Lung Cancer

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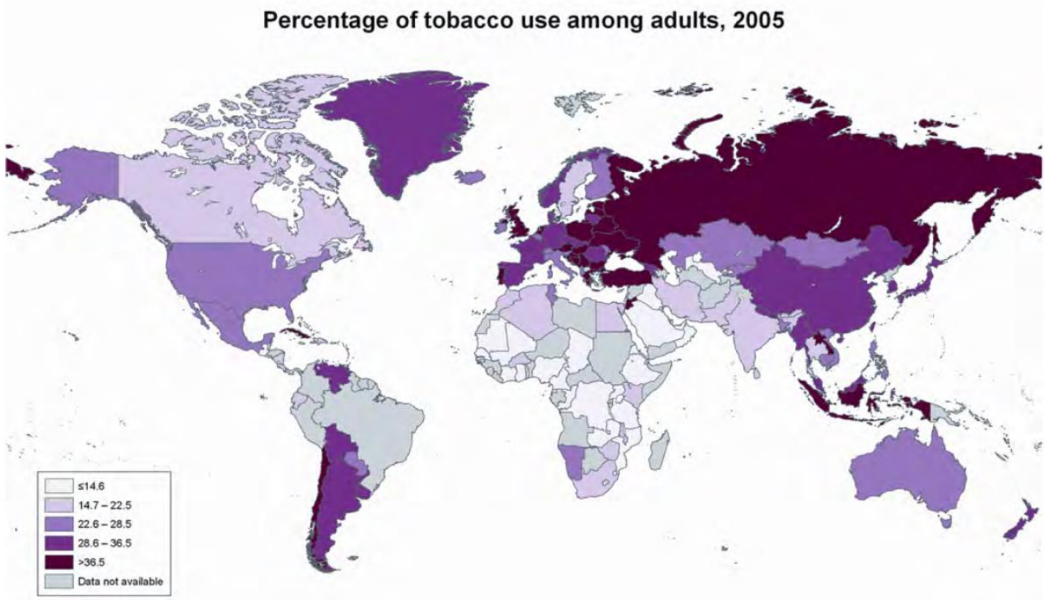
Epidemiology

Lung Cancer: Global Impact

- Most common cause of cancer death
- 1.8 million new lung cancer cases per year
- 1.6 million deaths per year (more than TB, malaria, HIV)



Question 1: In terms of incidence the most common cancer in males and females is:

A. Lung cancer in both

B. Breast cancer in females and lung cancer in males

C. Prostate cancer in males and lung cancer in females

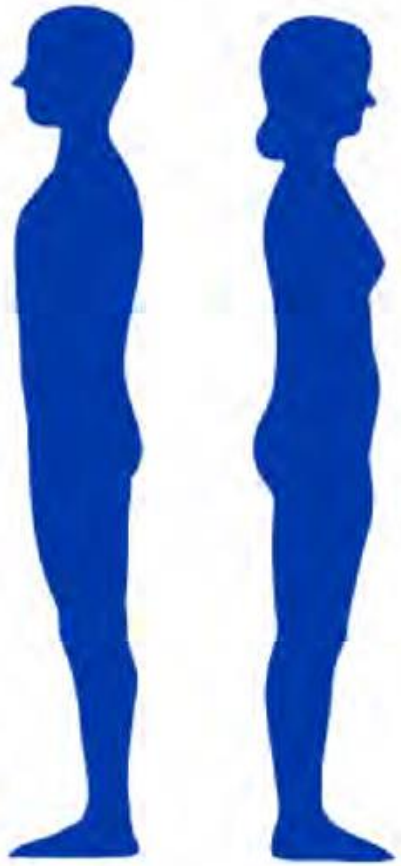
D. Prostate cancer in males and breast cancer in females

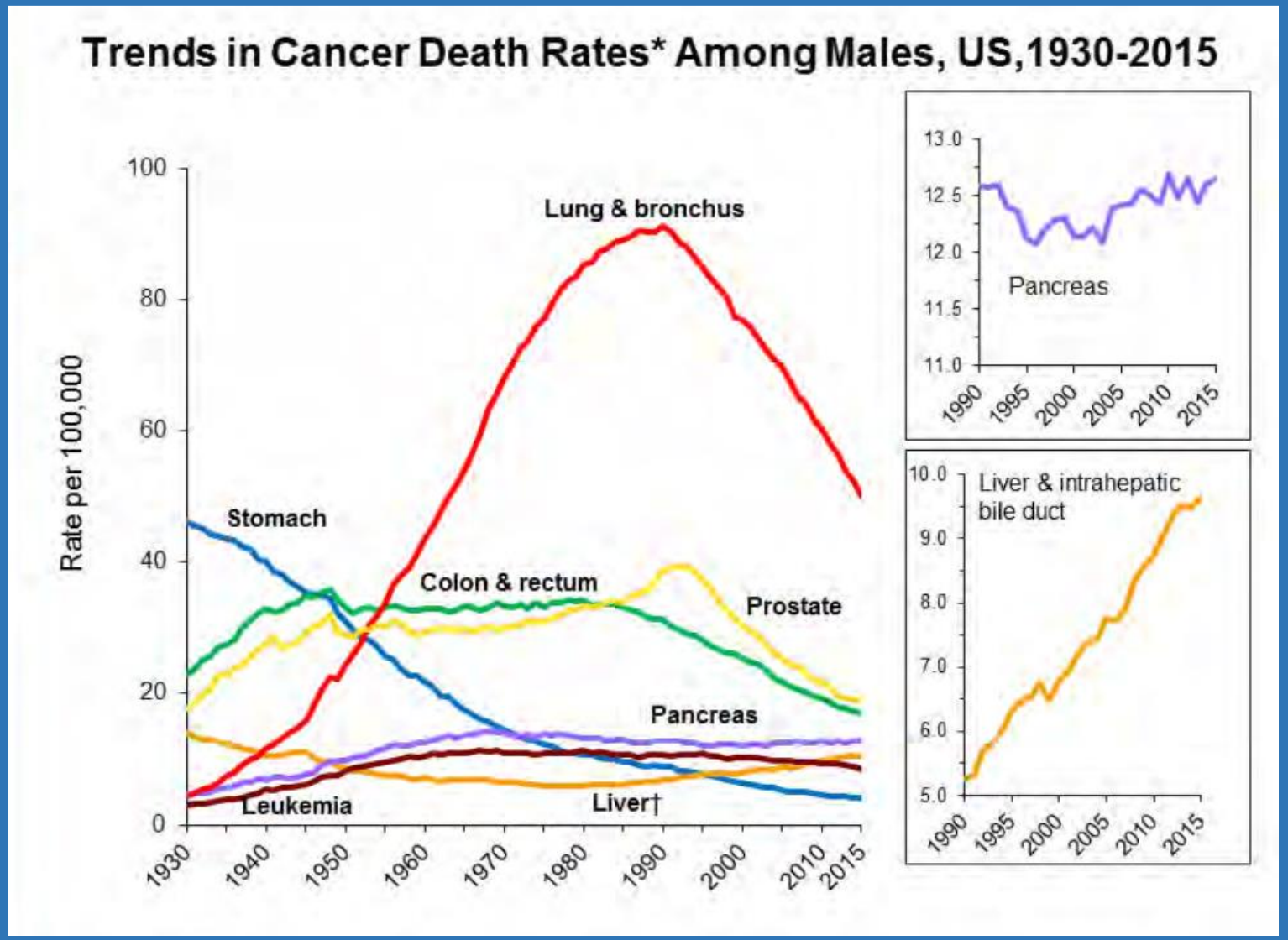
Estimated New Cancer Cases* in the US in 2018

