Introduction to CT Ventilation Imaging:

Principles, Validation and Clinical Translation

Tokihiro Yamamoto, Ph.D.

UC DAVIS COMPREHENSIVE CANCER CENTER Radiation Oncology

AAPM 2016 | 7/31-8/4 | WASHINGTON, DC
SAM JOINT IMAGING-THERAPY SCIENTIFIC SYMPOSIUM

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

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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

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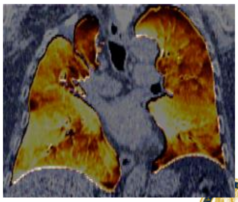
Why Pulmonary Functional Imaging?

- 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



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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

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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.*, ^{99m}Tc-DTPA)
  - PET with tracer gas/aerosol (*e.g.*, ^{68}Ga-Galligas)
- **MR**
  - Hyperpolarized He/Xe
  - Oxygen-enhanced proton

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CT Ventilation Imaging

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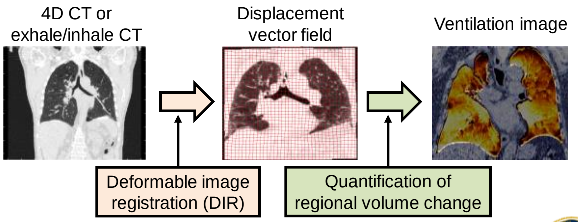
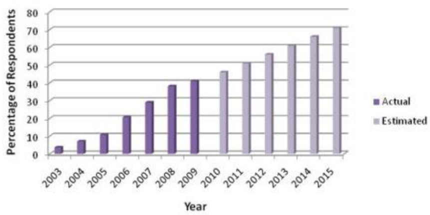
CT Ventilation Imaging



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

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



Simpson *et al.* (*J Am Coll Radiol* 2009)

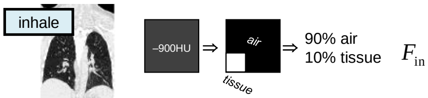
Quantification of Regional Volume Change

- Assumption: *Regional ventilation is proportional to regional volume change*
- Class of ventilation metric
  - Hounsfield unit (HU) change
    Simon (*J Clin Monit Comput* 2000); Guerrero *et al.* (*IJROBP* 2005)
  - Jacobian determinant of deformation
    Reinhardt *et al.* (*Med Image Anal* 2008)
  - Hybrid
    Ding *et al.* (*Med Phys* 2012)

HU-based Metric

$F(x,y,z) = -\frac{\text{HU}}{1000}$ 0 HU → 0% air
-1000 HU → 100% air

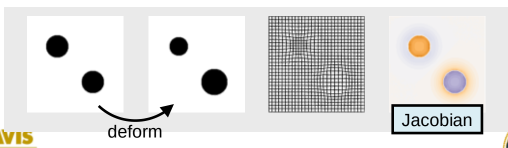
$$\Delta\text{Vol} = \frac{F_{\text{in}}\{x+u_x(x,y,z), y+u_y(x,y,z), z+u_z(x,y,z)\} - F_{\text{ex}}(x,y,z)}{F_{\text{ex}}(x,y,z)[1-F_{\text{in}}\{x+u_x(x,y,z), y+u_y(x,y,z), z+u_z(x,y,z)\}]}\text{Vol}_{\text{ex}}^{\text{air}}(x,y,z)$$



Simon (*J Clin Monit Comput* 2000)
Guerrero *et al.* (*IJROBP* 2005)

Jacobian-based Metric

$$\Delta\text{Vol} = \text{Vol}_{\text{ex}}^{\text{voxel}}\left(\begin{vmatrix} 1+\frac{\partial u_x(x,y,z)}{\partial x} & \frac{\partial u_x(x,y,z)}{\partial y} & \frac{\partial u_x(x,y,z)}{\partial z} \\ \frac{\partial u_y(x,y,z)}{\partial x} & 1+\frac{\partial u_y(x,y,z)}{\partial y} & \frac{\partial u_y(x,y,z)}{\partial z} \\ \frac{\partial u_z(x,y,z)}{\partial x} & \frac{\partial u_z(x,y,z)}{\partial y} & 1+\frac{\partial u_z(x,y,z)}{\partial z} \end{vmatrix} - 1\right)$$



Reinhardt *et al.* (*Med Image Anal* 2008)

Comparison of Ventilation Imaging Modalities

Ventilation imaging modalities	Spatial resolution (mm)	Time for exam (min)	Effective dose (mSv)	Imaging measures
CT w/o contrast (CT ventilation)	**1-2**	**5**	**30 (4D)**	**Volume change**
CT w/ contrast – single breath	1-2	5	7-15	Inhaled gas distribution
CT w/ contrast – multiple breath	1-2	10	High	Specific ventilation
SPECT	8-20	20	0.2	Inhaled gas distribution
PET	4-8	10	1	Inhaled gas distribution
Hyperpolarized He/Xe MR	3-10	5	0	Inhaled gas distribution

Simon *et al.* (*J Appl Physiol* 2012); Castillo *et al.* (*J Appl Clin Med Phys* 2015); Hofman *et al.* (*J Nucl Med* 2011); Mettler *et al.* (*Radiology* 2008)

Comparison of Ventilation Imaging Modalities

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

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Cross-Modality Comparison Studies for CT Ventilation Imaging

