Mapping Anatomically Sensitive Bone Marrow Regions

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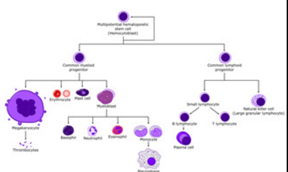
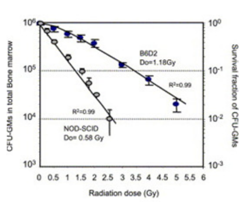
Hematopoietic Functions of Bone Marrow

- 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

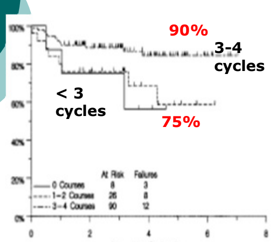
- Therapeutic Gain
  - Total Body Irradiation
  - Total Nodal Irradiation
- Complications
  - Myelosuppression with Magna Fields (e.g. Lymphoma)
  - Chemo-RT (e.g. Pelvic Malignancies)
- Myelosuppression – Barrier to Optimal Treatment Delivery
- Reduce BM Injury → Improve Treatment

Chemotherapy Increases Grade 3-4 Myelosuppression

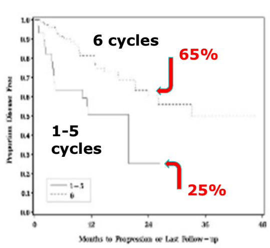
Toxicity	RT	ChemoRT	Odds Ratio	p
Hemoglobin	4%	6%	1.5	0.06
WBC	8%	16%	2.2	<0.001
Platelets	0%	2%	3.7	0.004
Any Hematologic	**1%**	**29%**	**8.6**	**<0.001**

