Role of Medical Physics in the Era of Precision Medicine

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PRECISION MEDICINE
"4 P’s of medicine": Individuals respond differently to environmental conditions, according to their genetic endowment and their own behavior. In the future, research will allow us to predict how, when, and in whom a disease will develop. We can envision a time when we will be able to precisely target treatment on a personalized basis to those who need it, avoiding treatment to those who do not. Ultimately, this individualized approach will allow us to preempt disease before it occurs, utilizing the participation of individuals, communities, and healthcare providers in a proactive fashion, as early as possible, and throughout the natural cycle of a disease process.

Elias A. Zerhouni, M.D.
Director, National Institutes of Health (NIH), 2008
Ten years later…

Cancer Moonshot

The Precision Medicine Initiative
What is precision medicine?

Peter Hoey; Source: Bayer Healthcare pharmaceuticals
Precision medicine (example)

Sequist et al. 2011, Ann Oncol, 22:2616
How do we assess tumor biology?

**Microscopy**

- Proliferation
- Hypoxia

**Molecular imaging**

- PET/CT

Courtesy of A. van der Kogel
Have you noticed HETEROGENEITY?

Microscopy

| 1 mm |

Molecular imaging

| 5 cm |

Proliferation

Hypoxia

PET/CT

Courtesy of A. van der Kogel
The problem of tumor BIOPSY…

Microscopy

Molecular imaging

1 mm

5 cm

Proliferation

Hypoxia

PET/CT

Courtesy of A. van der Kogel
Tumors are heterogeneous…

- Clonal Selection
- Parallel Evolution
- Dynamic Heterogeneity
- Clonal Dominance
- Stem Cell

Talmadge 2007, Cancer Res 67: 11471-75
...and they are heterogeneous a lot!

Imaging can assess tumor HETEROGENEITY

Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

Marco Gerlinger, M.D., Andrew J. Rowan, B.Sc., Stuart Horswell, M.Math., James Larkin, M.D., Ph.D.,
David Butler, B.Sc., Aengus Stewart, B.Sc.,
Neil Quarmby, B.Sc.,
Claudia Szallasi, M.D.,
Graham Clarke

...branched evolutionary tumor growth, with 63 to 69% of all somatic mutations not detectable across every tumor region...

Tumors are evolving…

Yates and Campbell 2012, Nat Rev Gen 13, 795-806
...and they are evolving a lot!

Imaging can assess tumor EVOLUTION

Johnson et al 2014, Science 343, 189-193
Heterogeneity + Evolution = Resistance

Imaging can assess tumor RESISTANCE

Meacham and Morrison 2013, Nature 501, 328–337
Qualitative vs Quantitative Imaging

Qualitative Imaging (Diagnostics)

Quantitative Imaging (Biomarkers)

Precision Medicine requires PRECISION IMAGING!
QUANTITATIVE IMAGING
How much variability is there?

SNMMI’s Clinical Trials Network (CTN) sent the same phantom to 170 sites, and collected and analyzed the PET/CT images.
How much variability is there?

SNMMI’s Clinical Trials Network (CTN) sent the same phantom to 170 sites, and collected and analyzed the PET/CT images.

What should we do?

Problem

Cause

Sources of Variance

Differences in:
- Patient Handling
- Acq. Protocols
- Reconstruction
- Segmentation
...
What should we do?

Problem: Treat vs. Wait

Measure = 7 ±6

Goal: Treat

Measure = 7 ±1

Cause: Sources of Variance

Differences in:
- Patient Handling
- Acq. Protocols
- Reconstruction
- Segmentation

Solution:

When all participating actors conform...

