The Future of (IM)RT: Integration of Molecular Imaging

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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)
Imaging in oncology

ANATOMICAL IGRT MOLECULAR

BEFORE DURING AFTER THERAPY

DIAGNOSIS and STAGING
TARGET DEFINITION

EARLY LATE TREATMENT ASSESSMENT
Target definition

~1980
Discrete volume

~1990
Conformal therapy
IMRT
Current state of affairs…

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

Hong and Harari, 2005
Adding PET information HELPS!

However, there is still a significant variability in contouring...

50% (30%-70%) decrease of the contouring standard deviation!

How can we increase reproducibility

- **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)
  - …
However, we should not forget...

- 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**)
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**
  - Scan acquisition parameters (15%)
  - Image reconstruction parameters (30%)
  - Use of contrast agents (15%)

- **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%)

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Inherent variability of PET scans

<table>
<thead>
<tr>
<th>SUV measure</th>
<th>CV (%)</th>
<th>min - max (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$SUV_{max}$</td>
<td>9</td>
<td>4 - 15</td>
</tr>
<tr>
<td>$SUV_{mean}$</td>
<td>5</td>
<td>1 - 8</td>
</tr>
</tbody>
</table>
We still need to rely on margins

Auto segmentation is better but still not the full answer

<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>
Do we really trust what we see?

Being more precise does not guarantee we are more accurate!

50% (30%-70%) decrease of the contouring standard deviation!

What is the real tumor extent?

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

We are still missing a gold standard – watch this space!

Daisne et al 2004, Radiology 233, 93.
And here comes DOSE PAINTING…

Dose painting workflow

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

What are extra challenges?
Microscopy → Macroscopy

Microscopy

PET/CT imaging

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)
Correlation between phenotypes

HNSCC, N = 11 (Age: 43-75, T2-4)

<table>
<thead>
<tr>
<th></th>
<th>Correlation (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDG:FLT</td>
<td>0.76 (0.53-0.85)</td>
</tr>
<tr>
<td>FDG:CuATSM</td>
<td>0.64 (0.51-0.79)</td>
</tr>
<tr>
<td>FLT:CuATSM</td>
<td>0.61 (0.21-0.80)</td>
</tr>
</tbody>
</table>

FDG:FLT  → highest correlation
FLT:CuATSM  → most heterogeneous
Correlation between phenotypes

Spatial correlations should be considered very carefully
Histology dependence

Sarcomas

Carcinomas

Pre FDG SUV

Pre Cu-ATSM SUV

Pre FLT SUV

Pre FL SUV
How to combine this information?

Proliferation

$[^{18}\text{F}]\text{FLT}$

Hypoxia

$[^{64}\text{Cu}]\text{Cu-ATSM}$

Proliferative and hypoxic

Proliferative

Hypoxic

Other
Biologically-based prescription

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

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

\[
\text{Cu}^{I}\text{ATSM} \rightleftharpoons \text{Cu}^{I}\text{ATSM}
\]

\[
\text{H}_2\text{ATSM} \rightleftharpoons \text{H}_2\text{ATSM}
\]

\[
\text{Cu}^{I}\text{RS} \rightleftharpoons \text{Cu}^{I}\text{RS}
\]

\[
\text{FRNO} \rightleftharpoons -2\text{FRNO} \cdot
\]

REDOX compartment

BOUND compartment

DISSOCIATION compartment

Bowen et al 2011, Nucl Med Biol


\textbf{pO}_2 \textit{ transformation functions}

\begin{itemize}
    \item \textbf{Cu-ATSM model}
    \item \textbf{FMISO model}
\end{itemize}

\begin{itemize}
    \item \textbf{Cu-ATSM meas. Lewis et al. 1999}
    \item \textbf{FMISO meas. Lewis et al. 1999}
    \item \textbf{FMISO meas. Piert et al. 2000}
\end{itemize}
Prescription function

Cu-ATSM

Prescribed Dose (Gy)

$pH = 7.1$

$pH = 7.3$

$pDose$
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>
</tr>
</thead>
<tbody>
<tr>
<td>$\rho H$</td>
<td>pH Intracellular Acidity</td>
<td>7.1 – 7.3</td>
<td>4 % (10 %)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Gerweck 1998)</td>
<td></td>
</tr>
<tr>
<td>$HP_{2.5}$</td>
<td>Dose Boost vs. Hypoxic</td>
<td>95 % CI</td>
<td>5 % (14 %)</td>
</tr>
<tr>
<td>$P_{mid}$</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>1 % (2 %)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Chan 2008)</td>
<td></td>
</tr>
</tbody>
</table>

**Translating biological imaging uncertainty to dose is uncertain**

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>10 % (17 %)</th>
<th>Patient</th>
<th>20 % (60 %)</th>
</tr>
</thead>
</table>

**Overall**

**Patient**
Extraction of biological information

Tracer pharmacokinetics needs to be carefully considered

FLT PET/CT
Planning and delivery

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

- PET/CT
- Prescription Function
- PET Imaging Rx
- Dose Discretization
- Sub-PTV Contours

Planning/Delivery
- $D_{ROI}$
- $\min(D_{ROI}) \& \max(D_{ROI})$
- $\min(DVH_{ROI}) \& \max(DVH_{ROI})$

Clinical Planned Dose

Deveau et al 2010, Acta Oncol 49:991
Hi-Art vs. RapidArc

MLC Leaf Width: 6.25 mm
Jaw Width: 1.05 cm
Pitch: 0.43
Modulation Factor: 3.0

MLC Leaf Width: 2.50 mm
Two arcs
Collimator angles: 45°, 315°

- Plan Quality:
  - A piece of good news – we can already deliver what we want!
- Treatment Time:
  - 17 min. vs. 6 min.

- We can plan and deliver any dose we want with the current technology

Korreman et al 2010, Acta Oncol 49:964
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
Correlating dose to the outcome

PET

Dose

Recurrence
Dose vs. PET for recurrence

Real clinical world is not perfect – hard to extract reliable information
How many patients need dose painting?
How many patients need dose painting?

- Imaging → 1/12 or 8.3%
- Eppendorf → 6/69 or 8.7%

Only a small number of patients might benefit at the end.
Dose painting workflow

Heuristic Modeling and Empirical Data

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

Clinical outcome

Many problems – many challenges, BUT extremely exciting!!!

Uncertainty Characterization and Validation

Micro→Macro
Which biology
Tracer
Extraction of biology
Set-up
Motion
Outcome uncertainties
Uniform dose $\rightarrow$ Non-uniform dose

Reggio Emilia – 20??

Anatomical imaging
Population-based
Uniform dose IMRT

Molecular imaging
Patient-specific
Non-uniform dose IMRT
Thanks to:

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  - Benny Titz
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  - Mark Juckett

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  - Chris Jaskowiak

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