Green et al. Lancet 2001

Outcomes Improved with More Chemotherapy



Peters et al. JCO 2000



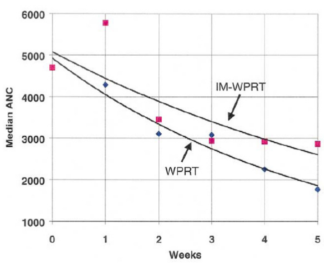
Nugent et al. Gyn Oncol 2010

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

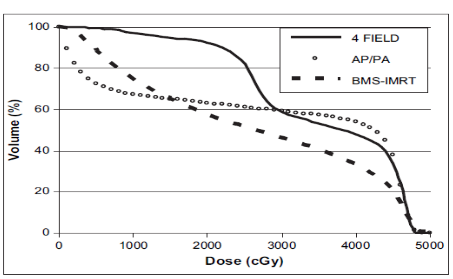
Dueñas-González et al. JCO 2011

Less Hematologic Toxicity with IMRT

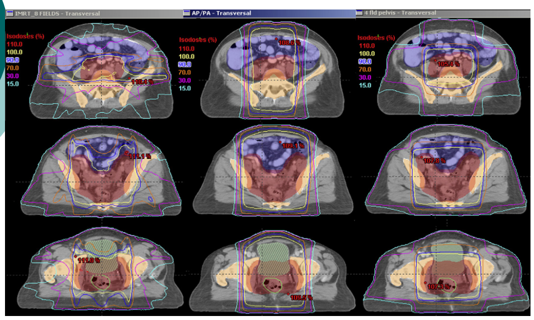


Brixey et al. IJROBP 2002

IMRT vs. Conventional Techniques

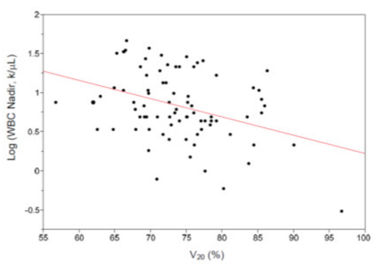


IMRT AP/PA 4F-Box



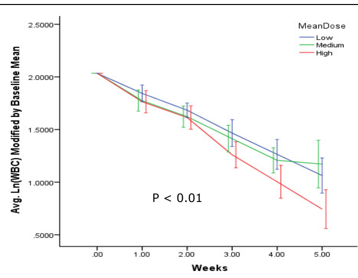
Mell et al. IJROBP 2008

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



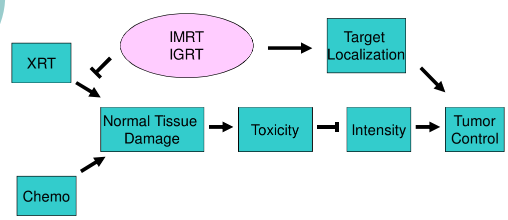
Rose et al. IJROBP 2011

Longitudinal Analysis of Myelosuppression



Zhu et al. ASTRO 2012

Hypothesis: Radiation Technologies Could Improve Therapeutic Ratio of ChemoRT



Bone Marrow Dose-Volume Constraints

- Endpoint: Grade ≥ 2 neutropenia
- *Mell IJROBP 2006*:
  - V_{20} > 75% – 69%
  - V_{20} ≤ 75% – 24%

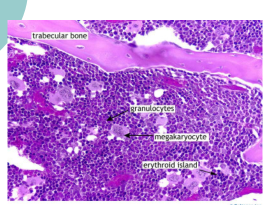
  p<0.01
- *Rose IJROBP 2011*:
  - V_{20} > 76%– 58%
  - V_{20} ≤ 76%– 22%

  p=0.001
- Recommended Constraints:

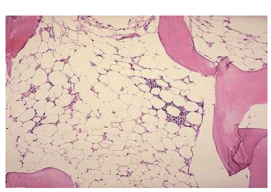
  V_{10} ≤ 90%, V_{20} ≤ 75%

Heterogeneity of Bone Marrow

Red Marrow



Yellow Marrow



Properties of Bone Marrow

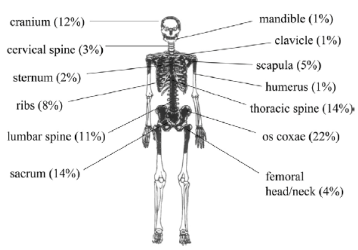
Red Marrow

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

Yellow marrow

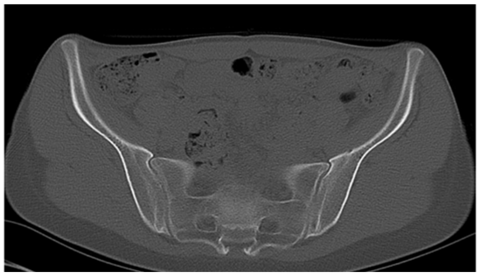
- Higher fat content (80-95%)
- Lower cellularity
- Lower hematopoietic activity

Distribution of Red Bone Marrow



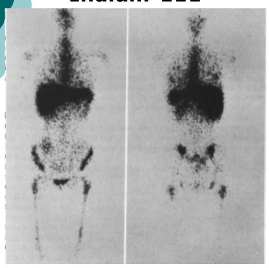
~50% of red marrow located within pelvis and lumbar spine in adults

Bone Marrow Imaging - CT



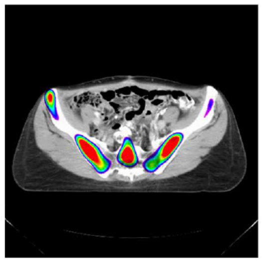
Bone Marrow Imaging – Scintigraphy / SPECT

Indium-111



Sacks et al. Cancer 1978

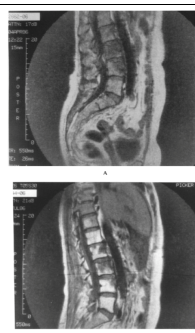
Tc-99m Sulfur Colloid



Roeske et al. Radiother Oncol 2003

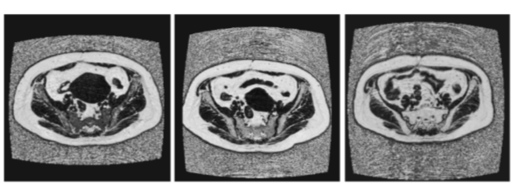
Bone Marrow Imaging - MRI

- 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



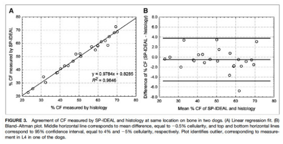
Functional Bone Marrow Imaging – Quantitative MRI (IDEAL)

