Brigham and Women's Hospital
Founding Member, Mass General Brigham

Lung Cancer

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Titles:

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Education and Training:

- AB and MD: Brown University, Providence, RI
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Specialty:

- Thoracic Oncology
- 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 that of a nonsmoker.

C. More than half of new lung cancers are already metastatic at the time of diagnosis.

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.

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?

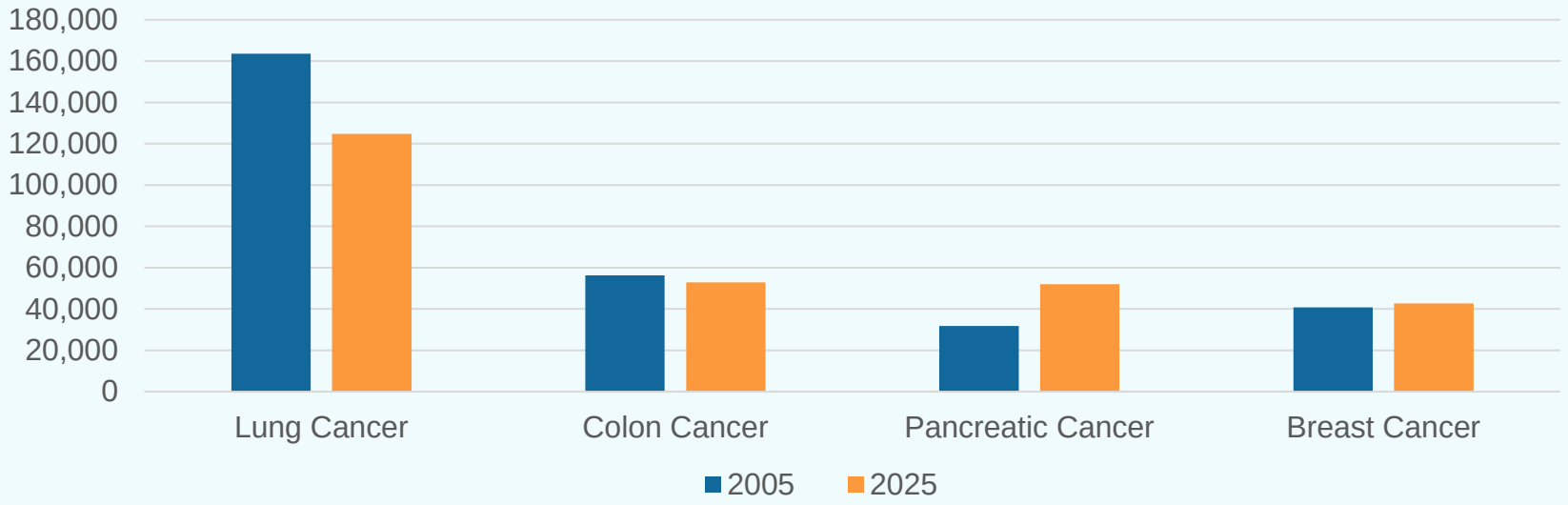
It is still too early to say.

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)

Number of deaths among leading causes of cancer mortality, 2005 vs 2025



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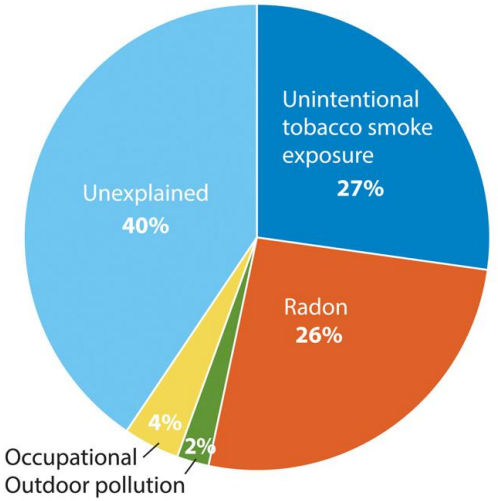

Causes of lung cancer in non-smokers

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

Lung Cancer Epidemiology

at a glance

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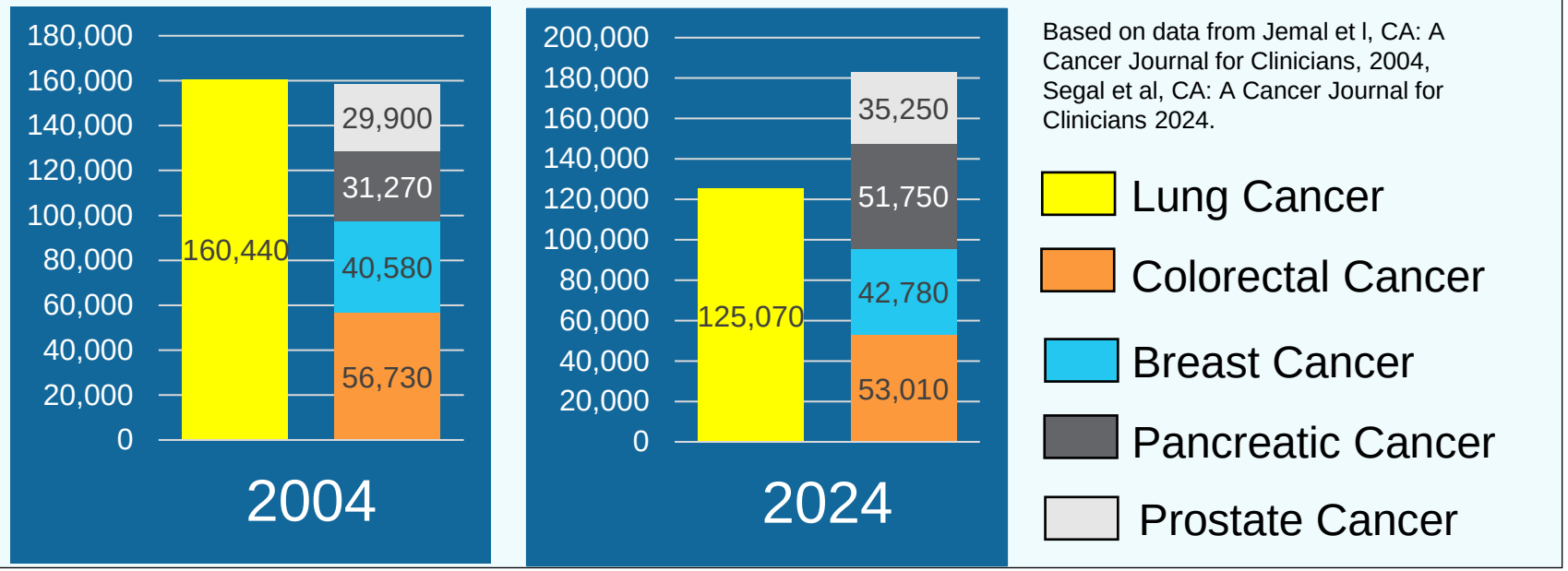

