ACRODeck

Early-Stage 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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ACRODeck

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Clinical Presentation and Differential Diagnosis

Exposure to radon is responsible for an estimated 3 – 14% of lung cancers

- Symptomology is dependent on extent of disease and location:
  - Central lesions can present with cough, dyspnea, hemoptysis, postobstructive pneumonia, weight loss
  - Peripheral lesions are often asymptomatic

- Differential Diagnosis:
  - Neoplasm
  - Granuloma
  - Fibroma
  - Hamartoma
  - Infections (fungal, bacterial, parasitic)
  - Pulmonary infarct

Screening Guidelines

Per NCCN; USPSTF recommendations slightly differ

- As most early-stage lung cancers are secondary to tobacco exposure and initially present asymptomatically, NCCN endorses annual low-dose CT (LDCT) for patients with a:
  - ≥ 20 pack year history of smoking cigarettes and
  - Age ≥ 50

- Per the Agency for Healthcare Research and Quality (AHRQ):
  - A LDCT provides 1.4 mSv of radiation
  - A diagnostic CT provides 7 mSv of radiation
  - Natural background of radiation in the U.S. is 3 – 5 mSv annually

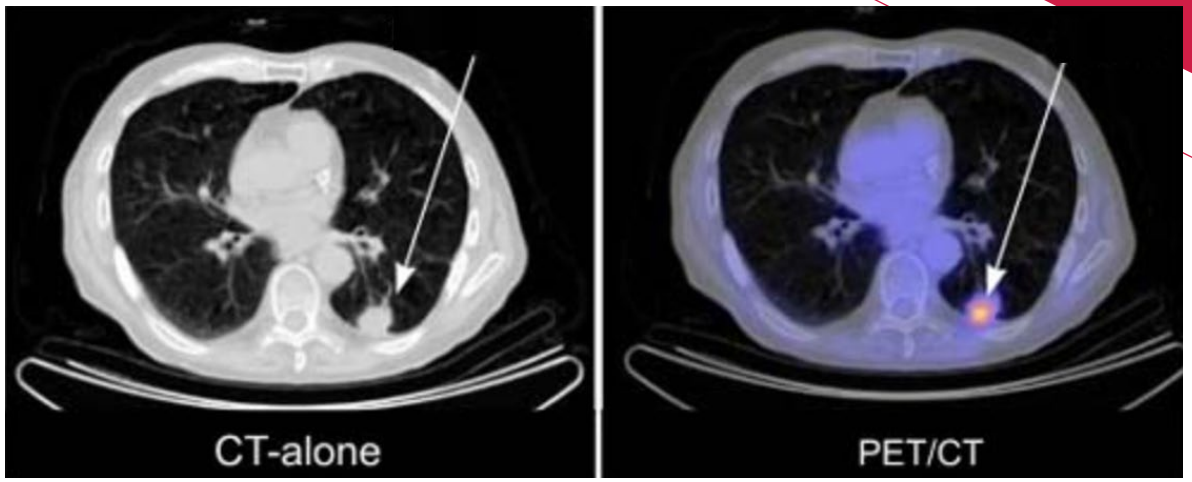
Initial Workup

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

- H/P
  - Focus on smoking history, occupational exposures, weight loss
- CBC, CMP, PFTs

- CT chest and abdomen
- PET CT
- MR brain
  - For stage II and above (IB optional)

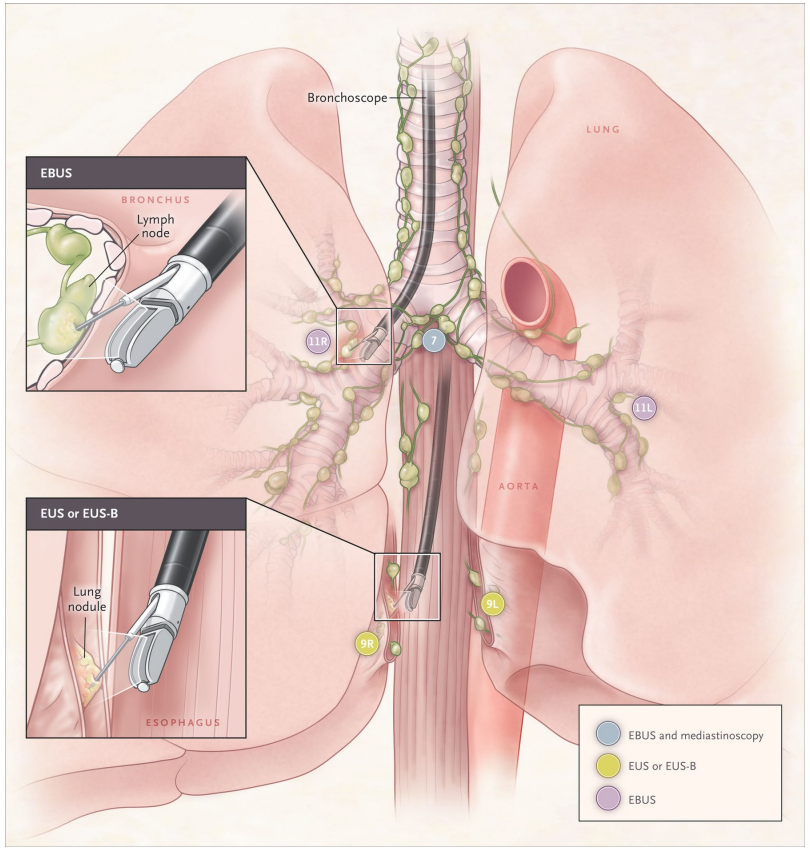
- Invasive mediastinal staging
  - Typically done via EBUS, EUS, or mediastinoscopy
  - For solid tumors < 1 cm and non-solid tumors < 3 cm, pathologic mediastinal evaluation is optional in the setting of a negative CT and PET
- Bronchoscopy
  - Required prior to surgical resection
- Biopsy
  - Typically done via bronchoscopy or CT guidance
  - This is not required if the patient is proceeding to surgery, and there is a strong clinical suspicion for malignancy



