Introduction to
CT Ventilation Imaging:
Principles, Validation and Clinical Translation
Tokihiro Yamamoto, Ph.D.

Learning Objectives
• To understand the principles of CT ventilation imaging
• To understand the physiological significance and challenges of CT ventilation imaging
• To learn about the current status and future prospects for clinical translation of CT ventilation imaging

Outline
• Pulmonary functional imaging
• Principles of CT ventilation imaging
• Cross-modality comparison: SPECT, PET, MR and dual-energy CT
• Clinical translation
• Challenges: Lung CT attenuation variations, validation of DIR and ventilation computation

Summary
Outline

• Pulmonary functional imaging
• Principles of CT ventilation imaging
• Cross-modality comparison: SPECT, PET, MR and dual-energy CT
• Clinical translation
• Challenges: Lung CT attenuation variations, validation of DIR and ventilation computation

Summary

Why Pulmonary Functional Imaging?

• Clinical symptoms and global lung function measurements insensitive to early stages of pulmonary diseases
• Growing economic and social burdens of pulmonary diseases
• Trend toward precision medicine

Roles of Pulmonary Functional Imaging

• **Physiology**: Investigate unanswered questions in pulmonary physiology
• **Diagnosis**: Phenotype pulmonary diseases (*e.g.*, COPD and asthma)
• **Therapy**: Personalize therapy (*e.g.*, functional avoidance radiotherapy), monitor response to therapy, and assess and predict toxicity
Pulmonary Ventilation Imaging Modalities

- CT
  - Single-energy CT without contrast agent (e.g., 4D, exhale/inhale breath-hold)
  - Single/dual-energy CT with contrast agent (e.g., Xe-CT)
- Nuc Med
  - SPECT with tracer gas/aerosol (e.g., 99mTc-DTPA)
  - PET with tracer gas/aerosol (e.g., 68Ga-Galligas)
- MR
  - Hyperpolarized He/Xe
  - Oxygen-enhanced proton

Outline

- Pulmonary functional imaging
- Principles of CT ventilation imaging
- Cross-modality comparison: SPECT, PET, MR and dual-energy CT
- Clinical translation
- Challenges: Lung CT attenuation variations, validation of DIR and ventilation computation

Summary
CT Ventilation Imaging

- Higher resolution, lower cost, or shorter scan time than other modalities

4D CT or exhale/inhale CT → Displacement vector field → Ventilation image

Deformable image registration (DIR) → Quantification of regional volume change

4D CT is in routine clinical use at many RT centers

- Assumption: Regional ventilation is proportional to regional volume change
- Class of ventilation metric
  - Hounsfield unit (HU) change
  - Jacobian determinant of deformation
  - Hybrid

Quantification of Regional Volume Change

- Simpson et al. (J Am Coll Radiol 2009)
- Guerrero et al. (IJROBP 2005)
- Reinhardt et al. (Med Image Anal 2008)
- Ding et al. (Med Phys 2012)
HU-based Metric

\[
F(x,y,z) = \begin{cases} 
0 \text{ HU} & \rightarrow 0\% \text{ air} \\
-1000 \text{ HU} & \rightarrow 100\% \text{ air}
\end{cases}
\]

\[
\Delta \text{Vol} = \frac{F_\text{ex}(x,y,z) + u(x,y,z) + v(x,y,z) - F_\text{in}(x,y,z)}{F_\text{ex}(x,y,z) + u(x,y,z) + v(x,y,z)} \text{Vol}_\text{ex}(x,y,z)
\]

\[
h_{\text{inhale}} \Rightarrow 90\% \text{ air} \rightarrow F_\text{ex}
\]

\[
h_{\text{exhale}} \Rightarrow 10\% \text{ tissue} \rightarrow F_\text{in}
\]

Jacobian-based Metric

\[
\Delta \text{Vol} = \text{Vol}_{\text{in}} - \text{Vol}_{\text{ex}} = \begin{bmatrix} \frac{\partial x}{\partial x} & \frac{\partial x}{\partial y} & \frac{\partial x}{\partial z} \\
\frac{\partial y}{\partial x} & \frac{\partial y}{\partial y} & \frac{\partial y}{\partial z} \\
\frac{\partial z}{\partial x} & \frac{\partial z}{\partial y} & \frac{\partial z}{\partial z} \end{bmatrix} \begin{bmatrix} x \\
y \\
z \end{bmatrix}
\]

