

GUIDELINES

Chinese guidelines on the diagnosis and treatment of primary lung cancer (2011)

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Introduction

Primary lung cancer (PLC) is one of the most common malignant tumors in China. According to the *Health Statistics Yearbook 2010*, PLC was the first leading cause of cancer death nationwide in 2005.

These guidelines are developed to standardize the diagnosis and treatment protocols for this condition and enhance the related practice at medical institutions, so as to improve the prognosis of PLC patients and the quality and safety of healthcare services.

Diagnostic techniques

Risk factors

Populations at risk of PLC include those have a history of

smoking with a smoking index of greater than 400 cigarettes/year; a history of high-risk occupational exposure (eg. exposure to asbestos) and family history of PLC; or at the age of 45 years or above.

Clinical manifestations

At the early stage, patients with PLC may have few, if any, obvious symptoms. With the progression of disease, the following symptoms may occur:

1. Irritating cough;
2. Blood in the sputum or bloody sputum;
3. Chest pain;
4. Fever; and
5. Shortness of breath.

Respiratory symptoms that persist longer than two weeks unresponsive to treatment, particularly blood in the sputum, irritating cough, or exacerbation of existing respiratory symptoms, can be a sign of PLC.

If invasion of the surrounding tissues or metastasis occurs, the following symptoms may be present:

1. Hoarse voice if the recurrent laryngeal nerve is affected;
2. Superior vena cava obstruction syndrome such as facial and neck edema, when the superior vena cava is involved;
3. Pleural effusion, often bloody, due to pleural invasion, and shortness of breath if a large amount of fluid is present;
4. Severe, persistent chest pain if the pleura and chest wall is affected;
5. Cervical sympathetic syndrome such as severe chest pain,

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upper extremity venous engorgement, edema, arm pain and upper limb movement disorder, ipsilateral ptosis, miosis, enophthalmos, and facial anhidrosis, as a result of invasion and compression of organs at the thoracic inlet (eg. first rib, subclavian vein, brachial plexus, cervical sympathetic) by cancer located at the tip of the upper lobe;

6. Newly-occurring neurological symptoms and signs such as headache, nausea, dizziness and blurred vision, which may indicate brain metastases;
7. Persistent bone pain at a fixed site with elevated serum alkaline phosphatase or calcium, which may indicate bone metastasis;
8. Right upper quadrant pain, hepatomegaly, and elevated alkaline phosphatase, aspartate aminotransferase, lactate dehydrogenase or bilirubin, which can be suggestive of liver metastasis;
9. Palpable subcutaneous nodules in the case of subcutaneous metastasis; and
10. Symptoms as a result of hematogenous metastasis to other organs.

Physical examination

Most PLC patients do not have symptoms on examination;

Some have unexplained, persistent extrapulmonary signs such as clubbing (toes), non-migratory pulmonary joint pain, gynecomastia, dark skin or dermatomyositis, ataxia, and phlebitis;

Findings of vocal cord paralysis, superior vena cava obstruction, Horner's syndrome and Pancoast syndrome in patients with clinical manifestations highly suspicious for PLC are indicative of local invasion and metastasis; and

Findings of nodular hepatomegaly, subcutaneous nodules and swollen supraclavicular lymph nodes in patients with highly suspected PLC are indicative of distant metastasis.

Imaging

Chest X-ray: this is an important tool for early detection of PLC, and is also used in postoperative follow-up;

Chest CT scan: an essential technique in the diagnosis of PLC, it can further verify the location and extension of any lesion and generally identify benign and malignant tumors. Low-dose spiral chest CT can effectively detect early PLC, while CT-guided transthoracic biopsy is critical for cytological and histological diagnosis;

Ultrasound: this is mainly used to identify metastasis to abdominal organs and retroperitoneal lymph nodes, as well as supraclavicular lymph nodes; it can identify cystic and solid lesions on the chest wall or lung tissues nearby and provide

guidance for biopsy. Ultrasound is also commonly used as a positioning guidance for pleural aspiration;

MRI: it is useful for staging of PLC, and particularly identification of metastases to the spine, ribs, and brain;

Bone scan: it is a routine examination for bone metastases. When a suspected bone metastasis is suggested by bone scan, MRI of that area could be conducted for confirmation; and

PET-CT: this is not recommended for routine use. It is more sensitive and specific in diagnosing mediastinal lymph node metastases than CT scan.

Endoscopy

Bronchoscopy: this is the most common tool for diagnosis of PLC -- it enables brush biopsy under direct vision with a bronchoscope, biopsy and bronchoalveolar lavage for cytological and histological diagnosis; the combination of these methods can improve the detection rate;

Transbronchial needle aspiration (TBNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA): they are helpful to accurate N2 staging of PLC before treatment, although not recommended as routine screening methods. Some well-equipped hospitals are encouraged to use these tools to facilitate diagnosis when applicable. EBUS-TBNA provides more reliable evidence for accurate pathological diagnosis of N1 and N2 PLC in a safe manner;

Mediastinoscopy: it is useful in confirmation of PLC and evaluation of N staging, and is regarded as the gold standard for clinical assessment of mediastinal lymph nodes. Although CT, MRI and the latest PET-CT are good enough to furnish valuable evidence on pre-treatment staging of PLC, mediastinoscopy has still been indispensable for diagnosis; and

Thoracoscopy: it enables accurate diagnosis and staging of PLC, and is particularly useful for diagnosing early-stage lesions (such as small lung nodules), of which pathological specimen can not be obtained through bronchoscopy or transthoracic needle aspiration biopsy (TTNA), by thoracoscopic excision. Lymph node, pleural and pericardial biopsy, and pleural and pericardial effusion cytology can be performed under thoracoscopy to provide a reliable basis for the development of comprehensive treatment programs for mid- to late-stage lung cancer.

