Lung Cancers

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Epidemiology

- Most common cause of cancer- related deaths in both M & F. (30%)
- kills more people than the next three most common cancers combined (breast, prostate, and colon).

- M : F = 2:1
- The overall 5-year survival rate for lung cancer is only 18%, primarily because the disease is usually advanced at presentation;
- diagnosis and treatment at an early stage makes the 5-year survival rate approaches 60%.

Risk factors:

1.Cigarette smoking.

- primary cause of more than 80% of lung cancers.

2. Radon exposure.

- second most common cause of lung cancer
- he main source of indoor radon is radon gas infiltration from soil into buildings. Rock and soil produce radon gas. Building materials, the water supply, and natural gas can all be sources of radon in the home.

3. Passive (secondhand) smoking

- Third most common cause
- increases the risk of lung cancer by 30%.

Despite the strong association between lung cancer and smoking, lung cancers develop in only 15% of heavy smokers.

4.Urban air pollution.

5.Industrial exposure (asbestos, uranium, arsenic)

6.Family history / somatic denovo mutations

Types of lung cancers :

- **Benign**

- **Malignant**
- **Primary**
- **Metastatic**

- **Primary malignant lung cancers :**
- **non–small cell lung carcinoma (NSCLC)**
- **(adenocarcinoma, squamous cell carcinoma, and large cell carcinoma)**

- **small cell lung carcinoma (SCLC).**

- **NSCLC is often managed with surgery when the tumor is localized, whereas SCLC is almost always managed with chemotherapy with or without radiation therapy**

Malignant primary LC

I. Non-small cell lung cancer (N.S.C.L).

1. Adenocarcinoma 40-50%.

- most common lung cancer found in nonsmokers and women.
- Usually peripheral , more likely to develop systemic metastases

a. Bronchioalveolar CA.

- tumor cells proliferating along the surface of intact alveolar walls
- Can be single/multiple nodules , indolent/aggressive course

b. Acinar adenocarcinoma.

c. Papillary adenocarcinoma.

d. Solid carcinoma with mucus formation.

2. Squamous cell carcinoma 25%.

- 65% as a central lesions +/- cavitation
- Unlike adenocarcinoma, (localized, spread within the pulmonary lobe/ regional lymph nodes
- invasion of the chest wall, mediastinum, or other intrathoracic organs is also known to occur.

3. Undifferentiated large cell carcinoma 7%.

- aggressive, with early metastases to the regional nodes in the mediastinum and distant sites such as the brain.

4. Adenosquamous carcinoma 1%.

II. Small cell lung carcinoma (S.C.L.C) 20%.(15-30%).

- Classified under neuroendocrine tumors because of structural similarities

- well-differentiated, benign/typical carcinoid tumor,
- Central , main bronchus, treatment mainly surgery
- Express (NSE, Chromogranin, Synaptophysin) tumor markers

- intermediate less differentiated atypical carcinoids or neuroendocrine carcinomas,

-more aggressive than typical carcinoids , surgery mainly but depends on stage

- undifferentiated malignant **small cell carcinomas**.

II. Small cell lung carcinoma (S.C.L.C) 20%.(15-30%).

- Highly malignant
- Rapid growth
- Early mets and invasion
- Production of peptides.
  1. Dopa decarboxylase.
  2. Adenocorticotropic hormone ACTH.
  3. Gastrin releasing peptide.
  4. Creatinine kinase.

TABLE 7.1

Frequency of Histologic Subtypes of Primary Lung Cancer

Cell Type	Estimated Frequency (%)
Non–Small Cell Lung Cancer	
Adenocarcinoma	40
Bronchoalveolar	2
Squamous cell carcinoma	25
Large cell carcinoma	7
Small Cell Lung Cancer	
Small cell carcinoma	20
Neuroendocrine, well differentiated	1
Carcinoids	5

Clinical Presentation

- Asymptomatic 5%. (discovered incidentally on CXR/CT)

I. Bronchopulmonary symptoms:

- cough 75%
- hemoptysis 57%
- chest pain
- dyspnea
- febrile respiratory symptoms. (infection in obstructed bronchus)
    - fever , wheezing , stridor.

Clinical Presentation

II. Extrapulmonary intrathoracic symptoms 15%.

- hoarseness of voice. (RLN paralysis)
- superior vena cava syndrome.
- Pancoast apical lung tumor :
  (pain in the upper extremity, Horner's syndrome).
- chest pain / chest wall invasion
- dysphagia. (esophagus)
- pleural effusion.
- phrenic / vagus nerve paralysis.

