

# Lung Cancer

David M. Jackman, MD

Senior Physician, Lowe Center for Thoracic Oncology  
Medical Director of Clinical Pathways and New Business Initiatives  
Medical Director, DFCI Collaborative and Strategic Alliances  
Dana-Farber Cancer Institute

Assistant Professor of Medicine  
Harvard Medical School



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### **Titles:**

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- Medical Director of Clinical Pathways and New Business Initiatives, Dana-Farber Cancer Institute
- Medical Director, DFCI Collaborative and Strategic Alliances, Dana-Farber Cancer Institute
- Assistant Professor, Harvard Medical School

### **Education and Training:**

- AB and MD: Brown University, Providence, RI
- Residency, Internal Medicine: Beth Israel Deaconess Medical Center, Boston, MA
- Fellowship, Medical Oncology: Dana-Farber/Massachusetts General Hospital, Boston, MA

### **Specialty:**

- Thoracic Malignancies
- Cancer Care Delivery

# Disclosures

- I have no conflicts to disclose

# Objectives

- Epidemiology
- Lung Cancer Screening
- Clinical Presentation, Diagnosis, Staging
- Overview of Lung Cancer Therapy



# Epidemiology

# Practice Question 1

Which of the following statements is true about lung cancer?

- A. Breast cancer causes more deaths in women than lung cancer.
- B. For former smokers, it takes ~ 10 years for the risk of lung cancer to decrease to the level of a nonsmoker.
- C. There are about 20,000 – 40,000 new cases of lung cancer in never smokers in the US each year.
- D. Tumor grade (level of differentiation under the microscope) is a more important prognostic factor than tumor stage (extent of disease on scans)
- E. Small cell lung cancer is both more aggressive and more common than non-small cell lung cancer.

Epidemiology

Screening

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# Lung Cancer Epidemiology

*at a glance*

## Impact of Smoking on Lung Cancer Risk: Rules of 20

**20x**

Smoking increases one's risk of smoking by ~ 20-fold.

**20%**

Up to 20% of new lung cancer cases in the US occur in never smokers.

**10 x 2**

10 years after smoking cessation, one's lung cancer risk is cut in two

## Does vaping cause lung cancer?

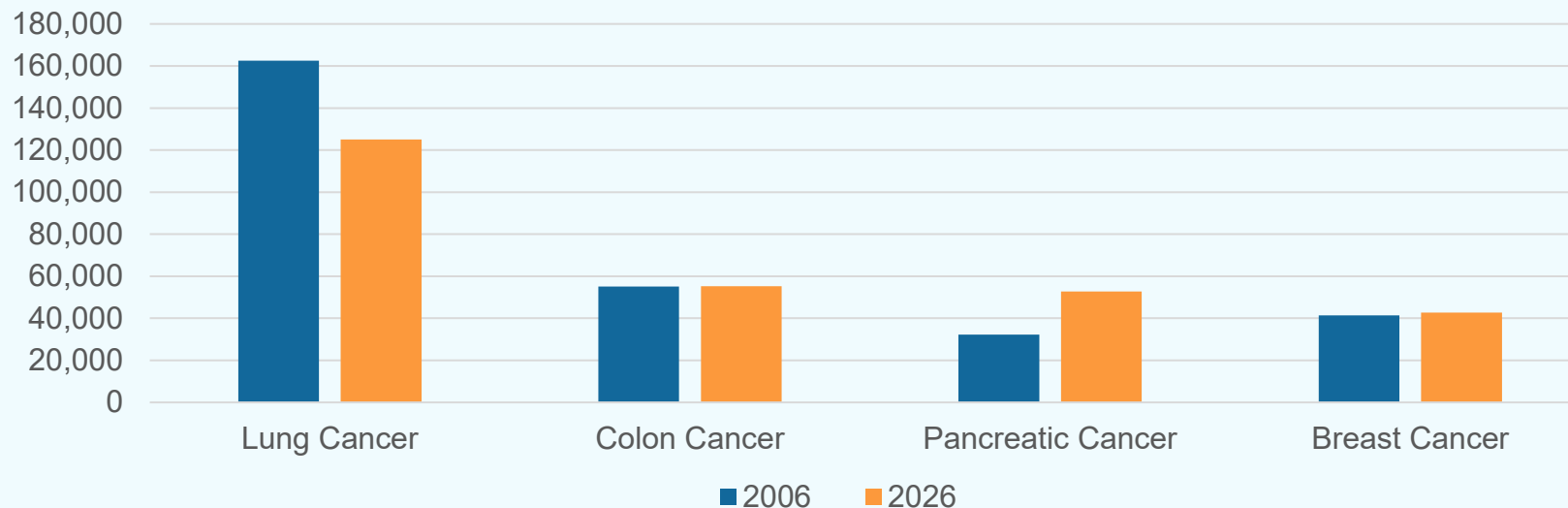
**It is still too early to say.**

However, we know that vape has been found to contain:

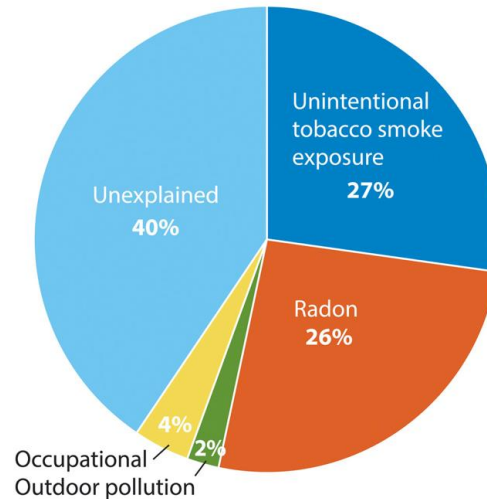
- Acetaldehyde
- Acrolein
- Benzene
- Cadmium
- Diacetyl
- Diethylene glycol
- Formaldehyde
- Heavy metals (lead, nickel, tin)

American Lung Association ([www.lung.org/quit-smoking/e-cigarettes-vaping/whats-in-an-e-cigarette](http://www.lung.org/quit-smoking/e-cigarettes-vaping/whats-in-an-e-cigarette))

## Number of deaths among leading causes of cancer mortality, 2006 vs 2026



Based on data from Jemal et al, CA: A Cancer Journal for Clinicians, 2006, Segal et al, CA: A Cancer Journal for Clinicians 2026.



