Validation, Clinical Endpoints and Opportunities for CT Ventilation

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Background

4DCT-Ventilation Imaging

CT-Ventilation
Learning objectives

1. Validation of CT ventilation
2. Clinical applications of CT ventilation in radiation oncology
3. Potential clinical applications outside of radiation oncology

Validation

Compare CT ventilation to other forms of functional imaging
Validation

Compare CT ventilation to other forms of functional imaging

<table>
<thead>
<tr>
<th>Study</th>
<th>CT Type</th>
<th>Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fuld et al. 2008</td>
<td>Prospective gating</td>
<td>Xenon-CT</td>
</tr>
<tr>
<td>Reinhardt et al. 2008</td>
<td>Prospective gating</td>
<td>Xenon-CT</td>
</tr>
<tr>
<td>Mathew et al. 2012</td>
<td>4D</td>
<td>Hyperpolarized 19F-MRI</td>
</tr>
<tr>
<td>Vinogradsky et al. 2014</td>
<td>4D</td>
<td>16F-DTPA SPECT</td>
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<tr>
<td>Clasiff et al. 2010</td>
<td>4D</td>
<td>16F-DTPA SPECT</td>
</tr>
<tr>
<td>Yamamoto et al. 2014</td>
<td>4D</td>
<td>PFT and 16F-DTPA SPECT</td>
</tr>
<tr>
<td>Kipritidis et al. 2014</td>
<td>4D</td>
<td>99mTc-sensor PET</td>
</tr>
<tr>
<td>Brennan et al. 2015</td>
<td>4D</td>
<td>PFT</td>
</tr>
<tr>
<td>Vida et al. 2016</td>
<td>4D</td>
<td>16F-DTPA SPECT-guided plan</td>
</tr>
<tr>
<td>Kanai et al. 2016</td>
<td>4D</td>
<td>99mTc scintigraphy</td>
</tr>
</tbody>
</table>

Validation again nuclear medicine

- Validation against nuclear medicine imaging
- 16 lung cancer patient receiving radiation therapy

VQ Ventilation Scan
Validation again nuclear medicine

- Correlation coefficient = 0.65
- Radiologist observations: Sensitivity = 90%, Specificity = 64%, Accuracy = 81%
Validation

- Kipritidis et al – PET 68Ga
- Reinhardt et al – xenon CT
- Yamamoto et al – SPECT
- Matthew et al – 3He MRI

Validation – conclusions/challenges

Conclusions
1. Moderate (~0.5) correlation between CT ventilation and other ventilation imaging
2. Good correlation in areas of major ventilation defects, decreasing correlation for minor features

Challenges
1. Uncertainties of CT ventilation and other ventilation imaging
2. True gold standard?
3. What is good enough correlation?

Learning objectives

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Clinical Applications

1. Assess lung response throughout and after RT
2. Functional avoidance – design RT plans to avoid function parts of the lung

Clinical Applications – assess lung response

Changes in lung function during RT
Functional planning concept

Avoid functional portions of the lung in favor of irradiating through less functioning lung tissue.
Can functional planning reduce toxicity???

• 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
• Is dose + function a better predictor of toxicity than dose alone
### Results – Toxicity reduction to functional lung

<table>
<thead>
<tr>
<th>Toxicity (grade 3+) reduction</th>
<th>NTCP Clinical Plan</th>
<th>NTCP Functional Plan</th>
<th>Difference Absolute</th>
<th>Difference Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal functional lung</td>
<td>10%</td>
<td>8%</td>
<td>2%</td>
<td>15.8%</td>
</tr>
<tr>
<td>Critical functional lung</td>
<td>17%</td>
<td>15%</td>
<td>2%</td>
<td>13.3%</td>
</tr>
<tr>
<td>Mildly functional lung</td>
<td>9%</td>
<td>5%</td>
<td>4%</td>
<td>27.8%</td>
</tr>
</tbody>
</table>

- Average reduction of 3-5% for grade 3+ RP probability with functional planning
- Reduction as high as 15% possible for individual patients
- Average reduction of 5-8% for grade 2+ RP probability with functional planning, with maximum reduction of 15-20% possible (results not shown)
Learning objectives

