Wang and Society of Lung Cancer of China Anti-Cancer Association
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CACA guidelines for holistic integrative management of lung cancer

Jun Wang[1*] and Society of Lung Cancer of China Anti-Cancer Association

Abstract

Lung cancer (LC) is among the malignant tumors with the highest disease burden in the world, accounting for approximately 11.4% of all cancer cases, and LC was the 2nd most common type of malignant tumor. The editing of the CACA Guidelines for Holistic Integrative Management of Lung Cancer aimed to facilitate the enhancement of lung cancer diagnosis and comprehensive treatment in China.

The CACA Guidelines for Holistic Integrative Management of Lung Cancer include the epidemiology, the early detection, the comprehensive diagnosis, the treatment (including surgical, medical and radiological treatment), rehabilitation, and some general principles for both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).

The main objective of this guideline is to standardize the clinical diagnosis and treatment process of lung cancer, with a specific focus on enhancing the management of this disease in China.

Keywords Lung cancer, China anti-Cancer Association (CACA), Non-small cell lung cancer, Small cell lung cancer, Diagnosis, Treatment, Integrated guideline, Chemotherapy, Immunotherapy, Neoadjuvant, Radiotherapy, Surgery, Targeted therapy

1 Monograph I: non-small cell lung cancer

1.1 Epidemiology

1.1.1 Current status and epidemiological trends

Lung cancer (LC) is among the malignant tumors with the highest disease burden in the world. Statistical data on cancer epidemiology [1] showed that the estimated worldwide number of new cases of LC was approximately 2.207 million in 2020, accounting for approximately 11.4% of all cancer cases, and LC was the 2nd most common type of malignant tumor. The 2019 Global Burden of Disease study [2] showed that the worldwide incidence rate of LC in 1990–2019 had increased by 39.02% from 21.01/0.1 million cases to 29.21/0.1 million cases, and the LC worldwide mortality rate had increased by 32.60% from 19.91/0.1 million to 26.40/0.1 million.

The burden of LC in China is heavy. An analysis of the registered data on tumors published by the National Cancer Centre [3] showed that there were a predicted 0.787 million new cases of LC in China in 2015. The incidence rate of LC was listed as No. 1 among malignant tumors suffered by males in China and as No. 2 in females. Both the incidence rate and mortality rate of LC were found to increase with age and reach peaks in the age range of 80–84 years [4]. Notably, cases of LC were found to present a sustained upward trend since the 1990s. An analysis of the survival rate data in the population cancer registry [5] showed that the 5-year survival rate of LC in China was only 19.7%, ranking 4th from the bottom among all malignant tumors, which was slightly higher than the incidence rate 10 years ago.

1.1.2 Cause of disease and hereditary susceptibility

Smoking is currently recognized as a risk factor for LC. Many studies have indicated that smoking is closely related to LC. The risk of LC onset in nonsmokers who were exposed to secondhand smoke was found to be

*Correspondence:
Jun Wang
wangjun@pkuph.edu.cn
[1] Society of Lung Cancer of China Anti-Cancer Association, Tianjin, China

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higher by approximately 20% than that in nonsmokers who were not exposed to secondhand smoke.

Work environments risk factors for LC including asbestos, radon, beryllium, chromium, cadmium, nickel, silicon, diesel exhaust gas, soot and ash of soot, all of which are listed as Class I carcinogens by the World Health Organization (WHO)-International Agency for Research on Cancer (IARC). Outdoor air pollution was also listed as a Class I carcinogen, and particulate matter (PM) was found to be the main component of outdoor air pollution.

A pooled analysis of 17 studies by the International Association for the Study of Lung Cancer [6] found that pulmonary emphysema, pneumonia, pulmonary tuberculosis and chronic bronchitis increased the risks of LC onset by 144%, 57%, 48% and 47%, respectively.

LC shows familial aggregation to some extent. Large analyses of tumor registration data [7, 8] have shown that the risk of illness in patients with a family history of LC was increased by approximately 2-fold that of patients without a family history.

1.2 *Early detection* [9]

1.2.1 Targeted screening

(1) Lung cancer (LC) screening was recommended for individuals between 50–74 years old who have a history of smoking (smoking amount of 20 packets/year) or quit smoking less than 15 years previously and for individuals with a family history of and high-risk factors for LC.
(2) Opportunistic screening could be considered for individuals ≥ 75 years old.

1.2.2 Screening technology

(1) Low-dose computed tomography (LDCT) was found to be the preferred method for LC screening, and chest X-ray examination was not recommended for LC screening.
(2) Tumor markers, bronchoscopy, sputum cytology and LC antibody screening could be used to assist in screening rather than as parts of a routine screening approach.

1.2.3 Screening frequency

Screening was recommended to be performed at an interval of 2 years.

1.2.4 Screening management

The screening population was divided into individuals in whom LC was detected during baseline screening and individuals for whom annual screening was being performed for detailed management.

2 Diagnosis of lung cancer

2.1 Clinical diagnosis

Main recommendations:

2.1.1 Risk factors for lung cancer (LC):

Smoking, environmental pollution, occupational exposure, a family history of neoplastic disease, age and a previous history of chronic pulmonary disease were found to be risk factors for LC onset.

2.1.2 Diagnosis of clinical manifestations:

The clinical manifestations were found to include a primary tumor, distant metastasis and other manifestations.

2.1.3 Imaging diagnosis:

1) One or more imaging examination approaches are reasonably and effectively selected according to different examination purposes for LC diagnoses.
2) Auxiliary imaging examinations include chest X-ray, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, radionuclide imaging and positron emission tomography (PET-CT), which were mainly used for diagnosis, staging, restaging, the monitoring of treatment efficacy and the prognosis evaluation of LC.

2.1.4 Histopathology typing:

1) The histopathological diagnosis of LC can include many approaches, and one or more approaches can be selected for the histopathological diagnosis of each individual patient.
2) The histopathological diagnosis of LC should be performed to specify the nature of the lesion, elucidate the pathological type, confirm the degree of invasion and identify whether a lesion is a primary or a metastatic tumor.

2.1.5 Laboratory serological diagnosis:

1) The serological examination of LC could be used as an auxiliary reference indicator for the diagnosis of lung tumors and the judgment of treatment efficacy, and the combined detection of different tumor markers could improve the corresponding sensitivity and specificity of this approach.
2) The detection of serum tumor markers of LC can help in auxiliary diagnosis and early differential diagnosis and to predict the potential pathological type of LC, and observation of the corresponding dynam-

ics is important for evaluating treatment efficacy and determining prognosis.

2.1.6 Staging of LC:

The staging of LC should be performed to define the extent of the growth and diffusion of cancer, and the LC staging defined in the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC), Edition 8, is commonly used.

Notes:

(1) The AJCC/UICC, Edition 8, staging system is most commonly used for the staging diagnosis of LC.
(2) LC staging consists of three parts, i.e., T (representing the range of the primary tumor), N (representing the degree of lymph node invasion) and M (representing distant metastasis). Therefore, the formed TNM staging integrates information related to the tumor and metastasis to adjacent lymph nodes and distant organs Table 1, 2, 3 and 4.

Table 1 Definition of T staging (T staging depends on the size of the tumor, its location in the lung and the extent of its spread)

Staging	Definition
Tx	The primary tumor cannot be evaluated, or tumor cells can be found in exfoliative cells of sputum and bronchial lavages, but the primary tumor is not found by imaging examination or bronchoscopy
T0	No evidence of a primary tumor is found
Tis	The primary tumor, i. e., the cancer, is limited to the endothelial cells of the respiratory tract and has not spread to other lung tissues
T1	The largest diameter of the tumor is ≤ 3 cm, and bronchoscopy shows that the tumor has invaded the bron- chus rather than main bronchus
T1a	The largest diameter of the tumor is ≤ 1 cm
T1b	The largest diameter of the tumor is > 1 cm and ≤ 2 cm
T1c	The largest diameter of the tumor is > 2 cm and ≤ 3 cm
T2	A tumor can be staged as T2 if it meets any one of the following conditions:
	The largest diameter of the tumor is > 3 cm and ≤ 5 cm
	The tumor has invaded the main bronchus, but the distance to the carina is > 2 cm
	The tumor has invaded the visceral pleura
	The patient suffers from obstructive pneumonia or partial pulmonary atelectasis, but the tumor has not spread throughout the whole lung
T2a	The largest diameter of the tumor is > 3 cm and ≤ 4 cm
T2b	The largest diameter of the tumor is > 4 cm and ≤ 5 cm
T3	A tumor can be staged as T3 if it meets any one of the following conditions:
	The largest diameter of the tumor is > 5 cm and ≤ 7 cm
	The tumor has invaded any one of the following organs/tissues: the thoracic wall (including the superior pulmonary sulcus tumor), phrenic nerve and pericardium The tumor has invaded the main bronchus with a distance to the carina of < 2 cm, but the tumor does not in- volve the carina
	Whole pulmonary atelectasis or obstructive pneumonia
	Single or multiple cancer nodules in the same lung lobe
T4	A tumor can be staged as T4 if it meets any one of the following conditions:
	The largest diameter of the tumor is > 7 cm
	The tumor has invaded any one of the following organs/tissues: the mediastinum, heart, great vessels, trachea, esophagus, recurrent laryngeal nerve, vertebral body, carina and diaphragm Single or multiple cancer nodules in a lung lobe that is different from the lobe where the primary lesion is located

2.1.7 Pathological diagnosis

Main recommendations:

1) The biopsy and cytological specimen analysis should be performed to comprehensively evaluate whether the tumor is benign or malignant, with malignant tumors being divided into adenocarcinoma, squamous carcinoma or neuroendocrine carcinoma. When advanced LC is identified during the pathological diagnosis, as many specimens as possible should be saved for subsequent molecular pathology tests.
2) The surgical specimens should be histologically classified following the most recent edition of the World Health Organization (WHO) standards for classification [10]. LCs such as adenocarcinoma in situ, minimally invasive adenocarcinoma, large cell carcinoma, adenosquamous carcinoma, carcinoid tumor and atypical carcinoid can be diagnosed only after surgical specimens are well analyzed. The pathological diagnosis must meet the requirements for clinical staging. Following neoadjuvant therapy, a cut specimen of a tumor should be sampled as per the related pathological specification and evaluated in terms of treatment efficacy, including for indicators of a major pathological response (MPR) and complete pathological response (pCR) [11, 12].
3) An analysis of immunohistochemical indicators, such as TTF-1, NapsinA, P40 and CK5 / 6, is recommended for the identification of adenocarcinoma and squamous carcinoma, and if the specimen is not sufficient, measuring the expression of two indicators, TTF-1 and P40, can be used for identification. CD56, Syno, CgA, Ki-67, CK and TTF-1 are recommended

Table 2 Definition of N staging (N staging depends on the degree to which the tumor has invaded lymph nodes)

Staging	Definition
Nx	Regional lymph nodes cannot be evaluated
N0	There is no regional lymph node metastasis
N1	Metastasis of ipsilateral lymph nodes around the bronchus and (or) in the ipsilateral hilus pulmonis and intra- pulmonary lymph node metastasis, including direct invasion by the primary tumor
N2	Mediastinal and (or) subcarinal ipsilateral lymph node metastasis
N3	Metastasis of contralateral mediastinal lymph nodes and hilar lymph nodes, and metastasis of ipsilateral or contralateral scalene lymph nodes or supraclavicular lymph nodes

Table 3 Definition of M staging (M staging depends on whether the tumor has metastasized to distant tissues or organs)

Staging	Definition
Mx	Distant metastasis cannot be determined
M0	There is no distant metastasis
M1	There is distant metastasis
M1a	The metastasis is limited to the thoracic cavity, including pleural spread (malignant pleural effusion, pericardial effusion or pleural nodules); single or multiple cancer nodes are identified in the contralateral lung lobe
M1b	Single metastasis in a distant organ
M1c	Multiple metastases in multiple organs or a single organ

Table 4 TNM staging of lung cancer

T/M	Subgroup	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	T3	IIB	IIIA	IIIB	IIIC
T4	T4	IIIA	IIIA	IIIB	IIIC
M1	M1a	IVA	IVA	IVA	IVA
	M1b	IVA	IVA	IVA	IVA
	M1c	IVB	IVB	IVB	IVB

as markers related to neuroendocrine tumors. Commonly used special indicators include elastic tissue stain for assisting in the determination of pleural involvement and mucus coccinellin and Alcian blue (AB)/periodic acid Schiff (PAS) stain for the determination of mucus ingredients.

2.1.8 Molecular pathology

Main recommendations:

Molecular testing of operable stage Ib- III LC: After surgery, EGFR mutation detection is usually conducted for non-squamous LC to guide targeted adjuvant therapy. Invasive adenocarcinoma has a risk of relapse or metastasis following surgery, and molecular subtyping is helpful for directly guiding options for antineoplastic protocols for relapse or subsequent metastasis.

Molecular testing of inoperable stage III and IV LC:

1) Upon pathological diagnosis, sufficient tissue specimens should be comprehensively reserved for molecular testing, and the treatment should be guided per molecular subtyping.
2) Testing for EGFR mutations, ALK fusions, ROS1 fusions, RET fusions and MET 14 exon skipping mutations is commonly conducted in non-squamous cancer tissue specimens.
3) If tumor specimens are not available or are limited and molecular testing cannot be performed, peripheral blood can be tested for EGFR mutations in tumor DNA (ctDNA).
4) For patients who are resistant to EGFR-tyrosine kinase inhibitors (TKIs), testing for the EGFR T790 M mutation is recommended when a subsequent biopsy is performed. For patients for whom tumor specimens are not available, the ctDNA EGFR T790 M test is recommended.
5) The expression of PD-L1 in tissue specimens should be examined via immunohistochemistry (IHC).
6) The expression of other driver genes, including gene variations such as the BRAF V600E mutation, KRAS mutation, ERBB2 (HER2) amplification/mutation, MET amplification and NTRK fusion, can be measured along with the presence driver gene mutations in tumor tissues. If no tissue specimen is available, the test can be conducted with ctDNA (which is controversial but recommended).
7) Tumor mutation burden (TMB) should be evaluated with a next-generation sequencing (NGS) technique (which is controversial but recommended).
8) For the first diagnosis/ first genetic mutation analysis of advanced LC, a disposable polygenetic test using multiple polymerase chain reaction (PCR) or small-panel NGS is recommended. Information on several gene variants can be provided. Large-panel high-performance genetic testing is not recommended. For patients with relapse, advanced LC or drug-resistant LC, appropriate testing items and methods can be

selected based on the testing purpose, clinical needs and specimen types.

2.2 Treatment of lung cancer

2.2.1 Surgical treatment of lung cancer

Surgical treatment of lung cancer in stage I-III Main recommendations.

(1) For all patients with lung cancer (LC) at clinical stages I-II without surgical contraindications, excision is the preferred treatment method.
(2) For patients with LC at clinical stages III, regardless of the reason, when the patient is considering a nonsurgical approach [such as percutaneous ablation or stereotactic body radiation therapy (SBRT)], it is recommended that they be evaluated by a multidisciplinary team, including a thoracic surgeon, for integrated diagnosis and treatment.
(3) For patients with LC at clinical stages I-II, the current standard method for excision extension is still anatomical pulmonary lobectomy. Sublobectomy (segmentectomy and wedge resection) is applicable only for patients at stage T1a-b and some patients at stage T1c and above and high-risk patients who cannot tolerate pulmonary lobectomy.
(4) For patients with central LC, as long as R0 tumors are excised, sleeve resection is superior to total pneumonectomy.
(5) For patients with LC at clinical stage I-II, pathological staging can be accurately conducted with anatomical resection in combination with systematic sampling of mediastinal lymph nodes or sweeping.
(6) For patients with LC at clinical stage I-II, during anatomical pneumonectomy, minimally invasive surgery (including thoracoscopy and robotic surgery) can be used to achieve resection at the same scope as thoracotomy but with fewer postoperative complications, a lower mortality rate and better effects on quality of life; therefore, minimally invasive surgery is a better choice.
(7) For excessively large tumors (>7 cm) or tumors that have invaded the mediastinum, aortic knuckle and main trachea, it is possible to resect them if they are T4N0M0 tumors. It is recommended that surgeries are conducted for resection. Adjuvant therapies may be conducted after surgery according to the incisal margin and degree of lymph node metastasis.
(8) For patients with T1-3 tumors and N2 positivity identified in the preoperative examination and assessment, neoadjuvant therapy is recommended to be used first, and in the event of no improvement after therapy, surgical excision is recommended.

Surgical treatment principles for LC at stage III: LC tumors at stage III are highly heterogeneous. Among others, stage IIIA tumors in the 8th edition include T4N0M0, T3-4N1M0 and T1-2N2M0 tumors, all of which can be surgically treated. Patients with T3N2M0 tumors under stage IIIA in the 7th edition but stage IIIB in the 8th edition are also widely recognized as potentially operable patients. The selected surgical indications may not differ despite the changes made in the 8th edition.

For excessively large tumors (>7 cm) or tumors invading the mediastinum, aortic knuckle and main trachea, surgical excision is recommended. Adjuvant therapies may be administered after surgery according to the incisal margin and degree of lymph node metastasis. It is also possible to administer neoadjuvant therapy first and then perform surgical excision.

For patients with N2-positive T1-3 tumors identified in the preoperative examination and assessment, neoadjuvant therapy is recommended to be used first, and in the event of no imagological improvement after therapy, surgical excision is recommended. Although evidence from randomized controlled trials that used surgery or chemotherapy as the local control technique for such patients does not indicate a therapeutic method with an overall survival (OS) advantage, combined therapy including surgery is one of the options for T1-3N2N0 patients in the diagnosis and treatment guidelines in various countries.

Details:

Excision extension for T1a-b tumors (pulmonary lobectomy vs. sublobectomy): The study by the Lung Cancer Study Group (LCSG) in 1995 remains the only randomized controlled trial published concerning the use of pulmonary lobectomy vs. sublobectomy (segmentectomy and wedge resection) [13]. However, within the context of the increasing incidence rate of small LC tumors due to detailed staging and the longterm development of staging and minimally invasive operation technologies, the conclusion of this study should be reviewed again [14].

LC of special types mainly refers to types of LC that have exhibited a significantly increasing rate of detection in recent years and those that have a subsolid nature in imaging examination. The information on such types of LC is mainly based on the prospective multicenter single-arm clinical research trial JCOG0804 [15].

Data on sublobectomy for LC tumors with small diameters originate from the stage III prospective clinical study JCOG0802 published by the American Association of Thoracic Surgery (AATS) in 2021 [16]. In this study, after a follow-up exceeding 7 years, the segment resection group featured a slightly higher local recurrence rate, and the OS of this group was superior to that of the pulmonary lobectomy group.

Lymph node biopsy vs. lymph node dissection: Several previous randomized controlled trials and retrospective studies [17–19] did not prove a survival benefit for the use of MLND in LC patients at stage I/II, including in those who received conventional systematic MLND and improved "selective" MLND (the extent of lymph node dissection is influenced by the representations of the cancer).

Surgical indications for III A (N2): For patients with pathologically confirmed N2 tumors, the role of surgery is still in dispute [20, 21]. It is recommended that the therapeutic risks, team experience and patients' options be comprehensively evaluated by the multidisciplinary diagnosis and treatment team consisting of doctors specializing in LC and thoracic surgery.

