Promise and challenges of PET for target definition and treatment response evaluation

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Role of imaging in oncology

Qualitative and quantitative imaging

PET imaging uncertainties

Imaging for target definition

Images are mostly used in diagnostic context – diagnostic imaging (qualitative)

Imaging in therapeutic context is completely different – therapeutic imaging (quantitative)

Very limited experience with imaging in treatment context, compared to diagnostic!

Very dangerous to use diagnostic quality imaging in a therapeutic context (qualitative ≠ qualitative)

Target definition – a mess

Close-up of the mess

<table>
<thead>
<tr>
<th></th>
<th>GTV_{H}</th>
<th>GTV_{vis}</th>
<th>GTV_{2.5}</th>
<th>GTV_{50}</th>
<th>GTV_{ref}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum</td>
<td>138</td>
<td>115</td>
<td>93</td>
<td>31</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>(+40%)</td>
<td>(+65%)</td>
<td>(+54%)</td>
<td>(-25%)</td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>22</td>
<td>12</td>
<td>8.8</td>
<td>1.7</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>(-55%)</td>
<td>(-60%)</td>
<td>(-92%)</td>
<td>(-90%)</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>76</td>
<td>58</td>
<td>60</td>
<td>17</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>(-20%)</td>
<td>(-16%)</td>
<td>(-76%)</td>
<td>(-63%)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>42</td>
<td>33</td>
<td>30</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>(+30%)</td>
<td>(+34%)</td>
<td>(+13%)</td>
<td>(+20%)</td>
<td></td>
</tr>
</tbody>
</table>


Why such a mess?

What is the real tumor extent?

Different modalities – different answers

Future – dose painting?

Daisne et al 2004, Radiology 233, 93.


Daisne et al 2004, Radiology 233, 93.


All numbers in ml (% difference)


Why such a mess?

Source to background ratio

Activity threshold (% of the max)

Objects: spheres from 2.1 to 92.9 ml
Reconstruction: 3D OSEM, 4 mm FWHM post filter

Daisne et al 2004, Radiology 233, 93.

Different modalities – different answers

Average Mismatch of Lacrimal GTV between Imaging Modalities and the Surgical Specimen

Daisne et al 2004, Radiology 233, 93.

Future – dose painting?


What targets to choose?

**Hypoxia:**

**Metabolism:**

Possible targets

- Increased cellular metabolism
  - Increased glycolysis
  - Increased amino-acid metabolism

- Rapid cellular proliferation

- Subverted cellular regulation
  - Intracellular signaling
  - Cell-to-cell signaling
  - Extracellular matrix signaling

- Evading cellular death

Altered tumor microenvironment:
- Hypoxia
- Changes in perfusion
- Changes in diffusion

FDG FLT CuATSM

Spatially robust target

FDG FLT CuATSM

Spatially ambiguous target

FDG FLT CuATSM

What to do with this information?

Proliferation

Prescription function

Dose painting

Proliferative and hypoxic

Proliferative

Hypoxic

Hypoxia

Hypoxic

Proliferation
Anatomic response criteria

- **WHO (Miller, Cancer, 207, 1981):**
  - The size of a tumor should be estimated based on two perpendicular diameters
  - Positive tumor response to therapy defined as a reduction of at least 50% in the product of these two diameters

- **RECIST (Response Evaluation In Solid Tumors) (Therasse, JNCI, 205, 2000):**
  - The size of a tumor is estimated based on unidimensional measurement
  - Positive tumor response to therapy is defined as at least 30% decrease in the largest dimension of the tumor

**EORTC response criteria**

- **Complete Metabolic Response (CMR):** Complete resolution of FDG uptake within the tumor volume

- **Partial Metabolic Response (PMR):** A reduction of a minimum of 15-25% in tumor FDG SUV after one cycle of chemotherapy, and greater than 25% after more than one treatment cycle. No recommendation for radiotherapy!

- **Progressive Metabolic Disease (PMD):** Increase in FDG tumor SUV of greater than 25% within the tumor region, or increase of extend of FDG uptake (20% in the longest direction) or appearance of new lesions

- **Stable Metabolic Disease (SMD):** Increase of less than 25% or a decrease of less than 15% in tumor FDG SUV and no visible increase in extent (20% in the longest dimension)

**Treatment assessment in RT**

- 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 and radiation therapy**

FDG PET and radiation therapy


Temporal development

Pre ~30 days ~3 months

Day 3 Day 6

FLT-PET/CT

Multimodality longitudinal assessment

Pre-treatment Mid-treatment (1 wk of XRT)


Predicting response

Treatment

<table>
<thead>
<tr>
<th>Hypoxia Status</th>
<th>Chemoboost</th>
<th>TPZ/CIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No hypoxia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoxia in primary tumor and/or nodes</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>No residual hypoxia</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Residual hypoxia in primary tumor and/or nodes</td>
<td>0</td>
<td>14</td>
</tr>
</tbody>
</table>


Predicting response

Adaptive radiotherapy

Adaptive radiotherapy

Pre-treatment

Mid-treatment
(1 wk of XRT)

Pre-treatment

Mid-treatment

Normal tissue response


Conclusions

- Molecular imaging for target definition
  - Still in its infancy
  - Understanding limitations of molecular imaging
  - Many uncertainties remain (GTV-PTV)
  - Great potential for dose painting
- Molecular imaging for treatment assessment
  - Still in its infancy
  - Many applications for tumor assessment (adaptation, dose painting)
  - Normal tissue assessment

Thanks to:

- Image-guided therapy group
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