

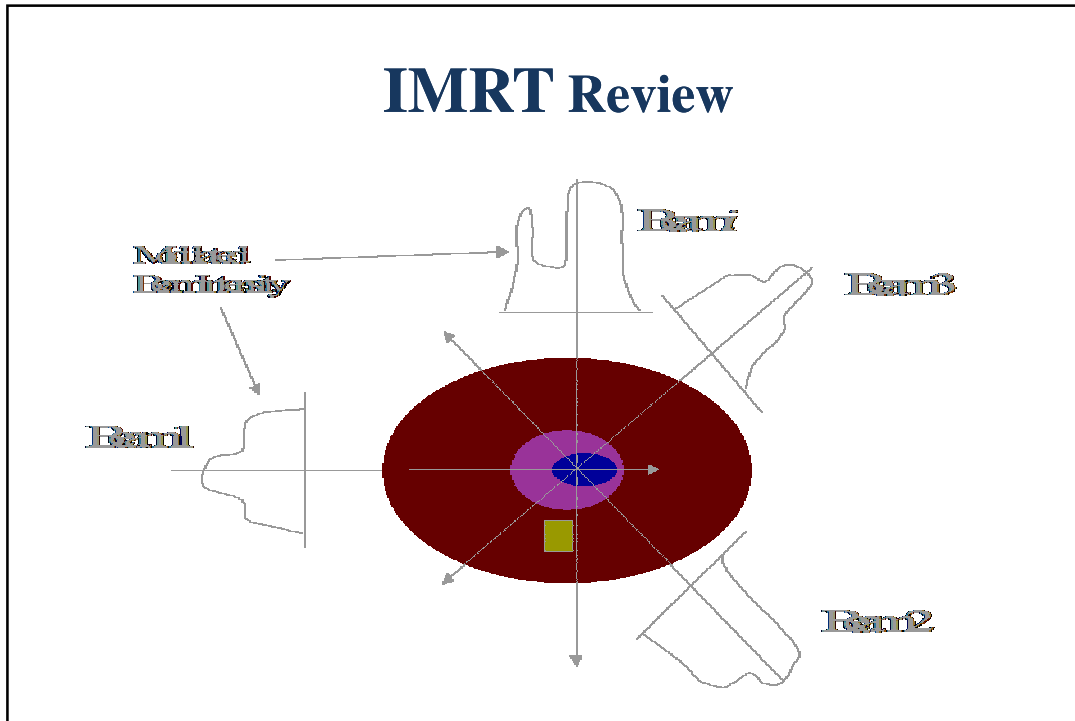
Bioanatomic IMRT

Mike Munley, Ph.D.
Department of Radiation Oncology
Wake Forest University School of Medicine
Winston-Salem, NC



IMRT Review

- **Automated computer-based technique that attempts to design and deliver very conformal radiation distributions**
- **Multileaf collimator (MLC) used to “paint” dose where desired intensity maps**
- **Combination of multiple fields (≥ 3) used to “sculpt” the dose distribution**



IMRT Objectives

- More accurately define/administer dose distributions
 - conform to complex 3D shape of target
 - deliver uniform dose to that complex shape
 - or
 - deliver non-uniform dose to meet an objective (i.e. bioanatomic and/or concomitant boost)
- Maximize the dose to the target
- Minimize the dose to normal tissues
- Optimize planning, treating, QA strategies for efficiency

Biology of IMRT

Simultaneously desire to:

Tumor Control Probability (TCP)

- increased target tissue dose

Normal Tissue Complication Probability (NTCP)

- reduced normal tissue dose

In order to:

Therapeutic Ratio

Current Radiation Treatment Planning

- Conventional anatomic imaging
 - Does not adequately image tumor anatomy
 - Ignores tumor biology
- Conventional radiation treatment planning and treatment delivery
 - Ignores tumor biology
 - Assumes dose homogeneity is preferable over dose inhomogeneity
- It is unlikely present approaches will result in significant improved outcomes ... **it's time for a paradigm shift**
BIOANATOMIC APPROACH



Paradigm Shift for Radiation Oncology

shift to.....

- Biological and Molecular Target Volumes
- Bio-physical Modeling
- Custom Dose Coverage of Target Volumes

made possible by.....

- *Quantitative* Use of Bio-molecular Images
- High-Tech Radiation Treatment: IMRT

Bioanatomic Imaging and Treatment

- Can tumor biology be imaged?
 - MRI, fMRI, MRS, PET, SPECT
- Can image-based tumor biology direct “biologically correct” cancer therapy
- RTP has been/is anatomically based
- What will molecular images contribute?

