Proton Treatment for Lung Cancer

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  • NSF-SBIR/STTR-1549509

Proton Therapy Rationale - Thoracic Tumors

Rationale | Potential Benefit
--- | ---
Reduce dose to normal tissues | Reduce treatment toxicities
More safely allows treatment of tumors close to critical organs (such as spinal cord) potentially not treatable with photon therapy | Chance of cure not otherwise achievable with proton therapy or chemotherapy alone
More safely allows for dose escalation | Improvement in local tumor control
More safely allows for radiotherapy to be combined with chemotherapy and surgery for immmunotherapy | Improvement in local tumor control and progression-free survival compared with definitive radiotherapy alone or immuno-oncology
More safely allows for retreatment of locally recurrent tumors potentially not treatable with photon therapy | Chance of cure not otherwise achievable with photon therapy or chemotherapy alone

Proton Therapy for Stage I NSCLC

- Prospective study of 80 patients with stage I NSCLC who were medically inoperable or refused surgery treated with protons (n=57) or carbon-ions (n=23) most commonly to 60 CGE in 10 fractions
  - 3-year overall survival 75%, cause-specific survival 86%, local control 82%
  - Grade 2 pneumonitis in 11%, grade 3 pneumonitis in 2%
- Phase II prospective study of 111 patients with stage I NSCLC who were medically inoperable or refused surgery treated in 10 fractions to escalated doses of 51 CGE, 60 CGE, 70 CGE
  - 4-yr overall survival increased with increasing dose level (18% vs. 32% vs. 51%, p<0.006)
  - No clinical radiation pneumonitis requiring steroid therapy
- Prospective study of 56 patients with stage I NSCLC
  - 66/6.6 Gy (peripheral) or 80/3.2 Gy (central)
  - 3-yr OS 81.3%, LC 96.0% (no differences based on dose)
  - Late toxicity: 13.4% grade 2, 1.5% grade 3


Proton Therapy for Stage I NSCLC

Meta-analysis comparing hypo-fractionated particle beam therapy (PBT) to photon SBRT for early stage (cT1-T3 N0 M0) NSCLC

- 72 SBRT studies, 9 hypo-fractionated PBT studies
- PBT patients had large median tumors (2.92 cm vs. 2.41 cm, p=0.02) and were less likely to have T1 disease (37% vs. 71%, p=0.05)
- PBT had improved overall survival (5 yr OS 60% vs. 41.3%, p=0.005) and progression-free survival (57.2% vs. 37.7%, p=0.01) on univariate analysis
- 3-year local control improved for PBT (p=0.03) on multivariate analysis
- Grade 3-5 toxicities lower with PBT (4.8% vs. 6.9%, p=0.05)
- Grade ≥3 pneumonitis: 0.9% vs. 3.4% (p=0.001)

Stereotactic Body Proton Therapy

Interplay effect between the target motion and scanning proton spots: can SBRT with protons be delivered in 5 or fewer fractions?


• 25 pts with stage I NSCLC prescribed to 60 Gy in 8 fractions
• Best potential indications are for tumors where photon SBRT risks are higher:
  • Large (>5 cm) tumors
  • Central and ultracentral tumors
  • Oligometastatic or oligoprogressive disease (systemic therapy)


ROCOCO Stage I Multinational Study

<table>
<thead>
<tr>
<th>Structure Measure</th>
<th>IMRT</th>
<th>RapidArc</th>
<th>CyberKnife</th>
<th>Protons</th>
<th>Carbon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Mean</td>
<td>5.0</td>
<td>4.4</td>
<td>4.6</td>
<td>4.1</td>
<td>2.3</td>
</tr>
<tr>
<td>Heart D2</td>
<td>6.1</td>
<td>4.7</td>
<td>7.6</td>
<td>2.4</td>
<td>0.71</td>
</tr>
<tr>
<td>Esophagus Mean</td>
<td>3.2</td>
<td>2.4</td>
<td>2.6</td>
<td>0.29</td>
<td>0.45</td>
</tr>
<tr>
<td>Cord D2</td>
<td>8.6</td>
<td>11.3</td>
<td>5.8</td>
<td>0.68</td>
<td>1.5</td>
</tr>
</tbody>
</table>

