
به‌نام مهربانترین
In the name of the most compassionate

LUNG CANCER

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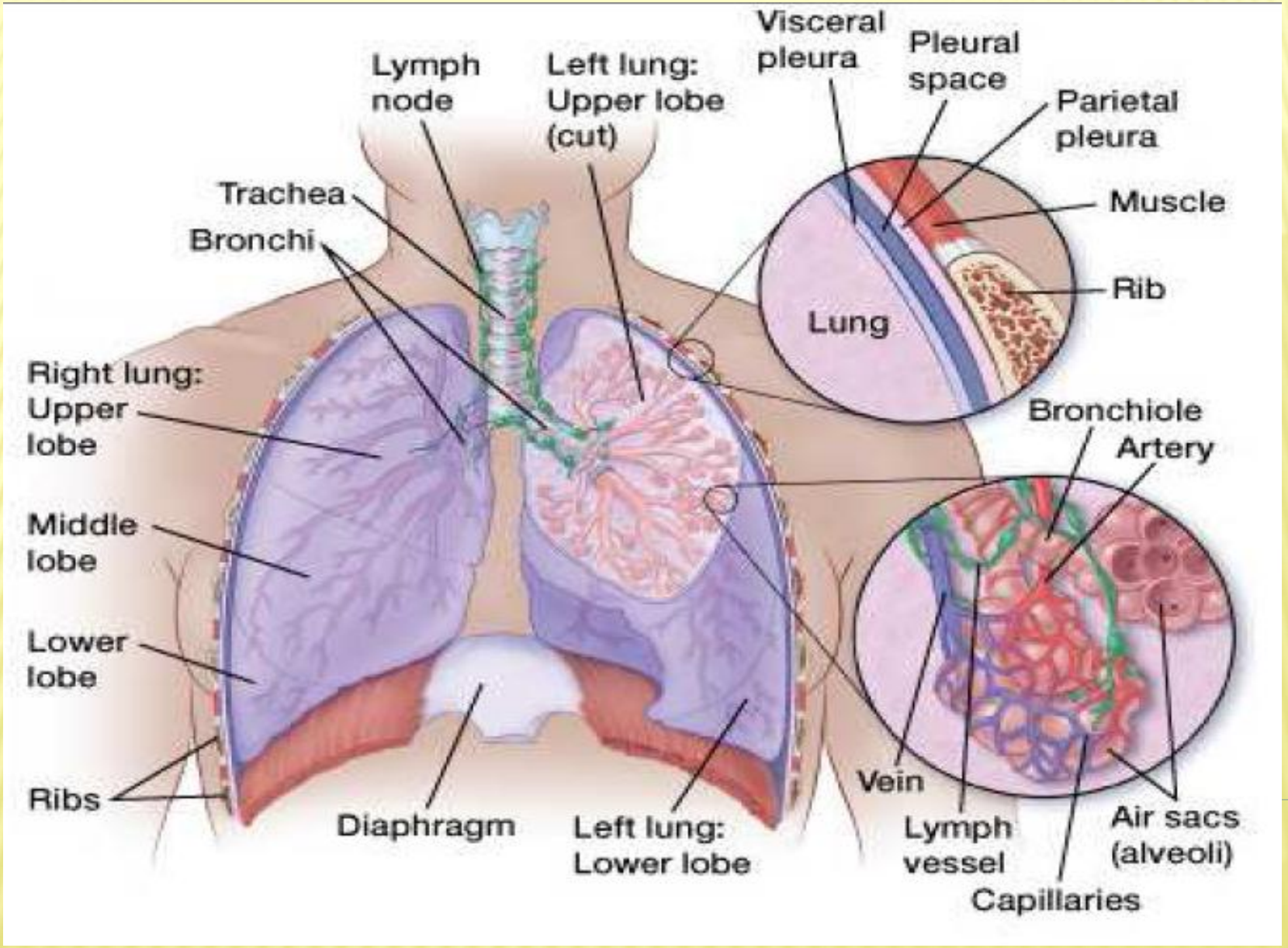
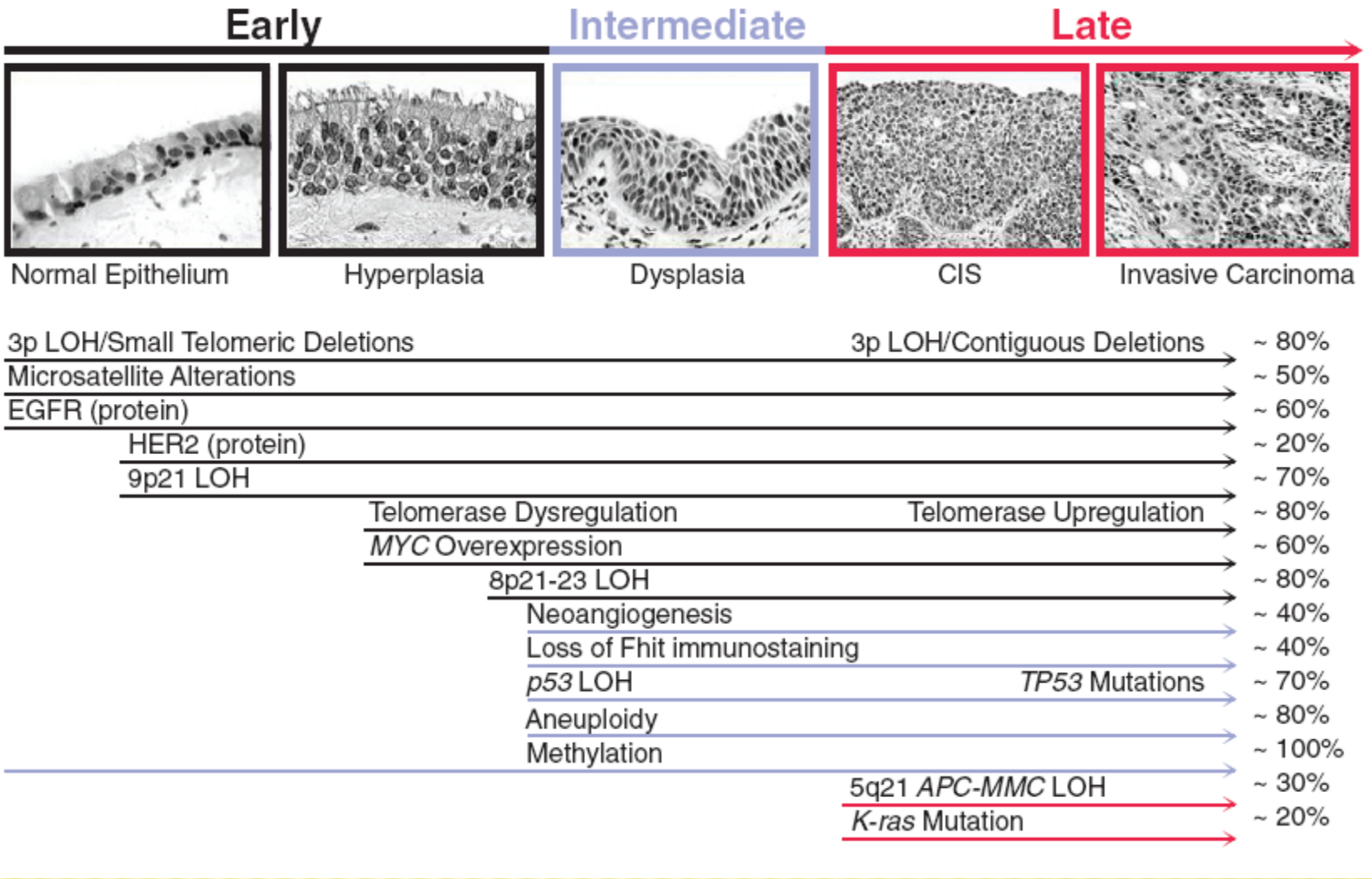
PULMONOLOGIST


Lymph node
Left lung: Upper lobe (cut)
Visceral pleura
Pleural space
Parietal pleura
Trachea
Bronchi
Muscle
Rib
Lung
Right lung: Upper lobe
Middle lobe
Lower lobe
Bronchiole
Artery
Ribs
Diaphragm
Left lung: Lower lobe
Vein
Lymph vessel
Air sacs (alveoli)
Capillaries

Lung cancer (e.g., bronchogenic carcinoma) arises from the respiratory epithelium. Lung cancer is divided into two major histologic groups: non–small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC accounts for approximately 85% of all lung cancer. Other less common pulmonary neoplasms include adenosquamous carcinoma, carcinoid tumors, bronchial gland tumors, soft tissue tumors (e.g., sarcomas), pulmonary blastomas, and lymphoma.