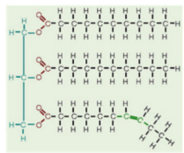
Pre-Treatment | Mid-Treatment | Post-Treatment



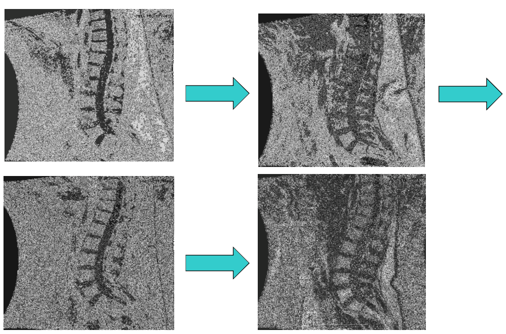
IDEAL / Fat Fraction Mapping

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





Functional Bone Marrow Imaging – Quantitative MRI (IDEAL)

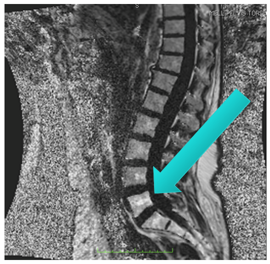


Changes in Fat Fraction During Chemoradiation

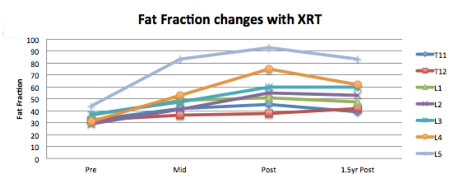
Patient	Baseline	Mid-treatment	Post-treatment
1	37	53	72
2	60	72	78
3	45	71	74
4	59	68	-
5	27	38	63
6	46	65	-
Avg	**46**	**61**	**72**

Spatial Analysis

Pre-Treatment | **18 Mos. Post-Treatment**

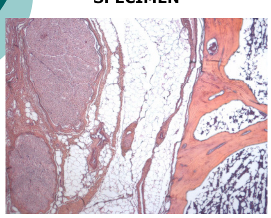


Vertebra	Mean Dose (Gy)	Fat Fraction % Pre	Fat Fraction % Mid	Fat Fraction % Post	Fat Fraction % 1.5yr Post
T11	<1	32	42	45	39
T12	<1	32	36	38	42
L1	<1	36	49	51	47
L2	<1	29	41	55	53
L3	1.03	37	47	60	60
L4	3.55	31	53	75	62
L5	40.9	44	83	93	83
FAT	<1	90	91	91	85

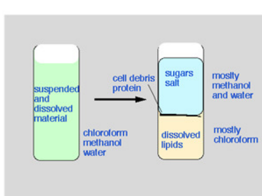


Histochemical Analyses

CADAVERIC VERTEBRAL SPECIMEN

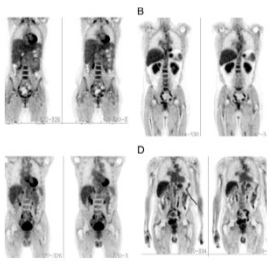


FOLCH METHOD



Functional Bone Marrow Imaging – PET

FDG-PET



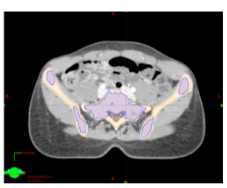
FLT-PET

Blebea et al. Semin Nuc Med 2007

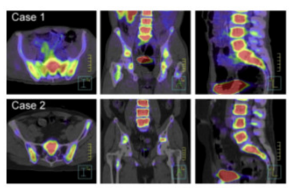
Hayman et al. IJROBP 2011

Functional Image-Guided BM-Sparing

FDG-PET + IDEAL



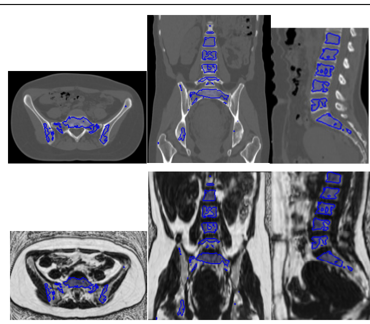
FLT-PET



Liang et al. IJROBP 2012

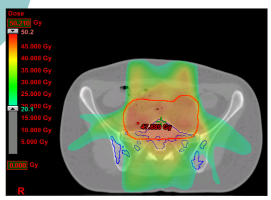
McGuire et al. Radiother Oncol 2011

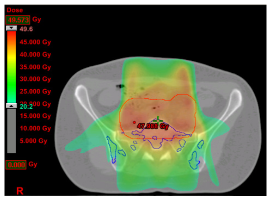
Functional bone marrow in cervical cancer patient



