Regional Functional Avoidance in Lung Radiotherapy Using Ventilation Mapping: Results of phase II trial

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Disclosures

Funding: R01CA200817, R01CA236857, UG3CA247605,
Cancer Center: CU Caner Center
Vendor funding: MIM Software
Pulmonary Toxicity in Lung Cancer Treatment

Palma et al, pneumonitis review

Results—The median radiotherapy dose was 60 Gy, and median follow-up was 2.3 years. Most patients received concurrent cisplatin/etoposide (38%) or carboplatin/paclitaxel (26%). The overall rate of symptomatic pneumonitis was 29.8% (n=249), with fatal pneumonitis in 1.9% (n=10).

QUANTEC

(a) Symptomatic Pneumonitis vs. Mean Lung Dose

RTOG 0617

<table>
<thead>
<tr>
<th>Dose Regimen</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 Gy (acute n=133; late n=111)</td>
<td></td>
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<tr>
<td>74 Gy (acute n=107; late n=93)</td>
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<tr>
<td>60 Gy plus cetuximab (acute n=137; late n=111)</td>
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<tr>
<td>74 Gy plus cetuximab (acute n=100; late n=80)</td>
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</tbody>
</table>

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Typical dose metrics (MLD, V20) assume homogenous lung function

QUANTEC Lung
Lung function is not homogenous

Vinogradskiy et al

Castillo et al

Kipritidis et al
The role of three dimensional functional lung imaging in radiation treatment planning: The functional dose-volume histogram

Conformal Avoidance for Lung Cancer
Conformal Avoidance For Lung Cancer

SPECT

4DCT-Ventilation
Functional Radiotherapy For Lung Cancer

4DCT-Ventilation

- 4DCT acquired for simulation (reduced time, cost, dose)
- Anatomical + Functional information
- Good spatial resolution
Calculating Ventilation Images

Calculating ventilation maps

4DCT – 10 phases
Calculating Ventilation Images

Link lung voxel elements from inhale to exhale using deformable registration

\[ \frac{V_{in} - V_{ex}}{V_{ex}} = 1000 \frac{HU_{in}^{voi} - HU_{ex}}{HU_{ex}(1000 + HU_{in}^{voi})} \]

Apply density-change-based equation

1Simon et al, 2Guerrero et al
Calculating Ventilation Images
Functional Imaging to Conformal Avoidance RT: Validation

VQ Ventilation Scan

4DCT Ventilation Map

Kipritidis et al – PET 68Ga, University of Sydney

Yamamoto et al – SPECT, UC Davis
Functional radiotherapy with CT Ventilation

Standard Plan No Avoidance

Ventilation Functional Avoidance

Functional radiotherapy objective: reduce pneumonitis rates
Predicting pneumonitis: dose + function > dose ???

- 96 NSCLC patients
- Radiation pneumonitis toxicity information using CTCAE grading
- Calculated dose metrics
  - Mean lung dose
  - V20 Gy = Volume of lung receiving 20 Gy or higher
- Calculated dose + function metrics
  - Functionally weighted mean lung dose
  - FV20 Gy = Amount of functioning lung getting 20 Gy or higher
4DCT-ventilation conformal avoidance – Will it work?

Ability of dose and dose + function metrics to predict for grade 3+ radiation pneumonitis: area under the curve (AUC) and logistic regression (Vinogradskiy et al 2013, Faught et al 2017)

<table>
<thead>
<tr>
<th></th>
<th>MLD</th>
<th>fMLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>0.55</td>
<td>0.66</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>V20</th>
<th>fV20</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>0.57</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Dose+function >> Dose alone
CT Ventilation Functional Radiotherapy Clinical Trial

- 67 lung cancer patients at University of Colorado + William Beaumont (NCT02528942)
- Use 4DCT to calculate ventilation imaging
- Use 4DCT-ventilation to design functional radiation plans
- Reduce functional dose metrics using favorable arc geometry + optimization
- Single-arm, early phase trial looking at feasibility, safety, toxicity rates to be compared to current standard of care techniques
Inclusion/Exclusion Criteria

• Trial inclusion/exclusion criteria
  • No SBRT, No palliative RT
  • Curative intent Rx dose ≥ 45Gy
  • Planned curative intent (concurrent) chemotherapy regimen
• Image heterogeneity criteria

Eligible

Not Eligible
Trial Design

• Study phase: II
• Primary endpoint: grade ≥ 2 Radiation Pneumonitis
• Hypothesis: Rate of grade ≥ 2 Radiation Pneumonitis can be reduced to 12% with functional radiotherapy compared to 25% rate of grade ≥ 2 Radiation Pneumonitis with historical control
• Historical control pneumonitis rate of 25%: QUANTEC Lung, Pneumonitis review by Palma et al (IJORBP, 2013), single institutional experiences published at the time of study design (MSKCC, MDA)
• Trial design: Simon’s Two-Stage, futility analysis at 17 patients
• Stats: Using one-sided alpha=0.05, power = 0.8, trial would be positive if ≤ 11 (11/67 = 16.4%) patient experience ≥ grade 2 radiation pneumonitis
Outcome assessments