## Causes of lung cancer in non-smokers

Adapted from American Cancer Society Facts & Figures 2006. Special section Environmental Pollutants.

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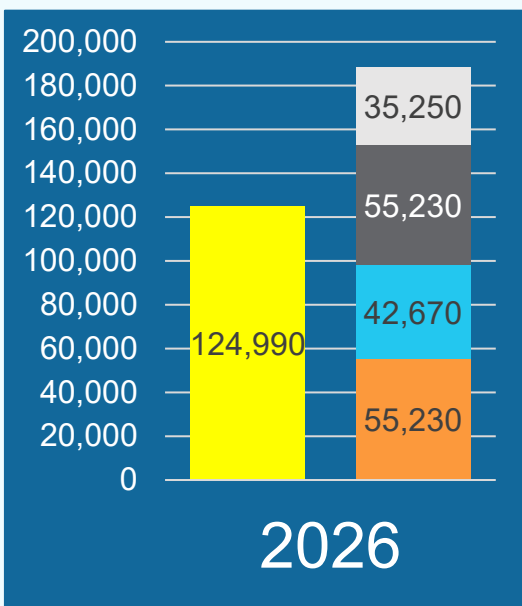
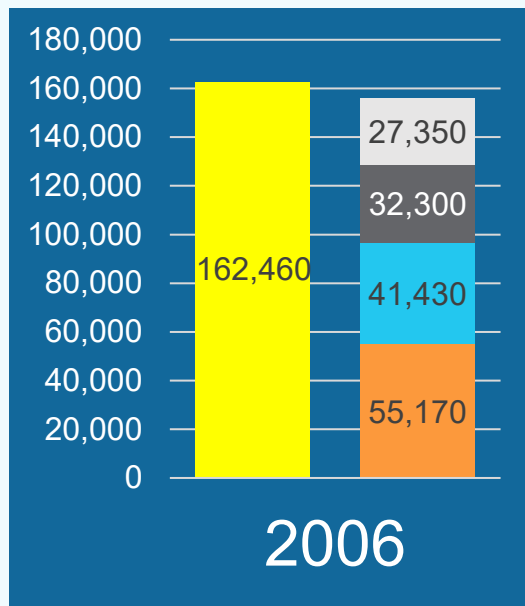
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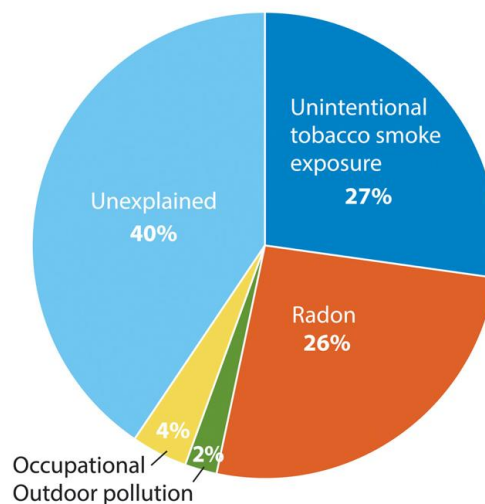
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- Lung Cancer
- Colorectal Cancer
- Breast Cancer
- Pancreatic Cancer
- Prostate Cancer



**Causes of lung cancer in non-smokers**  
Adapted from American Cancer Society Facts & Figures 2006. Special section Environmental Pollutants.

