Personalized radiation therapy through functional lung avoidance and response

Adaptive dose escalation (FLARE RT)

AAMD Annual Meeting Indianapolis
Patricia Sponseller, MS, CMD, RTT, (R)(T)
June 14, 2017
I have no relevant financial or nonfinancial relationships in the products or services described, reviewed, evaluated or compared in this presentation.
WWAMI Network
Phase II Study

FRED HUTCHINSON CANCER RESEARCH CENTER
UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE
Current version: 2/16/2016

Personalized radiation therapy through functional lung avoidance and response-adaptive dose escalation: utilizing multimodal molecular imaging to improve the therapeutic ratio (FLARE RT)
Proposal

• Improve therapeutic ratio by limiting pulmonary toxicity risk
• Avoidance of functional defined on P/V on SPECT/CT
• Increasing local control through FDG-PET/CT tumor guided dose escalation
• Select group of patient that are at high risk of local failure
Pulmonary Toxicity

- Limit pulmonary toxicity by identifying perfused lung
- Use in objectives in RT planning
- Use highly perfused lung as a surrogate for toxicity
FDG PET/CT

- Baseline scan
- Mid-Tx scan which determines if patient is a responder to RT
- If non-responder then dose escalation last 3 weeks of RT
Background

- RT major Tx option for pts with NSCLC
- Current Tx options suboptimal tumor control
- Local failure up to 50% and 5 year OS 10-20%
- Carry substantial toxicity
- Risk of Grade 3+ pulmonary toxicity in 20% patients Tx’d
Local control impacts survival in NSCLC

- RT still suboptimal treatment-current treatments local control around 50%
- Lack of LC is clearly correlated with worse survival, death-rate for intra-thoracic similar to metastatic
CHART trial
(Continuous hyperfractionated radiation therapy)

• The trial in non-small-cell lung cancer included 563 patients and showed improvement in survival; 30% of the CHART patients were alive at 2 years compared with 20%.

• In this interim analysis there was a trend for those with more advanced disease (T3 and T4) to show advantage.

• Local control does impact OS!
Dose Escalation

Promising local control rates

122 patients receiving definitive RT, without surgery

Each 1Gy increase in dose

1.25 % improvement in 5 yr LC.

Clinical investigation

High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non–small-cell lung cancer: Long-term results of a radiation dose escalation study


https://doi.org/10.1016/j.ijrobp.2005.02.010
RTOG 0617

- Showed uniform escalation inferior to the standard
- Local control worse in 74 Gy arm than 60 Gy
- Higher heart dose in 74 Gy arm
- Did more harm than good for big bad disease
- Key to identify only patients that would benefit from dose escalation
Patient Identification

• Given standard treatment 50% of NSCLC patients develop LC recurrences

• Data shows dose escalation in all patients leads to worse outcomes

• Strategies to identify patients at high risk of local failure
FDG PET/CT

- Fluorodeoxyglucose is a radiopharmaceutical used in Positron imaging (PET)
- Uptake of FDG is a marker for tissue uptake of glucose
- Uptake is closely correlated with tissue metabolism
Poor tumor response identified early in treatment

Response assessment using 18F-FDG PET early in the course of chemo-radiotherapy is correlated with survival in advanced stage non-small cell lung cancer

Wouter van Elmpt,¹ Michel Öllers,¹ Anne-Marie C. Dingemans,² Philippe Lambin,¹ and Dirk De Ruysscher¹
Baseline vs Mid-treatment FDG-PET

- High uptake = poor OC
- Dutch study 60% patients were classified as early non-responders
- 33% OS compared to responders 92%
- Highlights prevalence of poor tumor response early in TX and impact on patient OC
Netherlands PET Boost Trial

- Discrete dose escalation
- FDG PET avid regions (50% SUV\textsubscript{max})
- Pre-TX assessment
- Individualize target boost based on MLD
- Does not account for patient variability in early response
RTOG 1106

• Tumor dose escalation
• FDG-PET/CT at 40-46 Gy, late in therapy
• Increased toxicity with little survival benefit from dose escalation in responders
• Limited RBE with small # fx left
• Enhancement of radiation-induced inflammatory response signal late in therapy may confound target definition
Earlier Assessment

- Patients at high local failure risk can be selected as early as 2-3 weeks in TX
- Earlier assessment vs at 40-46 Gy earlier dose escalation to regions at risk of local failure
Earlier Assessment

• 2-3 week mid-Tx FDG PET/CT can select for patients who are at high risk of local failure and treat this subpopulation with dose escalation in order to improve cancer control

• Target residual disease
Another step towards personalized medicine!

