SABR: Central Lung Early Stage NSCLC

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Case Presentation

- 70 year old Male, presents with worsening cough and pink sputum x 4 weeks
- No weight loss, no fevers/chills, review of systems negative
- Chest X-Ray: left hilar mass, possible left lower lobe pneumonia
- Treated with Levofloxacin x 10 days → pink sputum resolved, but cough persisted

Case Presentation

Past Medical History:

- COPD- previous exacerbation 4 years ago requiring ICU admission
- Previous NSTEMI
- Past smoker: 50 pack year history, quit x 4 years

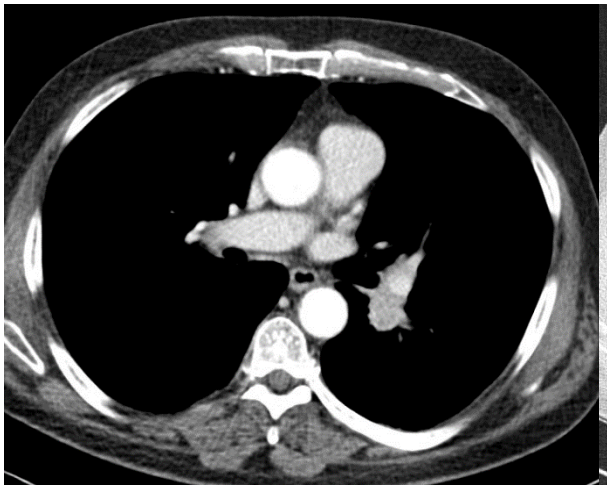
Physical Examination:

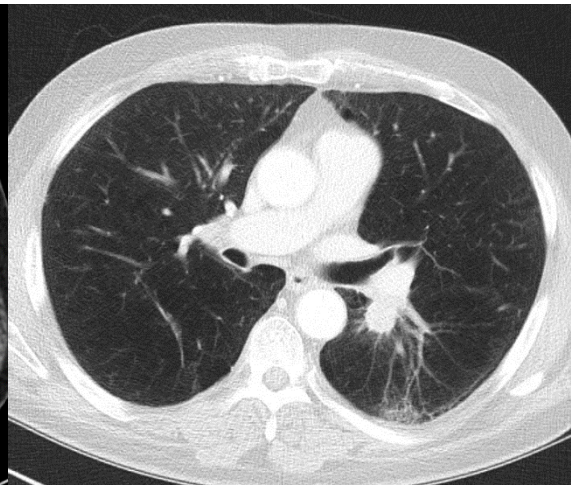
- Appeared well, vital signs normal
- No H&N lymphadenopathy
- Chest auscultation- clear bilaterally, no adventitious sounds

Workup

CT Chest:

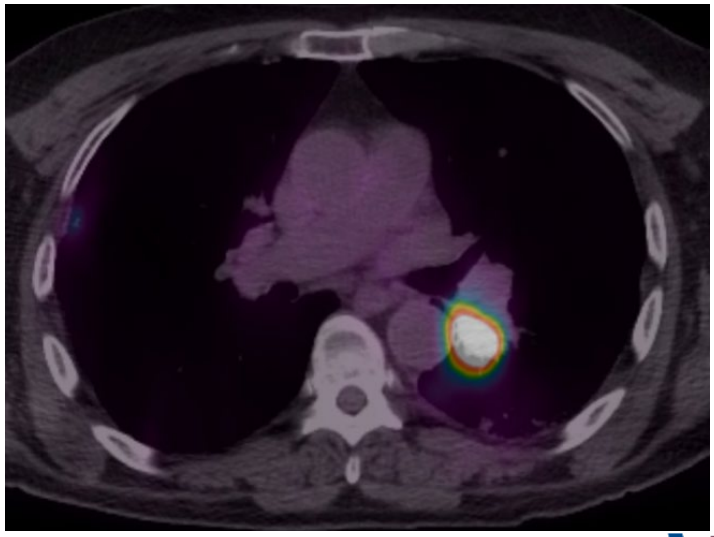
- Left lower lobe spiculated mass, 3.3 cm in greatest dimension, abutting left lower lobe bronchus
- No hilar/mediastinal lymphadenopathy





PET/CT Scan:

- Left lower lobe perihilar hypermetabolic lesion, SUVmax 15.0
- No FDG avid lymphadenopathy
- No distant metastases



Workup

Laboratory values: Normal

CT Head & MR Brain: Negative for metastases

Pulmonary Function Tests:

- FEV1/FVC Ratio = 42%
- FEV1= 45% predicted (1.19 L)
- DLCO = 44% predicted

Echocardiogram:

- LV Ejection fraction = 58%, no wall motion abnormalities, normal diastolic function, normal RV function, no valvular dysfunction

