

The logo consists of a red hexagon with a white border, containing the text "ACRODeck" in white.

ACRODeck

Locally Advanced NSCLC

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Introduction to ACRODeck



ACRODeck

- The goal of ACRODeck is to introduce standard treatments of oncologic malignancies for early radiation oncology residents
- Please note that there is often considerable variation in standard treatment recommendations
- Moreover, the landscape of oncology is ever-changing; for practice changing landmark studies and feedback, please email: resident@acro.org

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Clinical Presentation and Differential Diagnosis

Locally advanced lung cancer is typically defined as stage III disease

- Advanced lung cancer typically presents with symptoms of cough, dyspnea and weight loss
 - Hemoptysis, hoarseness, brachial plexopathy, SVC syndrome, and Horner's syndrome may also be present
- Differential Diagnosis:
 - Neoplasm (NSCLC, SCLC, metastases)
 - Infections (fungal, bacterial, parasitic)

Initial Workup

If a pleural effusion is present, thoracentesis with cytology should be performed: if positive, this is M1a disease

- H/P & Labs
 - Focus on smoking history, occupational exposures, weight loss
 - Counsel regarding smoking cessation
 - CBC, CMP, PFTs
- Imaging
 - CT chest and abdomen (must include liver and adrenals)
 - PET CT
 - MRI Brain for stage II+ disease
 - Consider MRI of spine/thoracic inlet for superior sulcus tumors and those abutting the spine, subclavian vessels, or brachial plexus
- Invasive mediastinal staging
 - Typically done via EBUS, EUS, or mediastinoscopy
 - Can be done during the same procedure as the primary resection, with evaluation of frozen mediastinal pathology prior to lung resection
- Bronchoscopy
 - Done prior to surgical resection
- Biopsy
 - Typically done via bronchoscopy or CT guidance

Adequate pulmonary function for
resection is based on ACCP guidelines
(PMID: 23649437)

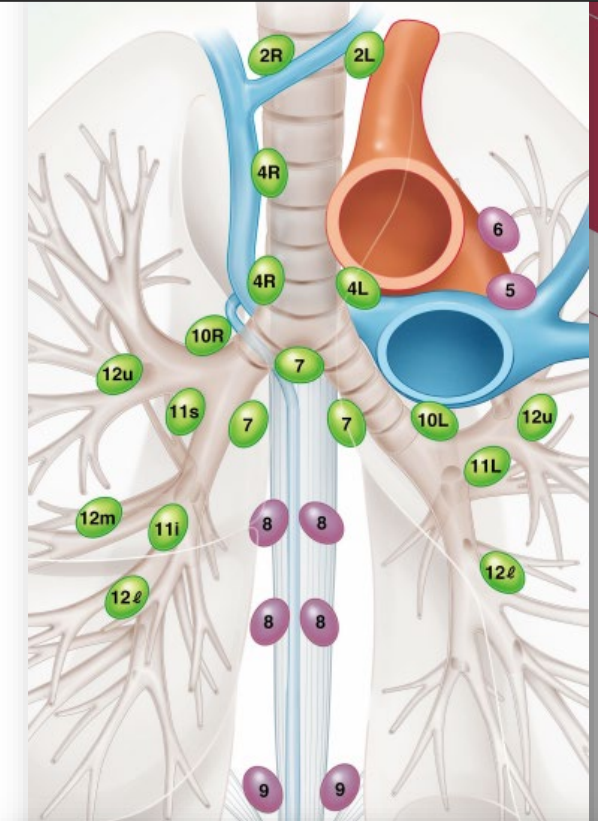
PFTs and Surgery

- Pulmonary Function Tests should measure:
 - FEV1 (Forced Expiratory Volume in 1 second)
 - DLCO (Diffusion Capacity of Carbon Monoxide)
- Generally, $FEV1 \geq 80\%$ predicted with $DLCO \geq 80\%$ predicted indicates a low risk for surgery, and needs no further testing
 - If either number is $< 80\%$ of predicted, further testing is required to calculate “Predicted Postoperative Pulmonary Function”

