Validation, Clinical Endpoints and Opportunities for CT Ventilation

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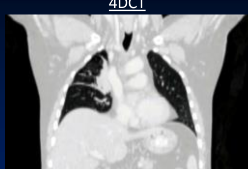
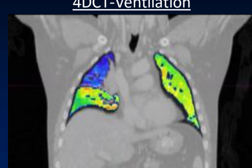
Background

4DCT-Ventilation Imaging

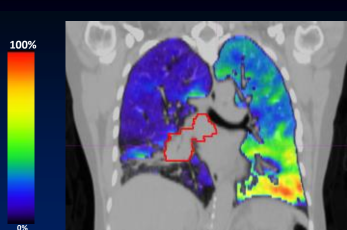
4DCT



4DCT-Ventilation



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

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Validation

Compare CT ventilation to other forms of functional imaging

Validation

Compare CT ventilation to other forms of functional 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

Slide courtesy of Tokihiro Yamamoto

Validation

Kipritidis et al, Medical Physics

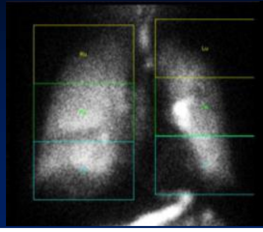
TABLE IV. Comparison of the present study and previous studies comparing CT with other modalities. Average values of r and d are shown; ROI = region of interest.

Study	Modality	CT ventilation metric	Subjects	Dice similarity $\bar{d}$	Spearman $\bar{r}$
Fuld *et al.* (Ref. 21)	Xe-CT	HU	4 sheep	N/A	0.81 (small ROIs)
Reinhardt *et al.* (Ref. 31)	Xe-CT	Jacobian	5 sheep	N/A	0.85 (small ROIs)
Yamamoto *et al.* (Ref. 26)	SPECT V /Q	Jacobian / HU	1 patient	N/A	0.18 / 0.48 (whole lung)
Castillo *et al.* (Ref. 24)	SPECT V	HU	7 patients	0.35 (low function)	N/A
Castillo *et al.* (Ref. 25)	SPECT Q	HU	10 patients	0.78 (low function)	N/A
Mathew *et al.* (Ref. 23)	^{3}He MRI	HU	11 patients	0.88 (good function)	N/A
This work	PET-Galligas	HU (density-scaled)	12 patients	0.52 (low function) 0.88 (good function)	0.42 (whole lung)

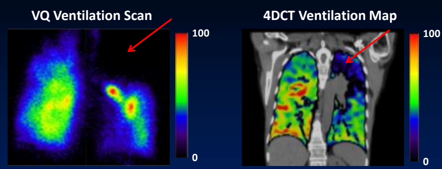
Validation again nuclear medicine

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

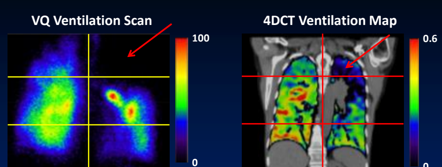
VQ Ventilation Scan



Validation again nuclear medicine

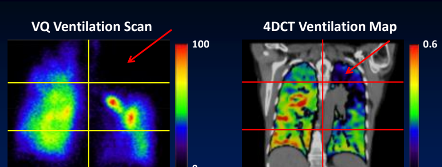


Validation again nuclear medicine



	SPECT Ventilation		4DCT Ventilation	
	Right (%)	Left (%)	Right (%)	Left (%)
Top	9.5	2.7	16.8	8.1
Middle	30.2	21.1	21.9	12.4
Lower	21.4	15.1	23.2	17.7
Total	61.1	38.9	61.8	38.2

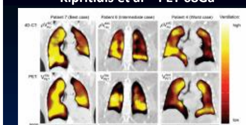
Validation again nuclear medicine



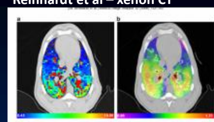
- Correlation coefficient = 0.65
- Radiologist observations: Sensitivity = 90%, Specificity = 64%, Accuracy = 81%

