Towards Personalized Therapy in Lung Cancer with Functional Imaging

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Disclosures

- No conflicts of interest
Objectives

• Understand different imaging modalities, contouring, and treatment planning for functional lung avoidance radiation planning
• Understand different imaging modalities, contouring, and treatment planning for response-adaptive radiation planning in lung cancer

Clinical Challenge

How do we continue to improve outcomes in unresectable stage III NSCLC?
• Decrease toxicity
• Improve cancer control

Radiation Pneumonitis is a Problem!

- PACIFIC trial: most frequent AE leading to discontinuation of trial regimen
  - Pneumonitis (4.8%)
  - Radiation pneumonitis (1.3%)
  - Pneumonia (1.1%)

MVA:
- V20 Gy
- Chemo
- Age (trend)

We Are Not Great At Predicting It

**Table 5** Risk of radiation pneumonitis based on V20 (volume of lung receiving 20 Gy or more) in the whole cohort of patients (training and validation set combined)

<table>
<thead>
<tr>
<th>Lung volume receiving ≥20 Gy</th>
<th>Symptomatic pneumonitis (% of patients)</th>
<th>Fatal pneumonitis (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20%</td>
<td>18.4%</td>
<td>0.0%</td>
</tr>
<tr>
<td>20%-29.99%</td>
<td>30.3%</td>
<td>1.0%</td>
</tr>
<tr>
<td>30%-39.99%</td>
<td>32.6%</td>
<td>2.9%</td>
</tr>
<tr>
<td>≥40%</td>
<td>35.9%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

**SPECT Perfusion Imaging in NSCLC**

- 123 pts tx with RT for thoracic cancers at Duke
- Serial SPECT scans, registered with simulation CT


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**Clinical Utility of Lung Perfusion MAA SPECT for Pneumonitis Prediction**

- 55 Duke patients and 65 NKI patients
- MLD, OpRP, pre-RT DLCO unable to accurately segregate patients into high vs. low risk groups for RP

SPECT/CT Lung Perfusion Imaging

Single Institution Modern SPECT/CT

- SPECT/CT=better spatial resolution and quantitative accuracy than SPECT
- 26 patients with lung cancer and pre-RT perf/vent SPECT/CT
- SPECT-based DFH parameters outperformed standard DVH parameters as predictors of RP in ROC

SPECT/CT Perfusion Imaging at UW

- 2013: Protocol-Specific Research Support grant, part of Fred Hutchinson Cancer Center Support Grant
- Supporting clinical trial: “Pulmonary Functional Imaging for Radiation Treatment Planning for Lung Cancer”
- Three SPECT/CT scans with $^{99m}$Tc-MAA and $^{99m}$Tc-DTPA
  - Pre-radiation treatment
  - Mid-radiation treatment
  - 3 months post-radiation treatment

PI: Zeng
Maybe We Could Predict Pneumonitis?


Functional Lung Avoidance RT?

1. Correlation to outcome: imaging biomarker association to radiation pneumonitis or PFT decline
2. Spatial stability: functional lung imaging-based avoidance regions must be spatially stable / reproducible
3. Dose modifying effect: changes in functional lung imaging must be linked to local radiation dose magnitude
4. Avoidance plan feasibility: functional lung avoidance RT planning must show dosimetric advantage while meeting conventional target + normal tissue objectives
2. Stable Perfusion Imaging for Functional Lung Avoidance RT

MAA SPECT perfusion: median Pearson $R = 0.95$ (IQR 0.83-0.96)

Unpublished data.

3. Regional Perfusion Response at 3 Months Post RT

Unpublished data.
3. MAA SPECT/CT Lung Perfusion Dose Response Curves

- Perfusion reduction normalized to lung regions < 5 Gy EQD2
- Shape of individual dose-response curves sensitive to baseline lung function and treatment regimen

Baseline perfusion defect (VQ mismatch)

SBRT Regimen

Baseline lung function normal


4. Functional Avoidance RT Plan

- Redistribute lung dose away from perfused regions
- Highly functional lung = >70% of max perfusion (best AUC=0.93 with grade 2+ PNM prediction), normalized to aortic arch on SPECT/CT

• Mean perfused lung dose reduced to < 10 Gy over cohort of patients
4. Functional Lung Avoidance RT Plan

- Define sub-lung perfusion level contours for differential functional avoidance planning
- Autosegmentation via threshold levels
- Evaluate pMLD (goal < 10 Gy) and pV20 (goal < 15%)