Clinical Presentation

III. Extrathoracic nonmetastatic symptoms

- Paraneoplastic syndromes. (10%)
- More with SCLC

- Cushing's syndrome (ACTH production).
- Excessive Anti-diuretic hormone production (SIADH)
- Hypercalcemia of malignancy
- Hypertrophic pulmonary osteoarthropathy.
- Lambert-Eaton myasthenic syndrome (LEMS)
- Clubbing of fingers.
- Thrombophlebitis.
- Dermatomyositis , limbic encaphilitis, opsoclonus, ….etc

Clinical Presentation

IV. Extrathoracic metastatic symptoms.

- Neurologic symptoms.
- Bone pain, pathological fracture.
- Jaundice, ascites, abdominal mass.
- Non-specific symptoms.

  - Wt loss , weakness , anorexia , malaise.

Metastasis

1. Direct extension.
2. Lymphatic metastasis.
3. Hematogenous spread.

   - brain, liver, lungs, bone, adrenal glands, kidney, pancreas, skin, subcutaneous tissue.

   - bone : ribs, spine, femur, humerus, pelvis.

Diagnosis

•Imaging :

- CXR (initial test)

- Chest CT scan with IV contrast (including liver and adrenals)
  - confirms dx, assess tumor extension, mediastinal LN, help staging)

- MRI (adds little to CT , mainly in superior sulcus tumor with spine / neurovascular involvement)

- PET/ PET-CT scans : (accuracy 90%)
- Performed routinely for diagnosis and staging.
- Distinguish Benign vs malignant mass
- False –ve in carcinoid and Bronchoalveolar adeno.

Histological diagnosis:

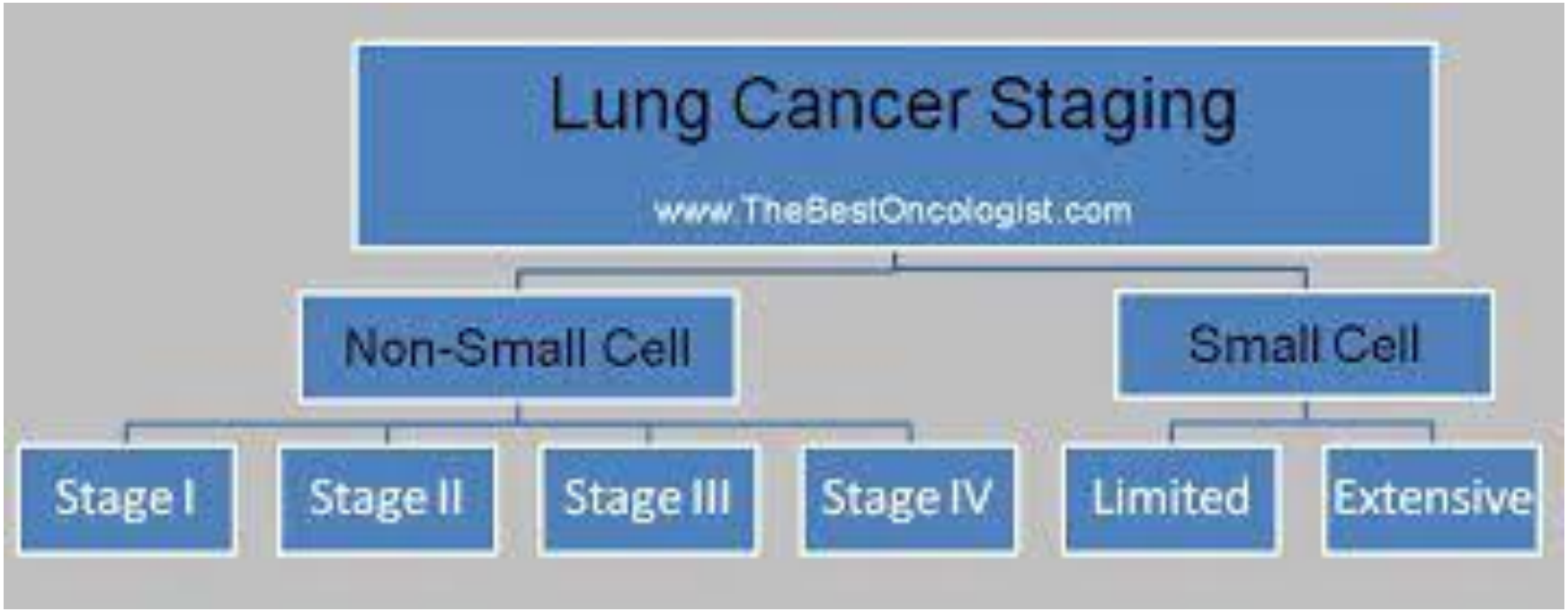
- Always required to confirm dx

- Sputum cytology +ve 45-90%.
- Bronchial Lavage cytology.