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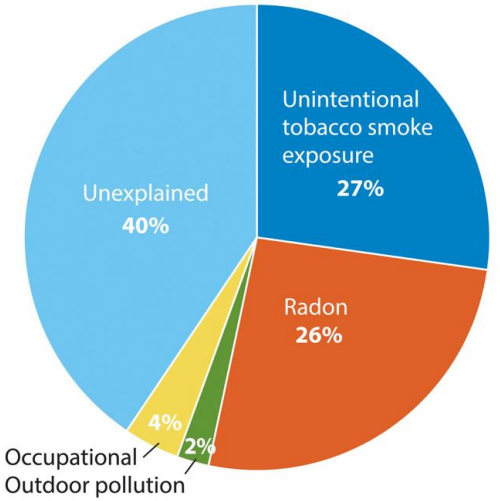
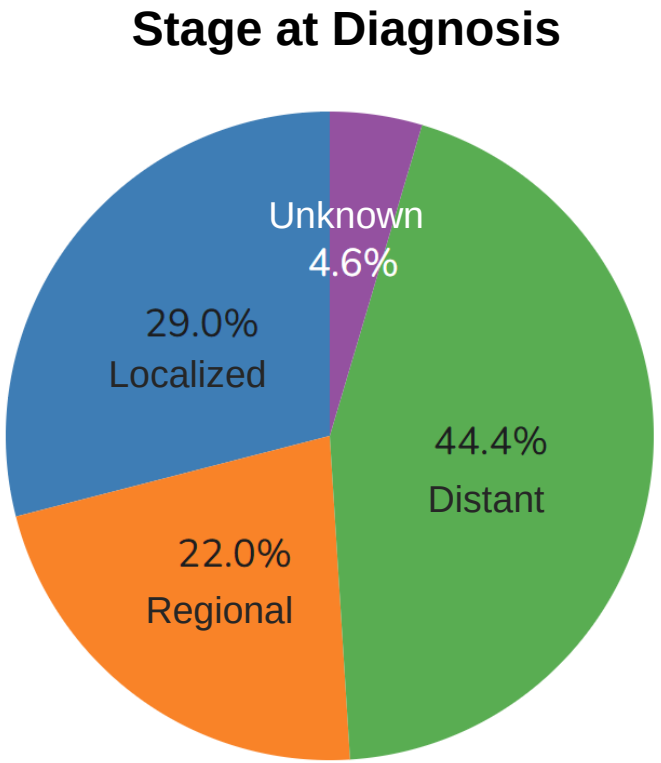
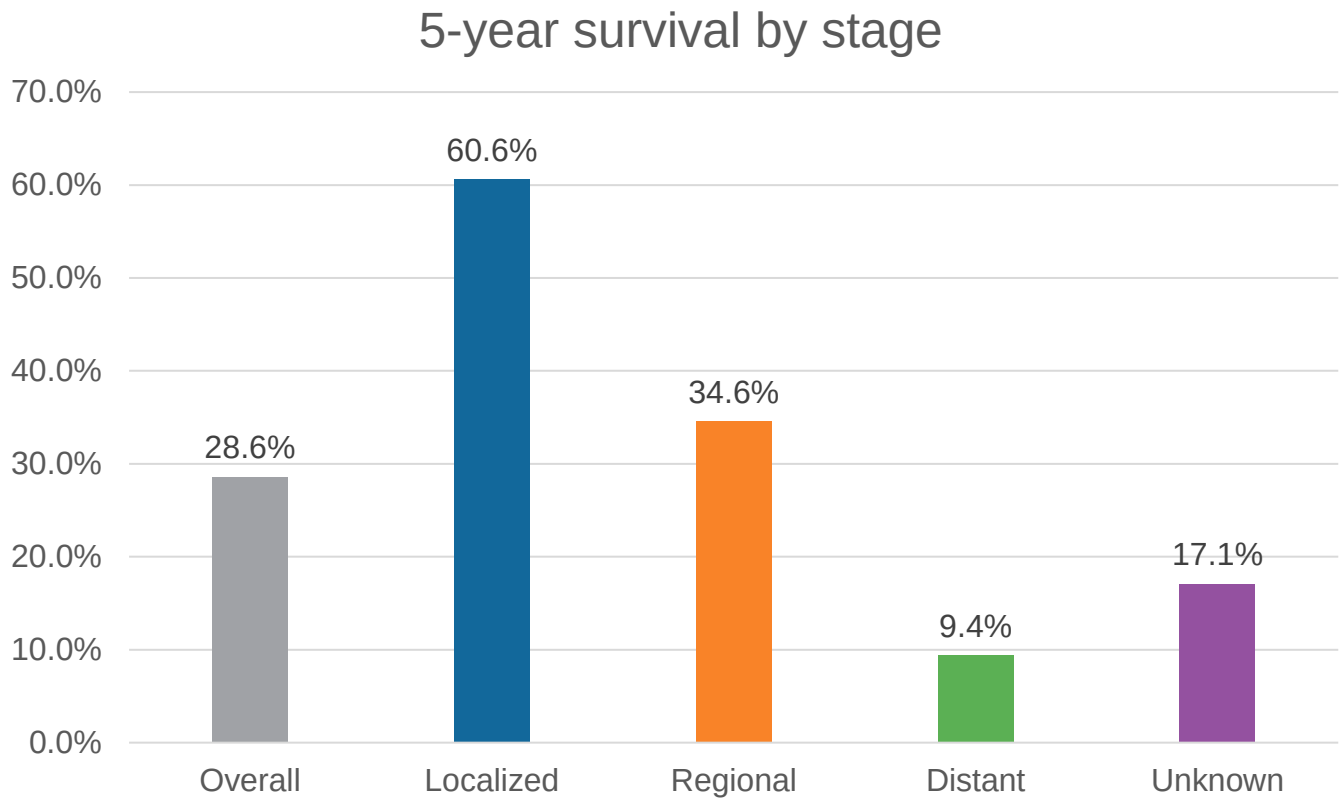