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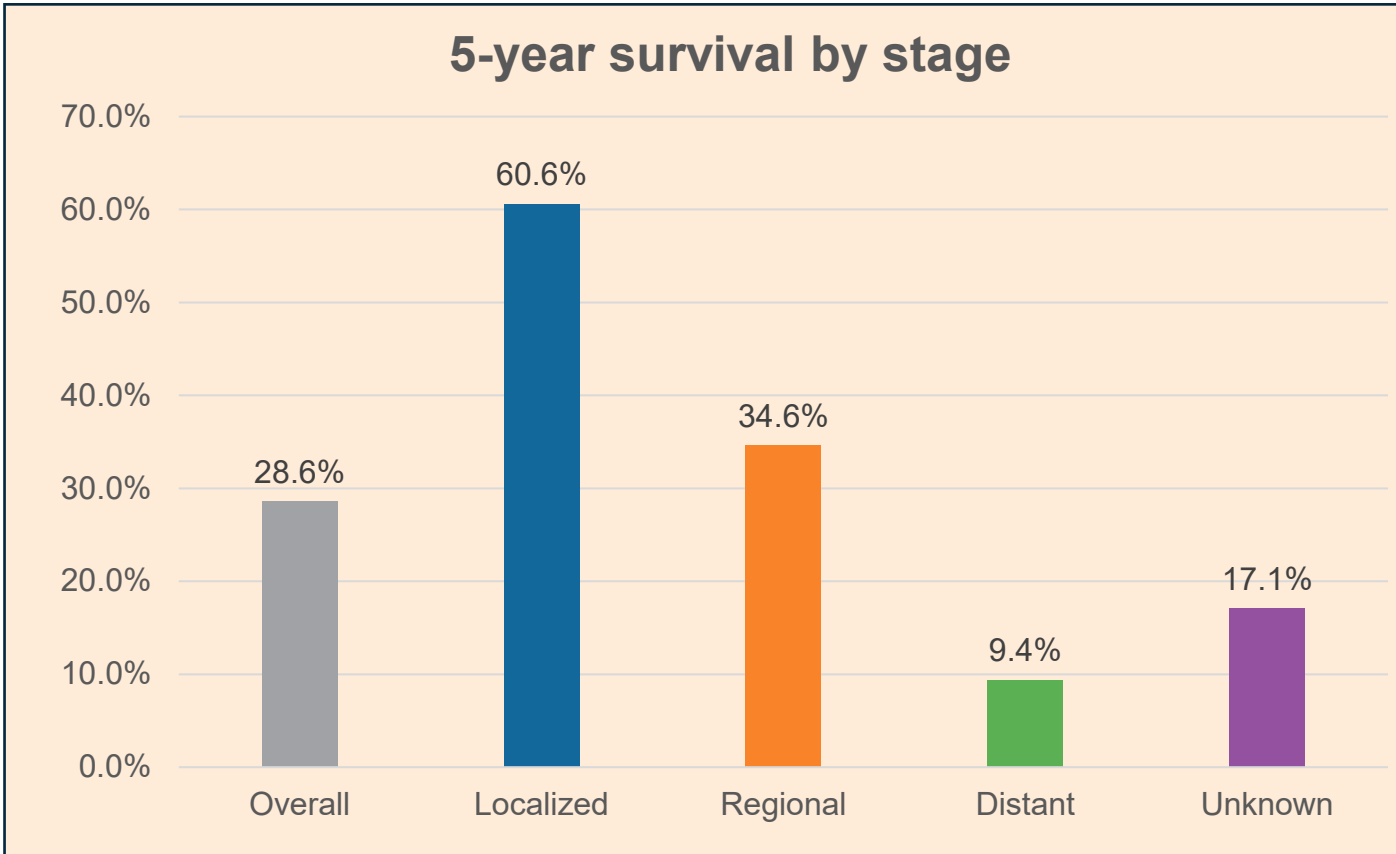
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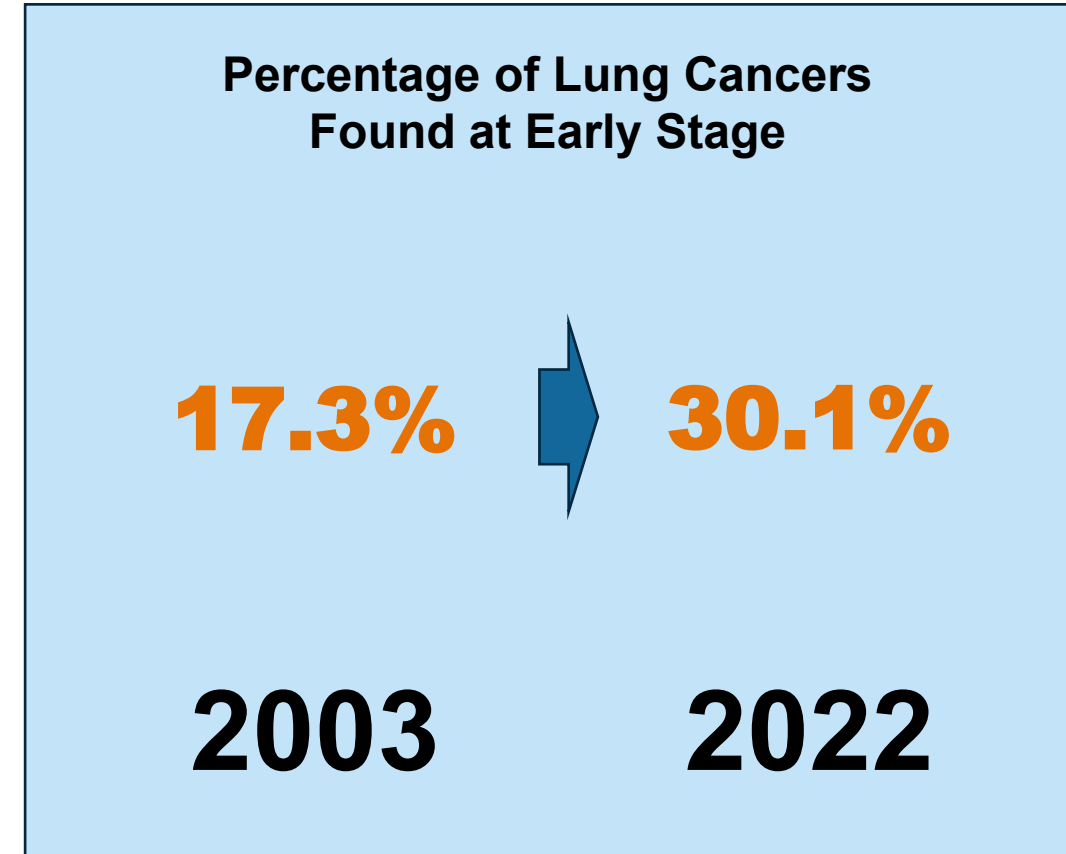
Lung Cancer Therapy

Summary

# Stage remains a critical prognostic factor



These data from [www.cdc.gov](https://www.cdc.gov) are based on cancers diagnosed from 2015-2021 and follow-up of patients through 12/31/21.



