What Can Anatomical Treatment Assessment Tell Us?

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Cancer: Phenomenological View

- Cancer: An abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize.

Grizzi et al., 2006

RT and Cell Death

- The model for describing the cell survival curve is the linear-quadratic model with constants $\alpha$ and $\beta$.
  - The ratio $\alpha/\beta$ gives the dose at which the linear and quadratic components of cell killing are equal.
More than a mass of cells.

In the late thirties in vivo images of tumour blood vessels began being published. Shown here is an image of a rabbit epitheloma obtained by Gordon Ide and collaborators at Rochester University. These dark streaks represent the tumour vasculature the Brown-Pearce rabbit epithelial carcinoma (malignant tumor of the epithelial tissue) in a transparent chamber in the rabbit ear.

Getting Beyond the Cell as a Target

Figure 2: The principle of anti-angiogenic agents. Judah Folkman was convinced that tumour angiogenesis was a necessary component of tumour growth and based on this was the premise that the inhibition of the angiogenic process could constitute a new form of cancer therapy. He made this idea in the 1971 New England Journal of Medicine paper which was the first to use the term “antiangiogenesis” to describe a potential therapeutic approach.


Growing appreciation of the complexity.

Hypoxia/Proliferation; The Role of Cellular Sub-populations; Inflammatory/Immune Components; Microenvironmental Feedback/Memory/Niche; Vascular and Lymphatic Compromises;

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“The term molecular imaging can be broadly defined as the in-vivo characterization and measurement of biologic processes at the cellular and molecular level. In contradistinction to “classical” diagnostic imaging, it sets forth to probe the molecular abnormalities that are the basis of disease rather than to image the end effects of these molecular alterations.”

Weissleder et al., Volume 219 (2), Molecular Imaging, 2001

Anatomical Imaging for Treatment Assessment:
Imaging the end of effect of molecular alterations induced by disease and therapy.
3D Anatomical Imaging

- Computed Tomography (CT)
  - Measures x-ray attenuation coefficient, density
- Magnetic Resonance Imaging (MRI)
  - Water proton relaxation
  - Proton Density, Spin-Spin ($T_1$), Spin-Lattice ($T_2$)
- Ultrasound (US)
- Exogenous Contrast Agents
  - Small molecule (Iodine-CT, Gadolinium-MR)
  - Macro-molecular agents (non-diffusing; bubbles)

It was also found that the differences between the relaxation rates of malignant tumors and normal liver could be used to distinguish the two malignancies from all of the normal tissues studied ($P$ values less than 0.01) (Table 2). The values of $T_1$ in Walker carcinosarcoma (0.716 second) and Novikoff hepatoma (0.626 second) were significantly greater than the values of $T_2$ in any of the normal tissues (0.293 to 0.595 seconds). The

Table 5. Analysis of $T_1$, and $T_2$ relaxation times for the normal liver.

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>$T_1$ (sec)</th>
<th>$T_2$ (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Liver</td>
<td>0.50</td>
<td>0.25</td>
</tr>
<tr>
<td>Walker Carcinosarcoma</td>
<td>0.716</td>
<td>0.61</td>
</tr>
<tr>
<td>Novikoff Hepatoma</td>
<td>0.626</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Give us a "water-weighted" assessment of the intra and extra-cellular organization in tissues.

Damadian, Science, 1971

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COMPUTED MEDICAL IMAGING

NUCLEAR IMAGING

Table 1. Imaging reagents as biomarkers or surrogate parameters for the assessment of therapeutic interventions.

<table>
<thead>
<tr>
<th>Imaging Reagent</th>
<th>Imaging Parameter</th>
<th>Therapeutic Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tracer</td>
<td>Activity</td>
<td>Response</td>
</tr>
<tr>
<td>Radiolabeled</td>
<td>PK</td>
<td>PK</td>
</tr>
<tr>
<td>conjugate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibody</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peptide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligonucleotide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNA</td>
<td></td>
<td></td>
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<tr>
<td>RNA</td>
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It shows a series of pictures demonstrating the progression of a primary tumor (a very radio-sensitive tumor). The radiation is applied at a low level while the tumor is large, but as the lesion regress, the smaller area is taken advantage of and larger doses are then applied. In this particular case the tumor was completely removed by accurate intense radiation.

