Predicting Symptomatic Radiation Pneumonitis using Exhaled Nitric Oxide and $^{18}$F-Fluorodeoxyglucose Positron Emission Tomography

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- Dr. Tom Buchholz who initiated this collaboration.
Radiation Pneumonitis

• First reported 1898 (J Bergonie Arch Electr Med (1898) 6:334)

• Incidence 5-50%, 1 - 6 months post-XRT

• V20 correlates with RP. Four fatal cases reported (V20 range 22 to 57). V20 range of severe RP overlaps asymptomatic.

Fatal Radiation Pneumonitis

- Dosimetric parameters set population guidelines but not predictive for individuals.
- Fatal RP rates as high as 46% reported (Allen et al. IJROBP 2006).

Nitric Oxide in the Airway

Nitric Oxide and Thoracic Radiation

• Koizumi JJCO (2001)
  29 lung cancer patients who received thoracic XRT, 5 had elevated NO after XRT 3x > pre-XRT. 3 of the 5 patients had radiation pneumonitis.

• Guerrero IJROBP (2011)
  28 esophagus cancer patients who received 50.4 Gy thoracic XRT with concurrent chemo-therapy, elevated NO in every symptomatic patient.

• McCurdy Radiother Oncol (2011)
  50 esophagus and lung cancer patients who received thoracic XRT. A threshold of 1.4 separated symptomatic from asymptomatic patients.
Exhaled Nitric Oxide

• Non-invasive, inexpensive, point-of-care device.
• FDA approved device available.
• Approved to monitor asthma.
• NIOX Mino optimized for airway NO evaluation in asthmatic patients.

NIOX Mino (Aerocrine)
Exhaled NO Measurement
Study Design

• Respiratory survey and eNO
  – Baseline
  – End of radiotherapy
  – 4-8 week follow-up visit (limited f/u)

• 78 esophagus cancer patients

• Part of NIH funded phase II study to evaluate PMRR
NIH Common Toxicity Criteria for Adverse Events version 4 (CTCAE v4.0) summarized below in Table 1 (CTEP, 2009).

**Table 3. RP¹ grading using NIH Common Toxicity Criteria for Adverse Events version 4.**

<table>
<thead>
<tr>
<th>Grade</th>
<th>None</th>
<th>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</th>
<th>Symptomatic; medical intervention indicated; limiting instrumental ADL</th>
<th>Severe symptoms; limiting self care ADL; oxygen indicated</th>
<th>Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
<td>Symptomatic; medical intervention indicated; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self care ADL; oxygen indicated</td>
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<td>Death</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ADL = activities of daily living.

¹Definition (Pneumonitis): A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.
# Pneumonitis Scores

<table>
<thead>
<tr>
<th>CTCAEv4 Toxicity Grade</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>35 (45)</td>
</tr>
<tr>
<td>1</td>
<td>33 (45)</td>
</tr>
<tr>
<td>2</td>
<td>9 (12)</td>
</tr>
<tr>
<td>3</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*Abbreviation: CTCAEv4 = Common Toxicity Criteria for Adverse Events version 4 pneumonitis toxicity grade.*
## Dosimetric Parameters & Symptoms

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Asymptomatic (n = 68)</th>
<th>Symptomatic (n = 10)</th>
<th>$p^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLD</td>
<td>6.6 (1.0 - 14.7)</td>
<td>6.6 (2.8 - 14.3)</td>
<td>0.83</td>
</tr>
<tr>
<td>$V_5$</td>
<td>32.4 (3.9 - 63.8)</td>
<td>38.6 (13.1 - 64.9)</td>
<td>0.77</td>
</tr>
<tr>
<td>$V_{10}$</td>
<td>22.3 (3.5 - 44.1)</td>
<td>22.1 (8.5 – 47.7)</td>
<td>0.72</td>
</tr>
<tr>
<td>$V_{20}$</td>
<td>12.9 (2.2 - 26.3)</td>
<td>10.2 (4.6 - 32.8)</td>
<td>0.41</td>
</tr>
<tr>
<td>$V_{30}$</td>
<td>6.3 (1.0 - 18.8)</td>
<td>4.1 (1.3 – 20.2)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

**Abbreviations:** MLD = mean lung dose; $V_5$ = percentage of lung receiving $\geq 5$ Gy; $V_{10}$ = percentage of lung receiving $\geq 10$ Gy; $V_{20}$ = percentage of lung receiving $\geq 20$ Gy; $V_{30}$ = percentage of lung receiving $\geq 30$ Gy.

Data presented as median with range in parentheses. P-values calculated using the Mann-Whitney test with $p \leq 0.05$ or less were considered statistically significant.
Distribution of Exhaled Nitric Oxide Ratio

Number of Cases

Ratio Exhaled Nitric Oxide (End RT / Before RT)

Number of Cases

Ratio Exhaled Nitric Oxide (1-2 mos After RT / Before RT)
Grade 3 Pneumonitis

Number of Cases

Ratio Exhaled Nitric Oxide
(End RT / Before RT)
Nitric Oxide Ratio and Dosimetric Parameters

![Graphs showing the relationship between Ratio Exhaled Nitric Oxide and Mean Lung Dose (Gy) and Percentage Lung >20 Gy ($V_{20}$). The graphs demonstrate the correlation between these dosimetric parameters and the ratio of exhaled nitric oxide, with different markers indicating different groups (e.g., none, symptomatic).]
Radiation pneumonitis appears “hot” on PET imaging.

The PET-dose response is linear.

This slope is independent of treated volume.

The slope (PMRR) is a surrogate biomarker of RP, not predictive.

Guerrero 2007 Int J Radiat Oncol Biol Phys
Hart 2008 Int J Radiat Oncol Biol Phys
McCurdy 2010 Int J Radiat Oncol Biol Phys
Pre-treatment PET

SUV of highest 5% of voxels

none

symptomatic
Radiation Dose Response on Post-Treatment PET

![Bar chart showing radiation dose response on post-treatment PET. The x-axis represents PMRR (probably malignant radiation-induced) and the y-axis shows the number of cases. The chart compares cases with and without symptoms, indicated by different colors.](image)
Future Work

- Weekly nitric oxide measurement
- Correlation of airway versus alveolar NO with RP
- Longer follow-up, 6 months post-XRT

Thoracic XRT Patients (MLD > 12 Gy)

XRT

Weekly eNO

↑ eNO

Concurrent trial

Inhaled Beclomethasone

Standard of Care

↔ or ↓ eNO

Observe

6 Monthly post-XRT respiratory symptom assessments

- Detection of chemotherapy-induced lung damage
Conclusions

- Symptomatic patients had higher NOR of $2.1 \pm SD 1.6$ (range 0.4 - 6.7) vs. $0.73 \pm 0.3$ (0.28 - 2.3) ($p<0.0001$).
- Post-treatment FDG-PET dose response ($p=0.28$), mean lung dose (MLD) ($p=0.81$) and volume of lung receiving at least 20 Gy (V20) ($p=0.41$) were not significant.
- Using an NOR threshold of 1.1 gave an associated sensitivity of 60%, specificity of 89%, positive predictive value of 46% and negative predictive value of 93% using a 13% prevalence found in this study.