Tissue Diagnosis and Staging

- Flexible Bronchoscopy:
  - tumor seen within left bronchial tree, partially occluding superior segment of the left lower lobe
- Transbronchial Biopsy:
  - Pathology: invasive squamous cell carcinoma
  - PDL-1 weak positive (41 - 49%)
- EBUS-FNA for mediastinal staging:
  - No visibly enlarged nodes
  - Stations 7 and 10 negative by FNA

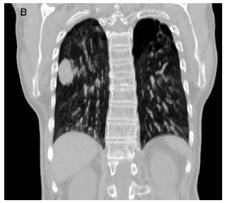
Curative Intent Treatment Options

- Surgical Resection
  - Requires lobectomy or pneumonectomy
- Definitive Radiation Treatment
  - Stereotactic Ablative Radiation Therapy (SABR) or Stereotactic Body Radiation Therapy (SBRT)
    - Considered standard of care for medically inoperable early stage NSCLC
  - Conventionally Fractionated Radiation Therapy

SABR

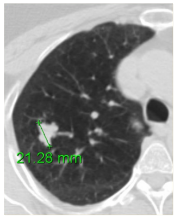
- Delivery of very high (ablative) radiation doses in a few fractions using highly conformal techniques
- Generally 1-5 fractions (ASTRO Evidence-Based Guidelines 2017)
- Alternatives include 6-10 fractions, used more frequently outside of the U.S.
- $BED_{10} \geq 100\ Gy_{10}$ needed to maximize local control

SABR Features



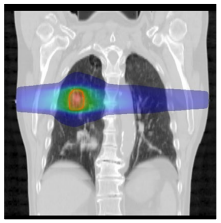
Accounting for Motion

- 4D Planning



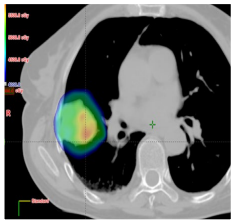
Small tumour volumes

- Small margins



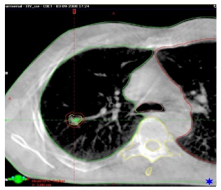
Many Beam Directions

- 7-11 Beams / Arc Therapy



Steep dose gradients

- Inhomogeneous target dose



Accurate Targeting

- e.g. CBCT pre-RT

High dose per fraction

- Short total treatment duration

SABR vs. Conventional RT: RCTs

SPACE (Nyman *et al.* 2016)

- Planned as Phase III, scaled down to Phase II
- Randomized N=102 to SABR (66 Gy in 3 Fr; 45 Gy at periphery of PTV) vs. conventional RT (70 Gy in 35 Fr)
- Excluded central tumors, or tumors > 6 cm
- OS & PFS: no difference between SBRT and conventional RT
- Potential better disease control rate in SBRT with better QoL and less toxicity

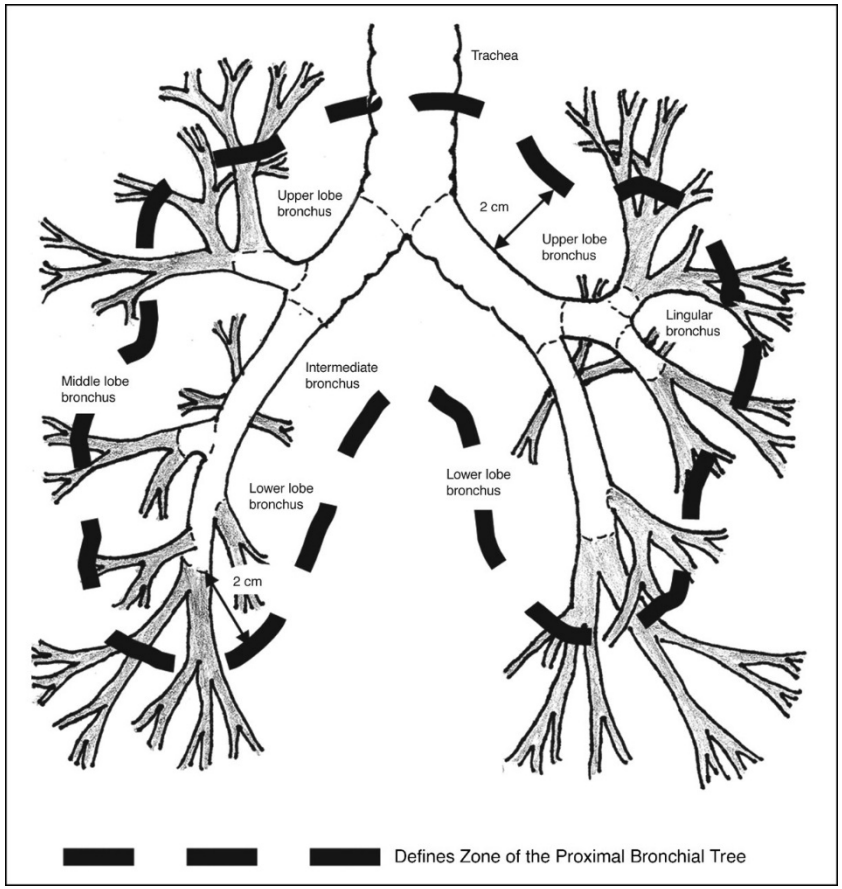
CHISEL (Ball *et al.* 2019)

