Functional/Molecular Imaging: MRI for Planning/Assessment of RT

Advanced MRI Techniques: Current & Future Applications in RT

Andrea Pirzkall, M.D.

Associate Adjunct Professor
Departments of Radiation Oncology, Radiology, and Neurological Surgery
Center for Molecular and Functional Imaging
Imaging in RT?
Issues of Interest..

- Target definition
  1. Subregions, -volumes? (GTV, BTV)
  2. Margins? (CTV)
  3. Lymph nodal involvement; distant spread?

- Treatment Response
  1. Treatment effect or tumor recurrence?
  2. Surrogate for therapeutic effectiveness?

- Predictors of outcome
aMRI for RT at UCSF

- 2 major disease sites
  - Brain gliomas
  - Prostate cancer
Brain Gliomas - Glioblastoma Multiforme (GBM)  
- Background -  

- Most malignant type of brain tumor in adults  
- **Standard of care:** surgery, radiation therapy, concurrent chemotherapy (Temozolomide)  
  - Median survival 15 mos *  
  - RT: 3D-CRT, 60 Gy/30 Fx (2 Gy/day); >80% local failure  
- Newer, molecularly targeted and/or antiangiogenic, agents increasingly added to standard therapy and tested in clinical trials  
- Early assessment of therapy response is critical but often hindered by questionable changes in morphological appearance  

* Stupp R, NEJM 2005
Brain Gliomas – Characteristics & Challenges

• Infiltrative
• Spatially heterogeneous → difficulty to define treatment margins and/or plan focal therapy

→ Tumor vessels are structurally and functionally abnormal
→ impairs delivery of therapeutic agents
→ creates abnormal microenvironment (e.g. hypoxia) that reduces effectiveness of RT and CHT
Brain Gliomas - Challenges

- Monitoring/assessing response to therapy

Contrast enhancement represents an area of BBB breakdown, and may not be synonymous with tumor progression or angiogenesis.

Initial scan → Treatment effect or Tumor recurrence? → Pseudo-progression

Follow-up
Brain Gliomas - Challenges

- Patient selection

Can non-invasive MR measurements provide surrogate markers for biologic behavior and patient outcome (survival, time-to-progression)?
• Advanced MRI techniques prove valuable to assess the metabolic and physiologic aspects of brain and tumor tissue:
  – 3D Proton Magnetic Resonance Spectroscopy Imaging (MRSI)
  – Perfusion weighted Imaging (PWI)
  – Diffusion weighted Imaging (DWI)

• @ UCSF: Brain tumor SPORE imaging protocol 2002 – 2007, renewed 2007-2012
Assesses metabolic status of brain and tumor tissue based on measurements of cellular metabolites that reflect the biological behavior of each respective volume compartment.

Parameters:

1. Metabolites: 
   1. $^{1}$Cho, 2. $^{2}$Cr, 3. $^{3}$NAA, 4. $^{4}$Lip, 5. $^{5}$Lac

2. Metabolic Indices:
   CNI, CrNI, CCrl
MRSI: Metabolic Indices, i.e. CNI

CNI measures the increase in Cho, decrease in NAA relative to normal.
Perfusion Weighted Imaging (PWI)

Assesses overall cerebral blood volume, tissue micro-vasculature and angiogenesis as well as vessel permeability.

Peak Height → Angiogenesis
Recovery → Vessel leakiness
CBV
Perfusion Weighted Imaging (PWI)
Perfusion Imaging with DSC (T2*) and DCE

Diffusion Weighted Imaging (DWI)

Assesses water diffusivity in brain tissue which has been used to
- infer changes in cellularity, cell membrane permeability, and extra-cellular space ⇒ Apparent Diffusion Coefficient (nADC)
- and structural integrity ⇒ Fractional Anisotropy (nFA)

(normalized to normal appearing white matter, NAWM)
Diffusion Tensor Imaging (DTI)

- DTI sensitive to anisotropic or directionally dependent diffusion, describes 3D diffusivity of water
  ⇒ to measure and tract fiber orientation (esp in large WM tracts)
Diffusion Tensor Imaging (DTI): Structure Avoidance

- DTI Fiber tracks match cortical mapping
- Motor pathways tracked from cortex to midbrain

aMRI in RT: Results so far..