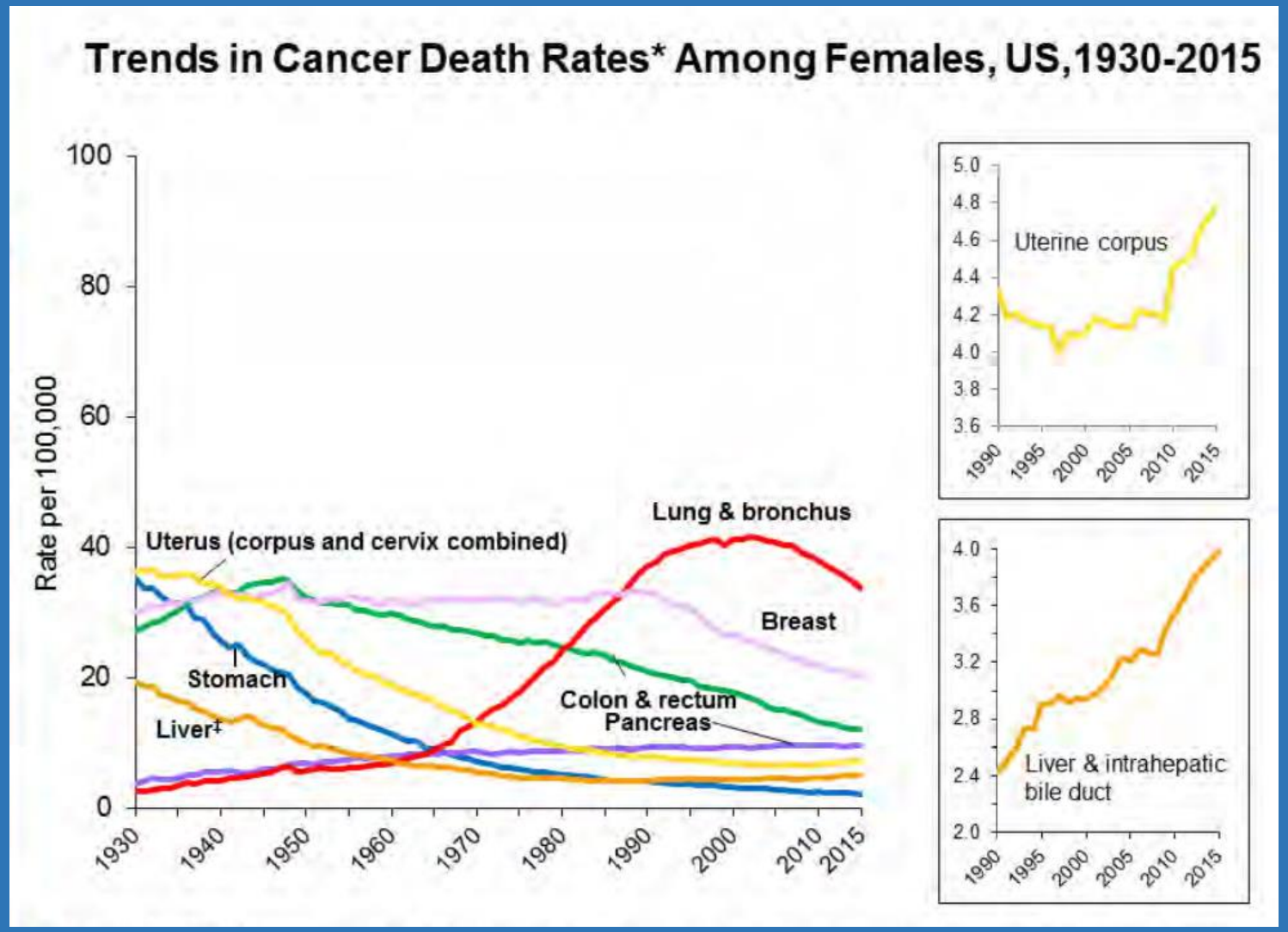
Males		Females	
856,370		878,980	
Prostate	19%	30%	Breast
Lung & bronchus	14%	13%	Lung & bronchus
Colon & rectum	9%	7%	Colon & rectum
Urinary bladder	7%	7%	Uterine corpus
Melanoma of skin	6%	5%	Thyroid
Kidney & renal pelvis	5%	4%	Melanoma of skin
Non-Hodgkin lymphoma	5%	4%	Non-Hodgkin lymphoma
Oral cavity & pharynx	4%	3%	Pancreas
Leukemia	4%	3%	Leukemia
Liver & intrahepatic bile duct	4%	3%	Kidney & renal pelvis
All other sites	22%	21%	All other sites

Estimated Cancer Deaths in the US in 2018

Males 323,630		Females 286,010	
Lung & bronchus	26%	25%	Lung & bronchus
Prostate	9%	14%	Breast
Colon & rectum	8%	8%	Colon & rectum
Pancreas	7%	7%	Pancreas
Liver & intrahepatic bile duct	6%	5%	Ovary
Leukemia	4%	4%	Uterine corpus
Esophagus	4%	4%	Leukemia
Urinary bladder	4%	3%	Liver & intrahepatic bile duct
Non-Hodgkin lymphoma	4%	3%	Non-Hodgkin lymphoma
Kidney & renal pelvis	3%	3%	Brain & other nervous system
All other sites	24%	24%	All other sites




Trends in Cancer Death Rates* Among Males, US,1930-2015
Rate per 100,000
100
80
60
40
20
0
1930
1940
1950
1960
1970
1980
1990
2000
2010
2015
Lung & bronchus
Stomach
Colon & rectum
Prostate
Pancreas
Leukemia
Liver†
13.0
12.5
12.0
11.5
11.0
Pancreas
1990
1995
2000
2005
2010
2015
10.0
9.0
8.0
7.0
6.0
5.0
Liver & intrahepatic bile duct


Trends in Cancer Death Rates* Among Females, US,1930-2015
Rate per 100,000
100
80
60
40
20
0
1930
1940
1950
1960
1970
1980
1990
2000
2010
2015
Uterus (corpus and cervix combined)
Lung & bronchus
Breast
Stomach
Colon & rectum
Pancreas
Liver‡
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
Uterine corpus
1990
1995
2000
2005
2010
2015
4.0
3.6
3.2
2.8
2.4
2.0
Liver & intrahepatic bile duct