Other examination techniques

Sputum cytology: this is a simple, non-invasive diagnostic method for PLC, in which the cytological result is obtained through smear examination of early morning deep-cough specimens on three consecutive days;

Transthoracic needle aspiration biopsy (TTNA): this is a sensitive and specific detection tool for peripheral PLC

performed under CT or ultrasound guidance;

Thoracentesis: this may be warranted in a pleural effusion of unclear cause for cytological diagnosis and definite staging of PLC;

Pleural biopsy: this is used to increase the positive detection rate if thoracentesis fails to yield positive cytological results; and

Superficial lymph node biopsy: enlarged superficial lymph nodes in patients with any space-occupying lesion of the lung or confirmed PLC lesions necessitate routine superficial lymph node biopsy for pathological diagnosis and definite staging of PLC to inform the clinical treatment.

Blood immunology and biochemistry

Blood biochemistry: no specific test panel is currently available for PLC. Elevated alkaline phosphatase or calcium in PLC patients will suggest bone metastases, while elevated plasma alkaline phosphatase, aspartate aminotransferase, lactate dehydrogenase or bilirubin would indicate liver metastasis;

Blood tumor markers: there are no specific markers for clinical diagnosis of PLC at the present, and thereby this test is not routinely arranged. However, physicians could still consider the following tests to support evaluation of the disease:

1. Carcinoembryonic antigen (CEA): serum CEA is basically used for prognosis assessment and treatment monitoring;
2. Neuron-specific enolase (NSE): this is the preferred marker for small cell PLC and is used in the diagnosis and treatment response monitoring;
3. Cytokeratin 19 fragment (CYFRA21-1): it provides a sensitive and specific aid for the diagnosis of squamous cell carcinoma; and
4. Squamous cell carcinoma antigen (SCC): this is helpful in efficacy monitoring and prognosis determination for patients with squamous cell carcinoma.

Histological diagnosis

The confirmation and treatment of PLC is based on histopathological findings. Biopsy confirmed PLC warrants standardized treatment. If definite biopsy confirmation is not possible due to limited access to tumor tissues, repeat biopsy or other treatment options based on imaging results are recommended; in this case, pathology consultation can be useful to confirm the diagnosis, if necessary.

Differential diagnosis of PLC

Benign tumor: including pulmonary hamartoma, bronchial pulmonary cyst, giant lymph node hyperplasia, inflammatory myofibroblastic tumor, sclerosing hemangioma, tuberculoma, arteriovenous fistula and pulmonary sequestration. These

benign tumors are characterized by varying imaging findings, but excision is always considered if there is concern about the possibility of a malignancy;

Tuberculosis and associated diseases: they are common and most easily confused with PLC, leading to misdiagnosis or delay in clinical treatment. Repeated sputum cytology, bronchoscopy and other laboratory examinations are necessary if a definite diagnosis is difficult to make before thoracotomy. Radiotherapy and chemotherapy are prohibited unless justified by definite pathological or cytological diagnosis. Diagnostic anti-TB treatment with close follow-up, however, is allowed. A positive tuberculin test is not enough to rule out PLC;

Pneumonia: about a quarter of PLC patients present with pneumonia in their early stages. Pneumonia characterized by slow onset and mild symptoms that are irresponsive to anti-inflammatory treatment or recurrent in the same position is highly suspicious for PLC; and

Others: some rare benign and malignant tumors, such as lung fibroma and lipoma, are not easily distinguished from PLC without surgical intervention.

Pathological assessment

Fixation procedures for lung cancer specimens

Fixative: Use 10% neutral buffered formalin and avoid any fixative containing heavy metals;

Fixative volume: at least 10 times that of the specimen;

Fixation temperature: room temperature;

Based on the site of origin and state of the tumor specimen on arrival at the pathology department, there are two options:

1. Directly put the specimen into 10% neutral buffered formalin; or
2. When necessary, inject a sufficient volume of 10% neutral buffered formalin into the bronchi followed by ligation or clamping, and preserve the specimen overnight.

Fixation Time: biopsy specimens: ≥ 6 hours and ≤ 48 hours; surgical specimens: ≥ 12 hours and ≤ 48 hours.

Sampling requirements

Biopsy specimens

Verify the number of biopsy specimens sent for test -- all of them must be sampled;

Make sure each wax block contains at most five biopsy specimens; and

Wrap the specimens in gauze or a soft permeable paper to prevent loss.

Surgical specimens

Partial lung resection (segmental resection and wedge resection)

1. Remove surgical sutures or staples;
2. Document the sample size and condition of the pleural surface;
3. Cut in the parenchyma tissue along the vertical margin to obtain a specimen block, and identify the size, conditions of the cut surface (with/without bleeding/necrosis/cavitation), relationship with the pleura and lung parenchyma, and distance from the mass margin to the cutting edge.
4. Cut 1-4 tissue blocks based on the site and size of lesion, and collect those containing the edges between the mass and the pleura, the tumor and the lung parenchyma; and
5. Collect non-tumor lung tissue.

Lobectomy and pneumonectomy specimens

1. Verify the five major structures of the lungs: airway, lung parenchyma, pleura, blood vessels and lymph nodes. Measure their sizes and locate the specimens based on the hilum;
2. Collect those containing the bronchial resection, vascular and pleural margins;
3. For pneumonectomy specimens, locate the hilar lymph nodes;
4. Based on the site of origin and state of the tumor specimen on arrival at the pathology department, there are two options: first, use scissors to open all main bronchi and their branches along the vertical axis to expose the plane where the structural relationship between the lesion and surrounding lung tissues is best demonstrated. Second, cut specimens injected with formalin in the main bronchi at intervals of 0.5-1.0 cm on the frontal plane perpendicular to the hilum;
5. Describe the tumor size, conditions of the cut surface (with/without bleeding/necrosis/cavitation), location in the lung lobe/segment and the relationship with bronchi, extent (local or metastasis), and the adequacy of resection. Cut adequate tissue blocks based on the tumor size, location and extent (typically 4 pieces), and collect those exposing the relationship between the lesion and surrounding lung tissues (typically 2 pieces); and
6. Collect non-tumor lung tissue.