[Henley et al, JAMA Oncology 2026](#)

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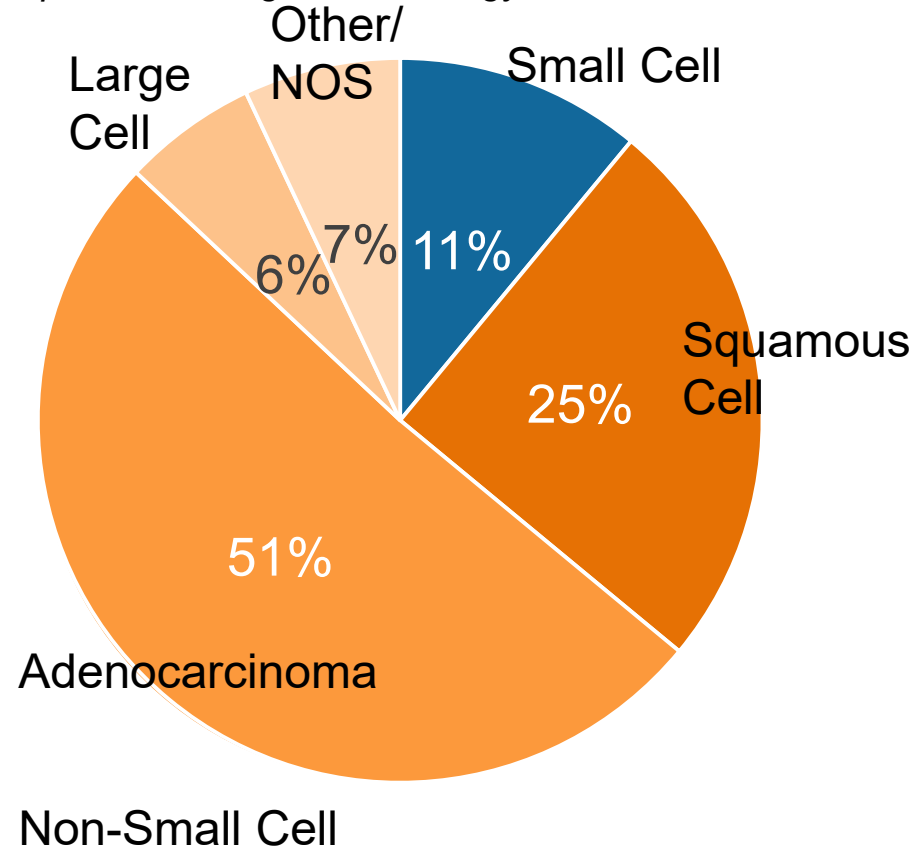
Lung Cancer Therapy

Summary

# Impact of Lung Cancer Histology



Adapted from Targeted Oncology, 11/20/17



|                                    | Non-Small Cell                 |               |                                    |
|------------------------------------|--------------------------------|---------------|------------------------------------|
|                                    | Small Cell                     | Squamous      | Adenocarcinoma                     |
| Most Common Location               | Central                        | Central       | Central or Peripheral              |
| Found in non-smokers?              | Exceedingly Rare               | Rare          | Yes                                |
| Targetable genomic alterations     | Extremely unlikely             | Unlikely      | Possible, especially in nonsmokers |
| Classic Paraneoplastic Syndrome(s) | SIADH, Cushings, Lambert-Eaton | Hypercalcemia | -                                  |

# Practice Question 1

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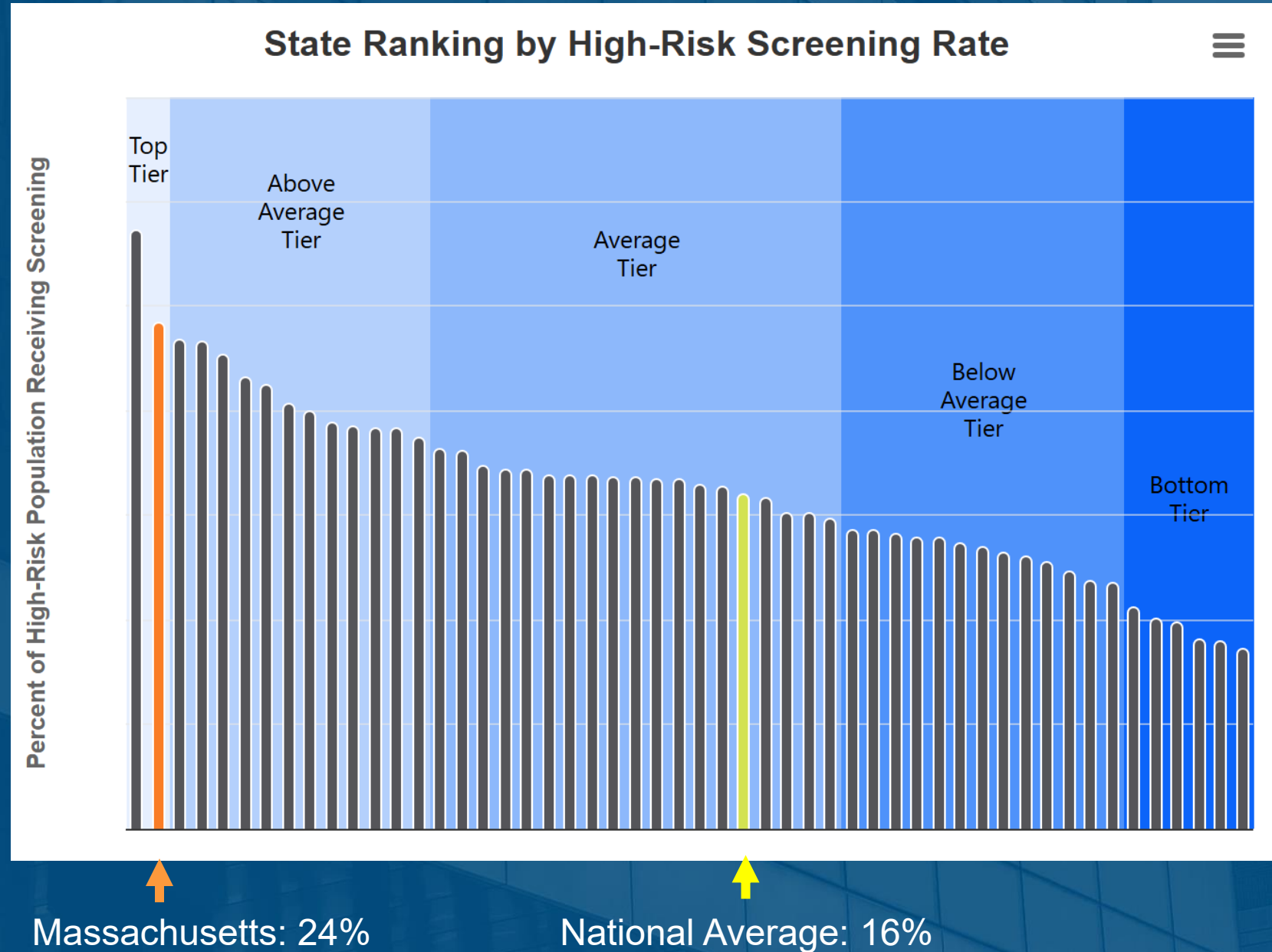
# Lung Cancer Screening