Etiology of lung cancer

- Tobacco causes 80 – 90%
  - Clear dose response relationship
  - Passive smoking may cause up to 25% of lung
- cancer in non-smokers (2.5 – 5% of all)
- Individual (genetic) susceptibility
- 10 – 15% of active smokers will develop lung cancer
- Other causes include asbestos, radon, polycyclic hydrocarbons, cadmium, chloromethyl ether, chromium,
- nickel, arsenic may cause lung cancer
- Age is a risk factor
  - Average age at dx is 70
- COPD is a risk factor
  - More so than just shared etiology (3-6x more likely than smoking alone)

WHO Classification of Lung cancer

Major types	%
• Adenocarcinoma	32
– 3% of total are pure BAC	
• Squamous cell carcinoma	29
• Small cell carcinoma	18
• Large cell carcinoma	9
• Unclassified/undifferentiated	12

Lung cancer

- **Squamous cell:**
    - 95% are smokers, Usually centrally located, can cavitate,

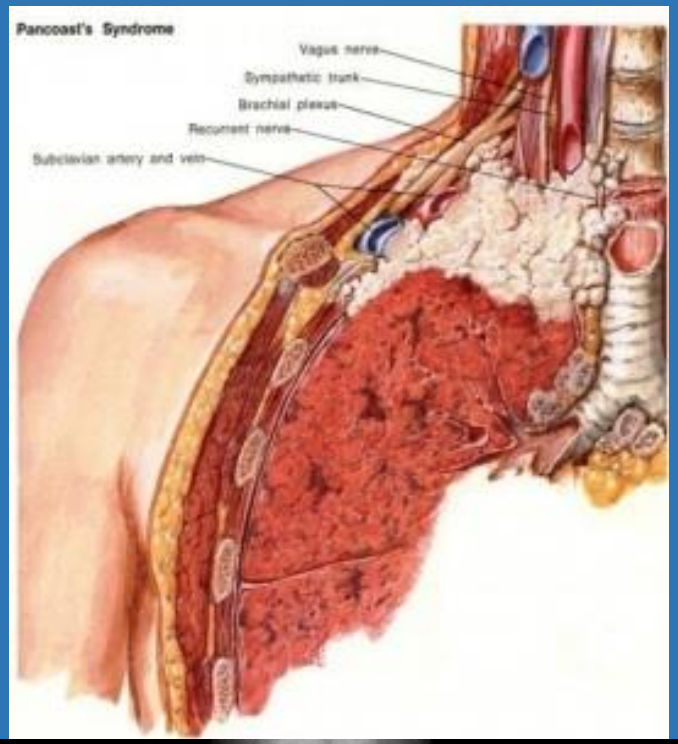
    Associated with HPO and hypercalcemia
- **Adenocarcinoma:**
    - Most common histologic subtype, Increased incidence in never smokers, peripheral, metastatic
- **Small cell:**
    - Almost all smokers, central, metastatic at presentation,
    - If you have to choose paraneoplastic syndromes related to lung cancer **(other than hypercalcemia)** pick **small cell.**

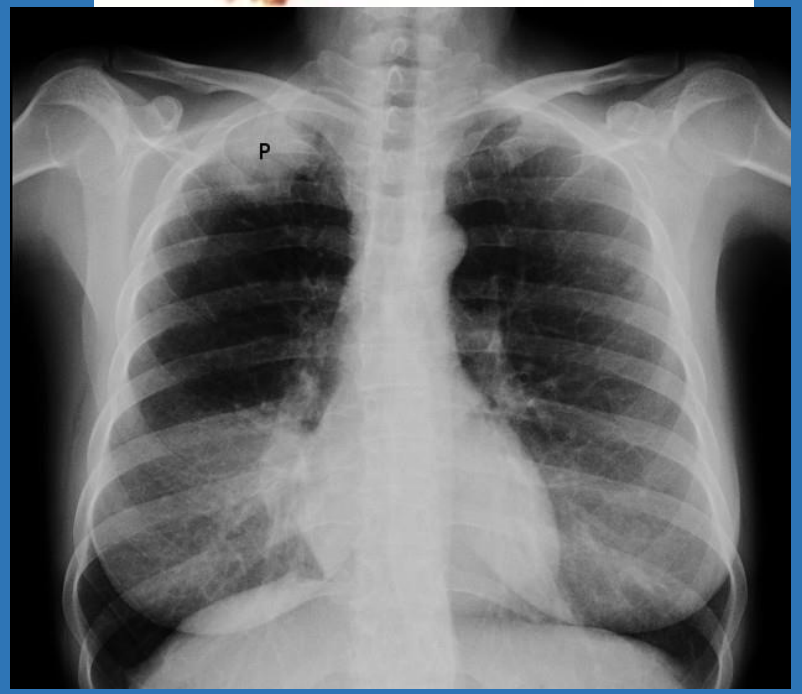
Adenocarcinoma of lung cancer

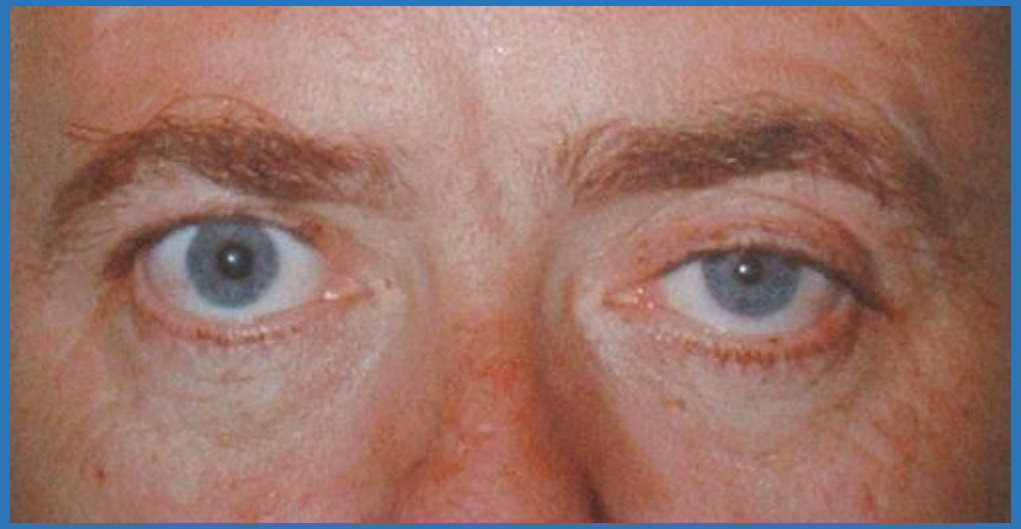
- Adenocarcinoma pathology consists of either
  - neoplastic gland formation, pneumocyte marker expression (thyroid transcription factor 1 (TTF-1) with or without napsin expression OR
  - intracytoplasmic mucin
- It is further classified based on the extent and architecture of the neoplastic gland formation as:
  - mucinous or nonmucinous. Acinar, papillary, micropapillary, lepidic, and solid are nonmucinous subtypes.
- Solid, micropapillary, and cribriform (a subtype of acinar nonmucinous adenocarcinoma) patterns have adverse prognostic significance
- Minimally invasive adenocarcinoma (MIA) is a small, solitary adenocarcinoma less than or equal to 3 cm with minimal invasion (less than 5 mm) and a predominant lepidic growth pattern, resembling other similar precursor glandular lesions.
- If the invasion is greater than 5 mm, it is defined as lepidic-predominant adenocarcinoma