Neoadjuvant therapy in stage I-III Main recommendations:

(1) For clinical single-region N2 mediastinal lymph nodes, if there is no massive-type metastasis (lymph node < 3 cm), these lymph nodes should be resected completely, and the recommended methods include surgical excision + adjuvant chemotherapy or neoadjuvant chemotherapy + surgery.
(2) Clinically, multiregion N2 mediastinal lymph nodes should be resected completely, and the recommended methods include radical concurrent radiochemotherapy or neoadjuvant chemotherapy ± radiotherapy + surgery.
(3) For T3-4N1 and T4N0 tumors not involving the superior pulmonary sulcus (invading the chest wall, main bronchus or mediastinum), the recommended methods include neoadjuvant chemotherapy ± radiotherapy + surgery or surgery + adjuvant chemotherapy.
(4) For T3-4N1 superior pulmonary sulcus tumors, the recommended methods include neoadjuvant radiochemotherapy + surgery.
(5) For resectable tumors at stage IIIA, in the event that an EGFR gene-sensitive mutation is identified, the recommended methods include neoadjuvant targeted therapy.
(6) For resectable tumors at stage II-IIIB that are EGFR / ALK-negative, in compliance with the neoadjuvant therapy indications, participation in a neoadjuvant immunotherapy clinical trial is recommended.
(7) For locally advanced LC (LA-LC) that is supercritical and resectable, it is recommended that restaging is performed and the possibility for surgery be reassessed after the administration of induction chemotherapy, immunotherapy, targeted therapy and many other therapeutic techniques.

Notes:

The conventional neoadjuvant therapies for LC include induction chemotherapy and concurrent and sequential radiochemotherapy. Other options are on their way.

(1) Neoadjuvant chemotherapy and radiochemotherapy:

For partial LC at stage IIIA/N2, the conventional neoadjuvant combined therapeutic mode includes surgery after induction chemotherapy, surgery after induced concurrent radiochemotherapy [22] and surgery after induced sequential radiochemotherapy [23]. The EORTC08941 research trial [24] showed that there was no significant difference in OS (16.4 months vs. 17.5 months, $p = 0.596$) or PFS (9.0 months vs. 11.3 months, $P = 0.605$) between the groups. A total of 429 patients with stage IIIA LC were enrolled in the INT 0139 research trial [25]. The results showed that both groups showed a similar OS (23.6 months vs. 22.2 months, $P = 0.24$); the surgery group showed a certain PFS advantage (12.8 months vs. 10.5 months, $P = 0.017$). A total of 558 patients with stage IIIA and IIIB LC (at stage IIIB, exceeding 40% is defined as a T4N1 lesion, which is actually stage IIIA LC now) were enrolled in the GLCCG research trial [26]. The results showed no significant difference in PFS (9.5 months vs. 10.0 months, $P = 0.87$) or OS (15.7 months vs. 17.6 months, $P = 0.97$) between the groups.

(2) Neoadjuvant immunotherapy:

For operable stage I-IIIA LC, in the CheckMate-159 study, [27] nivolumab was adopted for neoadjuvant therapy and was associated with an MPR rate of 42.9%. In LCMC3 study [28] the MPR rate was 18%, and 4 patients achieved a pCR with a 12-month disease-free survival (DFS) rate of 89%. In the NADIM study, [29] neoadjuvant therapy of chemotherapy combined with nivolumab was given with postoperative nivolumab adjuvant therapy

for 1 year; the pCR rate was 71.4%, and the MPR rate was 85.36%, with a downstaging rate of 93%; and the 18-month PFS and OS rates were 81% and 91%, respectively. The CheckMate-816 study is the only stage III controlled trial for which the initial results have been released. The MPR rates of the combined chemotherapy and immunotherapy group and the chemotherapy group were 36.9% and 8.9%, respectively, and the pCR rates were 24% and 2.2%, respectively. This study reached the main study endpoint, but the survival data require follow-up.

(3) Neoadjuvant small-molecule targeted therapy:

Clinical studies on neoadjuvant therapy for LC patients positive for driver gene mutations are quite limited. In CTONG1103 study [30] an erlotinib vs. GP regimen was adopted for neoadjuvant therapy. The erlotinib group showed a longer PFS than the chemotherapy group (21.5 months vs. 11.4 months, $P < 0.001$).

2.2.2 Adjuvant therapy after complete tumorectomy of stage I-IIIB LC

Main recommendations:

(1) Adjuvant therapy after complete tumorectomy of stage I-IIIB LC positive for EGFR mutations:

1) Regular follow-up after complete tumorectomy of LC at stage IA positive for EGFR mutations is needed. Adjuvant chemotherapy or adjuvant targeted therapy is not recommended.
2) After complete tumorectomy of LC at stage IB positivity for EGFR mutations, osimertinib adjuvant therapy can be considered.
3) After complete tumorectomy of stage IIA and IIB LC positive for EGFR mutations, EGFR-TKI (osimertinib, gefitinib or icotinib) adjuvant therapy is recommended.
4) After complete tumorectomy of stage IIIA and IIIB LC positive for EGFR mutations, EGFR-TKI (osimertinib, gefitinib, icotinib or erlotinib) adjuvant therapy is recommended, and osimertinib adjuvant therapy is preferred.

(2) Adjuvant therapy after complete tumorectomy of stage I-IIIB LC negative for EGFR mutations:

1) Regular follow-up after complete tumorectomy of LC at stage IA negative for EGFR mutations is needed. Adjuvant chemotherapy or adjuvant targeted therapy is not recommended.
2) After complete tumorectomy of LC at stage IB negative for EGFR mutations, adjuvant chemotherapy is generally not recommended. For patients with high-risk factors, a multidisciplinary integration discussion [a holistic integrative medicine (HIM) multidisciplinary team (MDT)] is recommended. Based on the discussion assessment and the patient's condition, postoperative adjuvant chemotherapy can be considered (with discrepancy but recommended).
3) For stage II-IIIB LC negative for EGFR mutations, adjuvant chemotherapy after complete tumorectomy is recommended.

Notes:

(1) Principle of adjuvant chemotherapy:

The cisplatin-based double-drug regimen is a recommended adjuvant chemotherapy regimen, [31] and the combined drugs include vinorelbine, gemcitabine, docetaxel, paclitaxel, pemetrexed (for nonsquamous cell carcinoma only) and etoposide. After the patient recovers from surgery, adjuvant chemotherapy may commence, usually at 4–6 weeks after surgery [32]. Four cycles of postoperative adjuvant chemotherapy are recommended.

(2) Principle of adjuvant targeted therapy:

Based on the results of randomized controlled clinical trials [33], adjuvant therapy can extend the DFS of patients with early and mid-stage LC positive for EGFR mutations. When an EGFR-TKI is applied for adjuvant therapy, the use of either single-drug or adjuvant chemotherapy sequential TKI therapy is recommended [34, 35]. The time to start EGFR-TKI adjuvant therapy should be no later than 10 weeks after the surgery. Postoperative EGFR-TKI adjuvant therapy should last for at least 2 years.

(3) Other adjuvant therapy:

Patients with N0 and N1 stage I-IIIB LC are conventionally not recommended to receive postoperative adjuvant radiotherapy [36]. For N2 LC, the findings from the Lung ART showed that for N2 patients who underwent complete tumorectomy, adjuvant radiotherapy could not significantly improve the postoperative recurrence or survival rate but did significantly increase cardiac toxicity [37]. Therefore, the use of adjuvant radiotherapy is not recommended after complete tumorectomy for stage I-IIIB LC.

Details:

(1) Adjuvant therapy after complete tumorectomy for stage I-IIIB LC positive for EGFR mutations:

The global multicenter phase III study ADAURA included patients with stage IB-IIIA LC after complete tumorectomy [38]. The research findings indicated that postoperative osimertinib adjuvant therapy can be considered for stage IB EGFR positive patients. For stage II-IIIB LC positive for EGFR mutations, The findings from the ADAURA [39], the ADJUVANT, the EVIDENCE, the EVEN study indicated that EGFR-TKI (osimertinib, gefitinib or icotinib) adjuvant therapy is recommended after complete tumorectomy. It is important to note that for stage III patients, osimertinib adjuvant therapy is preferred.

(2) Adjuvant therapy after complete tumorectomy for stage I-IIIB LC negative for EGFR mutations:

LACECG conducted meta-analysis [40] indicated that the adjuvant chemotherapy group of patients with LC at stage IA did not show an OS benefit over the observation group. Therefore, for LC at stage IA negative for EGFR mutations, adjuvant chemotherapy is not recommended.

For LC at stage IB negative for EGFR mutations, adjuvant chemotherapy is usually not recommended for such patients. However, the findings from CALGB9633 and retrospective research in 2013 indicated that partial LC at stage IB may benefit from postoperative adjuvant chemotherapy. As a result, for patients with high-risk factors, discussion by the HIM MDT is recommended.

After complete tumorectomy for LC at stage IIA negative for EGFR mutations, postoperative adjuvant chemotherapy is still recommended.

The results of a 2008 LACECG meta-analysis [41] and another results of a 2010 meta-analysis, 2010 JBR10 clinical study also showed that postoperative chemotherapy for stage II LC could lower the mortality risk. Therefore, for stage IIB IIIB LC negative for EGFR mutations, conventional adjuvant chemotherapy is recommended after complete tumorectomy.

2.2.3 Surgical treatment of LC "oligometastasis"

Main recommendations:

(1) Surgical treatment of LC brain oligometastasis:

1) Surgical treatment is recommended when the pulmonary primary tumor is resectable LC, and the synchronous LC brain oligometastasis is solitary metastasis [42].
2) Surgical treatment is recommended when the pulmonary primary tumor is resectable LC, and the synchronic brain oligometastasis is a large metastatic tumor with severe intracranial hypertension.
3) After the pulmonary primary tumor is resected, surgical treatment is recommended if the heterochronous brain oligometastasis is a solitary metastasis. After systematic examination and assessment, if no tumor recurrence is observed in other areas, surgical treatment can be performed if the patient can tolerate intracranial single oligometastatic tumor resection.
4) After the pulmonary primary tumor is resected, surgical treatment is recommended if heterochronous and solitary brain oligometastasis is observed after systematic examination and assessment and no tumor recurrence is observed in other areas. Surgical treatment is also recommended if heterochronous brain oligometastasis is accompanied by poor efficacy of internal medicine treatment and intracranial hypertension.

(2) Surgical treatment of LC adrenal gland oligometastasis:

1) With synchronic unilateral LC adrenal gland oligometastasis, the primary LC can be resected. Additionally, synchronous unilateral LC adrenal gland oligometastasis should be resected in stage I.
2) After complete primary LC resection is performed, surgical treatment is recommended if solitary heterochronous adrenal gland oligometastasis is observed after systematic examination and assessment, no tumor recurrence or metastasis is observed in other areas, and it is possible to perform heterochronic adrenal gland oligometastatic tumor resection.
3) Surgical treatment is recommended if synchronic opposite LC adrenal gland oligometastasis is observed 1 month after primary LC resection after systematic examination and assessment, and no tumor recurrence or metastasis is observed in other areas; synchronous opposite LC adrenal gland oligometastasis should be resected in stage II.
4) After complete primary LC resection is performed, surgical treatment is recommended if bilateral heterochronic adrenal gland oligometastasis is observed after systematic examination and assessment, no tumor recurrence or metastasis is observed in other areas, and it is possible to perform heterochronic bilateral adrenal gland oligometastasis tumor resection.

(3) Surgical treatment of LC bone oligometastasis:

1) By principle, LC bone oligometastasis is not recommended for treatment with surgery, and internal medicine involvement in HIM MDT diagnosis and treatment is recommended.
2) Surgical treatment is recommended for subsequent LC bone oligometastasis.

(4) Heterochronous, single-site and single metastasis focus bone oligometastasis after complete resection of primary LC, without metastasis in other areas after systematic assessment.
(5) Heterochronous bone solitary oligometastasis arising after complete resection of primary LC, with the bone oligometastasis area being a load-bearing area of the lower limbs, e.g., thighbone or shin bone, without metastasis in other areas after systematic assessment.
(6) Heterochronous bone oligometastasis arising after complete resection of primary LC, which results in severe bone-related events, e.g., vertebral oligometastasis accompanied by spinal cord compression, without metastasis in other areas after systematic assessment (with discrepancy but recommended).
(7) Surgical treatment of LC pulmonary oligometastasis:

1) For resectable LC accompanied by unilateral synchronous pulmonary oligometastasis, resection of the primary LC and unilateral synchronous pulmonary oligometastatic tumor in the same stage is recommended.
2) For resectable LC accompanied by opposite synchronous pulmonary oligometastasis, the resection of the primary LC should be performed first, and then resection of the opposite synchronous pulmonary oligometastatic tumor in several stages is recommended.
3) For unilateral heterochronic pulmonary oligometastasis, after the resection of primary tumors, surgery is recommended if recurrence or metastasis in other areas is not observed after systematic assessment and the patient can tolerate unilateral pulmonary oligometastatic tumor resection.
4) For opposite heterochronic pulmonary oligometastasis, after the resection of primary tumors, surgery is recommended if tumor recurrence or metastasis in other areas is not observed after systematic assessment and the patient can tolerate opposite pulmonary oligometastatic tumor resection.

Notes:

"LC oligometastasis" (LCO) refers to the intermediate state in the LC metastatic process, which is a stage between the onset of regional primary LC and the development of extensive metastatic tumors with mild biological invasion. During this stage, primary LC results in only a few local secondary tumors, and LCO is defined as ≤ 2 LC metastatic areas and ≤ 5 metastatic foci. M1b in the 8th edition of international LC staging (single metastasis of isolated extrapulmonary organs) corresponds to "oligometastasis", which differs from the extensive metastasis of LC.

Most scholars believe that as the number of LC "oligometastatic" metastatic lesions increases, the prognosis is usually poorer [43]. LCO may be divided into synchronous oligometastasis and heterochronous oligometastasis according to the chronological order of discovery. Synchronous "oligometastasis" refers to the finding of the primary tumor and metastatic foci at the same time, while heterochronous "oligometastasis" refers to the discovery of metastatic foci 2 months after the diagnosis of primary tumors. LCs with different "oligometastatic" states are associated with different survival rates after surgical treatment [44]. The indications for surgical treatment include many clinical conditions, that is, heterochronous "oligometastasis" and oligorecurrence: ① The patient is found to have a limited number of metastatic foci upon diagnosis. ② Although the patient had multiple metastatic foci, the number of residual foci was limited after systemic therapy. ③ Only 1 lesion develops after treatment (i.e., oligoprogression). ④ The illness is subject to limited recurrence after treatment (i.e., oligorecurrence). Under the above conditions, surgical treatment leads to benefits for patients with "oligometastatic" LC.

2.3 Medical therapy for advanced LC

2.3.1 Treatment of LC positive for driver gene mutations

Treatment of advanced LC positive for EGFR mutations Main recommendations:

(1) 1. First-line treatment for patients with EGFR mutations:

1) EGFR-TKIs, including gefitinib [45], erlotinib, icotinib, afatinib [45], dacomitinib, osimertinib, and almonertinib, are recommended.
2) Regimens that can be considered are gefitinib/erlotinib + chemotherapy and erlotinib + bevacizumab.

(2) Other-line treatment for patients with EGFR mutations:

1) First-line treatment for oligometastasis should be used. It is recommended that a biopsy is performed to clarify the drug-resistance mechanism; it is also possible to continue the original TKI treatment + local treatment.
2) For patients with substantial progression treated with 1st-/2nd-line EGFR-TKIs whose tumors are T790 M+, osimertinib, almonertinib and furmonertinib are recommended.
3) For patients with substantial progression with the 1st-/2nd-line EGFR-TKIs whose tumors are T790 M- (nonsquamous cell carcinoma), platinum-based double-drug chemotherapy or platinum-based double-drug chemotherapy + bevacizumab are recommended.
4) For patients whose tumors are T790 M- with 3rd-generation TKI failure, treatment should progress with reference to that recommended for advanced LC treatment without driver genes.

Notes:

(1) First-line treatment of advanced LC with EGFR-sensitive mutations:

The findings from the LUX-LUNG7 and ARCHER 1050 studies and the AENEAS and FLAURA studies indicate that afatinib, dacomitinib and osimertinib show better efficacy than first-generation TKIs [46, 47]. 7 drugs have been approved by the NMPA for application in the first-line treatment of advanced LC positive for EGFR mutations. Afatinib was also approved by the Food and Drug Administration (FDA) to be applied in the treatment of patients with tumors with site point mutations in exons 18–21 (Leu861Gln, Gly719Ser, Gly719Ala, Gly719Cys, Ser768lle) [48].

Combination therapy mode: EGFR-TKI first-line combination therapy includes EGFR-TKI combination chemotherapy, antiangiogenic therapy or other EGFR-TKI therapies. The FASTACT-2 [49], JMIT, NEJ009, NEJ005 study evaluated the difference in the efficacy of TKI combined with chemotherapy and TKI alone. These results indicated that targeted therapy with chemotherapy can provide certain benefits.

The phase II study JO25567 and the phase III randomized controlled trial ARTEMIS demonstrated the efficacy and safety of the combined bevacizumab and EGFR-TKI regimen globally. Combined therapy led to a significantly longer PFS than erlotinib monotherapy (median 18.0 vs. 11.3, $P < 0.001$) [50]. A domestic phase III clinical study (SINDAS) found that additional local radiotherapy for all foci could significantly improve the PFS and OS of patients with lung adenocarcinoma positive for EGFR mutations with oligometastasis (≤5 metastatic foci, no brain metastasis before randomized grouping).

(2) Treatment of patients with EGFR mutations after drug resistance:

The postdrug-resistance progression mode can be divided into the following two types according to the area of progression and oligoprogression: oligoprogression or central nervous system (CNS) progression, which refer to the progression of local isolated foci or the progression of CNS foci, respectively; extensive progression refers to the progression of multiple systemic or significant foci.

1) For patients who received 1st-/2nd-generation EGFR-TKIs during first-line and maintenance therapy, the T790 M mutation is the most common cause of drug-resistance. The AURA3 study used osimertinib and pemetrexed combined with platinum-based chemotherapy; the modified PFS (mPFS) values for the two groups were 10.1 months and 4.4 months, and their ORRs were 71% and 31%, respectively [51].

Several 3rd-generation EGFR-TKIs that are made in China have also shown good efficacy in the treatment of LC positive for the T790 M mutation after the development of TKI drug resistance. NMPA has approved almonertinib for the treatment of patients with other LCs positive for the EGFR T790M mutation with progression during or after EGFR-TKI therapy. The findings from a phase IIb study on furmonertinib indicated that the ORR for patients with advanced LC positive for the EGFR T790 M mutation treated with furmonertinib was 74.1%, the DCR was 93.6%, the PFS was 9.6 months, and the clinical benefit rate (CBR) was 79.5%. NMPA has also approved the use of methanesulfonic acid, with its indications being the same as those for almonertinib. Complete phase III clinical trial data concerning the above drugs have not yet been published.

2) For patients with the EGFR T790M mutation after the development of drug resistance or with 3rd-generation TKI treatment failure, platinum-based double-drug chemotherapy ± bevacizumab (nons-

quamous cell carcinoma) can be administered. For patients with oligoprogression / CNS progression, the original EGFR-TKI therapy combined with local therapy may be continued [52]. If permitted, the specific therapeutic regimen should be determined according to the reassessment of pathology in the biopsy sample and molecular subtyping results.

3) Regarding third-line and multiline treatment of EGFR-sensitive mutation patients, the results of the ALTER 0303 study showed that in the third-line and beyond treatment of advanced LC, compared anlotinib could lead to significantly longer OS and PFS than placebo with satisfactory tolerance, indicating that the drug can be selected for third-line treatment.

Treatment of advanced LC positive for ALK mutations Main recommendations:

(1) First-line treatment of LC positive for ALK mutations:

1) Alectinib, crizotinib and ceritinib are recommended.
2) Drugs that can be considered include ensartinib, brigatinib, and lorlatinib (with dispute but recommended).

(2) Other-line treatment of LC positive for ALK mutations:

1) With oligoprogression after first-line treatment, it is recommended that another biopsy is performed to clarify the drug-resistance mechanism and select the 2nd-/3rd-generation TKI therapy; the original TKI therapy + local therapy can also be continued.
2) With extensive progression after first-line treatment, it is recommended that another biopsy be performed to clarify the drug-resistance mechanism and select the 2nd-/3rd-generation TKI therapy; 2nd-generation drugs can also be exchanged.
3) With repeated progression, it is possible to refer to the treatment for advanced LC with nondriver gene mutations.