Worldwide, lung cancer accounts for approximately 13% of all cancer; more than 1.1 million cases of lung cancer are diagnosed annually, and more than 1 million deaths are caused by the disease. In the United States, 28% of all annual cancer deaths (30% in men, 26% in women) are due to lung cancer; lung cancer is the leading cause of cancer death in both men and women.

in men in the 1950s and in women 10 to 15 years later. Cancer death rates from lung cancer decreased in men by 37% between 1990 and 2005; however, in women, the cancer death rate from lung cancer between 1991 and 2005 increased approximately 8%. Worldwide, increasing lung cancer rates are predicted to continue in less developed countries as a result of increasing endemic use of tobacco.



Sequential changes during the pathogenesis of lung cancer.
CIS = carcinoma in situ; LOH = loss of heterozygosity.

Tobacco

It is estimated that cigarette smoking is responsible for approximately 85 to 90% of all cases of lung cancer, including 90% of cases in men and 80% in women. More than 40 carcinogens have been identified in cigarette smoke

The risk for development of lung cancer correlates with the number of cigarettes smoked per day, lifetime duration of smoking, age at onset of smoking, degree of inhalation, tar and nicotine content of the cigarettes, and use of unfiltered cigarettes.

Environmental Tobacco Smoke

Exposure to environmental tobacco smoke (i.e., passive smoking) by nonsmokers, especially in the workplace, increases the risk for the development of lung cancer. The exposure levels of environmental tobacco smoke depend on the size of the enclosed space and the intensity of smoking.

Other Exposure

The International Agency for Research on Cancer classified the following as group 1 known carcinogens for lung cancer: radon, asbestos, arsenic, beryllium, bis(chloromethyl)ether, cadmium, chromium, nickel, vinyl chloride, and polycyclic aromatic hydrocarbons (PAHs)

Group 2A probable carcinogens include acrylonitrile, formaldehyde, and diesel exhaust.

Group 2B possible carcinogens include acetaldehyde, silica, and welding fumes.

It is estimated that 9% of lung cancers in men and 2% in women are caused by occupational exposure.

Preexisting Lung Disease

Patients with COPD have an approximately four-fold increased risk for lung cancer. In addition, patients in whom idiopathic pulmonary fibrosis or pulmonary fibrosis from asbestosis or silica develops are at increased risk for the development of lung cancer.

Dietary Factors

Increased consumption of fruits and green and yellow vegetables is associated with a reduced risk for lung cancer, whereas low serum concentrations of antioxidant vitamins such as vitamins A and E are associated with the development of lung cancer. However, β-carotene supplementation increases the
incidence of lung cancer.

Increased consumption of dietary fat is also associated with an increased incidence of lung cancer. High blood concentrations of selenium, a mineral involved in the protection of cellular membranes, has been associated with a lower risk for lung cancer.

Gender and Racial Differences

Women who smoke have a 1.2- to 1.7-fold higher risk ratio than men, especially for adenocarcinoma and SCLC. Possible explanations for this difference in lung cancer risk include (1) effects of hormones such as estrogen on the development of lung cancer, (2) gender differences in nicotine metabolism, and (3) gender variations in cytochrome P-450 enzymes involved in the bioactivation of toxic components in cigarette smoke condensate.

The high incidence and mortality of lung cancer in African American males may be due, in part, to (1) increased tobacco use, (2) differences in the metabolism of tobacco smoke, and (3) higher intake of dietary fat.

Inheritance

First-degree relatives of patients with lung cancer have a two- to six-fold increase in the risk for lung cancer after adjusting for tobacco use. Second-degree relatives of lung cancer patients have a relative risk of 1.28, and third-degree relatives have a relative risk of 1.14. Nonsmokers with a family history of lung cancer have a two- to four-fold increased risk for lung cancer.

The familial risk may be due to shared exposure, such as environmental tobacco smoke, or to shared genetic susceptibility to environmental carcinogens.

The development of lung cancer is the result of a multistep process from a premalignant lesion to frank cancer after a number of years. Tobacco smoke or other carcinogens promote sequential genetic and epigenetic changes that result in the loss of normal control mechanisms of cellular growth.

These changes affect (1) oncogenes, which are homologues of normal cellular genes and, when mutated, result in activation and gain of function; (2) tumor suppressor genes, which are "cancer" genes, in which loss of function by mutation removes inhibitions to control cell growth;

Oncogenes

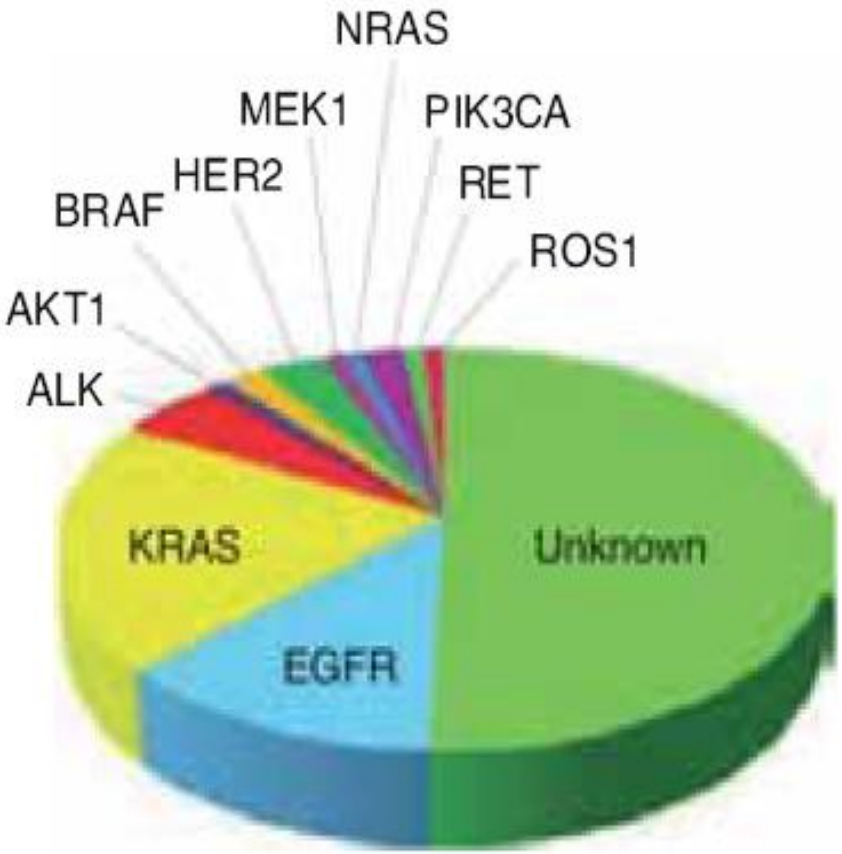
The oncogenes that play a role in the pathogenesis of lung cancer include ras, the myc family, HER-2/neu (ERBB2), and Bcl-2. The ras family of oncogenes

Tumor Suppressor Genes

Tumor suppressor genes include p53, Rb, and 3p

Growth Factors

Autocrine (peptide) growth factors that areimportant in the growth of lung cancer cells, particularly SCLC, include gastrin-releasing peptide (GRP),insulin-like growth factor type I (IGF-I), and hepatocyte growth factor



Frequency of driver mutations in NSCLC	
AKT1	1%
ALK	3–7%
BRAF	1–3%
EGFR	10–35%
HER2	2–4%
KRAS	15–25%
MEK1	1%
NRAS	1%
PIK3CA	1–3%
RET	1–2%
ROS1	1–2%

FIGURE 107-2 **Driver mutations** in adenocarcinomas.

Epigenetics

Epigenetics refers to a change in gene expression that is heritable but does not involve a change in DNA sequence. One of these epigenetic modifications involves changes in DNA methylation. These changes, which are very common in lung cancer, can include hypomethylation, dysregulation of DNA methyltransferase I, and hypermethylation. Genes that are methylated in NSCLC include p16, RAR-β, RASSFIA, methylguanine-methyltransferase, and death-associated protein kinase (DAP-kinase). This hypermethylation can silence tumor suppressor

As many as 15% of patients in whom lung cancer is diagnosed are initially asymptomatic. The diagnosis is usually made incidentally on a chest radiograph obtained for other reasons (e.g., a preoperative study). However, most patients have symptoms and signs that are (1) caused by the pulmonary lesion itself—local tumor growth, invasion, or obstruction; (2) intratho-racic—regional tumor spreading to lymph nodes and adjacent structures; (3) extrathoracic—distant spread of disease; and (4) paraneoplastic syndromes.

COUGH
(persistent or worsening)

COUGHING UP BLOOD

CHEST PAIN

SHORTNESS OF BREATH

WHEEZING

HOARSENESS

UNEXPLAINED WEIGHT LOSS

BONE PAIN

HEADACHE

Pulmonary Lesion

Intrathoracic Spread

Dysphagia
Hoarseness
hemidiaphragmatic elevation
pleural effusion
pericardial effusion

Extrathoracic Spread

Bone metastasis
Liver metastases
Adrenal metastases
Brain metastases

Paraneoplastic Syndromes

Apical tumors, such as superior sulcus NSCLC (Pancoast's syndrome), may cause Horner's syndrome ,pain secondary to rib destruction, atrophy of hand muscles, and pain in the distribution of the C8, T1, and T2 nerve roots because of tumor invasion of the brachial plexus.

miosis (a constricted pupil), partial ptosis (a weak, droopy eyelid), apparent anhidrosis (decreased sweating), with or without enophthalmos (inset eyeball).

