Molecular Imaging in Radiation Oncology: What and Where?

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Current state of affairs...

Hong and Harari, 2005

FDG PET/CT or CT?

GTV_{PET} < GTV_{CT}
75%

GTV_{PET} > GTV_{CT}
20%

FDG PET/CT or CT?

“Physicians B and C used contradictory techniques. Physician B would contour the suspected GTV on the basis of the CT but often totally disregard this information when given the PET information and contour only PET avidity. Physician C, on the other hand, would contour the suspected GTV on the basis of the CT, and then, for the fusion contour, draw the union of the CT contour and PET avidity.”

“Physician A’s method tended to be a mixture of the methods of Physicians B and C. Often, Physician A would “split the difference” and contour the compromise between the drawn CT contour and PET avidity.”


Whatever, adding PET info HELPS!

CT

PET/CT

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


How to increase reproducibility?

- AAPM TG211 - Classification, Advantages and Limitations of the Auto-Segmentation Approaches for PET
  - Manual segmentation is NOT the way to go!
  - Auto segmentation
    - Thresholding (Erdi 1997, Paulino 2004)
    - Gradient-based (Geets 2007)
    - Region-growing (Drever 2006)
    - Feature-based (Yu 2009)
    - ...
  - Reference benchmark dataset
Auto-segmentation, but which one?

Troost et al. 2010, Radiother Oncol, 96(3): 328

There are inherent uncertainties

Impact on volume definition

Impact of post-reconstruction filter width on target volumes

Threshold-based
Gradient-based
Region-growing
**Need for imaging margins**

<table>
<thead>
<tr>
<th>Margin plane</th>
<th>Mean ± SD (mm)</th>
<th>Maximum (mm)</th>
<th>Reg. 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>10.8 ± 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>

**Is imaging itself enough?**

CT+PET or CT+MRI

CT+MRI+PET+P.E. > CT+PET or CT+MRI

CI (CT+PET, CT+MRI) = 0.62


**Using FDG PET for target definition helps because:**

1. It better defines where the tumor is
2. Increases consistency of target definition
3. It will make hospital administrators happy (more revenue)
4. Doctors think so
5. It actually doesn’t help
And here comes DOSE PAINTING…

Dose painting workflow

What are extra challenges?

Microscopy → Macroscopy

8/2/2012
Spatial resolution

40 µm  0.5 mm  1 mm  2 mm

We do not see small heterogeneities

Partial volume effects  Recovery coefficients

Sphere Diameter (mm)

Extraction of biological information

1 min  15 min  60 min

FLT PET/CT
What to dose paint?

FDG PET/CT (metabolism)
FLT PET/CT (proliferation)
Cu-ATSM PET/CT (hypoxia)

FDG PET vs Time-to-progression

<table>
<thead>
<tr>
<th>FDG SUV measure</th>
<th>Pre-treatment p-val (N=19)</th>
<th>3 months post RT p-val (N=16)</th>
<th>6 months post RT p-val (N=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUVmean</td>
<td>0.34</td>
<td>0.005</td>
<td>0.001</td>
</tr>
<tr>
<td>SUVmax</td>
<td>0.86</td>
<td>0.017</td>
<td>0.003</td>
</tr>
<tr>
<td>SUVpeak</td>
<td>0.39</td>
<td>0.006</td>
<td>0.002</td>
</tr>
<tr>
<td>SUVtotal</td>
<td>0.51</td>
<td>0.047</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Regression analysis

**Sarcomas**
3mo FDG Regression, N=7

<table>
<thead>
<tr>
<th>SUVmean</th>
<th>FDGpre</th>
<th>FLTpre</th>
<th>CuPre</th>
<th>FLTmid</th>
<th>CuMid</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean</td>
<td>0.42</td>
<td>-0.23</td>
<td>0.03</td>
<td>0.21</td>
<td>0.25</td>
</tr>
<tr>
<td>p-val</td>
<td>0.01</td>
<td>0.35</td>
<td>0.84</td>
<td>0.29</td>
<td>0.13</td>
</tr>
</tbody>
</table>

**Carcinomas**
3mo FDG Regression, N=11

<table>
<thead>
<tr>
<th>SUVmean</th>
<th>FDGpre</th>
<th>FLTpre</th>
<th>CuPre</th>
<th>FLTmid</th>
<th>CuMid</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean</td>
<td>0.15</td>
<td>-0.25</td>
<td>-0.14</td>
<td>0.21</td>
<td>0.47</td>
</tr>
<tr>
<td>p-val</td>
<td>0.11</td>
<td>0.01</td>
<td>0.24</td>
<td>0.45</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Which tracer to assess biology?