• Best potential indications are for tumors where photon SBRT risks are higher:
  • Large (>5 cm) tumors
  • Central and ultracentral tumors
  • Oligometastatic or oligoprogressive disease (systemic therapy)

Median overall survival: 28.7 months (60 Gy) vs. 20.3 months (74 Gy), p=0.0042

<table>
<thead>
<tr>
<th>Grade ≥3</th>
<th>Pulmonary</th>
<th>20%</th>
<th>19%</th>
<th>0.71</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥3</td>
<td>Pneumonitis</td>
<td>7%</td>
<td>4%</td>
<td>0.21</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>Esophagitis</td>
<td>7%</td>
<td>21%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>Any</td>
<td>70%</td>
<td>78%</td>
<td>NS</td>
</tr>
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</table>

Median overall survival: 28.7 months (60 Gy) vs. 20.3 months (74 Gy), p=0.0042


Did increased heart dose in the 74 Gy arm (V50 – 11% vs. 7%) lead to an increase in intercurrent cardiac deaths?

Authors: “heart dose might best explain why patients given 74 Gy did worse than patients given the 60 Gy”

“Did increased heart dose in the 74 Gy arm (V50 – 11% vs. 7%) lead to an increase in intercurrent cardiac deaths?”


Pathogenesis of Radiation-Related Heart Disease

- Pericarditis
  - Acute within weeks of RT
  - Late = 150-200 days after RT
  - Effusion, tamponade

- Others Events
  - Generally believed >10 yrs after RT

- Cardiomyopathy

- Coronary artery disease
  - → Atherosclerosis → Ischemia

- Valvular disease
- Conduction abnormalities
- Autonomic dysfunction (loss of circadian rhythm)
- Vascular changes (e.g. pulmonary artery stenosis)
RTOG 0617 Cardiac Analysis

- 5 thoracic radiation oncologists recontoured cardiac structures on 495 analyzable pts from RTOG 0617
  - Pericardium, ventricles, atria, coronary space
  - Recontoured percardial and PTV overlap with pericardial volumes larger than submitted
- Univariate analysis: all volumetric and mean heart and pericardial doses were associated with increased risk of death (p<0.001)
  - Similar for atrium and ventricles (p<0.01)
- Multivariate analysis: pericardial mean dose (HR=1.019, p=0.007), atria V45 (HR=1.007, p=0.022), ventricle V45 (HR=1.015, p=0.0043), and coronary space V45 (HR=1.005, p=0.0022) each negatively impacted OS
  - Pericardial mean dose (OR 1.044, p=0.0372) and stage IIIIB disease (OR 2.51, p=0.0342) were associated with grade ≥3 pneumonitis

Conclusion: cardiac doses are associated with survival and pneumonitis

Goren EM, et al. 2016 ASTRO Annual Meeting

Cardiac Toxicity and Protons

- 532 patients with NSCLC treated with concurrent chemoradiation
  - Mean heart dose: 22.3 Gy – 3DCRT
    15.1 Gy – IMRT
    6.5 Gy – PBT
- Retrospective multivariate analysis: mean heart doses >25th percentile associated with increased risk of death (HR 1.4)

OS with mean heart dose above or below the median per RT dose subgroup

Liao Z, et al. ASTRO 2012

Prospective Study – 103 Patients

Liao Z. RTOG 1308 Protocol
**Proton Therapy Clinical Studies**

- MDACC phase II trial of 44 pts with stage III NSCLC
  - Protons to 74 CGE with concurrent carboplatin + paclitaxel
  - MS 29.4 mo
  - Best survival reported in a phase II or III chemorads conventionally fractionated trial for stage III NSCLC
  - 20.5% local failure
  - Toxicity: 11% grade 3 esophagitis and dermatitis, 2% grade 3 pneumonitis, no grade 4-5 toxicity

- 2017 JAMA Oncology Update
  - 64 pts, median OS 26.5 months, local failure 16%
  - Grade 3 esophagitis 8%
  - Grade 3 pneumonitis 12%


**Proton Therapy Clinical Studies**

- 2017 JAMA Oncology Update
  - 64 pts, median OS 26.5 months, local failure 16%
  - Grade 3 esophagitis 8%
  - Grade 3 pneumonitis 12%