# Practice Question 2

According to current USPSTF Guidelines, low-dose CT screening for lung cancer is currently recommended for which of the following asymptomatic patients?

- A. A 42 year-old nonsmoking former naval midshipmen with a history of asbestos exposure
- B. A 56 year-old non-smoker whose father had died of lung cancer at age 64.
- C. A 76 year-old who had smoked 1 pack per day for 30 years (from age 16-46), quit 30 years ago.
- D. A 70 year-old who had smoked 1 pack per day for 20 years (from age 45-65), quit 5 years ago
- E. A frail 84 year-old with Class III CHF who has continued to smoke 2 packs per day since age 14.

# State-by-State Lung Cancer Screening Rates in High-Risk Patients, 2024



# ABCs of Lung Cancer Screening (USPSTF)



## Audience

- **Asymptomatic adults, and**
- **Aged 50 to 80 years, and**
- **Heavy and recent smoking history:**
  - **$\geq 20$  pack-years, and**
  - **Currently smoke or quit smoking within the past 15 years.**

## Benefit

**NLST** (NEJM 2011. 365: 395-409):

- 20% decrease in lung cancer mortality
- 6.7% decrease in all cause mortality

**NELSON** (de Koning et al, WCLC 2018):

- 26% decrease in lung cancer mortality

**USPSTF: Grade B**

## Calendar

- **Annual Low-Dose Chest CT**
- Screening can be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.

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# Follow-up of Radiographic Findings

| Setting                                                                     | Guidelines                        |
|-----------------------------------------------------------------------------|-----------------------------------|
| Screening of an asymptomatic patient                                        | LUNG-RADS <sup>1</sup>            |
| Incidental finding on a scan performed for another reason                   | Fleishner Guidelines <sup>2</sup> |
| Radiographic study performed as part of evaluation of a symptomatic patient | Aggressive evaluation             |

1. LUNG-RADS: American College of Radiology. <https://www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/LungRADSAssessmentCategoriesv1-1.pdf>
2. Fleishner Guidelines: MacMahon et al, Radiology 2017. <https://pubs.rsna.org/doi/10.1148/radiol.2017161659>

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# Clinical Presentation, Diagnosis, and Staging

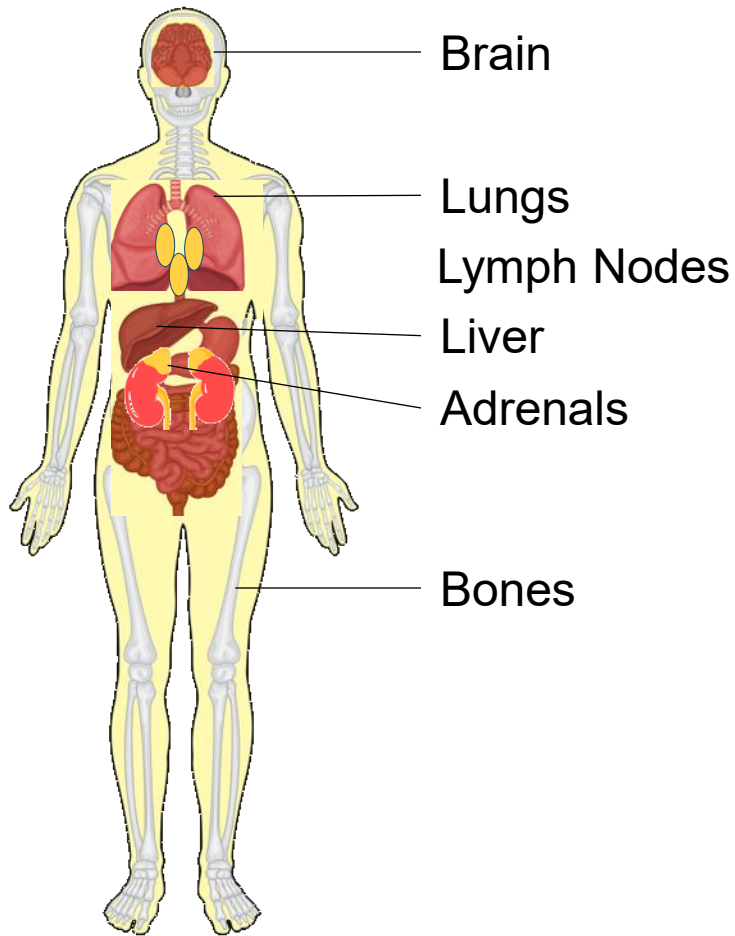
# Practice Question 3

A 68 year-old man with ongoing tobacco use (1ppd x 50 years) presents with worsening shortness of breath over 2 months time, along with hoarseness. CT angiogram is negative for pulmonary embolus, but it does show a large left hilar mass, along with subcarinal and left supraclavicular adenopathy and concerns for lesions in the liver and left adrenal. Serum chemistries are notable for a sodium of 124.