Squamous cell carcinoma

- Squamous cell pathology is defined by the presence of keratin and/or intercellular desmosomes on cytology or by immunohistochemistry (IHC) evidence of p40, p63, CK5, CK5/6, or desmoglein expression.
- Subtypes of squamous cell carcinoma include nonkeratinizing, keratinizing, and basaloid.
- Squamous cell carcinomas show extensive central necrosis with resulting cavitation.
- Squamous cell cancers can present as Pancoast tumors and hypercalcemia.
- A Pancoast tumor is a tumor in the superior sulcus of the lung. The brain is the most common site of recurrence postsurgery in cases of Pancoast tumors







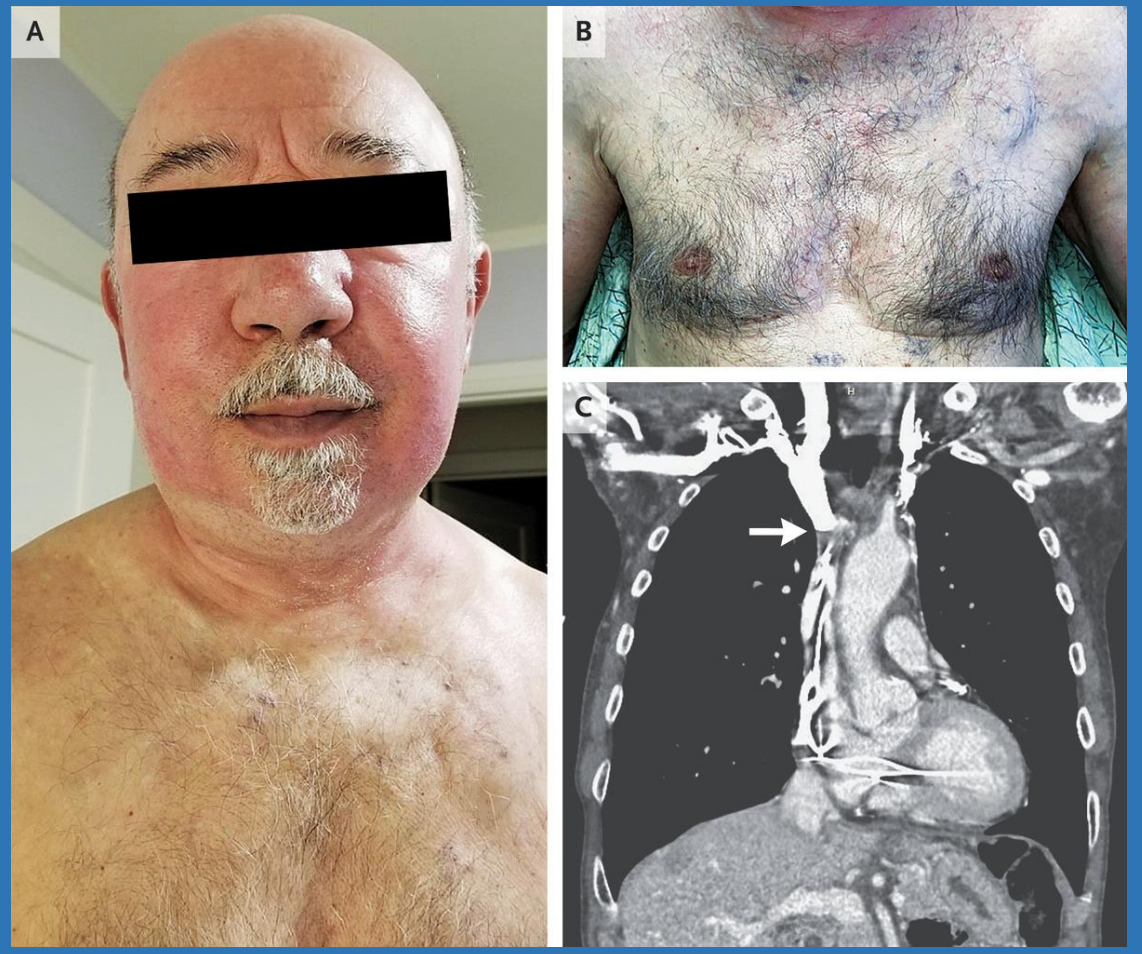
- Shoulder pain is present in up to 96% of patients and is the most common initial presenting symptom.
- The pain could potentially be secondary to the invasion of brachial plexus, pleural invasion, extension into ribs or vertebral bodies, and is generally progressive
- Horner syndrome is a combination of ipsilateral ptosis miosis and anhidrosis due to invasion or sympathetic trunck

Diagnosis

- History
  - Most common symptoms are:
    - Cough (75%), Dyspnea, Chest Pain, Hemoptysis (15-30%)
  - Less common symptoms:
- Clubbing, Hoarseness, Dysphagia, Wheeze, 15% pleural effusion
- Only 5 - 15% are asymptomatic
- 15% have extra-pulmonary symptoms
- 5% may present with a paraneoplastic syndrome
- Ask questions related to a cancer dx: new onset
- headaches, bone pain, etc

SVC syndrome

- Superior vena cava syndrome with dilated neck veins, edema of the face, neck, and upper extremities, and a plethoric appearance is a common feature of small cell lung cancer.
- It might be the primary presentation of the disease. The chest radiograph will show widening of the mediastinum or a right hilar mass.



Paraneoplastic Syndromes Associated with Lung Cancer

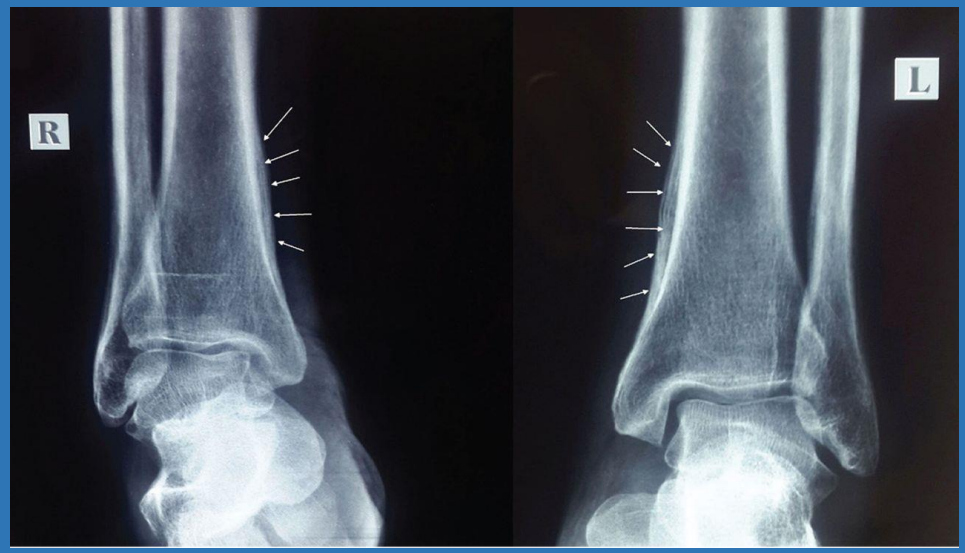
- Symptomatic hypercalcemia secondary to lung cancer may be due to secretion of the parathyroid hormone-related protein or due to extensive bony metastases.
- They present with anorexia, nausea, constipation, and lethargy as typical symptoms of hypercalcemia and have an overall poor prognosis as they tend to be associated with advanced disease.
- The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is associated with SCLC and presents with symptoms of hyponatremia.