Validation

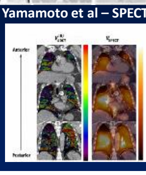
Kipritidis et al – PET 68Ga



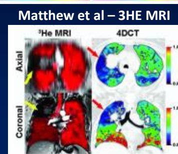
Reinhardt et al – xenon CT



Yamamoto et al – SPECT



Matthew et al – 3HE MRI



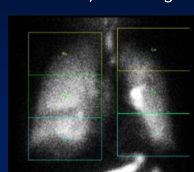
Validation – conclusions/challenges

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

1. Validation of CT ventilation
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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


International Journal of Radiation Oncology*Biology*Physics

Volume 84, Issue 3, Supplement, 1 November 2012, Pages S31–S32

Proceedings of the American Society for Radiation Oncology 54th Annual Meeting

ASTRO's 54th Annual Meeting

Establishing a Relationship Between Radiosensitivity of Lung Tissue and Ventilation

J. Bayouth[1], K. Du[2], G. Christensen[3], B. Smith[4], J. Buatti[1], J. Reinhardt[2]

Show more

doi:10.1016/j.ijrobp.2012.07.086

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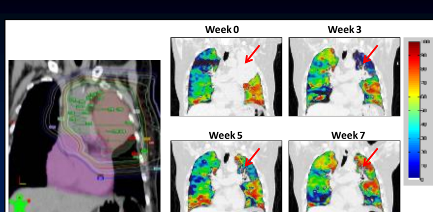
Changes in lung function during RT



Functional planning concept

Avoid functional portions of the lung in favor of irradiating through less functioning lung tissue


Incorporation of functional imaging data in the evaluation of dose distributions using the generalized concept of equivalent uniform dose

Received 15 January 2004
Published 1 April 2004


International Journal of Radiation Oncology*Biology*Physics

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


Radiotherapy and Oncology

Volume 77, Issue 3, December 2005, Pages 271–277

SPECT in treatment planning

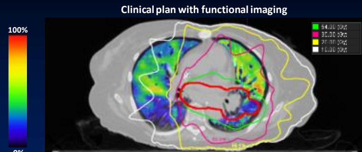
The incorporation of SPECT functional lung imaging into inverse radiotherapy planning for non-small cell lung cancer

Functional planning concept

Clinical plan

Functional planning concept

Clinical plan with functional imaging

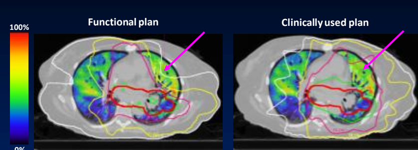


Functional planning concept

Functional plan with functional imaging

Functional planning concept

Can functional planning reduce toxicity???

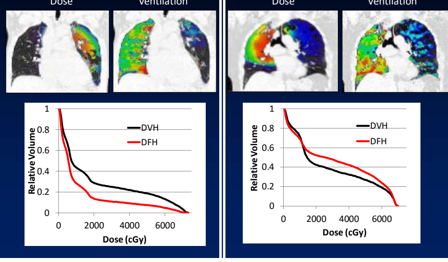


Functional planning – Will it work?

- 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

Functional planning

MLD = 22.9 Gy No pneumonitis	MLD = 23.2 Gy Grade 3 pneumonitis
Dose / Ventilation	Dose / Ventilation



Functional planning

- Area under the curve (AUC) and logistic regression p value

MLD	fMLD	V20	fV20
0.55 (p=0.29)	0.62 (p=0.07)	0.57 (p=0.23)	0.66 (p=0.04)

Results –Toxicity reduction to functional lung

Toxicity (grade 3+) reduction

	NTCP Clinical Plan	NTCP Functional Plan	Difference Absolute	Difference Relative
Mean Functional lung	19%	16%	3%	15.8%
V20Gy Functional lung	17%	14%	3%	17.6%
V30Gy Functional lung	18%	13%	5%	27.8%