Notes:

(1) First-line treatment of advanced LC positive for ALK fusion mutations:

Crizotinib was the first approved 1st-generation ALK-TKI drug applied in the first-line treatment of advanced LC positive for ALK mutations in the world [53], Ceritinib was the second, Alectinib was the third one which was approved for use in the world [54, 55]. In 2018, the NMPA approved alectinib for the first-line treatment of ALK mutation-positive locally advanced or metastatic LC and for second-line treatment after progression on crizotinib.

The ALTA-1 L research results showed that the median PFS of patients treated with brigatinib was significantly superior to that of patients treated with crizotinib, namely, 29.4 months and 9.2 months, respectively (HR, 0.49; 95% CI, 0.33–74; $P=0.0007$), which lowered the disease progression rate by 51% [56].

Ensartinib is a second-generation ALK-TKI that was independently developed in China. The phase III eXalt3 test compared the efficacy and safety of ensartinib and crizotinib in the treatment of advanced LC patients positive for ALK mutations who did not receive ALK-TKI therapy. The initial results have been released recently. The interim analysis results showed that among the targeted intent-to-treat population, in the BIRC assessment, the median PFS in the ensartinib group was 25.8 months, which was significantly superior to that in the crizotinib group, 12.7 months (HR = 0.51, $P=0.0001$).

The results of the phase III CROWN study, a head-to-head comparison of the efficacy and safety of lorlatinib and crizotinib in the first-line treatment of untreated advanced LC positive for ALK mutations, showed that the PFS benefit of lorlatinib was significant [57].

(2) Second-line and beyond treatment of patients with AKL fusion mutations:

After the development of resistance to first-line targeted drugs, the subsequent therapeutic regimen should be selected according to the general condition of the patient, the status of metastasis and the drug-resistance mechanism. Regarding different types of ALK-TKI drug-resistance mutations, different therapeutic strategies should be applied. For example, lorlatinib can be applied to treat tumors with drug resistance due to the G1202R mutation.

After progression with the first-line application of ALK inhibitors, two conditions can be defined based on the area of progression and oligoprogression: oligoprogression / CNS progression and extensive progression. For oligoprogression / CNS progression, use of the original ALK-TKI can be continued, and the treatment may focus on local foci. In the event of progression with first-line

application of crizotinib in treatment, crizotinib can be replaced with alectinib or ceritinib.

For therapy after progression on first-line crizotinib therapy for advanced LC positive for ALK mutations, alectinib and ceritinib are uniformly approved by the NMPA. In a single-arm multicenter phase II clinical study with ensartinib applied to treat advanced LC with ALK mutation positivity after the development of crizotinib resistance, the results showed that the ORR was 52%, the intracranial metastasis ORR was 70% and the median PFS was 9.6 months [58]. Recently, ensartinib was approved to be marked in China for second-line treatment. If the first-line treatment with 2nd-generation drugs fails, platinumbased double-drug chemotherapy ± bevacizumab can be selected.

Other ALK inhibitors that have not been marketed in China, including brigatinib and lorlatinib, can be selected for the treatment of advanced LC positive for ALK mutations with the development of resistance to a TKI as first-line treatment.

In the treatment of LC positive for ALK mutations after progression on a TKI and platinum-based double therapy, for patients with an ECOG PS of 0–2 points, single-drug chemotherapy can be considered.

Treatment of advanced LC positive for ROS1 mutations Main recommendations:

(1) First-line treatment of LC positive for ROS1 mutations:

1) Crizotinib is recommended.
2) Drugs that can be considered include ceritinib or entrectinib (with dispute but recommended).

(2) Other-line therapy for LC positive for ROS1 mutations:

1) With oligoprogression after first-line treatment, it is recommended that another biopsy is performed to determine the drug-resistance mechanism; it is also possible to proceed with the original TKI therapy + local therapy.
2) With oligoprogression after first-line treatment, platinum-based double-drug chemotherapy + local therapy or platinumbased double-drug chemotherapy + bevacizumab (nonsquamous cell carcinoma) + local therapy can be considered.
3) With extensive progression after first-line treatment, platinum-based double-drug chemotherapy + local therapy or platinumbased double-drug chemotherapy + bevacizumab (nonsquamous cell carcinoma) are recommended.
4) With extensive progression after first-line treatment, participation in a clinical study can be considered.
5) With repeated progression on second-line treatment, clinicians can refer to the treatment for advanced LC without driver gene mutations.

Notes:

(1) First-line treatment of advanced LC positive for ROS1 rearrangements:

Crizotinib is the only targeted drug approved by the FDA for the treatment of LC positive for ROS1 and ALK mutations [59]. This recommendation is mainly based on evidence from clinical studies, including A8081001, EUCROSS, EUROS1, and OO12-01. All of these clinical studies have proven that crizotinib shows significant efficacy in the treatment of advanced LC with ROS1 mutation positivity.

Entrectinib is a targeted drug for the treatment of solid tumors with NTRK1/2/3, ROS1 and ALK gene fusion mutations. Three clinical studies, STARTRK-2, STARTRK-1 and ALKA-372–001, concluded that entrectinib is superior to crizotinib. In 2019, the FDA approved entrectinib for use in the first-line treatment of advanced LC positive for ROS1 gene fusions. However, entrectinib has not been marketed in China.

Brigatinib may be applied in the treatment of LC positive for ROS1 mutations based on the results of a multicenter phase I clinical study (ALTA, NCT02094573), but more prospective research is needed to draw specific conclusions.

Lorlatinib is an ROS1 and ALK double-spot mutation targeted inhibitor. Some phase I-II clinical study subgroup analyses concerning advanced LC positive for ROS1 mutations have shown that lorlatinib has certain efficacy for patients with or without past treatment with crizotinib, including brain metastasis patients.

Repotrectinib is a new-generation ROS1 / TRK TKI. In 2021, the World Conference on Lung Cancer (WCLC) published phase II clinical study results on repotrectinib

in the treatment of advanced LC positive for ROS1 fusions and advanced solid tumors positive for NTRK fusions. High safety with good tolerance was demonstrated for all regimens.

(2) Second-line and beyond therapy for advanced LC positive for ROS1 rearrangements:

The results from a clinical study showed that repotrectinib has a strong inhibitory effect on tumors with the most common drug-resistance mutations (i. e., G2032R and D2033N), but its inhibitory effect on tumors with other drug-resistance mutations remains unclear. Loratinib has a strong inhibitory effect on tumors with common drug-resistance mutations, except for G2032R, and cabozantinib has a strong inhibitory effect on tumors with various drug resistance mutations.

Treatment for advanced LC positive for other driver gene mutations Main recommendations:

(1) First-line treatment of LC positive for BRAF-V600E:

1) The guidelines for the first-line treatment of advanced LC without driver gene mutations should be referred to.
2) Drugs that can be considered include dabrafenib combined with trametinib (with dispute but recommended).

(2) Other-line treatment of LC positive for BRAF-V600E:

1) For patients who received targeted drugs in the first-line treatment, the guidelines for the treatment of advanced LC without driver gene mutations after progression should be referred to.
2) For patients who did not receive targeted drugs in the first-line treatment, targeted therapy can be considered (with dispute but recommended).

(3) First-line treatment of LC positive for NTRK mutations:

1) The guidelines for the first-line treatment of advanced LC without driver gene mutations should be referred to.
2) Drugs that can be considered include entrectinib or larotrectinib (with dispute but recommended).

(4) Other-line therapy for LC positive for NTRK mutations:

1) For patients who received targeted drugs in the first-line treatment, the guidelines for the treatment of advanced LC without driver gene mutations after progression should be referred to.
2) For patients who did not receive targeted drugs in the first-line treatment, targeted therapy can be considered (with dispute but recommended).

(5) First-line treatment for LC positive for a C-met14 exon skipping mutation:

1) The guidelines for the first-line treatment of advanced LC without driver gene mutations should be referred to.
2) Drugs that can be considered include savolitinib, crizotinib, capmatinib, and tofacitinib (with dispute but recommended).

(6) Other-line treatment for LC positive for a C-met14 exon skipping mutation:

1) For patients who received targeted drugs in the first-line treatment, guidelines for the treatment of advanced LC without driver gene mutations after progression should be referred to.
2) For patients who did not receive targeted drugs in the first-line treatment, the recommended drugs include savolitinib, and other drugs that can be considered include crizotinib, capmatinib, and tofacitinib (with disputes but recommended).

(7) First-line treatment of LC positive for RET fusions:

1) Guidelines for the first-line treatment of advanced LC without driver gene mutations should be referred to.
2) Drugs that can be considered include pralsetinib and selpercartinib (with dispute but recommended).

(8) Other-line treatment for LC positive for RET fusions:

1) For patients who received targeted drugs in the first-line treatment, guidelines for the treatment of advanced LC without driver gene mutations after progression should be referred to.
2) For patients who did not receive targeted drugs in the first-line treatment, the recommended drugs include pralsetinib, and selpercartinib can also be considered (with dispute but recommended).

Notes:

BRAF mutations occur in 1% 3% of LCs. Single-drug BRAF inhibitor (vemurafenib or dabrafenib) treatment shows efficacy in the form of partial tumor regression in LCs with BRAF mutations. The results of a phase II clinical study (NCT01336634) on the first-line treatment of advanced LC with BRAF V600E combined with dabrafenib and trametinib showed that the ORR was 64%, the median PFS was 10.9 months, and the median DOR was 10.4 months. In China, the combined application of dabrafenib and trametinib has not been approved for first-line treatment, nor have any relevant targeted drugs been approved for use in LC treatment. The guidelines for the treatment of stage IV LC with the BRAF V600E mutation/ NTRK fusion mainly refer to those for the treatment for stage IV advanced LC treatment without driver gene mutations.

NTRK gene rearrangements have been discovered in several solid tumors, including LCs, but with an occurrence rate of only 0.1%-1%. NTRK gene fusions differ according to age, sex, smoking history and histological changes. FDA approved larotrectinib for use in the treatment of several solid tumors with NTRK gene fusion mutations. The pooled results of three clinical studies (STARTRK 2, STARTRK1 and ALKA372-001) showed that after entrectinib therapy, the ORR of solid tumors with NTRK fusions was 57.0%, the median PFS was 11.2 months [60]. In 2019, the FDA approved entrectinib for use in the treatment of solid tumors positive for NTRK gene fusions.

Among patients with LC, the rate of MET exon 14 mutation is 1%-3%. The PROFILE 1001 study showed that the PFS was 7.3 months, and the ORR of the crizotinib group was 32%. The findings of the phase II GEOMETRY mono-1 study indicated that the capmatinib DCR was 82% (28 cases of initial treatment, 69 treated patients in cohort 4), and the ORR in initial treatment was 68%, with a DOR of 12.6 months. The ORR in treated patients was 41%, and the DOR was 9.7 months. In May 2020, the FDA accelerated the approval of the marketing of capmatinib in the first-line treatment of locally advanced or metastatic LC positive for a MET exon 14 skipping mutation.

Savolitinib is a reversible MET small-molecule kinase inhibitor with a strong effect and ATP competitiveness. In a phase II study, the ORR as assessed by an IRC was 49.2%, the DCR was 93.4%, and the DOR was 9.6 months (maturity of 40.0%) [61]. Based on such research results, the NMPA approved savolitinib for use in the treatment of locally advanced or metastatic LC with a MET exon skipping mutation in June 2021 (with chemotherapy failure or intolerability).

The phase II VISION trial was performed to assess the efficacy and safety of the single drug tepotinib in the treatment of LC with a MET exon 14 skipping mutation (cohort A) or MET amplification (cohort B). In the Asian subgroup in the VISION study, the ORR was 61.9%, and the ORR as assessed by researchers was 71.4%.

RET gene fusion has been identified as an LC driver gene, with an occurrence frequency of 1%-2%. The findings from the phase I/II ARROW study demonstrated that pralsetinib had a good effect on antitumor activity. The ORR in Chinese patients reached 56%, but the DOR endpoint was not met in the study. Eighty-three percent of patients showed a 6-month DOR, and the brain metastasis ORR was 56%, with a CR rate of 33%. The efficacy and safety of pralsetinib in Chinese patients were the same as those observed in the global population.

In the phase I/II LIBRETTO-001 test, the retreatment DOR of LOXO-292 reached 20.3 months, and the PFS reached 18.4 months. The ORR, DOR and PFS did not vary with different types of previous treatment.

2.3.2 Treatment of LC without driver gene mutations

First-line treatment for nonsquamous cell LC without driver gene mutations Main recommendations:

(1) Conducting PD-L1 immunohistochemistry before the initial treatment of LC* without driver gene mutations is recommended.
(2) Single-drug treatment with pembrolizumab or atezolizumab is recommended for the first-line treatment of advanced LC*without driver gene mutations with ≥ 50% PD-L1 expression (pembrolizumab 22C3 antibody, atezolizumab SP142 antibody). For the first-line treatment of advanced LC* with 1% 49% PD-L1 (22C3) expression that lacks driver gene mutations, single-drug treatment with pembrolizumab is optional in the first-line treatment.
(3) Combined pembrolizumab and pemetrexed + platinum therapy is recommended as an option in the first-line treatment of LC* without driver gene mutations, regardless of PD-L1 expression. After 4–6 cycles, treatment can proceed with maintenance therapy with pembrolizumab and pemetrexed.

(4) Combined atezolizumab and pemetrexed + platinum (APP) therapy is recommended as an option in the first-line treatment of LC* that lacks driver gene mutations, regardless of PD-L1 expression. After 4–6 cycles, treatment can proceed with maintenance therapy with combined atezolizumab and pemetrexed.
(5) Combined camrelizumab and pemetrexed + carboplatin is recommended as an option in the first-line treatment of LC* without driver gene mutations, regardless of PDL1 expression. After 4–6 cycles, treatment can proceed with maintenance therapy with combined camrelizumab and pemetrexed.
(6) Combined tislelizumab, sintilimab or sugemalimab and pemetrexed + platinum therapy is recommended as an option for the first-line treatment of LC* without driver gene mutations, regardless of PD-L1 expression. After 4–6 cycles, treatment can proceed with maintenance therapy with combined immunotherapy and pemetrexed.
(7) Maintenance immunotherapy is recommended. Immunotherapy should last for 2 years in total unless disease progression or intolerable adverse events occur.
(8) Bevacizumab or pemetrexed or combined bevacizumab and pemetrexed maintenance treatment is recommended after combined bevacizumab and platinum-based double-drug chemotherapy (recommended) until disease progression or the occurrence of intolerable adverse events#.
(9) Combined human endostatin and vinorelbine / cisplatin + recombinant human endostatin maintenance therapy can be selected#.
(10) Single-drug chemotherapy can be considered in the first-line treatment of patients with advanced nonsquamous cell carcinoma negative for driver gene mutations with an ECOG PS = 2. The chemotherapy regimens include single-drug treatment with gemcitabine, paclitaxel, vinorelbine, docetaxel, and pemetrexed.

[Remarks]

*LC without driver gene mutations refers to LC without EGFR-sensitive mutations or ALK rearrangements.

#Regarding combined antivascular therapy and chemotherapy, its use is always recommended for patients with LC without driver gene mutations who are not suitable for combined immunotherapy and chemotherapy.

Notes:

KEYNOTE-024 was a phase III randomized controlled clinical trial. In comparisons of the use of pembrolizumab monotherapy with platinum-based double-drug chemotherapy for the treatment of advanced non-small-cell LC negative for driver gene mutations but with a PD-L1 Tumor Proportion Score (TPS) (Dako 22C3) ≥50%, pembrolizumab significantly extended the PFS (median 10.3 months vs. 6.0 months, HR=0.50) and OS (median 30.0 months vs. 14.2 months, HR= 0.63) and significantly improved the ORR (44.8% vs. 27.8%) [62]. In 2016, the FDA approved pembrolizumab for use in the first-line treatment of advanced LC without driver gene mutations but with a PD-L1 TPS≥50%.

KEYNOTE-042 was another phase III randomized controlled clinical trial on the treatment of advanced LC negative for driver gene mutations but with a PD-L1 TPS (Dako 22C3) ≥1%. The KEYNOTE-042 China extension study proved that first-line pembrolizumab led to better OS than chemotherapy (median OS PD-L1 expression ≥50%: 24.5 months vs.13.8 months, HR=0.63; PD-L1 expression ≥1%: 20.2 months vs. 13.5 months, HR=0.67) for all PD-L1 expression (≥50%, ≥ 20%, ≥1%) populations. The China extension study follow-up data updated this year showed that the use of pembrolizumab significantly lowered the mortality risk by 33%, and the median OS reached 20.2 months with a 2-year OS rate of 43.8% [63]. In 2019, the FDA and NMPA approved pembrolizumab for use as a first-line treatment.

IMpower110 was a randomized, open-label, phase 3 clinical trial on the initial treatment of patients with LC with tumor cell or tumor-invading immune cell PD-L1 expression ≥1% (SP142). Among patients with high PD-L1 expression (TC3 / IC3) and wild-type EGFR/ ALK, the median survival of the atezolizumab monotherapy group was longer than that of the chemotherapy group (20.2 months vs. 13.1 months; HR=0.59) [64]. In 2021, the NMPA approved the use of indications for atezolizumab use in the first-line treatment of patients with high PDL1 expression.

The final data of IMpower132 published showed that the APP group had a significantly higher PFS benefit than the pemetrexed and platinum (PP) therapy group (7.7 months vs. 5.2 months; HR=0.56). The Chinese cohort was consistent with global data. Interim analysis OS data are not yet complete, but the tendency of a benefit of combined atezolizumab and chemotherapy was observed [65].

The findings from the KEYNOTE-189 study showed that when pembrolizumab, pemetrexed and platinum were combined and applied in the treatment of nonsquamous LC with wild-type EGFR / ALK, the ORR (47.6% vs. 18.9%, *P*<0.0001), PFS(median 8.8 months vs. 4.9 months, HR= 0.52, *P*<0.001) and OS of the combined therapy group [66]. The FDA and NMPA approved the use of the combination of pembrolizumab and platinum-based double drugs in the first-line treatment of advanced nonsquamous LC without driver gene mutations in 2017 and 2019, respectively.

The CameL study compared the efficacy and safety of combined camrelizumab and pemetrexed/carboplatin with those of singledrug chemotherapy in the first-line treatment of advanced nonsquamous LC negative for EGFR / ALK mutations. The results showed that the camrelizumab + chemotherapy group had a significantly longer PFS (median 11.3 months vs. 8.3 months, HR= 0.61, *P*=0.0002) and a significantly better ORR (60.0% vs. 39.1%, *P*<0.0001) than the chemotherapy group [67]. In 2020, the NMPA approved the combined use of camrelizumab and pemetrexed/ carboplatin in the first-line treatment of locally advanced or metastatic nonsquamous LC negative for EGFR / ALK mutations that cannot be resected through surgery.

The RATIONALE 304 study results showed that if combined tislelizumab and pemetrexed / platinum were applied in the firstline treatment of stage IIIB-IV nonsquamous LC, the PFS could be significantly improved (9.7 months vs. 7.6 months, HR= 0.645), and a higher ORR and longer DOR could be obtained than with pemetrexed / platinum monotherapy. The combined tislelizumab and chemotherapy showed controllable safety and did not exhibit significantly more toxicity than the singledrug chemotherapy [68].