Pathologic Mediastinal Lymph Node Evaluation

Different techniques allow access to different nodal stations

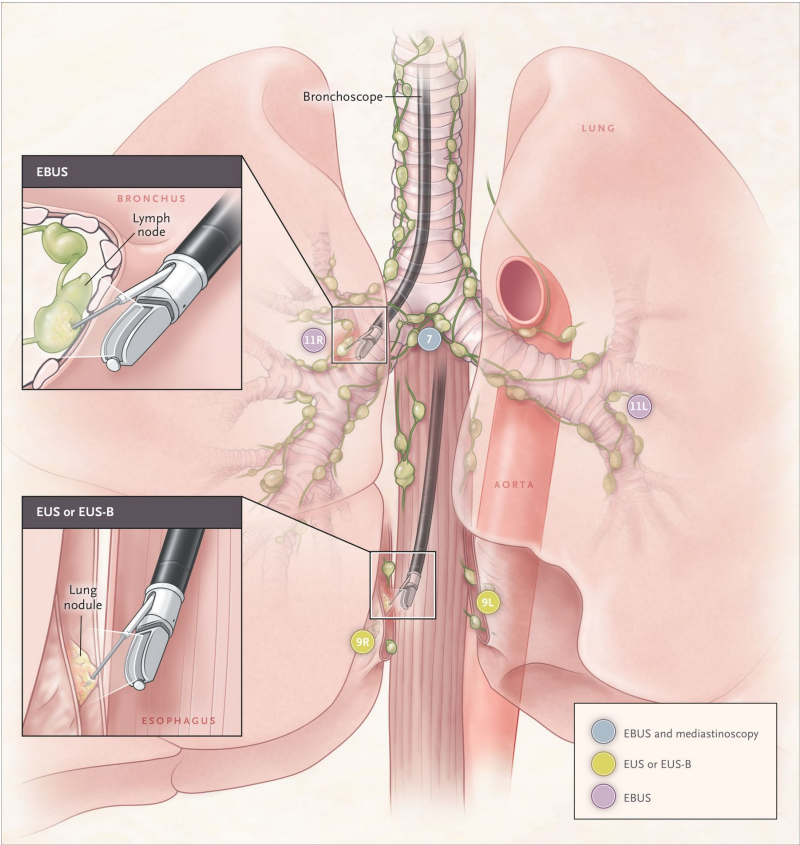
- Endobronchial Ultrasound (EBUS)
 - Can access nodes near the airways
- Cervical Mediastinoscopy
 - Can access nodes near the airways
 - Inserts scope through an incision above the sternum
- Endoscopic Ultrasound (EUS)
 - Can access nodes near the esophagus
 - Only modality that can reach levels 8-9
- Anterior Mediastinoscopy (Chamberlain Procedure)
 - Only modality that can reach levels 5-6
 - Inserts scope through an incision in the parasternal 2nd left intercostal space



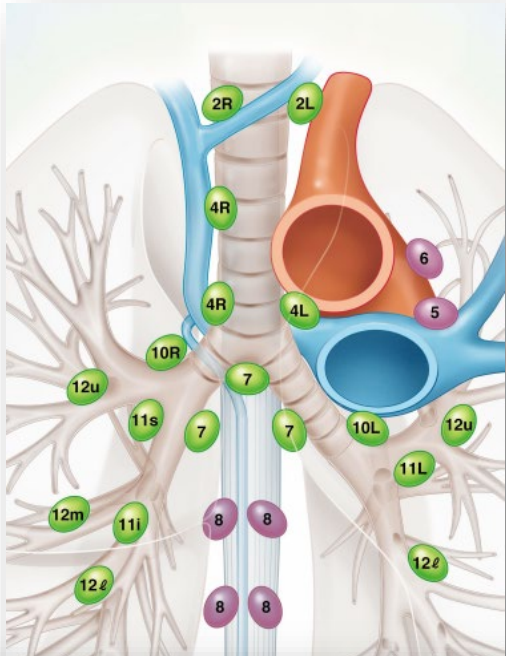
	Lymph Node Levels						
	2	4	5	6	7	8-9	10
EBUS-FNA	✓	✓			✓		✓
EUS-FNA		✓			✓	✓	
Mediastinoscopy: Cervical	✓	✓			✓		✓
Mediastinoscopy: Chamberlain		✓	✓	✓	✓		