1. Target definition
   - Spatial extent
   - Spatial heterogeneity
   - Pattern of recurrence

2. Treatment response
   - Treatment effect or tumor recurrence
   - Surrogate for therapeutic effectiveness
   - Radiation changes in normal tissue

3. Prediction of outcome
   - Survival
   - Time-to-progression
   - Focal failure
Target Definition
Spatial Extent
Discordance according to MRI/MRSI

- **CNI 2**: T2 hyperintensity
  - T2h: 48 cc
  - 8 mm
  - 8 cc
  - 8 mm

- **CNI 3**: Contrast Enhancement
  - 12 cc
  - 14 mm
  - 15 cc

- **CNI 4**: Contrast Enhancement
  - 15 cc
  - 10 mm
  - 10 cc

*Pirzkall A, et al. IJROBP 2001*
Treatment margins?
Pattern of Recurrence post 3D-CRT relative to pre-RT MRI/MRSI

- Clinical example: Increasing CE during FU residing within pre-RT MRI/S and 60 Gy
- Increased CE during FU occurred within the combined MRI/MRSI volume as defined at pre-RT in 8/9 patient
- Normal tissue exposure to 60 Gy nearly double that of the MRI/MRSI volume (median 78.5 cc vs 38.8 cc, respectively)

* Park I, et al. IJROBP 2007
Treatment margins?
- Early Delayed RT Changes -

• Radiation changes in **normal appearing brain tissue**

→ Dose dependent increase in Cho/NAA ratio & vessel permeability

Also, vessels in NAWM become leaky and have decreased rCBV 2 months after XRT

* Lee M. J Magn Reson Imag 2004
Treatment margins?
- Late Delayed RT Changes-

- Radiation changes assessed at high field strength MRI (7T)
  - Astrocytoma ° III, 5 yrs post therapy (60 Gy CRT + 6 cycles BCNU)
Spatial heterogeneity
MRSI
Spatial heterogeneity
MRI vs MRSI vs PWI

Difference between the spatial distribution of regions with increased metabolism (high Cho) and those with increased rCBV
Guiding RT Delivery: IMRT

MRI T1w post Gad + MRSI

CTV (FLAIR + CNI2)

GTV (CNI3,4 + CE)

72 Gy
60 Gy

30 Fx

IMRT treatment plan
Predictors of outcome & Treatment Response
### Predictors of worse survival @ pre-surgery

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Volume</th>
<th>pre-surgery (56 pts)</th>
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</thead>
<tbody>
<tr>
<td>Volume</td>
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<td></td>
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<tr>
<td>Parameter</td>
<td>↑ vol% CEL/T2all</td>
<td>↑ vol% Nec/T2all</td>
</tr>
<tr>
<td></td>
<td>↓ 25% ADC/T2all</td>
<td>↑ Lac &amp; Lip/T2all</td>
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</table>

* Crawford F, et al. ISMRM 2006*
**Predictors of worse survival @ pre-Tx**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Volume</th>
<th>pre-Tx (70 pts)</th>
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<tbody>
<tr>
<td>MRI, PWI, DWI, MRSI</td>
<td>CEL, NEL, T2all, rCBV&gt;3, ADC&lt;1.5, CNI&gt;2, Lac&gt;0.25</td>
<td>↑ rCBV (75, 90%)/NEL, ↑ Lac (max, 75, 90%)/NEL</td>
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* Saraswathy S, et al. ISMRM 2007*
Predictors of worse survival @ prior to surgery & prior to adjuvant therapy

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<thead>
<tr>
<th>Parameter</th>
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<th>pre-Tx</th>
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<tbody>
<tr>
<td>Volume</td>
<td>none</td>
<td>CEL, NEL, T2all</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rCBV&gt;3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADC&lt;1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CNI&gt;2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lac&gt;0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amount residual functional tumor left behind is critical!!</td>
</tr>
<tr>
<td>vol% CEL/T2all</td>
<td>↑</td>
<td>↑ rCBV (75, 90%)/NEL</td>
</tr>
<tr>
<td>vol% Nec/T2all</td>
<td>↑</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Lac &amp; Lip/T2all</td>
<td>↑</td>
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More malignant phenotype? (high cell density, regions of hypoxia & necrosis)

Suggestive of poor response to RT and CHT
Predictors of shorter Time-to-progression following surgery and adjuvant cytotoxic therapy

- Temporal changes $\Delta$ pre-/post-RT
  - %Recovery [within NEL]
    - $\uparrow$ vascular leakiness correlates with shorter TTP

- @ pre-Tx
  - Higher peak heights of Cho and Cr as well as related indices (CNI, CCrl, CrNI) [within NEL > CEL]
    - Suggest heightened proliferation and predict shorter TTP
  - Higher CBV and PH [within NEL]
    - Suggest increased angiogenesis and predict shorter TTP

* Pirzkall A, et al. ISMRM 2007*
Predictors of shorter Time-to-progression following surgery and adjuvant cytotoxic therapy

High Cho and Lac prior to RT

Pre-RT

Post-RT
Customized image-guided therapy

- Resection Cavity (RC)
- Contrast enhancement (CE)
- T2 hyperintensity (T2 h)
- 60 Gy CRT
- m/p low-risk volume (LRV)
- m/p high-risk volume (HRV)

"New" target definition:

- CTV: RC+T2h+CE+LRV
  \[\rightarrow 2 \text{ Gy/day} \quad \text{BED}\]
  \[\rightarrow 60 \text{ Gy} \quad \rightarrow 60 \text{ Gy}\]

- GTV: HRV
  \[\rightarrow 2.5 - 3 \text{ Gy/day}\]
  \[\rightarrow 72 - 90 \text{ Gy} \quad \rightarrow 84-120 \text{ Gy}\]

OR: \[\rightarrow \text{focal therapy (RS, CED, else)}\]
Focal therapy: Image guided CED

- Clinical phase I study for newly diagnosed GBM s/p GTR in preparation
  - CED of liposomal CPT-11
  - Adjuvant RT + Temozolomide
Prognostic Value of MRSI - Radiosurgery in recurrent GBM -

Patients with MRSI abnormal regions that were beyond the conventional radiosurgical target volume do worse compared to others in whom MRSI abnormality was confined to the volume treated with RS.