PERF MAA SPECT Avoidance Objectives

<table>
<thead>
<tr>
<th>Copy Data Below ↓</th>
<th>Lung-CTV</th>
<th>PERF L1</th>
<th>PERF L3</th>
<th>PERF L5</th>
<th>PERF L7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max (CNTS) Value</td>
<td>1817.00</td>
<td>265.00</td>
<td>782.00</td>
<td>1299.00</td>
<td>1817.00</td>
</tr>
<tr>
<td>Mean (CNTS) Value</td>
<td>640.21</td>
<td>160.43</td>
<td>656.66</td>
<td>1162.10</td>
<td>1604.42</td>
</tr>
<tr>
<td>Median (CNTS) Value</td>
<td>628.00</td>
<td>164.00</td>
<td>657.00</td>
<td>1158.00</td>
<td>1581.00</td>
</tr>
<tr>
<td>Min (CNTS) Value</td>
<td>7.00</td>
<td>7.00</td>
<td>524.00</td>
<td>1041.00</td>
<td>1558.00</td>
</tr>
<tr>
<td>Volume (ml) Value</td>
<td>3564.89</td>
<td>617.11</td>
<td>1003.66</td>
<td>322.61</td>
<td>10.59</td>
</tr>
</tbody>
</table>

- Functional dose painting tool: MIM workflow → RayStation plan integration
Functional Lung Imaging Options

- **Perfusion**
  - $^{99m}$Tc-MAA SPECT/CT
  - $^{68}$Ga-MAA PET/CT

- **Ventilation**
  - $^{99m}$Tc-DTPA SPECT/CT
  - $^{99m}$Tc-Technegas SPECT/CT
  - 4DCT-derived
  - $^3$He MRI
  - $^{68}$Ga-Galligas PET/CT

- **Inflammation**
  - FDG PET/CT

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**Pros**

- $^{99m}$Tc-MAA SPECT most widely studied for lung function
- Fully quantitative
- Can be gated to respiratory motion
- No radiation
- Functional sequences
- Predominant modality in RT imaging

**Cons**

- Uses radiation for imaging
- Poorer spatial and temporal resolution than CT/MRI/PET
- Gallium-68 MAA for perfusion
- Galligas for ventilation
- Multiple tissue interfaces & lack of protons in lung
- Special equipment, expertise, and compounds
- CT registration
- Uses radiation for imaging
- Expertise to interpret 4D scans for function
- Conflicting results in validation against established imaging methods
**Functional Lung Avoidance RT**

a) fV20

<table>
<thead>
<tr>
<th>Source</th>
<th>MD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfusion</td>
<td>10.17 [6.46; 13.89]</td>
</tr>
<tr>
<td>Shioyama et al., 2007</td>
<td></td>
</tr>
<tr>
<td>Agrawal et al., 2012</td>
<td>6.40 [0.95; 11.86]</td>
</tr>
<tr>
<td>Tian et al., 2014</td>
<td>3.14 [1.82; 4.66]</td>
</tr>
<tr>
<td>Siva et al., 2015</td>
<td>3.80 [0.39; 7.21]</td>
</tr>
<tr>
<td>Siva et al., 2016</td>
<td>0.88 [-0.84; 2.60]</td>
</tr>
<tr>
<td>Total</td>
<td>4.42 [1.66; 7.16]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 21.84$ (P < 0.01), $I^2 = 82\%$

<table>
<thead>
<tr>
<th>Source</th>
<th>MD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilation</td>
<td>3.40 [0.81; 5.99]</td>
</tr>
<tr>
<td>Yaremko et al., 2007</td>
<td></td>
</tr>
<tr>
<td>Siva et al., 2015</td>
<td>1.90 [-3.07; 6.87]</td>
</tr>
<tr>
<td>Waxweiler et al., 2017</td>
<td>5.60 [4.52; 6.68]</td>
</tr>
<tr>
<td>Total</td>
<td>4.41 [2.37; 6.45]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 4.07$ (P = 0.13), $I^2 = 51\%$

Total: $\chi^2 = 4.19$ (P < 0.01), $I^2 = 80\%$

b) fMLD

<table>
<thead>
<tr>
<th>Source</th>
<th>MD (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Perfusion</td>
<td>0.77 [0.54; 1.00]</td>
</tr>
<tr>
<td>St-Hilaire et al., 2011</td>
<td></td>
</tr>
<tr>
<td>Agrawal et al., 2012</td>
<td>7.93 [4.62; 11.24]</td>
</tr>
<tr>
<td>Siva et al., 2015</td>
<td>1.70 [0.27; 3.13]</td>
</tr>
<tr>
<td>Siva et al., 2016</td>
<td>1.22 [0.20; 2.24]</td>
</tr>
<tr>
<td>Total</td>
<td>1.96 [0.57; 3.39]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 19.92$ (P < 0.01), $I^2 = 86\%$