Elements of the Bioanatomic Imaging in RT

- Advanced imaging tools
 - CT-PET Scanner/Simulator
 - MRI Scanner/Simulator
- Sophisticated image integration tools for image registration
- Quantify biologic imaging data
- Define relationship between quantitative biologic imaging data and radiation dose

Bioanatomic Imaging for RTP

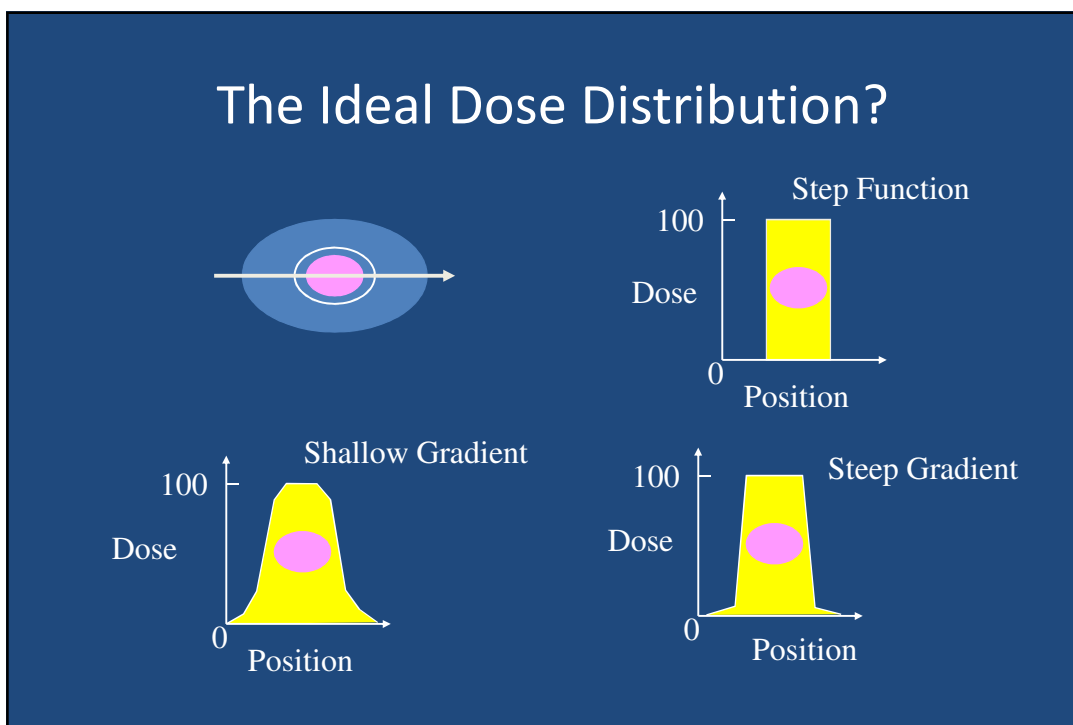
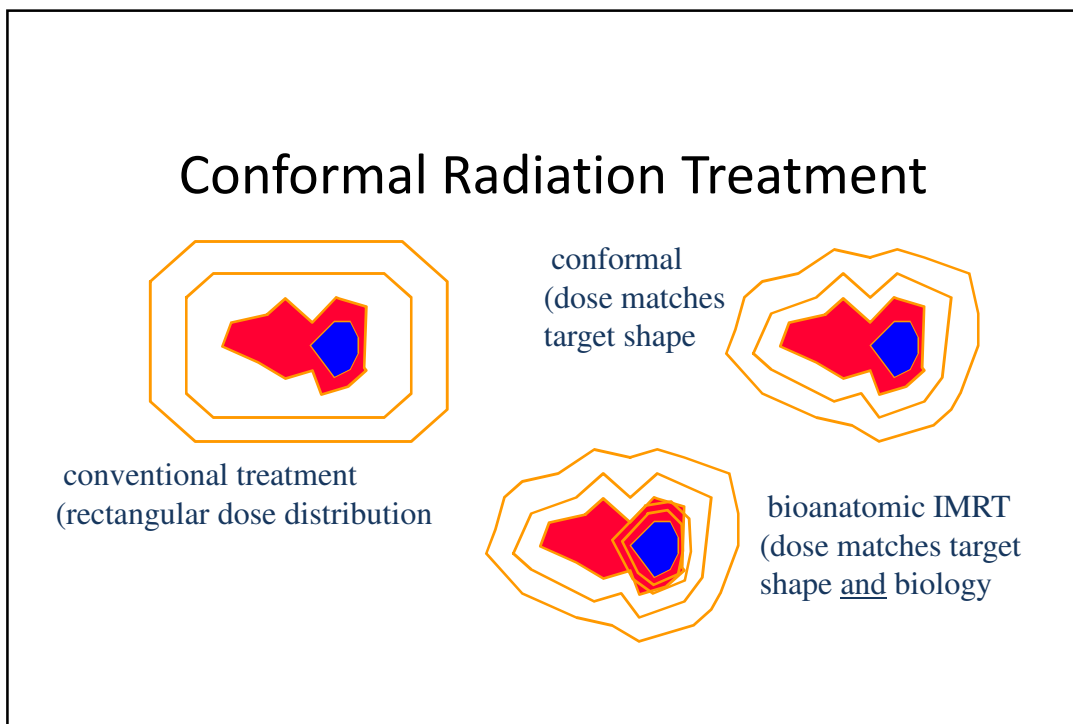
- | | |
|---|--|
| <ul style="list-style-type: none"> • MRI <ul style="list-style-type: none"> – MR Spectroscopic Imaging <ul style="list-style-type: none"> • Proton <ul style="list-style-type: none"> – Choline/creatine ratio – Choline/NAA ratio – Choline/citrate ratio • Other Nuclei (Na, P, F) – Functional MRI <ul style="list-style-type: none"> • BOLD imaging • Contrast enhanced dynamic MR • Diffusion MR • Perfusion MR – Novel contrast agents | <ul style="list-style-type: none"> • PET <ul style="list-style-type: none"> – F-18 FDG: glucose utilization (proliferation) – C-11 Methionine: amino acid (protein) synthesis – C-11 Thymidine: nucleic acid (DNA) synthesis – F-18 Misonidazole and Cu-ATSM: hypoxia and angiogenesis – O-15: blood flow (water) and oxygen delivery/utilization – Others: receptor imaging, reporter gene imaging, ...more |
|---|--|

