Mapping Anatomically Sensitive Bone Marrow Regions

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Hematopoietic Functions of Bone Marrow

- White Blood Cells
  - Lymphocytes
  - Mast Cells
  - Myeloblasts
  - Immune System
- Red Blood Cells
  - Oxygen Delivery
- Megakaryocytes
  - Platelets (Clotting)

Radiosensitivity of Bone Marrow
Significance to Radiation Oncologists

- Therapeutic Gain
  - Total Body Irradiation
  - Total Nodal Irradiation
- Complications
  - Myelosuppression with Magna Fields (e.g. Lymphoma)
  - Chemo-RT (e.g. Pelvic Malignancies)
- Myelosuppression – Barrier to Optimal Treatment Delivery
- Reduce BM Injury → Improve Treatment

Chemotherapy Increases Grade 3-4 Myelosuppression

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>RT</th>
<th>ChemoRT</th>
<th>Odds Ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>4%</td>
<td>6%</td>
<td>1.5</td>
<td>0.06</td>
</tr>
<tr>
<td>WBC</td>
<td>8%</td>
<td>16%</td>
<td>2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelets</td>
<td>0%</td>
<td>2%</td>
<td>3.7</td>
<td>0.004</td>
</tr>
<tr>
<td>Any Hematologic</td>
<td>1%</td>
<td>25%</td>
<td>8.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Green et al. Lancet 2001

Outcomes Improved with More Chemotherapy

Peters et al. JCO 2000
Nugent et al. Gyn Oncol 2010
Improved Outcomes with Multi-agent Chemotherapy

- Pathologic CR: 78% vs. 55%  $p=.02$
- 3-year PFS: 74% vs. 65%  $p=.03$
- Grade 3-4 toxicity: 87% vs. 46%  $p<.01$
- Predominant Toxicity = Hematologic

Dueñas-González et al. JCO 2011

Less Hematologic Toxicity with IMRT

Brixey et al. IJROBP 2002

IMRT vs. Conventional Techniques

Brixey et al. IJROBP 2002
**IMRT**

**AP/PA**

**4F-Box**

Meli et al. IJROBP 2008

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Hematologic toxicity as a function of bone marrow volume irradiated to >20 Gy

Rose et al. IJROBP 2011

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Longitudinal Analysis of Myelosuppression

Zhu et al. ASTRO 2012
**Hypothesis:** Radiation Technologies Could Improve Therapeutic Ratio of ChemoRT

![Diagram showing IMRT, IGRT, Target Localization, Normal Tissue Damage, Toxicity, Intensity, Tumor Control, and Chemo]

**Bone Marrow Dose-Volume Constraints**
- Endpoint: Grade ≥ 2 neutropenia
- **Mell IJROBP 2006:**
  - $V_{20} > 75\%$ – 69% $p < 0.01$
  - $V_{20} \leq 75\%$ – 24%
- **Rose IJROBP 2011:**
  - $V_{20} > 76\%$ – 58% $p = 0.001$
  - $V_{20} \leq 76\%$ – 22%
- Recommended Constraints:
  - $V_{10} \leq 90\%$, $V_{20} \leq 75\%$

**Heterogeneity of Bone Marrow**

![Images of red and yellow marrow]
Properties of Bone Marrow

**Red Marrow**
- Lower fat content (20-40%)
- Higher cellularity
- Higher Hematopoietic Activity

**Yellow marrow**
- Higher fat content (80-95%)
- Lower cellularity
- Lower hematopoietic activity

Distribution of Red Bone Marrow

~50% of red marrow located within pelvis and lumbar spine in adults

Bone Marrow Imaging - CT
Bone Marrow Imaging – Scintigraphy / SPECT

- Indium-111
- Tc-99m Sulfur Colloid

Sacks et al. Cancer 1978
Roeske et al. Radiother Oncol 2003

Bone Marrow Imaging - MRI

- Acute increases in T1 signal in response to radiation therapy
- Conversion of red to yellow marrow
- May be used as a measure of degree of bone marrow injury

Functional Bone Marrow Imaging – Quantitative MRI (IDEAL)

Pre-Treatment  Mid-Treatment  Post-Treatment
IDEAL / Fat Fraction Mapping

- Fat and water have different chemical shifts
- Gradient echo
- Iterative Decomposition Echo
  Asymmetry and Least Squares
  Estimation

Functional Bone Marrow Imaging – Quantitative MRI (IDEAL)

Changes in Fat Fraction During Chemoradiation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Baseline</th>
<th>Mid-treatment</th>
<th>Post-treatment</th>
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<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>53</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>72</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>71</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>68</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>38</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>46</td>
<td>65</td>
<td>-</td>
</tr>
<tr>
<td>Avg</td>
<td>46</td>
<td>61</td>
<td>72</td>
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</tbody>
</table>
Spatial Analysis