Paraneoplastic Syndromes Associated with Lung Cancer

- Neurologic paraneoplastic syndromes are immune-mediated syndromes associated with SCLC and include
  - Lambert-Eaton myasthenic syndrome (LEMS)
  - Encephalomyelitis
  - limbic encephalitis
  - cerebellar ataxia
  - sensory neuropathy
  - autonomic neuropathy.
- Ectopic adrenal corticotropin production can cause Cushing syndrome and is associated with SCLC, large cell neuroendocrine carcinoma, and carcinoid tumors of the lung, and it portends a worse prognosis.
- Other extrapulmonary clinical manifestations of lung cancers include hypertrophic pulmonary osteoarthropathy, dermatomyositis, and polymyositis.

Hypertrophic osteoarthropathy (HOA),

- Hypertrophic osteoarthropathy (HOA), consists of the presence of digital clubbing, increased periosteal activity of the tubular bones, arthralgias, and joint effusion and is characterized by abnormal proliferation of the skin, soft tissues, and osseous tissues in the distal parts of extremities



Evaluation

- The overall goal is a timely diagnosis and accurate staging
- As per the American College of Chest Physicians (ACCP) guidelines, the initial evaluation should be complete within six weeks in patients with tolerable symptoms and no complications
- Only 26% and 8% of cancers are diagnosed at stages I and II respectively
- 28% and 38% are diagnosed at stages III and IV respectively. Therefore, curative surgery is an option for only a minority of patients.

Evaluation

- Lung cancer evaluation can be divided as:
  - ➢ Radiological staging
- Every patient suspected of having lung cancer should undergo the following tests:
  - Contrast-enhanced CT chest with extension to upper abdomen up to the level of adrenal glands
  - Imaging with PET directed at sites of potential metastasis when symptoms or focal findings are present or when chest CT shows evidence of advanced disease.
  - MRI barin for tumors larger than 5 cm
  - ➢ Invasive staging
- Bronchoscopic endobronchial ultrasound-transbronchial needle aspiration (TBNA)
- Endoscopic-TBNA
- Mediastinoscopy
- Thoracoscopy or video-assisted thoracoscopy(VATS)

Staging

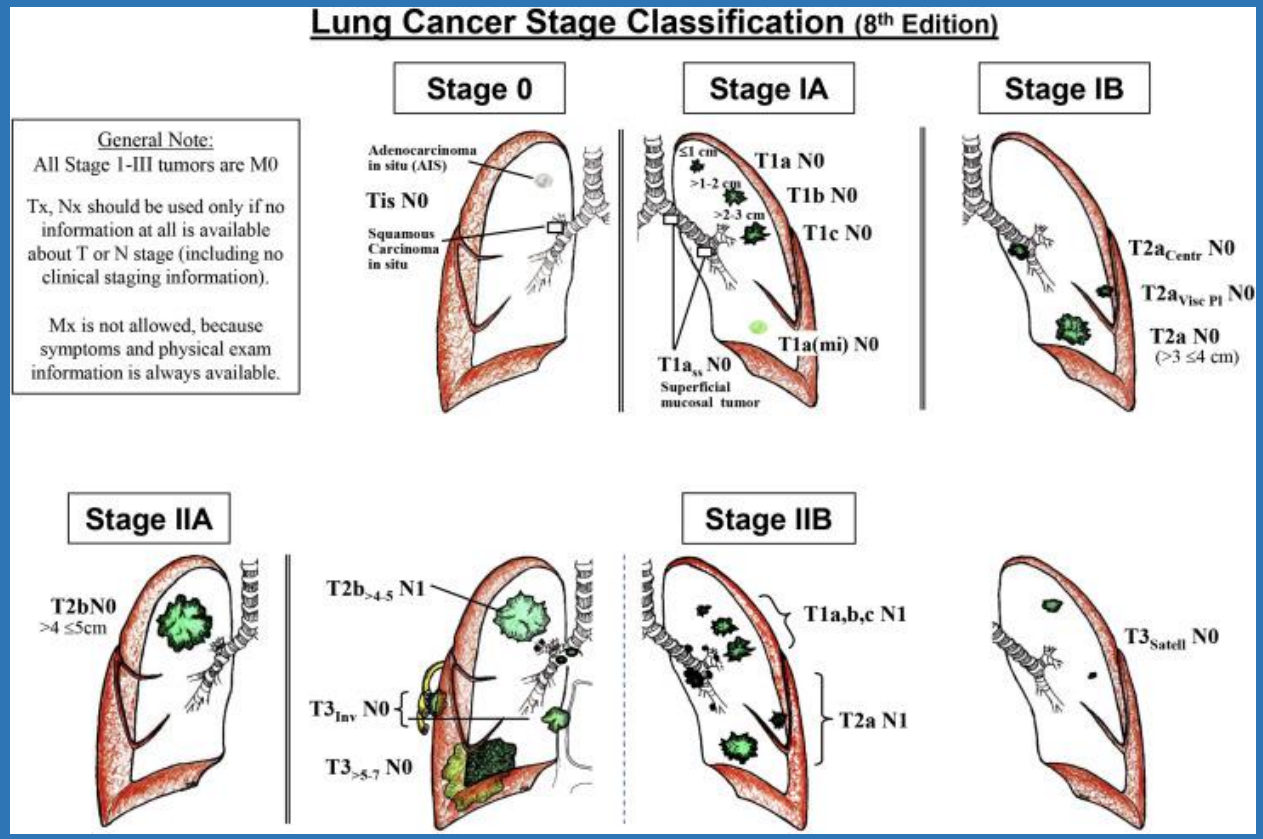
TABLE

Descriptors and T and M categories in the 7th Edition and as proposed for the 8th Edition. The resulting stage groupings proposed for the 8th Edition are highlighted in bold where changes have been implemented (the 7th Edition stage is given in parentheses). [1,2]