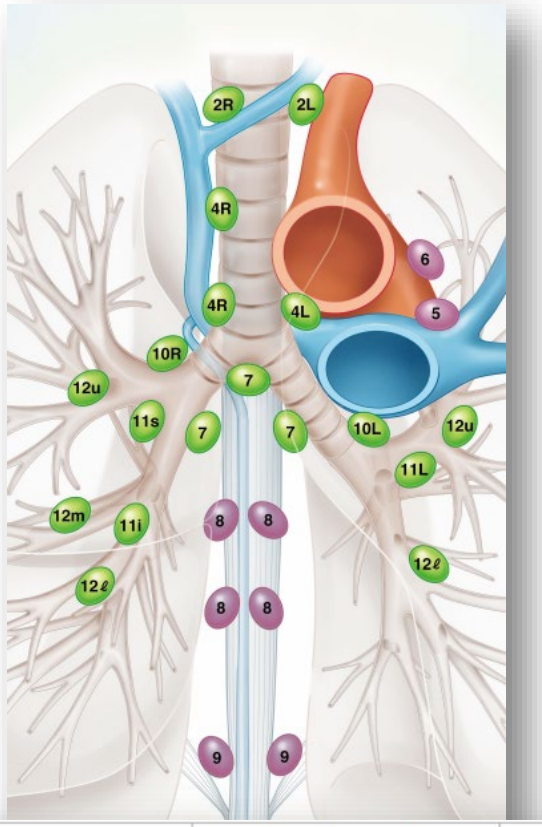
PET/CT Imaging of Berkeley

Pathologic Mediastinal Lymph Node Evaluation

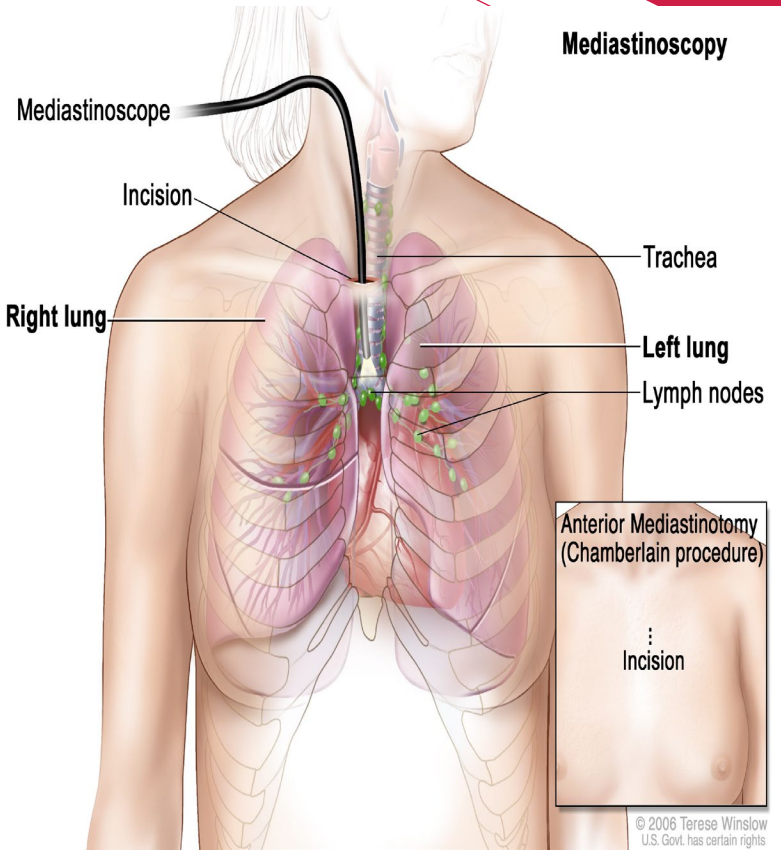
Consider performance status and comorbidities before pathologic mediastinal staging