<table>
<thead>
<tr>
<th>Source</th>
<th>MD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilation</td>
<td>5.62 [3.27; 7.97]</td>
</tr>
<tr>
<td>Munawar et al., 2010</td>
<td></td>
</tr>
<tr>
<td>Kadoya et al., 2015</td>
<td>1.43 [0.47; 2.39]</td>
</tr>
<tr>
<td>Siva et al., 2015</td>
<td>1.20 [-1.11; 3.51]</td>
</tr>
<tr>
<td>Total</td>
<td>2.63 [0.14; 5.12]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 10.88$ (P < 0.01), $I^2 = 82\%$

Total: $\chi^2 = 2.18$ [1.09; 3.26], $I^2 = 84\%$

**Functional Lung Avoidance RT Challenges**

- Perfusion or ventilation, or both?
- Image registration of functional images to treatment planning CT
- Timing between scans
- Perfusion deficits due to tumor and reperfusion
- Large variations in definition of functional lung, and dose constraints for avoidance
From Functional Lung Avoidance Onto Response Adaptive Therapy

RTOG 0617: More is Not Better?

- Uniform dose escalation to 74 Gy is detrimental in unresectable stage III NSCLC
- But more radiation must kill more cancer?!!
- Who would most likely benefit from dose escalation?

FDG PET/CT Response During RT Correlates with Lung Cancer Survival

Outcome prediction improves with mid-tx response relative to baseline FDG PET

van Elmpt JNM 2012
Huang EJNMMI 2011

FDG PET Spatial Correlation with Lung Cancer Recurrence/Progression

Project Funding Timeline

- 2014-2016: RSNA Research Scholar Grant
  - PI: Dr. Stephen Bowen, Medical Physics
- 2016: 5-year R01CA204301
  - Co-PIs: Dr. Stephen Bowen and Dr. Jing Zeng
  - Supporting clinical trial: “Personalized radiation therapy through response-adaptive dose escalation and functional lung avoidance (FLARE RT)”
    - Salary support for Co-PIs
    - Post-docs
    - Research coordinator
    - Statistician
    - Scan costs
    - Supplies

FLARE RT Trial Schema

- All patients get functional lung avoidance RT → potential toxicity benefit
- Only high local failure risk patients get FDG PET-guided dose escalation → potential survival benefit
- Primary endpoint: 2 year overall survival
Multi-Disciplinary Team Effort!

- Medical Oncology
- Thoracic Surgery
- Radiation Oncology

Upstaging with Repeat PET/CT

- 20 patients required a repeat PET/CT for the trial
- All 20 patients had an initial PET/CT performed for staging
- Median days between initial and repeat PET/CT was 35 days

Change in Management

- 2/20 patients (10%) were found to have metastatic disease on repeat PET/CT
- 5/20 patients (25%) had increased nodal involvement, increasing size of their radiation fields


Predicting Change in Management?

- No statistically significant differences between two groups
- Trend towards larger, more FDG avid tumors being upstaged

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients</th>
<th>Median Days Between Scans</th>
<th>Median SUV_{max}</th>
<th>Median SUV_{mean}</th>
<th>Median SUV_{peak}</th>
<th>Median MTV (ml)</th>
<th>Median TLG (SUV ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>20</td>
<td>35</td>
<td>11</td>
<td>6</td>
<td>9</td>
<td>36</td>
<td>283</td>
</tr>
<tr>
<td>Upstaged</td>
<td>7</td>
<td>34</td>
<td>13</td>
<td>8</td>
<td>13</td>
<td>115</td>
<td>883</td>
</tr>
<tr>
<td>Not-Upstaged</td>
<td>13</td>
<td>36</td>
<td>11</td>
<td>6</td>
<td>9</td>
<td>35</td>
<td>201</td>
</tr>
</tbody>
</table>

Predicting Change in Management?

Quartiles by TLG


Mid-Treatment Response Assessment

- **PET Responder**: required anatomic adaptation to 60 Gy in 30 fx
- **PET Non-responder**: required functional adaptation to 74 Gy in 30 fx
Mid-Tx PET Response Assessment

- Assessment from panel of FDG PET metrics + Radiology report
- **PET Responders:** $\Delta$SUV$_{\text{max}}$ decrease 36% (23-41%)
- **PET Non-responders:** $\Delta$SUV$_{\text{max}}$ decrease 8% ([−28]−23%)

Baseline Pre RT

3 week Mid RT

Unpublished data.