7th Edition descriptor	Proposals for 8th Edition				
	T/M	N categories overall staging			
		N0	N1	N2	N3
T1 ≤ 1 cm	T1a	**IA1** (IA)	**IIB** (IIA)	IIIA	IIIB
T1 > 1 – 2 cm	T1b	**IA2** (IA)	**IIB** (IIA)	IIIA	IIIB
T1 < 2 – 3 cm	T1c	**IA3** (IA)	**IIB** (IIA)	IIIA	IIIB
T2 > 3 – 4 cm	T2a	**IB**	**IIB** (IIA)	IIIA	IIIB
T2 > 4 – 5 cm	T2b	**IIA** (IB)	**IIB** (IIA)	IIIA	IIIB
T2 > 5 – 7 cm	T3	**IIB** (IIA)	**IIIA** (IIB)	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 structures	T3	**IIB**	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 > 7 cm	T4	**IIIA** (IIB)	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 diaphragm	T4	**IIIA** (IIB)	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 endobronch: location/atelectasis 3 – 4 cm	T2a	**IB** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T3 endobronch: location/atelectasis 4 – 5 cm	T2b	**IIA** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T4	T4	**IIIA**	IIIA	IIIB	**IIIC** (IIIB)
M1a	M1a	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1b single lesion	M1b	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1c multiple lesions	M1c	**IVB** (IV)	**IVB** (IV)	**IVB** (IV)	**IVB** (IV)

Staging

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



Treatment of lung cancer

- Two Main Questions:
  - Is the tumor resectable (staging)?
    - No benefit from debulking
    - Answerable from work-up
  - Is the patient operable (general health)?
    - Can the patient withstand the stress of surgery?
    - Do the potential benefits outweigh the risks?

Treatment of lung cancer –Stage I(NSCLC)

- Surgery is the mainstay of treating stage 1 NSCLC. The procedure of choice is either lobectomy or pneumonectomy with mediastinal lymph node sampling.
- The 5-year survival is 78% for IA and 53% for IB disease.
- In patients who do not have the pulmonary reserve to tolerate pneumonectomy or lobectomy, a more conservative approach with wedge resection or segmentectomy can be done.
- The disadvantage is a higher local recurrence rate, but survival is the same.
- Local postoperative radiation therapy or adjuvant chemotherapy has not been shown to improve outcomes in stage I disease.

Treatment of lung cancer –Stage II(NSCLC)

- The survival of stage IIA and IIB lung is 46% and 36%, respectively.
- The preferred treatment is surgery followed by adjuvant chemotherapy. If the tumor has invaded the chest wall, then an en-bloc resection of the chest wall is recommended.

Pancost tumor

- Pancoast tumor is a unique tumor of stage II. It arises from the superior sulcus and is usually diagnosed at a higher stage, IIB or IIIA.
- The treatment of choice in cases of Pancoast tumor is neoadjuvant chemotherapy, usually with etoposide and cisplatin and concurrent radiotherapy followed by resection.
- Overall survival is 44% to 54% depending on postsurgery presence or absence of microscopic disease in the resected specimen.

Treatment of lung cancer –Stage III(NSCLC)

- This is the most heterogeneous group, consisting of a wide variety of tumor invasion and lymph node involvement, Survival is 40% to 45% in the first two years, but five-year survival is only 20%.

- In stage IIIA disease with N1 lymph nodes, surgery with curative intent is the treatment of choice. Unfortunately, a significant number of patients are found to have an N2 disease at the time of resection.
- Stage IIIA tumors with N2/N3 lymph nodes. If the patient has good performance status and no weigh-loss, then concurrent chemo-radiotherapy affords the best outcome

Treatment of lung cancer –Stage III(NSCLC)

- Stage IIIB tumors are treated the same way unresectable IIIA cancers are treated, with concurrent chemo-radiotherapy.
- For a select few patients, post-induction chemo-radiotherapy, surgery might be an option. The trials on the survival of patients with IIIB tumors also included inoperable IIIA tumors; therefore, the survival in IIIB patients is unknown.

Treatment of lung cancer –Stage IV(NSCLC)

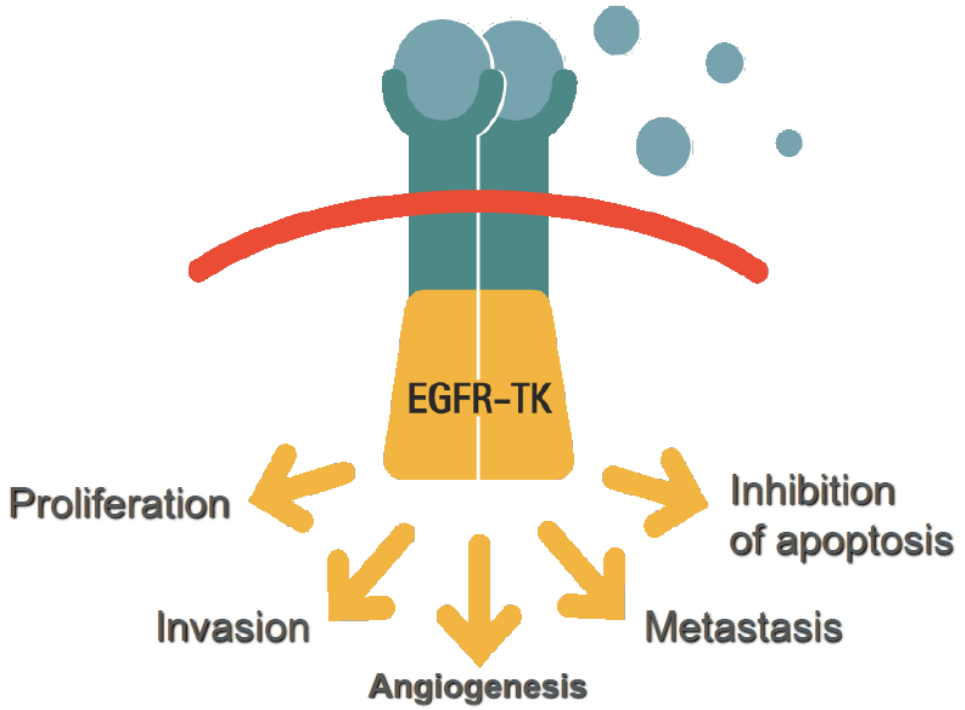
- Stage IV disease is considered incurable, and therapy is aimed at improving survival and alleviating symptoms. Only 10% to 30% of patients respond to chemotherapy, and only 1% to 3% survive five years after diagnosis
- Single or double drug-based chemotherapy is offered to patients with functional performance status. There is a small survival benefit from chemotherapy.

Targeted therapy

- In the early 2000s, researchers discovered that specific mutations encode critical proteins for cell growth and replication. These mutations were named “driver mutations.”
- It was proposed that blocking these mutation pathways may improve survival in lung cancer patients.
- The current practice is to check for the following mutations in every advanced NSCLC. Each of these mutations has a specific inhibitor available:
  - EGFR (epidermal growth factor receptor) is a mutation inhibited by tyrosine kinase inhibitors erlotinib, gefitinib, and afatinib.[36]
  - ALK (Anaplastic lymphoma kinase) includes the specific inhibitors crizotinib, ceritinib, and alectinib. A structurally similar mutation is ROS-1. The FDA recently approved crizotinib for treating cancers expressing ROS-1 mutation.