NEJM



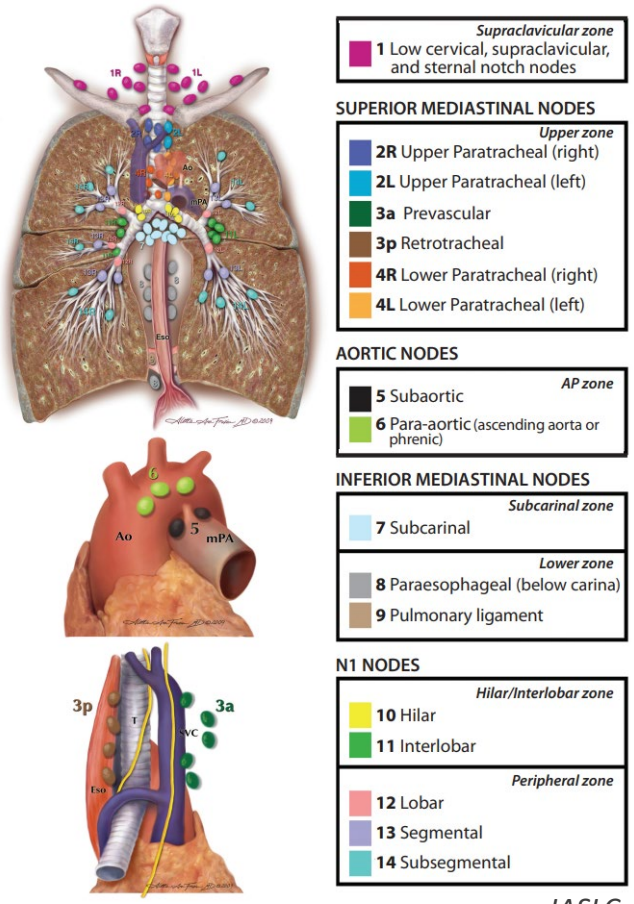
	Lymph Node Levels						
	2	4	5	6	7	8-9	10
EBUS-FNA	✓	✓			✓		✓
EUS-FNA		✓			✓	✓	
Mediastinoscopy: Cervical	✓	✓			✓		✓
Mediastinoscopy: Chamberlain		✓	✓	✓	✓		



NCI

Staging

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



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

Early-stage lung cancer is classically defined as stage I – II; note, SBRT is typically not performed for node positive disease

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

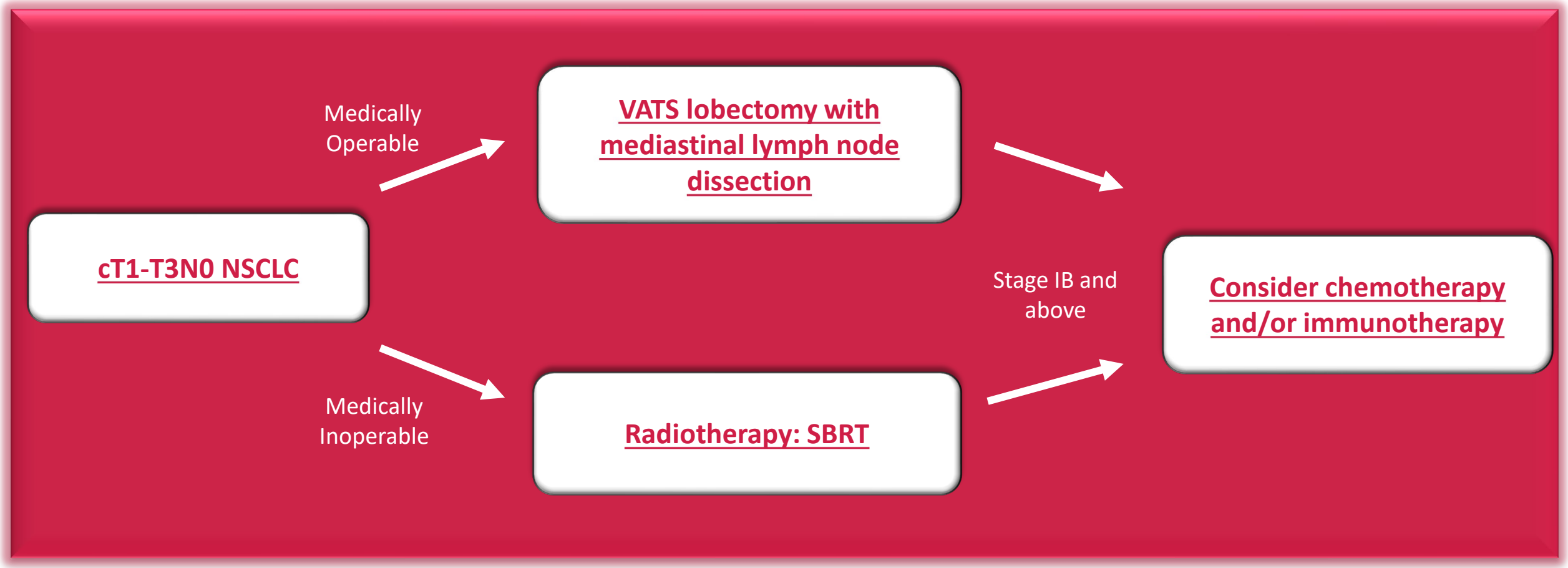
T/M \ N		cN0	cN1	cN2	cN3
T1	a ≤1 cm[1]	IA1	IIB	IIIA	IIIB
	b 1.1–2 cm	IA2			
	c 2.1–3 cm	IA3			
T2[2]	a 3.1–4 cm	IB			
	b 4.1–5 cm	IIA			
T3	• 5.1–7 cm • Invasion[3] • Same lobe nodules	IIB	IIIA	IIIB	IIIC
T4	• >7 cm • Invasion[4] • Separate lobe nodules	IIIA			
M1a	• Separate nodules in contralateral 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: Early-Stage NSCLC



