ACRODeck

Small Cell Lung Cancer

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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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ACRODeck

Clinical Presentation and Differential Diagnosis

SCLC classically appears as a large hilar mass with bulky mediastinal adenopathy

- SCLC typically presents with cough, weight loss, and dyspnea
  - Symptoms of hemoptysis, hoarseness, brachial plexopathy, SVC syndrome may also be present
  - 3-5% of cases will present with paraneoplastic symptoms
- Most cases present with extensive disease
- Differential Diagnosis:
  - Neoplasm (NSCLC, SCLC, metastases)
  - Infections (fungal, bacterial, parasitic)

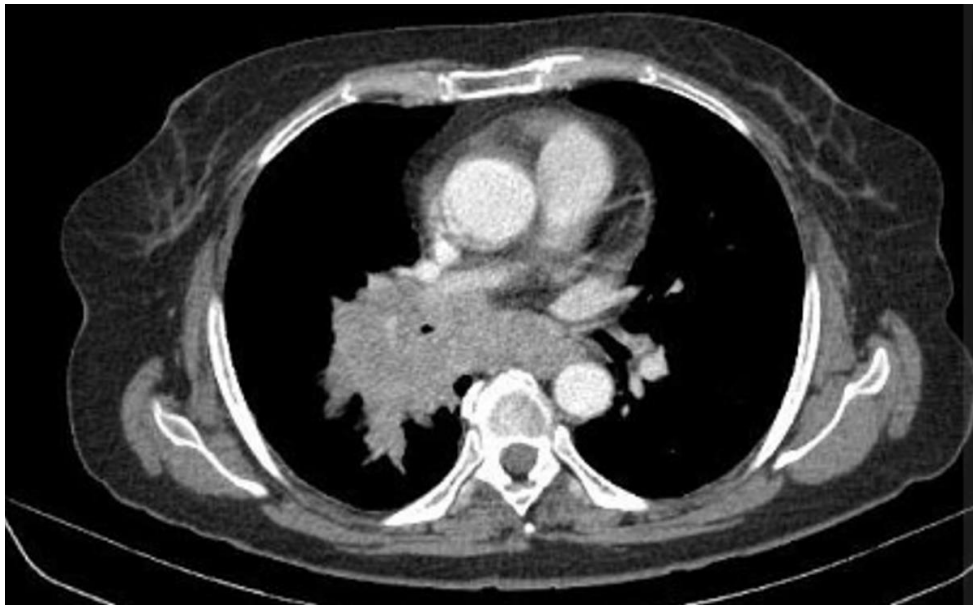
TABLE 27.2: Paraneoplastic Syndromes Commonly Diagnosed in SCLC	
SIADH	Overproduction of ADH with euvolemic hyponatremia. May present with altered mental status, seizures. Treat with water restriction, hypertonic saline, demeclocycline, vasopressin inhibitors, and/or lithium.
Cushing syndrome	Ectopic production of ACTH. Treat with ketoconazole.
Lambert–Eaton	Auto-antibodies to presynaptic calcium channels. Proximal muscle weakness that improves later in day. Treat with pyridostigmine, prednisone, IVIG and by treating cancer.

Essentials of Clinical Radiation Oncology

Initial Workup

In the case of emergent SVC syndrome, placement of an intravascular stent is critical

- H/P & Labs
  - Focus on smoking history and cessation
  - CBC, CMP, PFTs
- Imaging
  - CT CAP with contrast
  - PET CT
  - MRI Brain
- Biopsy
  - Typically done via bronchoscopy or CT guidance
- Pathologic mediastinal staging
  - Typically done via EBUS, EUS, or mediastinoscopy
- Thoracentesis if pleural effusion is present