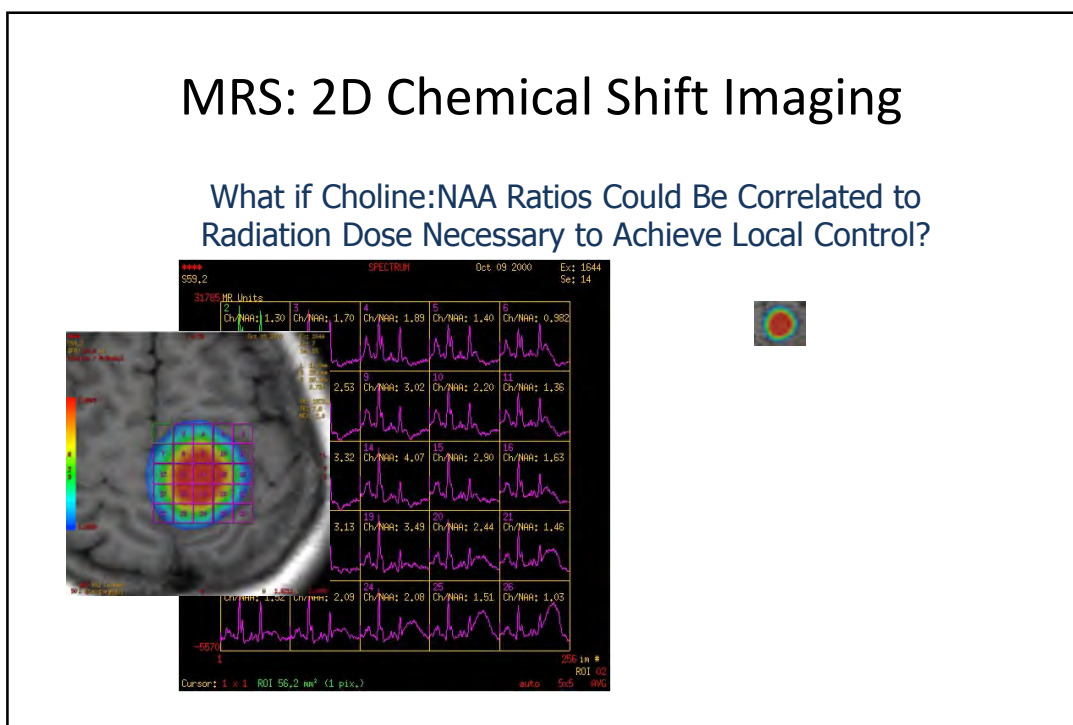
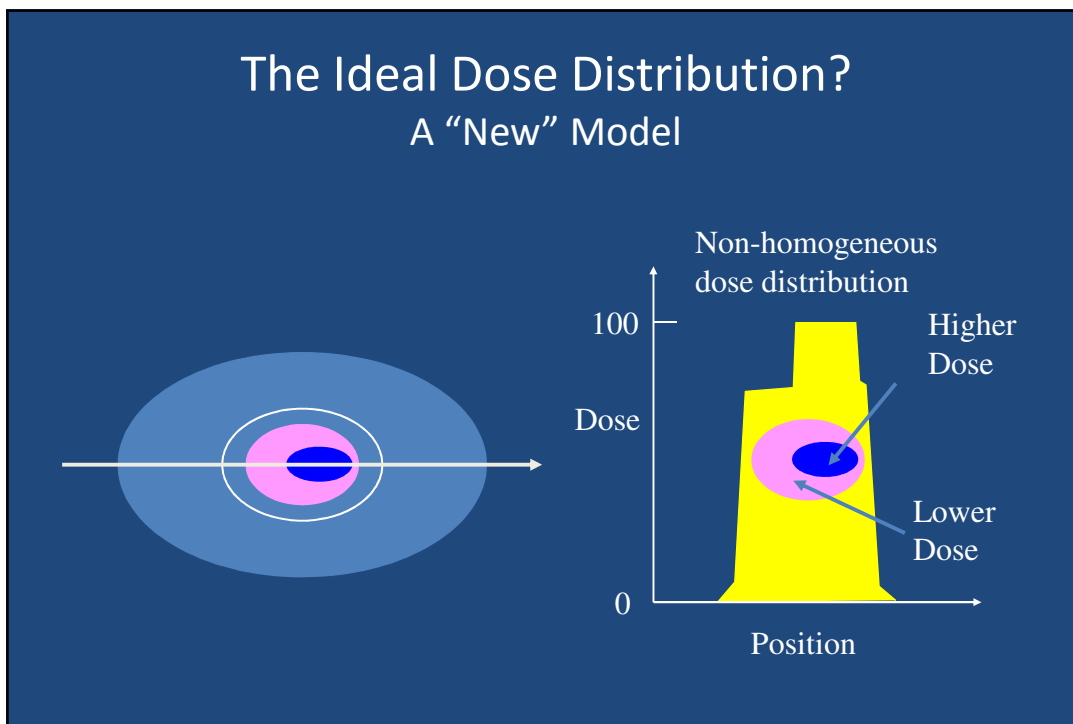
Elements of the Bioanatomic RTP Process