Impact of Functional Imaging on Active Bone Marrow Sparing

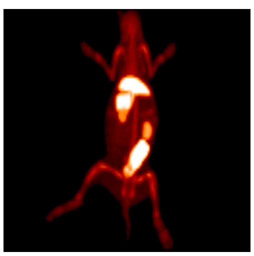
Image-Guided IMRT | **Non-Image-Guided IMRT**





Liang et al. IJROBP 2012

^{68}Ga-DTPA-Mannosyl-Dextran PET/CT of Rabbit



Courtesy: David Vera, Ph.D.

Radiation Effects on Active BM

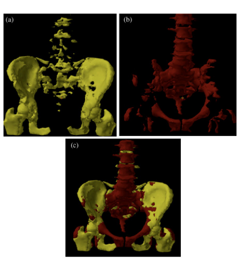


Fig. 1. Representative distribution of active (red) and inactive (yellow) bone marrow.

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

Rose et al. IJROBP 2012

Rose et al. IJROBP 2012

Table 3 Univariable linear regression of hematologic nadirs as a function of mean radiation dose to active and inactive bone marrow

	BM_{ACT} Mean dose (Gy)			BM_{INACT} Mean dose (Gy)		
Hematologic nadir	β	95% CI	*p*	β	95% CI	*p*
Log(WBC) (k/μL)	−0.04	−0.07 to −0.01	0.009*	−0.01	−0.06 to 0.05	0.84
Log(ANC) (k/μL)	−0.05	−0.08 to −0.02	0.006*	−0.03	−0.10 to 0.04	0.39
Hemoglobin (g/dL)	−0.16	−0.27 to −0.05	0.01*	−0.09	−0.31 to 0.14	0.45
Platelet (k/μL)	−6.16	−9.37 to −2.96	<0.001*	−3.47	−10.44 to 3.50	0.34

Abbreviations: BM_{ACT} = active bone marrow; BM_{INACT} = inactive bone marrow; β = regression coefficient (*e.g.*, 1 Gy increase in mean BM_{ACT} dose corresponds to a reduction in platelet count of 6.16 k/μL); CI = confidence interval; WBC = white blood cell count; ANC = absolute neutrophil count.

* Statistically significant.

- Radiation to "active" bone marrow correlated with significant decrease in WBC, ANC, Hgb, and Plt
- Radiation to "inactive" marrow not correlated with changes
- ^{18}F-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 & b are parameters.

D = **d*****w** — **d** is the vector defining the dose distribution in bone marrow; **w** vector defining the distribution of a weighting factor (e.g. given by functional image)

V = **v*****w** = (**d** > c) * **w** **v** = (**d** > c), for threshold dose level c

$P(T;\, \mathbf{d},\mathbf{w},k,a,b,c) = k\, (\mathbf{d}*\mathbf{w})^a\, ((\mathbf{d} > c)\, *\mathbf{w})^b$

$\log(P(T)) = k + a \log(\mathbf{d}*\mathbf{w}) + b \log((\mathbf{d} > c)\, *\mathbf{w})$

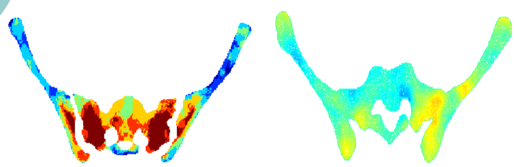
Given **d, w,** P(T), we can estimate model parameters k, a, b

Critical Bone Marrow Subregions

- All bone marrow is not created equal
- Which regions matter most?
- Two approaches:
  - "Bottom-up": Image → spare
  - "Top-down": Statistical mapping → spare