Causes of lung cancer in non-smokers

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

Stage remains a critical prognostic factor

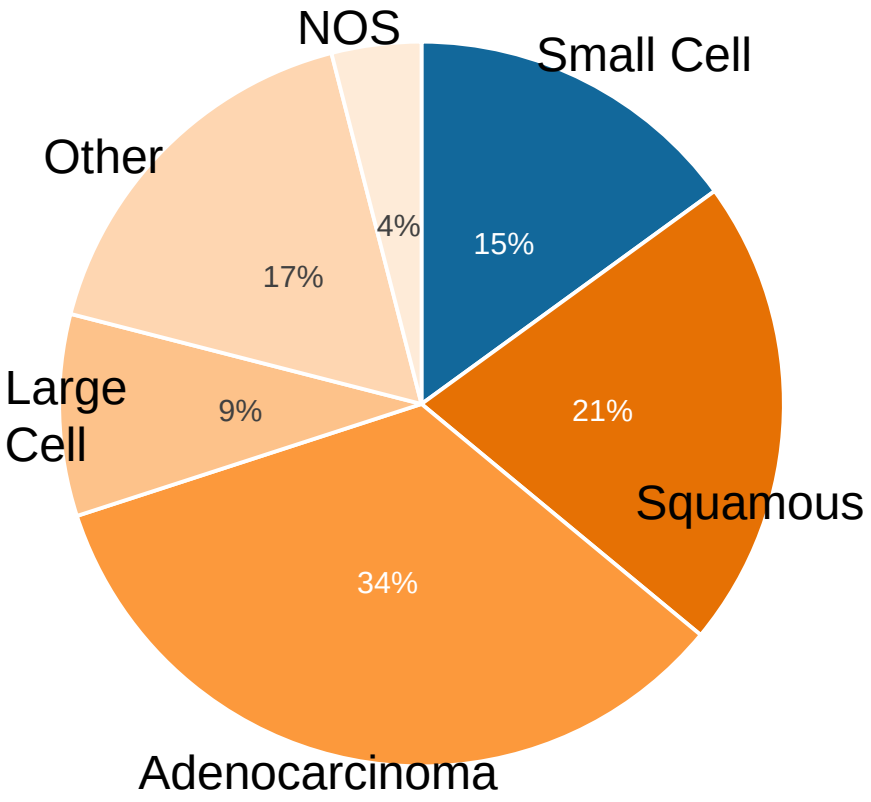




This data from www.cdc.gov is based on cancers diagnosed from 2015-2021 and follow-up of patients through 12/31/21.

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

Which of the following statements is true about cancer?

A. Breast cancer is the most common cause of cancer death in women.

B. For former smokers, it takes ~ 10 years for the risk of lung cancer to decrease to that of a nonsmoker.

C. More than half of new lung cancers are already metastatic at the time of diagnosis.

D. Tumor grade (level of differentiation under the microscope) is a more important predictor 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.