- Inverse radiation treatment planning system with optimization tools (IMRT)
 - Dose Volume Histogram analysis
 - Dose Function Histogram analysis
- Contemporary linear accelerator with dMLC
- Electronic imaging (QA)
- Clinical trials: Phase I, II, and III

Biological Models

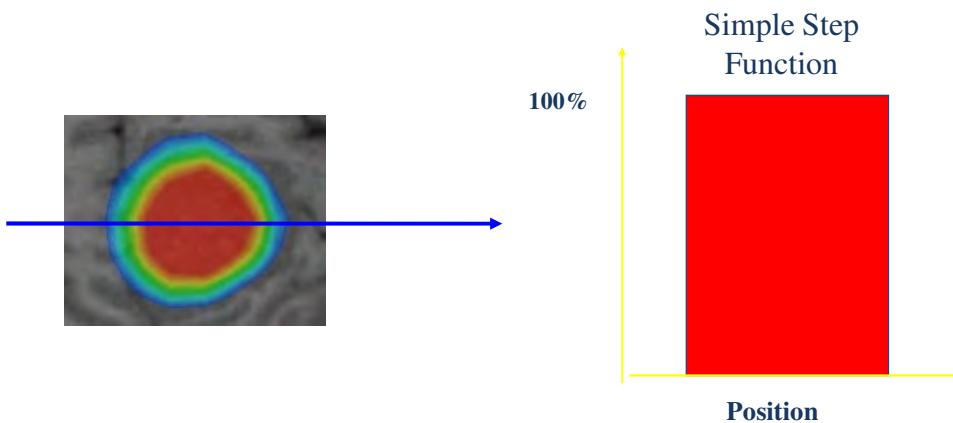
- Mathematical Representations of Effect
- Model Generation
 - Theoretical models: bio-physio-molecular principles
 - Micro models: fit of bio-molecular observations
 - Macro models: fit of clinical observations
- Model Application
 - Predictive models: guidance of therapeutic decisions
 - Predictive models: estimation of prognosis/injury