- Invasive Diagnostic Procedures.
  - Bronchoscopy - endobronchial US (EBUS).
  - Percutaneous transthoracic needle BX (CT guided FNA/CNB).
  - VAT.(video assisted thoracoscopy).
  - Supraclavicular lymph node biopsy.
  - mediastinoscopy.

Staging of primary lung cancers :

- Essential to determine extent of disease , formulate proper treatment plan and predict prognosis / survival .



Staging of SCLC :

- In SCLC, most patients present with metastatic or advanced locoregional disease.

- A simple **two-stage** system classifies the SCLC as **limited or extensive disease.**

- **Limited disease** is confined to one hemithorax, ipsilateral or contralateral hilar or mediastinal nodes, and ipsilateral supraclavicular lymph nodes.

- Extensive disease has spread to the contralateral supraclavicular nodes or distant sites such as the contralateral lung, OR liver, brain, bone marrow.

- Staging for SCLC requires CT scan /PET-CT and brain MRI
- May need mediastinoscopy / EBUS for LN staging

Staging of NSCLC :

- According to the 8th AJCC (TNM) – released in 2016
- CXR
- CT scan of the chest and upper abdomen (liver/adrenals)
- PET-CT (detect occult mets)
- Brain MRI (for stage II and more)
- May need EBUS , mediastinoscopy to confirm mediastinal LN mets (not indicated in early tumors T1N0)

TNM 8th - Primary tumor characteristics

T_x	**Tumor in sputum/bronchial washings but not be assessed in imaging or bronchoscopy**
T_0	**No evidence of tumor**
T_{is}	**Carcinoma in situ**
T_1	≤ 3 cm surrounded by lung/visceral pleura, not involving main bronchus
$T_{1a(mi)}$	**Minimally invasive carcinoma**
T_{1a}	**≤ 1 cm**
T_{1b}	**> 1 to ≤ 2 cm**
T_{1c}	**> 2 to ≤ 3 cm**
T_2	> 3 **to ≤ 5 cm** *or* **involvement of main bronchus without carina, regardless of distance from carina** or invasion visceral pleural *or* atelectasis or post obstructive pneumonitis extending to hilum
T_{2a}	**>3 to ≤4cm**
T_{2b}	**>4 to ≤5cm**
T_3	**>5 to ≤7cm in greatest dimension** *or* tumor of any size that involves chest wall, pericardium, phrenic nerve *or* satellite nodules in the same lobe
T_4	**> 7cm in greatest dimension** *or* any tumor with invasion of mediastinum, **diaphragm**, heart, great vessels, recurrent laryngeal nerve, carina, trachea, oesophagus, spine *or* separate tumor in different lobe of ipsilateral lung
N_1	Ipsilateral peribronchial and/or hilar nodes and intrapulmonary nodes
2	Ipsilateral mediastinal and/or subcarinal nodes
3	Contralateral mediastinal or hilar; ipsilateral/contralateral scalene/ supraclavicular
M_1	Distant metastasis
M_{1a}	Tumor in contralateral lung or pleural/pericardial nodule/malignant effusion
M_{1b}	**Single extrathoracic metastasis, including single non-regional lymphnode**
M_{1c}	**Multiple extrathoracic metastases in one or more organs**

T/M	Subcategory	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

Pre- treatment assessment :

- to determine the patient's ability to tolerate various therapeutic modalities

Includes :

- overall medical status (comorbidities, drugs, nutritional status)
- Full cardiovascular assessment (hx, PEx, CXR, ECG, ECHO,
- +/- exercise testing, nuclear cardiac perfusion, cardiac cath)

- Full pulmonary evaluation

- Especially when going for pulmonary resection as the lung reserve is usually less in those patients due to smoking/COPD and the cancer itself.