- Phase III RCT
- Randomized N = 101 to SABR (54 Gy/3Fr or 48 Gy/4Fr) vs. conventional RT (66 Gy/33Fr or 50 Gy/20Fr)
- Excluded central tumors
- SABR: improved freedom from local failure (HR 0.32; 95% CI 0.13-0.77; p=0.008)
- 2 yr Local Control: SABR 89% vs. conventional 65%
- Median OS: SABR 5 years vs. conventional 3 years (HR 0.53; 95% CI 0.3- 0.94, p=0.03)

Central Lung Tumours

Background

- Early SABR studies showed increased toxicities when treating central tumors compared to peripheral tumors
- Indiana University (Timmerman *et al.* 2007)
  - Phase II Study of SABR 60 - 66 Gy in 3 Fr
  - Hilar/pericentral tumors have 11x increased risk of severe toxicity compared to peripheral tumors
  - Location strong predictor of grade 3-5 toxicity (p=0.004)
  - 2-yr freedom from severe toxicity 83% peripheral vs. 54% perihilar/central
  - 4 of 6 deaths from toxicity were in patients with perihilar/central tumors
- "No-Fly Zone"- within 2 cm of proximal bronchial tree



Definitions

"Central":

- Most common definition/RTOG: Tumor within 2 cm radius in all directions from the proximal bronchial tree (PBT):
  - Distal 2 cm of Trachea, Carina
  - Right & left mainstem bronchi
  - Right: upper lobe, bronchus intermedius, middle lobe, lower lobe bronchus
  - Left: upper lobe, lingular bronchus, lower lobe bronchus
- Other definitions: within 2 cm of any mediastinal critical structure (bronchi, esophagus, heart & major vessels etc.)

"Ultracentral":

- More recent term, no consensus definition, varied by study
- PTV touches or overlaps central bronchial tree (PBT), esophagus, pulmonary artery or pulmonary vein (definition per SUNSET trial)
  - at risk of serious toxicities

NRG Oncology/RTOG 0813 Trial

- Phase I/II study to determine maximum tolerated dose (MTD), efficacy, and toxicity of SABR for central NSCLC; N= 120 pts
- Central definition: tumors within or touching 2 cm zone around the PBT or immediately adjacent to mediastinal or pericardial pleura
- Tumors no larger than 5 cm
- Ultracentral tumors: 17% of patients
- Dose-escalating, 5 fraction SABR schedule of 10 to 12 Gy per fraction (i.e. starting at 50 Gy escalated to 60 Gy)

- **MTD:** 12 Gy per Fr (60 Gy in 5 fractions)
- Probability of Dose-limiting Toxicity (DLT) at the MTD = 7.2% (95% CI: 2.8-14.5%)
- Total of 5 patients experienced DLT's (death NOS, gr. 5 sinus bradycardia, gr. 3 hypoxia, gr. 3 pneumonitis, gr. 3 pleural effusion)
- **2-yr LC** in 11.5 Gy/Fr (57.5 Gy) cohort: 89.4% and in 12 Gy/Fr (60 Gy) cohort: 87.9%
- **2-yr OS** 67.9% and 72.7%, respectively

Washington University Phase I/II Trial

- N= 74 patients enrolled to prospective study (23 to phase I, 51 to phase II)
- Tumors within or touching zone of PBT, within 5 mm or invading mediastinal pleura, within 5 mm or invading parietal pericardium
- Tumor 7 cm or less
- Phase II dose = 55 Gy / 5 Fr
- Acute toxicities: gr. 3 and 4 cardiac or pulmonary toxicities in 3 patients (6%)
- Late toxicities: gr. 3 cardiac or pulmonary in 11 pts (27%), gr. 4 in 5 pts (12%), 1 patient (4%) died of gr. 5 toxicity
- 2-yr LC: 85% (95% CI: 62-95%) using 55 Gy / 5 Fr
- 2-yr OS: 43% (95% CI: 28-57%)