**Proton Therapy for LA-NSCLC – Dose Escalation**

<table>
<thead>
<tr>
<th>1st Author</th>
<th>Year Published</th>
<th>Number of Patients</th>
<th>Stage Fractionation Regimen</th>
<th>Overall Survival</th>
<th>Local Control</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang JY</td>
<td>2011</td>
<td>44</td>
<td>74 CGE in 37 fractions</td>
<td>1 yr 79.5%</td>
<td>1 yr 86%</td>
<td>11% grade 3 dermatitis, 11% grade 3 esophagitis, 2% grade 3 pneumonitis, 2% late pulmonary/pleural fistula</td>
</tr>
<tr>
<td>Nakayama H</td>
<td>2011</td>
<td>35</td>
<td>74 CGE in 37 fractions (n=3), 77 CGE in 35 fractions (n=13), 83.6 CGE in 38 fractions (n=7), 72.6 CGE in 38 fractions (n=6), other (n=6)</td>
<td>2 yr 58.9%</td>
<td>2 yr 65.9%</td>
<td>14% grade 2 lung, 3% grade 2 esophagitis</td>
</tr>
<tr>
<td>Xiang ZL</td>
<td>2012</td>
<td>84</td>
<td>74 CGE in 37 fractions</td>
<td>3 yr 37.2%</td>
<td>2 yr 83%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Oshiro Y</td>
<td>2012</td>
<td>57</td>
<td>Median 74 CGE in median 2 CGE fractions</td>
<td>2 yr 39.4%</td>
<td>2 yr 64.1%</td>
<td>12% acute grade ≥2 pneumonitis, 15% grade 3 pneumonitis, grade 5 hemoptysis, grade 4 pneumonitis, grade 3 pneumonitis</td>
</tr>
</tbody>
</table>


**LA-NSCLC Proton Randomized Data**

- MDACC/Harvard Bayesian randomized trial of protons versus photons
  - Stage II-III NSCLC to 74 Gy with IMRT vs. protons (2 Gy/CGE fractions) and concurrent chemo
  - Primary outcomes: grade ≥ 3 radiation pneumonitis or local recurrence within 12 mo
  - Of 272 enrolled patients, 149 were randomly allocated to IMRT (n=92) or 3DPT (n=57)
  - Among randomized patients, proton target volumes were larger (p<0.071) and more patients received higher doses to tumors and had larger lung volumes receiving ≥30-80 Gy than IMRT
  - Failure rates: not significant
  - Pneumonitis rates: not significant

NCDB study of 140,383 NSCLC treated with thoracic radiation from 2004-2012, 99+% with photons and <1% with protons

- Multivariate analysis: receipt of photons was associated with an increased risk of death relative to protons (HR 1.46, p < 0.001)
- Stage II-III: 5-yr OS 15% photons vs. 22% protons, p=0.01
- Propensity score matching: 14% vs. 23%, p=0.024


**LA-NSCLC Proton Therapy Enrolling Studies**

- RT0G 1308: Phase III Randomized Trial Comparing Overall Survival After Photon Versus Proton Chemoradiotherapy for Inoperable Stage II-IIIB NSCLC
  - Protons vs. photons up to 70 Gy with concurrent chemotherapy (platinum-based doublet) +/- consolidation chemotherapy
  - Primary outcome: overall survival
  - Secondary outcomes: progression-free survival, grade ≥3 adverse events, QOL/PROs, cost-effectiveness outcomes, PFT changes
  - 560 patient targeted accrual, enrollment started 2014
- Proton Collaborative Group LUN005: Phase I/II Study of Hypofractionated Proton Therapy for Stage II-III NSCLC
  - Phase I: Proton RT with concurrent chemotherapy to 60 CGE in 24 → 20 → 17 → 15 fractions [find maximum tolerated dose]
  - Phase II: 61 patients treated with MTD [primary endpoint: 1-yr OS]

**Mediastinal LN Assessment**

<table>
<thead>
<tr>
<th>Lymph Node Levels</th>
<th>2</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8-9</th>
<th>10</th>
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<tbody>
<tr>
<td>EBUS-FNA</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>EUS-FNA</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Mediastinoscopy:</td>
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<tr>
<td>Cervical</td>
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<tr>
<td>Mediastinoscopy:</td>
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<td>✓</td>
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<td>Chamberlain</td>
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</tbody>
</table>
**NSCLC TRIMODALITY THERAPY**