- 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

Investigation of four-dimensional computed tomography-based pulmonary ventilation imaging in patients with emphysematous lung regions

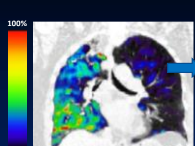
Tokihiro Yamamoto[1,4], Sven Kabus[2], Tobias Klinder[3], Cristian Lorenz[2], Jens von Berg[2], Thomas Blaffert[2], Billy W Loo Jr[1] and Paul J Keall[1]

Medical Physics

Toward automatic regional analysis of pulmonary function using inspiration and expiration thoracic CT

Keelin Murphy, Josien P. W. Pluim, Eva M. van Rikxoort, Pim A. de Jong, Bartjan de Hoop, Hester A. Gietema, Onno Mets, Marleen de Bruijne, Pechin Lo, Mathias Prokop, and Bram van Ginneken

Clinical application outside of RT



4DCT-Ventilation Metrics
Coefficient of Variation = 91%
V20 = 34%

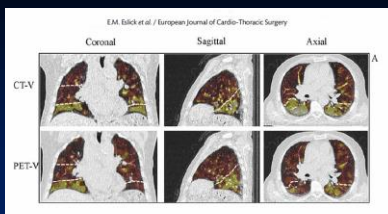
PFT Metrics
FEV1 = 36%
FEV1/FVC = 45%

Physics Contribution

Clinical Validation of 4-Dimensional Computed Tomography Ventilation With Pulmonary Function Test Data

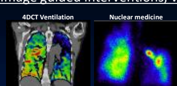
Douglas Brennan, MPH, Leah Schubert, PhD, Quentin Diot, PhD, Richard Castillo, PhD, Edward Castillo, PhD, Thomas Guerrero, MD, PhD, Mary K. Martel, PhD, Derek Linderman, MD, Laurie E. Gaspar, MD, MBA, Moyed Miften, PhD, Brian D. Kavanagh, MD, MPH, and Yevgeniy Vinogradskiy, PhD

CT ventilation for surgical assessment



CT ventilation for surgical assessment

Vinogradskiy et al – Image guided interventions, Wednesday at 7:30



	4DCT-ventilation	Nuclear medicine
	Imaging characteristics	
Spatial resolution	1-2 mm	4-10 mm
Type of imaging	Anatomical, Mechanical, Functional	Functional
Aerosol Artifact	No	Yes
Quantitative	Yes	No
	Patient considerations	
Cost	~$2000	~$4000
Imaging Time	30 seconds	15-30 minutes
Contrast required	No	Yes
Radiation dose	3 cGy	3 cGy

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

Validation, Clinical Endpoints and Opportunities for CT Ventilation

Thank you

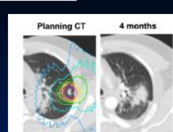
University of Colorado Anschutz Medical Campus

University of Colorado Cancer Center

Radiation toxicity in the lung

5% – 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

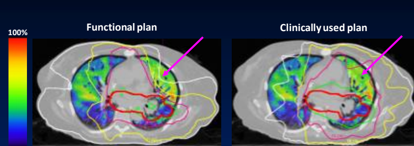


Diot et al

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

Functional planning concept

Can functional planning reduce toxicity???