The ORIENT-11 study compared the efficacy and safety of combined sintilimab and pemetrexed / platinum with those of monotherapy in the first-line treatment of advanced nonsquamous LC negative for EGFR / ALK mutations. The results showed that the combination of sintilimab and pemetrexed/ platinum could significantly improve the median PFS (8.9 months vs. 5.0 months, HR=0.48) and median OS (failed to meet the OS endpoint of 16.0 months in the comparison, HR=0.61) [69]. In 2021, the NMPA approved the combination of sintilimab and pemetrexed/platinum for use in the first-line treatment of nonsquamous LC.

The GEMSTONE-302 study intended to assess the efficacy and safety of combined sugemalimab and platinumbased chemotherapy (*n*=320) in the first-line treatment of stage IV squamous or nonsquamous nonsmall-cell LC (SQ/NSQ-NSCLC) negative for driver gene mutations compared with those of combined placebo and platinum-based chemotherapy (*n*=159). As of March 15, 2021, the median PFS assessed by the researchers in the sugemalimab group and the chemotherapy group was 9.0 months and 4.9 months, respectively (HR=0.48; 95% CI 0.39-0.60); among patients with nonsquamous NSCLC, the median PFS in the suge malimab group and chemotherapy group was 9.6 months and 5.6 months, respectively (HR=0.59; 95% CI 0.45-0.79). In December 2021, the NMPA approved the combination of sugemalimab and pemetrexed and carboplatin for use in the first-line treatment of metastatic nonsquamous NSCLC negative for driver gene mutations.

The BEYOND study was a randomized, controlled, national multicenter phase III clinical trial aiming to prove the efficacy and safety of a combined bevacizumab and carboplatin/ paclitaxel regimen for the treatment of advanced LC in China. The results showed that the combined bevacizumab and carboplatin/ paclitaxel group had a significantly longer PFS (9.2 months vs. 6.5 months, HR=0.40, 95% CI: 0.29-0.54, *P*<0.001), better ORR (54.4% vs. 26.3%, *P*<0.001) and longer OS (24.3 months vs. 17.7 months, HR=0.68, 95% CI: 0.50-0.93, *P*=0.0154) than the chemotherapy group [70]. In 2018, the NMPA approved the combined platinum-based double-drug chemotherapy and bevacizumab for use in a first-line therapeutic regimen.

In the PARAMOUNT trial, after 4 cycles of combined pemetrexed and cisplatin, patients without progression continued to receive pemetrexed maintenance therapy until disease progression or intolerance. The regimen led to significantly longer PFS (median 4.1 months vs. 2.8 months) and OS (median 13.9 months vs. 11.0 months) than the placebo [71]. The use of bevacizumab ± pemetrexed maintenance therapy was evaluated in the treatment of advanced nonsquamous LC in a randomized phase III study known as the COMPASS study. In this study, patients who received 4 cycles of pemetrexed, carboplatin and bevacizumab therapy without progression were divided into the bevacizumab maintenance group, the pemetrexed maintenance group and the pemetrexed + bevacizumab double-drug maintenance group. The double-drug maintenance group did not show a significantly longer OS than the single-drug group following statistical analysis, but the wild-type EGFR subgroup and those younger than 70 years did exhibit more benefits [72].

The results of a randomized, double-blind, multicenter and head-to-head phase III clinical trial, QL1101-002,

showed that a bevacizumab analog achieved an 18-week ORR, reaching the main research endpoint (52.3%vs. 56%, HR=0.933) and similar safety to that achieved using the original bevacizumab drug [73]. On this basis, in 2019, the NMPA approved the use of first-line indications for combined bevacizumab analog and platinum-based double-drug chemotherapy.

The combination of recombinant human endostatin, vinorelbine and cisplatin as firstline chemotherapy in the treatment of advanced LC significantly improved the ORR and extended the time to progression without a significant difference in adverse reactions [74].

For patients with an ECOG PS of 2 points, several clinical studies have proven that single-drug chemotherapy can lead to longer survival and better QOL than the best supportive care (BSC). The optional single-drug chemotherapy regimens include gemcitabine, vinorelbine, paclitaxel, docetaxel and pemetrexed. Patients with ECOG PSs ≥3points are not recommended to receive chemotherapy; instead, BSC is recommended.

First-line treatment of advanced squamous cell carcinoma negative for driver gene mutations Main recommendations:

(1) PD-L1 immunohistochemistry is recommended before the initial treatment of LC without driver gene mutations.
(2) Single-drug treatment with pembrolizumab or atezolizumab is recommended in the first-line treatment of advanced LC without driver gene mutations with a PD-L1 TPS (22C3) ≥ 50%. For the first-line treatment of advanced LC without driver gene mutations and a PD-L1 TPS (22C3) of 1% 49%, the single drug pembrolizumab may be selected as the first-line treatment.
(3) A combination of pembrolizumab and paclitaxel or albumin paclitaxel + carboplatin is recommended, regardless of the PD-L1 expression status.
(4) Combined tislelizumab and paclitaxel or albumin paclitaxel + carboplatin are recommended, regardless of the PD-L1 expression status.
(5) Combined sintilimab and gemcitabine + platinum are recommended, regardless of the PD-L1 expression status.
(6) Combined treatment with sugemalimab and paclitaxel or albumin paclitaxel + platinum is recommended, regardless of the PDL1 expression status.
(7) It is possible to select combined treatment with camrelizumab and paclitaxel + carboplatin, regardless of the PD-L1 expression status.
(8) Patients not suitable for platinum may receive nonplatinum-based double-drug regimens, including gemcitabine + docetaxel or gemcitabine + vinorelbine.
(9) Immune maintenance therapy is recommended. Immunotherapy should last for 2 years in total or until the disease progresses or the patient can no longer tolerate the side effects.
(10) In the first-line treatment of advanced squamous cell LC without driver gene mutations and an ECOG PS = 2, single-drug chemotherapy can be considered. The chemotherapy regimens include the single-drug regimens gemcitabine, paclitaxel, vinorelbine, and docetaxel.

Notes:

KEYNOTE-407 study: This study assessed the efficacy and safety of combining pembrolizumab and paclitaxel or albumin paclitaxel / carboplatin in the first-line treatment of advanced squamous cell carcinoma LC and compared them with those achieved using chemotherapy [75]. Regardless of the PD-L1 expression level, use of the combination of pembrolizumab and chemotherapy led to significantly better OS than the use of chemotherapy alone. The KEYNOTE-407 China extension study [76] was parallel to the global data. In 2019, the NMPA approved this regimen for use in the first-line treatment of metastatic squamous LC.

RATIONALE 307 study: Combined tislelizumab and carboplatin / paclitaxel or combined carboplatin / albumin / paclitaxel were applied in the first-line treatment of stage IIIB-IV squamous LC, the median PFS was 7.6 months, which was significantly longer than the 5.5 months observed in the chemotherapy group. However, among the three groups, the occurrence rate and frequency of AEs (including ≥grade 3) were similar. In 2021, the NMPA approved the combination of tislelizumab and paclitaxel or albumin-paclitaxel/carboplatin for use in the first-line treatment of advanced squamous LC [77].

ORIENT-12 study [78]: The combination of sintilimab and gemcitabine / platinum in the first-line treatment of squamous LC led to significantly longer median PFS than chemotherapy (5.5 months vs. 4.9 months, HR= 0.54). This was the first study with a positive conclusion concerning the application of a PD-1 inhibitor combined with a gemcitabine + platinum-based chemotherapy regimen in the treatment of LC squamous cell carcinoma

The CameL-sq study [79] showed that in the first-line treatment of squamous LC, use of the combination of camrelizumab and paclitaxel / carboplatin led to significantly longer median PFS than the use of chemotherapy alone (8.5 months vs. 4.9 months, HR=0.37). The GEMSTONE-302 study showed that among patients with squamous NSCLC, the median PFS of the sugemalimab group and chemotherapy group was 8.3 months and 4.8 months, respectively (HR=0.34; 95% CI 0.24-0.48). In December 2021, the NMPA approved the combination of sugemalimab, paclitaxel and carboplatin for use in the firstline treatment of metastatic squamous NSCLC.

Second or beyond-line treatment of advanced LC without driver gene mutations Main recommendations:

(1) Nivolumab, pembrolizumab (PD-L1 expression ≥ 1%), atezolizumab, and tislelizumab are recommended in the second-line treatment of advanced LC negative for driver gene mutations (if the first-line treatment does not include an ICI).In the case of progression after a PD-1 / PD-L1 inhibitor alone or combined with chemotherapy therapy, administering other PD-1 / PD-L1 inhibitors in the subsequent therapeutic regimens is not recommended.
(2) Docetaxel or pemetrexed is recommended in the second-line treatment of advanced LC negative for driver gene mutations (if the first-line treatment does not include the same drug but the ICI).
(3) Third-line treatment with the recommended anlotinib can be used for patients with progressive or recurrent locally advanced or metastatic squamous NSCLC (limited to the peripheral type) after at least 2 types of systemic chemotherapy.Sintilimab can be applied in the secondline treatment of advanced or metastatic squamous LC.
(4) Third-line treatment is recommended, and therapeutic regimens that have not been used in previous lines may be used, e.g., nivolumab monotherapy or docetaxel or pemetrexed monotherapy.
(5) Patients are encouraged to participate in clinical trials.

Notes:

The results from three phase III studies, CheckMate 017, CheckMate 057 and CheckMate 078 [80, 81], showed the efficacy of nivolumab in the treatment of advanced squamous and nonsquamous cell carcinoma. Evidence from advanced squamous cell carcinoma and nonsquamous cell carcinoma patients in China showed that nivolumab had better efficacy than docetaxel (median OS of 11.9 months vs. 9.5 months, HR=0.75). The FDA and NMPA approved nivolumab for use in the secondline treatment of advanced LC negative for mutated genes in 2015 and 2018, respectively.

The findings from the KEYNOTE-010 [82] showed that for patients with locally advanced or metastatic LC positive for PD-L1 expression (PD-L1 TPS≥1%, Dako 22C3), the standard pembrolizumab showed OS that were significantly superior to that of the docetaxel group (10.4 months vs. 12.7 months vs. 8.5 months). Based on the above research findings, in 2015, the FDA approved pembrolizumab for use in the second-line treatment of patients with locally advanced or metastatic LC that has progressed after first-line chemotherapy and with PD-L1≥1%. The Pembrolizumab showed no statistical significance in terms of OS among patients with PD-L1 ≥50%; among patients with PD-L1≥1%, pembrolizumab still showed a tendency for OS benefit for Chinese patient in KEYNOTE-033 study.

The POPLAR study (phase II) and OAK study (phase III) [83] assessed the efficacy and safety of PD-L1 antibody and atezolizumab in the second-line treatment of recurrent local advanced or metastatic LC compared with docetaxel. Atezolizumab significantly improved the median OS (POPLAR: 12.6 months vs.9.7 months, HR=0.76; OAK:13.3 months vs. 9.8 months, HR=0.78). In 2016, the FDA approved atezolizumab monotherapy for use in the second-line treatment of advanced LC, regardless of the PDL1 expression level.

The RATIONALE 303 study [84] results showed that for the second-line or third-line treatment of locally advanced or metastatic LC with disease progression after platinumbased chemotherapy, the tislelizumab group showed significantly better results in the main endpoint OS than the docetaxel group (ITT population, PD-L1≥25% population) (median OS 17.2 months vs. 11.9 months, 19.1 months vs. 11.9 months). The tislelizumab group had a significantly low er ≥grade 3 AE occurrence rate (38.6% vs. 74.8%).

Nevertheless, the NMPA has not approved pembrolizumab, atezolizumab or tislelizumab for use in the second-line treatment of LC.

ORIENT-3 was a randomized, open, multicenter, parallel, phase III clinical study in China on the effectiveness and safety of sintilimab in the second-line treatment of advanced or metastatic squamous LC [85]. For the second-line treatment of advanced / metastatic sqLC, sintilimab led to significantly better OS than docetaxel (median OS 11.79 months vs. 8.25 months; HR=0.74, P= 0.02489).

In terms of the median PFS, sintilimab (4.30 months, 95% CI: 4.04-5.78) was also significantly superior to docetaxel (2.79 months, HR: 0.52, P<0.00001).

ALTER0303 was a randomized, doubleblind, placebo-controlled, national multicenter phase III clinical study that aimed to assess the efficacy and safety of anlotinib hydrochloride as monotherapy in the secondline treatment of recurrent or progressive LC after therapy [86]. The results from 440 patients showed that the anlotinib hydrochloride group showed an OS that was longer by 3.3 months that in the placebo group (9.6 months vs. 6.3 months, HR=0.68, P= 0.0018), the PFS was longer by 4.0 months that in the placebo group (5.4 months vs. 1.4 months, HR=0.25, P<0.0001), and the ORR was significantly better than that in the placebo group (9.2% vs. 0.7%, p =0.002). The NMPA approved the use of indications for anlotinib as third-line treatment in May 2018.

2.4 Radiotherapy for LC

2.4.1 Treatment for patients with stage I LC not suitable for surgery or who refuse surgery

Main recommendations:

For patients with stage I LC not suitable for surgery due to medical reasons or who refuse surgery, stereotactic body radiotherapy (SBRT) is preferred.

Notes:

Many clinical studies have shown that unlike conventional radiotherapy technology, SBRT or stereotactic ablative radiotherapy (SABR) is associated with a 3-year survival rate of nearly 90% in the treatment of early LC [87]. For patients with early LC not suitable or refuse surgery, SBRT is preferred [88]. The indications for SBRT are as follows: ① Patients with stage I LC who cannot tolerate surgery. ② Patients with stage I LC who refused surgery. ③ For stage I LC patients which are considering SBRT while pathological diagnosis is not available, multidisciplinary integrated diagnosis and treatment (by the HIM MDT) is required or the review and approval of the ethics committee of the local hospital are needed. SBRT could be considered when the following criteria are met: at least 2 types of imagological examinations for identification (e.g., chest thin-layer CT and systemic PET-CT indicate malignant properties); a clear imagological diagnosis (existence of foci during the long-term follow-up > 2 years) showing progressive enlargement, a ground glass shadow density increase, or vascular pass and edge burr changes and other malignant properties; determination after HIM MDT discussion; and full informed consent is obtained from the patient and family. ④ Relative indications include T3N0M0 disease and synchronous multiprimary LC.

Regarding SBRT for early-stage LC, the literature shows that a better local tumor control rate can be obtained, along with improved long-term survival, when the biological effective dose (BED) is ≥ 100 Gy. For central-type LC (within 2 cm of the main bronchus tree, adjacent to the mediastinal pleura), as the healthy organs and tissues surrounding the tumor cannot tolerate high-dose radiotherapy (e.g., reradiotherapy), dose fractionation should be properly reduced, and the frequency can be enhanced. For ultracentral LC (e.g., the tumor is adjacent to or involves the main bronchus or great vessels), the extent of the irradiation field planning treatment volume (PTV) overlaps with important organs (e.g., the esophagus), and SBRT is associated with an enhanced risk of fatal bleeding; thus, SBRT should be used with caution.

2.4.2 Radiotherapy for LA-LC

Main recommendations:

(1) Surgery-centered LA-LC radiotherapy strategy:

1) If the incisal margin is positive or there is residual tumor visible under any form of microscopy or with the naked eye, postoperative radiotherapy (PORT) is recommended.
2) This approach is recommended for patients with pathological N2 tumors after complete resection (with dispute but recommended).

(2) Radiotherapy-centered strategy for LA-LC:

1) Durvalumab after concurrent radiochemotherapy for consolidation therapy is recommended [89].
2) Sequential radiochemotherapy or single radiotherapy can be recommended for patients who cannot tolerate concurrent radiochemotherapy.
3) Concurrent radiochemotherapy should be conducted after chemotherapy is applied to reduce the tumor size (with dispute but recommended).
4) Consolidation chemotherapy after concurrent radiochemotherapy can be performed (not recommended).
5) Conventional application of targeted drugs after concurrent radiochemotherapy for patients with driver gene mutations can be performed (not recommended).

Notes:

For LC tumors at stage II / III, especially stage III, heterogeneity is significant. Stage II / III LC can be divided into three surgery-related categories according to whether the tumor can be resected through surgery: ① resectable: stage

II or IIIAN0-1, partial N2 with a single-segment mediastinal lymph node metastasis with a short diameter (< 2 cm) and partial T4 (satellite nodule existing in the same pulmonary lobe) N1; ② unresectable: partial stages IIIA and IIIB and all IIIC, usually including a single-segment N2 mediastinal lymph node with a short diameter (≥ 3 cm) or multisegment lymph node fusion conglobation (lymph node short diameter determined through CT ≥ 2 cm) N2, T4 and all N3 invading the esophagus, heart, aorta and pulmonary veins; and ③ potentially resectable: partial IIIA and IIIB, including stage IIIA LC with a single-segment N2 mediastinal lymph node short diameter < 3 cm, a potentially resectable superior pulmonary sulcus tumor and a potentially resectable T3 or T4 central tumor.

For patients with LA-LC who undergo surgery, if the clinical comments state that there is postoperative microscopic residual cancer or if residual tumor is visible with the naked eye, PORT is needed [90]. Although no prospective studies have evaluated the best time for radiotherapy, the US National Cancer Database (NCDB) shows that in most clinical cases [91], radiotherapy is performed for advanced patients, and concurrent radiochemotherapy can be considered. The immunotherapy drug that has phase III prospective study evidence is durvalumab [89].

(1) Surgery-centered LA-LC radiotherapy strategy:

Patients with complete surgical excision should receive postoperative adjuvant chemotherapy, radiotherapy and other therapeutic methods. Complete resection covers the following conditions: ① negative incisal margins, including the bronchus, artery, veins, areas surrounding the bronchus, and tissues surrounding the tumor; ② dissection of at least 6 groups of lymph nodes, including 3 groups inside the lungs and 3 groups in the mediastinum (required to include 7 segments); ③ negative pathological results for the resected lymph node with the highest class; and ④ no external lymph node invasion. Positive incisal margins, extracapsular spread, and positive and unresectable lymph nodes are included in the definition of incomplete resection.

For patients with stage III tumors that are unsuitable for complete resection, it is possible to reassess the condition after 2 cycles of neoadjuvant therapy and then conduct complete resection or radical radiochemotherapy. Patients who undergo pulmonary lobectomy after effective neoadjuvant therapy (especially for T4N0-1 and T3N2) may benefit more from surgical excision.

(2) Radiotherapy-centered strategy for LALC:

Patients with stage IIIC LC and most patients with stage IIIB LC are categorized as having unresectable stage III LCs. The combined therapy of radiotherapy and chemotherapyis a standard therapeutic method for inoperable LA-LC. For patients with good general condition (PS 0–1), concurrent radiochemotherapy is recommended; for patients with poor general condition and severe underlying conditions who cannot tolerate concurrent radiochemotherapy, sequential radiochemotherapy or single radiotherapy / chemotherapy (targeted therapy ± radiotherapy for patients with tumors positive for driver gene mutations) may be conducted, or individualized or supportive therapy may be provided according to the situation. The local control rate of tumors is significantly improved to lower the mortality risk by 16%.

Concurrent radiochemotherapy should include a cisplatin-based regimen as much as possible. The EP regimen and PC daily regimen are the chemotherapy regimens most widely applied in concurrent radiochemotherapy. The CAMS study showed that the EP regimen led to a greater survival benefit than the PC regimen. Based on the data from PROCLAIM, the EP regimen is preferred in concurrent radiochemotherapy. For nonsquamous cell carcinoma, combined pemetrexed and cisplatin can be administered.

The results of the CALGB39801, LAMP, HOG LUN, KCSG-LU05-04, START, SWOG0023 and other randomized controlled phase II / III studies showed that induction chemotherapy, consolidated chemotherapy and consolidated targeted therapy fail to further improve the efficacy after concurrent radiochemotherapy. For patients receiving induction chemotherapy + concurrent radiochemotherapy, it is necessary to conduct a comprehensive image examination prior to induction chemotherapy to guide target volume outlining after induction chemotherapy.