We Can personalize MEDICINE
Pulmonary Toxicity

- Dose escalation weighed against increased toxicity
- RT can cause a spectrum of changes to the lungs
- Most clinically relevant are radiation pneumonitis and fibrosis
Pulmonary Toxicity

- RP can be mild or severe
- Worsening if patients have underlying diseases such as COPD and emphysema
Pulmonary Toxicity

• Approx 15-40% patients Tx’d develop clinically significant RP with conventional doses

• Symptomatic lung damage is the major impediment to safely dose escalate in the lung!
Current radiation planning methods are unable to accurately predict which patients will develop pulmonary toxicity.
V20 and MLD most common metrics

- Other studies have incorporated other variables into predicting radiation pneumonitis and other pulmonary dysfunction
Recent study of a large group of patients, V20 found to be predictive for radiation pneumonitis
Standard of Practice

- All lung functions equally
- Lung tissue is heterogeneous
- Patients with baseline lung disease
- Gas exchange becomes compromised
- Standard is still MLD and V20
Need a better way!
SPECT/CT $^{99m}$Tc-labeled MAA and DPTA

- VQ scan examine airflow and blood flow in the lungs
- $^{99m}$Tc-labeled DPTA is and aerosol tracer for lung ventilation
- $^{99m}$Tc-labeled MAA (albumin) is a tracer injected for lung perfusion
SPECT/CT

- Prior studies used planar scintigraphy and MAA-SPECT perfusion scans.
- Long term FU provided strong rationale for modeling regional dose reduction RT dose to perfused lung.
SPECT can be used in RT planning

- Modern SPECT/CT allows for accuracy to achieve spatial resolution when identifying regional deficits
- Need to identify and imaging surrogate
Phase II study

- Stage IIB-III NSCLC
- Non-randomized study
- Patients are assigned to 1 of 2 arms
- 60 Gy responders, 74 Gy non-responders
- All patients are receiving chemotherapy
- All imaging is FDA approved
- Endpoint will be 2 year overall survival
General Design

• Study to deliver personalized RT plans
• Combining differential tumor dose escalation
• Based on residual tumor SUV of mid-RT FDG-PET/CT
• Classify patients as responders or non-responders
Pilot Study

• 50 patients
• Improve the therapeutic ratio by limiting pulmonary toxicity
• Defining functional lung on ventilation/perfusion SPECT/CT
• Increasing local control through FDG-PET/CT guided dose escalation
• Predict 72% 2 yr OS
Study ?’s

- Combination of selective tumor dose escalation and functional lung imaging affect outcomes
- Patient selection early FDG PET response can improve survival
Study ?’s

- Whether radiation dose affects functional lung rather than anatomic lung
- Whether image parameters of spatial and functional heterogeneity in lung can select patients who are at high risk for pulmonary toxicity
Patient eligibility
IIB-III Stage NSCLC
definitive RT

Pretreatment imaging
including 4D PET/CT and
V/Q SPECT/CT

Week 1 RT

Week 2 RT

Mid-Tx
FDG
PET/CT

Responder cont with
current plan to 60 Gy

Non-responder dose
esc to 74 Gy

Week cont
to 60
Gy or
plan
DE

Weeks
4-6 RT
to 60
Gy or
74 Gy
<table>
<thead>
<tr>
<th>Study Calendar</th>
<th>Prior to Start of Radiation Treatment</th>
<th>Mid-Radiation Treatment (~24 Gy)</th>
<th>3-Months Post-Radiation Treatment</th>
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<td>Lab Work***</td>
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<td>Pulmonary Function Tests (PFTs) including FEV1</td>
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<td>$^{18}$F-FDG PET/CT Scan#</td>
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<td>X##</td>
<td>X###</td>
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<tr>
<td>SPECT/CT with $^{99m}$Tc-MAA and $^{99m}$Tc-DTPA# performed at UWMC</td>
<td>X</td>
<td>*</td>
<td>X###</td>
</tr>
<tr>
<td>Blood and urine collection for future correlative studies</td>
<td>**</td>
<td>**</td>
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</tr>
</tbody>
</table>

X  Required for study  
*  Optional for study  
**  Optional but highly encouraged  
***CBC with absolute neutrophil count and platelet count. Serum chemistries include BUN, creatinine, sodium, potassium, bicarbonate, chloride, glucose, total protein, total bilirubin, AST, ALT, alkaline phosphatase, and albumin  
#  Scans should ideally be performed in the treatment position with treatment immobilization  
##  The Mid-Radiation Treatment PET/CT scan can be performed when the patient radiation dose is in the range between 20 – 30 Gy.  
###  The three month SPECT/CT and PET/CT scans are permissible between 2-4 months after patient finishes radiotherapy.
Dose

• In agreement with RTOG 0617, mid-treatment FDG PET responders patients will receive 60Gy.