1. Validation of CT ventilation
2. Clinical applications of CT ventilation in radiation oncology
3. Potential clinical applications outside of radiation oncology

Clinical application outside of RT
Use CT ventilation to assess other thoracic diseases

<table>
<thead>
<tr>
<th>4DCT - Ventilation Metrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coefficient of Variation = 91%</td>
</tr>
<tr>
<td>V20 = 34%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PFT Metrics</th>
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</thead>
<tbody>
<tr>
<td>FEV1 = 36%</td>
</tr>
<tr>
<td>FEV1/FVC = 45%</td>
</tr>
</tbody>
</table>

Clinical application outside of RT

Use CT ventilation to assess other thoracic diseases

Investigation of four-dimensional computed tomography-based pulmonary ventilation imaging in patients with emphysema lung region

Medical Physics
CT ventilation for surgical assessment

Summary

1. Validation of CT ventilation
   1. Modest correlation of CT ventilation with other forms of ventilation imaging. Highest correlation in regions of ventilation defects.
2. Clinical applications of CT ventilation in radiation oncology
   1. Assessment of lung response to RT
   2. Functional radiotherapy – decrease toxicity
   3. Clinical trials underway
3. Potential clinical applications outside of radiation oncology
   1. Non-oncologic lung disease
   2. Surgical assessment
Radiation toxicity in the lung

6% – 20% of patients treated with RT get radiation toxicity

- Radiation pneumonitis
- Radiation fibrosis
- Imaging presentations
- Oxygen needed
- Steroids needed
- Impact on activities of daily living

- Poor quality of life
- Limits radiation doses that can be given

Diot et al

Functional planning concept

Can functional planning reduce toxicity???
Outline

4DCT-Ventilation Imaging
- Image formation
- Validation
- Clinical applications in radiation oncology
- Clinical trial

4DCT-Ventilation Clinical Trial
- 70 lung cancer patients between 2 institutions
- Use 4DCT to calculate ventilation imaging
- Use 4DCT-ventilation to design functional radiation plans
- Hypothesis: 4DCT-ventilation functional planning results in less pulmonary toxicity than toxicity with current standard of care techniques
- Assess lung function in a variety of ways
  - CTCAE Toxicity (Pneumonitis, esophagitis)
  - QOL Questionnaires
  - PFTs
  - CT/4DCT-Ventilation Imaging
  - Nuclear Medicine VQ Imaging
  - PET Imaging

Eligibility

Nothing to spare

[Image of brain with color coding]

Impertinent balancing

[Image of brain with color coding]

Good for sparing

[Image of brain with color coding]

Nothing to avoid

[Image of brain with color coding]

Avoid

[Image of brain with color coding]

No need to avoid

[Image of brain with color coding]

Courtesy of Tim Waxweiler, MD
**Protocol Basics**
- Functional planning
- Structure based functional approach

**Planning techniques**

**Calculating Ventilation Images**
- Link lung vessels from inhale phase to exhale phase using deformable image registration
- 4D deformable registration using trajectory modeling [Castillo et al., 2010]
Calculating Ventilation Images

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

Guerrero et al., 2006; Fuld et al., 2008

Protocol Basics

- Functional planning
- Structure based functional approach
- Start with standard (non-functional plan)
- Planning priorities 1) Target coverage 2) OAR constraints 3) Reducing dose to functional lung

Summary

4DCT 4DCT-Ventilation Validation

Clinical Trial Randomized national clinical trial Functional RT

???
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- Thomas Guerrero MD, PhD, Beaumont

Clinical Trial team
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- Kyra Anderson
- Robin Swing
- Chelsea Schoefrer
- Monica Robischon

Conclusions

- 4DCT-Ventilation calculates lung ventilation maps from 4DCT data
- 4DCT-Ventilation has been validated against established methods of measuring lung function
- Retrospective work suggests toxicity can be reduced with functional planning
- Clinical trials are underway to evaluate 4DCT-Ventilation based functional planning

Calculating Ventilation Images

Calculating ventilation maps

4DCT – 10 phases

0% 10% 20% 30% 40% 50%
Movie of 4DCT-ventilation

An aside about imaging...