Ultracentral (UC) Tumors

- Raman (2018): 60 Gy in 8 Fr
  - UC= PTV contact/overlap PBT, esophagus, pulmonary vessels
  - No excessive risk of toxicity of UC vs. central
- Tekatli (2016): 60 Gy in 12 Fr; 4 fr per week over 3 weeks
  - UC= PTV overlapping trachea or main bronchi
  - 15% fatal pulmonary hemorrhage
  - Gr. 3 toxicity or higher: 38%
- Chaudhuri (2015): 50 Gy in 4 or 5 Fr
  - UC= GTV directly abut PBT or Trachea (excluded esophagus, mediastinum)
  - No significant toxicity difference between central vs. UC
- Hasbeek (2011): 60 Gy in 8 fr
  - Overlap with high-risk mediastinal structures (aorta, esophagus)
  - Acute gr. 3 toxicity 2%; late gr. 3 toxicity 6% (dyspnea, chest wall pain, fracture)

Current Trial: SUNSET

- Multicenter phase I dose-finding study to determine MTD for ultracentral NSCLC
- Ultracentral definition: PTV touches or overlaps the central bronchial tree, esophagus, pulmonary vein, or pulmonary artery
- Starting Dose: 60 Gy in 8 fr; 7.5 Gy/fr (common in many Canadian centers)
- CT Simulation with contrast required
- Hot spot limited to 120%

Dose Options

- Central:
  - 50-55 Gy in 5 Fr (common in the U.S.)
  - 60 Gy in 8 Fr (common in Canada / Europe)
  - 48 Gy in 4 Fr
  - 60 Gy in 5 Fr (MTD as per RTOG 0813)

- Ultracentral:
  - 60 Gy in 8 Fr
  - 50 Gy in 5 Fr
  - 60 Gy in 15 Fr (Hypofractionated)
  - Conventional RT

- Enroll in clinical trials

Case: Our Patient's Treatment

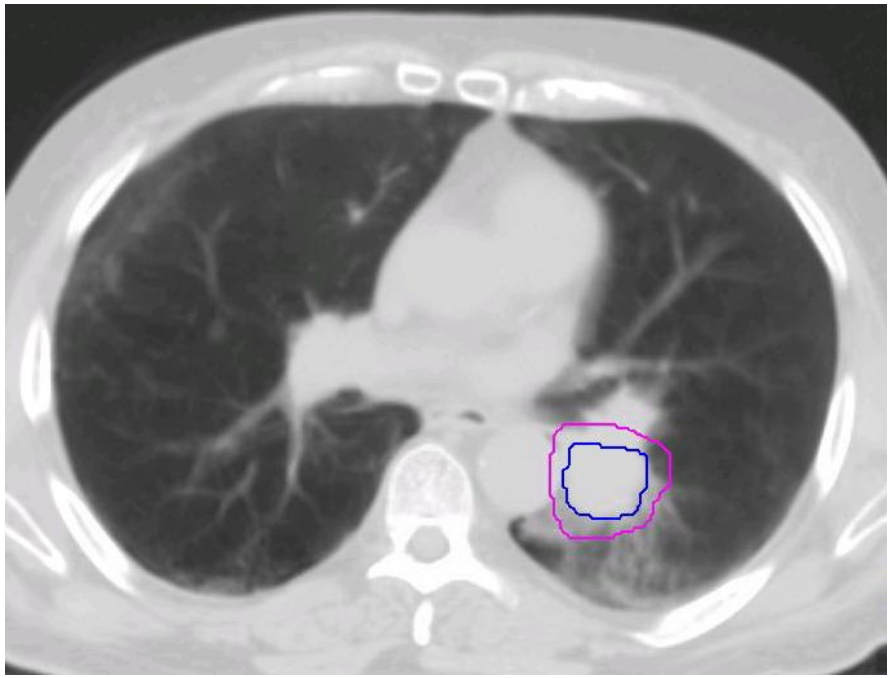
- Offered sleeve lower lobectomy by thoracic surgeon as well as SABR
- Patient decided on SABR
- Enrolled onto SUNSET Clinical Trial
- Dose on trial: 60 Gy in 8 fractions

Radiation Planning

- Simulation:
  - 4D CT, IV contrast preferred
  - Position: Supine, arms above head
  - Immobilization: Vac Lok
- Physics:
  - Observe 4D-Cine “loop” playback of tumor motion from 4D CT
  - Ensures no hysteresis (tumor takes different path between inspiration and expiration)
    - If hysteresis, can use Maximum Intensity Projection (MIP) or delineate on all phases of breathing cycle
  - Our institution uses respiratory gating if tumor motion > 7 mm
  - Ungated: Rad Onc delineates tumor using the Average Intensity Projection (AIP), Phase 0 (full inspiration), Phase 50 (full expiration)
    - Alternative: delineate using the MIP or contour all phases of 4DCT