Pathologic Mediastinal Lymph Node Evaluation

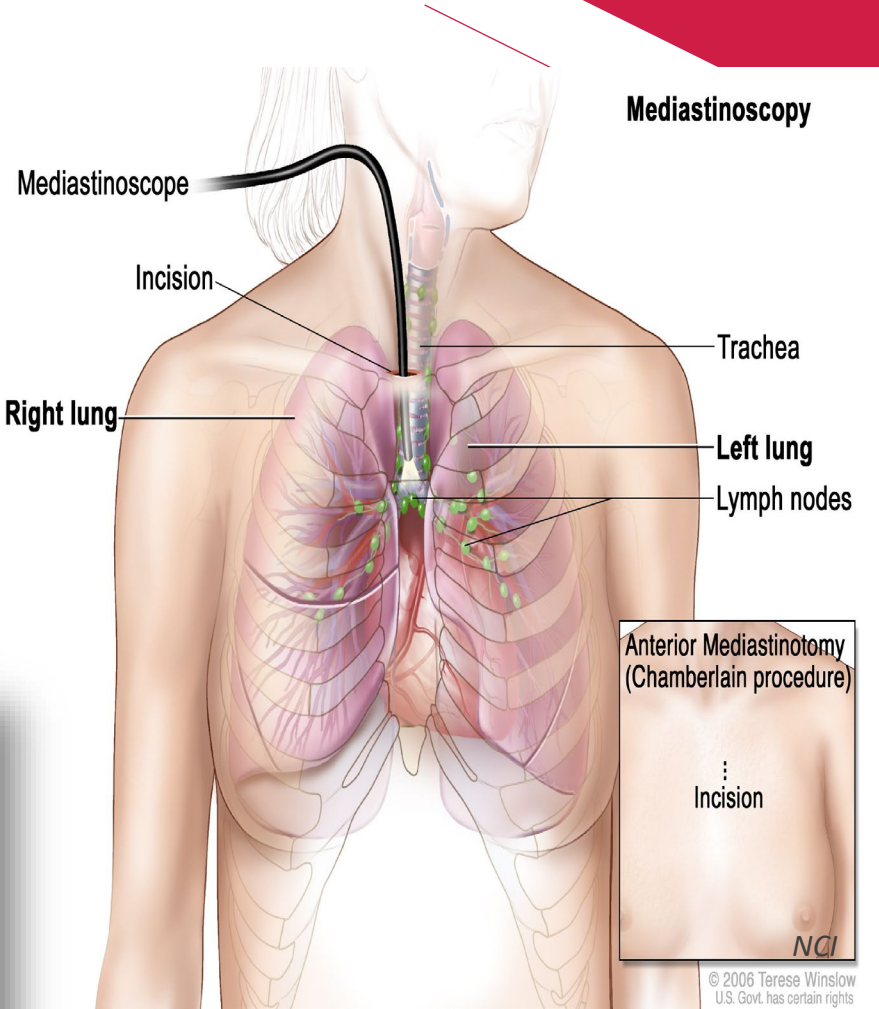
Consider performance status and comorbidities before pathologic mediastinal staging