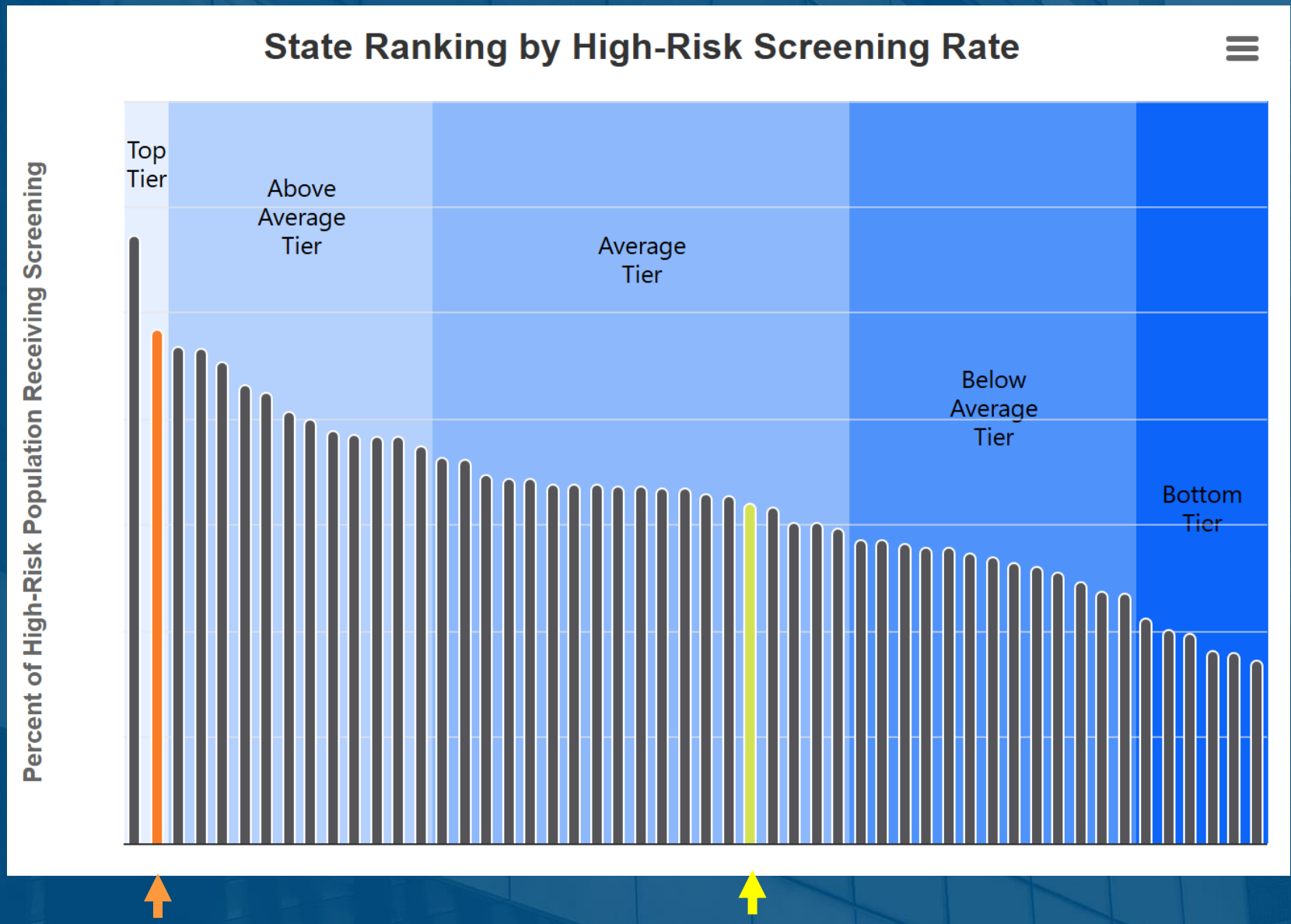
Lung Cancer Screening

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).
D. A 70 year-old who had smoked 1 pack per day for 20 years (from age 45-65).
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



From State Data | Massachusetts | American Lung Association

Dana-Farber Cancer Institute

ABCs of Lung Cancer Screening (USPSTF)

Audience

- **Asymptomatic adults, and**
- **Aged 50 to 80 years, and**
- **Heavy and recent smoking history:**
  - **≥ 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.

Follow-up of Radiographic Findings

Setting	Guidelines
Screening of an asymptomatic patient	LUNG-RADS[1]
Incidental finding on a scan performed for another reason	Fleishner Guidelines[2]
Radiographic study performed as part of evaluation of a symptomatic patient	Aggressive follow-up

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

Screening Follow-up: LUNG-RADS (reference)

From 2022 LUNG-RADS from ACR

Lung-RADS	Category Descriptor	Findings	Management
0	**Incomplete** Estimated Population Prevalence: ~ 1%	Prior chest CT examination being located for comparison (see note 9)	Comparison to prior chest CT;
		Part or all oflungs cannot be evaluated	Additional lung cancer screening CT imaging needed;
		Findings suggestive of an inflammatory or infectious process (see note 10)	1-3 month LDCT
1	**Negative** Estimated Population Prevalence: 39%	**No lung nodules OR**	12-month screening LDCT
		Nodule with benign features: • Complete, central, popcorn, or concentric ring calcifications **OR** • Fat-containing	
2	**Benign -** Based on imaging features or indolent behavior Estimated Population Prevalence: 45%	**Juxtapleural nodule:** • < 10 mm (524 mm^3) mean diameter at baseline or new **AND** • Solid; smooth margins; and oval, lentiform, or triangular shape	
		Solid nodule: • < 6 mm (< 113 mm^3) at baseline **OR** • New < 4 mm (< 34 mm^3)	
		Part solid nodule: • < 6 mm total mean diameter (< 113 mm^3) at baseline	
		Non solid nodule (GGN): • < 30 mm (< 14,137 mm^3) at baseline, new, or growing **OR** • ≥ 30 mm (≥ 14,137 mm^3) stable or slowly growing (see note 7)	
		Airway nodule, subsegmental - at baseline, new, or stable (see note 11)	
		Category 3 lesion that is stable or decreased in size at 6-month follow-up CT **OR** Category 4B lesion proven to be benign in etiology following appropriate diagnostic workup	

Screening Follow-up: LUNG-RADS (reference)