Surgery

Multidisciplinary discussion is highly recommended

- Surgery (VATS lobectomy with a N1/N2 mediastinal lymph node dissection) is the current standard of care for early-stage lung cancer
  - A segmentectomy can be considered for selected patient populations (i.e.: major co-morbidities)

- Evolving treatment paradigms include:
  - Increased utilization of segmentectomies and wedge resections
  - SBRT as an equivalent standard of care to surgery

Radiation – SABR / SBRT

“No-Fly Zone” = Proximal Bronchial Tree (PBT) + 2 cm

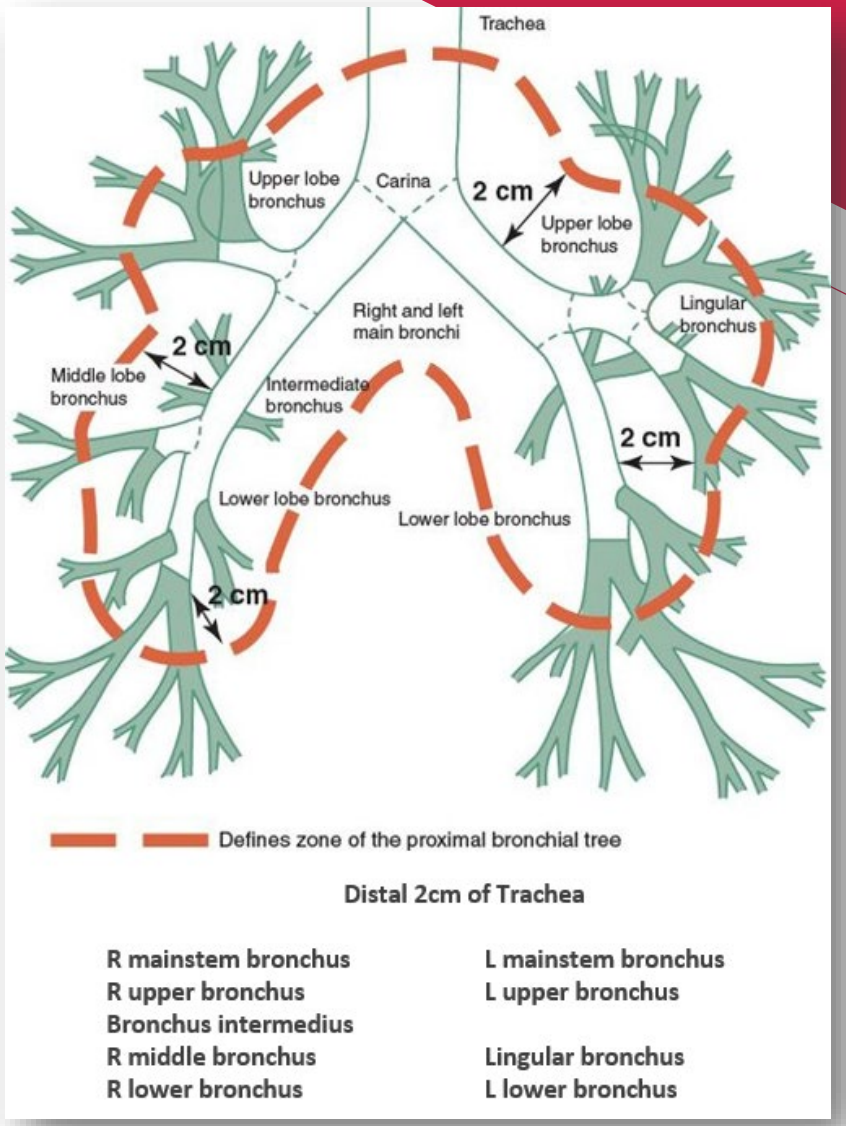
Simulation

- 4DCT (± IV contrast)
- Supine, arms above head in an arm-board

Treatment

- Dosing for lung SBRT is quite variable between institutions, as are the definitions of ultracentral, central, and peripheral lesions
  - It is important to note that BED > 100 Gy is associated with better local control

Dose / Fractionation	Location	Definition
60 / 8	Ultracentral	Tumor touching the PBT, esophagus, pulmonary artery or vein
50 / 5	Central	Tumor touching the “No-Fly Zone”
54 / 3	Peripheral	Tumors that do not meet the above criteria



