Predictors of response in patients and radiation-dose impact

Session: An Immuno-oncology Primer for Physicists.
AAPM 2020: Wed July 15th 1:00-2:00 pm EDT

Eric Ford, PhD FAAPM
Professor
University of Washington
Seattle, WA
Disclosures

- None
Learning Objectives

• Understand the fundamental biological underpinnings of the interaction between the immune response and radiation therapy.

• Learn about emerging data connecting immune response to radiation dose and biophysical models that describe this interaction.

• Appreciate how medical physicists might participate in IO efforts in the clinical and research space.
Outline

• RT has a systemic effect on the immune system
• Translates into outcomes
• Major challenge for combined therapies with ICI
Bone Marrow RT and Hematological Toxicity

<table>
<thead>
<tr>
<th>RTOG grade 2+ leukopenia</th>
<th>Odds ratio*</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic BM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{10}$</td>
<td>2.09</td>
<td>1.24–3.53</td>
<td>0.006†</td>
</tr>
<tr>
<td>$V_{20}$</td>
<td>1.40</td>
<td>1.06–1.85</td>
<td>0.017†</td>
</tr>
<tr>
<td>Ilium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{10}$</td>
<td>1.04</td>
<td>0.88–1.22</td>
<td>0.66</td>
</tr>
<tr>
<td>$V_{20}$</td>
<td>1.06</td>
<td>0.96–1.16</td>
<td>0.27</td>
</tr>
<tr>
<td>LSS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{10}$</td>
<td>1.66</td>
<td>0.96–2.88</td>
<td>0.070</td>
</tr>
<tr>
<td>$V_{20}$</td>
<td>1.25</td>
<td>1.01–1.57</td>
<td>0.048†</td>
</tr>
<tr>
<td>Lower pelvis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{10}$</td>
<td>1.35</td>
<td>1.06–1.70</td>
<td>0.013†</td>
</tr>
<tr>
<td>$V_{20}$</td>
<td>1.25</td>
<td>1.04–1.52</td>
<td>0.021†</td>
</tr>
</tbody>
</table>

Effects of RT on the immune system.
Is it all about bone-marrow?
THE EFFECTS OF SEQUENTIAL VERSUS CONCURRENT CHEMOTHERAPY AND RADIOTHERAPY ON SURVIVAL AND TOXICITY IN PATIENTS WITH NEWLY DIAGNOSED HIGH-GRADE ASTROCYTOMA

LAWRENCE KLEINBERG*, STUART A. GROSSMAN,† STEVEN Piantadosi,‡ MICHEL ZELTZMAN,† AND MOODY WHARAM*

Divisions of *Radiation Oncology, †Medical Oncology, and ‡Biostatistics, Johns Hopkins Oncology Center, Baltimore, MD
Hematological Toxicity & RT: Brain

Protocol 1: Sequential

BCNU + Cisplatin → Radiation

4.5 months

Mean WBC Nadir

Sequentially

Cycle
Hematological Toxicity & RT: Brain

**Protocol 1: Sequential**

BCNU + Cisplatin → Radiation

4.5 months

**Protocol 2: Concurrent**

BCNU + Cisplatin → Radiation

3 months

**Graph:**

- **Mean WBC Nadir**
- **Cycle:** 1, 2, 3, Lowest

Sequentially
Hematological Toxicity & RT: Brain

**Protocol 1: Sequential**

BCNU + Cisplatin → Radiation

4.5 months

**Protocol 2: Concurrent**

BCNU + Cisplatin

Radiation

3 months
Systemic effects not explained by dose to bone-marrow
GBM Study: RT + TMZ