From 2022 LUNG-RADS from ACR

3	**Probably Benign -** Based on imaging features or behavior Estimated Population Prevalence: 9%	**Solid nodule:** • ≥ 6 to < 8 mm (≥ 113 to < 268 mm³) at baseline **OR** • New 4 mm to < 6 mm (34 to < 113 mm³)	6-month LDCT
		Part solid nodule: • ≥ 6 mm total mean diameter (≥ 113 mm³) with solid component < 6 mm (< 113 mm³) at baseline **OR** • New < 6 mm total mean diameter (< 113 mm³)	
		Non solid nodule (GGN): • ≥ 30 mm (≥ 14,137 mm³) at baseline or new	
		Atypical pulmonary cyst: (see note 12) • Growing cystic component (mean diameter) of a thick-walled cyst	
		Category 4A lesion that is stable or decreased in size at 3-month follow-up CT (excluding airway nodules)	
4A	**Suspicious** Estimated Population Prevalence: 4%	**Solid nodule:** • ≥ 8 to < 15 mm (≥ 268 to < 1,767 mm³) at baseline **OR** • Growing < 8 mm (< 268 mm³) **OR** • New 6 to < 8 mm (113 to < 268 mm³)	3-month LDCT; PET/CT may be considered if there is a ≥ 8 mm (≥ 268 mm³) solid nodule or solid component
		Part solid nodule: • ≥ 6 mm total mean diameter (≥ 113 mm³) with solid component ≥ 6 mm to < 8 mm (≥ 113 to < 268 mm³) at baseline **OR** • New or growing < 4 mm (< 34 mm³) solid component	
		Airway nodule, segmental or more proximal - at baseline (see note 11)	
		Atypical pulmonary cyst: (see note 12) • Thick-walled cyst **OR** • Multilocular cyst at baseline **OR** • Thin- or thick-walled cyst that becomes multilocular	

Screening Follow-up: LUNG-RADS (reference)

From 2022 LUNG-RADS from ACR

4B	**Very Suspicious** Estimated Population Prevalence: 2%	**Airway nodule**, segmental or more proximal - stable or growing (see note 11)	Referral for further clinical evaluation
		Solid nodule: • ≥ 15 mm (≥ 1767 mm^3) at baseline **OR** • New or growing ≥ 8 mm (≥ 268 mm^3)	Diagnostic chest CT with or without contrast; PET/CT may be considered if there is a ≥ 8 mm (≥ 268 mm^3) solid nodule or solid component; tissue sampling; and/or referral for further clinical evaluation Management depends on clinical evaluation, patient preference, and the probability of malignancy (see note 13)
		Part solid nodule: • Solid component ≥ 8 mm (≥ 268 mm^3) at baseline **OR** • New or growing ≥ 4 mm (≥ 34 mm^3) solid component	
		Atypical pulmonary cyst: (see note 12) • Thick-walled cyst with growing wall thickness/nodularity **OR** • Growing multilocular cyst (mean diameter) **OR** • Multilocular cyst with increased loculation or new/increased opacity (nodular, ground glass, or consolidation)	
		Slow growing solid or part solid nodule that demonstrates growth over multiple screening exams (see note 8)	
4X	Estimated Population Prevalence: < 1%	Category 3 or 4 nodules with additional features or imaging findings that increase suspicion for lung cancer (see note 14)	
S	**Significant or Potentially Significant** Estimated Population Prevalence: 10%	**Modifier:** May add to category 0-4 for clinically significant or potentially clinically significant findings unrelated to lung cancer (see note 15)	As appropriate to the specific finding

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?

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C. A 76 year-old who had smoked 1 pack per day for 30 years (from age 16-46).

D. A 70 year-old who had smoked 1 pack per day for 30 years (from age 35-65).

E. A frail 84 year-old with Class III CHF who has continued to smoke 2 packs per day since age 14.

Clinical Presentation, Diagnosis, and Staging

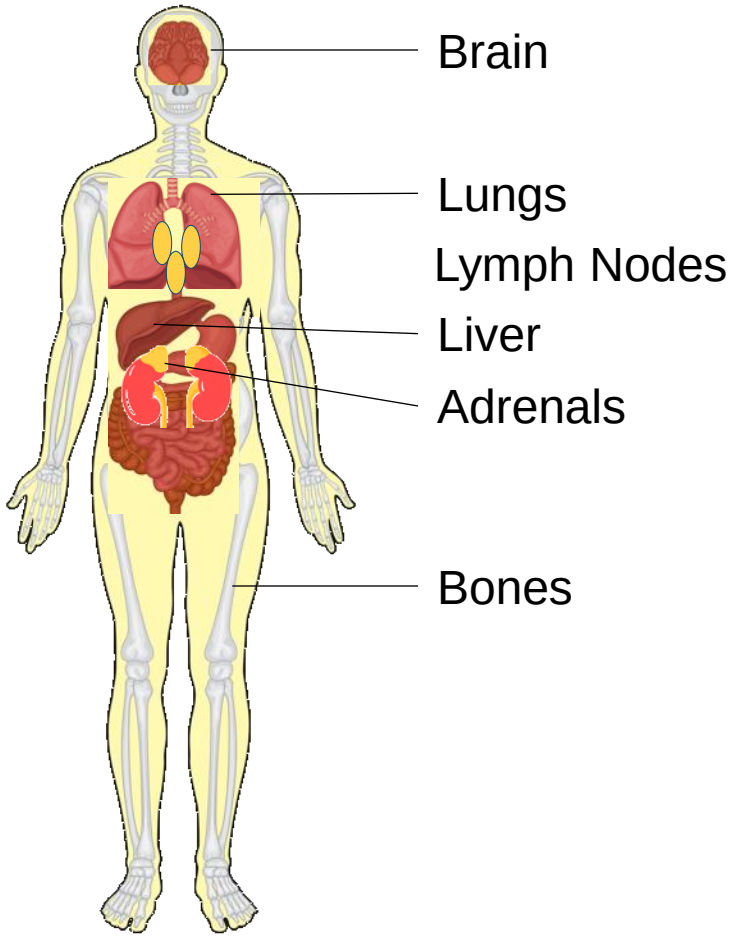
Practice Question 3

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 andidiuretic hormone (SIADH)
D. Laboratory error