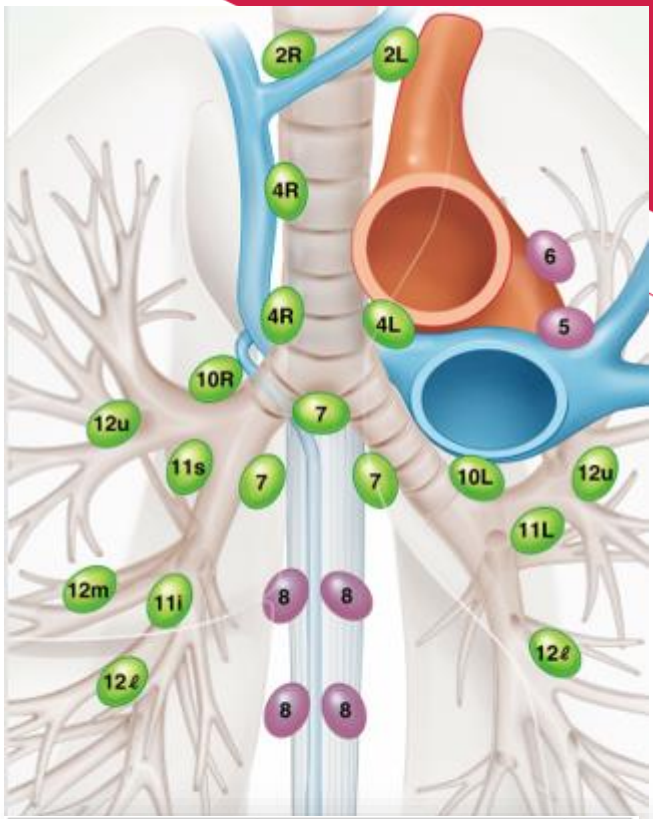


Radiopaedia

Pathologic Mediastinal Lymph Node Evaluation

- 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

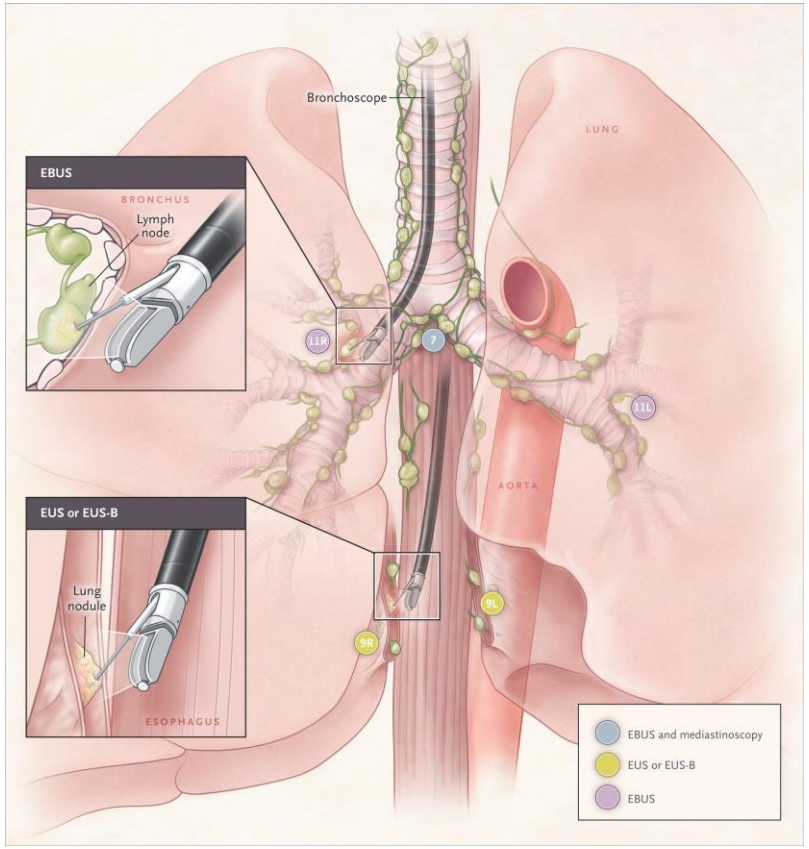
Different techniques allow access to different thoracic nodal stations