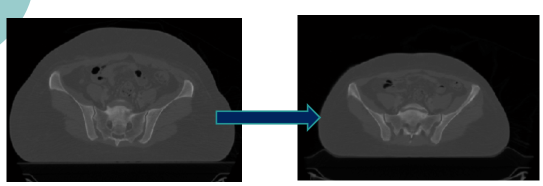
Mapping Critical Bone Marrow

Bottom Up **Top Down**



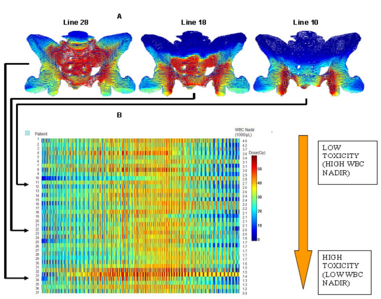
Mapping Critical Bone Marrow

New Instance **Canonical Template**



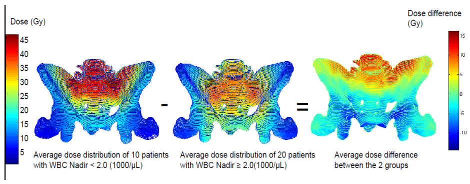
Deformable Image Registration

High Dimensional Data Analysis



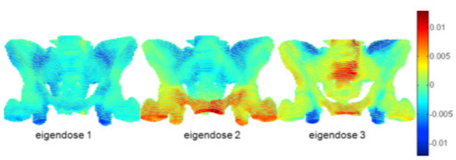
Liang et al. IJROBP 2010

Differencing Mean Vectors



Liang et al. IJROBP 2010

Dimensionality Reduction

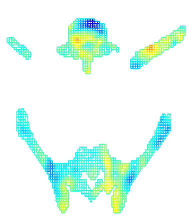


$$\widehat{y} = \widehat{b}_o - \widehat{\beta} \cdot \widehat{E^*} \cdot \boldsymbol{d} = \widehat{b}_o - \widehat{\mathbf{v}} \cdot \boldsymbol{d}$$

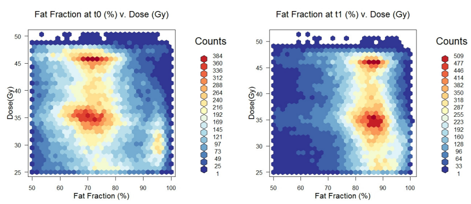
Statistical “Images”

Image Subtraction

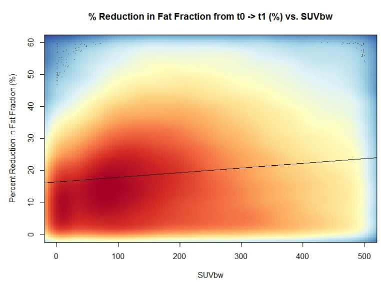
PCA



Determining Dose Effects in Active Bone Marrow Subregions



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***

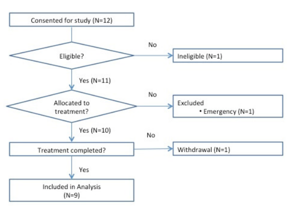
45

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

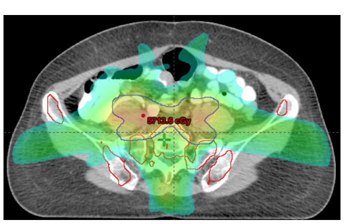
INTERTECC - PHASE II/III TRIAL OF IMRT FOR CERVICAL CANCER

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

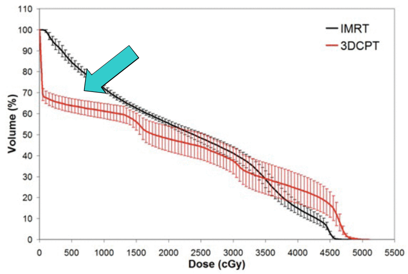


INTERTECC – Image-Guided BM-Sparing IMRT Sub-Study

- FLT-PET-guidance
- Serial IDEAL



Protons vs. IMRT for BM Sparing



Song et al. JACMP 2010

Center for Advanced Radiotherapy Technologies (CART)