Guiding RT Delivery: Radiosurgery

Conventional RS Target

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CNI ≥ 2
Guiding RT Delivery: Radiosurgery

- Conventional RS Target
- CNI ≥ 2
- PIDL based on MRSI
Treatment Effect or Tumor Recurrence?

Pre-treatment  
MRI ⇒ progression,  
MRSI ⇒ radiation response  
Histology ⇒ NECROSIS

5 mos. post-GK  
MRSI ⇒ progression

Chan et al, 2003

Pre-treatment  
Histology ⇒ TUMOR

5 mos. post-GK  
MRSI ⇒ progression

Chan et al, 2003
Treatment Response following surgery + adjuvant cytotoxic AND cytostatic therapy

- **Antiangiogenic Tx**
  - Avastin + CPT-11
    - Recurrent GBM

- **Molecularly targeted Tx**
  - Enzastaurin + Temozolomide + RT
    - Newly dx GBM

  → Data acquisition/evaluation ongoing

- Avastin + Temozolomide
  +/- Tarceva

  *(in patients stable post XRT+Temozolomide, EGRF status dependent?)*

  - Newly dx GBM
  → To be launched (~6 mos)
Treatment Response
following surgery + adjuvant cytotoxic AND cytostatic therapy

<table>
<thead>
<tr>
<th></th>
<th>Historic</th>
<th>Avastin/Irinotecan</th>
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<tbody>
<tr>
<td>6 mos PFS</td>
<td>15%</td>
<td>30%</td>
</tr>
<tr>
<td>Med PFS</td>
<td>9 wks</td>
<td>20 wks</td>
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</table>

Q:
- Anti-VEGF effect only?
- Improved drug delivery?
- Synergistic effects?

aMRI in Prostate Cancer
Cancer vs. Healthy

- MRI: Reduced signal intensity on T2w
- MRSI: Increased choline and decreased citrate and polyamines on MRSI
Step-section histopathological tumor maps were used to identify MRSI voxels of unequivocally benign (n = 306) or malignant (n = 81) peripheral zone tissue in 22 patients with MRI/MRSI studies prior to radical prostatectomy.

- The score is based primarily on the choline + creatine/citrate ratio
- Secondarily on choline/creatine ratio, levels of citrate, polyamines and spectral S/N

Jung JA, Radiology 2004; 233:701-708
Use of MRSI for Radiation Planning

- IMRT
- RS
- PPI (seeds)
- HDR

Use of MRSI for Radiation Planning
- HDR -

MRI planning scan with the HDR catheters in place, manually aligned with a MRI/MRSI staging exam

An average of 2 DIL’s were contoured on CT images based on concordant MRI/MRSI findings

Dose to DIL >120%, while simultaneously treating the entire prostate (100%) w/o increasing the dose to surrounding normal tissues

After therapy, difficult to detect cancer based on MRI alone.
The presence of three or more abnormal voxels with \textit{choline/creatine} \textgreater 1.5 demonstrated a sensitivity and specificity of 87\% and 72\%, respectively, and an overall accuracy of 81\% for the diagnosis of local recurrent/residual disease.

• Increasing metabolic atrophy paralleled decreasing serum PSA with time after Brachytherapy and EBRT, but occurred significantly earlier.
• The presence of residual abnormal metabolism did not correlate with PSA in individual patients after radiation.

Brachytherapy was associated with an earlier more dramatic decrease in prostate metabolism than EBRT resulting in a significantly larger % of the prostate demonstrating metabolic atrophy at the 6-12 and 13-24 month time points.

Pickett B et al, IJROBP 65(1):65-72, 2006
The median time to resolution of abnormalities for Brachytherapy patients was 24.8 mos, 7.4 mos sooner than for EBRT patients (32.2 months).

All patients receiving Brachytherapy had resolution of metabolic abnormalities by 60 mos, while 10% of patients receiving EBRT still had metabolic abnormalities at 60 mos.

Pickett, B., Int J Radiat Oncol Biol Phys, 2006
• There are many new MR methods that are likely to impact the diagnosis and management of patients with cancer.
• These methods give information about changes in tissue structure and function rather than merely anatomy.
• They can be acquired as an add-on to a conventional anatomic MR exam being used for treatment planning or follow-up.
• Quantitative analysis and integration of the results from multiple parameters are critical aspects of this technology.
• Validation of the biological significance of these parameters requires correlations with histology and outcome.
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