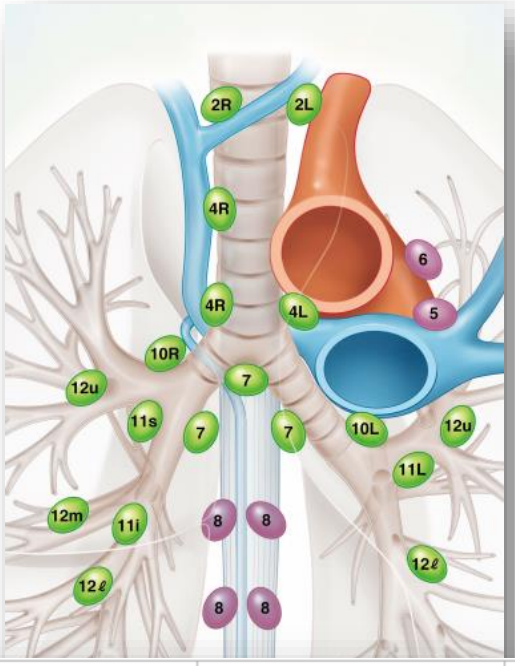
	Lymph Node Levels						
	2	4	5	6	7	8-9	10
EBUS-FNA	✓	✓			✓		✓
EUS-FNA		✓			✓	✓	
Mediastinoscopy: Cervical	✓	✓			✓		✓
Mediastinoscopy: Chamberlain		✓	✓	✓	✓		

Pathologic Mediastinal Lymph Node Evaluation

Consider performance status and comorbidities before pathologic mediastinal staging