- Assess lung function in a variety of ways
  - CTCAE Toxicity (Pulmonary toxicity, pneumonitis, esophagitis)
  - PFTs
  - QOL Questionnaires
  - Imaging: CT, 4DCT-Ventilation, PET, VQ/SPECT
Implementation: Treatment planning

- Structure-based treatment planning
- Start with standard lung plan (has to be clinically approved), proceed to functional avoidance plan using favorable arc geometry/optimization
- Priorities 1) Target coverage, 2) Standard OAR constraints, 3) Functional dose reduction
Futility analysis

• Trial met futility criteria, progressed with accrual
Results

Patient, clinical, and treatment parameters for the study cohort

• 101 consented patients, 67 patients (≥ 3 month f/u)
• 60% Female
• KPS: 90 (range 60 – 100)
• 55% with COPD
• 93% smokers or former smokers
• 79% NSCLC
• 76% stage III disease
• 16% had surgery (lobectomy, pneumonectomy)
• Rx: 60 Gy (range 45 – 66 Gy), in 30 fractions (range 15 to 33 fractions)
• 25% treated with I/O
• Median f/u 312 days (range 78 to 427 days)
Results: Toxicity

- 10 patients experienced ≥ grade 2 radiation pneumonitis (10/67, 14.9%, upper 95% CI of 24.0%)
- Trial outcome positive

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 0 Number (%)</th>
<th>Grade 1 Number (%)</th>
<th>Grade 2 Number (%)</th>
<th>Grade 3 Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>42 (62.7)</td>
<td>15 (22.4)</td>
<td>7 (10.4)</td>
<td>3 (4.5)</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>7 (10.4)</td>
<td>27 (40.3)</td>
<td>28 (41.8)</td>
<td>5 (7.5)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>15 (22.4)</td>
<td>38 (56.7)</td>
<td>10 (14.9)</td>
<td>4 (6.0)</td>
</tr>
<tr>
<td>Cough</td>
<td>7 (10.4)</td>
<td>47 (70.1)</td>
<td>13 (19.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (7.5)</td>
<td>48 (71.6)</td>
<td>12 (17.9)</td>
<td>2 (3.0)</td>
</tr>
</tbody>
</table>
Patient plan example

- Functional avoidance plan
- Standard lung plan
### Functional and Standard Dosimetry

- Standard, non-lung metrics get worse, differences are not clinically significant
- Functional dosimetry improved with functional avoidance

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Functional Avoidance Plan: mean ± sd</th>
<th>Non-functional Plan: mean ± sd</th>
<th>t test p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV Coverage of Rx dose (%)</td>
<td>94.7 ± 3.5</td>
<td>95.5 ± 3.7</td>
<td>0.002</td>
</tr>
<tr>
<td>PTV Hotspot (%)</td>
<td>21.7 ± 10.0</td>
<td>21.0 ± 10.4</td>
<td>0.043</td>
</tr>
<tr>
<td>Mean Lung Dose (Gy)</td>
<td>14.2 ± 3.8</td>
<td>14.9 ± 3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lung V20 (%)</td>
<td>24.3 ± 8.6</td>
<td>26.3 ± 9.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Max Spinal Cord Dose (Gy)</td>
<td>33.5 ± 8.7</td>
<td>32.1 ± 9.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean Esophagus Dose (Gy)</td>
<td>22.0 ± 8.3</td>
<td>22.7 ± 8.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart V40 (%)</td>
<td>5.2 ± 6.3</td>
<td>5.3 ± 6.0</td>
<td>0.646</td>
</tr>
<tr>
<td>Functional Avoidance Structure Mean (Gy)</td>
<td>13.5 ± 3.8</td>
<td>14.9 ± 3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>fV5 (%)</td>
<td>67.7 ± 14.2</td>
<td>71.1 ± 13.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>fV10 (%)</td>
<td>42.2 ± 13.5</td>
<td>48.6 ± 14.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>fV20 (%)</td>
<td>21.6 ± 8.9</td>
<td>25.1 ± 9.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>fV30 (%)</td>
<td>12.9 ± 6.8</td>
<td>14.7 ± 7.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Functional and Standard Dosimetry

Average reduction in fV20 = 3.5% (range 0% – 12%)
Discussion

- More recent comparison: RTOG 0617: 21.6% ≥ grade 2 radiation pneumonitis, 20% ≥ grade 3 pulmonary events in 60 Gy arm
- IMRT/3D
- Performance status/PFT requirement
- Surgery allowed
- I/O
  - I/O: 24% ≥ grade 2 radiation pneumonitis
  - No I/O: 12% ≥ grade 2 radiation pneumonitis
- Lung function heterogeneity requirement
- Next steps: secondary outcomes, phase III?, is a phase III needed?
Summary

- 4DCT-based ventilation provides a way to generate lung function images with no extra imaging procedure
- Phase II study positive: Functional avoidance reduces rates of side-effects for lung cancer patients
- Future work to include robustness, QA, IO