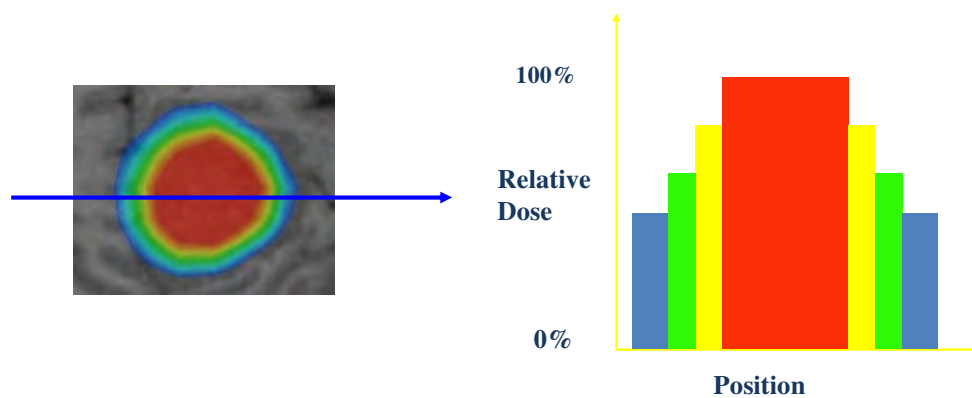
MRS: 2D Chemical Shift Imaging

Instead of a Conventional Dose Distribution That Looks



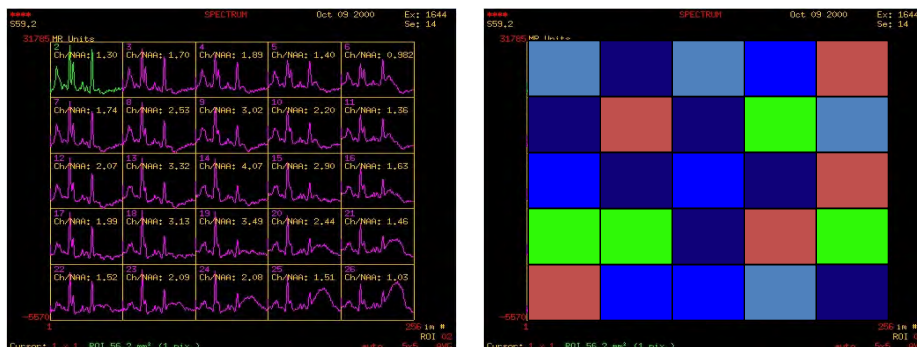
MRS: 2D Chemical Shift Imaging

The Dose Distribution Would Look Like



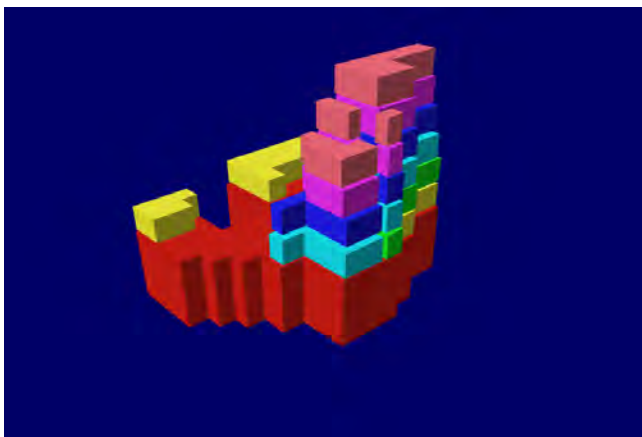
MRS: 2D Chemical Shift Imaging

Correlate 3D Chemical Shift Imaging of Choline:NAA Ratios to the 3D Radiation Dose Distribution Necessary



New Concept in RTP: Bioanatomic IMRT

Dose Distributions Will Eventually Look Like This



Challenges

- Image quantitation/interpretation
- Image registration accuracy
- Patient positioning/motion/warping
- Need precise patient setup for every fraction
- Heterogeneous target dose
- Depends on complete knowledge of partial volume organ tolerances and accurate contouring
- Increased physics and dosimetry effort
- Integral dose effects?
- Shielding requirements (IMRT+biologic dose escalation)
- Demonstrate clinical benefit for multiple disease sites

General Method Summary

- Traditional RT treatment strategies are based on physical parameters (i.e. dose)
- Proposed methodology based on biologic data
- Structure definition using biologic information
- Biologic optimization for IMRT treatment planning
- Biologic dose response models to predict tumor response and symptomatic injury prior to RT

Bioanatomic Radiation Treatment Planning

Related Clinical Studies

Bioanatomic Imaging: MRS UCSF Experience

- Low-grade gliomas (Pirzkall et al, IJROBP 53:1254-1264, 2002)
 - MRS volume > T2MR volume in 9/20 pts by median 2.3cc (range, 1.4-5.2cc)
 - Diameter MRS tumor volume up to 2.2cm larger than T2MR volume
- High-grade gliomas (22 AAs, 12 GBMs)
 - T2MR underestimates volume of microscopic disease in 95% AAs and 75% GBMs
 - MRS volume > T2MR volume by average diameter 9mm (range, 3-12mm) and average volume of 5cc

Bioanatomic Imaging: MRS UCSF Experience (continued)

- High-grade gliomas
 - T1MR underestimates volume of gross disease in AA and GBM
 - AA – average extension MRS volume beyond T1MR volume 38mm (range, 31-50mm)
 - GBM - average extension MRS volume beyond T1MR volume 24mm (range, 16-28mm)

Pirzkall et al, IJROBP 50:915-928, 2001

Bioanatomic Imaging: MRS UCSF Experience

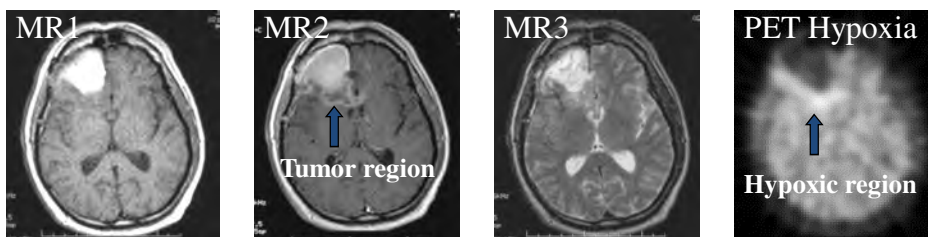
- High-grade gliomas
 - 30 pts (27 GBM, 3AA) underwent MRI/MRS prior to surgery and RT treatment planning
 - T1+C = gross dz, T2 = micro dz, CNI >2 = tumor
 - Differences in MRS vs MRI tumor volume and diameter on T1 images
 - Observed in 27/30 pts
 - Volume difference 20-21cc, diameter 8-36mm
 - Differences based on T2 images
 - Observed in 19/30 pts
 - Volume difference 7-8cc, diameter 15-23mm

Wake Forest Work

- WFU Brain Tumor Pilot: 5 Patients
 - CT, MR, PET Perfusion, PET Hypoxia (1 MRS)
 - Registration methods, Biological volumes, and Quantitative analysis
 - IMRT for multi-compartments
 - Show feasibility

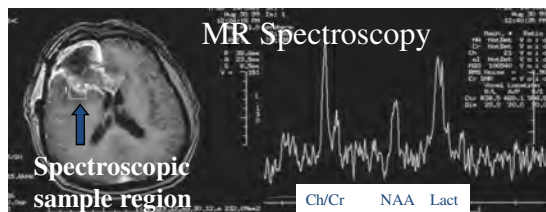
WFU Brain Pilot Study

F-18 Misonidazole PET and MR Spectroscopy



Applications

- 3D RTP (IMRT)
 - Targeting
 - Dose escalation/modulation
 - Spare functional normal tissue
- “Biologically targeted” therapy
- If serial F/U, then response