NEJM



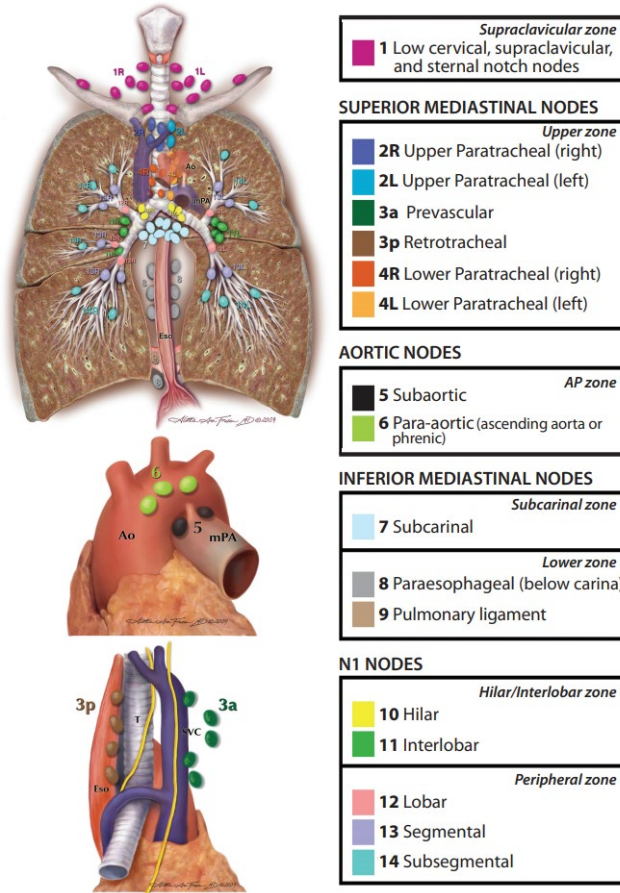
	Lymph Node Levels							
	2	4	5	6	7	8-9	10	
EBUS-FNA	✓	✓			✓		✓	
EUS-FNA		✓			✓	✓		
Mediastinoscopy: Cervical	✓	✓			✓		✓	
Mediastinoscopy: Chamberlain		✓	✓	✓	✓			



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Staging

- Nodal Staging:
 - N1: double digit LN levels
 - 10 – 14
 - N2: single digit LN levels
 - Excluding N3 disease
 - N3: contralateral LN levels and/or the level 1 station



IASLC

N2 disease is at least Stage III

TABLE 25.2: AJCC 8th ed. (2017) Staging for Lung Cancer

T/M		N	cN0	cN1	cN2	cN3
T1	a ≤1 cm ¹		IA1	IIB	IIIA	IIIB
	b 1.1–2 cm		IA2			
	c 2.1–3 cm		IA3			
T2 ²	a 3.1–4 cm		IB			
	b 4.1–5 cm		IIA			
T3	• 5.1–7 cm • Invasion³ • Same lobe nodules		IIB	IIIA	IIIB	IIIC
T4	• >7 cm • Invasion⁴ • Separate lobe nodules					
M1a	• Separate nodules in contralateral lobe • Pleural nodules • Malignant pleural/pericardial effusion	IVA				
M1b	• Single extrathoracic metastasis in single organ • Single non-regional lymph node					
M1c	• Multiple extrathoracic metastasis	IVB				

Notes: ≤1 cm¹ = or rare superficial spreading tumor with invasive component limited to bronchial wall. T2² = or involves main bronchus, but not carina, invades visceral pleura, or atelectasis or obstructive pneumonitis extending to hilar region. Invasion³ = Invasion of parietal pleura, chest wall, phrenic nerve, or parietal pericardium. Invasion⁴ = Invasion of diaphragm, mediastinum, great vessels, trachea, carina, recurrent laryngeal nerve, esophagus, or vertebral body.

cN1, Ipsilateral peribronchial and/or ipsilateral hilar LNs (stations 10–14); cN2, ipsilateral mediastinal and/or subcarinal LNs (stations 2–9); cN3, contralateral mediastinal, hilar, or any scalene or supraclavicular LNs (station 1).