Treatment Volumes

- GTV = gross tumor from CT and PET imaging
- CTV = GTV
- CTV_0 = CTV on full inspiration
- CTV_50 = CTV on full expiration
- CTV_Avg = CTV on AIP
- ITV = CTV_0 + CTV_50 + CTV_Avg
  - Alternative use MIP instead of Avg
- Check ITV to ensure it covers all phases
- PTV = ITV + 0.5 cm (since using ITV)



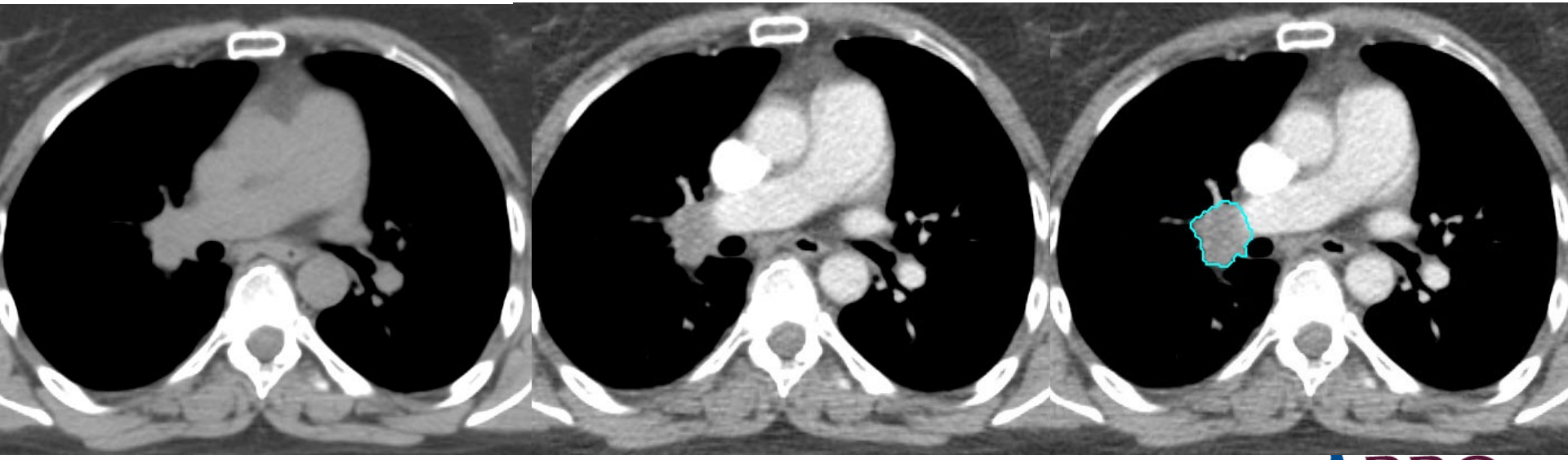
ITV in Blue
PTV in Pink

IV Contrast

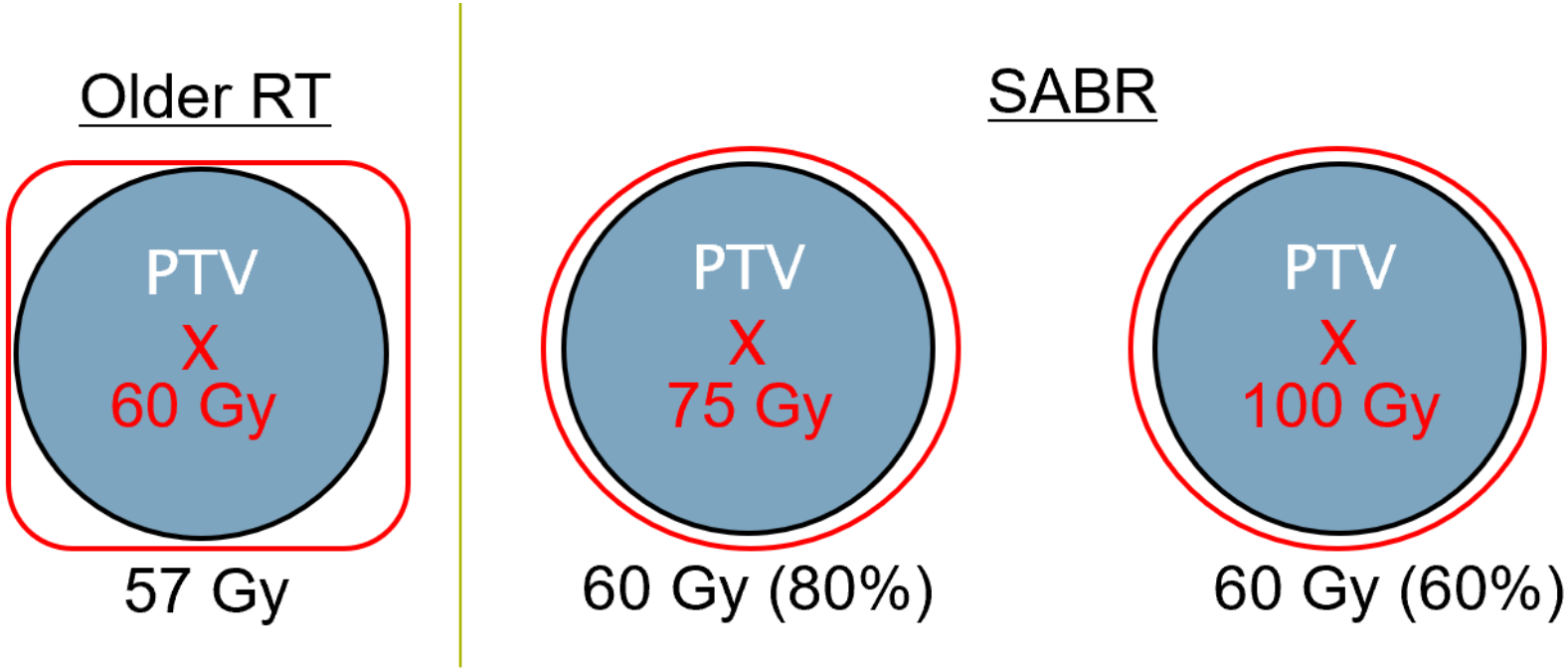
- IV Contrast was not used for this patient
- However, it can be helpful for central tumors for target delineation, especially if abutting vessels