System	Paraneoplastic Syndrome
Musculoskeletal	Clubbing Hypertrophic osteoarthropathy Polymyositis Osteomalacia Myopathy
Cutaneous	Dermatomyositis Acanthosis nigricans Pruritus Erythema multiforme Hyperpigmentation Urticaria Scleroderma
Endocrinologic	Cushing syndrome Syndrome of inappropriate secretion of antidiuretic hormone Hypercalcemia Carcinoid syndrome Hyperglycemia/hypoglycemia Gynecomastia Galactorrhea Growth hormone excess Calcitonin secretion Thyroid-stimulating hormone
Neurologic	Lambert-Eaton myasthenic syndrome Peripheral neuropathy Encephalopathy Myelopathy Cerebellar degeneration Psychosis Dementia
Vascular/ hematologic	Thrombophlebitis Arterial thrombosis Nonbacterial thrombotic endocarditis Thrombocytosis Polycythemia Hemolytic anemia Red cell aplasia Dysproteinemia Leukemoid reaction Eosinophilia Thrombocytopenic purpura
Miscellaneous	Cachexia Hyperuricemia Nephrotic syndrome

TABLE 107-4 PRESENTING SIGNS AND SYMPTOMS OF LUNG CANCER

Symptom and Signs	Range of Frequency
Cough	8–75%
Weight loss	0–68%
Dyspnea	3–60%
Chest pain	20–49%
Hemoptysis	6–35%
Bone pain	6–25%
Clubbing	0–20%
Fever	0–20%
Weakness	0–10%
Superior vena cava obstruction	0–4%
Dysphagia	0–2%
Wheezing and stridor	0–2%

Source: Reproduced with permission from MA Beckles: Chest 123:97-104, 2003

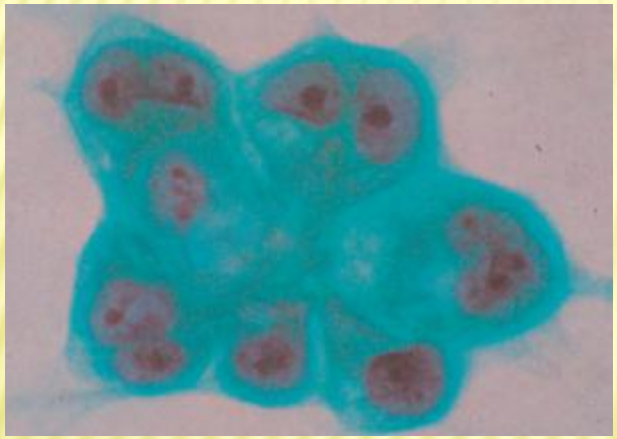
TABLE 107-5 CLINICAL FINDINGS SUGGESTIVE OF METASTATIC DISEASE

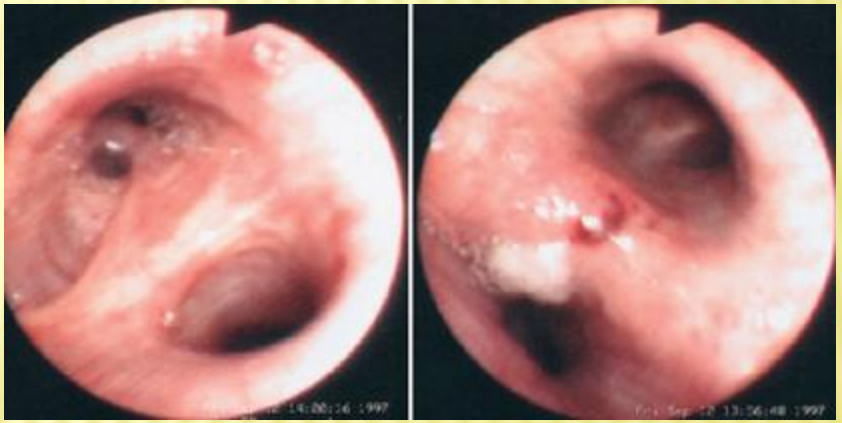
Symptoms elicited in history	• Constitutional: weight loss >10 lb • Musculoskeletal: focal skeletal pain • Neurologic: headaches, syncope, seizures, extremity weakness, recent change in mental status
Signs found on physical examination	• Lymphadenopathy (>1 cm) • Hoarseness, superior vena cava syndrome • Bone tenderness • Hepatomegaly (>13 cm span) • Focal neurologic signs, papilledema • Soft-tissue mass
Routine laboratory tests	• Hematocrit, <40% in men; <35% in women • Elevated alkaline phosphatase, GGT, SGOT, and calcium levels

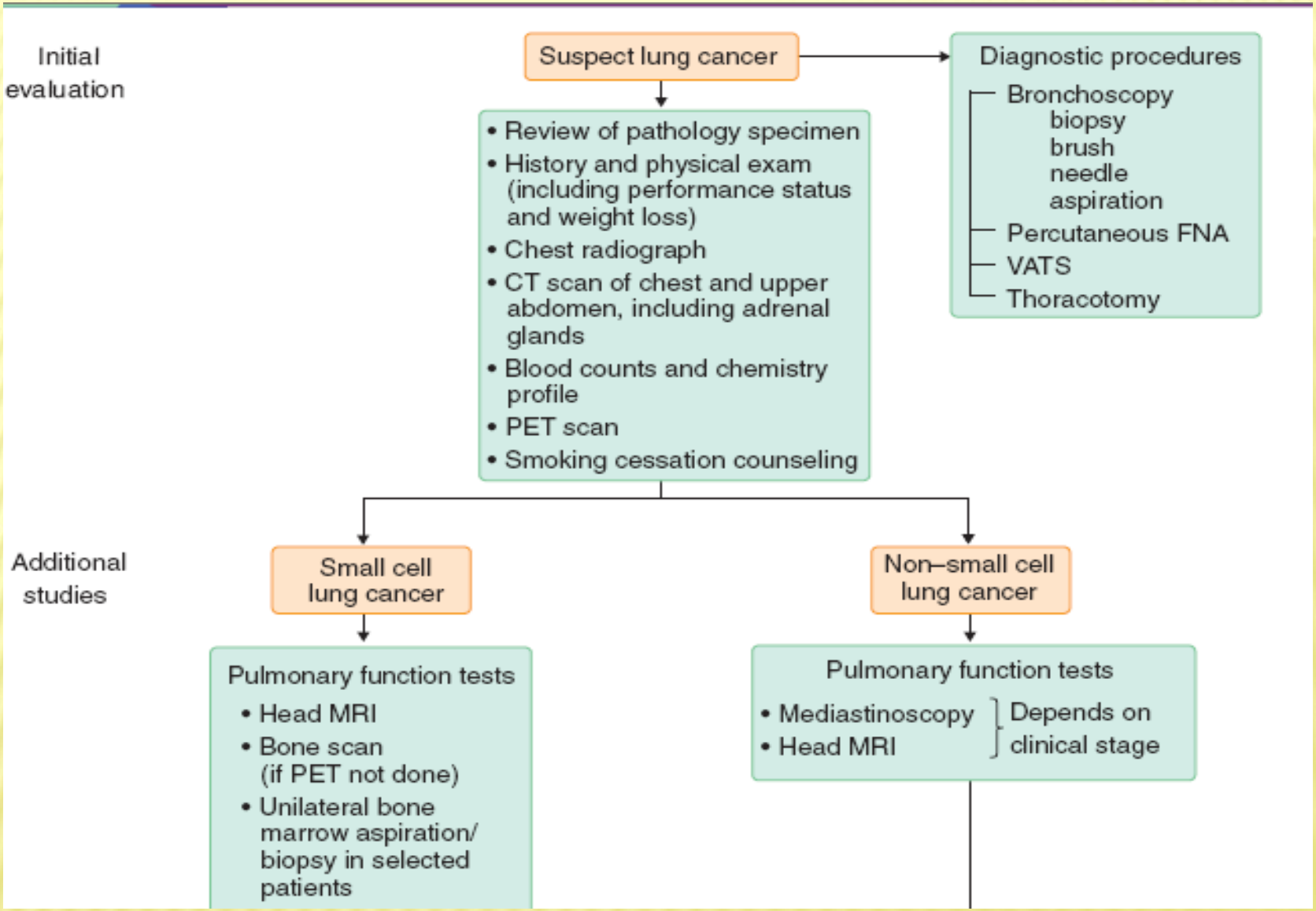
Abbreviations: GGT, gamma-glutamyltransferase; SGOT, serum glutamic-oxaloacetic transaminase.