Outline

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

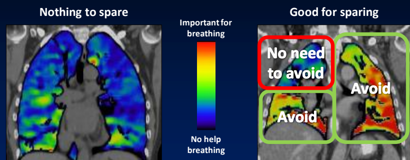
4DCT-Ventilation Clinical Trial

- **70 lung cancer patients between 2 institutions**
- **Use 4DCT to calculate ventilation imaging**
- **Use 4DCT-ventilation to design functional radiation plans**
- **Hypothesis: 4DCT-venitlation 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

Good for sparing

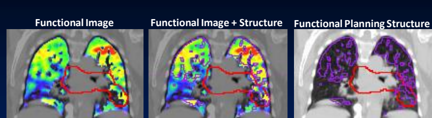


Courtesy of Tim Waxweiler, MD

Protocol Basics

- Functional planning
  - Structure based functional approach

Planning techniques



Calculating Ventilation Images

Link lung voxels from inhale phase to exhale phase
using deformable image registration

Deformable registration maps

4D deformable registration using trajectory modeling (Castillo et al., 2010)

Calculating Ventilation Images

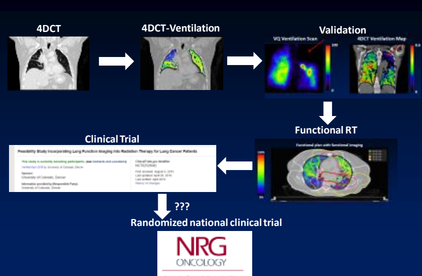
$$\frac{V_{in}-V_{ex}}{V_{ex}} = 1000\frac{\overline{HU}_{in}^{voi} - HU_{ex}}{HU_{ex}(1000+\overline{HU}_{in}^{voi})}$$

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



Acknowledgments

- NIH/NCI R01CA200817
- State of Colorado: Advanced Industries Accelerator grant

Radiation Oncology
Yevgeniy Vinogradskiy PhD
Timothy Waxweiler MD
Leah Schubert PhD
Quentin Diot PhD
Bernard Jones, PhD
Chad Rusthoven, MD
Laurie Gaspar, MD, MBA
Brian Kavanagh MD, MPH
Moyed Miften PhD

Thoracic Physicians
Phillip Koo, MD, Nuclear Medicine
John Mitchell, MD, Cardiothoracic Surgery
Derek Linderman, MD, Pulmonology

Other institutions
Mary Martel, PhD MD Anderson
Richard Castillo, PhD, UTMB
Edward Castillo, PhD, Beaumont
Thomas Guerrero MD, PhD, Beaumont

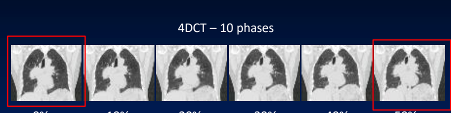
Clinical trial team
Kari Anderson
Kyra Anderson
Robin Swing
Chelsea Schaefer
Monica Robischon

Conclusions

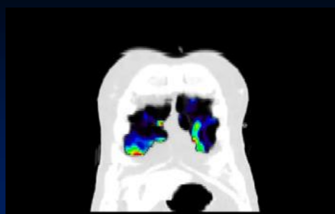
- 4DCT-Ventilation calculates lung ventilation maps from 4DCT data
- 4DCT-Ventilation has been validated against established methods of measuring lung function
- Retrospective work suggests toxicity can be reduced with functional planning
- Clinical trials are underway to evaluate 4DCT-Ventilation based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

Calculating Ventilation Images

Calculating ventilation maps

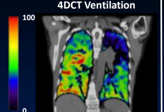


Movie of 4DCT-ventilation

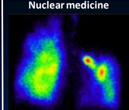


An aside about imaging…

4DCT Ventilation



Nuclear medicine



	4DCT-ventilation	Nuclear medicine	Advantage
Cost	$2000	$4000	4DCT-ventilation
Imaging Time	30 seconds	30 minutes	4DCT-ventilation
Contrast required	No	Yes	4DCT-ventilation
Spatial resolution	1 mm	5-10 mm	4DCT-ventilation
Type of imaging	Anatomical and Functional	Functional	4DCT-ventilation
Radiation dose	3 cGy	3 cGy	Even