EGFR-TK

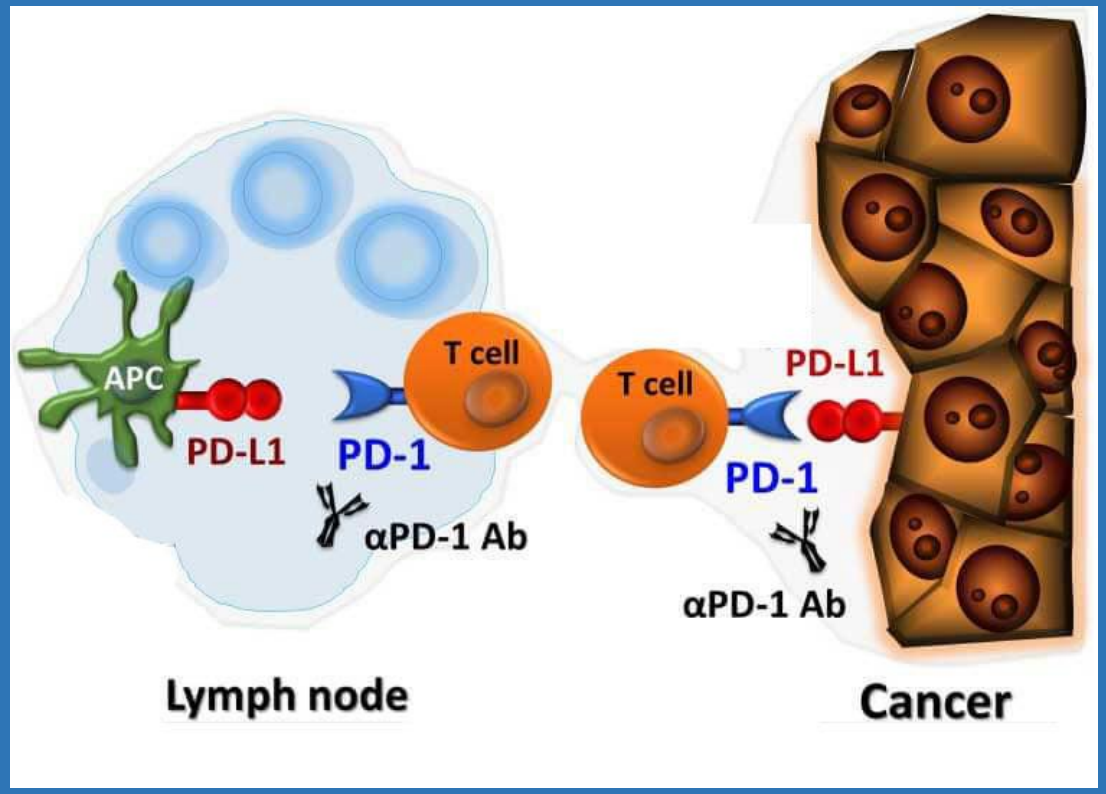
- In tumor cells, the EGFR-TK signal is inappropriately turned on by various mechanisms inside or outside the cell
- EGFR-TK enzyme activity drives uncontrolled tumor growth



Targeted therapy

Targeted oncogenic driver	FDA approved drugs	Drugs under study
EGFR	Gefitinib, erlotinib, afatinib, osimertinib	Dacomitinib, olmutinib (HM61713), ASP8273, nazartinib (EGF816), avitinib, PF-06747775, HS-10296
ALK	Crizotinib, ceritinib, alectinib, brigatinib	Ensartinib, entrectinib, lorlatinib
ROS1	Crizotinib	Ceritinib, cabozantinib, entrectinib, lorlatinib
RET1		RXDX-105, cabozantinib, vandetanib, sunitinib, sorafenib, alectinib, lenvatinib, nintedanib, ponatinib, regorafenib
NTRK1		Entrectinib, larotrectinib (LOXO-101), LOXO-195
BRAF	Dabrafenib and trametinib combination	Vemurafenib, PLX8394, selumetinib
HER2		Afatinib, dacomitinib, trastuzumab
MET		Crizotinib, cabozantinib, capmatinib, MGCD265
KRAS		Selumetinib, trametinib, ARS853

Immunotherapy

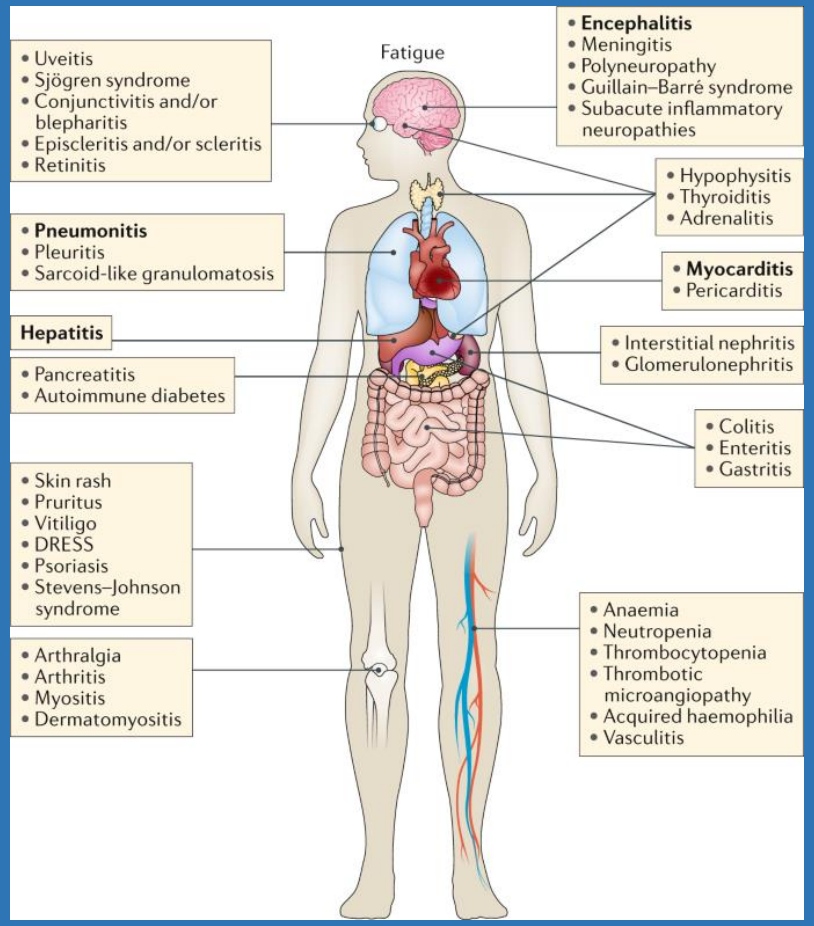


- PD-1 plays an important role in down-regulating T-cells and promotes self-tolerance. However, it also renders the immune system less effective against tumor cells.
- PD-1 interacts with two proteins: PD-L1 and PD-L2. This binding results in the inactivation of activated T-cells