- Images below show value of IV contrast for different patient

No Contrast | Post Contrast | Delineated target + contrast

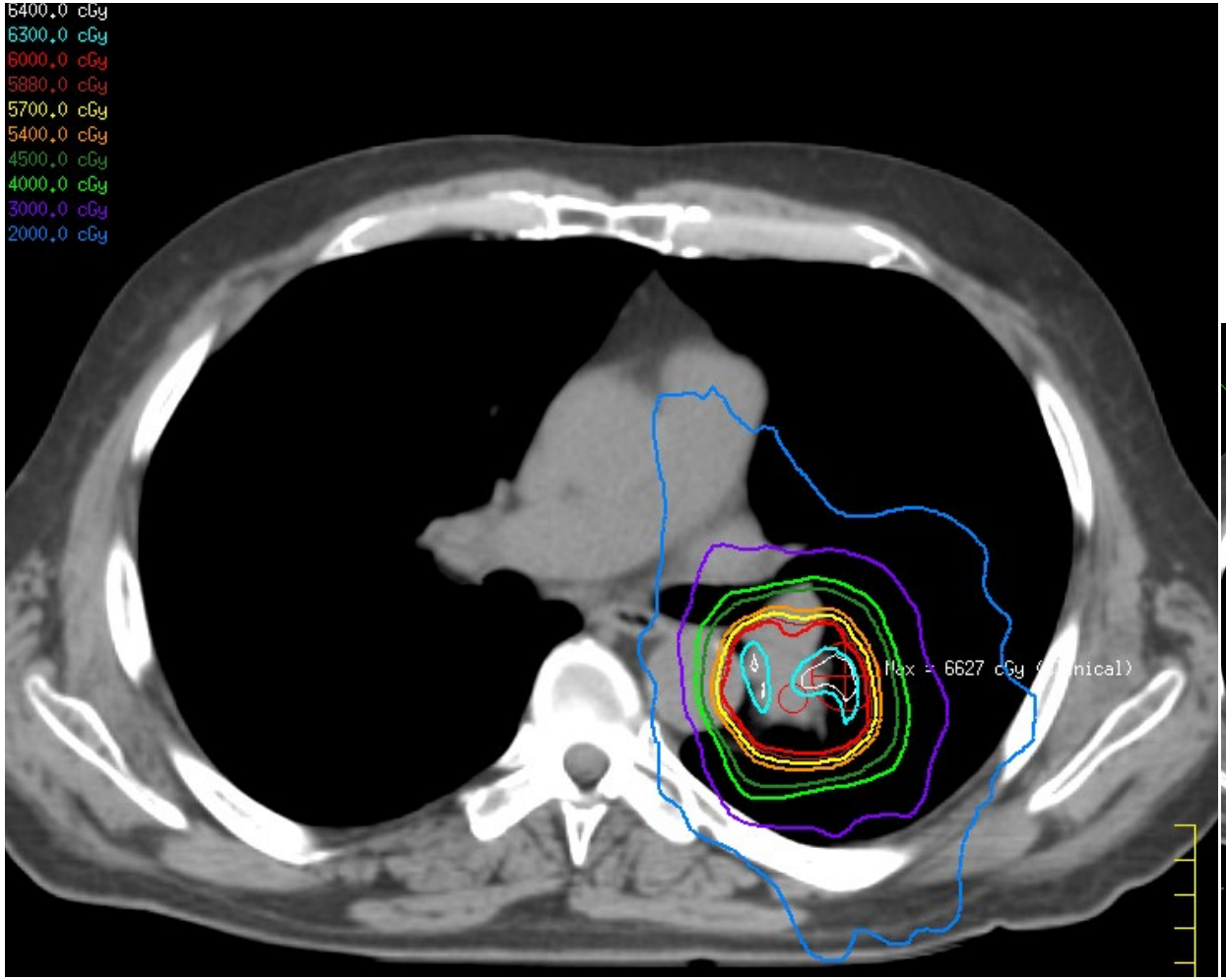


SABR Prescription



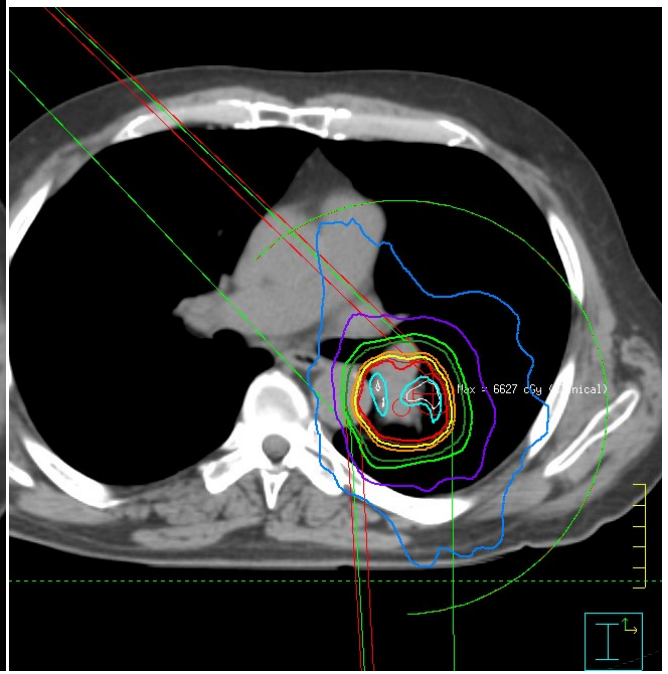
- SABR: dose prescribed to the periphery of PTV (e.g. 60-90% isodose line) such that a “hotspot” and dose heterogeneity will exist within the PTV
- To improve dose fall-off outside of target