Clinical Presentation of Lung Cancer:



Generalized Symptoms

- Fatigue
- Weight loss
- Night sweats

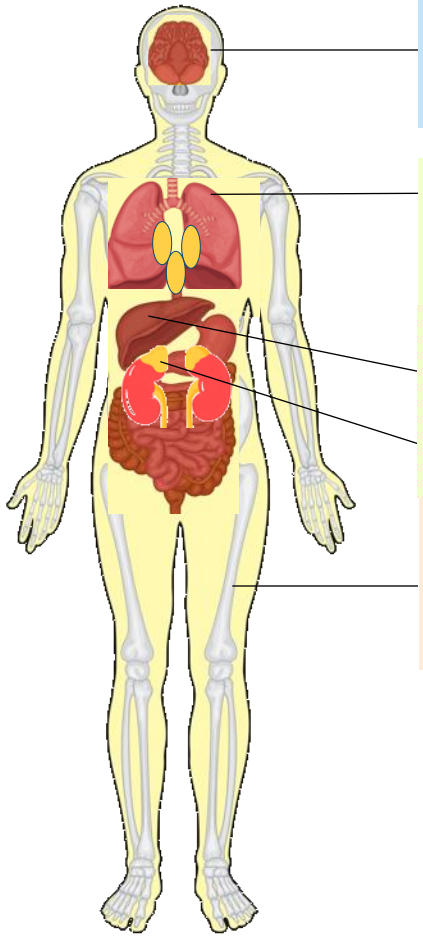
Symptoms related to local destruction, obstruction, or replacement

- 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

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

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.

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

Practice Question 3

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Overview of Therapy For Lung Cancer

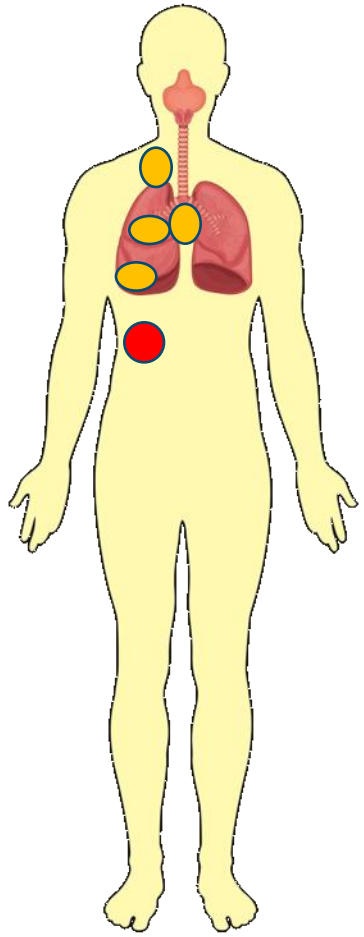
Practice Question 4

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

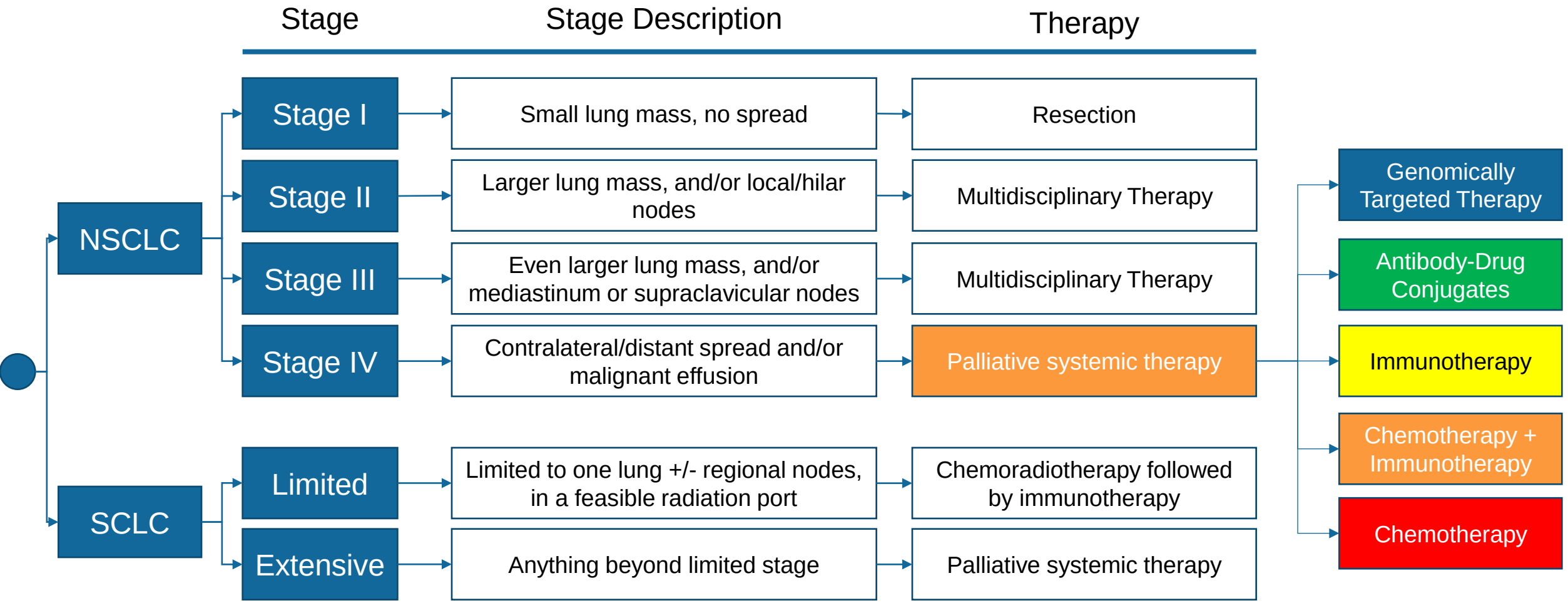
A. Pericardial effusion / cardiac tamponade
B. Pleural Effusion
C. Pneumonitis (treatment-associated)
D. Post-obstructive pneumonia
E. Progression of lung cancer
F. Pulmonary Embolism
G. All of the above