Immunotherapy

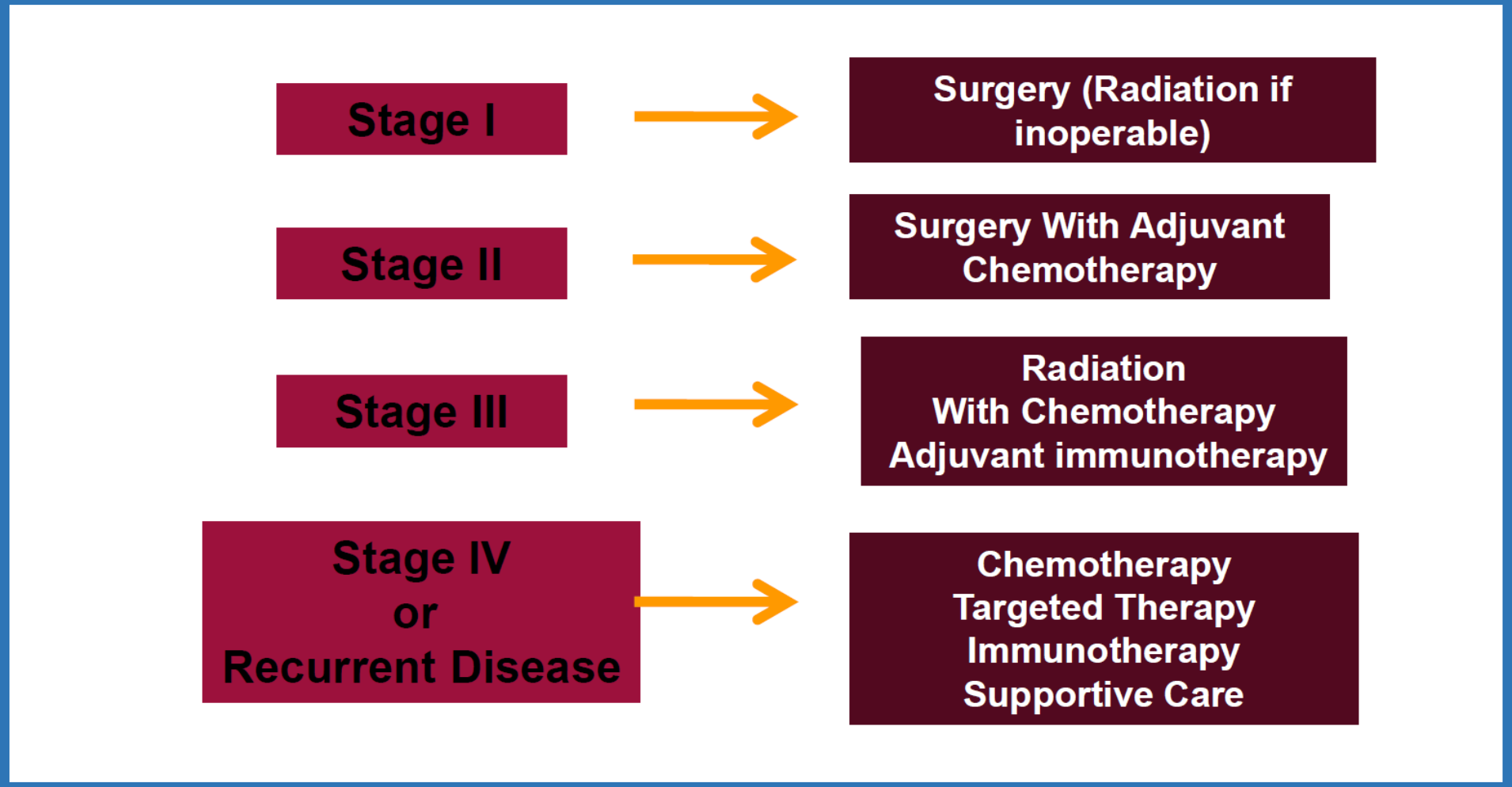
- Immunotherapy is used when tumors lack gentic mutation that can be targeted or failed targeted therapy.
- Nivolumab is an IgG4 monoclonal antibody against PD-1. It is approved by the FDA for squamous and non-squamous NSCLC that has progressed after platinum-based chemotherapy. It can be used in patients with high or low PD-L1 expression status
- Pembrolizumab is also an IgG4 monoclonal antibody against PD-1. It is approved for pre-treated metastatic NSCLC with greater than 50% expression of PD-L1 and does not harbor EGFR and ALK mutations.

Immunotherapy related adverse events



VEGF-A

- Bevacizumab is not considered immune therapy. It is an anti-angiogenesis antibody that inhibits vascular endothelial growth factor A (VEGF-A).
- It is primarily used in combination with platinum-based chemotherapy to treat non-squamous NSCLC.
- It is contraindicated in squamous cell NSCLC due to the risk of severe and often fatal hemoptysis.
- It is also used to treat breast, renal, colon, and brain cancers


Stage I
Surgery (Radiation if inoperable)
Stage II
Surgery With Adjuvant Chemotherapy
Stage III
Radiation
With Chemotherapy
Adjuvant immunotherapy
Stage IV
or
Recurrent Disease
Chemotherapy
Targeted Therapy
Immunotherapy
Supportive Care

Treatment of small cell cancer

- SCLC is very sensitive to chemotherapy, but unfortunately, has a very high recurrence rate. Treatment for SCLC is according to the stage of the disease.
- Limited stage vs extensive stage
- Stage I limited-stage small cell lung cancer (LS-SCLC) is lobectomy followed by adjuvant chemotherapy. These include SCLC presenting as peripheral nodules without mediastinal or hilar lymphadenopathy
- LS-SCLC with mediastinal or hilar lymph node involvement is 4 to 6 cycles of chemotherapy followed by radiation therapy.

Limited stage SCLC

- Radiation therapy is indicated to avoid recurrence since nearly 80% of SCLC will recur locally without radiation therapy.
- In patients who achieve remission, prophylactic whole brain radiation is also done. This significantly reduces symptomatic brain metastasis and increases overall survival

Extensive stage SCLC

- Extensive stage small cell lung cancer (ES-SCLC) includes distant metastasis, malignant pleural or pericardial effusions, contralateral hilar, or supraclavicular lymph node involvement.
- Treatment is with platinum-based chemotherapy.
- Up to 50% to 60% of patients show remission and should be offered radiation therapy followed by prophylactic whole-brain irradiation.
- Median survival from the time of diagnosis of ES-SCLC is only 8 to 13 months, and only about 5% of patients survive two years postdiagnosis.

National Lung Screening Trial

- 53,454 participants
- Age 55-74 (Medicare covers until 77)
- Current or former smokers – 30 pack years. If quit, had to quit within 15 years.
- Randomized to Low Dose CT (LDCT) vs CXR
- Scanned for 3 years followed for 3.5 years
- 20% reduction in lung cancer mortality
- 7% reduction in overall mortality