<2015
Standard field
• 46 Gy: T1 + T2 + 1-2 cm
• 14 Gy: T1 + 1-2 cm

>2015
Limited-field approach
• 46 Gy: T1 + 1.5 cm
• 14 Gy: T1 + 0.5 cm

Wash U
Acute Severe Lymphopenia

Wash U
# Acute Severe Lymphopenia


Wash U

## Table 2: Overall survival univariate and multivariate Cox regression analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate HR (95% CI)</th>
<th>P</th>
<th>Multivariate HR (95% CI) (n = 160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>1.014 (1.001-1.027)</td>
<td>.034</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Higher KPS</td>
<td>0.987 (0.974-1.001)</td>
<td>.062</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.811 (0.595-1.103)</td>
<td>.182</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian race</td>
<td>0.733 (0.406-1.323)</td>
<td>.302</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EOR GTR</td>
<td>1.395 (1.031-1.886)</td>
<td>.031</td>
<td>1.619 (1.126-2.327)</td>
<td>.009</td>
</tr>
<tr>
<td>STR biopsy</td>
<td>1.395 (1.031-1.886)</td>
<td>.031</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylated MGMT*</td>
<td>0.493 (0.339-0.717)</td>
<td>&lt;.001</td>
<td>0.469 (0.322-0.683)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Higher baseline TLC (100 cells/μL)</td>
<td>0.984 (0.963-1.007)</td>
<td>.166</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher baseline Dex Use (mg/d)</td>
<td>1.040 (1.003-1.079)</td>
<td>.034</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Limited-field RT</td>
<td>1.246 (0.827-1.877)</td>
<td>.293</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT technique (IMRT)</td>
<td>0.964 (0.634-1.464)</td>
<td>.863</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLC &lt; 500 cells/μL at week 6</td>
<td>1.454 (0.988-2.139)</td>
<td>.058</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>TLC &lt; 500 cells/μL at week 12</td>
<td>1.488 (0.806-2.748)</td>
<td>.204</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASL at any time point</td>
<td>1.867 (1.326-2.629)</td>
<td>&lt;.001</td>
<td>1.831 (1.196-2.803)</td>
<td>.005</td>
</tr>
<tr>
<td>GTV</td>
<td>1.005 (0.998-1.007)</td>
<td>.222</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What accounts for this effect?
Lymphocytes: RT exposure & sensitivity

$D_{50} \approx 2 \text{ Gy}$

Lymphocytes: RT exposure & sensitivity

CLINICAL TRANSLATIONAL RESEARCH

The Etiology of Treatment-related Lymphopenia in Patients with Malignant Gliomas: Modeling Radiation Dose to Circulating Lymphocytes Explains Clinical Observations and Suggests Methods of Modifying the Impact of Radiation on Immune Cells

Susannah Yovino, Lawrence Kleinberg, Stuart A. Grossman, Manisha Narayanan, and Eric Ford

Departments of Radiation Oncology and Medical Oncology, and Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
Lymphocytes: RT exposure & sensitivity

![Graph showing the percent blood pool with dose > 0.5 Gy (%) against the number of fractions.](image)

- Dose rate: 600 MU/min
- 8-cm diameter PTV
- 2 Gy/fraction
Lymphocytes: RT exposure & sensitivity

% Blood Pool with Dose > 0.5 Gy

Number of Fractions

- 8-cm PTV
- 2-cm PTV
Is there any independent validation of these effect?
Extracorporeal irradiation of blood
Patients receiving transfusions

Murine model: Focal RT

Piotrowski et al. Oncoimmunology, 7(7), e1445951 (2018)
Johns Hopkins
https://doi.org/10.1080/2162402X.2018.1445951
4Gy x 10 Fractions

T cells (CD45+CD3+)

2Gy x 30 Fractions

CD8+ T cell (CD45+CD3+CD4-)

Piotrowski et al. Oncoimmunology, 7(7), e1445951 (2018)
Radiation Suppresses Lymphocytes

Other clinical data
Lung cancer

Cardiac dose is associated with immunosuppression and poor survival in locally advanced non-small cell lung cancer

Jessika A. Contreras a,1, Alexander J. Lin a,1, Ashley Weiner b, Christina Speirs c, Pamela Samson a, Daniel Mullen a, Jian Campian d, Jeffrey Bradley a, Michael Roach a, Clifford Robinson a,*

a Radiation Oncology, Washington University Medical Center, St. Louis; b Radiation Oncology, The University of North Carolina; c Cancer Center of Hawaii; and d Medical Oncology, Washington University Medical Center, St. Louis, USA
91% of pts >Gr 3 lymphopenia at nadir

Neutrophil to Lymphocyte ratio

Treatment factors

Multivariate analysis (NLR at 4 mo):
Heart V50
Clinical Investigation

Lymphocyte Nadir and Esophageal Cancer Survival Outcomes After Chemoradiation Therapy

Rajayogesh Davuluri, MD,*, 1 Wen Jiang, MD, PhD,†, 1 Penny Fang, MD,†
Cai Xu, MD,† Ritsuko Komaki, MD,† Daniel R. Gomez, MD,†
James Welsh, MD,† James D. Cox, MD,† Christopher H. Crane, MD,†
Charles C. Hsu, MD, PhD,*, and Steven H. Lin, MD, PhD†

*Department of Radiation Oncology, The University of Arizona, Tucson, Arizona; †Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; and ‡Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York