Comparison of Ventilation Imaging Modalities

<table>
<thead>
<tr>
<th>Ventilation imaging modality</th>
<th>Spatial resolution (mm)</th>
<th>Time for exam (min)</th>
<th>Effective dose (mSv)</th>
<th>Imaging purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT w/o contrast (CT ventilation)</td>
<td>1-2</td>
<td>5</td>
<td>30 (4D)</td>
<td>Volume change</td>
</tr>
<tr>
<td>CT w/ contrast – single breath</td>
<td>1-2</td>
<td>5</td>
<td>7-15</td>
<td>Inhaled gas distribution</td>
</tr>
<tr>
<td>CT w/ contrast – multiple breath</td>
<td>1-2</td>
<td>10</td>
<td>0.2</td>
<td>Inhaled gas distribution</td>
</tr>
<tr>
<td>SPECT</td>
<td>8-20</td>
<td>20</td>
<td>1</td>
<td>Specific ventilation</td>
</tr>
<tr>
<td>PET</td>
<td>4-8</td>
<td>10</td>
<td>5</td>
<td>Inhaled gas distribution</td>
</tr>
<tr>
<td>Hyperpolarized He/Xe MRI</td>
<td>3-10</td>
<td>5</td>
<td>0</td>
<td>Inhaled gas distribution</td>
</tr>
</tbody>
</table>

Simon et al. (J Appl Physiol 2012); Castillo et al. (J Appl Clin Med Phys 2015); Hofman et al. (J Nucl Med 2011); Metter et al. (Radiology 2008).
Comparison of Ventilation Imaging Modalities

<table>
<thead>
<tr>
<th>Ventilation imaging modalities</th>
<th>Availability of hardware</th>
<th>Availability of contrast agents or tracers</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT w/o contrast (CT ventilation)</td>
<td>Excellent</td>
<td>N/A</td>
</tr>
<tr>
<td>CT w/ contrast – single breath</td>
<td>Excellent (single energy)</td>
<td>Good, not FDA-approved (Xe)</td>
</tr>
<tr>
<td></td>
<td>Limited (dual energy)</td>
<td></td>
</tr>
<tr>
<td>CT w/ contrast – multiple breath</td>
<td>Excellent (single energy)</td>
<td>Good, not FDA-approved (Xe)</td>
</tr>
<tr>
<td></td>
<td>Limited (dual energy)</td>
<td></td>
</tr>
<tr>
<td>SPECT</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>PET</td>
<td>Good</td>
<td>Limited, not FDA-approved</td>
</tr>
<tr>
<td>Hyperpolarized He/Xe MR</td>
<td>Limited</td>
<td>Limited</td>
</tr>
</tbody>
</table>

Outline

- Pulmonary functional imaging
- Principles of CT ventilation imaging
- Cross-modality comparison: SPECT, PET, MR and dual-energy CT
- Clinical translation
- Challenges: Lung CT attenuation variations, validation of DIR and ventilation computation

Summary

Cross-Modality Comparison Studies for CT Ventilation 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>Reinhart 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 He MRI</td>
</tr>
<tr>
<td>Vinogradsky et al 2014</td>
<td>4D</td>
<td>Tc-DTPA scintigraphy</td>
</tr>
<tr>
<td>Castillo et al 2010</td>
<td>4D</td>
<td>Tc-DTPA SPECT</td>
</tr>
<tr>
<td>Yamamoto et al 2014</td>
<td>4D</td>
<td>PFT and Tc-DTPA SPECT</td>
</tr>
<tr>
<td>Kipritidis et al 2014</td>
<td>4D</td>
<td>Ga-68 aerosol PET</td>
</tr>
<tr>
<td>Brennan et al 2015</td>
<td>4D</td>
<td>PFT</td>
</tr>
<tr>
<td>Kida et al 2016</td>
<td>4D</td>
<td>Tc-DTPA SPECT-guided plan</td>
</tr>
<tr>
<td>Kanai et al 2016</td>
<td>4D</td>
<td>Tc-99m scintigraphy</td>
</tr>
</tbody>
</table>

Details presented by Jenia Vinogradskiy, Ph.D.
Outline

• Pulmonary functional imaging
• Principles of CT ventilation imaging
• Cross-modality comparison: SPECT, PET, MR and dual-energy CT
• Clinical translation
• Challenges: Lung CT attenuation variations, validation of DIR and ventilation computation

Summary

Lung functional avoidance RT may reduce toxicity

First-in-Human CT Ventilation Image-guided RT at UC Davis
## Functional Image-guided IMRT vs. Anatomical Image-guided IMRT

![CT ventilation functional image-guided plan vs. Anatomical image-guided plan](image.png)

*Yamamoto et al. (Radiother Oncol 2016)*

## Clinical Trials of CT Ventilation: Functional Image-guided RT

**Novel Lung Functional Imaging for Personalized Radiotherapy**
This study is currently recruiting participants. See Contacts and Locations.

