inspection is based on image examination. For the early and middle stage lung cancer after comprehensive treatment including surgery, it is generally recommended to re-examine every 3 months within 2 years after treatment, once every half year from 2 to 5 years, and once every 1 year after 5 years.

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