Lymph node

Surgeons are recommended to use American Joint Committee on Cancer (AJCC) staging system for intraoperative lymph node (N) grouping. N2 lymph nodes usually arrive individually and are accurately grouped by surgeons. Therefore, they should be reported separately. N2 lymph nodes included in lung resection specimens should be handled accordingly based on the specific parts of origin. Look for the hilar soft tissues along the bronchi and lymph nodes in the lung parenchyma, sample all of the found lymph nodes and document their locations. All

grossly negative lymph nodes should be sent for pathological examination in their entirety. For grossly positive ones, partial submission is acceptable.

Recommended tissue sample volume: not larger than 2 cm×1.5 cm×0.3 cm.

Disposal of specimens and retention period after sampling

Preservation of the remaining specimens

The remaining tissues shall be preserved in a standard fixative. The volume and concentration of the formaldehyde fixative must be maintained to prevent the specimens from drying up or decaying as a result of insufficient volume or decreased concentration, so that gross review or additional sampling may be possible upon receipt of clinical feedback on the last pathological report.

Time to specimen disposal

The remaining specimens are disposed at the hospital's discretion one month after issuance of the pathological report should no clinical feedback is submitted or reevaluation is justified by discrepancy between the current report and consultation results provided by another hospital.

Pathological types

Gross type: describe the tumor site and document the distance from carina.

Histological type: refer to the 2004 WHO histological classification of lung cancer (Table 1).

Pathology report

Requirements for biopsy pathology reports:

1. Describe the basic information of the patient and the specimen;
2. If intraepithelial neoplasia (dysplasia) is found, describe the classification;
3. If tumor is found, identify the histological type.

Requirements for surgical specimen pathology report:

1. Describe the basic information of the patient and the specimen;
2. Describe the gross specimen: measure the lung size and specify any other attached structures; specify the relationship between the tumor and lung lobes, segments and/or the main airway and the pleura; specify the distance from tumor to the bronchial margin, as well as those to other margins when necessary (i.e. chest wall, soft tissues, hilar vessels); indicate the tumor size and the presence of satellite nodules; and describe non-tumor lung tissues;
3. Diagnostic reports must include: (I) tumor location: in which site of the lungs and which lung lobe is the tumor located; if possible, specify the lung segment; (II) type of surgery: segmental resection, lobectomy, or

pneumonectomy, including partial lung resection; and (III) histological type, specifically: histological grade, histological evaluation of margins, pleural involvement, lymphatic vessel invasion, invasion of the surrounding nervous tissues and lymph node metastasis.

4. Major immunohistochemical findings for differential diagnosis: key screening indicators for squamous cell carcinoma (CK14, CK5/6, 34 β E12 and p63); screening indicators for lung adenocarcinoma (CK7 and TTF-1); and screening indicators for neuroendocrine carcinoma (CK18, AE1/AE3, CD56, CgA, NSE and Syn);
5. Other optional tests to inform medication and prognosis, if necessary: HER2, VEGF, p53, p170, Top2A, PCNA, Ki-67.

A complete pathological report begins from a complete, detailed pathological request form, which describes surgical findings and auxiliary examination results with lymph node status explicitly marked. Correct clinical staging and proper treatment is built on adequate communication, trust and collaboration between clinicians and pathologists.

Staging of lung cancer

Non-small cell lung cancer

At present, TNM staging of non-small cell lung cancer complies with the 7th Edition of TNM in Lung Cancer of the International Association for the Study of Lung Cancer (IASLC) Staging Committee in 2009.

Definitions of T, N, and M in the TNM staging of lung cancer:

1. Primary tumor (T)

TX: primary tumor cannot be assessed or tumor proved by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.

T₀: No evidence of primary tumor.

T_{is}: Carcinoma in situ.

T₁: Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus).

T_{1a}: Tumor 2 cm or less in greatest dimension.

T_{1b}: Tumor more than 2 cm but 3 cm or less in greatest dimension.

T₂: Tumor with any of the following features of size or extent: more than 3 cm but less than 7 cm in greatest dimension; involves main bronchus, 2 cm or more distal to the carina; invades the visceral pleura; associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung.

T_{2a}: Tumor more than 3 cm but 5 cm or less in greatest dimension and with any of the following features: more than 3 cm in greatest dimension; involves main bronchus, 2 cm or more distal to the carina; invades the visceral pleura; associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung.

T_{2b}: Tumor more than 5 cm but 7 cm or less in greatest dimension.

T₃: Tumor more than 7 cm or one that directly invades any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (less than 2 cm distal to the carina but without involvement of the carina); or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe.

T₄: Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe.

2. Regional lymph nodes (N)

N_x: Regional lymph nodes cannot be assessed.

N₀: No regional lymph node metastasis.

N₁: Metastasis in ipsilateral peribronchial or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension.

N₂: Metastasis in ipsilateral mediastinal or subcarinal lymph node(s).

N₃: Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s).

3. Distant metastasis (M)

M_x: Distant metastasis can not be assessed.

M₀: No distant metastasis.

M₁: Distant metastasis.

M_{1a}: Separate tumor nodule(s) in a contralateral lobe tumor with pleural nodules or malignant pleural (or pericardial) effusion.

M_{1b}: Extrathoracic distant metastasis.

Most pleural (and pericardial) effusions are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonblood and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element.

Small-cell lung cancer

Staging of small-cell lung cancer: limited and extensive disease staging is applied to patients receiving non-surgical

Invisible lung cancer	T _x , N ₀ , M ₀
0	T _{is} , N ₀ , M ₀
IA	T _{1a,b} , N ₀ , M ₀
IB	T _{2a} , N ₀ , M ₀
IIA	T _{1a,b} , N ₁ , M ₀ T _{2a} , N ₁ , M ₀ T _{2b} , N ₀ , M ₀
IIB	T ₂ , N ₁ , M ₀ T ₃ , N ₀ , M ₀
IIIA	T ₁ , N ₂ , M ₀ T ₂ , N ₂ , M ₀ T ₃ , N ₁ , M ₀ T ₃ , N ₂ , M ₀ T ₄ , N ₀ , M ₀ T ₄ , N ₁ , M ₀
IIIB	T ₄ , N ₂ , M ₀ Any T, N ₃ , M ₀
IV	Any T, any N, M _{1a,b}

procedures, and IASLC 2009 will be used for patients undergoing surgery.