**Feasibility Study Incorporating Lung Function Imaging into Radiation Therapy for Lung Cancer Patients**
This study is currently recruiting participants. See Contacts and Locations.

**Improving Pulmonary Function Following Radiation Therapy**
This study is not yet open for participant recruitment. See Contacts and Locations.

## Comparison of UC Davis, U Colorado, and U Wisconsin Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>UC Davis</th>
<th>Colorado</th>
<th>Wisconsin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arm</strong></td>
<td>Single arm</td>
<td>Single arm</td>
<td>Two-arm, randomized</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>Grade ≥3 adverse events</td>
<td>Grade ≥3 pneumonitis</td>
<td>Ratio of Jacobian map following RT (3 months) to before RT</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>33</td>
<td>70</td>
<td>120</td>
</tr>
<tr>
<td><strong>Optimization technique</strong></td>
<td>Image/voxel-based optimization with dose-function objectives</td>
<td>Subvolume (ROI)-based optimization with dose-volume objectives</td>
<td>Subvolume (ROI)-based optimization with dose-volume objectives</td>
</tr>
</tbody>
</table>
Clinical Trials of Other Ventilation Imaging Modalities in Oncology

- 99mTc-DTPA SPECT
  - Ventilation (and perfusion) image-guided RT (NCT02773238, U of Washington)
- Hyperpolarized He/Xe MR
  - Ventilation image-guided RT (NCT02002052, London, Canada)
  - Assessment of toxicity after RT (NCT02151604, NHS Trust)
  - Assessment of toxicity after RT (NCT02478255, Duke U)
- Dual-energy Kr-CT
  - Prediction of postop lung function (NCT02377518, Strasbourg, France)

Outline

- Pulmonary functional imaging
- Principles of CT ventilation imaging
- Cross-modality comparison: SPECT, PET, MR and dual-energy CT
- Clinical translation
- Challenges: Lung CT attenuation variations, validation of DIR and ventilation computation

Summary

Sources of Variation in Lung CT Attenuation

- Inspiration/expiration level and breathing irregularity (including 4D CT artifacts)
- Imaging parameters
  - Dose
  - Reconstruction kernels
  - Manufacturers and models
- Scanner calibration
4D CT Artifacts

CT ventilation

- Phase-sorted 4D CT-based
- Anatomic similarity-sorted 4D CT-based

SPECT ventilation

Yamamoto et al. (Med Phys 2013)

Variation between Manufacturer-recommended Lung Kernels

GE Chest Kernel
- Philips YB Kernel
- Toshiba FCB Kernel
- Siemens B01 Kernel

Courtesy of Jered Sieren (VIDA Diagnostics)

Cross-Modality Comparison Studies for CT Ventilation

<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>Brennan et al. 2015</td>
<td>4D</td>
<td>PFT</td>
</tr>
<tr>
<td>Kid et al. 2016</td>
<td>4D</td>
<td>$^{99m}$Tc-DTPA SPECT-guided plan</td>
</tr>
<tr>
<td>Kanai et al. 2016</td>
<td>4D</td>
<td>$^{81m}$Kr scintigraphy</td>
</tr>
</tbody>
</table>

VAMPIRE Challenge aims to address the limitation (presented by John Kipritidis, Ph.D.)

- Limited to specific implementations and ground truth modalities
Outline

- Pulmonary functional imaging
- Principles of CT ventilation imaging
- Cross-modality comparison: SPECT, PET, MR and dual-energy CT
- Clinical translation
- Challenges: Lung CT attenuation variations, validation of DIR and ventilation computation

Summary

- CT ventilation imaging is based on CT, DIR and image analysis, and thus has great potential for widespread clinical translation
- CT ventilation imaging has been translated into clinic at a few centers
- Major challenges include variations in lung CT attenuation (including 4D CT artifacts) and validation

Acknowledgments