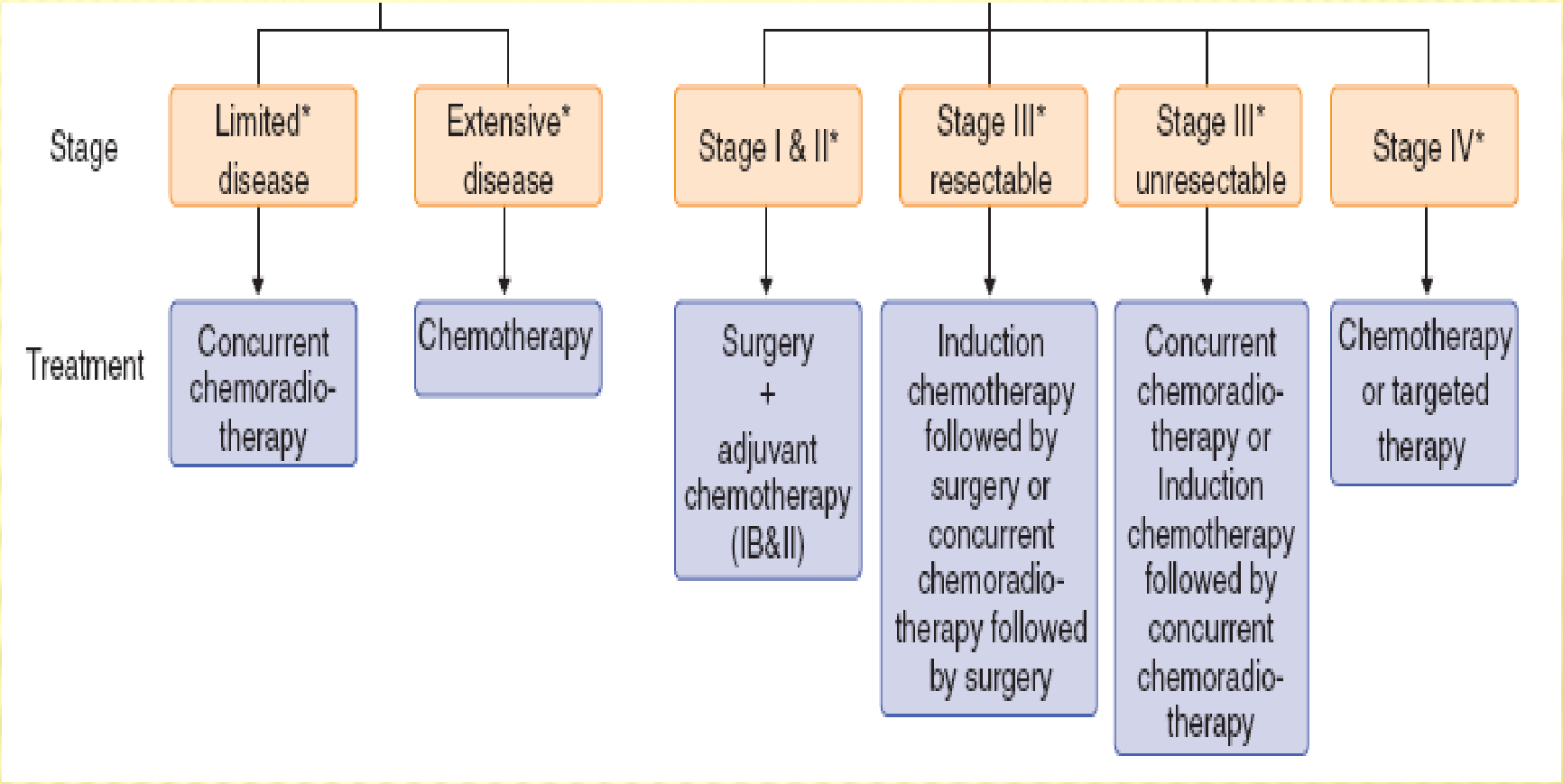
Source: Reproduced with permission from GA Silvestri et al: Chest 123(1 Suppl):147S, 2003.

The diagnosis of lung cancer is made by cytologic examination of tissue biopsy specimens, sputum (Fig. 197-2), bronchial washings and brushings of suspicious lesions (Fig. 197-3), bronchoalveolar lavage fluid, and transbronchial and transthoracic needle aspirates (Fig. 197-4).






Initial evaluation
Suspect lung cancer
Diagnostic procedures
Bronchoscopy
biopsy
brush
needle
aspiration
Percutaneous FNA
VATS
Thoracotomy
• Review of pathology specimen
• History and physical exam (including performance status and weight loss)
• Chest radiograph
• CT scan of chest and upper abdomen, including adrenal glands
• Blood counts and chemistry profile
• PET scan
• Smoking cessation counseling
Additional studies
Small cell lung cancer
Non–small cell lung cancer
Pulmonary function tests
• Head MRI
• Bone scan (if PET not done)
• Unilateral bone marrow aspiration/ biopsy in selected patients
Pulmonary function tests
• Mediastinoscopy
• Head MRI
Depends on clinical stage



CT = computed tomography;FNA = fine-needle aspiration;
MRI = magnetic resonance imaging; PET = positron emission tomography;VATS = video-assisted thoracic surgery.

(SPN)SOLITARY PULMONARY NODULE

A solitary pulmonary nodule is a asymptomatic lesion less than 3 cm indiameter surrounded by normal lung parenchyma that is incidentally found on a chest radiograph or computed tomography (CT) scan

on a chest radiograph or computed tomography (CT) scan . A SPN is found in up to 0.2% of all chest radiographs, and 10 to 70% are malignant.

Pathology

The histologic classification of lung cancer includes adenocarcinoma (about 40%), squamous cell (epidermoid) carcinoma (~30%), large cell carcinoma (~15%), and small cell carcinoma (~15%). These four histologic types represent more than 95% of all lung cancer.

Squamous cell carcinoma and adenocarcinoma are further classified by their
differentiation: well differentiated, moderately differentiated, and poorly differentiated. The latter types of cells are more aggressive and may have a worse prognosis than well-differentiated tumors.

Adenocarcinoma is the most frequent histologic type in women and nonsmokers. Bronchoalveolar carcinoma, a subtype of adenocarcinoma, is well differentiated, grows along intact alveolar septa, and can be localized, multinodular, multifocal, or diffuse.

Staging

Staging of NSCLC involves classification according to T (tumor size), N (regional lymph node involvement), and M (presence or absence of distant metastases).

For SCLC, TNM staging is not generally used; rather, SCLC is staged as limited disease, defined as disease that can be encompassed by a single radiation portal, or extensive disease, that
extending beyond a single radiation portal (usually metastatic).

Staging Procedures

All patients with lung cancer should be clinically staged using a complete history with a focus on performance status and weight loss; physical examination; pathologic review of all biopsy material; complete blood cell and platelet
counts; chemistry profile, including renal and liver function tests, electrolytes, glucose, calcium, and phosphorus; and chest radiograph and chest CT (including the upper part of the abdomen and adrenal glands).

Magnetic resonance imaging (MRI) of the brain and radionuclide scan of bones should be performed if metastases to these organs are suspected. Radiographs or MRI should be obtained if bone lesions are suggested by radionuclide scanning. PET is used to assess both regional and metastatic spread of tumor. Pulmonary function tests and arterial blood gas determinations should be obtained only if needed for treatment purposes.

For patients with SCLC, the initial pretreatment staging evaluation is similar to that used for NSCLC patients. For patients with peripheral blood count abnormalities, bone marrow aspiration and biopsy are recommended. Twenty to 30% of patients with SCLC will have tumor in bone marrow at the time of diagnosis.