NEJM



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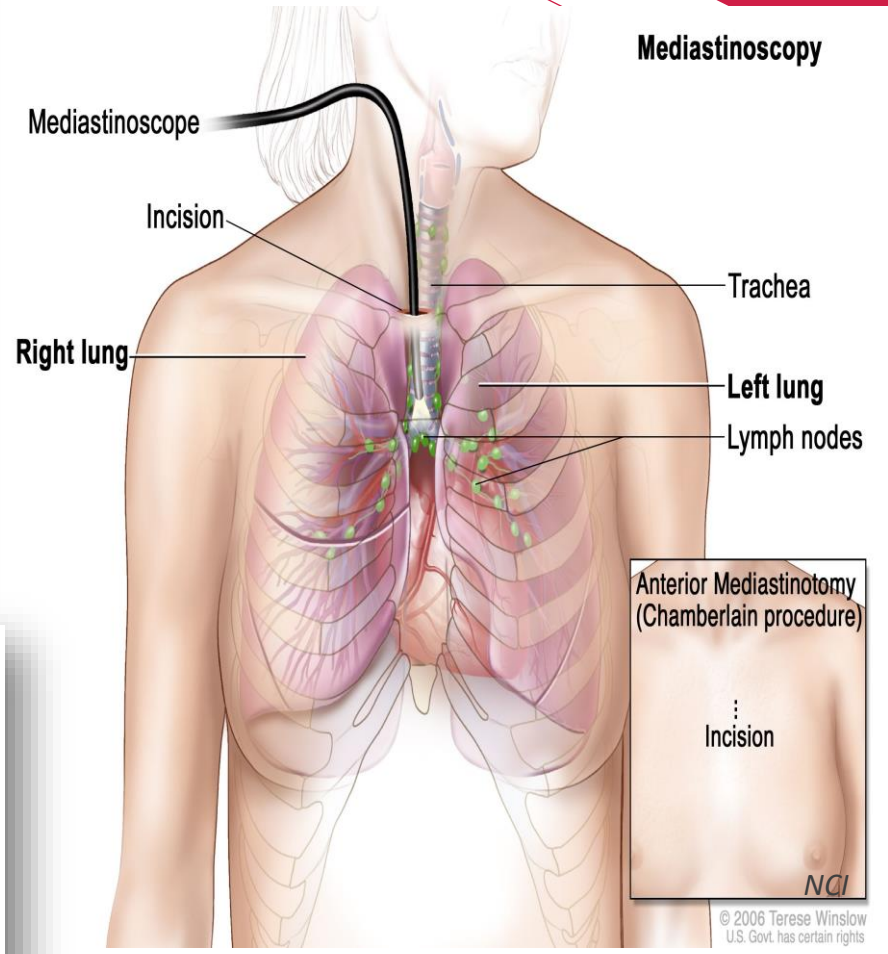
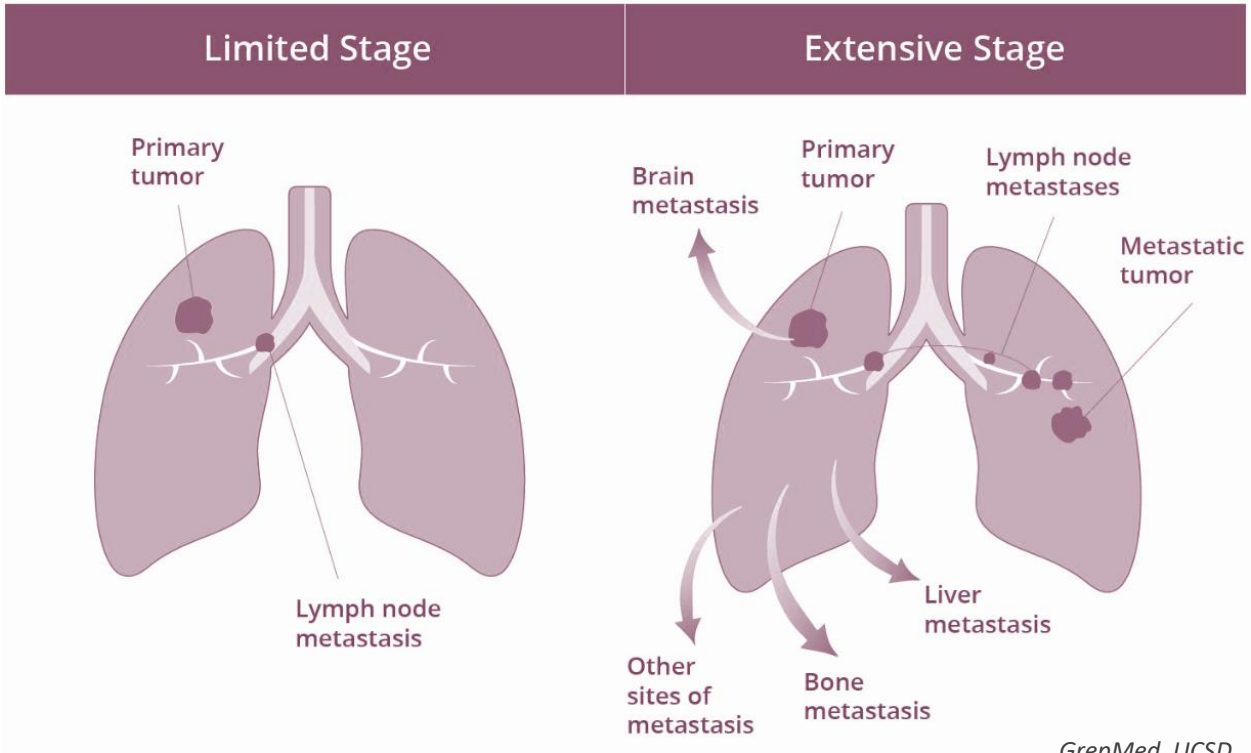
Mediastinoscopy: Chamberlain		✓	✓	✓	✓		



VA Staging

LS-SCLC is also defined as "disease confined to a single radiation port"