Pre-Treatment  18 Mos. Post-Treatment

<table>
<thead>
<tr>
<th>Vertebra</th>
<th>Mean Dose (Gy)</th>
<th>Fat Fraction % Pre-</th>
<th>Fat Fraction % Med</th>
<th>Fat Fraction % Post</th>
<th>Fat Fraction % 1.5yr Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>T11</td>
<td>&lt;1</td>
<td>32</td>
<td>42</td>
<td>45</td>
<td>39</td>
</tr>
<tr>
<td>T12</td>
<td>&lt;1</td>
<td>32</td>
<td>36</td>
<td>38</td>
<td>42</td>
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<tr>
<td>L1</td>
<td>&lt;1</td>
<td>36</td>
<td>49</td>
<td>51</td>
<td>47</td>
</tr>
<tr>
<td>L2</td>
<td>&lt;1</td>
<td>29</td>
<td>41</td>
<td>55</td>
<td>53</td>
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<tr>
<td>L3</td>
<td>3.55</td>
<td>31</td>
<td>53</td>
<td>75</td>
<td>62</td>
</tr>
<tr>
<td>L5</td>
<td>40.9</td>
<td>83</td>
<td>83</td>
<td>85</td>
<td></td>
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<tr>
<td>FAT</td>
<td>&lt;1</td>
<td>90</td>
<td>91</td>
<td>91</td>
<td>85</td>
</tr>
</tbody>
</table>

Histochemical Analyses

CADAVERIC VERTEBRAL SPECIMEN

FOLCH METHOD
Functional Bone Marrow Imaging – PET

- FDG-PET
- FLT-PET

Blebea et al. Semin Nuc Med 2007
Hayman et al. IJROBP 2011

Functional Image-Guided BM-Sparing

- FDG-PET + IDEAL
- FLT-PET

Liang et al. IJROBP 2012
McGuire et al. Radiother Oncol 2011

Functional bone marrow in cervical cancer patient
Impact of Functional Imaging on Active Bone Marrow Sparing

Image-Guided IMRT  Non-Image-Guided IMRT

Liang et al. IJROBP 2012

68Ga-DTPA-Mannosyl-Dextran PET/CT of Rabbit

Courtesy: David Vera, Ph.D.

Radiation Effects on Active BM

- 26 women with cervical cancer
- All underwent 18F-FDG PET/CT prior to treatment
- All underwent serial CBCs
- Pelvic RT 45-50.4 Gy + weekly cisplatin

Rose et al. IJROBP 2012
Radiation to "active" bone marrow correlated with significant decrease in WBC, ANC, Hgb, and Plt.
Radiation to "inactive" marrow not correlated with changes.
18F-FDG-PET may help identify regions of "active" bone marrow in which radiation dose is more likely to result in hematologic toxicity.

Spatial information-preserving toxicity model

\[ P(T) = k D^a V^b \]

- \( P(T) \) = probability of toxicity, \( k \) = constant, \( D \) = dose factor, \( V \) = volume factor, and \( a \) and \( b \) are parameters.
- \( D = d^w \) where \( d \) is the vector defining the dose distribution in bone marrow, \( w \) is the vector defining the distribution of a weighting factor (e.g., given by functional image).
- \( V = w^C = (d > c) \times w = (d > c) \), for threshold dose level \( c \).
- \( P(T; d, w, k, a, b, c) = k (d^w)^a (w^c)^b \)

\[ \log(P(T)) = k + a \log(d^w) + b \log((d > c) \times w) \]

Given \( d, w, P(T) \), we can estimate model parameters \( k, a, b \).

Critical Bone Marrow Subregions

- All bone marrow is not created equal.
- Which regions matter most?
- Two approaches:
  - "Bottom-up": Image \( \rightarrow \) spare
  - "Top-down": Statistical mapping \( \rightarrow \) spare
Mapping Critical Bone Marrow

Bottom Up  Top Down

New Instance  Canonical Template

Deformable Image Registration

High Dimensional Data Analysis

Liang et al. IJROBP 2010
Differencing Mean Vectors

Liang et al. IJROBP 2010

Dimensionality Reduction

\[
\hat{y} = \hat{b}_n - \hat{\beta} \cdot \hat{E}^T \cdot d = \hat{b}_n - \hat{\gamma} \cdot d
\]

Statistical “Images”

Image Subtraction  PCA
Determining Dose Effects in Active Bone Marrow Subregions

Obstacles / Pitfalls

- Impact of Compensatory Hematopoiesis
- Imaging Test / Re-Test Uncertainties
- Residual Spatial Uncertainties
  - Resolution of PET
  - Registration Errors
- Correct Model Specification?
- Controlled Clinical Trials
Prospective BM-Sparing IMRT Studies

- Prospective Pilot Study
  - 30 patients with cervical/anal cancer
  - FDG-PET + IDEAL
  - Published - Liang IJROBP 2012
  - IG-BMS IMRT dosimetrically and clinically feasible
- Phase I Trial of IMRT with Cisplatin and Gemcitabine
  - Locoregionally Advanced Cervix Ca
  - N=4 of 15

INTERTECC - PHASE II/III TRIAL OF IMRT FOR CERVICAL CANCER

- UCSD
  - Univ. Hradec Kralove (Czech Republic)
  - Xijing Medical Center (China)
  - Asan Medical Center (S. Korea)
  - Tata Hospital (India)
  - 7 other sites cREDENTIALED

INTERTECC – Image-Guided BM-Sparing IMRT Sub-Study

- FLT-PET-guidance
- Serial IDEAL
Protons vs. IMRT for BM Sparing

Song et al. JACMP 2010

Center for Advanced Radiotherapy Technologies (CART)