Overview of Therapy for Lung Cancer

	Stage	Stage Description	Therapy
NSCLC	Stage I	Small lung mass, no spread	Resection
NSCLC	Stage II	Larger lung mass, and/or local/hilar nodes	Multidisciplinary Therapy
NSCLC	Stage III	Even larger lung mass, and/or mediastinum or supraclavicular nodes	Multidisciplinary Therapy
NSCLC	Stage IV	Contralateral/distant spread and/or malignant effusion	Palliative systemic therapy
SCLC	Limited	Limited to one lung +/- regional nodes, in a feasible radiation port	Chemoradiotherapy followed by immunotherapy
SCLC	Extensive	Anything beyond limited stage	Palliative systemic therapy



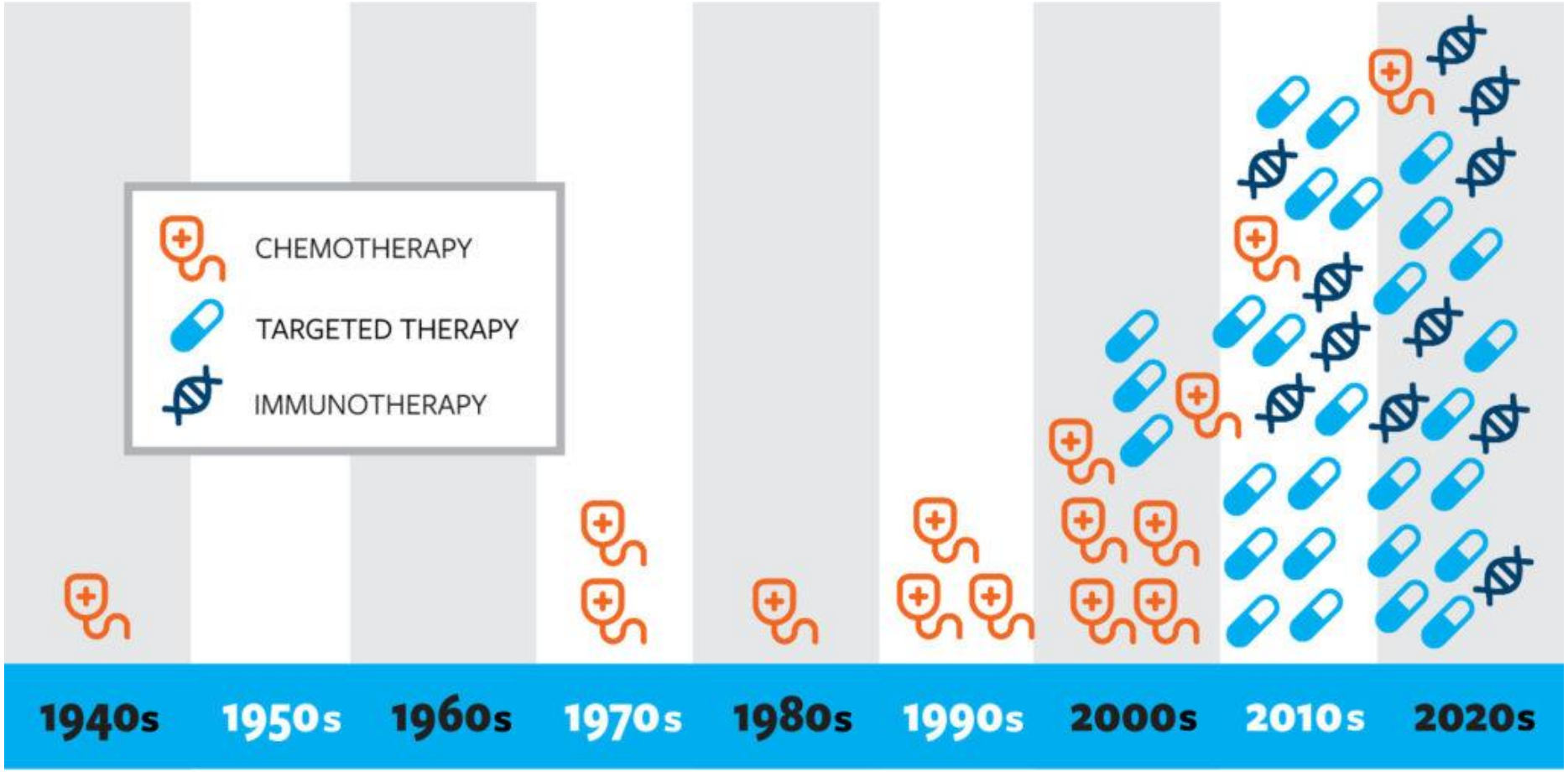
Overview of Therapy for Lung Cancer



Role of Radiation in Lung Cancer

Curative	Palliative	Other
• Early-stage: alternative to surgery in poor operative candidates • Locally advanced: with chemotherapy as a neoadjuvant (pre-operative) or definitive strategy	• To address an urgent symptom. e.g.: cord compression, SVC syndrome, airway or esophageal obstruction • To palliate: e.g., bone metastasis • Brain metastases	• Prophylactic cranial irradiation (small cell) • Consolidative chest radiation (small cell) • Oligo-progressive disease, particularly for patients on targeted tx or immunotherapy