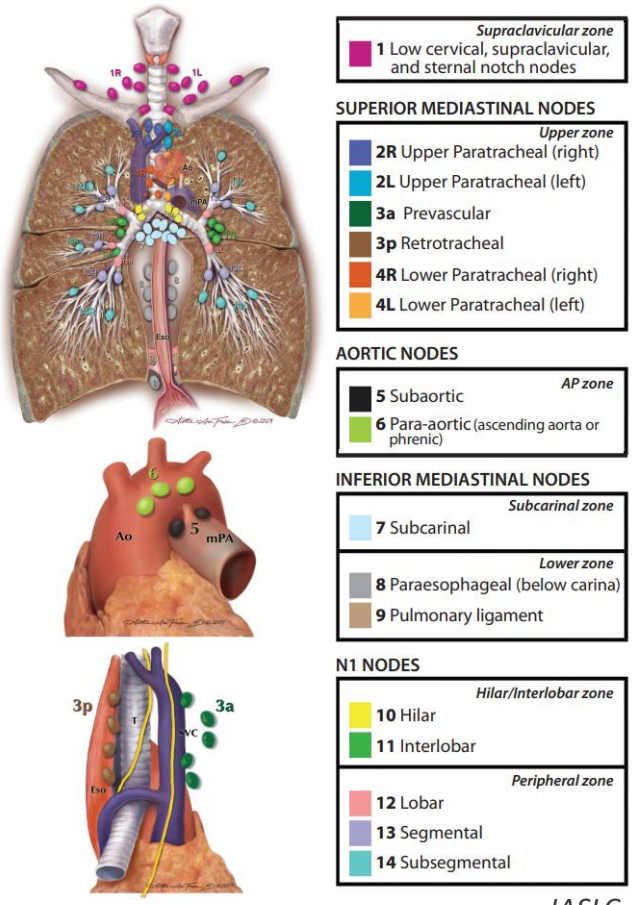
- Limited Stage
  - Confined to ipsilateral mediastinum and/or supraclavicular region
- Extensive stage
  - Not limited stage
    - Contralateral disease
    - Metastatic disease (including malignant effusions)



GrepMed, UCSD

AJCC 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



Supraclavicular zone
1 Low cervical, supraclavicular, and sternal notch nodes

SUPERIOR MEDIASTINAL NODES

Upper zone
2R Upper Paratracheal (right)
2L Upper Paratracheal (left)
3a Prevascular
3p Retrotracheal
4R Lower Paratracheal (right)
4L Lower Paratracheal (left)

AORTIC NODES

AP zone
5 Subaortic
6 Para-aortic (ascending aorta or phrenic)

INFERIOR MEDIASTINAL NODES

Subcarinal zone
7 Subcarinal

Lower zone
8 Paraesophageal (below carina)
9 Pulmonary ligament

N1 NODES

Hilar/Interlobar zone
10 Hilar
11 Interlobar

Peripheral zone
12 Lobar
13 Segmental
14 Subsegmental

IASLC

While the VA staging is more common, AJCC is used to determine surgical / SBRT candidates

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 • Invasion[3] • Same lobe nodules	IIB	IIIA	IIIB	IIIC
T4	• >7 cm • Invasion[4] • Separate lobe nodules	IIIA			
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 cm[1] = or rare superficial spreading tumor with invasive component limited to bronchial wall. T2[2] = or involves main bronchus, but not carina, invades visceral pleura, or atelectasis or obstructive pneumonitis extending to hilar region. Invasion[3] = Invasion of parietal pleura, chest wall, phrenic nerve, or parietal pericardium. Invasion[4] = 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).

Essentials of Clinical Radiation Oncology

Treatment Summary

Limited Stage

Radiotherapy*
BID Treatment: 45 Gy in 30 fx
Daily Treatment: 66 Gy in 33 fx

Chemotherapy
Cisplatin & Etoposide

→

Immunotherapy: Durvalumab

(Consider PCI vs. MRI Brain Surveillance)

Extensive Stage

Chemotherapy: Carboplatin & Etoposide

Immunotherapy: Atezolizumab

→

Immunotherapy: Atezolizumab

*Other radiotherapy fractionations are often used as well

T1-T2N0 (AJCC)

Prior to definitive treatment, pathologic mediastinal staging should be performed

- Lobectomy with mediastinal lymph node dissection
  - For positive margins and/or nodes, chemotherapy ± radiotherapy is considered
- If surgical resection is not performed (i.e.: medically operable patients), SBRT can be considered

Limited Stage (VA)

Radiotherapy fractionation and the role of immunotherapy are active areas of research in LS-SCLC