Functional planning

- Predicting toxicity as a function of dose and dose-function
- Area under the curve (AUC) and logistic regression p value

<table>
<thead>
<tr>
<th>MLD</th>
<th>MLD+</th>
<th>V20</th>
<th>IV20</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.57</td>
<td>0.62</td>
<td>0.67</td>
<td>0.64</td>
</tr>
<tr>
<td>(p=0.29)</td>
<td>(p=0.07)</td>
<td>(p=0.3)</td>
<td>(p=0.04)</td>
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</tbody>
</table>

• Bootstrap analysis

<table>
<thead>
<tr>
<th>Dose and function metrics</th>
<th>Bootstrap p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLD + fMLD</td>
<td>0.154</td>
</tr>
<tr>
<td>v20 + fV20</td>
<td>0.118</td>
</tr>
</tbody>
</table>
**Should all patients be eligible?**

Evaluate patient spatial lung function
- Observer defect presence (yes/no)
- Metrics based on regional (each third) lung function

**4DCT Imaging**

Calculate ventilation from 4DCT data

**Should all patients be eligible?**

Metrics based on regional (each third) lung function
- % ventilation in third with tumor, % ventilation in third with tumor or adjacent third
Validation against PFTs

4DCT Ventilation Image

Derived metrics

4DCT Ventilation Metrics

Coefficient of Variation = 91%

PFT Metrics

FEV1 = 36%

FEV1/FVC = 45%

Should all patients be eligible?

Patient spatial lung function

Heterogeneous ventilation

Suitable for functional sparing

Homogeneous ventilation

Not suitable for functional sparing

Results

- 69% of patients had observer identified defects

<table>
<thead>
<tr>
<th>Area under the curve</th>
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<tbody>
<tr>
<td>Ipsi/Contra</td>
</tr>
<tr>
<td>CoV (std/mean)</td>
</tr>
<tr>
<td>V20</td>
</tr>
<tr>
<td>% Ventilation in third with tumor</td>
</tr>
<tr>
<td>% Ventilation in third with tumor or adjacent third</td>
</tr>
</tbody>
</table>

- AUC: 0.72
- CoV (std/mean): 0.65
- V20: 0.55
- % Ventilation in third with tumor: 0.73
- % Ventilation in third with tumor or adjacent third: 0.83
Results

ROC analysis for % ventilation in third with tumor or adjacent

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>TP (%)</th>
<th>FP (%)</th>
<th>TN (%)</th>
<th>FN (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ventilation defect and user defect</td>
<td>85</td>
<td>15</td>
<td>47</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>ventilation no defect but user defect</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ventilation defect but user no defect</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>ventilation no defect  and user no defect</td>
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</table>

Optimal threshold based on AUC analysis was 14.8%, ~12% reduction in regional function

58% of stage III lung cancer patients could be replanned according to algorithm based on % ventilation in each lung third

Functional re-planning qualitative results

- Turn functional avoidance image into structure
- Use threshold techniques based on trial inclusion criteria
- Allow for post-processing

- Planning techniques
  - coplanar arcs
  - non-coplanar techniques may be needed

- In practice end up sparing contra-lateral lung

- What has to ‘give’ in the functional avoidance planning process
  - Tumor dose homogeneity (hot spot)

Should all patients be eligible?

Patient spatial lung function

- Heterogeneous ventilation
  - Suitable for functional sparing
  - Not suitable for functional sparing

- Heterogeneous ventilation
  - Suitable for functional sparing
  - Not suitable for functional sparing
Functional avoidance example (AAPM 2013)
Shape the radiation dose to avoid functional (ventilated) parts of the lung

Standard RapidArc Plan No Avoidance

RapidArc plan with ventilation Functional Avoidance

Functional Avoidance

Functional Avoidance example (AAPM 2013)