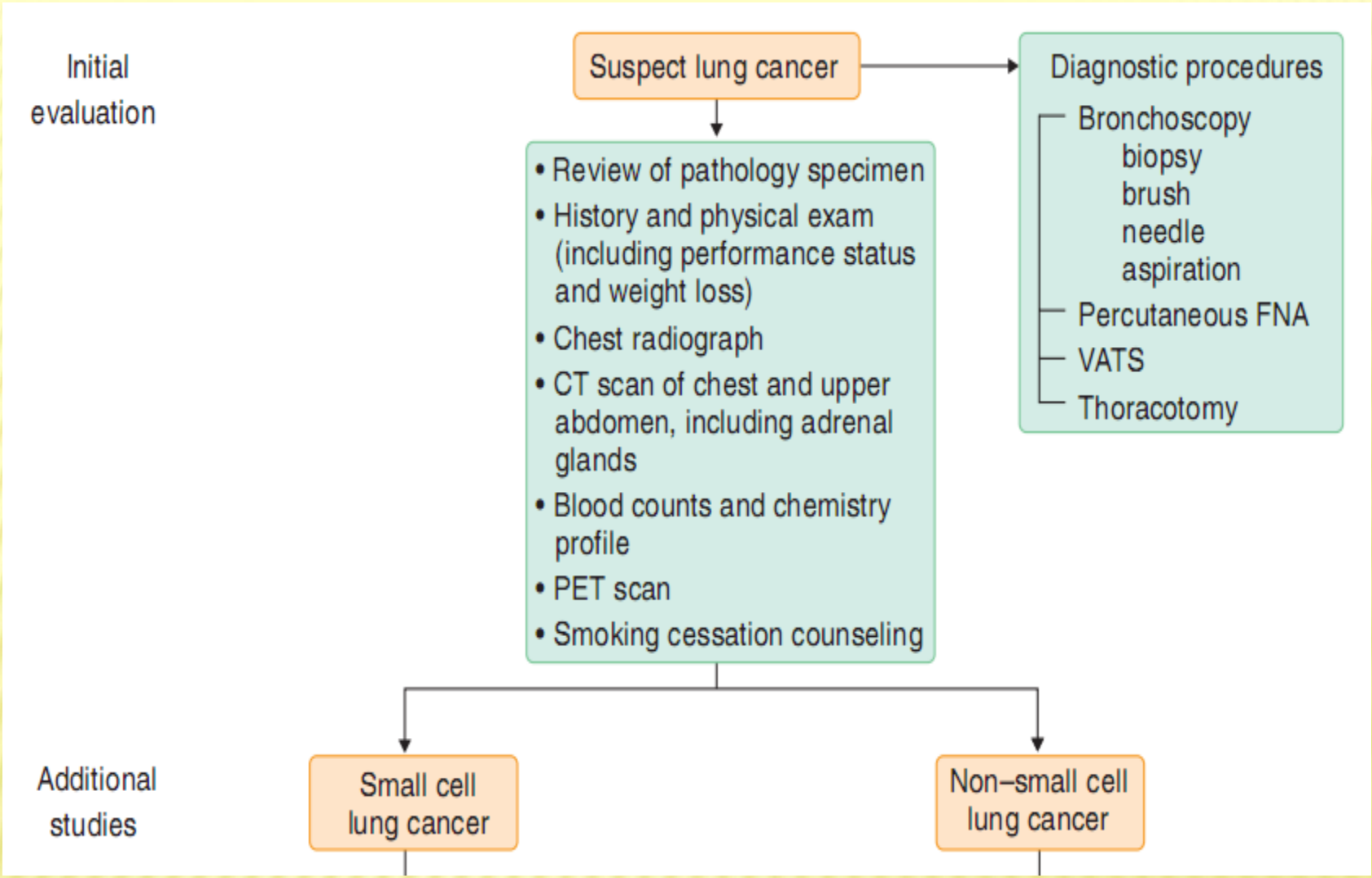
Imaging

Radiography

A standard posteroanterior and lateral chest radiograph, although inexpensive and easy to perform, has limited value in the staging of lung cancer.

Computed Tomography

A CT scan is commonly used to evaluate whether lung cancer is present in the hilar and mediastinal lymph nodes, liver, and adrenal glands, but its accuracy in identifying mediastinal lymph node involvement is suboptimal (sensitivity of 40 to 65% and specifcity of 45 to 90% versus either a PET scan or mediastinoscopy). PET, which uses 2-[18F]fuoro-2-deoxy-d-glucose to identify areas of increased glucose metabolism in lung tumors, is more sensitive than CT in staging lung cancer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• Review of pathology specimen
• History and physical exam (including performance status and weight loss)
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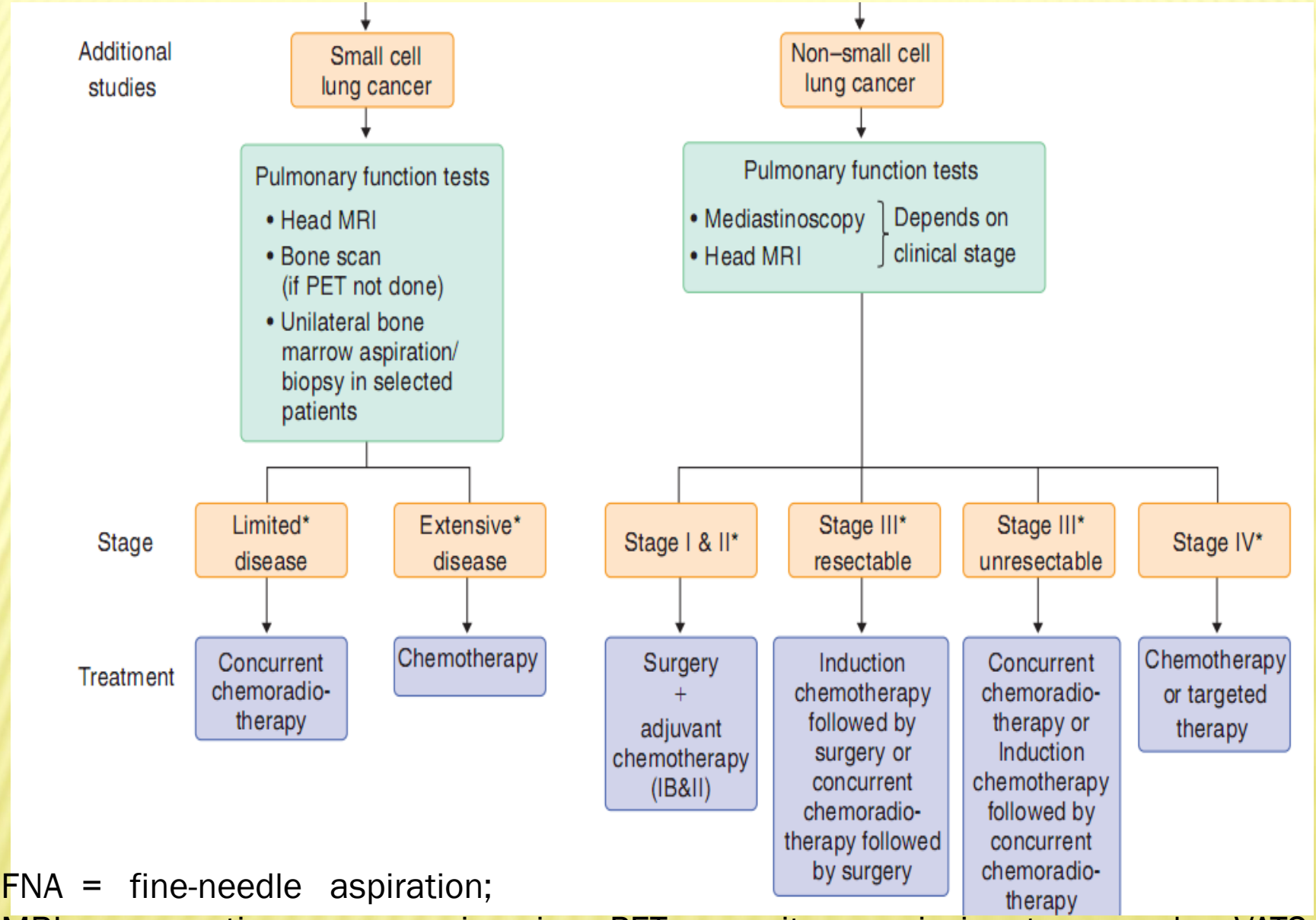
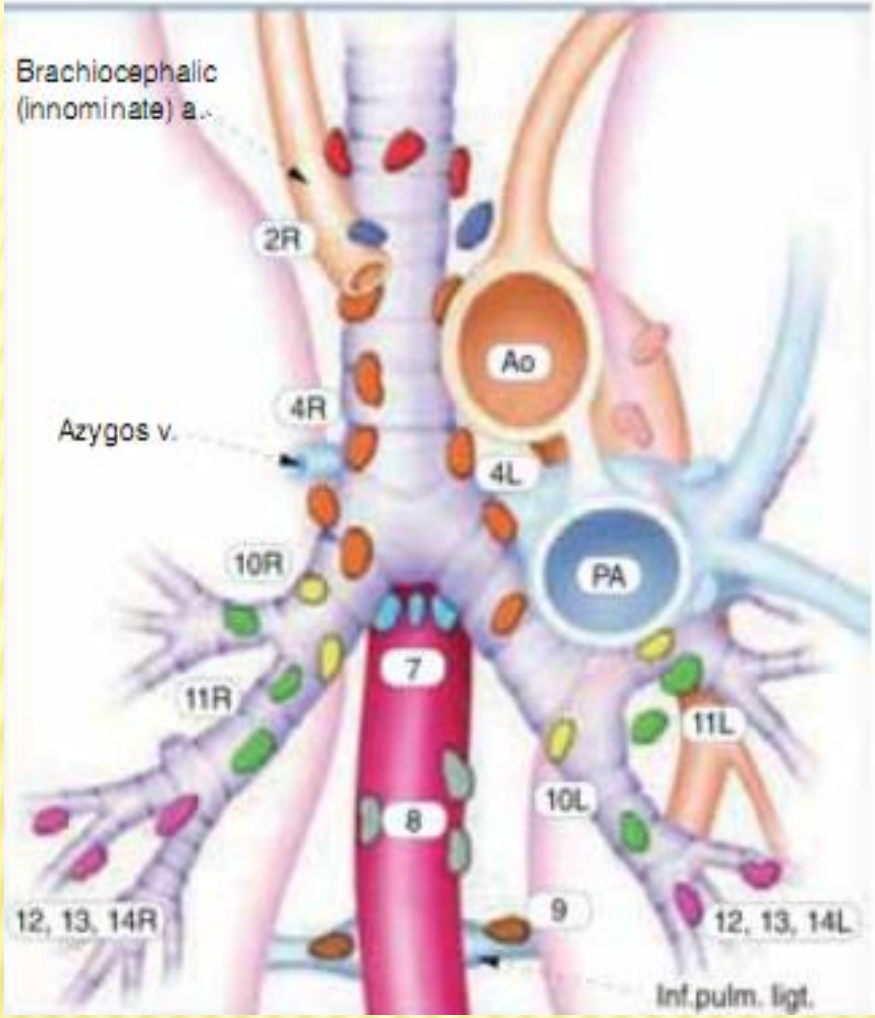
• PET scan
• Smoking cessation counseling
Additional studies
Small cell lung cancer
Non–small cell lung cancer



FNA = fine-needle aspiration;
MRI = magnetic resonance imaging; PET = positron emission tomography; VATS = video-assisted thoracic surgery.