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

\[ Cu^{I}\text{ATSM} + H_2O \rightarrow Cu^{II}\text{ATSM} + RSH \]

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

\[ Cu^{I}\text{RS} \rightleftharpoons Cu^{II}\text{ATSM} + H_2O \]

\[ BOUND \]

\[ DISSOCIATION \]


\[ pO_2 \text{ transformation functions} \]

\[ Cu-ATSM \text{ model} \]

\[ FMISO \text{ model} \]


\[ Prescription function \]

\[ pH = 7.1 \]

\[ pH = 7.2 \]

\[ pH = 7.3 \]

8/2/2012
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 Mean (Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>Intracellular Acidity</td>
<td>7.1 – 7.3 (Gerweck 1998)</td>
<td>4% (10%)</td>
</tr>
<tr>
<td>HP</td>
<td>Dose Boost vs. Hypoxic Proportion Function</td>
<td>95% CI</td>
<td>5% (14%)</td>
</tr>
<tr>
<td>Pmid</td>
<td>Half-max Sensitization pO₂</td>
<td>2 – 5 mmHg (Nilsson 2002)</td>
<td>1% (2%)</td>
</tr>
<tr>
<td>OER</td>
<td>Max Oxygen Enhancement Ratio</td>
<td>1.4 – 3.0 (Chan 2008)</td>
<td>1% (2%)</td>
</tr>
<tr>
<td>Overall</td>
<td>Patient</td>
<td>10% (17%)</td>
<td>20% (60%)</td>
</tr>
</tbody>
</table>

How many patients need dose painting?

- Imaging \(\rightarrow\) 1/12 or 8.3%
- Eppendorf \(\rightarrow\) 6/69 or 8.7%
Motion impact on dose painting

Dose painting workflow

Heuristic Modeling and Empirical Data

Uncertainty Characterization and Validation

Which biology

Micro → Macro

Tracer

Extraction of biology

Motion

Set-up

Outcome uncertainties

What phenotype should we dose paint?

1. Hypoxia (Cu-ATSM PET)
2. Metabolism (FDG PET)
3. Proliferation (FLT PET)
4. It depends on the histology
5. Whatever we have available in the hospital
WHAT AND WHERE TO TARGET?

- Using molecular imaging helps in target definition, but still many issues to resolve:
  - Choice of molecular imaging
  - Image quantification
  - Automatic segmentation
  - Validation clinical trials

- Molecular imaging-assisted target definition using molecular imaging in qualitative way is the way to go at present!

- Dose painting is an extremely exciting concept, but we are just at the beginning

Response during radiation therapy

FDG PET and radiation therapy

FDG PET and radiation therapy


FDG PET and radiation therapy


Radiation induced inflammation

- Radiation induced inflammation is a known effect – temporal and spatial dependence
- Not known how much it is a confounding factor in treatment assessment
- FDG PET shows increased uptake post therapy

FDG PET/CT

3 months post RT
FDG PET late response

- **HNSCC:** Negative FDG PET results post chemoRT have a high NPV (95%), but low PPV (50%) (Schöder et al 2009, J Nucl Med, 50:74S)

- **NSCLC:** 80% decrease in FDG PET SUV_{max} post chemoRT has 90% sensitivity, 100% specificity, and 96% accuracy for predicting pathologic response (Cerfolio et al 2004, Ann Thorac Surg, 78:1903)

- **Rectal cancer:** 70% decrease in FDG PET SUV_{max} post chemoRT has 79% specificity, 81% sensitivity, 77% PPV, 89% NPV and 80% accuracy for predicting pathological response (Caprici et al 2007, Eur J Nucl Med Mol Imaging, 34:1583)

- **Esophageal cancer:** Mixed results - in adenocarcinomas negative FDG PET post chemoRT has a high PPV, elsewhere inconclusive (Krause et al 2009, J Nucl Med, 50:S9)

FLT PET and radiation therapy

Application: Treatment adaptation
Application: Treatment adaptation

Application: Dose painting

Should we use FDG PET for treatment response assessment?

- 1. Absolutely
- 2. Yes, for post-treatment assessment
- 3. Yes, for early-treatment assessment
- 4. If there are enough hospital resources
- 5. If the physician requests it, it doesn’t matter anyway
WHAT AND WHERE TO ASSESS?

- PET imaging for response assessment in RT still in its infancy, but with some encouraging results
  - Late FDG PET response assessment has high predicting value of pathological response in many tumors
  - Early FDG PET response assessment limited because of radiation-induced inflammation
  - Alternatives, especially early FLT PET response assessment promising for early assessment but lacks clinical validation
- Normal tissue assessment should not be forgotten

Thanks to:

- Image-guided therapy group
  - Vikram Adhikari
  - Tyler Bradshaw
  - Enrique Cuna
  - Matt Le Fontaine
  - Paulina Galavis
  - Stephanie Harman
  - Koala Yip
  - Former students...

- Medical Oncology/Hematology
  - Glenn Liu
  - George Wilding
  - Mark Juckett
  - Brad Kahl
  - Anne Traynor

- Human Oncology
  - Søren Bentzen
  - Paul Harari
  - Mark Ritter

- Radiology
  - Scott Perlman
  - Chris Jakobovits

- Veterinary School
  - Lisa Fyfe
  - David Vall

- Medical Physics
  - Ross McDonald
  - Jerry Nichols
  - Onofre De Jesus

- Phase I Office

- Funding
  - NIH, PCF, UWCCC, Pfizer, AstraZeneca, Amgen, EntreMed

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