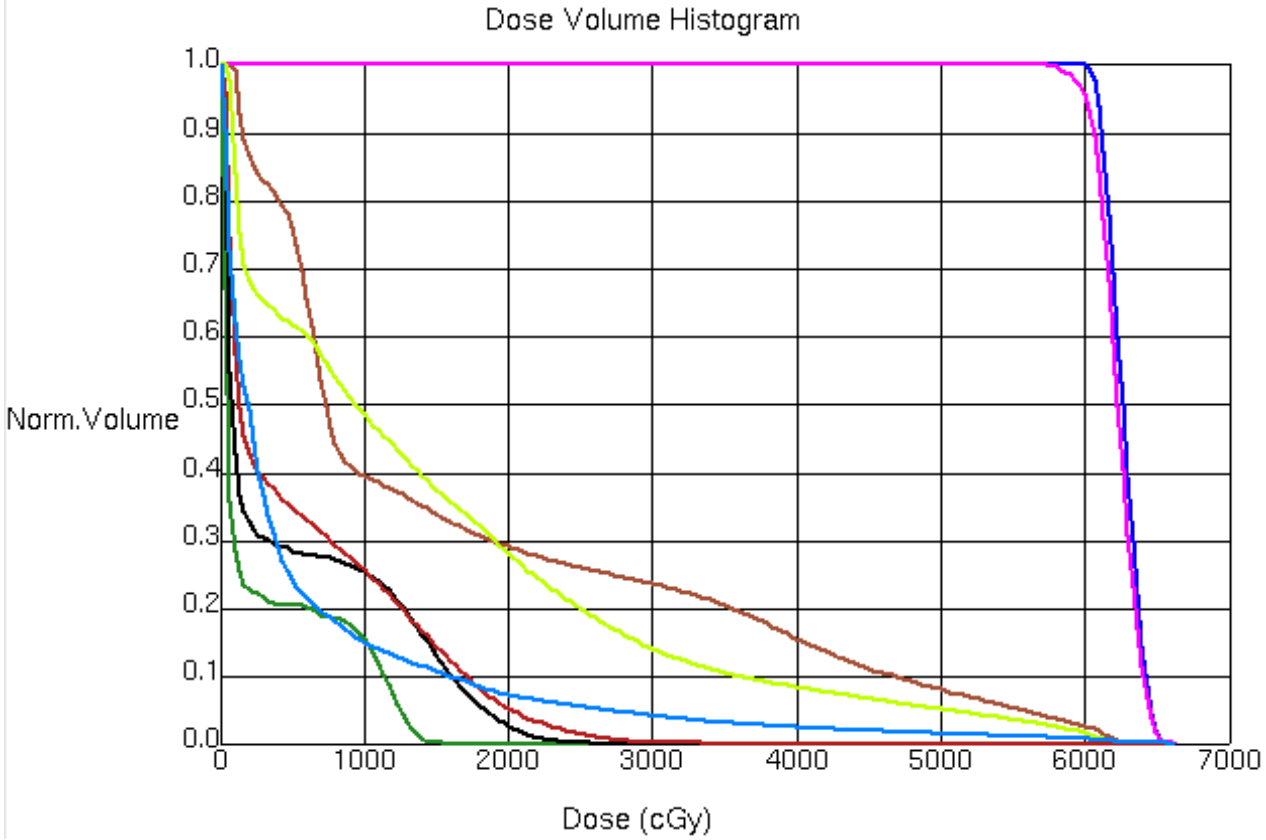
Patient Plan



VMAT 2 arcs:

315-178 degrees Clockwise & Counter clockwise





	SpinalCanal	Clinical	15.0	1547.0	247.5	424.1	7.34 %	0.00 %	--
	Esophagus	Clinical	18.5	2574.6	472.4	660.2	0.00 %	0.00 %	--
	Bronchus	Clinical	87.4	6331.1	1662.0	1759.4	0.00 %	0.00 %	--
	ITV	Clinical	5984.6	6615.9	6261.2	114.5	0.00 %	0.00 %	--
	PTV60	Clinical	5549.3	6615.9	6223.1	137.9	0.00 %	0.00 %	--
	Great Vessels	Clinical	53.3	6338.2	1426.4	1527.5	0.00 %	0.00 %	--
	Heart	Clinical	16.9	3339.1	559.4	702.2	0.00 %	0.00 %	--
	Lung_Eval	Clinical	1.2	6580.8	553.5	1003.0	0.00 %	0.00 %	--

Critical Structure Dose Constraints SUNSET

Organ	Metric	Fraction		
		5/6	8/10	15
Spinal canal	Max	30 Gy	32 Gy	39.5 Gy
Spinal canal PRV (3 mm)	Max	32 Gy	34 Gy	42 Gy
Esophagus	Max	40 Gy	45 Gy	50.5 Gy
	5 cc	35 Gy	40 Gy	48 Gy
Brachial plexus	Max	32 Gy	39 Gy	50 Gy
Heart	Max	62 Gy	64 Gy	66 Gy
	10 cc	50 Gy	60 Gy	62 Gy
Trachea	Max	62 Gy	64 Gy	66 Gy
	10 cc	50 Gy	60 Gy	62 Gy
Proximal bronchus	Max	62 Gy	64 Gy	66 Gy
	10 cc	50 Gy	60 Gy	62 Gy
Non-GTV lung	Mean	< 12 Gy	< 12 Gy	< 14 Gy
Aorta and major vessels	Max	62 Gy	64 Gy	64 Gy