Radiation: 4DCT and Gating

Per AAPM TG-76, if tumor motion is greater than 5 mm in any coordinate, motion management should be considered

- Four-dimensional computed tomography (4DCT) records multiple images over time
  - This allows tumor movement to be tracked and be played as a video
- With gating, treating the tumor only during certain phases of the respiratory cycle (i.e.: 40 – 60) reduces radiation exposure to normal organs (i.e.: heart and lungs)
- Other motion management techniques include compression and DIBH

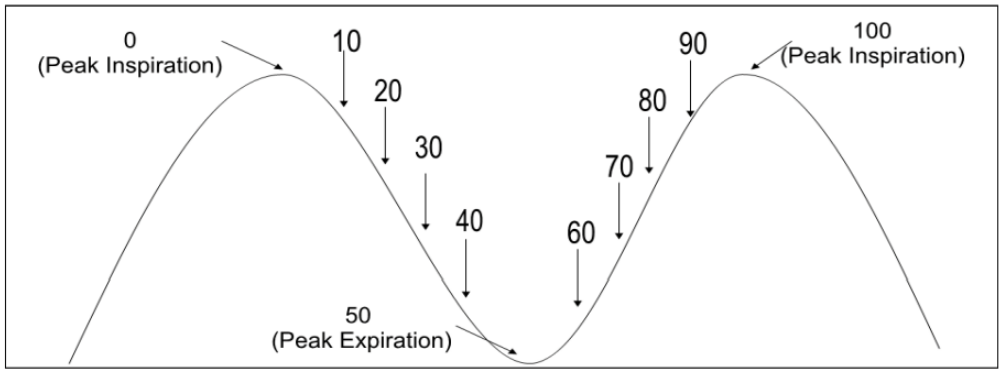
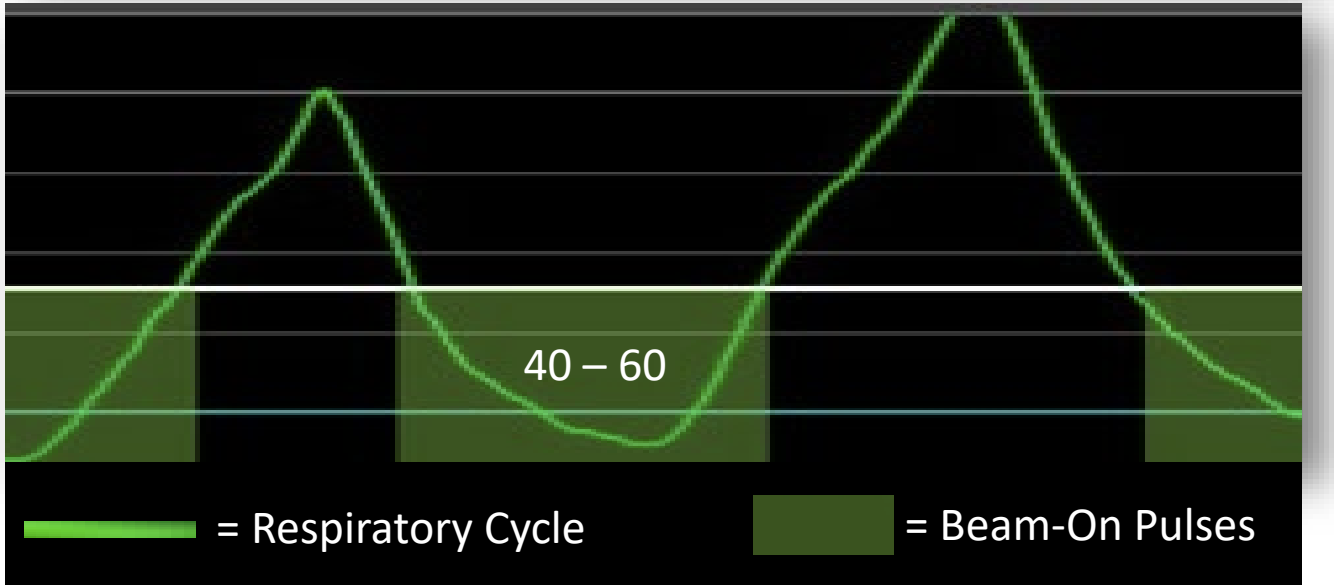


Figure 1: Schematic of a human breathing cycle in the form of a sinusoidal wave form. The numbers on the curve represent the location of various bins used to segregate the original 4DCT dataset with 0% & 50% representing maximum inhale and exhale states, respectively.