Study	CT type	Modality
Fuld *et al.* 2008	Prospective gating	Xenon-CT
Reinhardt *et al.* 2008	Prospective gating	Xenon-CT
Mathew *et al.* 2012	4D	Hyperpolarized ^{3}He MRI
Vinogradskiy *et al.* 2014	4D	^{99m}Tc-DTPA scintigraphy
Castillo *et al.* 2010	4D	^{99m}Tc-DTPA SPECT
Yamamoto *et al.* 2014	4D	PFT and ^{99m}Tc-DTPA SPECT
Kipritidis *et al.* 2014	4D	^{68}Ga-aerosol PET
Brennan *et al.* 2015	4D	PFT
Kida *et al.* 2016	4D	^{99m}Tc-DTPA SPECT-guided plan
Kanai *et al.* 2016	4D	^{81m}Kr scintigraphy

Details presented by Jenia Vinogradskiy, Ph.D.

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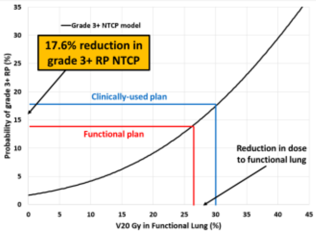
Lung functional avoidance RT may reduce toxicity



Vinogradskiy/Yamamoto *et al*. (Wed at 7:30am, Rm 202)

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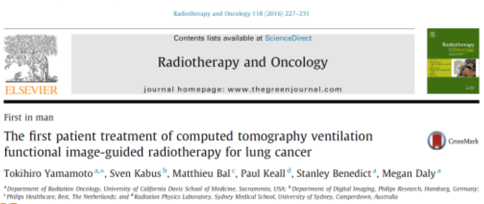
First-in-Human CT Ventilation Image-guided RT at UC Davis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ELSEVIER

First in man

The first patient treatment of computed tomography ventilation functional image-guided radiotherapy for lung cancer

CrossMark

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[a] Department of Radiation Oncology, University of California Davis School of Medicine, Sacramento, USA; [b] Department of Digital Imaging, Philips Research, Hamburg, Germany; [c] Philips Healthcare, Best, The Netherlands; and [d] Radiation Physics Laboratory, Sydney Medical School, University of Sydney, Camperdown, Australia

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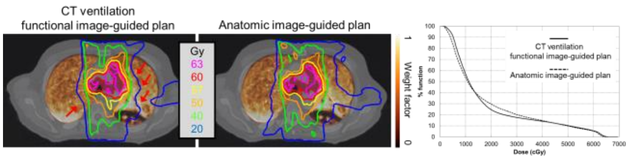
Yamamoto *et al*. (*Radiother Oncol* 2016)

Functional Image-guided IMRT vs. Anatomical Image-guided IMRT



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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)
Verified December 2014 by University of California, Davis
ClinicalTrials.gov Identifier: NCT02308709

Feasibility Study Incorporating Lung Function Imaging Into Radiation Therapy for Lung Cancer Patients

This study is currently recruiting participants. (see Contacts and Locations)
Verified April 2016 by University of Colorado, Denver
ClinicalTrials.gov Identifier: NCT02528942

Improving Pulmonary Function Following Radiation Therapy

This study is not yet open for participant recruitment. (see Contacts and Locations)
Verified July 2016 by University of Wisconsin, Madison
ClinicalTrials.gov Identifier: NCT02843568

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

	UC Davis	Colorado	Wisconsin
Arm	Single arm	Single arm	Two-arm, randomized
Primary endpoint	Grade ≥3 adverse events	Grade ≥3 pneumonitis	Ratio of Jacobian map following RT (3 months) to before RT
Sample size	33	70	120
Optimization technique	Image/voxel-based optimization with dose-function objectives	Subvolume (ROI)-based optimization with dose-volume objectives	Subvolume (ROI)-based optimization with dose-volume objectives

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Clinical Trials of Other Ventilation Imaging Modalities in Oncology

- ^{99m}Tc-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)

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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

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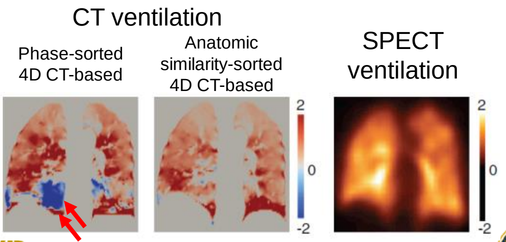
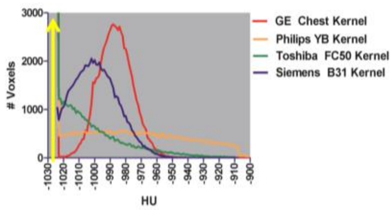
4D CT Artifacts



Yamamoto *et al*. (*Med Phys* 2013)

Variation between Manufacturer-recommended Lung Kernels



Courtesy of Jered Sieren (VIDA Diagnostics)

Cross-Modality Comparison Studies for CT Ventilation

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Reinhardt *et al.* 2008	Prospective gating	Xenon-CT
M		
V		
C		
Y		
K		
Brennan *et al.* 2015	4D	PFT
Kida *et al.* 2016	4D	^{99m}Tc-DTPA SPECT-guided plan
Kanai *et al.* 2016	4D	^{81m}Kr scintigraphy

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

- Limited to specific implementations and ground truth modalities

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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

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Jenia Vinogradskiy

American Cancer Society

PHILIPS

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