- spirometry , PFT, VQ scan

- Majorly impaired pulmonary reserve might be a contraindication to lung resection

Pre- treatment assessment :

- Preoperative incentive spirometer training
- initiation of bronchodilators
- weight reduction
- good nutrition
- cessation of smoking for at least 2 weeks before surgery

- All can help minimize complications and improve performance on spirometry for patients with marginal pulmonary reserve

TABLE 7.2

Pulmonary Assessment and Risk for Thoracic Resection

Average Risk	High Risk	Prohibitive Risk
ppoFEV1% > 40	ppoFEV1% 20–40	ppoFEV1% < 20
ppoDLCO% > 40	ppoDLCO% 20–40	ppoDLCO% < 20
pO_2 > 60	pO_2 45–60	pO_2 < 45
pCO_2 < 45	pCO_2 45–60	pCO_2 > 60
VO_2 max > 15	VO_2 max 10–15	VO_2 max < 10

Available Treatment modalities :

- Surgery.
- Chemotherapy.
- Radiotherapy.
- immunotherapy

Treatment of NSCLC

- Stage I, II (mainly surgery) if they can tolerate.
- Stage I,II not fit for surgery – (less resection or radiation-SBRT)
- Stage I (60-70% 5-year survival), Stage II 40%
- Stage IIB (chest wall invasion with N0) surgery+ chemo or definitive radiation + chemo if they can't tolerate
- Stage IIIA – induction chemoradiation +/- surgery
- Stage IIIB – definitive chemoradiation
- Stage IV – induction chemo + palliative radiotherapy
- Surgery for stage IV only in patients with resected primary and less than 3 mets to lung/brain