Functional planning

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

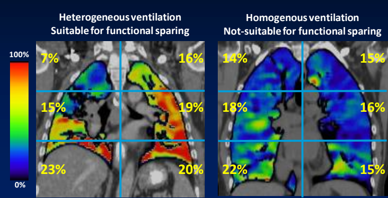
MLD	fMLD	V20	fV20
0.55 (p=0.29)	0.62 (p=0.07)	0.57 (p=0.23)	0.66 (p=0.04)

- Bootstrap analysis

Dose and function metrics	Bootstrap *p* value
MLD + fMLD	0.154
v20 + fv20	0.118

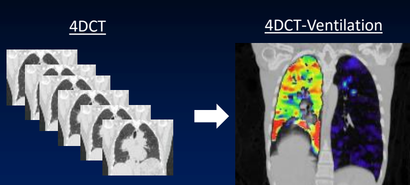
Should all patients be eligible?

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



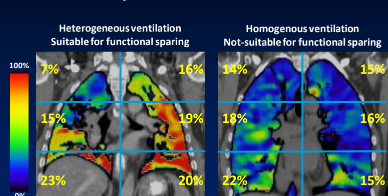
4DCT Imaging

Calculate ventilation from 4DCT data



Should all patients be eligible?

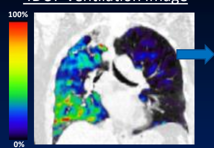
Metrics based on regional (each third) lung function
- % ventilation in third with tumor, % ventilation in third with tumor or adjacent third



Validation against PFTs

4DCT-Ventilation Image

Derived metrics



4DCT-Ventilation Metrics
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PFT Metrics
FEV1 = 36%
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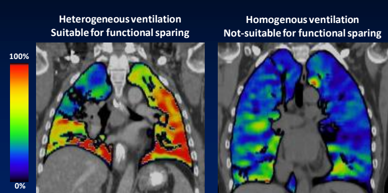
Should all patients be eligible?

Patient spatial lung function



Results

- 69% of patients had observer identified defects

Area under the curve

Metric	AUC
Ipsi/Contra	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

ROC Metric	Description	(%)
TP	% ventilation defect and user defect	85
FP	% ventilation no defect but user defect	15
TN	% ventilation defect but user no defect	47
FN	% ventilation no defect and user no defect	53

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

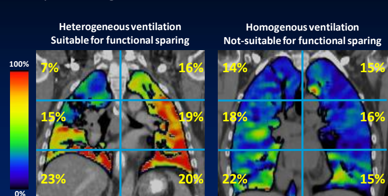
58% of stage III lung cancer patients could be replaned according to algorithm based on % ventilation in each lung third

Functional re-planning qualitative results

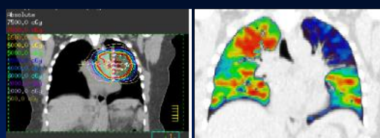
- Turn functional avoidance image into structure
  - Use threshold techniques based on trial inclusion criteria
  - Allow for post-processing
- Planning techniques
  - coplanar arcs
  - non-coplanar techniques may be needed
- In practice end up sparing contra-lateral lung
- What has to 'give' in the functional avoidance planning process
  - Tumor dose homogeneity (hot spot)

Should all patients be eligible?

Patient spatial lung function



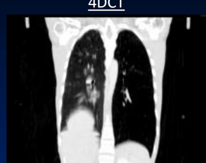
Calculating Ventilation Images



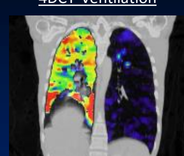
Background

4DCT-Ventilation Imaging

4DCT



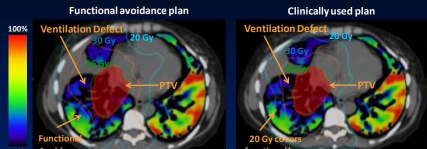
4DCT-Ventilation



Functional planning

Functional avoidance plan

Clinically used plan



Functional avoidance example (AAPM 2013)

Shape the radiation dose to avoid functional (ventilated) parts of the lung