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.
• $\text{BED}_{10} \geq 100 \text{ Gy}_{10}$ 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)
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
<table>
<thead>
<tr>
<th>Organ</th>
<th>Type</th>
<th>Dose (cGy)</th>
<th>Norm Volume</th>
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</thead>
<tbody>
<tr>
<td>Spinal Canal</td>
<td>Clinical</td>
<td>15.0</td>
<td>1547.0</td>
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<tr>
<td>Esophagus</td>
<td>Clinical</td>
<td>18.5</td>
<td>2574.6</td>
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<td>Bronchus</td>
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<tr>
<td>ITV</td>
<td>Clinical</td>
<td>5384.6</td>
<td>6615.9</td>
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<tr>
<td>PTV60</td>
<td>Clinical</td>
<td>5549.3</td>
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<td>Great Vessels</td>
<td>Clinical</td>
<td>53.3</td>
<td>6336.2</td>
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<tr>
<td>Heart</td>
<td>Clinical</td>
<td>16.9</td>
<td>3339.1</td>
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<tr>
<td>Lung Eval</td>
<td>Clinical</td>
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</table>
# Critical Structure Dose Constraints SUNSET

<table>
<thead>
<tr>
<th>Organ</th>
<th>Metric</th>
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<th>8/10</th>
<th>15</th>
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<tbody>
<tr>
<td>Spinal canal</td>
<td>Max</td>
<td>30 Gy</td>
<td>32 Gy</td>
<td>39.5 Gy</td>
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<tr>
<td>Spinal canal PRV (3 mm)</td>
<td>Max</td>
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<td>34 Gy</td>
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<tr>
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<td>45 Gy</td>
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<tr>
<td>Esophagus</td>
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<td>40 Gy</td>
<td>48 Gy</td>
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<tr>
<td>Brachial plexus</td>
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<tr>
<td>Heart</td>
<td>Max</td>
<td>62 Gy</td>
<td>64 Gy</td>
<td>66 Gy</td>
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<tr>
<td>Heart</td>
<td>10 cc</td>
<td>50 Gy</td>
<td>60 Gy</td>
<td>62 Gy</td>
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<tr>
<td>Trachea</td>
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<td>Trachea</td>
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<td>Proximal bronchus</td>
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<td>66 Gy</td>
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<td>10 cc</td>
<td>35 Gy</td>
<td>40 Gy</td>
<td>48 Gy</td>
</tr>
</tbody>
</table>

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
References


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