• Dose escalation same but higher dose to 74 Gy redistributed to target FDG-avid regions.
Simulation

- Immobilization made in CT sim in Radiation Oncology
- CT origin is marked at stable 3 point
- Setup documented
Simulation

- Simulation is performed in PET/CT suite in treatment position on Q-Fix couch top
- 4D CT sim with contrast
- Baseline PET/CT acquired
- Physics and Dosimetry present
Lasers
SPECT/CT
PET/CT to 4D average
Standard Uptake Value (SUV)

• Common place in imaging
• Can be used to assess tumor response to Tx
• Radioactivity concentration detected by the PET scanner
Standard Uptake Value (SUV)

- Ratio of image derived radiation concentration and the whole body concentration of injected radioactivity
- Measures metabolic active tumor volume
- Tumor glycolysis
Ventilation scan
Perfusion scan
Perfusion areas contoured in MIM
Study Validation

Medical Physics
The International Journal of Medical Physics Research and Practice

Explore this journal >

Research Article

Functional lung avoidance and response-adaptive escalation (FLARE) RT: Multimodality plan dosimetry of a precision radiation oncology strategy

Eunsin Lee, Jing Zeng, Robert S. Miyaoka, Jatinder Saini, Paul E. Kinahan, George A. Sandison, Tony Wong, Hubert J. Vesselle, Ramesh Rengan, Stephen R. Bowen
Methods

- 8 stage IIB-IIIB NSCLC patients
- FDG-PET/CT and MAA-SPECT/CT planning scans
- Perfused lung objectives MAA-SPECT/CT uptake relative to ITV-lung
- Maintain V20 lung
Methods

• Rx 60 Gy to PTV, 74 Gy to concominant boost vol
• Dose constraints for lungs, heart, cord, and esophagus defined

Plans were optimized for VMAT, proton pencil beam (PBS), and combination of PBS and VMAT (dose escalation)

High dose eval within the SUV_max

Dosimetric differences were evaluated
FDG PET/CT fusion with 4D TPCT
Conventional VMAT and FLARE
PBS and PBS with VMAT
Results

- No unacceptable violations of PTV and normal tissue objectives in the plans
- Compared to reference VMAT plans, FLARE RT achieved higher dose to SUV\text{max}
Results

• Lower doses to perfused lung (7.3 Gy vs 14.9 Gy)
• Higher mean dose to the heart (9.4 Gy vs 5.8 Gy)
• Higher maximum dose to the spinal cord (50.1 Gy vs 44.6 Gy)
Dose Evaluation to highly perfused Lung-CTV_{perf} (imaging surrogate)
Planning 60Gy
Planning objectives

• PTV min 95% cover Rx
• Heart Mean < 35 Gy
• Lungs-CTV MLD, V20, V10, V5
• Lung-CTV_{perf} Mean < 15 Gy
• Spinal cord (canal contoured) Max <50.5 Gy
• Brachial Plexus <66 Gy
• Esophagus Mean < 34 Gy
Perfusion areas added as objectives

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<th>1528</th>
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<td>Dose (cGy)</td>
<td>Volume (%)</td>
<td>Dose (cGy)</td>
<td>Volume (cm³)</td>
<td>Dose (cGy)</td>
<td>Volume at Primary Goal</td>
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<td>6000</td>
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<td>55</td>
<td>6666.1</td>
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<td>Max DVH (%)</td>
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<td>60</td>
<td>500</td>
<td>70</td>
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<td>2000</td>
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<td>30</td>
<td>6000</td>
<td>40</td>
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<td>60</td>
<td>4500</td>
<td>70</td>
<td>6715.1</td>
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<tr>
<td>Heart</td>
<td>Max DVH (%)</td>
<td>4000</td>
<td>100</td>
<td></td>
<td></td>
<td>6715.1</td>
<td>Max</td>
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</table>
Between weeks 2-3 mid-treatment PET/CT

- Patient setup in the treatment position
- Aim to start exam around the time of day of initial PET/CT
- Treatment response assessed
Mid-treatment response

• Assessed by relative changes between baseline and mid-treatment FDG PET SUV
• Incorporate Radiology findings
• Evaluate GTV, nodal volumes and their union
• Panel of metrics
### Lesion:

#### FDG PET: Baseline 08/04/2016 (60 min post injection)

<table>
<thead>
<tr>
<th>#</th>
<th>Location</th>
<th>Metabolic Tumor Volume (mL)</th>
<th>SUV max</th>
<th>SUV mean</th>
<th>SUV peak</th>
<th>TLG (SUV mL)</th>
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<tr>
<td>1</td>
<td>L Lobe + Mediastinum</td>
<td>97.74</td>
<td>6.72</td>
<td>5.01</td>
<td>7.63</td>
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#### FDG PET: 3 WK Mid RT 08/31/2016 (60 min post injection)

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<th>Metabolic Tumor Volume (mL)</th>
<th>SUV max</th>
<th>SUV mean</th>
<th>SUV peak</th>
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<td>59.72</td>
<td>7.00</td>
<td>3.73</td>
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### PERF SPECT: Baseline 08/04/2016

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<th>Lung CTV PERF voxel-weighted</th>
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<td>11.46</td>
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<tr>
<td>Mean EQD2 (Gy)</td>
<td>13.33</td>
<td>9.10</td>
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\[ \Delta (3wk/Baseline-1) (\%) \]
74Gy
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<td>SpinalCord</td>
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<tr>
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<tr>
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<tr>
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16 patients accrual
Special thanks!
Dr. Steve Bowen
References


References
