Targeting based on biological imaging

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Back to the DARK AGES
Biological/molecular imaging

- “Visualization, characterization and measurement of biological processes at the molecular and cellular levels in humans and other living systems”

- It can probe molecular abnormalities that are the basis of disease rather than to image the end effects

- Enabled by developments in cell and molecular biology, with better understanding of the cellular function and disease changes

- Various other “definitions” of molecular imaging exist (e.g., small animal imaging, PET imaging)
Current state of affairs...

Different levels of trust into imaging are the main reason for variability

Hong and Harari, 2005
What is the real tumor extent?

Daisne et al 2004, Radiology 233, 93.
Different modalities – different answer

Average Mismatch of Laryngeal GTVs between Imaging Modalities and the Surgical Specimen

<table>
<thead>
<tr>
<th>Pair</th>
<th>Mismatched Volume (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td></td>
</tr>
<tr>
<td>To MR imaging</td>
<td>26 (6.2/23.8)</td>
</tr>
<tr>
<td>To FDG PET</td>
<td>48 (7.8/16.3)</td>
</tr>
<tr>
<td>To specimen</td>
<td>81 (10.2/12.6)</td>
</tr>
<tr>
<td>MR imaging</td>
<td></td>
</tr>
<tr>
<td>To CT</td>
<td>45 (9.3/20.8)</td>
</tr>
<tr>
<td>To FDG PET</td>
<td>67 (11.0/16.3)</td>
</tr>
<tr>
<td>To specimen</td>
<td>107 (13.4/12.6)</td>
</tr>
<tr>
<td>FDG PET</td>
<td></td>
</tr>
<tr>
<td>To CT</td>
<td>17 (3.5/20.8)</td>
</tr>
<tr>
<td>To MR imaging</td>
<td>15 (3.6/23.8)</td>
</tr>
<tr>
<td>To specimen</td>
<td>46 (5.8/12.6)</td>
</tr>
<tr>
<td>Specimen</td>
<td></td>
</tr>
<tr>
<td>To CT</td>
<td>10 (2.0/20.8)</td>
</tr>
<tr>
<td>To MR imaging</td>
<td>9 (2.2/23.8)</td>
</tr>
<tr>
<td>To FDG PET</td>
<td>13 (2.1/16.3)</td>
</tr>
</tbody>
</table>

Note.—Data in parentheses are the average mismatched volumes in cubic centimeters.

Daisne et al 2004, Radiology 233, 93.
### SUV measure

<table>
<thead>
<tr>
<th>SUV measure</th>
<th>CV (%)</th>
<th>min - max (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUV(_{\text{max}})</td>
<td>9</td>
<td>4 - 15</td>
</tr>
<tr>
<td>SUV(_{\text{mean}})</td>
<td>5</td>
<td>1 - 8</td>
</tr>
</tbody>
</table>
This is a BIG, BIG problem!!!

- From **QUALITATIVE DIAGNOSTIC IMAGING** (Diagnosis and Staging)...
- ...To **QUANTITATIVE THERAPEUTIC IMAGING** (Target definition, Treatment assessment)

- **Limited experience** with imaging in treatment context, compared to diagnostic (except CT)!
- **Dangerous** to use diagnostic quality imaging in a therapeutic context (**Qualitative ≠ Quantitative**)
Problem: PET imaging uncertainties

- **Technical factors**
  - Relative calibration between PET scanner and dose calibrator
  - Residual activity in syringe
  - Incorrect synchronization of clocks
  - Injection vs calibration time
  - Quality of administration

- **Physical factors**
  - Scan acquisition parameters
  - Image reconstruction parameters
  - Use of contrast agents

- **Analytical factors**
  - Region of interest (ROI) definition
  - Image processing

- **Biological factors**
  - Patient positioning
  - Patient breathing
  - Uptake period
  - Blood glucose levels

Jeraj 2010
PET imaging uncertainties

- **Technical factors**
  - Relative calibration between PET scanner and dose calibrator (10%)
  - Residual activity in syringe (5%)
  - Incorrect synchronization of clocks (10%)
  - Injection vs calibration time (10%)
  - Quality of administration (50%)

- **Physical factors**

- **Analytical factors**
  - Region of interest (ROI) definition (50%)
  - Image processing (25%)