What is the most likely cause of hyponatremia?

- A. Dehydration
- B. Psychogenic polydipsia
- C. Syndrome of inappropriate antidiuretic hormone (SIADH)
- D. Laboratory error

# Clinical Presentation of Lung Cancer:



## Generalized Symptoms

- Fatigue
- Weight loss
- Night sweats

## Symptoms related to local destruction, obstruction, or replacement

- Cough
- Shortness of breath
- Hemoptysis
- SVC Syndrome
- Focal bone pain
- Fracture
- Cord Compression
- Focal CNS symptoms
- Seizure
- Altered Mental Status

## Paraneoplastic Syndromes

- SIADH
- Paraneoplastic Cushings
- Hypercalcemia

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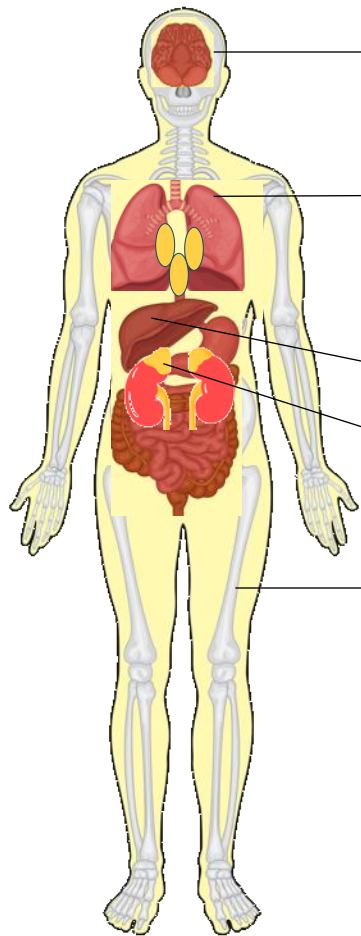
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# Lung Cancer Staging:



Brain

Brain MRI with gad (preferred), or  
CT head with IV contrast

Lungs

Lymph Nodes

CT chest with IV contrast

Liver

Adrenals

Bones

PET/CT (preferred), or  
Bone scan

## Mediastinal Nodes

- **Mediastinal staging:**
  - For potentially resectable patients
  - For patients with locally advanced disease
- **How:**
  - Mediastinoscopy
  - Bronchoscopy/EBUS
  - Lymph node dissection at the time of surgery

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# Lung Cancer Diagnosis:

## ENDS

- ☐ Safe, timely, accurate diagnosis
- ☐ Obtain sufficient tissue for subsequent biomarker studies, clinical trial eligibility
- ☐ Confirm spread (when applicable)

## MEANS

- ☐ CT-guided biopsy
- ☐ Bronchoscopy/EBUS
- ☐ Mediastinoscopy
- ☐ Thoracentesis, other drainage
- ☐ Surgical procedure
- ☐ Other

## Additional Information:

- ☐ Bone biopsies are usually inadequate for biomarker studies and trial eligibility. The decalcification process that bone biopsies undergo denatures DNA.
- ☐ If there appears to be only a single site of spread, it should be biopsied to confirm or rule out metastasis.

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# Paraneoplastic Syndromes



| Disease                | Paraneoplastic Syndrome                                | Mechanism                                        |
|------------------------|--------------------------------------------------------|--------------------------------------------------|
| Squamous NSCLC         | Hypercalcemia                                          | PTHrP                                            |
| Small cell lung cancer | Syndrome of inappropriate antidiuretic hormone (SIADH) | Anti-diuretic hormone (aka arginine vasopressin) |
|                        | Cushing syndrome                                       | Ectopic ACTH                                     |
|                        | Lambert-Eaton                                          | Ab against voltage-gated calcium channels        |
| Thymoma                | Myasthenia gravis                                      | Ab against nicotinic acetylcholine receptors     |
|                        | Pure red cell aplasia                                  | Suspect IgG against erythroblasts, epo           |

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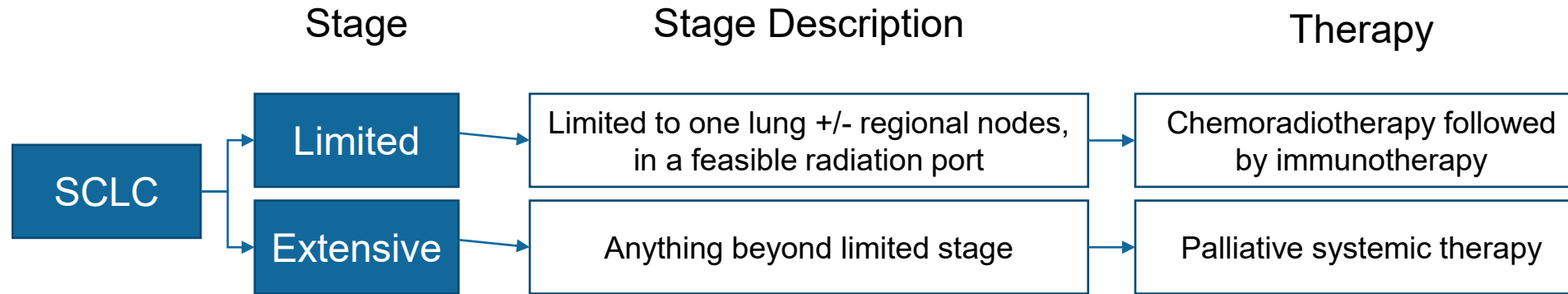
# Overview of Therapy For Lung Cancer