1. Concurrent chemoradiation
   - Chemotherapy = “Platinum-Doublet”
     - Cisplatin/Etoposide
     - Carboplatin/Etoposide (not an NCCN preferred regimen)
   - Radiation (start before cycle 2 of chemotherapy)
     - 45 Gy in 30 fx BID

     or
     - 66 – 70 Gy (in 2 Gy fractions)

2. Adjuvant durvalumab is now being utilized (per the ADRIATIC trial)

3. Consider Prophylactic cranial irradiation (PCI) or Surveillance with MRI brain

Extensive Stage (VA)

IMPOWER 133 demonstrated OS benefit of Atezolizumab in ES-SCLC (PMID: 30280641)

1. Concurrent chemoimmunotherapy regimens (4 cycles)
   - Cisplatin/Etoposide + Durvalumab
   - Carboplatin/Etoposide + Durvalumab
   - Carboplatin/Etoposide + Atezolizumab

2. Maintenance Immunotherapy (PD-L1 inhibitors)
   - Atezolizumab or Durvalumab continued until disease progression or unacceptable toxicities
     - Consolidative radiation is considered during (or before) maintenance immunotherapy (and is being explored on the NRG RAPTOR trial)
       - Many doses are used: 30 Gy in 10 fx is an option

3. Prophylactic cranial irradiation (PCI) or Surveillance with MRI brain

Thoracic Radiation Dosing in LS-SCLC

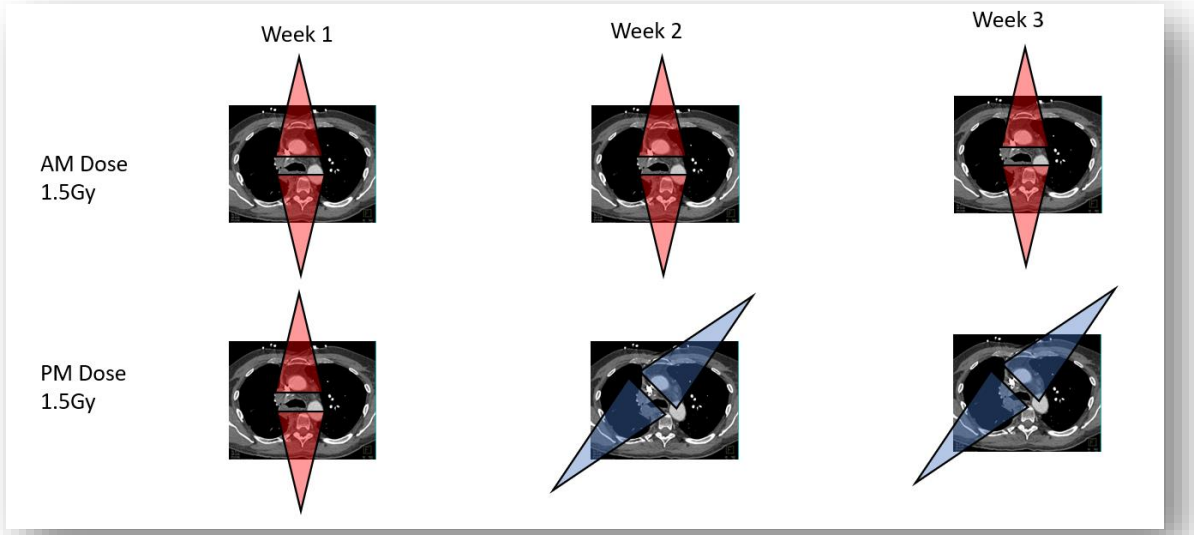
The Turrisi trial used AP/PA (and obliqued) fields; its toxicity profile is not likely relevant with modern RT

- In 1999, Turrisi published a landmark trial establishing 45 Gy in 30 fx BID as standard of care

- In 2017, the CONVERT trial did not demonstrate superiority of 66 Gy in 33 fx
  - However, many institutions have adopted this regimen

- Radiotherapy fractionation is an area of continued research:
  - 70 Gy in 35 fx daily (RTOG 0538)
  - 60 Gy in 40 BID (THORA Trial)
  - 42 Gy in 15 fx daily (Gronberg et al)