- **Biological factors**
  - Patient positioning (15%)
  - Patient breathing (30%)
  - Uptake period (15%)
  - Blood glucose levels (15%)

**Unacceptable imaging uncertainties for therapy applications!!!**

Jeraj 2010
Target definition using PET

- **Manual segmentation** by an expert physician

- **Auto segmentation**
  - Thresholding *(Erdi 1997, Paulino 2004)*
  - Gradient-based *(Geets 2007)*
  - Region-growing *(Drever 2006)*
  - Feature-based *(Yu 2009)*
  - …
Manual segmentation is NOT PRECISE and NOT ACCURATE
Auto segmentation: Number of iterations

Impact of Iteration on target volumes

Volume Variations (%)

128x128 grid size

Segmentation Techniques

- Threshold-based
- Gradient-based
- Region-growing

3D Acquisition, 6mm PF
2D Acquisition, 5mm PF
Auto segmentation: Post-iteration filter width

Impact of post-reconstruction filter width on target volumes

256x256 Grid-Size

128x128 Grid-Size

Segmentation Techniques

- Threshold-based
- Gradient-based
- Region-growing

Volume Variations (%)
Auto segmentation: Grid size

Impact of grid size on target volumes for 3mm PF

Auto segmentation is PRECISE but NOT ACCURATE

- Threshold-based
- Gradient-based
- Region-growing

Volume Variations (%)

Segmentation Techniques

3D Acquisition
2D Acquisition
## Margins

<table>
<thead>
<tr>
<th>Margin plane</th>
<th>Mean ± SD (mm)</th>
<th>Maximum (mm)</th>
<th>Avg. Max ± SD (mm)</th>
<th>Maximum (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial</td>
<td>1.0 ± 0.4</td>
<td>1.8</td>
<td>8.4 ± 6.0</td>
<td>26.0</td>
</tr>
<tr>
<td>Coronal</td>
<td>0.5 ± 0.3</td>
<td>1.2</td>
<td>10.6 ± 6.1</td>
<td>26.7</td>
</tr>
<tr>
<td>Sagittal</td>
<td>0.5 ± 0.3</td>
<td>1.2</td>
<td>10.2 ± 5.3</td>
<td>22.1</td>
</tr>
</tbody>
</table>
Summary

- **Biological imaging is not QUANTITATIVE**
  - Many national/international efforts focused on improving image quantification
    - IRAT, CQIE, QIBA
  - Physicists should carry the main burden/effort to improve quantification/educate physicians
    - Are YOU ready?

- **Target segmentation is not ACCURATE/PRECISE**
  - Manual segmentation is not an option
  - Auto-segmentation carries many uncertainties
  - Much more work to be done
    - AAPM TG211
Traditional approach

- Anatomical imaging - **GTV**

- **Uncertainties:**
  - Not seen on imaging - **CTV**
  - Motion, positioning - **PTV**
But, is it optimal?

Uniform dose \xrightarrow{X} \text{Uniform response}
How can we get uniform response?

Targeted dose ← Heterogeneous response
DOSE PAINTING
(Biologically targeted radiotherapy)

Dose painting

- Anatomical → Biological imaging – BTV
Dose painting

- Anatomical → Biological imaging – BTV

- Uncertainties:
  - All uncertainties - PTV
Dose painting workflow

1. Tumor biology
2. Biological imaging
3. Bio-based prescription
4. Planning & delivery

Clinical outcome

What are extra uncertainties?
Biological imaging
Microscopy → Macroscopy

Microscopy

PET/CT imaging

1 mm

5 cm

Proliferation
Hypoxia

Courtesy of A. van der Kogel, Nijmegen, NL
Spatial resolution

- 40 μm
- 0.5 mm
- 1 mm
- 2 mm
We do not see **hot** heterogeneities

**Very small localized high activities can not** be visualized
We do not see **small** heterogeneities

Partial volume effects

Recovery coefficients

**Even relatively large localized activities need to be corrected for**
Spatial distribution of tumor phenotypes

FDG PET/CT (metabolism)

FLT PET/CT (proliferation)