Mid-Tx PET Response

- 4 studies reporting on PET parameters at predicting tumor response (TR) or progression (TP)

FLARE-RT Boost to Non-Responders

3wk FDG PET/CT

FLARE RT Boost Plan

Unpublished data.

FLARE-RT Planning Technical Workflow

PET/CT

Prescription Function

Dose Discretization

Planning/Delivery

Sub-target Contours

Discrete Contour Prescriptions

• $D_{ROI}$

• $\min(D_{ROI})$ & $\max(D_{ROI})$

• $\min(DVH_{ROI})$ & $\max(DVH_{ROI})$

PET Imaging Rx

Clinical Planned Dose

Deveau, Bowen et al. 2010 Acta Oncol
FLARE-RT Dose Painting Plan Objectives

FDG PET Boost Objectives

<table>
<thead>
<tr>
<th>Copy Data Below ↓</th>
<th>FDG L1</th>
<th>FDG L2</th>
<th>FDG L4</th>
<th>FDG L7</th>
<th>PTV_midtx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max (SUVbw) Value</td>
<td>2.57</td>
<td>4.73</td>
<td>9.04</td>
<td>15.50</td>
<td>15.50</td>
</tr>
<tr>
<td>Mean (SUVbw) Value</td>
<td>1.85</td>
<td>3.61</td>
<td>7.97</td>
<td>13.89</td>
<td>6.74</td>
</tr>
<tr>
<td>Median (SUVbw) Value</td>
<td>1.89</td>
<td>3.58</td>
<td>7.94</td>
<td>13.78</td>
<td>6.47</td>
</tr>
<tr>
<td>Min (SUVbw) Value</td>
<td>0.54</td>
<td>2.57</td>
<td>6.88</td>
<td>13.36</td>
<td>0.42</td>
</tr>
<tr>
<td>Volume (ml) Value</td>
<td>44.59</td>
<td>63.07</td>
<td>57.41</td>
<td>6.94</td>
<td>314.15</td>
</tr>
<tr>
<td>Mean Dose (Gy)</td>
<td>63.84</td>
<td>67.50</td>
<td>76.56</td>
<td>88.85</td>
<td>74.00</td>
</tr>
<tr>
<td>Median Dose (Gy)</td>
<td>63.93</td>
<td>67.44</td>
<td>76.50</td>
<td>88.63</td>
<td>73.44</td>
</tr>
<tr>
<td>Min Dose (Gy)</td>
<td>61.12</td>
<td>65.34</td>
<td>74.29</td>
<td>87.75</td>
<td>60.88</td>
</tr>
<tr>
<td>Max Dose (Gy)</td>
<td>65.34</td>
<td>69.82</td>
<td>78.77</td>
<td>92.19</td>
<td>92.19</td>
</tr>
<tr>
<td>Weight</td>
<td>14.19</td>
<td>20.08</td>
<td>18.27</td>
<td>2.21</td>
<td>100.00</td>
</tr>
</tbody>
</table>

- Divide FDG avid volume into bins by FDG avidity
- Most avid regions receive >90 Gy, mean dose to boost region 74 Gy
- Functional dose painting tool: MIM workflow → RayStation plan integration

FDG PET/CT-guided Dose Escalation

- NKI+Maastricht: average dose increase to PET avid areas up to 85+ Gy in 24 fractions
- RTOG 1106: dose escalation based on mid Tx PET (up to 80.4 Gy in 30 fractions)
FLARE-RT Dosimetry

Normal tissue dosimetry not significantly different between PET responders and PET non-responders (p > 0.14)

Mid-Tx PET Outcome Stratification

Log rank p = 0.002

Unpublished data.
### Mid-Tx PET Toxicity Risk Stratification

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>6 mo (n=25)</th>
<th>6 mo PET-R (n=16)</th>
<th>6 mo PET-NR (n=9)</th>
<th>HR</th>
<th>p</th>
<th>Palma et al. 2013 historical control</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTCAE v4 Grade 2+ Pneumonitis (ε = 9)</td>
<td>26%</td>
<td>44%</td>
<td>11%</td>
<td>0.17</td>
<td>0.092</td>
<td>matched for age &amp; chemo risk factors 38%†</td>
</tr>
</tbody>
</table>

- Pulmonary toxicity risk linked to peak SUV change ($p = 0.033$) rather than tumor volume reduction ($p = 0.32$)
- Grade 3+ esophagitis in 2 patients, both PET-Responders
- Peripheral blood correlative analysis pending

Unpublished data.