Treatment Summary

Definitive ChemoRT

Radiotherapy: 60 Gy in 30 fx

Chemotherapy: Carboplatin and Paclitaxel



Immunotherapy: Durvalumab

Surgery

Surgery: VATS Lobectomy + Mediastinal
Lymph Node Dissection



Chemotherapy: Cisplatin Doublet

± Immunotherapy



Chemotherapy: Cisplatin Doublet

± Radiotherapy

Definitive ChemoRT → IT

ChemoRT has been historically preferred over surgery for N2/N3 disease. This preference is now controversial for N2 disease.

- Concurrent chemoradiation
 - Chemotherapy = “Platinum-Doublet”
 - Carboplatin/Paclitaxel
 - Cisplatin/Etoposide
 - Carboplatin/Pemetrexed (For non-SqCC histology)
 - Cisplatin/Pemetrexed (For non-SqCC histology)
 - Radiation
 - 60 – 70 Gy (in 2 Gy fractions)
- Consolidative Immunotherapy
 - Durvalumab (for up to 12 months)
 - Only for those with no disease progression after chemoRT

60 Gy is commonly used for definitive treatment

Radiation Dosing, per NCCN

- Definitive RT
 - 60 – 70 Gy (in 2 Gy fractions)
- Preoperative RT
 - 45 – 54 Gy (in 1.8 – 2 Gy fractions)
- Postoperative RT
 - R0 Resection (controversial since the publication of LungART)
 - 50 – 54 Gy (in 1.8 – 2 Gy fractions)
 - ECE or R1 Resection
 - 54 – 60 Gy (in 1.8 – 2 Gy fractions)
 - R2 Resection
 - 60 – 70 Gy (in 2 Gy fractions)

Radiation Simulation

Other motion management techniques
include compression and DIBH

Simulation

- 4DCT ($\pm$ IV contrast)
 - IV contrast strongly recommended for nodal disease
- Supine, arms above head in an arm-board

Dose Constraints

$V_{20\text{Gy}} \leq 30\text{-}40\%$ has a radiation
pneumonitis risk of around 15%

Organ at Risk (OAR)	Dose Constraint
Spinal Cord	Max ≤ 50 Gy
Lung	$V_{20\text{Gy}} \leq 35\%$ Mean ≤ 20 Gy
Heart	$V_{50\text{Gy}} \leq 25\%$ Mean ≤ 20 Gy
Esophagus	Max $\leq 105\%$ of prescription $V_{60\text{Gy}} \leq 17\%$ Mean ≤ 34 Gy
Brachial Plexus	Max ≤ 66 Gy