In the PACIFIC study, durvalumab led to significantly longer median PFS than the placebo, with PFS in the durvalumab group exceeding 11 months (16.9 months and 5.6 months; HR = 0.52, $P < 0.001$); the 5-year PFS rates were 33.1% and 19.0%; the median OS was 47.5 months vs. 29.1 months (HR = 0.68, $P = 0.0025$); and the 5-year survival rates were 42.9% and 33.4%, respectively.

There is no clinical evidence concerning the survival benefit of concurrent radiochemotherapy + TKI targeted therapy in patients with unresectable stage III LC, nor is there higher-level evidence concerning comparisons between different strategies for EGFR gene mutation targeted therapy and radiochemotherapy.

Radiotherapy target volume: For patients who have received induction chemotherapy, irradiation is limited to the residual primary foci and involved lymph node area after chemotherapy, and preventive lymph node irradiation may not be conducted. The recommended total radiotherapy dose for concurrent radiochemotherapy is

60–66 Gy, with daily conventional fractionation irradiation (1.8–2.0 Gy/time).

Radiotherapy for advanced LC Main recommendations:

(1) Oligometastasis:

1) For extracranial oligometastatic foci, the addition of local radiotherapy with SBRT to effective active systemic therapy is preferred.
2) For patients with intracranial oligometastatic foci and patients with a good prognosis, local stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) high fractionation radiotherapy (HFRT) is preferred.
3) For patients requiring quick symptom alleviation with stroke risks, large tumors and surgical involvement, surgery may be considered.

(3) Extensive metastasis:

1) Local radiotherapy based on systemic therapy and palliative treatment, symptomatic treatment and the reduction of the occurrence of bone-related events should be added.
2) For patients who have received immunotherapy, radiotherapy can achieve palliative treatment and symptomatic treatment, reduce the occurrence of bone-related events and enhance the efficacy of immunotherapy (with dispute but recommended).

Notes:

For advanced LC, combined therapy centered on systemic therapy should be adopted. Based on drug therapy, oligometastases should be treated in combination with radiotherapy / surgery and other local therapies to improve their symptoms and QOL and bring about survival benefits.

(1) Radiotherapy strategy for patients with oligometastases:

Oligometastasis is currently defined as the presence of no more than 3 metastatic organs (mediastinal lymph node metastasis is deemed as one organ) and no more than 5 metastatic foci, and the possibility of radical therapy is considered an important factor in defining the oligometastatic state. The results of a randomized controlled phase II trial involving oligometastatic LC showed that local therapy after effective systemic therapy could extend the median PFS by 9.8 months (14.2 months vs. 4.4 months, $P=0.022$) and the median OS by 24.2 months (41.2 months vs. 17.0 months, $P=0.017$). Patients showed satisfactory tolerance without grade 3 and above TRAEs. However, higher level of evidence is still needed. Local consolidated therapy after stage IV oligometastasis may be determined through HIM MDT discussion. Participation in clinical trials is recommended.

For LC with brain metastasis, the prognosis should be judged according to the score of the GPA or Lung-mol GPA scale system before therapy. Based on systemic therapy, HIM MDT discussion should be conducted to formulate a reasonable plan for combined therapy for brain metastasis to improve symptoms and QOL and extend survival. The N0574 study was a phase III clinical trial on the need for WBRT after SRS for 1–3 brain metastatic foci, and the results showed that although the SRS + WBRT group showed improved control of brain foci, their OS was poorer and QOL was worse [92]. Therefore, SRT therapy is recommended and preferred for locally advanced brain metastatic foci. Concerning refractory brain metastatic foci (≥ 3 cm, located at key structures, e. g., brain stem, inside and near the optic nerve and endocyst, several recurrent and progressive foci after WBRT progression, etc.), HFRT with a lower fractionated dose can significantly improve therapy-related toxicity with the local control rate ensured.

For stage IV brain metastasis positive with driver gene mutations, based on the effectiveness of molecular targeted therapy, SRS or SRT can be considered for patients with a good prognosis (e.g., limited brain metastatic foci). The stage III randomized controlled clinical trial BRAIN involved the head-to-head comparison of the efficacy of two methods, EGFR-TKI and WBRT ± chemotherapy, in the treatment of asymptomatic LC negative for EGFR mutations with ≥ 3 brain metastatic foci. The results showed that icotinib significantly extended the intracranial PFS and was superior to WBRT ± chemotherapy. Patients with limited foci smaller than 4 cm, if permitted, should receive combined SRT and TKI therapy to maximize the OS benefit.

The results of the NCCTG N107C / CEC · 3 randomized phase III clinical trial showed that the groups receiving localized SRS or WBRT showed no difference in OS after brain metastatic tumor resection [93]. The SRS group exhibited a significant advantage over the WBRT group in terms of the protection of neurocognitive function. Therefore, if permitted, localized SRS is recommended after the resection of brain metastatic foci to further reduce the occurrence of neurological side effects.

(2) Radiotherapy strategy for extensive metastasis:

For stage IV LC, primary foci and regional lymph node recurrence are the earliest and most common causes (>90%). Under such circumstances, radiotherapy can be considered in combination with systemic therapy. In addition to palliative and symptomatic effects, this approach can improve the clinical efficacy of tumor control to a certain extent: ① For patients after effective systemic therapy, effective localized therapy, e. g., radiotherapy and surgery, may be considered. Researchers have found that radiotherapy for advanced patients results in a significant survival benefit, especially when local radiotherapy at a radical dose achieves better survival; local radiotherapy for primary foci can be considered, and the preferred dose is >60 Gy. ② For advanced LC positive for driver gene mutations, the application of targeted drugs in the treatment of oligoprogression or slow progression can also benefit from radiotherapy and other localized therapies. ③ For patients with combined chemotherapy and immunotherapy, the findings from the KEYNOTE-001, PEMBRO-RT and Bauml studies indicated that in stage IV LC treatment involving targeted therapy and immunotherapy, radiotherapy bring about more opportunities [94, 95]. Currently, clinical trials suggest that immunotherapy should be considered after radiotherapy, and the preferred radiotherapy technology is SBRT.

2.5 Traditional Chinese medicine (TCM) treatment of LC

Main recommendations:

(1) For patients who are not suitable for or refuse surgery, radiotherapy, chemotherapy, molecular targeted therapy or immunotherapy, TCM syndrome differentiation treatment is recommended.
(2) During the perioperative period, radiotherapy, chemotherapy, molecular targeted therapy or immunotherapy, or concurrent TCM syndrome differentiation treatment is recommended.
(3) In the event that there is no need for postoperative adjuvant therapy or after the end of postoperative adjuvant therapy, more than 3 years of TCM treatment is recommended.
(4) For patients with tumors and a controlled condition after therapy, TCM treatment is recommended for the long term.

Notes:

(1) TCM LC treatment characteristics:

    (1) Human-centeredness and a combination of disease and syndrome: A deficiency of vital qi in the human body is the essential etiology for LC onset and is key to prognosis and outcome.
    (2) Idea of "preventive treatment of disease": LC treatment with TCM is not only applicable to advanced patients, elderly patients and others intolerable to Western medicine treatment. The combined application of TCM during the use of Western medicine treatment can mitigate symptoms, reduce the occurrence of TRAEs, improve the rate of treatment completion and enhance treatment efficacy. To a certain extent, TCM can control tumor recurrence and metastasis, extend survival and improve QOL. The longterm application of TCM is beneficial to rehabilitation and recuperation [96].
    (3) Mechanistic study on LC prevention and treatment with TCM: Modern scientific research technologies have been applied to clarify the scientific implications of LC prevention and treatment with TCM.

(2) Method of LC prevention and treatment with TCM:

    (1) Methods of LC prevention and treatment include strengthening body resistance and eliminating pathogenic factors. These two factors constitute a dialectical unity and supplement each other. Strengthening the body's resistance is the root, and eliminating pathogenic factors is the purpose. Comprehensive consideration is needed according to the resistance of the human body and the conditions of pathogenic factors.
    (2) Strengthening the body resistance and supporting healthy energy means adopting the qi supplement, blood supplement, and yang or yin supplement method to adjust the imbalanced yin and yang situation and the qi and blood deficiency and achieve yin and yang balance and the recovery of body resistance. During therapy, the patient must be given syndrome differentiation. It is far from an "all nourishing" method [97].
    (3) Eliminating pathogenic factors is mainly applied for tumor patients with dominating pathogens. It is necessary to clinically differentiate phlegm stagnation, toxicity clustering (pathogenic toxin, heat toxin), qi stagnation and blood stasis. TCM should be applied according to the intensity of pathogenic factors as appropriate.

(3) TCM etiology and pathogenesis:

1) Deficient vital qi: Yin and yang imbalance in organs and deficient vital qi are the main internal causes for disease.
2) Lung invasion by pathogenic toxins: The external wind, coldness, heat, humidity, dryness and fire, the six pathogenic factors invading the lungs, cause the pulmonary disturbance of upbearing and downbearing, pulmonary qi stagnation, obstructed blood circulation, qi stagnation and blood stasis and mass.
3) Phlegmatic hygrosis and stagnation: Controlled diet, fatigue, emotional disorder and other factors may cause spleen deficiency and transport disorder, body dampness gathering and phlegm forming, phlegm in the lungs, pulmonary qi depression, a disturbance of upbearing and downbearing, phlegmatic hygrosis and toxin gathering and mass forming.

Details:

From the TCM perspective, the deficiency of the lungs mainly includes yin deficiency and qi and yin deficiency, and excess symptoms include qi stagnation, blood stasis, phlegmatic hygrosis and toxin gathering. As a result, an increasing number of doctors have combined deficient vital qi with pathogenic toxin and phlegmatic hygrosis opinions, arguing that deficient vital qi is the internal basis for LC onset as well as the essential pathogenesis throughout the development of this disease. LC is a disease featuring systemic deficiency and local excess. The instructive idea for LC treatment through resistance strengthening and tumor treatment ideas is centered on strengthening the body resistance and supporting the healthy energy, accompanied by therapy to remove heat and eliminate toxins, softening the solid and clearing phlegm so that good efficacy can be realized [98].

2.5.1 Treatment based on TCM syndrome differentiation [99–102]

(4) Therapeutic principle:

The top priority is human-centeredness; that is, the treatment should be conducted from a holistic view and should focus on the patient to differentiate the single or complex syndromes and treat cancer through treatment based on syndrome differentiation. The second principle is the combination of disease and syndrome. In other words, based on the treatment that is identified based on syndrome differentiation, herbs and Chinese patent medicines with antitumor effects proven by modern pharmacological research should be selected.

(5) Syndrome differentiation of TCM and treatment:

1) Main syndromes of spleen deficiency and phlegmatic hygrosis type: cough with much phlegm, chest distress and shortness of breath, poor appetite and loose stool, fatigue and weariness, pale complexion, a fat tongue light in color with tooth marks and a white and greasy coating, and a soft and slow or slippery pulse.

Treatment method: Invigorating the spleen to eliminate dampness, regulating qi flow to eliminate phlegm.

Prescription: Addition to or deduction of Liujunzi Decoction and Erchen Decoction. Codonopsis pilosula, atractylodes, poria cocos, coix seed, dried tangerine peel, pinellia ternata, licorice, trichosanthes peel, Selaginella doederleinii Hieron, Salvia chinensis, Oldenlandia diffusa, radix stemonae, aster, etc.

2) Yin deficiency with internal heat type:

Main syndromes: Cough with no or little phlegm or frothy sputum, phlegm with blood, shortness of breath and chest pain, low fever, thirst, night sweating, restlessness, red or purple– red tongue with little or no coating, and rapid pulse.

Treatment method: Nourishing yin to clear away the lung heat and moistening the lung to remove phlegm.

Prescription: Addition to and deduction of Baihegujin Decoction. Lily, Rhizome of rehmannia, radix glehniae, Radix Ophiopogonis, apricot kernel, total Fructus Trichosanthis, Houttuynia cordata, Oldenlandia diffusa, five-leaf akebia fruit, radix sophorae flavescentis, dried toad skin, etc.

3) Qi and yin deficiency type:

Main syndromes: Cough with little phlegm or blood, weak or no coughing sounds, fatigue and weariness and shortness of breath, spontaneous perspiration or night sweats, thirst with little water intake, red or pink tongue with teeth marks and a thin coating, and weak pulse.

Treatment method: Tonifying qi and yin and eliminating phlegm by cooling.

Prescription: Addition to Shengmai Powders and Radix Adenophorae and Radix Ophiopogonis Decoction and deduction. Raw Astragalus, raw atractylodes, radix glehniae, Radix Asparagi, Radix Ophiopogonis, apricot kernel, radix stemonae, trichosanthes peel, Schisandra chinensis, Selaginella doederleinii Hieron, Salvia chinensis, Oldenlandia diffusa, selfheal, raw oyster shell, etc.

4) Kidney yang deficiency type:

Main syndromes: Cough with shortness of breath, shortness of breath upon movement, chest distress and fatigue, tinnitus, soreness of the waist and weakness of the knees, intolerance of cold and cold limbs, frequent urination at night or concurrent weight loss, thirst without a desire to drink, pink tongue or pale but fat tongue with a thin and white coating, and a rapid but deep pulse.

Treatment method: Nourishing yin and the kidney and reducing swelling.

Prescription: Addition to and deduction of Radix Adenophorae and Radix Ophiopogonis Decoction and Procreation Elixir. Radix glehniae, Radix Asparagi, prepared rehmannia root, unprepared rehmannia root, radix scrophulariae, cistanche, rhizoma curculiginis, herba epimedii, Selaginella doederleinii Hieron, Salvia chinensis, Cowherb seed, Oldenlandia diffusa, selfheal, raw oyster shell, silkworm chrysalis, climbing fig fruit, etc.

5) Qi stagnation and blood stasis type:

Main syndromes: Cough with obstruction or phlegm with blood, chest distress and shortness of breath, chest and hypochondrium pain or severe pain, fixed site pain, exposed veins at neck and chest wall, dark purple lips and nails, dark red or slate-violet tongue and ecchymosis of the tongue with a thin and yellow coating, and a rapid or uneven pulse.

Treatment method: Regulating qi flow, eliminating swelling, and promoting blood circulation to remove blood stasis.

Prescription: Addition to and deduction of Fuyuan Huoxue Decoction. Peach kernel, Cowherb seed, Salvia miltiorrhiza, curcuma zedoary, hive, five-leaf akebia fruit, radix curcumae, total Fructus Trichosanthis, selfheal, raw oyster shell, seaweed, kelp, subprostrate sophora, Salvia chinensis, Oldenlandia diffusa, edible tulip, etc.

2.5.2 Combined treatment of LC with TCM and Western medicine

(4) Surgical treatment and TCM:

Surgery damages the vital qi of the human body, and there is a recurrence and metastasis risk after surgery. Through disease and syndrome differentiation, TCM can balance yin and yang; supplement qi, blood and liquid; regulate functions of the meridian and organs; and improve the inherent resistance of the human body. With TCM preoperative application, it is possible for vulnerable patients to meet the conditions for surgery, and TCM postoperative application can reduce the risk of recurrence, prevent metastasis and improve long-term efficacy. For stage IIIIA LC surgery, the postoperative syndrome differentiation of TCM mainly includes lung-spleen qi deficiency and qi-yin deficiency, and the main treatment method is reinforcing qi and nourishing blood, invigorating the spleen to eliminate dampness, and tonifying qi and yin. Long-term TCM treatment based on syndrome differentiation can prevent or slow recurrence and metastasis after LC radical surgery. The median DFSs for stages I, II and IIIA were found to be 67.36 months, 24.03 months and 15.9 months, respectively. It is recommended that TCM treatment is conducted based on syndrome differentiation to strengthen body resistance and eliminate pathogenic factors 1 week after surgery [103].

(5) Chemotherapy and TCM:

From the TCM perspective, chemotherapy is a kind of "drug toxin" and may cause toxicity and side effects to different extents and damage organs, restricting the clinical efficacy. On the one hand, combined TCM and chemotherapy can regulate qi flow to harmonize the stomach, benefit qi and nourish the blood, replenish the vital essence, remove heat, tonify the kidney and spleen, etc.; on the other hand, the two can support body resistance and balance yin and yang. Additionally, traditional Chinese drugs can soften hardness and transform phlegm, regulate qi flow, disperse blood stasis, and clear away heat and toxic materials. Therefore, TCM therapy should be selected as appropriate to enhance the support for resistance.

1) TCM treatment principle in adjuvant chemotherapy after LC surgery:

TCM treatment is an independent protective factor of DFS for LC. At stages IB-IIIA, for completely resected postoperative LC, it is recommended that the combined therapeutic regimen of TCM and adjuvant chemotherapy is selected [104]. Qi deficiency and yin deficiency are quite common in syndrome differentiation together with residual poison. Methods for tonifying qi, nourishing yin, softening hardness and clearing toxicity should be adopted to extend DFS, alleviate chemotherapy adverse reactions, and improve clinical symptoms and TCM syndromes. As the clinical stage progresses, the risks for metastasis and recurrence increase. After adjuvant chemotherapy, patients with stages IIA-IIIB LC should continue to receive TCM treatment based on disease and syndrome differentiation with methods for tonifying qi, supplementing essence and clearing toxicity. This approach can improve the patient's postoperative

recurrence and metastasis rate and improve the patient's QOL and immune function. Therefore, combined therapy with TCM is superior to adjuvant chemotherapy alone.

2) TCM treatment principle in palliative chemotherapy for advanced LC:

TCM intervention can extend the survival of patients with advanced LC. For advanced LC, a regimen combining TCM (TCM syndrome differentiation decoction, TCM injection, Chinese patent medicine) and chemotherapy should be adopted, as this can result in good efficacy in reducing the number of foci and stabilizing them, preventing distant metastasis, extending survival and increasing the survival rate and reducing the toxicity and side effects of chemotherapy as well as in improving the syndromes, regulating body weight, and improving QOL and immune function. For LC, the qi-yin deficiency type accounts for the highest percentage. Some scholars applied TCM Compound Yifei Kangliu Drinks (Jinfukang) [105] (comprising Astragalus membranaceus, radix glehniae, Radix Asparagi, glossy privet fruit, Selaginella doederleinii Hieron, Paris polyphylla, etc.) combined with chemotherapy. The use of a regimen including TCM resulted in a better median OS than the use of chemotherapy alone and provided a significant advantage in the long-term survival rate, distant metastasis rate, etc. In the maintenance therapy stage after first-line chemotherapy for advanced LC, a regimen combining TCM and chemotherapy showed equivalent clinical efficacy to chemotherapy alone concerning the extension of survival with a better QOL [106, 107].

(6) Radiotherapy and TCM:

Radiotherapy is included in the "eliminating pathogenic factors" category in the TCM field. However, radioactive rays also damage the cells in normal tissues, causing pathogenic "heat toxin". Heat toxin damages yin and reduces qi, resulting in thirst, coprostasis, tussiculation, shortness of breath, fatigue and other qi-yin damage syndromes. TCM strengthens body resistance to eliminate pathogenic factors and to do so without damaging body resistance. For patients with LC at any stage with radiotherapy indications, combined radiotherapy and TCM is recommended with the dialectic application of therapeutic principles of nourishing yin and generating body fluid, activating blood circulation and detoxicating, and cooling blood and tonifying qi to improve the completion rate of radiotherapy and increase the short-term efficacy of radiotherapy. In addition, TCM can reduce the loss of appetite, thirst and pharyngoxerosis, fatigue and other toxic and side effects after radiotherapy and improve QOL [108].

(7) Targeted therapy and TCM:

With the rapid development of molecular targeted therapy, partially advanced LC cases have greatly improved prognoses but with certain limitations, e.g., drug resistance and adverse reactions. The combination of targeted drug therapy and TCM treatment based on syndrome differentiation can improve treatment efficacy by enhancing the effect and reducing the toxicity.