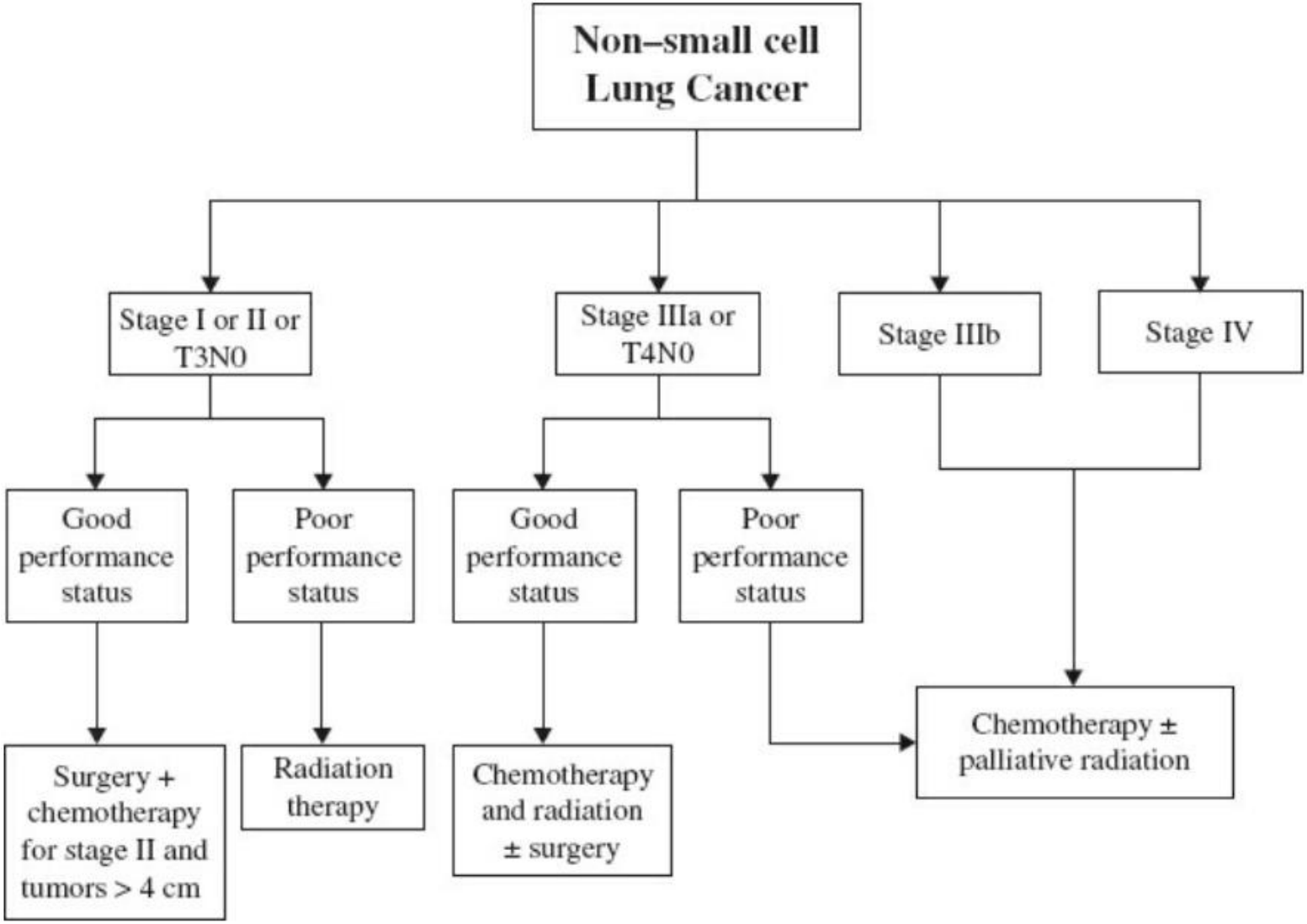


Figure 7.3 Algorithm for treatment of non–small cell lung cancer.

Surgical treatment includes :

- **Pneumonectomy (the whole lung) :**

- Was very commonly performed, now only 20% of surgeries
- Higher mortality 4-10% and morbidity
- Advances in surgical techniques reduced the need for pneumonectomy

- **Lobectomy : (tumor + lobe + lymphatic pathway)**

- The standard and most common surgery performed
- Mortality <2%

- **Segmentectomy and non anatomical wedge resections :**

- Higher recurrence rate
- Only in patients who can't tolerate lobectomy
- Still under investigation for early small lung cancers (no evidence on their efficacy for early lung cancer)
- The procedure of choice for metastatic lung cancer from another primary cancer but not for primary lung cancers

- **Video Assisted Thoracoscopic Surgery (VATS):**

- Ports inserted and resection under camera visualization
- similar outcome to open thoracotomy surgery (tumor resection) but less morbidity and pain

- **Robotic VATS**
- **Mediastinal Lymph Node Dissection**

- Decrease recurrence
- Improve survival ???? (not conclusive)
- More staging accuracy

- Stereotactic body radiation (SBRT) can be an alternative for resectable tumors not fit for surgery with inferior results

Treatment of NSCLC

- **Chemotherapy**
- **Radiotherapy**
- **Those can be Neoadjuvant / adjuvant or palliative according to stage**
- **Can be definitive in some patients without need for surgery**

- **Immunotherapy / targeted therapy :**
- Usually in metastatic NSCLC
- Anti PD-1 (Nivolumab) , Anti PD-L1 (pembrolizumab)
- anti-CTLA4 (Ipilimumab)
- EGFR antagonist (erlotinib)
- Anti- ALK (anaplastic lymphoma kinase – crizotinib)

Biologic or Genetic Markers and Their Prognostic Value

Biologic Variable	Prognostic Factor
bcl-2	Favorable
TTF1	Adverse
Cox2	Adverse
EGFR overexpression	Adverse
Ras	Adverse
Ki67	Adverse
HER2	Adverse
VEGF	Adverse
Microvascular density	Adverse
p53	Adverse
Aneuploidy	Adverse

Treatment of Small cell lung carcinoma SCLC

- Most of SCLC are disseminated at presentation
- SCLC is very sensitive to cemotherapy
- Mainstay of treatment is chemotherapy
- 2/3 of patient get partial response to chemo
- 20-50% have complete response but still 5 year survival is 10% only due to recurrence.
- +/- radiotherapy to chest sometimes
- 80% will develop **brain mets ,** so it is standard now that **ALL patients with SCLC should receive prophylactic brain irradiation**
- Surgery very rarely in early tumor with no mets (T1,T2) limited disease (only few patients) with brain radiation too