Radiation Toxicities

- Acute:
 - Fatigue
 - Skin Irritation
 - Cough
 - Esophagitis

- Subacute
 - Radiation Pneumonitis

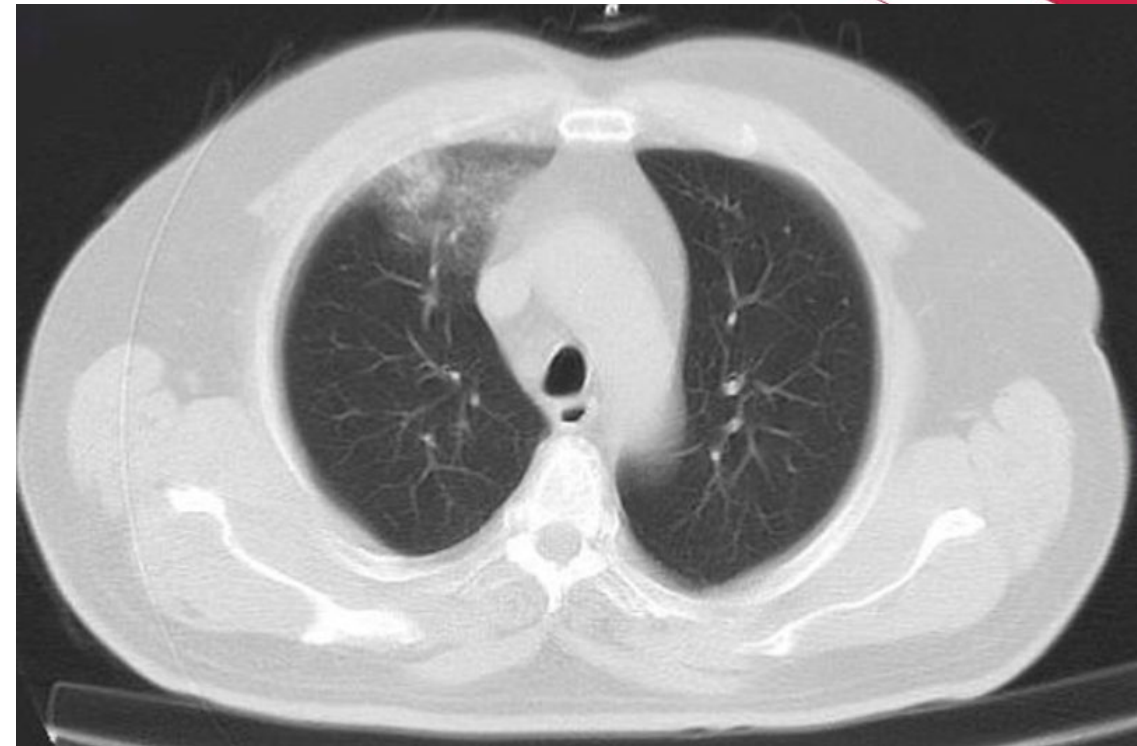
- Chronic:
 - Chest Wall Pain
 - Rib Fracture
 - Cardiac Toxicity
 - Bronchopulmonary Hemorrhage/Fistula
 - Pulmonary Fibrosis

A contralateral esophageal sparing technique can be used to reduce the risk of esophagitis

Radiation Pneumonitis

- Radiation pneumonitis typically presents 1 – 6 months after the completion of radiotherapy
 - Symptoms include cough, dyspnea, low-grade fevers, chest and pleuritic pain
 - Supplemental oxygen may be necessary
- The mainstay of treatment is steroids
 - There are a variety of dosing schedules, most including 40 – 60 mg steroids with a slow taper
 - Example 6-week schedule
 - Prednisone 60mg daily for 1 week
 - Prednisone 50mg daily for 1 week
 - Prednisone 40mg daily for 1 week
 - Prednisone 30mg daily for 1 week
 - Prednisone 20mg daily for 1 week
 - Prednisone 10mg daily for 1 week

On RTOG 0617, 3.5% of patients treated with IMRT developed grade 3 pneumonitis (n = 228) (PMID: 28034064)



Radiopaedia

Surgery (+ CHT $\pm$ PORT)

A minimum of three N2 nodal stations are required for sampling during surgery

- Surgery
 - VATS lobectomy with a N1/N2 mediastinal lymph node dissection
 - However, both open surgeries and pneumonectomies are sometimes performed depending on tumor location and extent
- Systemic Therapies (Given adjuvantly to stage II+, can be considered for stage IB)
 - 4 cycles of cisplatin/pemetrexed (nonsquamous histologies)
 - 4 cycles of cisplatin/gemcitabine (squamous histologies)
 - Adjuvant osimertinib can be added for EGFR mutated
 - Immunotherapy may be added for patients PD-L1 $\geq$ 1%
- Post-Operative Radiotherapy (PORT)
 - Classically used in cases of N2 disease, margin positivity, and ECE
 - However, the use of PORT in completely resected N2 disease has become an area of marked controversy given the results of LungART (PMID 34919827)
 - Consider for R1 and R2 resections

Neoadjuvant Treatment → Surgery

Often, the purpose of neoadjuvant treatments is to allow for surgical resection

■ Neoadjuvant Therapy

- Neoadjuvant chemoRT is an option
 - 45 Gy in 25 fx with platinum-doublet chemo
- Neoadjuvant chemo-immunotherapy is another option, per Checkmate 816 (PMID: 35403841)
 - Nivolumab with platinum-doublet chemo
 - “Platinum-doublet” options:
 - Carboplatin/Paclitaxel (for any histology)
 - Cisplatin/Paclitaxel (for any histology)
 - Cisplatin/Gemcitabine (for SqCC Histology)
 - Cisplatin/Pemetrexed (for non-SqCC histology)