Turrisi Fields



Thoracic RT Simulation

Other motion management techniques include compression and DIBH

Simulation

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

Thoracic Dose Constraints

If unable to meet dose constraints:
2 cycles of chemotherapy can be administered prior to resimulation for chemoRT

Organ at Risk (OAR)	Qday Dose Constraint	BID Dose Constraint
Spinal Cord	Max ≤ 48 Gy	Max ≤ 41 Gy
Lung	V_{20Gy} ≤ 35% Mean ≤ 18 Gy	V_{20Gy} ≤ 29% Mean ≤ 15 Gy
Heart	V_{50Gy} ≤ 25% Mean ≤ 20 Gy	V_{30Gy} ≤ 42% Mean ≤ 18 Gy
Esophagus	Max ≤ 105% of prescription V_{60Gy} ≤ 17% Mean ≤ 34 Gy	Max ≤ 49 Gy Mean ≤ 28 Gy
Brachial Plexus	Max ≤ 60 Gy	Max ≤ 50 Gy

Dose constraints vary widely in practice; safe and acceptable ranges can be found in the protocol of NRG LU-005

Radiation Toxicities

In the 1999 Turrisi trial, the rate of esophagitis was higher in the BID arm; this was not the case in CONVERT or RTOG 0538

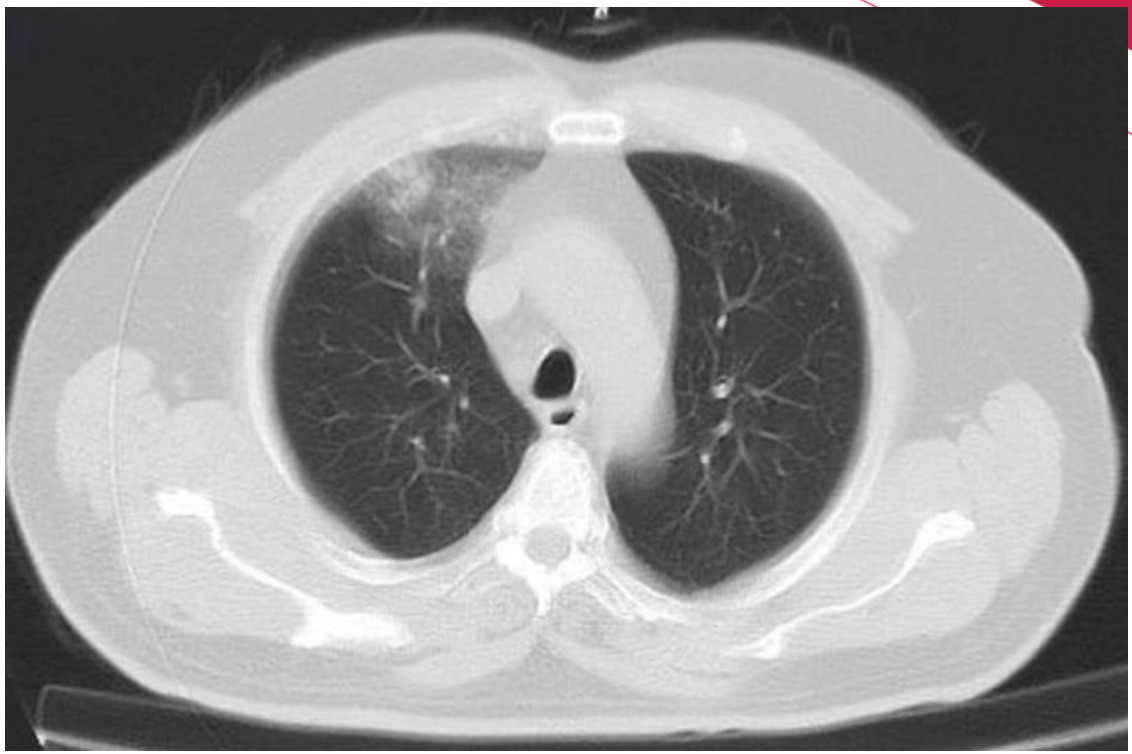
- Acute:
  - Fatigue
  - Skin Irritation
  - Cough
  - Esophagitis
- Subacute
  - Radiation Pneumonitis
- Chronic:
  - Chest Wall Pain
  - Rib Fracture
  - Cardiac Toxicity
  - Bronchopulmonary Hemorrhage/Fistula
  - Pulmonary Fibrosis