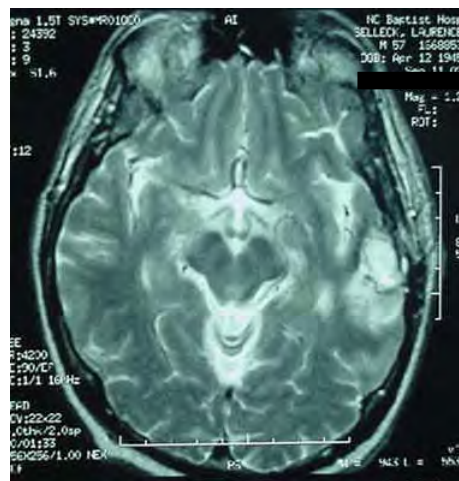


Hypoxia: Solid Tumors

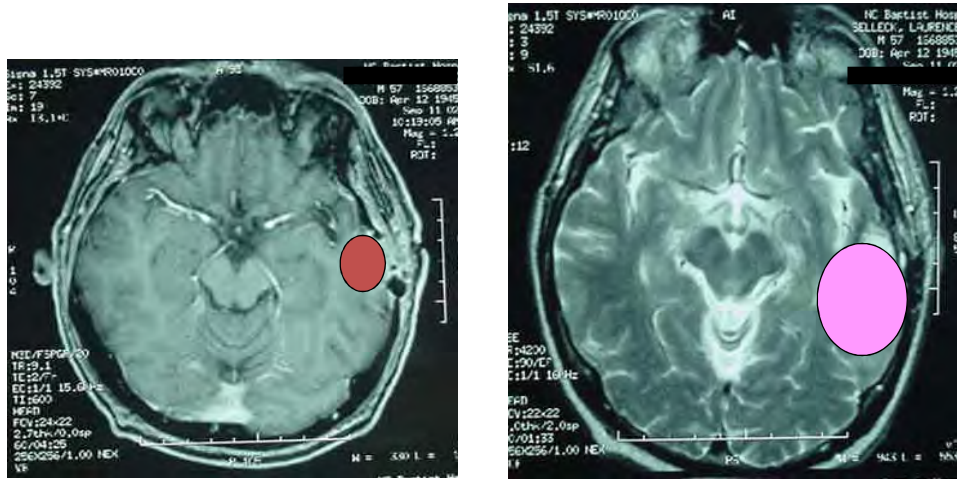
- The Oxygen Enhancement Ratio (OER) for solid tumors is ~ 3 (i.e., 3 times more dose is required for tumor cell kill in a hypoxic versus an oxic environment)
- F-18 Misonidazole PET in 37 patients with solid tumors were obtained prior to radiation therapy
 - Hypoxia was present in 36/37 tumors studied (NSCLC, H/N, prostate, ...)
 - No correlation between size and hypoxia

Rasey et al, IJROBP 36:417-428, 1996

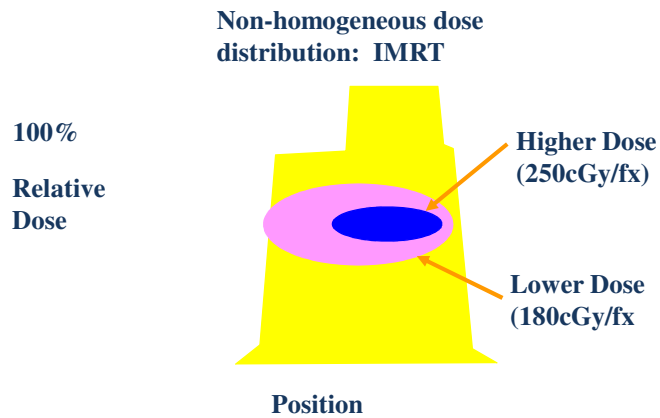
WFU IMRT Dose-Escalation Study



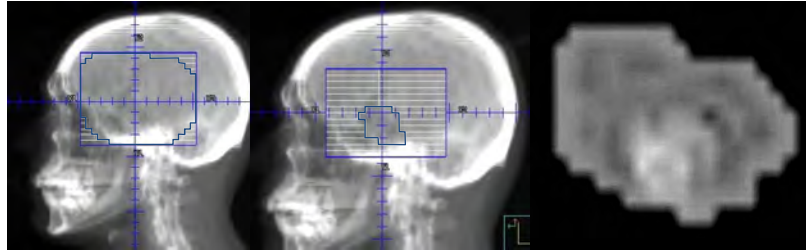
WFU IMRT Dose-Escalation Study



WFU IMRT Dose-Escalation Study



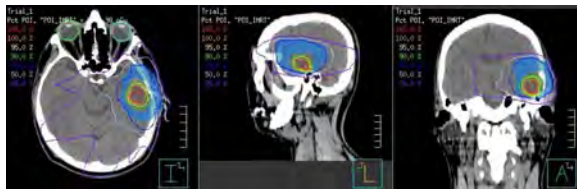
WFU IMRT Dose-Escalation Study



MLC pattern at start
of IMRT

MLC pattern at end
of IMRT

Dose intensity map for
the IMRT



Treatment plan for 80Gy in 32
fractions of 180/250cGy each
(on Phase I dose-escalation
study: 70Gy → 75Gy → 80Gy)

Since MRS may add important additional information and we can modulate dose heterogeneously in a desired fashion, now what?