Treatment

Treatment principles

A comprehensive treatment plan should be developed, i.e. to achieve radical cure or maximize the control of tumor and improve the cure rate, improve the patient's quality of life and prolong survival by a well-planned multidisciplinary treatment model (MDT) combining surgery, chemotherapy, radiotherapy and targeted biological therapy based on his/her conditions, tumor cytology, pathological type, extension (clinical stage) and development trends. Currently, the treatment of lung cancer is still built on surgery, radiotherapy and medication.

Surgery

Principles

Surgical resection is the mainstream treatment of lung cancer and the only way to achieve clinical cure. Common approaches include radical surgery and palliative surgery, where radical resection is always the ultimate goal as it may completely remove tumors, reduce tumor metastasis and recurrence, and conduct the final pathological TNM staging to inform postoperative comprehensive treatment. The following surgical principles must be observed for resectable lung cancer:

1. A comprehensive treatment plan and necessary imaging studies (clinical staging and examination) must be completed before non-emergency surgery. Surgical protocols should be based on a full assessment of the possibility of surgical resection;
2. Attempts should be made to completely remove tumors and regional lymph nodes while retaining functional lung tissues;
3. Video-assisted thoracoscopic surgery (VATS) is a rapidly developing minimally invasive surgical technique in recent years, particularly applicable to patients with stage I lung cancer;
4. Should the patient's physical condition allows, anatomic pulmonary resection (lobectomy, bronchial sleeve lobectomy or pneumonectomy) must be performed. Otherwise, limited resection -- pulmonary resection (preferred) or wedge resection -- or VATS may be chosen;
5. If complete resection (R0 surgery) is performed, hilar and mediastinal lymph nodes (N1 and N2 lymph nodes) must be removed, located and sent for pathology in addition to complete removal of the primary lesions. Sampling or dissection must be done at least for three mediastinal drainage areas (N2 groups) by making the best use of en bloc resection of lymph nodes. Preferably, dissection should include 2R, 3a, 3p, 4R and 7-9 groups of lymph nodes and the surrounding soft tissues of the right chest, and 4L and 5-9 groups of lymph nodes and the surrounding soft tissues of the left chest;
6. The surgery should in turn involve the pulmonary vein, pulmonary artery, and finally the bronchi;
7. The lung function (including bronchi or pulmonary artery) should be preserved as much as possible given that negative margins (including bronchial, pulmonary artery or vein ends) are confirmed by rapid intraoperative pathological examination in sleeve lobectomy. This may result in better quality of life after surgery compared with patients undergoing complete resection;
8. If recurrence or solitary pulmonary metastasis is present 6 months after complete resection of lung cancer, resection of the ipsilateral residual lung or metastatic lesions could be the choice as long as distant metastasis is excluded; and
9. Surgery-ineligible patients with stages I and II diseases due to cardiovascular conditions or other findings may receive radical radiotherapy, radiofrequency ablation and drug therapy as alternatives.

Indications

1. Stages I, II, III and some IIIa (T3N1-2M0, T1-2N2M0 and T4N0-1M0 can be completely resected) non-small cell lung cancer, and some small cell lung cancer (T1-

Squamous cell carcinoma	Squamous cell carcinoma, papillary subtype
	Squamous cell carcinoma, clear cell subtype
	Squamous cell carcinoma, small cell subtype
	Squamous cell carcinoma, basal cell subtype
Small cell carcinoma	Combined small cell carcinoma
Adenocarcinoma	Adenocarcinoma, mixed
	Alveolar adenocarcinoma
	Papillary adenocarcinoma
	Bronchioloalveolar carcinoma
	Bronchioloalveolar carcinoma, non-mucinous
	Bronchioloalveolar carcinoma, mucinous
	Bronchioloalveolar carcinoma, mucinous and non-mucus mixed or uncertain
	Solid carcinoma with mucus formation
	Fetal adenocarcinoma
	Mucinous (colloid) adenocarcinoma
Mucinous cystadenocarcinoma	
Signet ring cell carcinoma	
Clear cell adenocarcinoma	
Large cell carcinoma	Large cell neuroendocrine carcinoma
	Composite large cell neuroendocrine carcinoma
	Basal cell carcinoma
	Lymphoepithelial carcinoma
	Clear cell carcinoma
	Large cell carcinoma with rhabdoid phenotype
Adenosquamous carcinoma	
Sarcomatoid carcinoma	Pleomorphic carcinoma
	Spindle cell carcinoma
	Giant cell carcinoma
	Carcinosarcoma
	Pulmonary blastoma
Carcinoid	Typical carcinoid
	Atypical carcinoid
Salivary gland tumor	Mucoepidermoid carcinoma
	Adenoid cystic carcinoma
	Epithelial-myoepithelial carcinoma
Precancerous lesion	Squamous cell carcinoma in situ
	Atypical adenomatous hyperplasia
	Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

2N0-1M0);

2. Stage N2 non-small cell lung cancer responsive to neoadjuvant treatment (chemotherapy or chemotherapy plus radiotherapy);
3. Some stage IIIb non-small cell lung cancer (T4N0-1M0) if complete resection of localized lesion is possible,

including those involving the superior vena cava or adjacent to large blood vessels, heart, carina and so on;

4. Some stage IV non-small cell lung cancer with a single contralateral lung metastasis, single brain or adrenal metastasis; or
5. Surgical exploration is made when a definite diagnosis

Table 2. Karnofsky score (KPS, percentages).