**PORT Meta-Analysis and Toxicity**
- 2,343 patients from 11 trials
  - Using outdated RT techniques, significant adverse effect of PORT on survival HR 1.18
    - HR 1.33 for pN0, 1.24 for pN1, 0.97 for pN2
  - Benefit of improved local-regional control of PORT offset by excess toxicity and death from RT
  - Causes of death primarily cardiac and pulmonary

<table>
<thead>
<tr>
<th></th>
<th>NSCLC</th>
<th>Treatment</th>
<th>Other</th>
<th>Non-Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>PORT</td>
<td>82%</td>
<td>4%</td>
<td>14%</td>
<td>18%</td>
</tr>
<tr>
<td>No PORT</td>
<td>89%</td>
<td>2%</td>
<td>9%</td>
<td>11%</td>
</tr>
</tbody>
</table>


**Modern Population-Based PORT Studies**
- SEER: 7,465 patients from 1988-2002 with stage II-III NSCLC s/p lobectomy/pneumonectomy
  - 47% received PORT (more common in poor prognosis tumors)
  - PORT improved 5-yr survival for pN2 nodal disease (27% vs. 20%; HR 0.855; p=0.0077)
- NCDB: 4,483 patients with pN2 stage III NSCLC s/p R0 surgery from 2006-2010
  - All received chemo, 41% received PORT that included IMRT
  - PORT increased median (45.2 v 40.7 months) and 5-year OS (39.3% v 34.8%) [p=0.014]

Dosimetric Studies

• 20 patients treated to 66.6/1.8 Gy as part of RTOG 1308 pre-activation studies of new dose constraints

<table>
<thead>
<tr>
<th></th>
<th>IMRT</th>
<th>Protons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Mean V20</td>
<td>16.9 Gy</td>
<td>15.2 Gy</td>
</tr>
<tr>
<td>Mean V5</td>
<td>27%</td>
<td>27%</td>
</tr>
<tr>
<td>Heart Mean V20</td>
<td>14.9 Gy</td>
<td>7.7 Gy</td>
</tr>
<tr>
<td>Mean V5</td>
<td>47%</td>
<td>34%</td>
</tr>
</tbody>
</table>

• 10 patients treated to 50.4/1.8 Gy to mediastinum

<table>
<thead>
<tr>
<th></th>
<th>IMRT</th>
<th>Protons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Mean V20</td>
<td>15.0 Gy</td>
<td>9.3 Gy</td>
</tr>
<tr>
<td>Mean V5</td>
<td>27%</td>
<td>31%</td>
</tr>
<tr>
<td>Heart Mean V20</td>
<td>14.6 Gy</td>
<td>6.4 Gy</td>
</tr>
<tr>
<td>Mean V5</td>
<td>47%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Adjuvant Proton Studies

• Greater magnitude of benefit for adjuvant compared with definitive LA-NSCLC, especially for lung V20 and mean
• First-ever clinical report
  • 28 patients treated from 2011-2015 with proton PORT
  • Grade 3: pneumonitis 4%, esophagitis 7%
  • 1-yr OS 88.9%, local recurrence-free survival 93.9%

Proton Collaborative Group Phase III Randomized Trial

Primary Endpoint: combined rate of major cardiac events and grade ≥2 pneumonitis at 24 months (photons 30%, protons 15%)
**INT 0139: Definitive Chemorads vs Neoadjuvant Chemorads and Surgery for Stage IIIA NSCLC**

- 429 patients (396 eligible) with stage IIIA (T1-3, pN2, M0) NSCLC randomized to:
  - Cisplatin/etoposide with concurrent photon RT to 45 Gy → surgery → consolidative chemotherapy
  - Cisplatin/etoposide with concurrent photon RT to 61 Gy → consolidative chemotherapy

- Increased treatment-related deaths in surgery arm: 8% vs. 2%
- 26% perioperative mortality with pneumonectomy
- Progression-free survival
  - Sx: 12.8 mo vs. no sx: 10.5 mo, p=0.017
  - 5-yr PFS: 22% vs. 11%
- Overall survival
  - Median: 23.6 mo (surgery) vs. 22.2 mo (no surgery), p=0.24
  - 5-yr OS: 27% vs. 20%, p=0.10
- Hypothesis: if trimodality can be done more safely, survival would be improved