For stage IIIA-IV pulmonary adenocarcinoma patients positive for EGFR mutations, it is recommended that TCM is orally taken together with TKI therapy and the methods of supplementing qi and yang, nourishing yin, tonifying qi and yin, softening hardness and detoxifying are adopted to achieve a better PFS. The efficacy of first-line treatment is superior to that of second-line treatment. In 2020, a meta-analysis of 57 randomized controlled trials, with a total of 4266 patients with stage III-IV LC, showed similar results [109]. When TCM was combined with EGFR-TKI therapy, the effective rate was significantly higher than that when EGFRTKIs were applied alone. In combined treatment, it is recommended that the TCM method is selected based on TCM syndrome differentiation, including TCM intravenous injection, oral TCM decoction, Chinese patent medicine, and granules. For the treatment, the dominating principles include supplementing qi, nourishing yin, and eliminating phlegm by cooling. It is commonly believed that TCM can enhance the therapeutic effect of EGFR-TKIs on LC.

3 Lung cancer rehabilitation

Main recommendations:

3) Follow-up after curative therapy for lung cancer (LC):

1) After LC is treated with curative therapy (including surgery and radiotherapy in the HIM MDT plan for combined therapy with the aim of cure), it is necessary to implement close follow-up to identify tumor recurrence, metastasis, and new and recurrent LC in the early stage with timely treatment to extend survival and improve quality of life.
2) For LC patients without clinical symptoms or with stable symptoms after curative therapy, it is recommended that 1 follow-up every 6 months in the first 5 years and 1 follow-up every year for 5 years or longer is implemented after the therapy.

3) For patients with new symptoms or aggravated symptoms, immediate follow-up is recommended.
4) According to the recovery state after surgery, the initial follow-up time should be determined as appropriate.
5) Item recommendation: Inquiry regarding medical history, physical examination and chest CT (plain scan or enhanced) (recommended but with dispute) should be performed.
6) In the first two years, chest (including bilateral adrenal gland) plain scan or enhanced CT examination should be conducted; after two years, chest plain scan or low-dose CT examination should be conducted.
7) PET/ CT is not recommended as the conventional follow-up technique.
8) Conventional head MRI examination, bone scanning, and fiber bronchoscopy are not recommended for the monitoring of disease recurrence and metastasis in follow-up.
9) Measurements of peripheral blood tumor markers are not recommended to monitor disease recurrence.

4) Follow-up of locally advanced and advanced LC that has not undergone radical radiotherapy:

1) For patients without clinical symptoms or with stable symptoms, 1 follow-up at 6–12 weeks after therapy is recommended.
2) For patients with new symptoms or aggravated symptoms, immediate follow-up is recommended.
3) Recommended follow-up items include inquiry regarding medical history, physical examination and chest CT (plain scan or enhanced).
4) The choice of imaging examination, including head MRI and bone scanning, should be made according to the metastasis or tumor-invasive area, or suitable examinations for the corresponding symptomatic areas should be included.
5) PET/ CT is not recommended as the conventional follow-up technique.
6) Peripheral blood tumor markers are not recommended to monitor disease recurrence.

5) Other recommended follow-up examinations:

1) For patients not suitable for or unwilling to receive further clinical treatment, there is no need to perform imaging examinations. It is recommended that the health status, presence of complicating chronic diseases and the patient's personal options are comprehensively assessed during the follow-up strategy.
2) During the follow-up process, it is necessary to assess the patients'smoking condition, and patients who smoke should be encouraged to stop smoking.
3) It is recommended that the HIM MDT is employed to formulate the follow-up regimen and consider individualized adjustments.

Notes:

The purpose of cancer follow-up is to discover ① recurrence/ metastasis, ② new primary cancers, and ③ complications after treatment and other conditions that may threaten life / health. Currently, prospective randomized controlled trial results concerning the optimal follow-up frequency, timing and follow-up regimen are needed, and as of now, no large-scale randomized controlled trial has proven that the follow-up of patients with LC after treatment can bring about survival benefit.

4 General principles for lung cancer holistic integrative therapy by stage [7]

4.1 Overview of lung cancer holistic integrative therapy

Lung cancer (LC) Holistic Integrative Therapy refers to treatment according to the patient's physical condition and tumor pathological type, invasion scope (stage of disease), and cellular and molecular biological changes combined with cost – effective analysis. All kinds of effective treatment methods should be integrated and used in a planned and reasonable way to greatly improve the cure rate and quality of life. Integrated therapy aims to prolong survival and improve quality of life while preserving the main functions of organs as much as possible. The integrated therapy of LC depends on the comprehensive assessment, accurate diagnosis and effective coordination of a holistic integrative medicine (HIM) multidisciplinary team (MDT). It is recommended that the LC HIM MDT create a patient-centered, reasonable and integrated diagnostic and treatment plan. The LC MDT should include experts in thoracic surgery, respiratory medicine, oncology or thoracic medicine, radiotherapy, intervention department (endoscopy), imaging, pathology, traditional Chinese medicine and other disciplines. The LC HIM MDT will formulate the optimal integrated treatment scheme according to the individual situation of patients and the best medical evidence. Currently, surgery, radiotherapy, chemotherapy, molecular targeted therapy and immunotherapy are five conventional therapies for LC treatment. Other effective therapy supplements include

interventional therapy and traditional Chinese medicine (TCM) therapy.

LC can be divided into LC and small cell LC (SCLC), the molecular subtype plays an important role in the formulation of an integrated therapy regimen. SCLC is more malignant and prone to distant metastasis than LC. SCLC usually metastasizes at the time of diagnosis, and only a few patients have the opportunity for surgery. At present, integrated therapy for SCLC mainly involves chemotherapy, radiotherapy and immunotherapy, and molecular typing is still under exploration.

4.2 Integrated treatment principles for stage I LC

(1) The preferred therapy for stage I LC is anatomical lobectomy with systematic biopsy sampling or dissection of the hilar and mediastinal lymph nodes. Adjuvant therapy is not recommended for patients with stage IA LC. Osimertinib can be considered as adjuvant therapy after complete resection of stage IB LC positive for EGFR mutations. For stage IB LC negative for EGFR mutations, adjuvant chemotherapy is not routinely recommended after complete tumor resection. HIM MDT integrated assessment is recommended for patients with high-risk factors. Based on the comments made during the assessment and the patient's willingness to undergo treatment, adjuvant chemotherapy can be considered on a case-by-case basis (controversial but recommended).
(2) For patients with stage I LC who cannot undergo pulmonary lobectomy plus hilar mediastinal lymph node dissection for medical reasons, subpulmonary lobectomy (segmental resection and wedge resection) plus systematic hilar mediastinal lymph node biopsy sampling or dissection can be considered.
(3) Stereotactic radiotherapy (SBRT) is recommended for patients with stage I LC who are not suitable for or are unwilling to undergo surgical treatment.
(4) For stage I LC with incomplete resection, reoperation ± chemotherapy or postoperative three-dimensional conformal radiotherapy ± chemotherapy is recommended.

4.3 Integrated treatment principles for stage II LC

(1) The preferred treatment for stage II LC is anatomic lobectomy plus systematic hilar mediastinal lymph node biopsy sampling or dissection. EGFR-tyrosine kinase inhibitors (TKIs) (osimertinib, gefitinib or icotinib) are recommended after complete resection of stage II LC positive for EGFR mutations. Adjuvant chemotherapy is recommended after complete resection in stage II LC negative for EGFR mutations.
(2) Sublobectomy (lobectomy and wedge resection) plus systematic hilar and mediastinal lymph node biopsy sampling or dissection should be considered for patients with stage II LC who cannot undergo lobectomy plus hilar and mediastinal lymph node dissection.
(3) SBRT or concurrent radiochemotherapy is recommended for patients with stage II LC who are not suitable for or are unwilling to undergo surgical treatment.
(4) For incomplete resection of stage II LC, reoperation ± chemotherapy or postoperative three-dimensional conformal radiotherapy ± chemotherapy is recommended.

4.4 Integrated treatment principles for stage III LC

Stage III LC has high clinical, pathological and molecular heterogeneity. Before treatment, HIM MDT assessment is recommended for optimal multidisciplinary integrated therapy before starting treatment. Stage III LC can be divided into operable and inoperable categories.

(1) Surgical treatment is the preferred choice for operable stage III LC. Anatomic lobectomy + systematic hilar mediastinal lymph node biopsy sampling or dissection are recommended.

    1) A single group of N2 mediastinal lymph nodes (lymph node < 3 cm) should be completely resected and can be treated by surgical excision + adjuvant chemotherapy or neoadjuvant chemotherapy + surgery.
    2) Multiple groups of N2 mediastinal lymph nodes should be completely resected and can be treated with radical concurrent radiochemotherapy or neoadjuvant chemotherapy ± radiotherapy + surgery.
    3) For T3-4N1, T4N0 nonsuperior pulmonary sulcus tumors (involving the chest wall, main bronchus or mediastinum) can be treated with surgery + adjuvant chemotherapy or neoadjuvant chemotherapy ± radiotherapy + surgery.
    4) T3-4N1 superior sulcus tumors can be treated with neoadjuvant radiochemotherapy + surgery.
    5) For resectable stage IIIA LC, if an EGFRsensitive mutation is identified during the molecular diagnosis, EGFR-TKIs can be used in neoadjuvant targeted therapy.
    6) For resectable stage II-IIIB patients without driver mutations, in line with the guidelines for neoadjuvant chemotherapy, participation in a neoadjuvant immunotherapy clinical trial is recommended.

7) Critical resectable locally advanced (LA)LC can be treated by induction chemotherapy, targeted therapy (for patients with EGFR-sensitive mutations) and many other treatment options, and the possibility of surgery can be reevaluated after restaging.

(2) After complete resection of stage III LC, the selection of postoperative adjuvant therapy according to the EGFR mutation status is recommended.

1) EGFR-TKI (osimertinib, gefitinib, icotinib or erlotinib) adjuvant therapy is recommended after complete resection of stage III LC positive for EGFR mutations, and adjuvant therapy with osimertinib is preferred.
2) For stage III LC negative for EGFR mutations, adjuvant chemotherapy is recommended after complete resection; participation in an adjuvant immunotherapy clinical trial is recommended.
3) Adjuvant radiotherapy is not recommended for completely resected stage III LC.
4) For incompletely resected stage III LC, postoperative radiochemotherapy is recommended.

(3) Concurrent radiochemotherapy + durvalumab consolidation therapy is recommended for patients with stage III inoperable LC. Sequential radiochemotherapy can be used for those who cannot tolerate concurrent radiochemotherapy for medical reasons.

4.5 Treatment principles for stage IV LC with driver gene mutations

After molecular biological testing of stage IV LC, drug therapy is guided by the molecular subtype. Routine genetic testing includes tests for EGFR mutations, ALK fusions, ROS1 fusions, RET rearrangements, MET4 exon skipping mutations, the BRAF V600E mutation, the KRAS G12C mutation and NTRK fusions. With the development of next-generation sequencing (NGS) technology, one-time multigene testing is recommended. The principles of integrated therapy for stage IV LC positive for driver gene mutations are as follows:

(1) With the discovery of an increasing number of LC driver genes and the launch of corresponding specific therapeutic drugs, it is recommended that a high-throughput testing method is implemented to identify more driver genes at one time and that the corresponding targeted drugs are used during the first-line treatment.
(2) For these patients, there are an increasing number of available drugs and methods, and it is necessary to establish an integrated scoring system that takes into account the efficacy, safety, quality of life and insurance compensation so that patients can obtain more ideal treatment benefits.
(3) For patients with significant and lasting benefit from targeted therapy, localized therapy (including but not limited to surgery, radiotherapy, ablation, etc.) for residual disease is recommended after HIM MDT integration assessment. The choice of localized therapy is made based on the principles of "minimum trauma and maximum benefit".
(4) After first-line targeted therapy, patients with oligometastasis are recommended to continue the original TKI therapy + localized therapy after HIM MDT combined evaluation.
(5) For patients with multiple metastases after first-line targeted therapy, reperforming the biopsy or ctDNA testing is recommended. For patients with well-defined drug-resistance mechanisms and corresponding targeted treatment drugs to resist drug-resistance reactions, it is recommended that targeted treatment drugs are applied to overcome resistance, and targeted therapy drugs that overcome drug resistance are recommended. Patients without a well-defined drug-resistance mechanism or targeted therapy drugs that can overcome drug resistance can also participate in clinical trials of new drugs according to the treatment recommendation of stage IV LC negative for driver gene mutations.
(6) For patients with LC with brain metastasis who harbor driver gene mutations, firstline targeted therapy is preferred. In patients with stable extracranial lesions and the progression of intracranial lesions during targeted therapy, it is recommended that the original targeted therapy is continued plus localized therapy for intracranial lesions, and SRT or surgical resection of brain metastases can be used; if the number or size of the intracranial lesions is not suitable for SRT or surgical treatment, WBRT can be used.
(7) For patients with LC with meningeal metastasis positive for driver gene mutations, cerebrospinal fluid (CSF) analysis is recommended to guide the choice of targeted therapy and/ or WBRT and to explore the possibility of intrathecal injection therapy.
(8) For patients with LC with oligometastasis who harbor driver gene mutations (including brain oligometastasis, adrenal gland oligometastasis and lung oligometastasis), the principle of inte-

grated therapy is to pay equal attention to systemic treatment and localized treatment. The HIM MDT should be used to evaluate the possibility of surgery for primary lesions and regional lymph node and oligometastatic lesions. Based on the results of targeted therapy, primary lesions and oligometastatic lesions can be treated with synchronous or heterochronous surgery. Radiotherapy can be carried out if the patient is not suitable for surgical treatment. Targeted therapy can be continued after surgery or radiotherapy.

(9) CtDNA monitoring can be performed for patients with stage IV LC positive for driver gene mutations who have received targeted therapy. An analysis of the dynamic changes in ctDNA that occur during treatment is helpful to judge the prognosis and curative effect. CtDNA testing is helpful to identify the drug resistance mechanism in targeted therapy. For negative ctDNA tests, exploratory minimal residual disease (MRD) testing (controversial but recommended) can be performed for patients who have achieved a complete response (CR) with systemic treatment or systemic + localized treatment.

(10) Participation in a clinical trial of a new targeted drug is recommended for those patients who are positive for driver gene mutations.

4.6 Integrated therapy principles for stage IV LC without driver gene mutations

Patients without driver gene mutations are negative for EGFR mutations, ALK rearrangements, ROS-1 rearrangements, cMet14 exon skipping mutations, RET rearrangements and other obvious driver gene mutations. The integrated therapy principles for stage IV LC without driver gene mutations are as follows:

(1) It is recommended that PD-L1 expression is detected by immunohistochemistry before the initial treatment of LC negative for driver gene mutations.

(2) For tumors with ≥ 50% PD-L1 expression, immune monotherapy is preferred for first-line treatment, and immunotherapy combined with chemotherapy can also be considered.

(3) Regardless of PD-L1 expression, immunotherapy combined with chemotherapy can be recommended for first-line treatment. For tumors with 1%-49% PD-L1 expression, immune monotherapy can be selected for first-line treatment.

(4) For stage IV LC patients without driver gene mutations who are not suitable for combination chemotherapy, first-line antiangiogenic treatment combined with chemotherapy is recommended.

(5) Single-drug chemotherapy is recommended as a first-line treatment for patients with stage IV LC without driver gene mutations and an Eastern Cooperative Oncology Group (ECOG) performance score (PS) = 2.

(6) For patients with stage IV LC without driver gene mutations who have not received immunotherapy in first-line treatment, the use of immunotherapy alone is preferred as second-line treatment; for patients with stage IV LC without driver gene mutations who have received immunotherapy in first-line treatment, chemotherapy or chemotherapy combined with antiangiogenic therapy is preferred as second-line treatment.

(7) Anlotinib is recommended for patients with locally advanced or metastatic LC (limited to squamous cell carcinoma of the peripheral type) whose disease has progressed or recurred after they received at least 2 kinds of systemic chemotherapy in the past.

(8) Participation in clinical trials is recommended for patients without driver gene mutations.

5 Monograph II small cell carcinoma

5.1 Epidemiology of small cell lung cancer

Small cell lung cancer (SCLC) is an important subtype of lung cancer (LC), accounting for 15% of LC cases. Worldwide, there are 250, 000 new SCLC cases per year, and there are at least 200,000 deaths [110]. Investigation results from 12 Chinese hospitals showed an increasing tendency in the onset of SCLC from 2005 to 2010 [111]. The 2019 Chinese Cancer Registry Annual Report indicates that there were 230,000 new LC cases in 2016, 11.29% of which were SCLC cases [112]. SCLC is closely related to smoking and is a high-grade neuroendocrine lung tumor with rapid progression and early metastasis. Approximately 60%-70% of patients present metastasis upon diagnosis. Although SCLC is sensitive to initial treatment, it quickly develops drug resistance and recurs, and there are no effective therapeutic approaches after recurrence. The prognosis of SCLC is poor, and the 5-year overall survival is less than 7% [113].

5.2 Early detection of small cell lung cancer

Small cell lung cancer (SCLC) lacks specific symptoms at an early stage. Low-dose spiral computed tomography (CT) is the main method used for early lung cancer (LC) screening. However, researchers have found that low-dose spiral CT has a limited role in the detection of early-stage SCLC. As the SCLC tumor doubling time is short with strong invasive properties and rapid progression,

metastasis almost always exists at diagnosis. Thus, an effective screening method for early detection is still needed [114].

5.3 Diagnosis of small cell lung cancer

Main recommendations:

(1) Small cell lung cancer (SCLC) is a highgrade pulmonary neuroendocrine tumor, and the pathological diagnosis should follow the World Health Organization (WHO) standards. Histodiagnosis is more reliable thancytological diagnosis, and immunohistochemical examination is always needed for confirmation.
(2) For combined SCLC (C-SCLC), admixed non-small-cell cancer components must be clarified in the pathological report.
(3) In the diagnosis of transformed SCLC, the histodiagnosis of an additional biopsied tumor tissue sample is the current gold standard.
(4) It is recommended that both the American Joint Committee on Cancer (AJCC) TNM staging system and the Veterans'Affairs Lung Study Group (VALSG) staging method are applied to confirm the SCLC stage and identify the specific TNM stage after VALSG staging.
(5) Regarding molecular diagnosis, SCLC patients should undergo molecular subtyping diagnosis (recommended although with discrepancy).

Notes:

Precise diagnosis and staging are the basis for SCLC treatment. Based on the pathological classification of the WHO, SCLC is divided into two subtypes: pure SCLC (approximately 80%) and C-SCLC (approximately 20%). For C-SCLC, the most common non-small-cell LC (NSCLC) component is a large cell neuroendocrine lung tumor (LCNEC). SCLC was reported to be differentiated from other neuroendocrine lung tumors, NSCLC, extrapulmonary small cell cancer, lymphoma, and basal-like carcinoma. Immunohistochemistry demonstrated that SCLC can be differentiated from other diseases. Most SCLCs are reactive to at least one positive neuroendocrine marker (CD56, Syn, or CgA). In total, 85%-90% of SCLCs express TTF-1. Other pulmonary neuroendocrine tumors include lung carcinoid tumors, atypical carcinoid tumors, and LCNEC. Carcinoid tumors and atypical carcinoid tumors are different from SCLC in terms of tumor cell morphology, mitosis rate and proliferation index. The mitosis rate and proliferation index (Ki67) of SCLC are extremely high, but those of carcinoid tumors are quite low. In addition, regarding cell size, LCNEC always shows more abundant endochylema. There are distinct boundaries between cells in LCNEC. SCLC is usually negative for P40, which can be used to distinguish SCLC from basal-like cell carcinoma. Napsin A is a marker for lung adenocarcinoma and is usually negative in SCLC. Cytokeratin can help to differentiate SCLC from nonepithelial tumors, e.g., lymphoma [115].