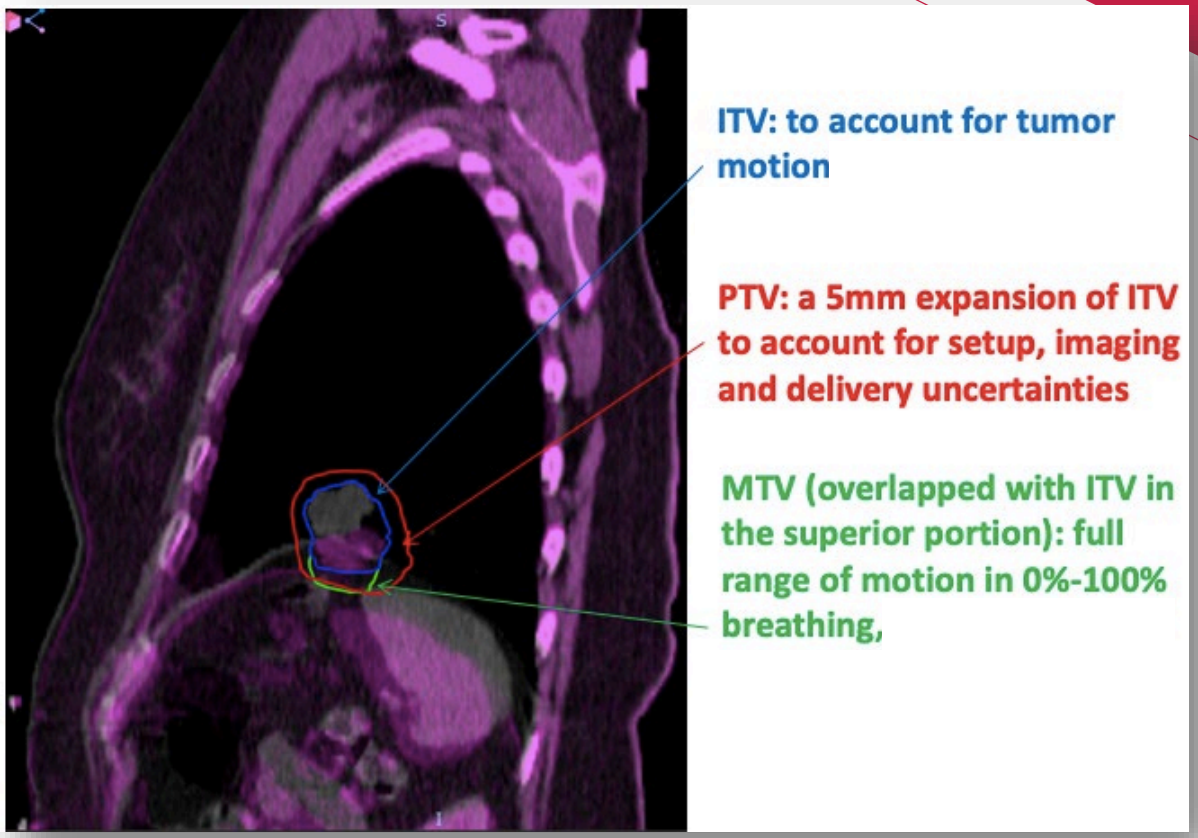
PMID: 31942567



Radiation – Contours

Often, an ITV to PTV expansion of 5 mm will be utilized (omitting a CTV)

- GTV = Gross Tumor Volume
  - This is the volume of disease contoured on all available datasets, on lung window
- ITV = Internal Target Volume
  - This is the volume of tumor motion when radiation is actively being delivered
- MTV = Maximum Tumor Volume
  - This is the volume of the full extent of tumor motion throughout the breathing cycle
  - It is sometimes used to align the patient for treatment



Selected SBRT Doses and Dose Constraints

PTV coverage may be compromised to meet critical OAR constraints (i.e.: great vessels, bronchi)

PRINCIPLES OF RADIATION THERAPY

Please note: Tables 2–5 provide doses and constraints used commonly or in past clinical trials as useful references rather than specific recommendations.

Table 2. Commonly Used Doses for SABR

Total Dose	# Fractions	Example Indications
25–34 Gy	1	Peripheral, small
45–60 Gy	3	Peripheral tumors
48–50 Gy	4	Central or peripheral tumors <4–5 cm
50–55 Gy	5	Central or peripheral tumors
60–70 Gy	8–10	Central tumors

Table 3. Maximum Dose Constraints for SABR*

OAR/Regimen	1 Fraction	3 Fractions	4 Fractions	5 Fractions
Spinal cord	14 Gy	18 Gy (6 Gy/fx)	26 Gy (6.5 Gy/fx)	30 Gy (6 Gy/fx)
Esophagus	15.4 Gy	27 Gy (9 Gy/fx)	30 Gy (7.5 Gy/fx)	105% of PTV prescription^
Brachial plexus	17.5 Gy	24 Gy (8 Gy/fx)	27.2 Gy (6.8 Gy/fx)	32 Gy (6.4 Gy/fx)
Heart/ pericardium	22 Gy	30 Gy (10 Gy/fx)	34 Gy (8.5 Gy/fx)	105% of PTV prescription^
Great vessels	37 Gy	NS	49 Gy (12.25 Gy/fx)	105% of PTV prescription^
Trachea & proximal bronchi	20.2 Gy	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy/fx)	105% of PTV prescription^
Rib	30 Gy	30 Gy (10 Gy/fx)	40 Gy (10 Gy/fx)	NS
Skin	26 Gy	24 Gy (8 Gy/fx)	36 Gy (9 Gy/fx)	32 Gy (6.4 Gy/fx)
Stomach	12.4 Gy	NS	27.2 Gy (6.8 Gy/fx)	NS

*Based on constraints used in recent RTOG SABR trials (RTOG 0618, 0813, & 0915).
^For central tumor location. NS = not specified.