■ Surgery

- VATS lobectomy with a N1/N2 mediastinal lymph node dissection
- However, both open surgeries and pneumonectomies are sometimes performed depending on tumor location and extent

Special Circumstances: Superior Sulcus Tumors

INT 0160 / SWOG 9416 was a phase II trial exploring preoperative chemoRT followed by surgery

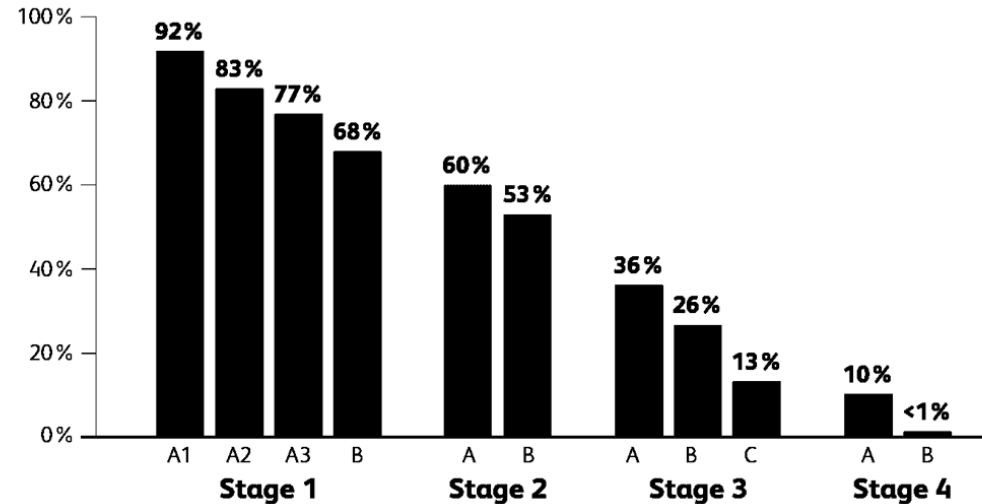
- Superior sulcus tumors are often in an eloquent location, with the brachial plexus and major vessels present
 - Surgical evaluation is critical to determine resectability
 - Get an MRI of primary site to evaluate local invasion
- For unresectable tumors:
 - Definitive chemoradiation → Durvalumab
- For potentially resectable tumors:
 1. Preoperative chemoradiation (45 Gy)
 2. Surgical re-evaluation with imaging (CT chest ± PET/CT ± MRI spine and thoracic inlet)
 3. Surgery
 - Followed by chemotherapy and immunotherapy (Atezolizumab or Osimertinib, based on PD-L1 and EGFR mutation status)