The combination of VALSG staging and TNM staging is recommended for SCLC. According to VALSG staging, SCLC is divided into limited-stage SCLC (LS-SCLC) and extensive-stage SCLC (ES-SCLC). LSSCLC refers to a tumor limited to one lung and a metastatic lymph node limited to the ipsilateral side of the chest. ES-SCLC refers to a tumor extending to the contralateral lung or lymph nodes or distant organs or with malignant pleural and pericardial effusion. VALSG staging has been extensively applied in clinical trials and studies. TNM staging provides a detailed description of the anatomical distribution of lesions, precise lymph node staging and a more accurate prognostic assessment to screen patients with LS-SCLC suitable for surgical treatment in earlier stages (T1-2N0). This approach helps to formulate the optimal therapeutic strategy.

Imaging examination is the foundation for SCLC staging. Chest, abdominal, and pelvic CT (enhanced scan); brain magnetic resonance imaging (MRI) (preferred); or brain CT (with contrast) and a bone scan are conventional staging methods for SCLC. Positron emission tomography (PET)—CT can provide a more accurate staging for SCLC. Brain MRI, especially MRI with contrast, is a more sensitive examination method for discovering brain metastasis. For patients not suitable for MRI, brain CT (with contrast) is recommended. Cytopathological examinations of pleural or pericardial effusions should be performed if pleural or pericardial effusion is suspected. When multiple cytopathological examinations of pleural or pericardial effusions are negative for malignant cells, nonbloody and nonexudative serosal effusions are irrelevant to tumor staging, and effusion should not be considered for staging. If nucleated red blood cells on a peripheral blood smear and a decrease in neutrophil and platelet counts are observed, then it is recommended that bone marrow aspiration and biopsy are conducted to clarify whether bone marrow infiltration has occurred. For patients with stage I-IIA SCLC who are considering surgery, it is recommended that systematic preoperative staging examinations, including mediastinoscopy, mediastinotomy, transtracheal or transesophageal ultrasound [endoscopic bronchial ultrasound (EBUS) and endoscopic ultrasound (EUS)] – guided biopsy and video-assisted thoracoscopy, are conducted to exclude the possibility of potential metastasis of the mediastinal lymph nodes.

SCLC molecular subtypes are still under exploration. According to differences in the expression of the 4 dominant transcription factors, ASCL1, NEUROD1, POU2F3, and YAP1, SCLC can be divided into the A, N, P and Y subtypes. In addition, some researchers have proposed the SCLC subtype I (SCLC-I, inflammatory type) classification, which does not express ASCL1, NEUROD1 or POU2F3 transcription factors but highly expresses immune-related genes. The results of a retrospective analysis found that SCLC-I patients benefit from immunotherapy [116].

5.4 Treatment of small cell lung cancer

5.4.1 Internal medicine treatment for small cell lung cancer (SCLC)

Main recommendations:

5.4.2 Initial treatment of limited-stage SCLC (LS-SCLC):

1) At clinical stage I-IIA, it is recommended that pulmonary lobectomy, hilar and mediastinal lymph node dissection and postoperative adjuvant chemotherapy are performed, but adjuvant chemotherapy is recommended only for pN0 patients. Chemotherapy ± radiotherapy is recommended for pN1 patients. Chemotherapy + radiotherapy is recommended for pN2 patients. Prophylactic cranial irradiation (PCI) is recommended after surgery [117].
2) Stage T1-T2N0 patients who are not suitable for or refuse surgery are recommended to receive stereotactic ablative radiotherapy (SABR).
3) Stage T1-2N0 patients who are not suitable for or refuse surgery and patients with LS-SCLC beyond stage T1-2N0 are recommended to receive concurrent or sequential radiochemotherapy.
4) Patients with LS-SCLC who achieve a complete response (CR) or a partial response (PR) after initial treatment are recommended to receive PCI treatment.

5.4.3 Initial treatment of extensive-stage SCLC (ES-SCLC):

1) Eastern Cooperative Oncology Group (ECOG) performance score (PS) 0–2: Firstline chemotherapy combined with immunotherapy: atezolizumab maintenance therapy after 4 cycles of an EC + atezolizumab regimen; durvalumab maintenance therapy after 4 cycles of an EC/EP + durvalumab regimen.
2) ECOG PS 2: First-line chemotherapy regimen: EP, EC, EL, IP, IC.
3) For patients with a CR / PR to first-line therapy, consolidation thoracic radiotherapy is recommended.
4) For patients with a CR / PR to first-line therapy, PCI is recommended (with discrepancy but recommended).
5) For patients with symptomatic brain metastasis, spinal cord compression, severe superior vena cava syndrome, bone metastasis with severe pain, or other conditions endangering life or severely harming quality of life, local radiotherapy is recommended according to the intensity and emergency nature of the clinical symptoms and chemotherapy efficacy.
6) ECOG PS 3–4: It is important to fully and comprehensively evaluate various factors and prudently select a suitable therapeutic regimen. For patients suitable for chemotherapy, if their ECOG PS is above 2 points after a single-drug regimen or combined reduction regimen treatment, thoracic radiotherapy is recommended. If ECOG PS 3–4 is not due to SCLC, symptomatic supportive therapy is recommended.

5.4.4 Second-line treatment of SCLC:

1) For patients with recurrence within 6 months, topotecan, participation in clinical trials, irinotecan, gemcitabine, paclitaxel or vinorelbine (with discrepancy but recommended) are recommended.
2) For patients with recurrence after more than 6 months, the original therapeutic regimen is recommended.
3) For third-line and beyond therapy, anlotinib and participation in clinical trials are recommended.

5.4.5 Treatment of combined SCLC (CSCLC):

1) For stage T1-2N0 C-SCLC, surgical treatment and postoperative adjuvant chemotherapy are recommended. If N1-2 is discovered after surgery, adjuvant radiotherapy is recommended, and postoperative PCI treatment should be conducted.
2) For limited-stage C-SCLC beyond stage T1-2N0, concurrent or sequential radiochemotherapy is recommended.
3) Systemic therapy is recommended for extensive-stage C-SCLC. The guidelines for the pure SCLC therapeutic regimen should be referred to.
4) For C-SCLC with adenocarcinoma, genetic testing is recommended. A tyrosine kinase inhibitor (TKI) can be tried for C-SCLC positive for EGFR or ALK mutations (with discrepancy but recommended).

5.4.6 Treatment of transformed SCLC:

1) For patients with rapid progression, the use of the EP / EC regimen, chemotherapy combined with TKI therapy, and chemotherapy combined with bevacizumab and anlotinib (with discrepancy but recommended) are recommended.
2) For patients with local progression, the EP/EC regimen combined with local radiotherapy (with discrepancy but recommended) or TKI therapy combined with local radiotherapy (with discrepancy but recommended) are recommended.
3) For patients with slow progression, the EP / EC regimen (with discrepancy but recommended), chemotherapy combined with TKI therapy (with discrepancy but recommended), chemotherapy combined with bevacizumab (with discrepancy but recommended), or anlotinib (with discrepancy but recommended) are recommended.

Notes:

1. Internal medicine treatment for LS-SCLC:

1) Internal medicine treatment can be used for patients with LS-SCLC who are suitable for surgery.

Postoperative adjuvant chemotherapy can reduce the risk of death in patients with LSSCLC. Retrospective studies have found that platinum-based adjuvant chemotherapy can significantly improve the 5-year survival rate after surgery in patients with LSSCLC. Therefore, the recommended adjuvant therapeutic regimen is always the EC / EP regimen [118].

2) Internal medicine treatment for patients with LS-SCLC who are not suitable for surgery or refuse surgery.

Concurrent or sequential radiochemotherapy is the standard therapeutic option for stage IIIA patients who are not suitable for or refuse surgery and patients with stage IIB-IIIA SCLC. Etoposide combined with platinum is a standard chemotherapy regimen in terms of LS-SCLC induction treatment. A meta-analysis found that cisplatin was similar to carboplatin as an induction therapy [119].

2. Internal medicine treatment for ES-SCLC:

1) First-line treatment of ES-SCLC:

Platinum combined with etoposide has always been the standard regimen for the initial treatment of ES-SCLC. Several phase III studies on the combination of irinotecan and platinum in first-line therapy for ES-SCLC found PFS benefits but inconsistent results for overall survival (OS) [120–122]. Chinese researchers have conducted a phase III noninferiority study on the first-line treatment of ES-SCLC with combined cisplatin and etoposide (EP) or combined lobaplatin and etoposide (EL) regimens, finding that the efficacy of the EL regimen was similar to that of the EP regimen and that loplatin was better than cisplatin in terms of renal toxicity and gastrointestinal reactions, with good patient tolerance [123]. The EL regimen is recommended as one of the available therapeutic regimens in the first-line treatment of ES-SCLC in China.

The recent development of immune checkpoint drugs has led to progress in SCLC therapy. The first-line treatment of ESSCLC was changed by the results of the Impower133 and CASPIAN studies, which found significantly better survival in patients who received atenizumab combined with EC in the first-line treatment of ESSCLC than in those who received etoposide / carboplatin (EC), and the median OS was prolonged by 2 months, with the mortality risk decreasing by 30% [124]. The CASPIAN study also found that combined durvalumab and chemotherapy led to a longer median OS than standard chemotherapy that was achieved by 13.0 months and a mortality risk that was lower by 27% [125]. The FDA approved atezolizumab and durvalumab combined with chemotherapy as first-line treatments for ES-SCLC in 2019 and 2020, respectively. Atezolizumab and durvalumab have also been approved by the National Medical Products Administration (NMPA) for the treatment of ESSCLC in China.

2) Treatment of patients with ES-SCLC with an ECOG PS of 3–4:

For patients with ES-SCLC with an ECOG PS of 3–4 due to SCLC, various factors should be considered comprehensively, and the therapeutic regimen should be carefully selected. Thoracic radiotherapy should be given if the ECOG PS is ≤ 2 after chemotherapy (single-drug or combined reduction regimen). Patients with an ECOG PS of 3–4 not due to SCLC are recommended to receive symptomatic supportive treatment. If these patients reach an ECOG PS of 0–2 after supportive treatment, the treatment strategy for patients with an ECOG PS of 0–2 points can be followed.

3. Second-line treatment of SCLC:

Topotecan is approved by the FDA for use as a first-line treatment for SCLC. A phase III study found that oral topotecan led to better survival of recurrent SCLC patients than the best supportive therapy (13.9 weeks

vs. 5.9 weeks), with better symptomatic control and a delayed decline in quality of life [126]. Researchers also found that oral topotecan and intravenous administration had similar efficacy in the treatment of relapsed SCLC [127]. The dose-limiting toxic effect of topotecan was granulocytopenia. Topotecan at 1.25 mg /m2 was similarly effective to topotecan at 1.5 mg/m2, with a significant reduction in ≥ 3 hematological toxicities [128]. Topotecan was approved in China at a dose of 1.25 mg/m2 intravenously administered for 1–5 days, with 1 cycle lasting 21 days. Currently, for SCLC relapse within 6 months after first-line treatment, in addition to topotecan, irinotecan, gemcitabine, paclitaxel or Navelbine are also recommended treatment options.

Chinese researchers have explored the efficacy of immunotherapy combined with anti-angiogenesis drugs in the treatment of relapsed SCLC. The PASSION study was a phase II study on the second-line treatment of ESSCLC. The objective response rate (ORR) of camrelizumab plus apatinib was 34.0%, and the median PFS and OS were 3.6 months and 8.4 months, respectively. Both sensitive relapsed and drug-resistant relapsed patients achieved treatment benefits [129]. The combined therapy was well tolerated, and camrelizumab plus apatinib is also an available therapeutic strategy for relapsed SCLC in China.

4. Third-line and beyond treatment for SCLC:

Patients with SCLC with disease progression after second-line treatment have a poor prognosis when only the best supportive therapy is administered [130–133]. A retrospective study found that approximately 20% of patients with progressive disease after second-line treatment received third-line treatment [131]. Chinese researchers have also conducted clinical trials on third-line and beyond-line treatment of SCLC. The ALTER1202 study was a randomized phase II study on patients with SCLC after at least two therapeutic regimens comparing anlotinib to placebo. The study found that anlotinib, a small-molecule multitarget anti-angiogenesis drug independently developed in China, led to significantly longer PFS (4.1 months vs. 0.7 months, $P < 0.0001$) and an 81% lower risk of disease progression than placebo. Anlotinib also significantly improved OS (7.3 months vs. 4.9 months, $P = 0.0210$) and reduced the mortality risk by 47% [134]. In 2019, the NMPA approved anlotinib for use in the third-line treatment of SCLC.

5. Internal medicine treatment for C-SCLC:

C-SCLC is a special type of SCLC, accounting for 2%—28% of all SCLC cases. The treatment of C-SCLC is mainly based on the results of retrospective studies and case reports [135–139]. Currently, there is a lack of prospective studies. The treatment of C-SCLC mainly refers to the therapeutic strategy for pure SCLC. Surgery, radiotherapy, chemotherapy and other multidisciplinary combined therapies are recommended for C-SCLC [140].

For stage T1-2N0 C-SCLC, surgery should be considered. A retrospective analysis found that the 5-year OS rate was higher (48.9% vs. 36.6%) in patients with limited stage C-SCLC who underwent surgery than in those who did not undergo surgery [138]. Another postoperative analysis found that among 181 patients with C-SCLC who underwent surgery, 153 patients received postoperative adjuvant chemotherapy, and 124 patients received the EP / EC regimen. Among 104 patients with N1-2, 53 patients (29.3%) received postoperative adjuvant radiotherapy, and 19 patients (10.5%) received PCI. In the multifactor analysis, postoperative adjuvant chemotherapy was an independent prognostic factor for disease-free survival (DFS) and OS. However, PCI had no effect on DFS or OS [141]. In an analysis of 91 postoperative C-SCLC patients, 11 patients received PCI, and multifactor analysis found that PCI was an independent prognostic factor with a tendency to reduce the occurrence rate of brain metastasis [142].

Systemic chemotherapy is basic for extensive-stage C-SCLC. C-SCLC is not sensitive to chemotherapy as is pure SCLC [143]. The EP / EC regimen remains the major therapeutic option for most C-SCLC patients. Researchers are also exploring other therapeutic regimens. In a retrospective study, the NIP regimen had higher and more serious toxicity [144]. Another retrospective study analyzed the effect of adding paclitaxel to the EP / EC regimen in the treatment of extensive stage CSCLC, and the three-drug regimen showed a higher ORR (90% vs. 53%, $P = 0.033$) with significantly increased the therapy-related toxicity [145].

TKIs are effective for C-SCLC with adenocarcinoma positive for EGFR mutations, which indicates the potential benefit of molecular targeted therapy for C-SCLC [139, 146].

6. Treatment of transformed SCLC:

The concept of transformed SCLC was first proposed as one of the mechanisms for resistance to TKI therapy in patients with NSCLC positive for EGFR mutations [147–150]. The occurrence rate of transformed SCLC is 5%-14% in patients with NSCLC positive for EGFR mutations [148, 151]. Subsequently, researchers reported that NSCLC with ALK fusion mutations or ROS1 fusion mutations may also undergo SCLC transformation [152]. Recently, there have been reports on

patients with immunotherapy for transforming NSCLC into SCLC [153].

A retrospective study of 8 centers analyzed 32 patients with EGFR-mutated lung adenocarcinoma who transformed to SCLC after TKI therapy. Among others, the 27 patients who accepted the EP regimen showed an ORR of 44.4% and a median PFS of 3.5 months. Five patients who were administered anlotinib therapy showed an ORR of 66.7% and a PFS of 6.2 months, which indicated that except with reference to the primary SCLC regimen, anlotinib is also worth trying [154]. One case report showed that 2 patients exhibited transformation to SCLC with oligometastatic progression after TKI treatment, provides a reference for the selection of treatment for local progression of transformed SCLC [155]. Recently, in another retrospective study, 12 of 21 patients accepted the EP / IP chemotherapy regimen and 9 of whom received combined chemotherapy and TKI or combined chemotherapy and bevacizumab. The combined therapy group showed a significantly better ORR (50% vs. 25%, $P=0.002$) and PFS (6.4 months vs. 2.9 months, $P=0.024$) than the chemotherapy group with the tendency of OS extension (10.7 months vs. 7.1 months, $P=0.237$). The results indicated that a combined therapy regimen may be a more promising therapeutic strategy for transformed SCLC [156] Table 5.

5.5 Surgical treatment for SCLC

At first, surgery is an option for the therapy of LC of all pathological types. The results of two prospective randomized controlled studies indicated that surgery did not lead to a survival benefit for SCLC over radiotherapy, and the use of surgery in SCLC was gradually replaced by the use of radiotherapy [157, 158]. SCLC TNM staging and a retrospective analysis based on a large number of cases in a database showed that, for early-stage SCLC, the selected patients (T1-2N0) had a 5-year survival rate exceeding 50% after surgical treatment, especially following pulmonary lobectomy [157]. Then, the value of surgery in SCLC was reestablished. Currently, it is commonly believed that SCLC at clinical stage I- II A (T1-2N0) may benefit from surgery. Clinical stage I- II A patients are recommended to receive pulmonary lobectomy and hilar and mediastinal lymph node dissection. There is still dispute as to whether stage IIB-IIIA SCLC patients can benefit from surgery [158].

5.6 Radiotherapy for SCLC

Main recommendations:

5.6.1 Radiotherapy for LS-SCLC [159–162]:

1) Radiotherapy for operable SCLC: Patients suitable for surgery include those with stage cT1-2N0M0 and stage I SCLC. Regarding N2, it is recommended that adjuvant chemotherapy combined with chest radiotherapy is conducted, either concurrently or sequentially. N1 patients should receive chemotherapy ± chest radiotherapy. N0 patients should receive adjuvant therapy and systemic chemotherapy. If a patient cannot benefit from adjuvant radiotherapy, postoperative adjuvant radiotherapy is not recommended. The recommended target volume includes the bronchial stump, unilateral hilus pulmonis, involved lymph node region before surgery, and pathologically positive lymph node region [117, 159].
2) LS-SCLC at a stage beyond cT1-2N0M0: Concurrent radiochemotherapy is preferred. Sequential radiochemotherapy can be selected for patients who cannot undergo concurrent radiochemotherapy. Regarding the chest radiotherapy dose and fractionation pattern in concurrent radiochemotherapy, 45 Gy/3 weeks (bid) or 60–70 Gy/6–7 weeks (qd) can be selected [160].
3) For patients who achieve a CR or PR after systemic therapy, PCI is recommended. PCI for stage I SCLC patients who have undergone radical surgery and systemic chemotherapy is still in dispute (recommended but with dispute). For patients with a Karnofsky Performance Score (KPS) > 75, an ECOG PS > 2 points and neurocognitive dysfunction, PCI therapy is not recommended. The common fractionation pattern is whole-brain 25 Gy/10f (2.5 Gy / f), which should commence 3–4 weeks after the completion of radiochemotherapy [117, 159, 160].

5.6.2 Radiotherapy for ES-SCLC:

1) Consolidating chest radiotherapy can be considered for patients with ES-SCLC, but there is no uniform best treatment dose or fractionation pattern. A pattern of 30 Gy/10f, 60 Gy/30f or other regimens of equivalent dose in this range can be selected. The target volume should include the postchemotherapy gross primary tumor volume (GTVp), the hilar region and the mediastinum (more than the involved region) [161, 162].
2) After effective systemic therapy, PCI or brain MRI can be considered for close follow-up (recommended but with dispute). The commonly used fractionation pattern includes whole-brain 25 Gy/10f (2.5 Gy/f) or whole-brain 20 Gy/5f.

