Positron Emission Tomography for Treatment Assessment

Robert Jeraj
Department of Medical Physics
University of Wisconsin – Madison, WI
rjeraj@wisc.edu

Why treatment assessment?

- Based on early treatment assessment one could modify treatment:
  - If likely not successful:
    - Escalate therapy
    - Change therapy
    - Selectively add dose (RT)
  - If likely successful:
    - Deescalate therapy
    - Stop therapy early

- Enormous benefits for the patient - improved tumor control, reduced side effects, and costs

Treatment assessment now

- Histopathological evaluation:
  - Typically by regression score (viable tumor vs. fibrosis), e.g., Salzer-Kuntschik for osteosarcomas
  - Limitations: need complete resection, problem with point biopsies because of tumor heterogeneities

- Radiological evaluation:
  - Defined by the therapy-induced reduction of tumor size: WHO, RECIST
  - Limitations: numerous
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 should be 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 **at least 30%** decrease in the largest dimension of the tumor

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**Ideal...**

![ideal CT scan image]

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**... and reality**

![reality CT scan image]

**Inherent inconsistencies in expert observers: 15-40%**

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**Ideal...**

![ideal CT scan image]

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**... and reality**

![reality CT scan image]
Other issues...

- **Tumor shrinkage** is only the final step in a complex cascade of cellular and subcellular changes after treatment.

- **Several cycles** of therapy (radiotherapy fractions, chemotherapy) are needed before treatment response can be assessed by anatomic imaging.

- **Residual mass** is often present after treatment – it is hard to differentiate between viable tumor posttreatment changes, such as scarring and fibrosis.

Visual example

CT scan and comparable FDG-PET scan in a patient with gastrointestinal stromal tumor (GIST) with hepatic metastatic lesions.

FDG PET response criteria

- **EORTC FDG PET response criteria** (Young et al, Eur J Cancer 35(13), 1773, 1999):
  - **Patient preparation** – overnight (6h) fasting
  - **Timing of scans** – within 2 weeks of Tx
  - **Attenuation corrections** – no recommendation
  - **Uptake measurements** – SUV<sub>GDA</sub> recommended
  - **Tumor sampling** – SUV<sub>max</sub> and SUV<sub>mean</sub>
  - **Response** – complicated

Typical behavior of FDG uptake
**EORTC response criteria**

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

- **Partial Metabolic Response (PR):** 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)

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**Prognostic relevance of FDG-PET AFTER therapy**

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Ref</th>
<th>No pat</th>
<th>Survival respond (mo)</th>
<th>Survival non-resp (mo)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head neck</td>
<td>Kunkel 2003</td>
<td>35</td>
<td>&gt;200</td>
<td>18</td>
<td>0.002</td>
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<tr>
<td>Esophagus</td>
<td>Flamen 2002</td>
<td>36</td>
<td>&gt;24</td>
<td>7</td>
<td>0.005</td>
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<tr>
<td>Lung</td>
<td>Retting 2004</td>
<td>34</td>
<td>&gt;20</td>
<td>18</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>Genit</td>
<td>Grigsby 2004</td>
<td>152</td>
<td>&gt;200</td>
<td>&gt;20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Several 2001-04</td>
<td>260</td>
<td>(130,400)</td>
<td>1.20</td>
<td></td>
</tr>
</tbody>
</table>

All chemoradiotherapy except lymphoma (chemo only)

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**Prognostic relevance of FDG-PET DURING therapy**

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Ref</th>
<th>Crit</th>
<th>Survival respond (mo)</th>
<th>Survival non-resp (mo)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Head neck</td>
<td>Bin 2002</td>
<td>47</td>
<td>50%</td>
<td>&gt;130</td>
<td>0.004</td>
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<tr>
<td>Esophagus</td>
<td>Flam 2002</td>
<td>36</td>
<td>50%</td>
<td>&gt;130</td>
<td>0.01</td>
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<tr>
<td>Lung</td>
<td>Retting 2004</td>
<td>34</td>
<td>50%</td>
<td>&gt;130</td>
<td>0.005</td>
</tr>
<tr>
<td>Stomach</td>
<td>Grigsby 2004</td>
<td>152</td>
<td>50%</td>
<td>&gt;130</td>
<td>0.001</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Kostakoglou 2002</td>
<td>30</td>
<td>Vis</td>
<td>&gt;24</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

All chemotherapy

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**FDG-PET and radiation therapy**

- **Mid-treatment metabolic response is highly predictive of overall survival**

[Graph showing FDG-PET activity over time with RT (radiation therapy) indicated]
FDG-PET and radiation therapy

Molecular imaging targets in oncology
- Increased cellular metabolism:
  - Increased glycolysis
  - Increased amino-acid metabolism
- Subverted cellular regulation:
  - Intracellular signaling
  - Cell-to-cell signaling
  - Extracellular matrix signaling
- Evading cellular death
- Altered tumor microenvironment:
  - Hypoxia
  - Changes in perfusion
  - Changes in cellularity

Response to targeted therapy in SCC
Avastin (bevacizumab) therapy

Response to chemotherapy in NHL
Guanine nucleotide analogue prodrug (GS-9219)
**Response to chemotherapy in AML**

Antracycline, cytarabine and/or etoposide

<table>
<thead>
<tr>
<th></th>
<th>Mean SUV</th>
<th>Max SUV</th>
<th>Coefficient of Variation</th>
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<tbody>
<tr>
<td>Responders</td>
<td>0.79 ± 0.04</td>
<td>3.4 ± 0.2</td>
<td>0.30 ± 0.01</td>
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<tr>
<td>Non-responders</td>
<td>1.00 ± 0.14</td>
<td>11.4 ± 0.8</td>
<td>0.71 ± 0.04</td>
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<tr>
<td>Partial-responder</td>
<td>0.88</td>
<td>5.1</td>
<td>0.41</td>
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</table>

**Response to molecular targeted therapy**

Sunitinib melate (Sutent)

- **Sunitinib treatment**
- **Withdrawal**

**Response to molecular targeted therapy**

Sunitinib melate (Sutent)

- Pre-treatment
- Week 4
- Week 6

**Response to combination therapy**

Bevacizumab + Bevacizumab/Cisplatin/RT

- Pre-Avastin: Week 1
- Pre-RT: Week 3
- Mid-RT: Week 5
- Post-RT: Week 2
Response to radiation therapy
Adaptive radiotherapy

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

Response to radiation therapy
Adaptive radiotherapy

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

Response to radiation therapy
Temporal development

Dose painting

Pre-treatment
Mid-treatment
Treatment response

Dose painting plan
Dose prescription
Prescription function
Conclusions

- **Treatment assessment** has enormous potential to change patient care
- **Anatomical imaging** used for treatment assessment has many limitations
- **Functional/molecular imaging** is more powerful and versatile in assessment of treatment response
- **Response criteria** are more complex, tumor and tracer dependent
- Need for **clinical trials** with extensive functional/molecular imaging component

Thanks to:

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