# Practice Question 4

A 66 year-old woman currently on therapy for her stage IV non-small cell lung cancer presents to her local ED with several days of worsening shortness of breath. The differential diagnosis includes which of the following

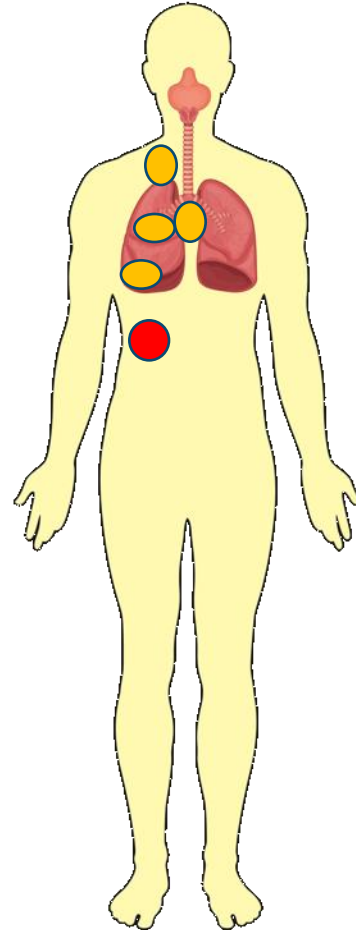
- A. Pericardial effusion / cardiac tamponade
- B. Pleural Effusion
- C. Pneumonitis (treatment-associated)
- D. Post-obstructive pneumonia
- E. Progression of lung cancer
- F. Pulmonary Embolism
- G. All of the above

# Broad Overview of Therapy for Small Cell Lung Cancer



## Key Pearls for Small Cell:

- Almost all SCLC patients have a significant smoking history.
- For previously untreated, metastatic small cell lung: prioritize starting chemotherapy urgently.



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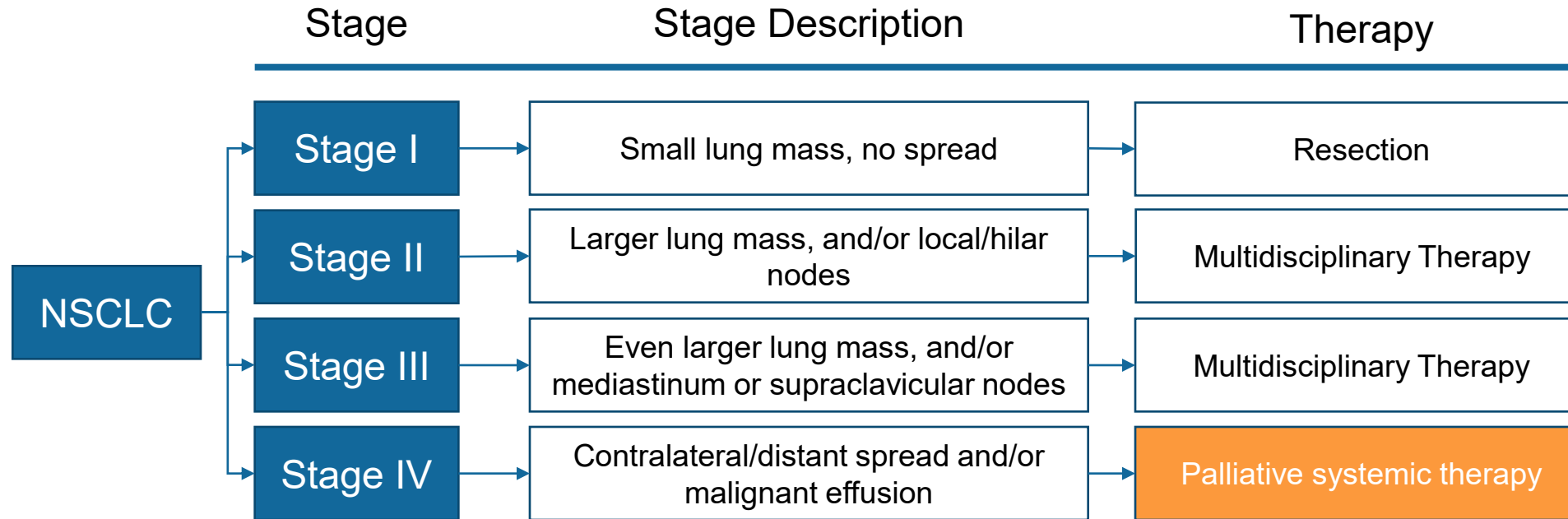
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# Overview of Therapy for Non-Small Cell Lung Cancer



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# Systemic Therapies for Lung Cancer

## Chemotherapies

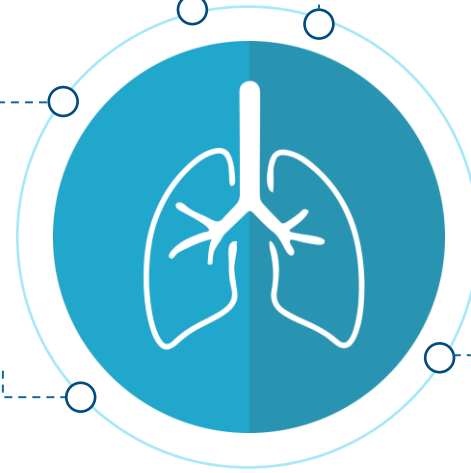
Target vital cell process like DNA synthesis or cell division.

## Antibody-Drug Conjugates

A disease-specific antibody with an anticancer payload

## Bispecifics

Dual-targeted antibodies that might simultaneous attack two targets/pathways, or might target and bind tumor cell and T-cell, bringing them into proximity.