Need to utilize MRS data to modulate dose to biology...

it is feasible

IMRT OPTIMIZATION

The DFH:
Dose-Function Histogram

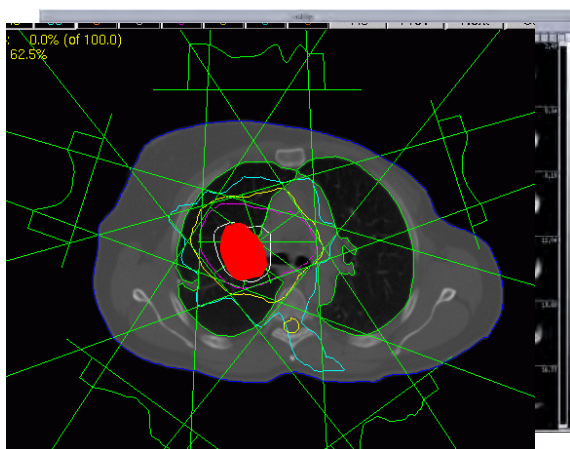
Objectives

- To simultaneously use functional and physical data during intensity modulated radiation therapy (IMRT) treatment planning.
- Demonstrate the use of the dose-function histogram (DFH) during IMRT planning to reduce the dose to regions of higher function in normal tissues.

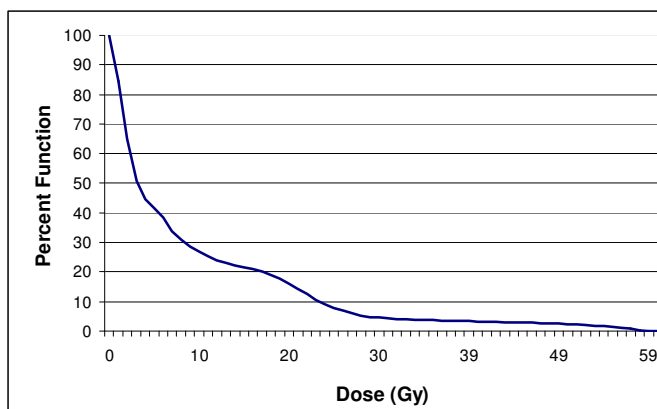
Dose-Function Histogram

- Similar to the dose-volume histogram (DVH), but displaying the percent relative function of a structure versus dose.
- Uses the value of each voxel element:
 - Targets: MR Spectroscopy (choline/citrate)
F-18 FDG
F-18 Misonidazole PET (hypoxia)
 - Normal: MAA SPECT (lung perfusion)

SPECT Lung Perfusion Image



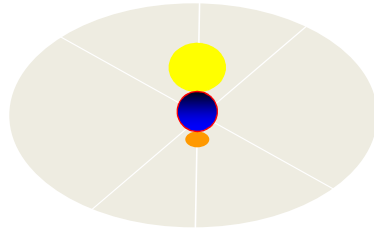
Corresponding DFH



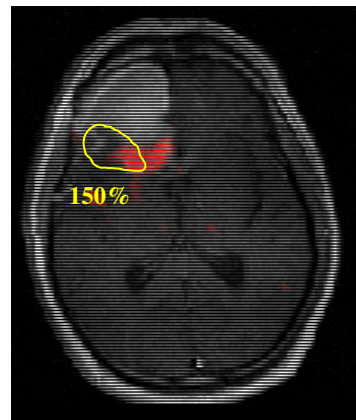
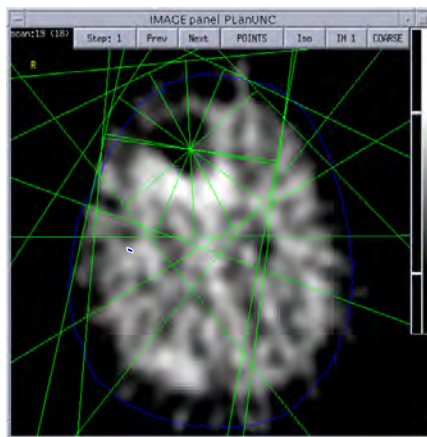
General Methodology

- Contour anatomic structures
- Define anatomic-based (DVH) planning objectives
- Calculate IMRT plan
- Register functional image set to planning CT
- Re-plan with same beam geometry, planning objectives and number of iterations, but also include a function-based (DFH) objective
- Escalate dose heterogeneously within target or reduce dose to critical normal tissues with respect to the relative function of a structure
- Determine feasibility of the DFH approach and compare resulting plans