Evaluation of Mediastinal Tissue After initial clinical staging, if a patient with NSCLC has potentially surgically resectable disease, the regional lymph nodes (mediastinum) must be sampled for possible metastases.

Te gold standard for evaluating the mediastinal lymph nodes for metastatic disease during life is transcervical mediastinoscopy Te subaortic and aortopulmonary window lymph nodes are inaccessible by routine mediastinoscopy, and the subcarinal lymph nodes may be difcult to access.



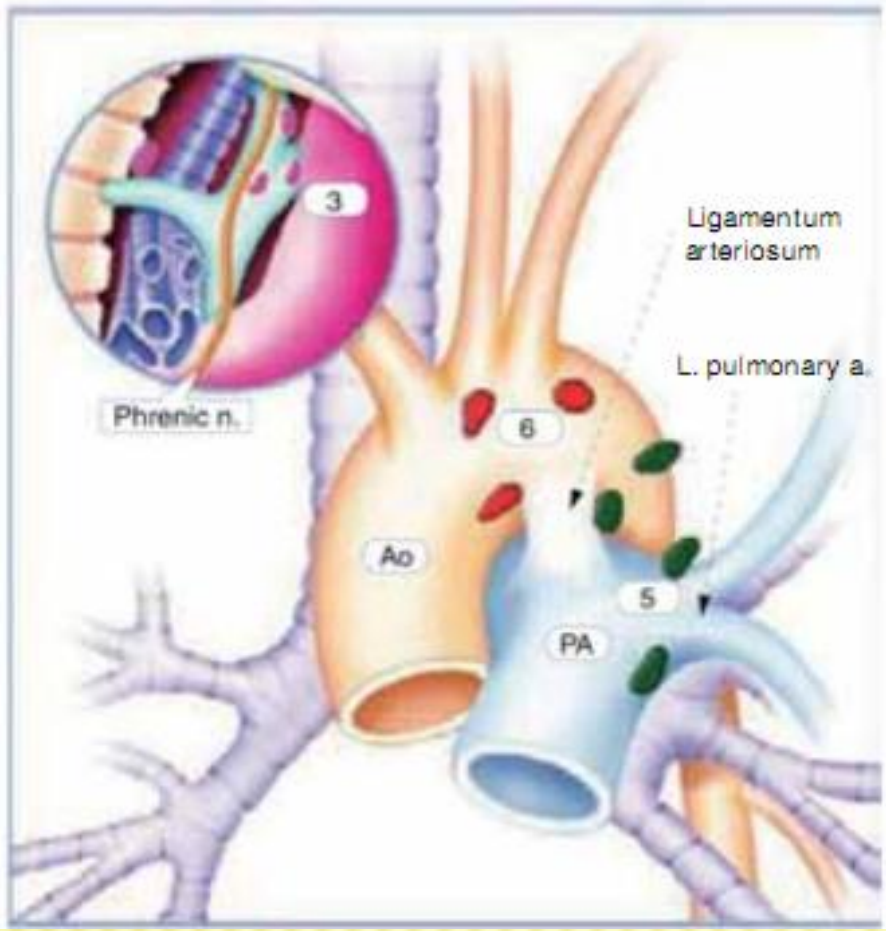
Superior mediastinal nodes

- 1 Highest mediastinal
- 2 Upper paratracheal
- 3 Prevascular and retrotracheal
- 4 Lower paratracheal (including azygos nodes)

N2 = single digit, ipsilateral
N3 = single digit, contralateral or supraclavicular

Aortic nodes

- 5 Subaortic (A-P window)
- 6 Para-aortic (ascending aorta or phrenic)



Inferior mediastinal nodes

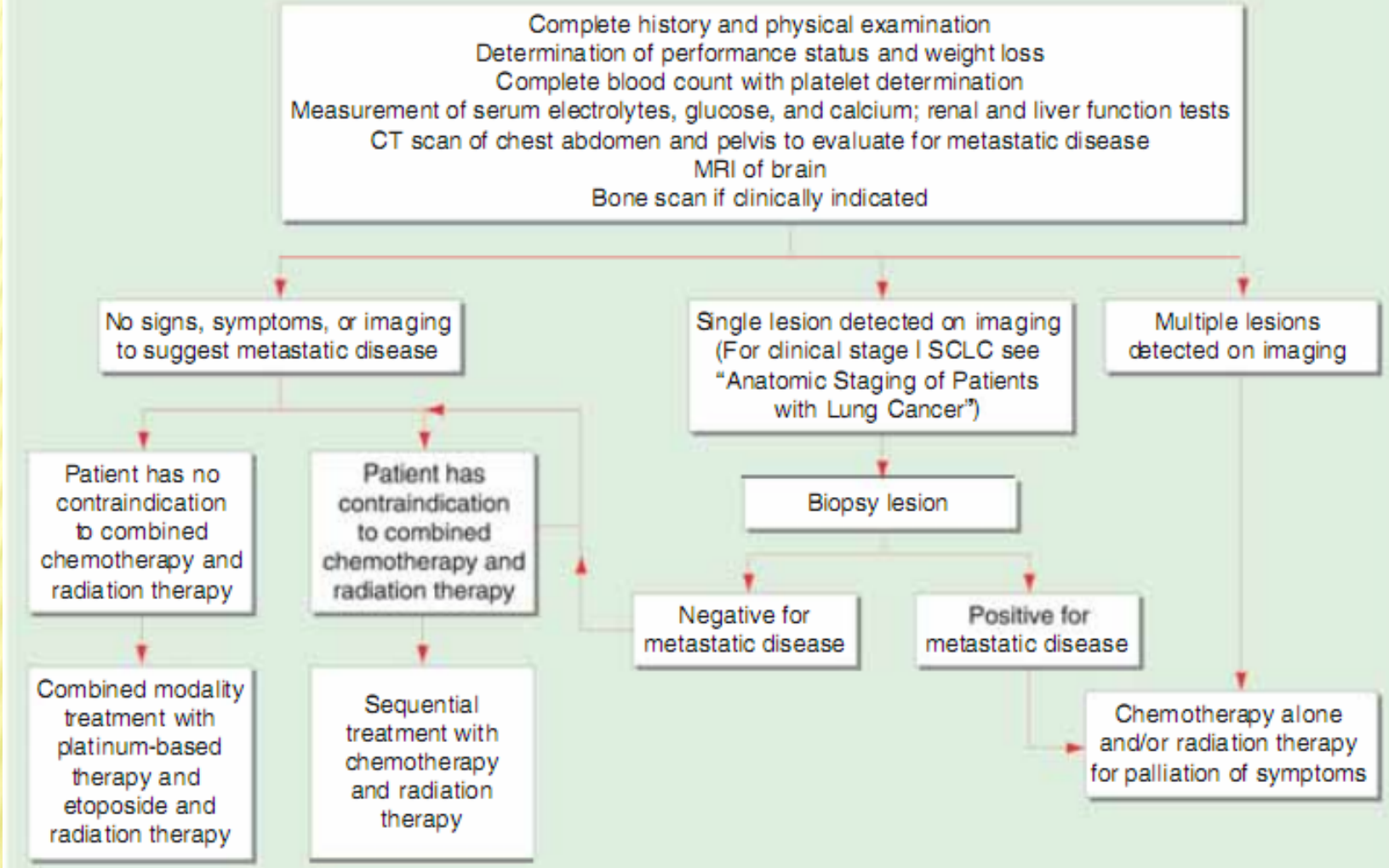
- 7 Subcarinal
- 8 Paraesophageal (below carina)
- 9 Pulmonary ligament

N1 nodes

- 10 Hilar
- 11 Interlobar
- 12 Lobar
- 13 Segmental
- 14 Subsegmental

a., artery; Ao, aorta; Inf. pulm. ligt., inferior pulmonary ligament; n., nerve; PA, pulmonary artery; v., vein.