NCCN

Radiation Toxicities

It is imperative to tailor dosing to the area of disease (i.e.: ultracentral vs. peripheral) to avoid fatal toxicities from radiotherapy

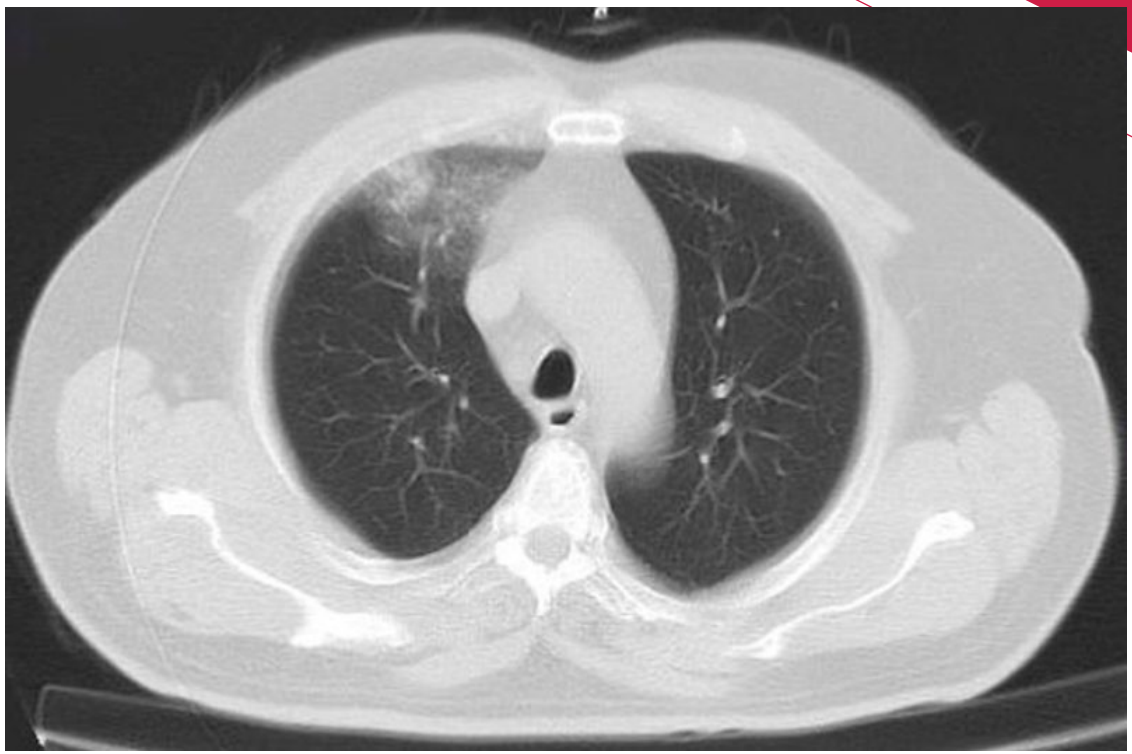
- Acute:
  - Fatigue
  - Skin Irritation
  - Cough
  - Esophagitis
  - Radiation Pneumonitis

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

Radiation Pneumonitis

Following SBRT, there is around a 10 – 15% risk of 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
- The mainstay of treatment is steroids
  - There are a variety of dosing schedules, most including 40 – 60 mg steroids with a slow taper
    - 10-week schedule
      - 50mg daily for 2 weeks
      - 40mg daily for 2 weeks
      - 30mg daily for 2 weeks
      - 20mg daily for 2 weeks
      - 10mg daily for 2 weeks
  - Supplemental oxygen may be necessary



Radiopaedia

Image Guided Thermal Ablation (IGTA)

Pneumothorax is a known event after IGTA: 20% of cases may require chest tube insertion (per NCCN)

- IGTA may be considered for patients whose tumors are < 3 cm, and who are ineligible for surgery or SBRT (those with significant co-morbidities, i.e.: interstitial lung disease)
  - However, many centrally located tumors are not amenable to IGTA
- IGTA includes radiofrequency ablation, microwave ablation, and cryoablation
- The local control rate of IGTA is inferior to that of SBRT
  - ACOSOG Z4033 reported 1- and 2-year local recurrence rates at 30% and 40% (for stage IA tumors)

Systemic Therapy

Adjuvant systemic therapy can be considered for high risk factors including vascular invasion, tumors > 4 cm, visceral pleural involvement