100	Normal no complaints; no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self; unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospital admission is indicated although death not imminent.
20	Very sick; hospital admission necessary; active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly.
0	Dead.

Table 3. WHO response evaluation criteria in solid tumors.

1	Complete remission (CR): tumor disappears for more than 1 month.
2	Partial response (PR): the product of maximum tumor diameter and maximum vertical diameter decreases up to 50% and none of the other lesions increase for more than 1 month.
3	Stable disease (SD): product of two diameters reduces less than 50% or increases less than 25% for more than 1 month.
4	Disease progression (PD): product of two diameters increases more than 25%.

Table 4. RECIST response evaluation criteria.

Evaluation of target lesions:	Complete Response (CR): Disappearance of all target lesions. Partial Response (PR): At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD. Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started. Progression (PD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Evaluation of non-target lesions:	Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits. Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.
Evaluation of best overall response:	The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence. In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

is not possible for an intrapulmonary nodule highly suspected of lung cancer.

Contraindications

Surgery ineligibility or intolerability due to systemic conditions or poor functions of the heart, lung, liver, kidney and other vital organs; or

Most of the confirmed stage IV, a majority of stage IIIb and

some stage IIIa non-small cell lung cancer, as well as small cell lung cancer beyond the T1-2N0-1M0 stage.

Radiation therapy

Radiation therapy for lung cancer includes radical radiotherapy, palliative radiotherapy, adjuvant radiotherapy and prophylactic radiotherapy.

Table 5. Radiation Therapy Oncology Group (RTOG) scale for assessment of acute radiation-induced lung injury.

Grade 0:	no change.
Grade 1:	mild dry cough or difficulty breathing when tired.
Grade 2:	persistent cough that requires narcotic medication/breathing difficulty upon slight activity, but no difficulty breathing at rest.
Grade 3:	severe cough inresponsive to narcotic cough medicine, or difficulty breathing at rest/clinical or imaging evidence of acute radiation pneumonitis/intermittent oxygen or steroid treatment may be required.
Grade 4:	severe respiratory insufficiency/continuous oxygen or assisted ventilation.
Grade 5:	fatal.

Table 6. Zubrod-ECOG-WHO score (ZPS, 5-point scale).

0	Asymptomatic.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hour.
4	Bedbound.
5	Dead.

Table 7. Common first-line chemotherapy for NSCLC.

Chemotherapy protocol	Dose (mg/m ²)	Medication time	Cycle and duration
NP:			
Vinorelbine	25	d1, d8	
Cisplatin	80	D1.	q21d×4
TP:			
Paclitaxel	135-175	d1	
Cisplatin	75	d1	
Or carboplatin	AUC=5-6	d1	q21d×4
GP:			
Gemcitabine	1250	d1, d8	
Cisplatin	75	d1	
Or carboplatin	AUC=5-6	d1	q21d×4
DP:			
Docetaxel	75	d1	
Cisplatin	75	d1	
Or carboplatin	AUC=5-6	d1	q21d×4

Principles

1. Radical radiotherapy is applicable to patients with a KPS score ≥ 70 points (refer to Karnofsky score in Table 2), including those with inoperable early-stage non-small cell lung cancer, unresectable locally advanced non-small cell lung cancer and limited-stage small cell lung cancer due to iatrogenic and/or personal factors;
2. Palliative radiotherapy is used to reduce symptoms associated with primary lesions and metastases of advanced lung cancer. Whole-brain radiotherapy can be performed in patients who have a single brain metastasis of non-small cell lung cancer that is surgically removed;
3. Adjuvant radiotherapy is suitable for patients who have received preoperative radiotherapy and have positive surgical margins. Postoperative pN2-positive patients are

- encouraged to participate in clinical research;
4. The postoperative radiotherapy protocol should be built on surgical pathology reports and surgical records;
 5. Prophylactic radiotherapy is used as a whole-brain approach for patients with small cell lung cancer responsive to systemic treatment;
 6. Radiotherapy is usually performed in combination with chemotherapy for lung cancer. In view of different stages, treatment objectives and patients' general conditions, it may be combined with concurrent chemotherapy or sequential chemotherapy. Concurrent radio-chemotherapy uses EP and paclitaxel-containing treatment regimens;
 7. Patients should be informed before treatment of increased potential toxic side effects as a result of chemotherapy. Radiotherapy should be designed and implemented in such a way that the lungs, heart, esophagus and spinal cord are well protected. The risk of unplanned interruption due to improper treatment of toxic side effects should be minimized during radiotherapy;
 8. The application of other advanced techniques, such as three-dimensional conformal radiotherapy (3DCRT) and intensity modulated radiotherapy (IMRT), are recommended; and
 9. Adequate monitoring and supportive care should be provided to patients undergoing radiotherapy or chemotherapy during the rest period.

Indications of radiotherapy for non-small cell lung cancer (NSCLC)

Radiotherapy can be used as a radical treatment for early-stage NSCLC that is inoperable due to poor health status, or as a pre- and post-operative adjuvant therapy for operable lesions, local treatment for advanced, unresectable local lesions, and an important palliative approach for advanced incurable patients.

Radiotherapy is an effective way of local lesion control for surgery-ineligible patients with stage I NSCLC. For NSCLC patients that have negative surgical margins but positive mediastinal lymph nodes (pN2), the addition of postoperative radiotherapy is recommended to routine adjuvant chemotherapy. Postoperative concurrent radio-chemotherapy is recommended, if tolerable, for pN2 tumors with a positive margin. Radiotherapy should be initiated as soon as possible for margin-positive patients.

For patients with stages II to III NSCLC who are ineligible for surgery due to poor health status, concurrent radio-chemotherapy may be administered if tolerable. A more suitable radiotherapy plan and more aggressive supportive care may be provided to those in whom cure is possible during their radiotherapy or chemoradiotherapy, so as to minimize treatment interruption and dose reduction.

Some patients with widespread metastatic stage IV NSCLC

may accept palliative radiotherapy for both the primary tumor and metastases in order to reduce symptoms.