Requirements for:
- Acquisition Params
- Recon Params
- Resolution
- Noise Reqs
- Processing Params
- Patient Prep & Operation
- Segmentation
- Calibration

Courtesy of Kevin O'Donnell
Qualitative imaging chain

Patient status

Scanning protocol → Data acquisition → Image reconstruction → Image interpretation

Imaging physics

Qualitative
Imaging Biomarkers require quantification of the whole imaging chain!
Role of medical physics

- **Improve image acquisition and reconstruction**
  - Develop more quantitative imaging systems
  - Develop scanner harmonization procedures
  - *Minimize differences between different scanners*

- **Improve image analysis**
  - Develop advanced methods of image analysis
  - *Minimize uncertainties due to “clinical reads”*

- **Understand/model the disease and its progression**
  - Develop models of tumor growth and response
  - *Guide clinical decisions based on observed changes*
How this impacts clinical decisions?

Lung Lesion

Maximum SUV vs. Months

- D710
- DVCT

-39% +89% -76% +74%

0 6 13
How this impacts clinical decisions?

Lung Lesion

Maximum SUV vs. Months

- Harmonized
- Original

D710

-39%
+89%
+13%
+19%
+74%
+3%
-62%
-76%
TUMOR HETEROGENEITY AND RESISTANCE
Let’s look at the metastatic disease

- **Metastasis**: μετά (“next”) + στάσις (“placement”)
  - Cancer-related deaths

- **Bone metastases** present in 90% of advanced prostate cancer patients
  - (Bubendorf et al, Hum Pathol. 2000)
  - Relative **5-year survival rate** is about **30%**
    - (SEER 2006-2012)

Image source: Wikimedia commons

Common destinations from solid tumors: bones, brain, lungs, liver

-

(Gupta and Massagué, Cell 2006; Tofe et al, J Nucl Med 1975)
How can molecular imaging help?

- **Whole body imaging** provides a complete snapshot of the progression of multiple metastases.

- The role of imaging in monitoring treatment response is **not well established** (Wallace et al, J Cancer 2014)
  - Often based on responses of **a few lesions** (Wahl et al, J Nucl Med 2009; Doot et al, Transl Oncol 2010)
    - Limited assessment in **disease burden**

- **¹⁸F-NaF PET/CT**, imaging of bone metabolism, ideal for monitoring bone metastases
  - **100% sensitivity and 70-100% specificity** (Even-Sapir et al, J Nucl Med 2006)
  - **Quantitative and reproducible** whole body scans (Kurdziel et al, J Nucl Med 2012)
Repeatability of NaF PET/CT

- **Multicenter** trial of metastatic castrate-resistant prostate cancer patients
  - received pre-treatment test-retest $^{18}$F-NaF PET/CT scans

<table>
<thead>
<tr>
<th>Site</th>
<th>Patients</th>
<th>Bone lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Wisconsin Carbone Cancer Center</td>
<td>18</td>
<td>265</td>
</tr>
<tr>
<td>Memorial Sloan Kettering Cancer Center</td>
<td>11</td>
<td>78</td>
</tr>
<tr>
<td>National Cancer Institute</td>
<td>6</td>
<td>68</td>
</tr>
<tr>
<td><strong>All</strong></td>
<td><strong>35</strong></td>
<td><strong>411</strong></td>
</tr>
</tbody>
</table>

Test/retest scans (3-5 days apart)

Standardized Uptake Value (SUV) metrics extracted from an ROI

$\text{SUV}_{\text{max}}$ – maximum uptake

$\text{SUV}_{\text{mean}}$ – average uptake

$\text{SUV}_{\text{total}}$ – total uptake
What is our quantitative accuracy?
What is our quantitative accuracy?
Quantitative Total Bone Imaging (QTBI)

Scan 1
- NaF PET/CT Scan
- Lesion segmentation
- Image feature quantification

Scan 2
- NaF PET/CT Scan
- Lesion segmentation
- Image feature quantification

Registration

Lesion matching

Difference quantification

Quantitative Total Bone Imaging (QTBI)

NaF PET/CT Acquisition

NaF PET Uptake Localization

Articulation Segmentation

Lesion Segmentation

Quantitative Total Bone Imaging (QTBI)