### Multiparametric Imaging of Functional Lung Response

- Correlation between ↓ perfusion in high dose regions and ↑ inflammation
- Increased post-Tx lung perfusion in low dose regions

Thomas H, Zeng J et al. Under review
Effect of FLARE-RT on Dose-Perfusion Response

- Relative lung perfusion increase in low-dose regions following FLARE-RT
- Baseline high perfusion regions have steeper (more sensitive) dose-response curves

Thomas H, Zeng J et al. Under review

Voxel Forecast Tool: PET Response Prediction for Decision Support

- PET Responder: NED 491 days
- PET Non-responder: Died 323 days

MAE = 1.1 SUV

MAE = 3.3 SUV

Anatomic Adaptation During Lung RT

Table 1 Lung Density Changes Observed Across Multiple Large Patient Studies During Radiation Therapy Treatments

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Patients</th>
<th>Tumor Anatomical Shift</th>
<th>Atelectasis</th>
<th>Pleural Effusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kwint (2014)</td>
<td>177</td>
<td>27%</td>
<td>19%</td>
<td>6%</td>
</tr>
<tr>
<td>Elsayad (2016)</td>
<td>71</td>
<td>10%</td>
<td>20%</td>
<td>25%</td>
</tr>
<tr>
<td>Moller (2014)</td>
<td>163</td>
<td>—</td>
<td>15%</td>
<td>8%</td>
</tr>
<tr>
<td>Van Zwienen (2008)</td>
<td>114</td>
<td>—</td>
<td>29%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Table 2 Tumor Regression Rates for Patients Diagnosed With Stage III NSCLC Treated With Definitive Radiation

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Patients</th>
<th>Imaging Modality</th>
<th>Volume</th>
<th>Median Fraction (Range)</th>
<th>Median Regression (Range)</th>
<th>Median Fraction (Range)</th>
<th>Median Regression (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kataria (2014)</td>
<td>15</td>
<td>Helical kVCT</td>
<td>GTVp</td>
<td>22nd-23rd</td>
<td>–</td>
<td>34% (–13.8% to –73.0%)</td>
<td>30th</td>
</tr>
<tr>
<td>Spoelstra (2008)</td>
<td>21</td>
<td>Helical kVCT</td>
<td>ITVp</td>
<td>15th(14th-17th)</td>
<td>Not reported (+47% to –25%)</td>
<td></td>
<td>25th (21st-33rd)</td>
</tr>
<tr>
<td>Berkovic (2015)</td>
<td>41</td>
<td>kV CBCT</td>
<td>GTVp</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fox (2013)</td>
<td>22</td>
<td>Helical kVCT</td>
<td>GTVp</td>
<td>15th(46-20th)</td>
<td>–</td>
<td>24% (–0.3% to –61.7%)</td>
<td>30th</td>
</tr>
<tr>
<td>Wald (2017)</td>
<td>52</td>
<td>kV CBCT</td>
<td>GTVp</td>
<td>11th</td>
<td>–</td>
<td>30% (–24.0% to –84.3%)</td>
<td>30th</td>
</tr>
<tr>
<td>Elsayad (2016)</td>
<td>37</td>
<td>kV CBCT</td>
<td>GTVp</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Remelle (2017)</td>
<td>50</td>
<td>Helical kVCT</td>
<td>GTV</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Selbert (2007)</td>
<td>17</td>
<td>MVCT</td>
<td>GTVp</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Kavanaugh J et al. Seminars in Rad Onc. 2019

Uncertainty of Anatomic Adaptation

- Subclinical disease extent
  - Inside initial CTV
  - Inside initial GTV
- When/how often to adapt?
- Accurate dose accumulation calculations?
Pathology

- Studies looking at microscopic tumor extension in surgery specimens
- Variation between studies, and by histology (squamous vs adenocarcinoma) and grade
- All pre-treatment, unclear what happens mid-radiation

Apolle R et al. Clin Trans Rad Onc 2017

MRI Adaptive RT

- Potential for MRI guided personalized/ adaptive RT
- Functional assessment of both target and normal tissues
- Superior soft tissue definition compared to CT

Bainbridge H et al. TLCR 2017.
Conclusions

• More sophisticated imaging modalities will continue to be integrated into the radiation oncology treatment planning & delivery workflow

• Movement towards more personalized radiation therapy
  – Radiation treatment plans that are more biologically targeted, for both tumor and normal tissue
  – More adaptive therapy
  – Continued investigations into the “how” of the process

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  – Ramesh Rengan

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  – Daniel Hippe

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