Indications of radiotherapy for small cell lung cancer (SCLC)

Complete remission is possible for some limited-stage SCLC patients through systemic chemotherapy. However, there is a high risk of intrathoracic recurrence if chest radiotherapy is not added. This addition may significantly reduce not only the local recurrence rate but also the risk of death.

In patients with extensive-stage SCLC, the addition of chest radiotherapy after chemotherapy of distant metastases also improves the tumor control rate and prolongs survival.

If the patient's conditions permit, radiotherapy for small cell lung cancer should be started as soon as possible -- simultaneous administration with chemotherapy may be considered. For large lesions where the lungs are at risk of being damaged by radiotherapy, 2-3 cycles of chemotherapy can be administered followed by radiotherapy as soon as possible.

Prophylactic cranial radiotherapy

For patients with limited-stage small cell lung cancer, prophylactic cranial radiotherapy is recommended following treatment if complete remission of intrathoracic lesions has been achieved. Prophylactic cranial radiotherapy may also reduce the risk of brain metastasis in patients with extensive-stage small cell lung cancer that is responsive to chemotherapy.

Decisions to start prophylactic whole-brain radiotherapy for patients with non-small cell lung cancer should be based on full communication between doctors and patients and the goal to balance individual benefits and risks.

Palliative radiotherapy for patients with advanced lung cancer

Palliative radiotherapy is provided for patients with advanced lung cancer to relieve local compression symptoms caused by primary tumors or metastases, pain caused by bone metastases, and neurological symptoms due to brain metastases. Low-dose fractionated radiotherapy may be considered in such patients for ease of treatment and rapid relief of symptoms.

Efficacy

Efficacy is assessed according to the WHO Response Evaluation Criteria in Solid Tumors (Table 3) or RECIST Response Evaluation Criteria (Table 4).

Protection

The lungs, heart, esophagus and spinal cord must be well protected when using conventional radiotherapy techniques to avoid serious radiological damage to vital organs. Acute radiation-induced lung injury is assessed according to the RTOG standards (Table 5).

Drug therapy for lung cancer

Drug therapy for lung cancer includes chemotherapy and molecular targeted therapy (EGFR-TKI therapy). Chemotherapy consists of palliative chemotherapy, adjuvant chemotherapy and neoadjuvant chemotherapy, which should be administered on strict indications and under the guidance of oncologists. The stages of disease, physical condition, adverse reactions, quality of life and patient's wishes should be taken into account when delivering chemotherapy to avoid over-treatment or inadequate treatment. Assessment of the chemotherapy efficacy should be conducted in a timely manner along with close monitoring and control of adverse reactions, so that drugs and/or doses could be adjusted accordingly.

Indications for chemotherapy: PS score ≤ 2 (5-point-scale ZPS score, Table 6), function reserve of vital organs enable the patient to tolerable chemotherapy; SCLC patients with a PS score up to 3 are also eligible. Patients are encouraged to participate in clinical trials.

Drug therapy for advanced NSCLC

1. First-line regimens: A platinum-based two-drug combination is the standard first-line treatment; patients with EGFR mutations may choose targeted therapy drugs. Anti-angiogenesis drugs may also be added when applicable. Currently available chemotherapy drugs are listed in Table 7. Patients who have achieved disease control (CR + PR + SD) by first-line therapy may choose maintenance therapy if conditions permit.
2. Second-line regimens: The second-line therapy options include docetaxel, pemetrexed and targeted drug EGFR-TKI; and
3. Third-line regimens EGFR-TKI may be used. Otherwise, patients may also be encouraged to participate in a clinical trial.

Drug therapy for unresectable NSCLC

A combination of radiotherapy and chemotherapy is recommended. The use of concurrent or sequential radio-chemotherapy may depend on the particular case. Etoposide/cisplatin or carboplatin (EP/EC) and paclitaxel or docetaxel/cisplatin are recommended for concurrent regimens. First-line therapy drugs can be used in sequential chemotherapy.

Perioperative adjuvant therapy for NSCLC

Three or four cycles of platinum-containing two-drug adjuvant chemotherapy are recommended after completely removal of stage II-III NSCLC. Postoperative adjuvant chemotherapy often begins 3-4 weeks after surgery when the patient's physical conditions have returned to normal.

Neoadjuvant chemotherapy: two cycles of preoperative

neoadjuvant chemotherapy with platinum-containing two-drug regimens may be considered for resectable stage III NSCLC. Timely assessment of the efficacy and monitoring of adverse reactions are needed to avoid surgical complications. Surgery is generally performed 2-4 weeks after the chemotherapy. Postoperative adjuvant therapy regimens are dependent on the preoperative staging and efficacy of neoadjuvant chemotherapy; maintenance or adjustment of the original protocol for tolerability considerations may be possible. The regimen may also be replaced if ineffective.

Drug therapy for small cell lung cancer (SCLC)

Radiotherapy and chemotherapy-based comprehensive treatment is recommended for limited-stage small cell lung cancer (stage II-III). EP or EC is recommended as chemotherapy regimens.

Chemotherapy-based comprehensive treatment is recommended for extensive-stage small cell lung cancer (stage IV). EP, EC or cisplatin plus topotecan (IP) or irinotecan (IC) are recommended as the chemotherapy drugs.

Topotecan is a recommended second-line option. Patients are encouraged to participate in new drug clinical studies.