SUV Segmentation

Lin et al., JNM 2016

Lesion-based Response

Yip and Jeraj, PMB 2014

Yip et al., PMB 2014

Articulated Registration

Yip et al., PMB 2014

Progressing

Stable

Responding

SUV

30
How much is repeatability?

Bland-Altman plots assess measurement agreement \cite{Bland and Altman, J Bioph Stat 2007}

\[ RC = 1.96\sqrt{\sigma} \]

**Imaging sites:**
- UWCCC
- MSKCC
- NCI

**UWCCC significantly narrower variance** \( (p < 0.001) \)

*Log-transformed*
Test-retest limits of agreement (LOA) can be used to define significant changes in imaging features in individual lesions (Lin et al, J Nucl Med 2016)

Limits of agreement:

\[ LOA_{95\%} = (e^{(B-RC)}, e^{(B+RC)}) \]

\[ B = \frac{m_2}{m_1} \]

\[ RC = 1.96\sqrt{\sigma} \]
Imaging site affects repeatability

<table>
<thead>
<tr>
<th>n</th>
<th>pROI</th>
<th>1UW</th>
<th>2MSK</th>
<th>3NCI</th>
<th>All</th>
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<tbody>
<tr>
<td>18</td>
<td>pSUV_{max}</td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>10</td>
<td>pSUV_{mean}</td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>6</td>
<td>pSUV_{total}</td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
</tbody>
</table>

95% LOA
Lesion location affects repeatability

Atlas-based segmentation identified lesion location *(Yip, Perk, and Jeraj, 2014)*

<table>
<thead>
<tr>
<th>Location</th>
<th>No. lesions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skull</td>
<td>9 (2.19)</td>
</tr>
<tr>
<td>Ribs</td>
<td>78 (18.98)</td>
</tr>
<tr>
<td>Cervical</td>
<td>17 (4.14)</td>
</tr>
<tr>
<td>Thoracic</td>
<td>62 (15.09)</td>
</tr>
<tr>
<td>Lumbar</td>
<td>54 (13.14)</td>
</tr>
<tr>
<td>Sacrum</td>
<td>31 (7.54)</td>
</tr>
<tr>
<td>Shoulder</td>
<td>34 (8.27)</td>
</tr>
<tr>
<td>Sternum</td>
<td>15 (3.65)</td>
</tr>
<tr>
<td>Arm</td>
<td>13 (3.16)</td>
</tr>
<tr>
<td>Pelvis</td>
<td>70 (17.03)</td>
</tr>
<tr>
<td>Leg</td>
<td>28 (6.81)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>411 (100%)</strong></td>
</tr>
</tbody>
</table>

Coefficient of variation (\(CV\))

\[
CV = \frac{\sigma_w}{\mu}
\]

Repeatability poorest in ribs
WHAT INFORMATION CAN WE EXTRACT FROM IMAGING?
Does this make an impact?

- 56 mCRPC patients receiving multiple NaF PET/CT scans early in treatment
  - Taxane-based therapy (N = 16)
  - Androgen Receptor (AR) pathway inhibitors (N = 40)

- QTBI* used for Quantitative NaF PET/CT analysis

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Patent No: US 9,161,720 (Exclusive license to AIQ)
Global correlation to PFS

Significant NaF PET/CT correlates

Baseline

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUV&lt;sub&gt;max&lt;/sub&gt;</td>
<td>1.51</td>
<td>0.01</td>
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<tr>
<td>SUV&lt;sub&gt;mean&lt;/sub&gt;</td>
<td>1.64</td>
<td>0.002</td>
</tr>
<tr>
<td>N&lt;sub&gt;lesions&lt;/sub&gt;</td>
<td>1.43</td>
<td>0.01</td>
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</table>

Mid-Tx

<table>
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<tr>
<th>Parameter</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUV&lt;sub&gt;max&lt;/sub&gt;</td>
<td>1.62</td>
<td>0.01</td>
</tr>
<tr>
<td>SUV&lt;sub&gt;mean&lt;/sub&gt;</td>
<td>1.84</td>
<td>0.0006</td>
</tr>
<tr>
<td>SUV&lt;sub&gt;total&lt;/sub&gt;</td>
<td>2.03</td>
<td>0.0002</td>
</tr>
<tr>
<td>N&lt;sub&gt;lesions&lt;/sub&gt;</td>
<td>1.61</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