Management of Small Cell Lung Cancer



Note: Regardless of disease stage, patients who have a good response to initial therapy should be considered for prophylactic cranial irradiation after therapy is completed.

TNM Staging System for Lung Cancer (7th Edition)	
Primary Tumor (T)	
T1	Tumor ≤3 cm diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus
T1a	Tumor ≤2 cm in diameter
T1b	Tumor >2 cm but ≤ 3 cm in diameter
T2	Tumor >3 cm but ≤7 cm, or tumor with any of the following features: Involves main bronchus, ≥2 cm distal to carina Invades visceral pleura Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor >3 cm but ≤5 cm
T2b	Tumor >5 cm but ≤7 cm
T3	Tumor >7 cm or any of the following: Directly invades any of the following: chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus <2 cm from carina (without involvement of carina) Atelectasis or obstructive pneumonitis of the entire lung Separate tumor nodules in the same lobe
T4	Tumor of any size that invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a different ipsilateral lobe

Regional Lymph Nodes (N)	
N0	No regional lymph node metastases
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion
M1b	Distant metastasis (in extrathoracic organs)

Abbreviation: TNM, tumor-node-metastasis

Source: Reproduced with permission from P Goldstraw et al: J Thorac Oncol 2:706, 2007.

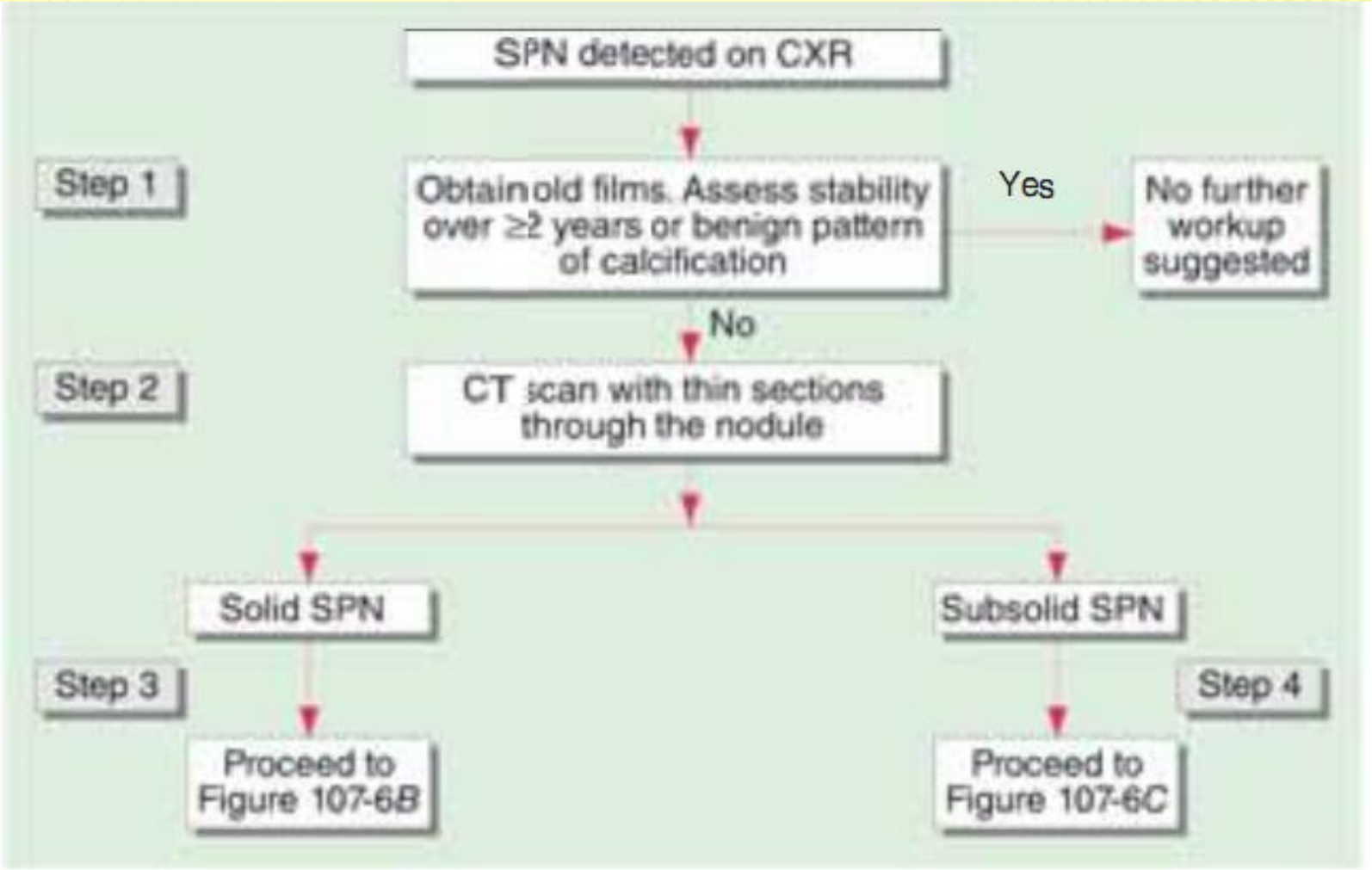
TABLE 107-7 SEVENTH EDITION TNM STAGING SYSTEMS FOR NON-SMALL-CELL LUNG CANCER

Stage groupings			
Stage IA	T1a-T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T1a,T1b,T2a	N1	M0
	T2b	N0	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a,T1b,T2a,T2b	N2	M0
	T3	N1,N2	M0
	T4	N0,N1	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1a or M1b

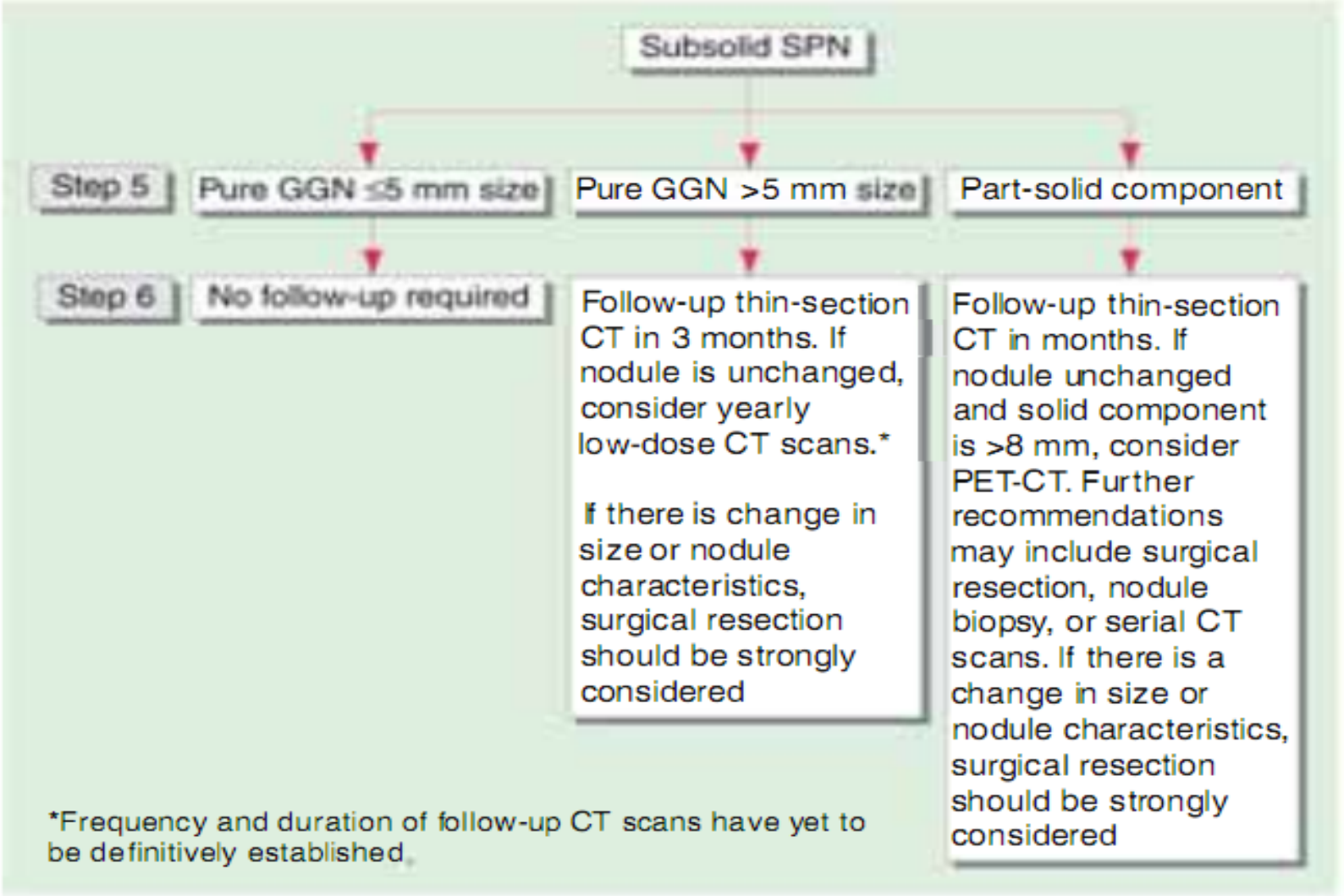
Abbreviation: TNM, tumor-node-metastasis.