Notes:

Radiotherapy is an important therapeutic technique for SCLC, and its value is reflected both in the limited

Table 5 Common therapeutic regimens for SCLC

Chemotherapy regimen	Dose and usage	Medication time	Treatment cycle
Initial treatment of LS-SCLC			
EP regimen			
Cisplatin	75 mg/m^2, intravenous injection	Day 1	Every 3–4 weeks × 4–6 cycles
Etoposide	100 mg / m^2, intravenous injection	Days 1–3	Every 3–4 weeks × 4–6 cycles
EP regimen			
Cisplatin	60 mg/m^2, intravenous injection	Day 1	Every 3–4 weeks × 4–6 cycles
Etoposide	120 mg / m^2, intravenous injection	Days 1–3	Every 3–4 weeks × 4–6 cycles
EP regimen			
Cisplatin	25 mg/m^2, intravenous injection	Days 1–3	Every 3–4 weeks × 4–6 cycles
Etoposide	100 mg / m^2, intravenous injection	Days 1–3	Every 3–4 weeks × 4–6 cycles
EC regimen			
Carboplatin	AUC = 5–6, intravenous injection	Day 1	Every 3–4 weeks × 4–6 cycles
Etoposide	100 mg / m^2, intravenous injection	Days 1–3	Every 3–4 weeks × 4–6 cycles
Initial treatment of ES-SCLC			
EC + atezolizumab regimen			
Atezolizumab	1200 mg intravenous injection on Day 1 (first infusion should last at least 60 min, and the subsequent infusion should last at least 30 min in case of good tolerance)	Day 1	Every 3 weeks × 4 cycles, followed by 3 weeks maintenance therapy until disease progression or intolerance to toxicity
Carboplatin	AUC = 5 intravenous injection	Day 1	Every 3 weeks × 4 cycles
Etoposide	100 mg / m^2 intravenous injection	Days 1–3	Every 3 weeks × 4 cycles
EP + durvalumab			
Durvalumab	1500 mg intravenous injection, infusion duration of 60 min	Day 1	Every 3 weeks × 4 cycles every 4 weeks after 4 cycles until disease progression or intolerance to toxicity
Cisplatin	75–80 mg/m^2 intravenous injection	Day 1	Every 3 weeks × 4 cycles
Etoposide	80–100 mg / m^2 intravenous injection	Days 1–3	Every 3 weeks × 4 cycles
EC + durvalumab regimen			
Durvalumab	1500 mg intravenous injection, infusion duration of 60 min	Day 1	Every 3 weeks × 4 cycles, repeated every 4 weeks after 4 cycles, until disease progression or intolerance to toxicity
Carboplatin	AUC = 5 intravenous injection	Day 1	Every 3 weeks × 4 cycles
Etoposide	80–100 mg / m^2 intravenous injection	Days 1–3	Repetition every 3 weeks, 4 cycles in total
EP regimen			
Cisplatin	75 mg/m^2 intravenous injection	Day 1	Every 3 weeks × 4–6 cycles in total
Etoposide	100 mg / m^2 intravenous injection	Days 1–3	Every 3 weeks × 4–6 cycles in total
EP regimen			
Cisplatin	80 mg/m^2 intravenous injection	Day 1	Every 3 weeks × 4–6 cycles in total
Etoposide	80 mg/m^2 intravenous injection	Days 1–3	Every 3 weeks × 4–6 cycles in total
EP regimen			
Cisplatin	^{2}5 mg/m^2 intravenous injection	Days 1–3	Every 3 weeks × 4–6 cycles in total
Etoposide	100 mg / m^2 intravenous injection	Days 1–3	Every 3 weeks × 4–6 cycles in total
EC regimen			
Carboplatin	AUC = 5–6 intravenous injection	Day 1	Every 3 weeks × 4–6 cycles in total
Etoposide	100 mg / m^2 intravenous injection	Days 1–3	Every 3 weeks × 4–6 cycles in total
EL regimen			
Lobaplatin	30 mg/m^2 intravenous injection	Day 1	Every 3 weeks × 4–6 cycles in total
Etoposide	100 mg / m^2 intravenous injection	Days 1–3	Every 3 weeks × 4–6 cycles in total
IP regimen			
Cisplatin	60 mg/m^2 intravenous injection	Day 1	Every 4 weeks × 4–6 cycles
irinotecan	60 mg/m^2 intravenous injection	Day 1, 8, 15	Every 4 weeks × 4–6 cycles

Table 5 (continued)

Chemotherapy regimen	Dose and usage	Medication time	Treatment cycle
IP regimen			
Cisplatin	30 mg/m^2 intravenous injection	Day 1, 8	Every 3 weeks × 4–6 cycles
irinotecan	65 mg/m^2 intravenous injection	Day 1, 8	Every 3 weeks × 4–6 cycles
IC regimen			
Carboplatin	AUC = 5 intravenous injection	Day 1	Every 4 weeks × 4–6 cycles
irinotecan	50 mg/m^2 intravenous injection	Day 1, 8, 15	Every 3 weeks × 4–6 cycles
SCLC second-line treatment			
Topotecan single-drug regimen			
Topotecan	1.25 mg / m^2 intravenous injection	Days 1–5	Every 3 weeks x
Topotecansingle-drugregimen			
Topotecan	3.2 mg/m^2 per os	Once every day, Days 1–5	Every 3 weeks
SCLC third-line and higher treatment			
Anlotinib single-drug regimen			
Anlotinib	12 mg per os	Once every day, Days 1–14	Every 3 weeks

and extensive stages. The time of radiotherapy intervention mainly depends on the stage. SCLC stage is obtained based on the two staging methods in the VALSG grading system. TNM staging is also recommended. LS-SCLC means that the tumor is limited to the hemithorax (stage I-III); that is, the extent of irradiation may be included in any target volume and can be subject to a sufficient irradiation dose. However, patients at stage T3-4 who could not tolerate the radiotherapy regimen due to multiple intrapulmonary metastatic foci or excessively large tumors were excluded. ES-SCLC includes stage IV and substages T3-4 in stages I III with multiple intrapulmonary metastatic foci or excessively large tumors.

(1) Recommended radiotherapy for operable SCLC:

Patients who are suitable for surgery include stage cT1-2N0M0 and stage I patients. The selection of postoperative adjuvant radiotherapy mainly relies on postoperative pathological staging [163, 164]. Regarding N2, it is recommended that adjuvant chemotherapy combined with chest radiotherapy are conducted, either concurrently or sequentially. N1 patients should receive chemotherapy ± chest radiotherapy. N0 patients should receive adjuvant therapy and systemic chemotherapy. If patients cannot benefit from adjuvant radiotherapy, postoperative adjuvant radiotherapy is not recommended. The recommended target volume includes the bronchial stump, unilateral hilus pulmonis, involved lymph node region before surgery, and pathologically positive lymph node region [163]. In the Lung ART study, it was proposed that the target volumes for postoperative radiotherapy (PORT) for patients with pN2 NSCLC may refer to those applied to patients with SCLC [164].

For patients with cT1-2N0M0 LS-SCLC who are not suitable for or refuse surgery, concurrent radiochemotherapy is preferred. Combined SBRT and chemotherapy may result in the same efficacy. The National Cancer Database (NCDB) shows that patients who receive SBRT sequential chemotherapy and patients who receive concurrent radiochemotherapy show no difference in OS [165]. A multicenter study reported that the 1-year and 3-year OS rates of SBRT (50 Gy/5f) were 69.9% and 34.0%, respectively, with little toxicity (a grade 2 pneumonia rate of 5.2%) [166]. Therefore, sequential chemotherapy after SBRT is also an available therapeutic strategy.

(2) Recommended radiotherapy for LSSCLC at stages beyond cT1-2N0M0:

Concurrent radiochemotherapy is preferred, and sequential radiochemotherapy can be selected for patients who cannot tolerate concurrent radiochemotherapy. It is recommended that chemotherapy is conducted in the 1st or 2nd cycle, which is determined according to the extent of radiotherapy and the injectivity of organs at risk. For patients with CR after chemotherapy, it is recommended that the GTVT be outlined according to the last primary focus in CT and the CTV-N is outlined according to the CT before chemotherapy [167, 168].

The SWOG prospective stage III randomized controlled study included 466 LSSCLC patients to compare the primary focus radiotherapy target volume before and after chemotherapy. The results showed that the OS of the two groups was not significantly different following statistical analysis [167]. The results from the CALGB 30610/RTOG0538/CONVERT study, and other

prospective randomized controlled trials indicate that the conventional selected lymph node region irradiation pattern is associated with an efficacy not superior to that of the prechemotherapy lymph node involvement region irradiation pattern, with more significant adverse reactions [168, 169].

Chest radiotherapy dose and fractionation pattern selection: Currently, 45 Gy/3 weeks (bid) or 60–70 Gy/6–7 weeks (qd) pattern can be selected. The two radiotherapy sessions per day pattern is associated with a higher occurrence rate of radiation esophagitis [168]. Therefore, this pattern is suitable for patients in good performance condition and patients with good baseline functions. The best radiotherapy pattern under concurrent radiochemotherapy for LS-SCLC is still under exploation. The INT0096 trial found that for two vs. one session of radiotherapy per day, the median survival was 23 months vs. 19 months,,the bid group showed a survival benefit, but the difference did not reach statistical significance, and their overall occurrence rate of esophagitis was higher [170]. In another randomized controlled CONVERT trial, the radiotherapy pattern for the bid group (274 patients) was 45 Gy/30 f/19 d, 1.5 Gy/f, bid; the radiotherapy pattern for the qd group (273 patients) was 66 Gy/33 f/45 d. The median OS of the bid and qd groups was 30 months and 25 months ($P=0.14$), respectively, and neither group showed a significant difference in the occurrence rates of grades 3–4 esophagitis (19% vs. 38%, $P=0.85$) and radiation pneumonia (3% vs. 2%, $P=0.70$). The hyperfractionation and conventional fractionation patterns showed no significant difference in survival with similar adverse reactions [168]. The results of a randomized group phase II trial, Grønberg BH, showed that if LS-SCLC is subject to the fractionation pattern of 1.5 Gy bid, the radiotherapy dose of 60 Gy results in a higher survival rate than that of 45 Gy but without additional toxicity [171]. These results indicate that chest radiotherapy with two irradiations per day up to 60 Gy is expected to become an optimized option for the existing regimen.

(3) Recommended PCI for LS-SCLC:

For patients with LS-SCLC who achieve a CR or PR after systemic treatment, PCI is recommended. PCI for stage I SCLC patients who have undergone radical surgery and systemic chemotherapy is in dispute. For patients with a KPS > 75, an ECOG PS > 2 points and neurocognitive dysfunction, PCI therapy is not recommended [172]. The common fractionation pattern is whole-brain 25 Gy/10 f (2.5 Gy/f), which is recommended to be initiated 3–4 weeks after the completion of radiochemotherapy. Common acute toxicities of PCI include fatigue, headache, nausea, and vomiting [173].

The results of a retrospective analysis of the US SEER database, including 7995 patients, showed that patients who received PCI had 2-year, 5-year and 10-year OS rates superior to those of the group who did not receive PCI, with statistical significance ($P<0.05$) [172]. For patients with poor general conditions, age > 75 years or cognitive deficiency, PCI is not recommended[173]. A partial cause of PCI-related neurocognitive deterioration is hippocampal irradiation. As a result, it is recommended that the hippocampus is protected during PCI, and the protection of the hippocampus does not add to the occurrence rate of brain metastasis.

(4) Recommended radiotherapy for ESSCLC:

For ES-SCLC, consolidated chest radiotherapy can be considered, but the benefited population needs to be further divided. A randomized controlled trial by Jeremic et al. included 210 ES-SCLC patients, and the results showed that for patients with a low metastatic burden who achieved or approached CR after chemotherapy, the subsequent addition of chest radiotherapy resulted in a significant survival benefit, with a median OS of 17 months, which was superior to that of the group who did not undergo radiotherapy (11 months) [174]. The Dutch CREST study found that patients with chest residual tumor after systemic therapy, effective systemic therapy and low metastatic focus burden may benefit from consolidated chest radiotherapy [175].

(5) PCI therapy for ES-SCLC:

There is dispute about the application of PCI in ES-SCLC. PCI or brain MRI can be selected for the close follow-up of patients with effective systemic treatment. The commonly used fractionation pattern includes whole-brain 25 Gy/10 f (2.5 Gy/f) or wholebrain 20 Gy/5 f.

An EORTC randomized controlled trial included 286 ES-SCLC patients, the results showed that PCI lowered the probability of brain metastasis and extended survival [176]. A Japanese stage III randomized controlled trial had the same design and included two groups, the PCI group and the MRI follow-up group. The results showed that PCI led to a lower occurrence rate of brain metastasis than MRI monitoring but without survival benefit [177].

(6) Radiotherapy for symptomatic ESSCLC:

Superior vena cava syndrome: Patients with severe clinical symptoms are recommended to receive radiotherapy first and then chemotherapy. Patients with mild clinical symptoms are recommended to receive chemotherapy

first and then radiotherapy together with symptomatic treatment of oxygen uptake, diuresis, sedation, pain relief, etc. In the early stage of radiotherapy, local edema may appear and can be treated with hormone and diuretic adjuvant therapy. For first-line chemotherapy, an aggressive dosage is recommended [174].

Spinal cord compression: Without special contraindications, local radiotherapy should be conducted first to control the compressive symptoms, and chemotherapy should be provided. The most commonly applied radiotherapy dose is 30 Gy/10 f/2 weeks or 40 Gy/20 f/4 weeks. For compression due to vertebral metastasis with rather isolated metastatic foci, large fractionated irradiation may be provided at 20 Gy/5f—8 Gy/f. As patients with spinal cord compression have a short survival period and poor quality of life, various factors should be considered in the selection of chest radiotherapy. The choice should be made with caution (e. g., patients with a CR or PR can receive radiotherapy). However, surgical decompression is usually not recommended [174].

Bone metastasis: Chemotherapy + palliative external irradiation radiotherapy ± diphosphonate therapy are recommended. Patients with a high risk of fracture may receive orthopedic fixation. Obstructive atelectasis: chemotherapy + chest radiotherapy is recommended [174].

Brain metastasis: For asymptomatic patients, for the initial treatment, chemotherapy is recommended, and if a CR or PR is achieved, whole-cerebrum radiotherapy (30 Gy/10 f) is available [176]. For symptomatic patients upon initial treatment, whole-brain radiotherapy and sequential chemotherapy are recommended, and radiotherapy must be conducted as soon as possible (30 Gy/10 f) [177]. For patients with brain metastasis after PCI, SRS/SRT is preferred. Patients who achieve a CR or PR after therapy may receive chest radiotherapy at the proper time [175].

(7) Reperforming radiotherapy for SCLC:

The use of reperforming radiotherapy for SCLC currently needs a large-scale prospective randomized controlled study, and most data originate from a retrospective study. It is necessary to fully consider the overlapping area and interval of the two radiotherapy programs to ensure the injectivity of organs at risk. If there is an overlapping region in the central tumor area, the risk of chronic toxicity is higher. A cumulative dose of 90–150 Gy to the central structure should be avoided. If the interval between the first radiotherapy and the reperformance of radiotherapy was less than 6 months, the dose to the spinal cord was less than 50 Gy (EQD2). If the interval exceeds 6 months, 40–45 Gy/20–25 f can be used, and the safe, cumulative and average dose is 87.4 Gy [178]. According to the existing data, palliative dose (< 40 Gy) repeat radiotherapy is useful in the treatment of hemoptysis, superior vena cava syndrome, costalgia and other symptoms. For asymptomatic patients without distant disease and a good PS, a high dose can improve the quality of life and OS [179]. Therefore, it is recommended that asymptomatic patients without metastasis are selected for radical radiotherapy; in other conditions, low fractionation reperformance of radiotherapy and supportive therapy can be considered to reduce toxicity.

(8) Radiotherapy technology for SCLC:

With the development of radiotherapy technology, various technologies have been tested in the treatment of SCLC. In general, each technology features unique advantages, and it is necessary to comprehensively consider the tumor position, tolerance of the patient's body and potency ratio. The application of image-guided radiotherapy (IGRT) in SCLC requires support from more data. In a study involving 132 patients with SCLC, no significant difference in OS was observed between those who received IGRT and those who received IMRT [179]. Nevertheless, retrospective study data on IMRT and 3D-CRT showed that the OS associated with IMRT is more advantageous [179]. For peripheral-type tumors, volumetric modulated arc therapy (VMAT) is associated with lower lung V5 than typical IMRT, and IMRT is associated with low lung V30. For centraltype tumors, the V20 of VMAT is lower than that of IMRT [180]. There are few studies on proton therapy. The results of a prospective study indicated that proton radiotherapy is associated with a significantly lower average dose to the spinal cord, heart and lungs than radiotherapy with modulated intensity with no difference in the average esophageal dose or V20 [181].

5.7 Small cell lung cancer rehabilitation

Main recommendations:

(1) For small cell lung cancer (SCLC) with a treatment efficacy evaluation of a complete response (CR), partial response (PR) or stable disease (SD), 1 follow-up visit every 3 months in the first 2 years after the therapy, 1 follow-up visit every 6 months in the 3rd year and 1 follow-up visit annually thereafter are necessary.
(2) For extensive-stage SCLC (ES-SCLC) with a treatment efficacy evaluation of CR, PR or SD, 1 follow-up visit every 2 months in the 1st year after the therapy, 1 follow-up visit every 3–4 months in the

2nd-3rd year, 1 follow-up visit every 6 months in the 4th-5th year and 1 follow-up visit annually after the 5th year are necessary.

(3) For patients with relevant new symptoms or aggravated symptoms, immediate follow-up is recommended.

(4) Recommended follow-up items include medical history, physical examination, and chest/abdominal / pelvic computed tomography (CT) (plain scan or enhanced). Cerebral enhanced magnetic resonance imaging (MRI) (preferred) or CT should be conducted once every 3–4 months in the 1st year and once every 6 months since the 2nd year. Positron emission tomography (PET)/CT is not recommended as the conventional follow-up technique.

Notes:

High-quality evidence is needed for the best follow-up regimen for SCLC.

Sugiyama T et al. [182] reviewed the cases of 94 SCLC patients who received first-line chemotherapy and in-depth or shallow follow-up after achieving CR/PR. The in-depth follow-up group (chest plus abdominal CT, cerebral MRI and bone scanning) was seen during follow-up every 2 months and every 3 months from the 6th month until the end of 2 years. The follow-up frequency of the shallow follow-up group was determined by the physician independently. The researchers found that the in-depth follow-up group had more asymptomatic recurrence cases and a higher effective rate of previous chemotherapy than the shallow follow-up group (61.8% vs. 37.9%, $P=0.04$), as well as a significantly extended overall median survival (20 months vs. 13 months, $P=0.001$).

Various guidelines recommend a high frequency of follow-up in the first 2 years after therapy: in the first 2 years after therapy, one CT follow-up every 2–3 months for patients with ES-SCLC and one CT follow-up every 3–6 months for patients with limited-stage SCLC are recommended. After 2 years, the recurrence risk is lowered, and the follow-up frequency can be reduced [183].

Currently, there is no prospective study assessing the effect of brain MRI in recurrence monitoring. Regardless of whether the patients have received prophylactic cranial irradiation (PCI), it is recommended that cerebral enhanced MRI (preferred) or CT is regularly conducted once every 3–4 months in the 1st year and once every 6 months in the 2nd year. The American Society of Clinical Oncology (ASCO) guidelines do not suggest regular cerebral MRI reexamination after 2 years of follow-up for asymptomatic patients who have achieved a CR. However, the European Society for Medical Oncology (ESMO) guidelines [184] and Canadian Society for Medical Oncology (CSCO) guidelines suggest regular monitoring with cerebral MRI after 2 years of follow-up. Due to the lack of evidence, these guidelines suggest that doctors and patients should discuss the options and make decisions together [7, 184].

No guidelines suggest the use of PET/CT as a conventional follow-up technique for SCLC [7].

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