	10 cc	50 Gy	60 Gy	60 Gy
Stomach and intestines	Max	40 Gy	45 Gy	50 Gy
	10 cc	35 Gy	40 Gy	48 Gy

Abbreviations: GTV = gross tumor volume; PRV = planning organ-at-risk volume.

SABR Plan Evaluation

- Target Coverage:
  - 95% of PTV receives at least 100% of prescription
  - 99% of PTV receives 90% of prescription
- High Dose Spillage:
  - Cumulative volume of all tissue outside the PTV receiving a dose of >105% of prescription should be ≤ 15% of PTV volume
- Dose Fall-off outside of target:
  - R50 = Ratio of 50% prescription isodose volume to the PTV volume
  - D2cm = Maximum dose (% dose prescribed) at 2cm from PTV in any Direction
- Plan Conformity:
  - R100 = Ratio of prescription isodose volume to the PTV volume <1.2 - 1.5
- Heterogeneity Index:
  - Ratio of the highest dose received by 5% of PTV to lowest dose received by 95% of PTV

Follow-Up

- NCCN: History and physical + CT Chest every 3 months: first 3 years
- H&P + CT Chest every 6 months: years 4-5
- Then H&P + Low-dose CT Chest annually
- PET/CT or MR Brain not routinely indicated

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