Principles of cancer chemotherapy

1. Patients with KPS < 60 or ECOG > 2 are not candidates for chemotherapy;
2. Patients whose white blood cell count is less than $3.0 \times 10^9/L$, neutrophil count less than $1.5 \times 10^9/L$, platelet count less than $6 \times 10^{10}/L$, red blood cell count less than $2 \times 10^{12}/L$ and hemoglobin less than 8.0 g/dl are not candidates for chemotherapy in principle;
3. Patients with liver and kidney dysfunction, abnormal laboratory indicators (higher than 2 times normal), or those who have serious complications and infections, fever or bleeding predisposition are not candidates for chemotherapy;
4. Discontinuation or change of chemotherapy regimens should be considered if the following occurs: Disease progression after 2 cycles of therapy, or deterioration again during the rest period, which requires discontinuation of the original regimen and switch to others; grade 3/4, obviously life-threatening adverse reactions; or serious complications, which requires discontinuation of the current regimen and switch to another for the next treatment course; and
5. Standardized and individualized chemotherapy protocols are key to successful treatment. The basic requirements of chemotherapy should be followed. In addition to routine antiemetic drugs, hydration and diuretics are required for platinum-based regimens except for carboplatin. Blood tests are performed twice a week after chemotherapy;

6. Efficacy is assessed according to the WHO Response Evaluation Criteria in Solid Tumors.

Stage-based treatment for non-small cell lung cancer

Combined treatment for stage I non-small cell lung cancer

1. Surgery is always the treatment of choice, including lobectomy plus hilar and mediastinal lymph node dissection; thoracotomy or VATS can be used;
2. For patients with poor lung function, anatomic pulmonary segment or wedge resection plus hilar and mediastinal lymph node dissection may be considered;
3. Patients undergoing complete resection of stage IA lung cancer are not candidates for postoperative adjuvant chemotherapy;
4. Routine use of adjuvant chemotherapy not recommended in patients with completely resected stage IB lesions;
5. Re-operation is recommended for stage I patients with positive surgical margins. Postoperative chemotherapy and radiotherapy is preferred for patients not suitable for reoperation, regardless of reasons.

Combined treatment for stage II non-small cell lung cancer

1. Surgical treatment is preferred, including lobectomy, double lobectomy or pneumonectomy plus hilar and mediastinal lymph node dissection;
2. For patients with poor lung function, anatomic pulmonary segment or wedge resection plus hilar and mediastinal lymph node dissection may be considered;
3. Postoperative adjuvant chemotherapy is recommended for those undergoing complete resection of stage 2 non-small cell lung cancer;
4. En bloc resection should be performed if pleural or chest wall invasion is present. Resection of ribs, at least from recent lesions of the upper and lower edge 2cm, invaded rib resection should be at least when away from the tumor 5cm.
5. Reoperation is recommended for stage II patients with positive surgical margins. Postoperative chemotherapy plus radiotherapy is preferred for patients not suitable for reoperation, regardless of reasons.

Combined treatment for stage III non-small cell lung cancer

Locally advanced non-small cell lung cancer refers to stage III lung cancer according to the TNM staging system. Comprehensive treatment is the best option for stage III non-small cell lung cancer. There are two types of locally advanced NSCLC: resectable and unresectable, where:

1. Resectable locally advanced non-small cell lung cancer includes:
T₃N₁ NSCLC, for which surgical treatment is preferred followed by postoperative adjuvant chemotherapy;

N₂ lung cancer, for which surgery is controversial. Preoperative mediastinoscopy is recommended for those with a single set of enlarged mediastinal lymph nodes, or two sets of enlarged mediastinal lymph nodes without fusion and complete resection is expected, as revealed by imaging approaches. Preoperative neoadjuvant chemotherapy followed by surgical treatment may be performed upon definite diagnosis;

For some T₄N₀₋₁ tumors: (I) satellite nodules within a single lobe: these are stage T₃ as per the new staging system and the treatment of choice is surgical resection; preoperative neoadjuvant chemotherapy and postoperative adjuvant chemotherapy can also be considered; (II) for other resectable T₄N₀₋₁ non-small cell lung cancer, neoadjuvant chemotherapy or surgical resection may be preferred. Adjuvant chemotherapy may be considered after complete resection. In the case of positive margins, postoperative radiotherapy and platinum-based chemotherapy are justified.

Treatment for Pancoast tumors: concurrent radio-chemotherapy followed by surgery plus adjuvant chemotherapy is recommended for some of the operable patients. For inoperable Pancoast tumor, radiotherapy and chemotherapy should be performed;

2. Unresectable locally advanced non-small cell lung cancer includes:
mediastinoscopy-positive non-small cell lung cancer with radiologically indicated massive mediastinal shadow; most of the T₄ and N₃ non-small cell lung cancer; T₄N₂₋₃ patients; patients with pleural metastases, malignant pleural effusion and malignant pericardial effusion have been classified as M1 as per the new staging system, and are not candidates for surgery. Some cases may receive thoracoscopic pleural biopsy or pleurodesis.

Treatment for stage IV non-small cell lung cancer

Before treatment is initiated, a testing may be necessary to identify mutations in the epidermal growth factor receptor (EGFR). Subsequent treatment strategies may be developed in view of the EGFR mutation status.

Systemic treatment is the main approach to managing stage IV lung cancer, as the treatment would aim to improve the patient's quality of life and prolong survival.

1. Treatment for solitary metastasis of stage IV lung cancer
For solitary brain metastasis from resectable non-small cell lung cancer, the brain lesion can be resected or subject to stereotactic radiotherapy, while the primary lesion is treated according to the stage-based treatment schemes; For solitary adrenal metastasis from resectable non-small cell lung cancer, the adrenal lesions may be resected while