Normal

Diseased

Perfusion (CT) or Dynamic Contrast Enhancement (DCE-MR) methods seek to characterize the vascular/intra-tumoral transport as a metric of the disease and its response to therapy.


Low-molecular weight agent: Omnipaque

Diffusion Weighted MR

- Diffusion-weighted magnetic resonance imaging (DW-MRI) depends on the microscopic mobility of water.
- This mobility, classically called Brownian motion, is due to thermal agitation and is highly influenced by the cellular environment of water.
- Motion in gradients encodes for diffusion.
- Findings on DW-MRI could be an early harbinger of biologic abnormality or an early harbinger of therapeutic response.

What Can Anatomical Treatment Assessment Tell Us?

- Gross Anatomical Change (CT/MR)
  - Cell death, inflammation, edema
- ‘Meso’-scopic transport changes
  - Vascular structure, function
  - Permeability, intra-tumoral transport
- Cellular/Intra-cellular Structure (Water Diffusion)
- RT: Opportunity for Geometric Adaptation

In the context of therapy, anatomical change contributes as a biomarker for predicting response.

Does any of this happen quickly enough to detect during a course of radiation therapy?

Yes.

IG Technologies for RT

- kV CBCT
- kV Radiography
- MV CT
- MV CBCT
IGRT Detected Changes in Lung Targets

- Siker ML et al. “Tumor volume changes on serial imaging with megavoltage CT for non-small-cell lung cancer during intensity-modulated radiotherapy: how reliable, consistent, and meaningful is the effect?”


Anatomical Treatment Assessment and the Domain of Adaptation in RT

- Concerns regarding the true extent of disease (in planning and during RT).
- Is there opportunity to reduce target volumes as therapy progresses?
  - Depends on what is changing – normal tissue vs target volumes (mass effect)
- Need to reflect on the definition of GTV and CTV
  - State-of-the-art IGRT imaging systems are not standard of care for use in target definition
  - Redefinition of target volumes is not standard of care in RT
- Greater value as a biomarker? To be determined.
Mayr et al: Translating Response During Therapy into Ultimate Treatment Outcome … in Cervical Cancer.

- Serial MRI in cervix cancer patients to define the regression parameters’ prognostic value validated with local control and survival correlation.
  - 115 patients with Stage IB(2)-IVA cervical cancer treated with RT
  - Serial MRI before, during RT (2-2.5 wks and 4-5 wks), and after (80/115 - 2 months)
  - Mean follow-up was 5.3 years

**CONCLUSION:**
- Tumor response can now be directly translated into individual patients’ outcome for clinical application.
- In patients with ≥20% residual volume at 40-50 Gy and ≥10% post-RT, the risk for local failure and death are so high that aggressive intervention may be warranted.

Radioresistant tumors with an $SP_{0.71} > 0.71$ were significantly more hypoxic (HPmed, Eppendorf) at the start of therapy than were radiosensitive ($SP_{0.71} < 0.71$) tumors.

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Cluster Analysis:
100% sensitivity and specificity of 100% for distinguishing Partial Response patients from Stable or Progressive Disease patients

The predictive values and overall accuracy for discriminating PR, SD, and PD patients at 3 weeks post-treatment initiation were found to be 100% for all 20 patients.

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Next Generation IG Technologies for RT

Edmonton Solution

Utrecht Solution

Viewray Solution

MR-Guided RT

Summary

• Imaged ‘anatomical’ changes will play a role in predicting outcome in RT.
  – Image-guidance technologies will heighten our awareness of these changes.
• Can capitalize on changes in anatomical target to reduce normal tissue irradiation
  – Caution - Re: target delineation
• Given the ‘biomarker’ nature of the observations, it is unclear what the feedback to the intervention should be.
  – Within RT, outside RT.

Adaptive Management of Cervical Cancer Radiotherapy