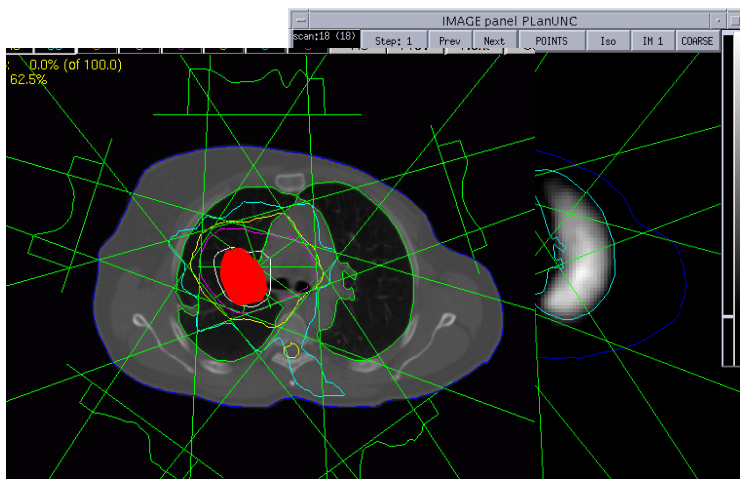
DFH-based IMRT Targeting



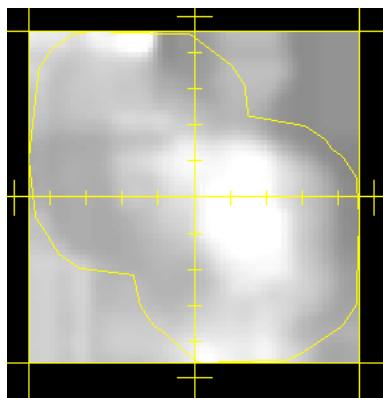
Boosting Regions of Hypoxia



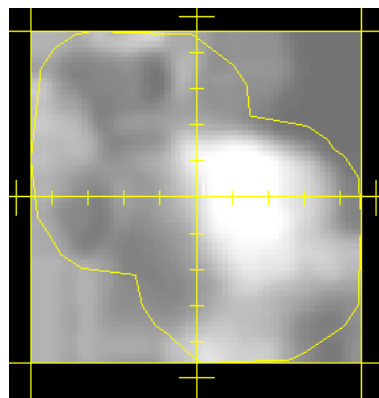
Reduction of Dose to Functional Lung



Fluence Map Comparison

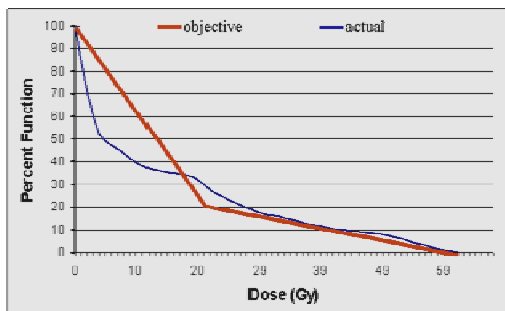


Anatomic

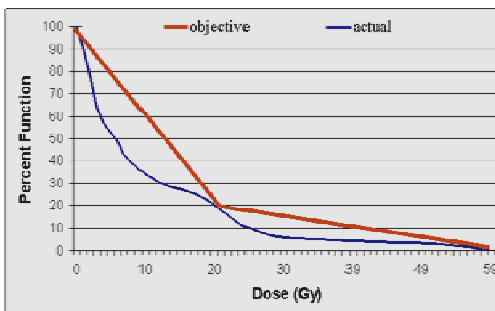


Bioanatomic

Normal Lung DFH Comparison



Anatomic



Bioanatomic

Comparison of Lung IMRT Approaches

Anatomic IMRT

V20: 20%

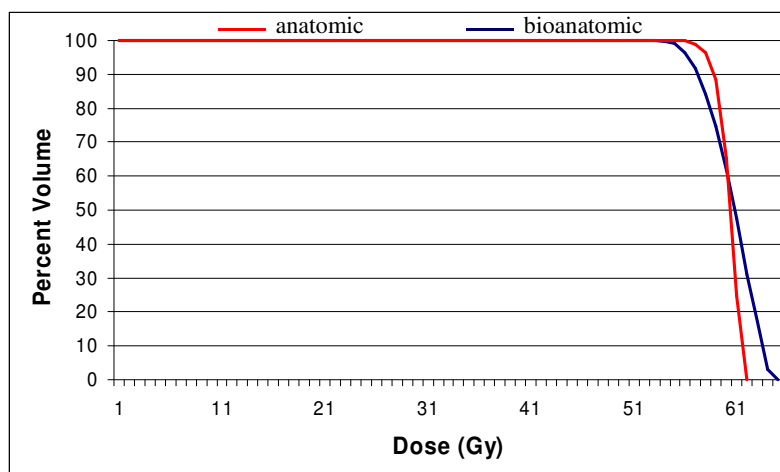
F20: 29%

Bioanatomic IMRT

V20: 17%

F20: 19%

PTV DVH Comparison



Challenges

- Multimodality image quality/quantitation/registration
- Selection of optimal beam geometry
- What do functional images represent?
- What is the dose response of heterogeneous dose distributions?
- Effect on patient outcome?

DFH Optimization Summary

- The use of functional data for dose escalations within targets requires spatial information
- The DFH can be used to decrease the dose proportional to the function of normal critical structures (parallel)
- Both the fluence maps and relative beam weights were changed due to the inclusion of functional data during treatment planning
- The dose to the PTV became more heterogeneous for the same number of optimization iterations
- The potential reduction in dose to a normal structure depends on the functional distribution of that structure, the target location and the beam geometry

Conclusions

- IMRT has become a clinical standard
- The next step will be to use IMRT to modulate dose as a function of biology
- This mode of treatment may become routine for all RT patients

THANK YOU!