- For early-stage lung cancer, systemic therapy can be considered adjuvantly for stage IB and higher disease
  - Squamous: cisplatin/gemcitabine or cisplatin/docetaxel
  - Non-squamous: cisplatin/pemetrexed

- The role of adjuvant immunotherapies is expanding. For example:
  - Atezolizumab can be given for completely resected, stage IIB – IIIA tumors with PD-L1 ≥ 1%
  - Osimertinib can be given for completely resected, stage IB – IIIA tumors with an EGFR mutation

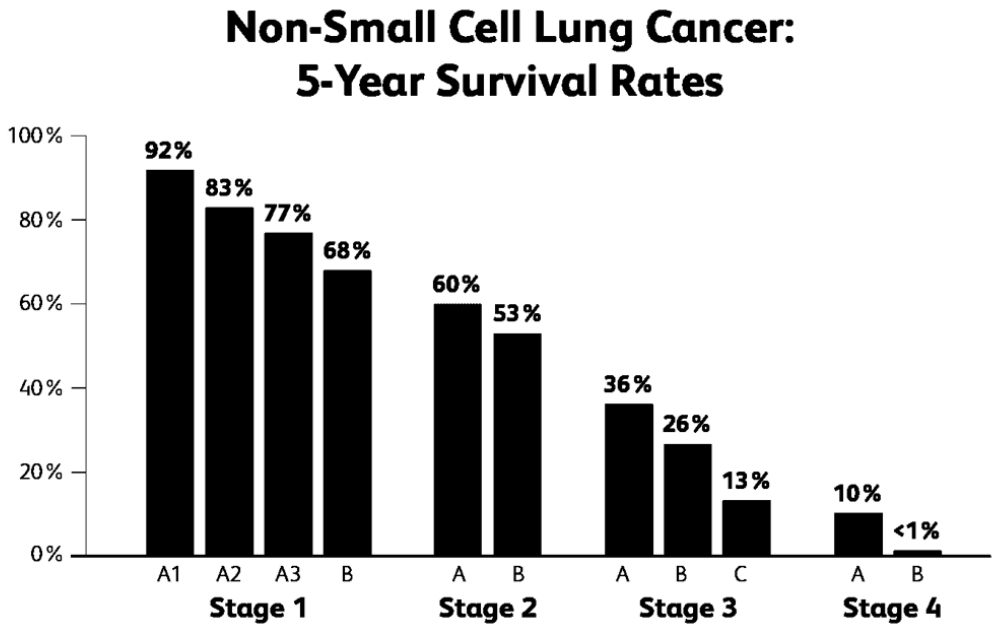
Prognosis

In the era of modern therapies, (i.e.: immunotherapy), survival rates are improving

- While lung cancer remains the most lethal cancer in the United States, survival rates for early-stage lung cancer are promising
  - Local control rates with SBRT are near 90%

T/M	Sub-Category	N0	N1	N2	N3
T1	T1a T1b T1c	1A1 1A2 1A3	2B 2B 2B	3A 3A 3A	3B 3B 3B
T2	T2a T2b	1B 2A	2B 2B	3A 3A	3B 3B
T3		2B	3A	3B	3C
T4		3A	3A	3B	3C
M1	M1a M1b M1c	4A 4A 4B	4A 4A 4B	4A 4A 4B	4A 4A 4B

Gunderson and Tepper's Clinical Radiation Oncology



Source: American Cancer Society 2017

Review

Review #1: Challenging the standard of care

PMID: 25981812

For early-stage NSCLC, what did the pooled analysis of STARS and ROSEL demonstrate comparing SBRT vs. Lobectomy with Mediastinal Lymph Node Dissection?

(A) Superior OS with surgery

(B) Superior OS with radiotherapy

(C) Significantly lower grade 3 – 4 toxicities with SBRT

(D) B + C

Review #2: Staging

LN stations 5 and 6 are considered left sided levels

What is the AJCC 8th edition TNM staging for a 55-year-old female with a 3.1 cm RML mass and a positive subaortic lymph node?

(A) T1cN2M0

(B) T1cN3M0

(C) T2aN2M0

(D) T2aN3M0

Review #3: Dose Constraints

Per NCCN

What is the 3 fraction SBRT dose constraint to the trachea and proximal bronchus?

(A) 25 Gy

(B) 30 Gy

(C) 35 Gy

(D) 40 Gy

Review #4: SBRT Dosing

Certain institutions currently utilize this fractionation for peripheral tumors

What was the single fraction SBRT dose utilized in RTOG 0915?

(A) 20 Gy / 1 fx

(B) 34 Gy / 1 fx

(C) 40 Gy / 1 fx

(D) 54 Gy / 1 fx

Review #5: Managing Toxicities

NCCN recommends H&P with chest CT every 3 - 6 months initially after treatment

Which of the following is the most appropriate initial treatment for the development of symptomatic radiation pneumonitis after delivery of SBRT?

(A) 10-week course of steroids

(B) Hyperbaric oxygen

(C) Lobectomy

(D) Avastin

Answer Key

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

VALOR and STABLE-MATES are randomized trials comparing SBRT and surgery