**Neoadjuvant Chemorads to Definitive RT Dose**

- RTOG 02-29: phase II trial of 57 pt with pathologically proved N2 or N3 stage III NSCLC
  - Induction carboplatin/paclitaxel → concurrent chemoradiation (50.4 Gy mediastinum + primary, boost to 61.2 Gy to all gross disease) → surgery
  - Primary endpoint: 63% pCR in mediastinum
  - 14% grade 3 pulmonary toxicity, 3% grade 5 postop toxicity
  - 2-yr OS 54% (75% if pCR in mediastinum, 52% if residual nodal disease, 23% if not eligible/no surgery, p=0.0002)
  - Hypothesis: if dose escalation of RT with trimodality therapy can be done safely, survival would be improved

**Neoadjuvant Proton Therapy**

- Protons may allow safer implementation of trimodality therapy
- MDACC experience of 444 patients treated with surgery after chemoradiation for esophageal cancer from 1998-2011
- Multicenter Phase III Trial of Preoperative Proton Beam Radiotherapy with Concurrent Chemotherapy for Resectable Stage IIIA or Superior Sulcus NSCLC
  - 50.4 Gy → 59.4 Gy → 66.6 Gy

**References**

REIRRADIATION

Rationale for Thoracic Reirradiation and Protons

- Local failures occur in 30-50% of patients with LA-NSCLC
  - Isolated first failures occurs locoregionally in 20-30% after chemoradiation and are potentially curable with additional RT but are traditionally treated with systemic therapy alone due to excessive toxicities associated with photon reirradiation
  - Cytotoxic chemotherapy: <6 month PFS
- Protons provide opportunity for reirradiation in the thorax when there would otherwise be few radiotherapy options
  - Lack of exit dose may allow for complete sparing of structures “maxed out” by the prior RT course and significantly decreases doses to cord, contralateral lung, heart, esophagus
  - May also be critical for distal wall of mainstem bronchus/carina
  - Allows for escalation of reirradiation dose

Prior Thoracic Photon Reirradiation Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Histology</th>
<th>Median histologic relRT (min)</th>
<th>Initial RT dose (Gy) (median)</th>
<th>Re-RT dose (Gy) (median)</th>
<th>Median OS (mo) (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green &amp; Melbye</td>
<td>29</td>
<td>NSCLC &amp; SCLC (6%)</td>
<td>18</td>
<td>53</td>
<td>35</td>
<td>5 (1-56)</td>
</tr>
<tr>
<td>Jackson &amp; Bell</td>
<td>22</td>
<td>NSCLC &amp; Other (14%)</td>
<td>15</td>
<td>55</td>
<td>30</td>
<td>5.4 (NS)</td>
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<tr>
<td>Mastruboli et al.</td>
<td>30</td>
<td>NSCLC &amp; Other (18%)</td>
<td>12</td>
<td>60</td>
<td>30</td>
<td>5 (NS)</td>
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<tr>
<td>Green et al.</td>
<td>23</td>
<td>NSCLC &amp; Other (27%)</td>
<td>15</td>
<td>58</td>
<td>30</td>
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<tr>
<td>Kramer et al.</td>
<td>28</td>
<td>NSCLC</td>
<td>17</td>
<td>40-60</td>
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<td>Okamoto et al.</td>
<td>34</td>
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<td>23</td>
<td>66</td>
<td>50</td>
<td>8 (NS)</td>
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<td>Wu et al.</td>
<td>23</td>
<td>NSCLC &amp; SCLC (20%)</td>
<td>13</td>
<td>66</td>
<td>51</td>
<td>16 (2-37)</td>
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<tr>
<td>Tada et al.</td>
<td>19</td>
<td>NSCLC</td>
<td>16</td>
<td>50-70</td>
<td>50</td>
<td>7.1 (NS)</td>
</tr>
</tbody>
</table>
Prospective Reirradiation Multicenter Study

- Multi-center trial of 57 patients with recurrent LA-NSCLC
  - Inclusion Criteria
    - Previously irradiated with tumor recurrence in or near prior radiation fields (50% isodose line)
    - KPS ≥ 60, life expectancy ≥ 3 months
  - Treatment
    - Median dose of first course 65 Gy
    - Median dose of reirradiation course 66.6 Gy
    - 68% received concurrent chemotherapy
  - Results
    - Local (16%), regional (9%), and distant (11%) failures
    - Median survival after reirradiation 16 months
    - 1-yr OS 59%, PFS 58%
    - Increased grade ≥ 3 toxicities with increased overlap with the central airway region, mean esophagus and heart doses, and concurrent chemotherapy
    - Decreased survival with greater central airway overlap, higher esophageal dose