FDA Approvals for Lung Cancer



From the Lung Cancer Research Foundation
https://www.lungcancerresearchfoundation.org/research/why-research/treatment-advances/#decades

FDA Approvals for Lung Cancer

Genomic alterations in lung cancer associated with an FDA-approved targeted therapy	
Mutations	*BRAF* V600E *EGFR* HER2 *KRAS* G12C *MET* exon 14
Fusions/Rearrangements	*ALK* *NRG* *NTRK* *RET* *ROS1*

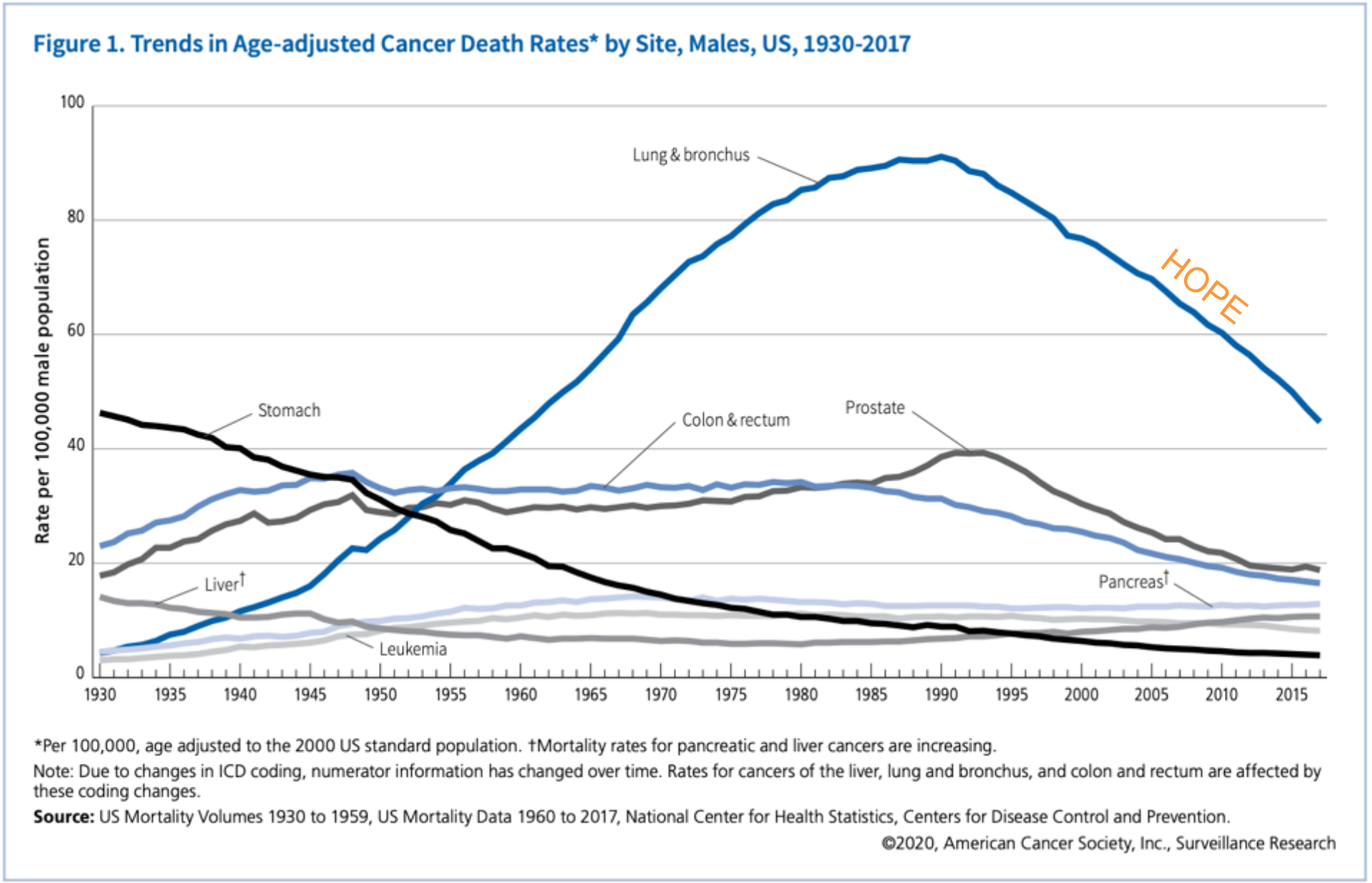
Considerations with Targeted Therapies

- 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

Cancer statistics, 2020. Siegel et al, Ca Cancer J Clin



Take Home Points, Test Prep version

- Stage is still the most prognostic factor
- Small cell lung cancer is the most likely to be associated with smoking and with paraneoplastic syndromes (esp SIADH)
- Lung cancer screening: in smokers heavy (≥ 20 pk-yrs) and recent (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