Radiation Pneumonitis

Risk of grade 3+ pneumonitis was 2.9% on RTOG 0538

- 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



Radiopaedia

Prophylactic Cranial Irradiation

EORTC/RTOG 0212 compared PCI dosing:
(25 Gy in 10 fx, 36 Gy in 18 fx and 36 Gy in 24 fx BID)
Increasing dose to 36 Gy led to increased neurotoxicity, with no oncologic benefit

- The utility of PCI is an area of debate in radiation oncology
  - Side effects included profound fatigue, nausea, hair loss, impaired neurocognition
  - Worse neurotoxicity is seen in patients aged ≥ 60 years
- If offered (instead of MR brain surveillance):
  - Patients must have had a partial response or complete response to initial therapy (determined by MR Brain and CT CAP)
  - Patients must have a good performance status and not be neurocognitively impaired
- Dose = 25 Gy in 10 fx
  - May consider memantine and hippocampal avoidance using IMRT
- The MAVERICK trial is exploring replacing PCI with surveillance MRIs, although many institutions already have adopted this as standard

Prognosis

NRG-LU005 showed no benefit to concurrent atezolizumab with chemoRT in LS-SCLC (The ADRIATIC trial demonstrated improved OS and PFS with adjuvant durvalumab in LS-SCLC)

- Distant failure (intracranially) is the most common pattern of failure

- Overall survival is dismal
  - Median OS
    - LS-SCLC: ~30 months
    - ES-SCLC: ~10 months
  - 5 Yr OS
    - LS-SCLC: 25%
    - ES-SCLC: 5%

Review

Review #1: CONVERT to Daily RT

More grade 3 esophagitis (followed by stricture or fistulation) was seen in the daily arm of the CONVERT trial

What was the radiation regimen used in the CONVERT trial (PMID 38521132), which attempted to prove the superiority of daily RT?

(A) 30 Gy in 10 fx

(B) 45 Gy in 25 fx

(C) 66 Gy in 33 fx

(D) 70 Gy in 35 fx

Review #2: Dose Constraints

RTOG 0538 used the "rule of thirds" for the heart dose constraint: 60 Gy to <1/3, 45 Gy to <2/3, and 40 Gy to <100% of the heart

Per RTOG 0538, what is the spinal cord dose constraint for BID radiation in SCLC?

(A) 31 Gy

(B) 41 Gy

(C) 51 Gy

(D) 61 Gy

Review #3: PCI

NRG CC003 (PCI ± HA) did not meet its primary endpoint; however, hippocampal avoidance did prevent "neurocognitive failure" with non-inferior intracranial relapse and OS

Per Takashai's phase 3 RCT of PCI vs. surveillance MRIs (PMID 28343976), how often were MRIs performed in the first year?

(A) Every month

(B) Every 3 months

(C) Every 6 months

(D) Every 12 months

Review #4: Consolidative RT in ES-SCLC

NRG-LU007 (RAPTOR) is exploring the addition of consolidative RT in ES-SCLC for improving PFS, in the era of PD-L1 immunotherapy

Per the CREST Trial (PMID 25230595), consolidative thoracic RT of 30 Gy improved which of the following:

(A) 1 yr OS

(B) 2 yr OS

(C) Neurocognition

(D) Grade 4 toxicity

Review #5: Stage IA

Medically inoperable patients can be referred for SBRT

For peripheral stage IA disease, with negative mediastinal nodes demonstrated pathologically, what is the recommended treatment regimen per NCCN?

(A) Observation

(B) Immunotherapy alone

(C) Radiation alone

(D) Exploration/resection with mediastinal lymph node dissection

Answer Key

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

The pattern of failure for advanced lung cancer is typically distant