NRG Oncology Planned Reirradiation Study

Phase I: Safety Assessment
- Locally Recurrent NSCLC
  1) Received prior RT for lung cancer
  2) Received prior platinum-based chemotherapy
  3) Recurrence within 50% isodose line
  4) Not a candidate for surgery or SABR
  5) Candidate for systemic therapy
  6) Patients who have received prior systemic therapy for recurrence are eligible

Phase II: Randomization/Efficacy Assessment
- Pilot Safety Arm
  Radiation (60 Gy in 2 Gy fractions) with IMRT or PBT + Adjuvant Anti-PD-1
- Primary Endpoint: PFS
- Secondary Endpoints:
  - OS
  - LFFS
  - DMFS

Overall sample size = 72 pts

Phase II Stratification:
1) Histology (SCC vs. non-SCC)
2) Prior Systemic Therapy for Recurrence (yes vs. no)

OTHER THORACIC SITES
Prospective Trial of Proton Therapy for LS-SCLC

- First prospective study of proton therapy for small cell lung cancer
  - 30 pts with LS-SCLC treated with proton therapy (median 63.9 CGE, range 45.6-66.6 CGE) delivered daily (N=18) or twice-daily (N=12) beginning with C1 or C2 of concurrent platin/etoposide
  - Proton therapy allowed for significant dose reductions to the cord, heart, and lungs compared with IMRT backup plans
- Results
  - 1-yr and 2-yr local control 85% and 69%
  - 1-yr and 2-yr overall survival 72% and 58%
  - Median OS 28.2 months
- Toxicity
  - One (3.3%) case each of grade ≥3 esophagitis, pneumonitis, anorexia, pericardial effusion
  - Grade 2 pneumonitis in 10% and esophagitis in 43%


Protons for Thymic Tumors

- Largest report and only prospective experience
  - 27 consecutive patients with thymoma (85%) or thymic carcinoma (15%) treated with proton therapy from 2011-2015
  - Adjuvant (63%), definitive (22%), or salvage (15%) RT
  - Median of 61.2/1.8 Gy [CGE]
- Toxicity
  - No grade ≥3 acute or late
  - Acute grade 2:
    - 7% esophagitis (n=2)
    - 4% acute pneumonitis (n=1)
  - Late grade 2:
    - 4% chronic dyspnea (n=1)
- Clinical outcomes at 3 yrs:
  - Local control 100%
  - OS: 94%


Whole Pleural Intensity-modulated Proton Therapy
**TREATMENT PLANNING CONSIDERATIONS**

**Tumor Motion**

- Account for motion from respiration using a 4D simulation
- Can mitigate tumor motion with:
  - Abdominal compression
  - Accelerator beam gating with the respiratory cycle
  - Dynamic tumor tracking
  - Active breathing control
  - Coaching/biofeedback techniques
**Anatomical Changes and Verification Simulations**

- Anatomical changes during treatment warrant verification scans to see the effects of these changes on proton beam range
  - Target volumes changes in size and density
  - Port implanted during treatment (range of anterior fields for cranial targets would be affected)
  - Changes in arm positioning (especially important for apical targets)
  - Other interfractional changes: effusions, pneumonia, atelectasis, weight changes

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**Impact of Tumor Regression to Organs at Risk**


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**LA-NSCLC PBS vs. DS Proton Therapy**

• Proton therapy has an increasingly well-demonstrated role in the treatment of both early stage and locally advanced NSCLC
  • Can reduce normal tissue doses that may lead to fewer toxicities
  • Can treat lesions potentially not treatable with photon therapy
  • May more safely allow for dose escalation
  • May more safely allow for trimodality therapy
  • May allow for retreatment of recurrent tumors
• Proton therapy has emerging roles in the treatment of small cell lung cancer, thymic tumors, mesothelioma, cardiac sarcomas and other thoracic malignancies
  • Reirradiation may allow for prolonged disease control in well selected patients
  • Pencil beam scanning offers even greater dosimetric benefits over scattered proton therapy
  • Prospective comparative trials are needed and are underway