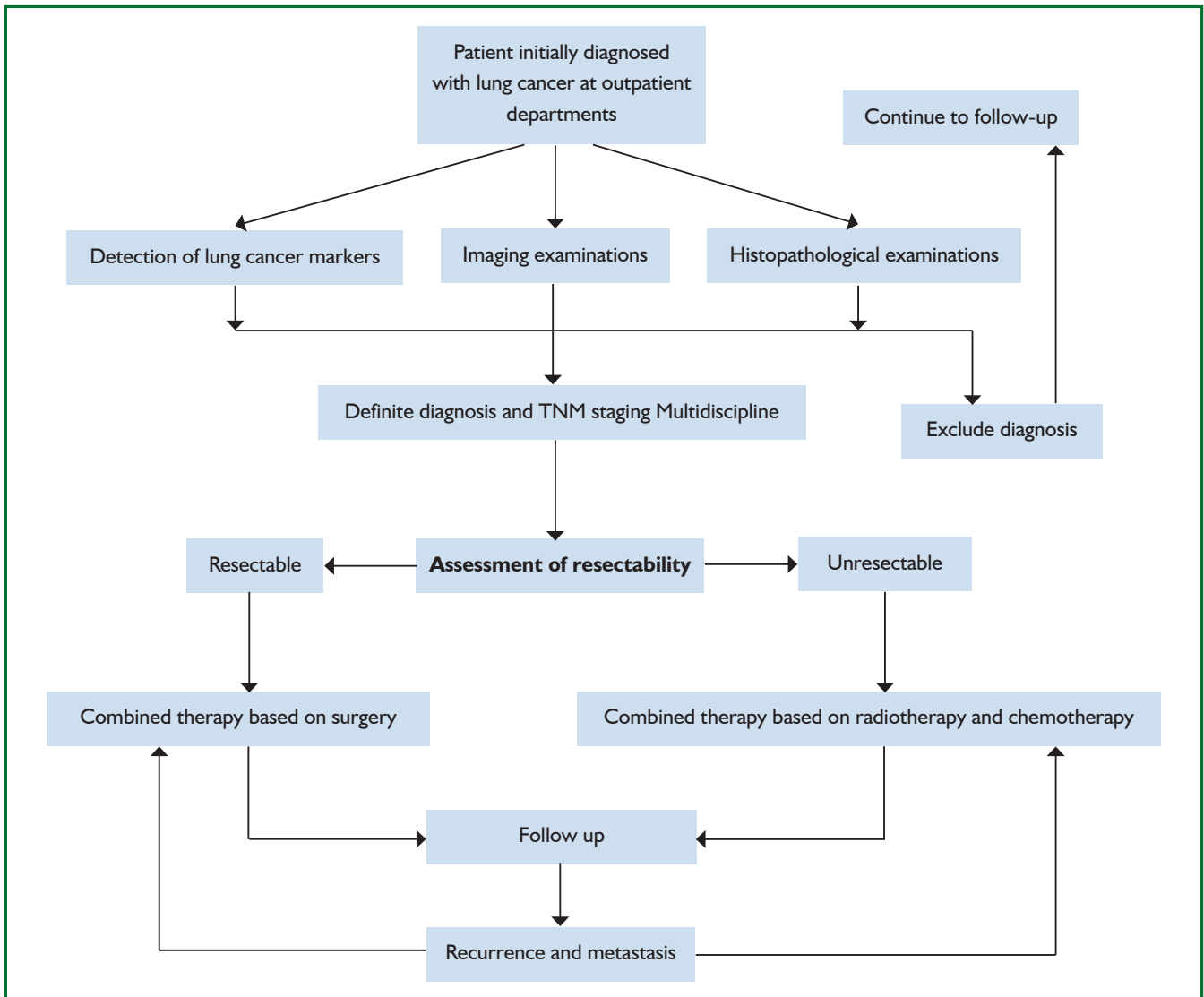


Figure 1. Process of lung cancer diagnosis and treatment.

the primary lesion is treated according to the stage-based treatment schemes;

Stage-specific treatment is conducted for other solitary nodules in the ipsilateral or contralateral lung.

2. Systemic treatment for stage IV lung cancer

Gefitinib or erlotinib first-line treatment is recommended for stage IV non-small cell lung cancer harboring sensitive EGFR mutations;

For stage IV non-small cell lung cancer with wild-type or unknown mutant EGFR status and a functional status score PS between 0 and 1, platinum-containing two-drug chemotherapy should be initiated as soon as possible. Non-platinum-based two-drug regimens may be considered for those ineligible for platinum-containing chemotherapy;

Cytotoxic single-drug chemotherapy is used for advanced non-small cell lung cancer with PS=2, though there is no evidence that it is suitable for patients with PS>2;

Current evidence does not support age as a basis for chemotherapy selection;

Docetaxel and pemetrexed second-line chemotherapy, as well as gefitinib or erlotinib second- or third-line oral treatment, are recommended following failure of first-line chemotherapy for non-small cell lung cancer;

Optimal supportive care alone can be considered for patients with stage IV non-small cell lung cancer whose PS is higher than 2.

In addition to systemic treatment, proper local treatment may be used based on specific local conditions in order to improve symptoms and the patient's quality of life.

Stage-based treatment for small cell lung cancer

Stage I SCLC: Surgery plus adjuvant chemotherapy (EP/EC, 4-6 cycles).

Stage II-III SCLC: radiotherapy plus chemotherapy.

1. Sequential or concurrent protocols may be selected;
2. Recommended sequential therapy includes 2 cycles of induction chemotherapy followed by concurrent radio-chemotherapy;
3. Prophylactic cranial irradiation (PCI) is recommended for patients who have achieved disease control after standard treatment.

Stage IV SCLC: Chemotherapy-based comprehensive therapy with a view to improve the quality of life.

Recommended first-line drugs include EP/EC, IP and IC. Patients with recurrence or progression within 3 months of standard treatment are encouraged to participate in clinical trials. Topotecan, irinotecan, gemcitabine or paclitaxel may be considered for patients with recurrence within 3-6 months. The initial treatment program may be used for those having disease

progression beyond 6 months.

Treatment and follow-up process

Process of lung cancer diagnosis and treatment

Refer to Figure 1 for the general diagnosis and treatment process.

Follow-up

A complete set of medical records and related documents should be maintained for patients newly diagnosed as lung cancer, and regular follow-ups should be scheduled for necessary examinations. Examinations may involve medical history, physical examination, blood tests, imaging and endoscopy, with an attempt to monitor recurrence or treatment-related adverse events and/or evaluate the quality of life. The follow-up frequency is every 3 to 6 month in the first 2 years after treatment, every 6 months from 2 to 5 years, and every one year from the fifth year.

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