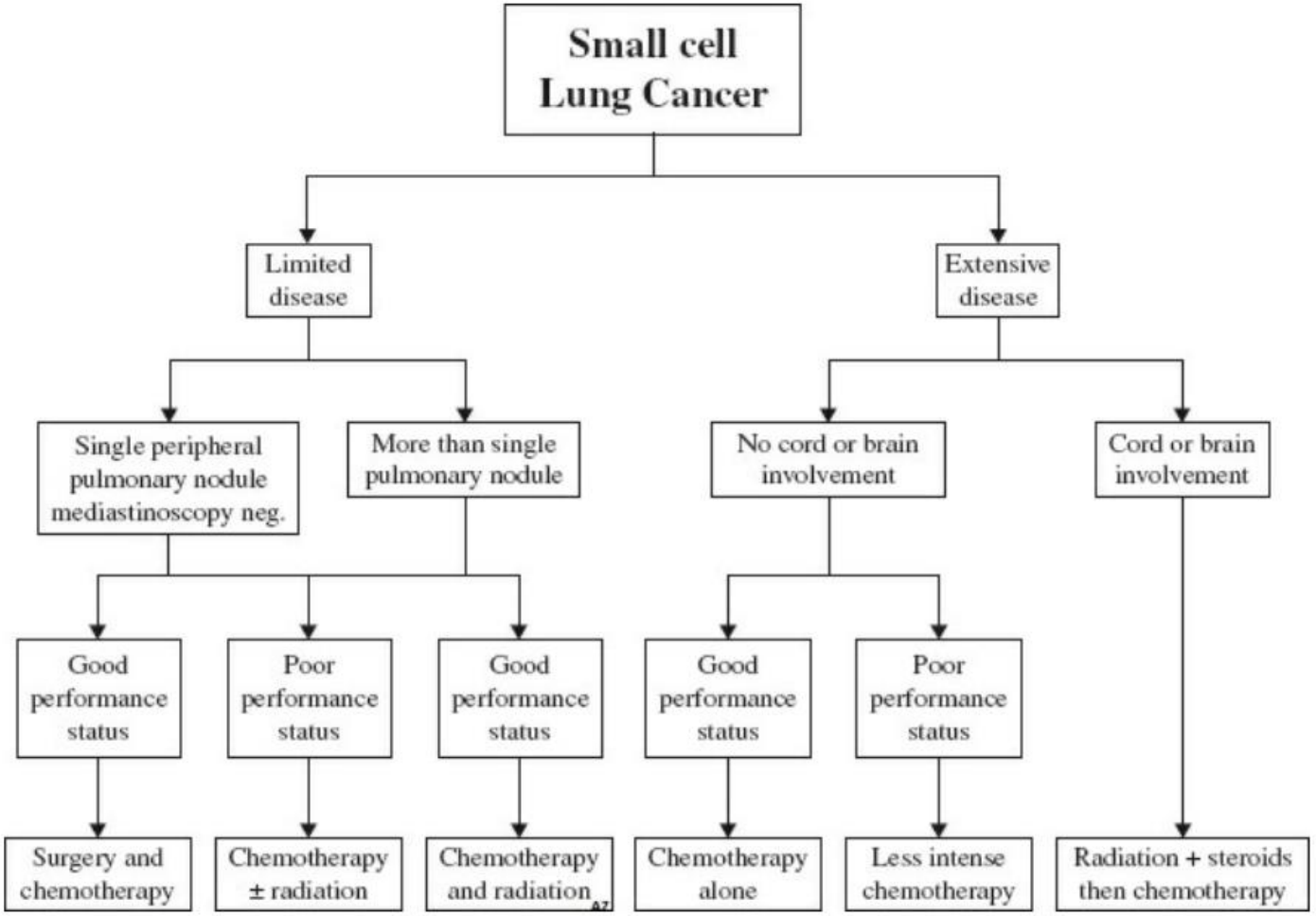


Figure 7.4 Algorithm for treatment of small cell lung cancer.

Metastatic Secondary Neoplasms To The Lung

- Any malignant tumor can have mets to lungs
- Mostly from colorectal, breast, thyroid …. etc
- Secondary lung mets are **Less common** than primary lung cancer (unlike liver)
- Usually multiple , peripheral
- 95% asymptomatic (discovered during follow up of the primary cancer)
- New multiple pulmonary nodules in a patient with known other cancers is highly suggestive (100%)
- New single nodule is more likely to be a new primary lung cancer (not secondary mets)
- Prognosis depend on resectability, disease free interval and number of mets

treatment

- Surgery (metastatectomy / wedge resection)
- Can improve survival in some cancers
- require

- Ability to remove all mets
- control of the primary tumor
- adequate predicted postoperative pulmonary reserve
- no other organ metastases

- Follow the treatment guidelines for the primary tumor (some benefit resection e.g.colorectal, some not – e.g gastric)

- Chemotherapy , radiotherapy (palliative)

THANK YOU