Cu-ATSM PET/CT (hypoxia)
Spatial distribution of tumor phenotypes

- **FDG PET/CT** (metabolism)
- **FLT PET/CT** (proliferation)
- **Cu-ATSM PET/CT** (hypoxia)
How to combine this information?
Biologically-based prescription

1. Tumor biology
2. Biological imaging
3. Bio-based prescription
Tracer retention mechanisms

\[ \text{Cu}^{II} \text{ATSM} \leftrightarrow \text{Cu}^{II} \text{ATSM} \]

\[ \text{CR} \rightarrow \text{O}_2 \]

\[ \text{FMISO} \leftrightarrow \text{FRNO}_2 \]

\[ \text{H}_3\text{O}^+ \leftrightarrow \text{H}_2\text{O} \]

\[ \text{RSH} \rightarrow \text{H}_2\text{ATSM} \]

\[ \text{Cu}^{I} \text{HATSM} \rightarrow \text{Cu}^{I} \text{ATSM}^{-} \]

\[ \text{Cu}^{I} \text{RS} \rightarrow \text{Cu}^{I} \text{HATSM} \]

\[ \text{H}_2\text{ATSM} \leftrightarrow \text{Cu}^{I} \text{RS} \]

\[ \text{REDOX} \text{ compartment} \]

\[ \text{BOUND} \text{ compartment} \]

\[ \text{DISSOCIATION} \text{ compartment} \]

Bowen et al. 2011, Nucl Med Biol
pO$_2$ transformation functions

Cu-ATSM model

1 SD CI

Cu-ATSM meas.
Lewis et al. 1999

FMISO model

1 SD CI

FMISO meas.
Lewis et al. 1999

Piert et al. 2000
Prescription function

Cu-ATSM

Prescribed Dose (Gy)

Cu-ATSM SUV

pDose_2

pH = 7.1

pH = 7.2

pH = 7.3

Cu-ATSM

pH = 7.1

pH = 7.3
Overall uncertainty in a patient

- Mean uncertainty of 20% (max 60%) in prescribed dose to individual patient
# Uncertainties in population

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Parameter</th>
<th>Range</th>
<th>Dose Uncertainty</th>
<th>Mean (Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$pH$</td>
<td>Intracellular Acidity</td>
<td>7.1 – 7.3</td>
<td></td>
<td>4 % (10 %)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Gerweck 1998)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$HP_{2.5}$</td>
<td>Dose Boost vs. Hypoxic</td>
<td>95 % CI</td>
<td></td>
<td>5 % (14 %)</td>
</tr>
<tr>
<td>$P_{mid}$</td>
<td>Half-max Sensitization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$OER_{max}$</td>
<td>Max Oxygen Enhancement Ratio</td>
<td>1.4 – 3.0</td>
<td></td>
<td>1 % (2 %)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Chan 2008)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>10 % (17 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient</td>
<td></td>
<td>20 % (60 %)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Translating biological imaging uncertainty to dose is uncertain.

Gerweck 1998
Nilsson 2002
Chan 2008
Tracer pharmacokinetics can lead to large uncertainties.
Setup uncertainties

Axial shift

Radial shift
Even small setup errors will lead to significantly different appearance of tumor heterogeneity.
Quantification errors due to respiration motion

- Blurring of recovered activity – loss of spatial and functional info
- Delineation errors – what/where are the targets?
Motion uncertainties

Motion can have a detrimental impact on accuracy
Clinical outcome correlation

1. Tumor biology
2. Biological imaging
3. Bio-based prescription
4. Planning & delivery
5. Clinical outcome
Dose vs. PET for recurrence

- Recurrence at Time Point
- No Recurrence at Time Point

Empirical fit
Upper 95% C.I.
Lower 95% C.I.

Real clinical world is not perfect

Dose 1
Dose 2
Dose 3

PET Uptake
Summary

1. Tumor biology (Micro → Macro)
2. Biological imaging (Tracer)
3. Bio-based prescription (Set-up)
4. Planning & delivery (Motion)
5. Clinical outcome (Outcome uncertainties)

Which biology
Extraction of biology
Thanks to:

- **Image-guided therapy group**
  - Vikram Adhikarla
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  - George Wilding
  - Mark Juckett

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  - Chris Jaskowiak

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  - Dhanabalan Murali
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