## Oral Targeted Therapies

Genomic testing identifies presence of a targetable genomic aberration. We now have over twenty agents targeting an array of aberrant proteins:

- Mutations: BRAF, EGFR, HER2, KRAS, MET
- Fusions: ALK, NRG, NTRK, RET, ROS1
- Overexpression: MET

## Immunotherapy: Checkpoint Inhibitors

Disrupt regulatory checkpoints of the immune response, exposing cancer cells to recognition and attack by the body's immune system

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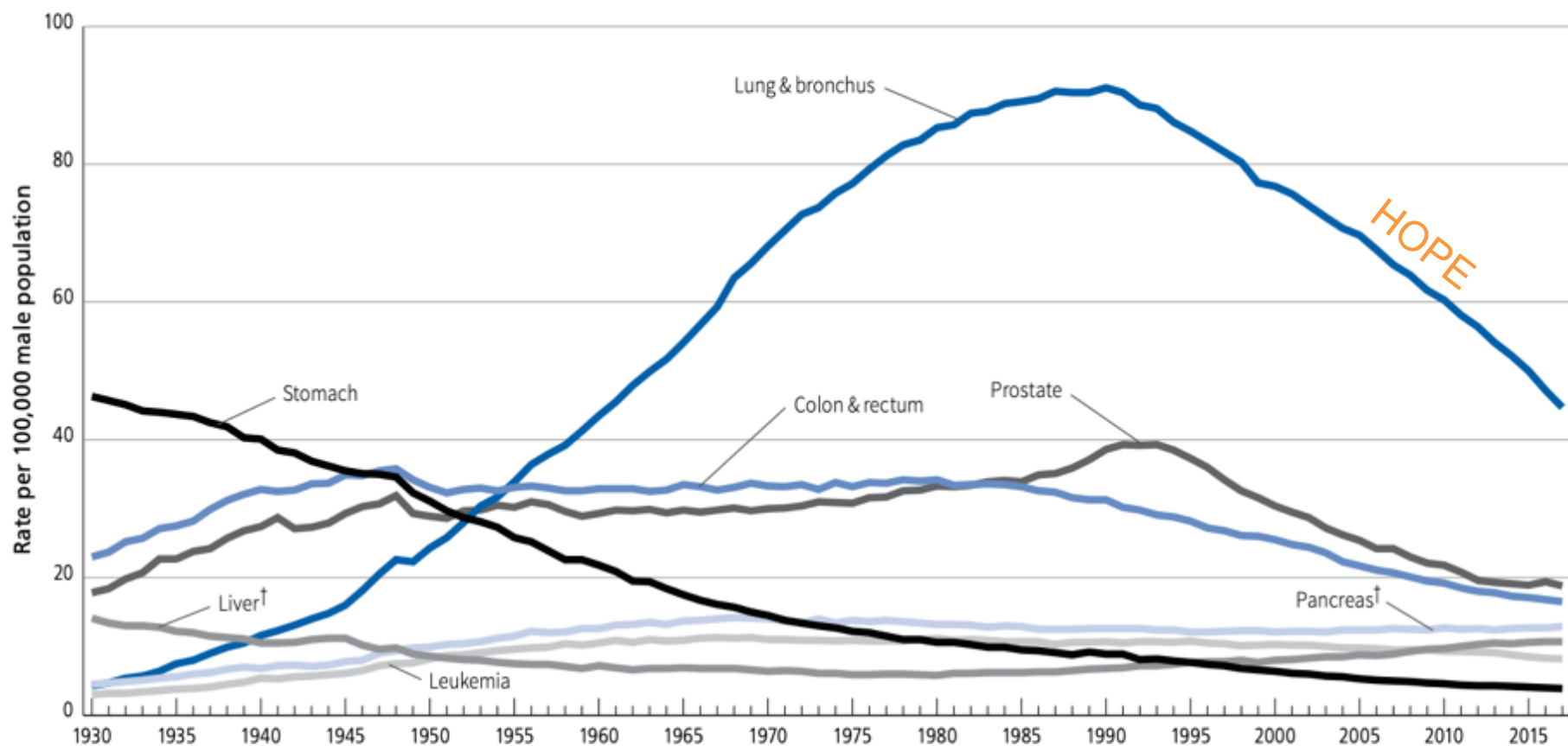
# Considerations with Targeted Therapies

- Caution with CYP3A4 inhibitors/inducers
  - Many anti-virals, some antibiotics
  - Many anti-epileptics
  - grapefruit, St. John's wort
- Don't assume toxicity patterns across class

# Considerations with immunotherapy

- Side effects can occur at any point in treatment course
- Can get immune-mediated toxicity of essentially any system
- Some severe but rare side effects include: pneumonitis, hepatotoxicity, CNS toxicity, cardiotoxicity, SJS
- For severe toxicity: consult, hospitalization, steroids, immunomodulators

Figure 1. Trends in Age-adjusted Cancer Death Rates\* by Site, Males, US, 1930-2017



\*Per 100,000, age adjusted to the 2000 US standard population. †Mortality rates for pancreatic and liver cancers are increasing.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the liver, lung and bronchus, and colon and rectum are affected by these coding changes.

Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2017, National Center for Health Statistics, Centers for Disease Control and Prevention.

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# Take Home Points, Test Prep version

- Stage remains a critical prognostic factor
- Small cell lung cancer is the most likely to be associated with smoking and with paraneoplastic syndromes (esp SIADH)
- Lung cancer screening: for smokers heavy ( $\geq 20$  pk-yrs) and recent (current or quit within the last 15 years)
- Staging: Chest CT w/ contrast, PET/CT, Brain MRI

# Take Home Points, Clinical Practice Version

- Staging: Brain imaging needs IV contrast
- The importance of adequate tissue for diagnosis and testing (core > FNA, non-bone > bone)
- Many targeted therapies are metabolized via CYP3A4 – drug interactions
- Lung Cancer Screening