Δ (%) 

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔSUV&lt;sub&gt;total&lt;/sub&gt;</td>
<td>1.65</td>
<td>0.003</td>
</tr>
<tr>
<td>ΔN&lt;sub&gt;lesions&lt;/sub&gt;</td>
<td>1.52</td>
<td>0.02</td>
</tr>
<tr>
<td>New Lesions</td>
<td>1.64</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Harmon et al 2017, J Clin Oncol, 7(1):9370
Mid-Tx functional burden

High NaF burden

3900 g/mL·cm³
30 lesions

Mid-Treatment SUV<sub>total</sub>

Low NaF burden

2900 g/mL·cm³
57 lesions

Tumor burden is predictive of the outcome

Harmon et al 2017, J Clin Oncol, 7(1):9370
Local disease heterogeneity

Does heterogeneity in lesion response impact our prediction?

43 patients with paired baseline and mid-Tx scans
- 3228 lesions tracked across scans
- 75.2 lesions/patient (range: 3 – 315)

Classify lesion response based on local test-retest analysis (volume dependent)

Record the proportion (%) of lesions contained within each response classification group

- New
- Progressing
- Stable
- Responding
- Disappeared

Harmon et al., AAPM (2016)
40/43 patients exhibit response heterogeneity regardless of burden.

**Local disease heterogeneity**

Inter-lesion heterogeneity is HUGE and variable!
40/43 patients exhibit response heterogeneity regardless of burden.

Non-favorable response dominates progression events!

**Local disease heterogeneity**

- Proportion of iSUV\textsubscript{total} favorably (iCR + iPR) responding lesions
- Prop. of iSUV\textsubscript{mean} non-favorably (iPD + iND) responding lesions

Radiographic Progression-Free Survival

![Graph showing progression-free survival](image)

**Inter-lesion heterogeneity is predictive of outcome**

![Graph showing progression rates](image)
Sample patient

- 73 year old, diagnosed in 2/2012 w/ PSA=764 and diffused bony mets (biopsy confirmed)
- Treated with combined androgen blockade; developed CRPC by 12/2012
- Palliative XRT (T6-L1) in 1/2013
Sample patient

Baseline Scan (B1) 12 week response (T1) 54 week response (T2) 62 week response (T3)

Abiraterone Docetaxel

Progression scan
“Oligo-resistance”

Inter-lesion heterogeneity could be targeted
Evolution of resistance

Medivation/Pfizer: MDV3100-18 clinical trial
All imaging aspects (coordination, analysis) managed by AIQ
Bridging the gap…

Understanding biological basis of heterogeneity

PCF Global Challenge 2014
Jeraj, Liu, Tomlins, Perlman, Simoncic
Summary

- Precision Medicine is powerful, but needs to better incorporate **molecular imaging** to fully assess:
  - Spatial information (Heterogeneity)
  - Temporal information (Evolution)
  - Change information (Resistance)

- **Medical physics** is an integral (but often “hidden”) part of Precision Medicine that enables:
  - Quantitative image acquisition
  - Advanced image analysis

  - Better understanding of the disease (my next talk 😊)
Role of medical physics in the era of precision medicine: Prof. Robert Jeraj, PhD

We invite you to the 18th Institute colloquium in the academic year 2017/18. The colloquium will be held on Wednesday June 27, 2018 at 1 PM in the main Institute lecture hall, Jamova 39, Ljubljana. To read the abstract click here. Past colloquia are posted on this website. 

prof. dr. Robert Jeraj

University of Wisconsin, Madison, USA
University of Ljubljana, Ljubljana
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  - Amy Weisman
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  - Mark Albertini
  - Ruth O’Regan
  - …

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