TABLE 107-9 ASSESSMENT OF RISK OF CANCER IN PATIENTS WITH SOLITARY PULMONARY NODULES

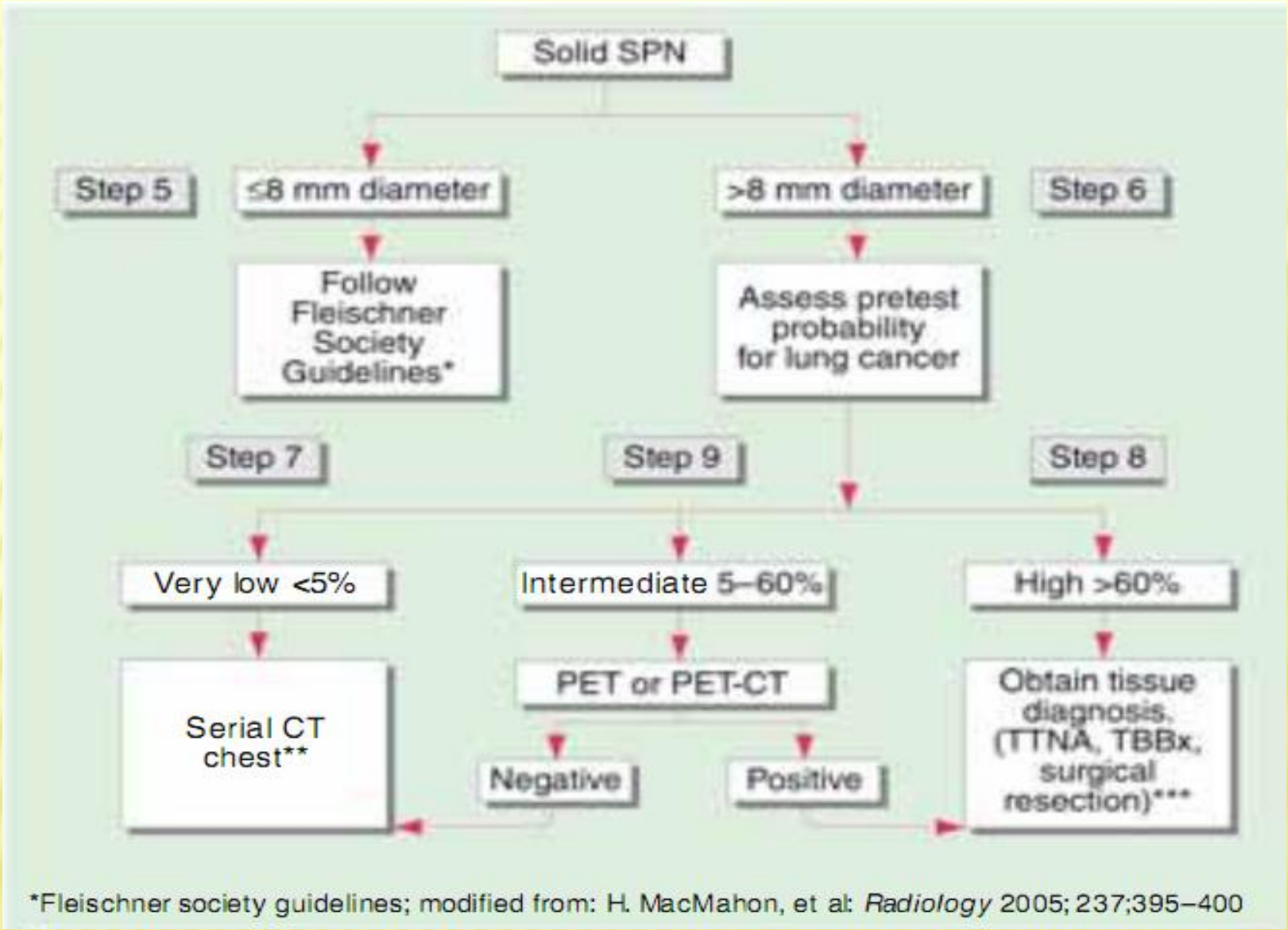
	Risk		
Variable	**Low**	**Intermediate**	**High**
Diameter (cm)	<1.5	1.5–2.2	≥2.3
Age (years)	<45	45–60	>60
Smoking status	Never smoker	Current smoker (<20 cigarettes/d)	Current smoker (>20 cigarettes/d)
Smoking cessation status	Quit ≥7 years ago or quit	Quit <7 years ago	Never quit
Characteristics of nodule margins	Smooth	Scalloped	Corona radiata or spiculated


SPN detected on CXR
Step 1
Obtain old films. Assess stability over ≥2 years or benign pattern of calcification
Yes
No further workup suggested
No
Step 2
CT scan with thin sections through the nodule
Solid SPN
Subsolid SPN
Step 3
Step 4
Proceed to Figure 107-6B
Proceed to Figure 107-6C

A


Subsolid SPN
Step 5
Pure GGN ≤5 mm size
Pure GGN >5 mm size
Part-solid component
Step 6
No follow-up required
Follow-up thin-section CT in 3 months. If nodule is unchanged, consider yearly low-dose CT scans.*
If there is change in size or nodule characteristics, surgical resection should be strongly considered
Follow-up thin-section CT in months. If nodule unchanged and solid component is >8 mm, consider PET-CT. Further recommendations may include surgical resection, nodule biopsy, or serial CT scans. If there is a change in size or nodule characteristics, surgical resection should be strongly considered
*Frequency and duration of follow-up CT scans have yet to be definitively established.

C



*Fleischner society guidelines; modified from: H. MacMahon, et al: *Radiology* 2005; 237;395–400

Nodule size (a):	Low-risk patient (b):	High-risk patient (c):
≤4 mm	No follow-up needed (d)	Follow-up at 12 months; if unchanged, no further follow-up
>4–6 mm	Follow-up CT at 12 months; if unchanged, no further follow-up	Follow-up CT at 6–12 months; then 18–24 months if no change
>6–8 mm	Follow-up CT at 6–12 months; then 18–24 months if no change	Follow-up CT at 3–6 months; then 9–12 and 24 months if no change
>8 mm	Follow-up CT at 3, 9, and 24 months; dynamic contrast-enhanced CT, PET, and/or biopsy	Same as low-risk patient

(a) Average of largest and smallest axial diameters of the nodule
(b) No smoking history and absence of other risk factors
(c) Previous or current smoking history or other risk factors
(d) Risk of malignancy (<0.1%) is substantially lower than for an asymptomatic smoker

**ACCP guidelines (see MK Gould et al: *Chest* 2007;132(suppl 3):108s-130S.
***Consider patient preference, severity of medical comorbidities, center specific expertise prior to tissue diagnosis.

B

TABLE 107-8 FIVE-YEAR SURVIVAL BY STAGE AND TNM CLASSIFICATION OF NON-SMALL-CELL LUNG CANCER (SEVENTH EDITION)

Stage	TNM Seventh Edition	5-Year Survival (%)
IA	T1a-T1bN0M0	73%
IB	T2aN0M0	58%
IIA	T1a-T2aN1M0 T2bN0M0	46%
IIB	T2bN1M0 T3N0M0	36%
IIIA	T1a-T3N2M0 T3N1M0 T4N0-1M0	24%
IIIB	T4N2M0 T1a-T4N3M0	9%
IV	Any T Any N plus M1a or M1b	13%

Abbreviation: TNM, tumor-node-metastasis.

TABLE 197-3 GENERAL APPROACH TO THE TREATMENT OF LUNG CANCER ACCORDING TO STAGE*

STAGE	PRIMARY TREATMENT	ADJUVANT THERAPY
NON–SMALL CELL LUNG CANCER		
I	Surgical resection	Chemotherapy (stage 1B)
II	Surgical resection	Chemotherapy
IIIA (resectable)	Preoperative chemotherapy followed by surgical resection (preferable) or chemotherapy followed by radiation therapy	Chemotherapy with or without radiation therapy
IIIA (unresectable) or IIIB (involvement of the contralateral or supraclavicular lymph nodes)	Chemotherapy plus concurrent radiation therapy (preferable) or chemotherapy followed by radiation therapy	None
IV	Chemotherapy with 2 agents for 4-6 cycles Chemotherapy + bevacizumab (selected patients) EGFR-TKI (erlotinib, gefitinib) in patients with positive *EGFR* gene mutation Surgical resection of solitary brain metastasis and surgical resection of primary (T1) lesion	None
SMALL CELL LUNG CANCER		
Limited disease†	Chemotherapy plus concurrent radiation therapy	None
Extensive disease†	Chemotherapy	None