Prognosis

Recent immunotherapies have led to better prognosis

- Lung cancer remains the most lethal cancer in the United States

**Non-Small Cell Lung Cancer:
5-Year Survival Rates**



Source: American Cancer Society 2017



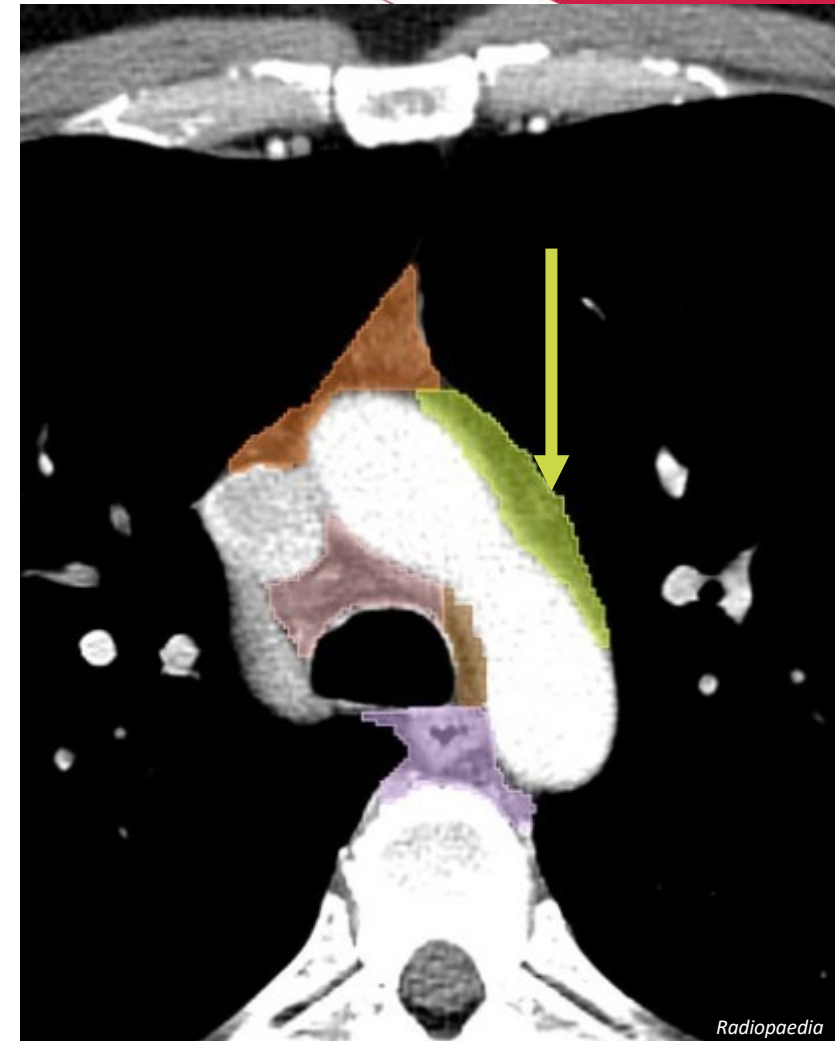
Review

Review #1: Nodal Anatomy

What is the marked lymph node station?

- (A) 4
- (B) 5
- (C) 6
- (D) 7

When scrolling inferiorly, the para-aortic LN station appears before the sub-aortic LN station



Review #2: RTOG 0617

Which of the following statements is true regarding the landmark study, RTOG 0617?

- (A) Lung V5 was associated with grade 3 pneumonitis
- (B) IMRT (vs. 3DCRT) was associated with lower rates of pneumonitis
- (C) Dose escalation to 74 Gy was associated with improved OS
- (D) IMRT was associated with improved overall survival

Review #3: PORT

PORT was considered the standard of care prior to Lung ART, but was made the experimental arm on the trial

In the post-operative radiotherapy trial Lung ART, what percent of patients were treated with IMRT?

- (A) 91%
- (B) 71%
- (C) 41%
- (D) 11%

$V_{60\text{Gy}} < 17\%$ is also an accepted
dose constraint for the
esophagus

Review #4: Dose Constraints

Per NCCN, what mean dose is allowed to the esophagus in a conventionally fractionated definitive chemoradiation plan for NSCLC?

- (A) Mean ≤ 14 Gy
- (B) Mean ≤ 24 Gy
- (C) Mean ≤ 34 Gy
- (D) Mean ≤ 44 Gy

Durvalumab blocks the action of
PD-L1

Review #5: Adjuvant Therapy

Per the PACIFIC trial, the addition of Durvalumab after definitive chemoradiation resulted in which of the following?

- (A) Improvement in PFS and OS for all patients
- (B) Improvement in PFS only in patients with PD-L1 expression > 25%
- (C) Increased Grade 3 Pneumonitis

Answer Key

1. C
2. B
3. D
4. C
5. A

The pattern of failure for advanced lung cancer is typically distant