No Gr 4 lymphopenia

Gr 4 lymphopenia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MVA without mean body dose</th>
<th>MVA with mean body dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age at diagnosis, y</td>
<td>1.02</td>
<td>1.00-1.04</td>
</tr>
<tr>
<td>CAD</td>
<td>0.81</td>
<td>0.45-1.44</td>
</tr>
<tr>
<td>DM</td>
<td>1.01</td>
<td>0.59-1.75</td>
</tr>
<tr>
<td>Tumor length</td>
<td>1.04</td>
<td>0.95-1.13</td>
</tr>
<tr>
<td>Tumor location, lower vs mid</td>
<td>2.60</td>
<td>1.08-6.24</td>
</tr>
<tr>
<td>Poor vs moderate diff</td>
<td>0.89</td>
<td>0.58-1.37</td>
</tr>
<tr>
<td>Adeno vs SCC</td>
<td>1.16</td>
<td>0.58-2.30</td>
</tr>
<tr>
<td>Tumor stage III vs I-II</td>
<td>1.27</td>
<td>0.79-2.05</td>
</tr>
<tr>
<td>Having surgery</td>
<td>0.55</td>
<td>0.35-0.88</td>
</tr>
<tr>
<td>Protons vs IMRT</td>
<td>0.29</td>
<td>0.17-0.48</td>
</tr>
<tr>
<td>Mean body dose*</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Induction chemotherapy</td>
<td>1.08</td>
<td>0.65-1.82</td>
</tr>
<tr>
<td>Chemo regimen 2 vs 1</td>
<td>0.69</td>
<td>0.34-1.40</td>
</tr>
<tr>
<td>Chemo regimen 3 vs 1</td>
<td>0.49</td>
<td>0.29-0.85</td>
</tr>
<tr>
<td>Chemo regimen 4 vs 1</td>
<td>1.41</td>
<td>0.64-3.13</td>
</tr>
</tbody>
</table>
Clinical Investigation

Lymphocyte Nadir and Esophageal Cancer Survival Outcomes After Chemoradiation Therapy

Rajayogesh Davuluri, MD,* 1 Wen Jiang, MD, PhD,† 1 Penny Fang, MD, Cai Xu, MD,† Ritsuko Komaki, MD,† Daniel R. Gomez, MD,† James Welsh, MD,† James D. Cox, MD,† Christopher H. Crane, MD,† Charles C. Hsu, MD, PhD,* and Steven H. Lin, MD, PhD†

*Department of Radiation Oncology, The University of Arizona, Tucson, Arizona; †Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; and ‡Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York

Lymphocytes: RT exposure & sensitivity

![Graph showing % Blood Pool with Dose > 0.5 Gy vs Number of Fractions for 8-cm PTV and 2-cm PTV]
Clinical Investigation

Lymphocyte-Sparing Effect of Stereotactic Body Radiation Therapy in Patients With Unresectable Pancreatic Cancer

Aaron T. Wild, MD, * Joseph M. Herman, MD, MSc, † Avani S. Dholakia, MD, † Shalini Moningi, BA, † Yao Lu, ScM, ‡ Lauren M. Rosati, BS, † Amy Hacker-Prietz, PA-C, † Ryan K. Assadi, BS, † Ali M. Saeed, PhD, † Timothy M. Pawlik, MD, MPH, PhD, § Elizabeth M. Jaffee, MD, || Daniel A. Laheru, MD, || Phuoc T. Tran, MD, PhD, † Matthew J. Weiss, MD, § Christopher L. Wolfgang, MD, PhD, § Eric Ford, PhD, ‡ Stuart A. Grossman, MD, || Xiaobu Ye, MD, † and Susannah G. Ellsworth, MD†

Conclusions

• Radiation affects the immune system ... more than bone-marrow irradiation
• Field (tumor) size has an enormous effect
• Modality, technique, dose/fractionation all seem to have some impact
• Impacts overall survival
What is the impact of these effects when combining RT with immune-modulating agents (e.g. inhibitors to CTLA-4 or PDL-1)?
Clinical Investigation

The Impact of Radiation Therapy on Lymphocyte Count and Survival in Metastatic Cancer Patients Receiving PD-1 Immune Checkpoint Inhibitors

Luke R.G. Pike, MD, DPhil,*,† Andrew Bang, MD,*,† Brandon A. Mahal, MD,*,† Allison Taylor, RNP,*,† Monica Krishnan, MD,*,† Alexander Spektor, MD, PhD,*,† Daniel N. Cagney, MD,*,† Ayal A. Aizer, MD,*,† Brian M. Alexander, MD,*,† Osama Rahma, MD,*,† Tracy Balboni, MD,*,† Patrick A. Ott, MD, PhD,*,† F. Stephen Hodi, MD,*,† and Jonathan D. Schoenfeld, MD MPH*

*Brigham and Women’s Hospital and Dana-Farber/Harvard Cancer Center, Boston, Massachusetts;†Harvard Radiation Oncology Program, Massachusetts General Hospital, Boston, Massachusetts; and Department of Radiation Oncology, Princess Margaret Cancer Centre, Toronto, Ontario, Canada

Int J Radiation Oncol Biol Phys, Vol. 103, No. 1, pp. 142–151, 2019
Pts receiving RT before ICI
Pts receiving RT before ICI
Fraction surviving

Days from PD-1 ICI Onset

ALC > 500
ALC < 500

P < .0001
The Future (physics)

• Small fields
• Hypofractionation
• Control dose distribution
• Fast delivery
• Need good models!
Thank you!

eford@uw.edu