Translational imaging research at the UWCCC

Robert Jeraj, PhD
Associate Professor of Medical Physics, Human Oncology, Radiology and Biomedical Engineering
Director of Translational Imaging Research Program
University of Wisconsin Carbone Cancer Center, Madison, WI

rjeraj@wisc.edu
Problem of tumor heterogeneity

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

How do we assess heterogeneity?

Microscopy

1 mm

Molecular imaging

5 cm

Proliferation
Hypoxia

Courtesy of A. van der Kogel, Nijmegen, NL
MICAD: Molecular Imaging and Contrast Agent Database

Molecular Imaging and Contrast Agent Database (MICAD)

Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

Copyright and Permissions

1444 agents listed

MICAD is a key component of the NIH Common Fund (formerly NIH Roadmap); it is developed by the National Center for Biotechnology Information (NCBI), at the National Institutes of Health (NIH). More about MICAD »

After June 30 of 2013, new and revised chapters will no longer be uploaded to the MICAD website. However, the current chapters remain available online.

1444 agents currently listed. Latest update: June 27, 2013.

MICAD available through PubMed: MICAD chapters are now accessible through PubMed. To retrieve a list of all MICAD records, query PubMed for "Molecular Imaging and Contrast Agent Database (MICAD)"[book].

FDA Approved Contrast Agents: Download a list of FDA approved contrast agents (Latest update: January 2013).

FDA approved: 119 active; 241 total (incl. discontinued)
Tumor heterogeneity

FDG PET/CT (metabolism)

FLT PET/CT (proliferation)

Cu-ATSM PET/CT (hypoxia)

Nyflot, … Jeraj 2012, Radiother Oncol 105(1):36-40
Tumor heterogeneity

FDG PET/CT (metabolism)

FLT PET/CT (proliferation)

Cu-ATSM PET/CT (hypoxia)
Biological heterogeneity

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

Nyflot, ... Jeraj 2012, Radiother Oncol 105(1):36-40
Biological heterogeneity

Sarcoma Example

Carcinoma Example

Bradshaw, … Jeraj 2013, J Nucl Med 54(11),1931.
Inter-patient heterogeneity

FDG  FLT  Cu-ATSM  SARCOMA

Carcinoma

Bradshaw, ... Jeraj 2013, J Nucl Med 54(11), 1931.
RT: Dose painting

Anatomical imaging
Population-based
Uniform dose

Molecular imaging
Patient-specific
Non-uniform dose

Imaging as a biomarker

Tumor effects
- Target effect
  - Imaging biomarker

IMAGING

Manifestation
- Clinical outcome
  - Imaging biomarker as a surrogate endpoint
Imaging as a biomarker

Normal tissue effects

Local tissue damage

Organ dysfunction

Resolution

Subclinical

Clinical

Manifestation

Imaging as a biomarker

Imaging biomarker

Imaging biomarker as a surrogate endpoint

Conventional response assessment

- **WHO (1979, 1981)**\(^1,2\)
  - anatomic

- **RECIST (2000, 2009)**\(^3,4\)
  - **Response Evaluation Criteria In Solid Tumors**
  - anatomic, CT/MR based
  - unidimensional
  - 4 response categories (CR, PR, SD, PD)

<table>
<thead>
<tr>
<th>complete response</th>
<th>partial response</th>
<th>stable disease</th>
<th>progressive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>-100%</td>
<td>-60%</td>
<td>-30%</td>
<td>0%</td>
</tr>
</tbody>
</table>

\(^1\)WHO 1979, \(^2\)Miller et al. 1981, \(^3\)Therasse et al. 2000, \(^4\)Eisenhauer et al. 2009
PET-based response assessment

- **EORTC, NCI Recommendations** (1999, 2005)\(^1,^2\)
  - SUV-based approach
  - \(\text{SUV}_{\text{mean}}\) and \(\text{SUV}_{\text{max}}\)
  - Response categories with thresholds (\(\text{CR}, \text{PR}, \text{SD}, \text{PD}\))
  - Problems
    - \(\text{SUV}_{\text{mean}}\) – collapse information, sensitivity issues
    - \(\text{SUV}_{\text{max}}\) – noise contamination
    - fails to use all available functional data
      - distribution
      - heterogeneity
    - no response threshold validation
    - few sensitivity studies
    - alternative measures

- **PET Response Criteria in Solid Tumors (PERCIST)** (2009)\(^3\)
  - \(\text{SUV}_{\text{peak}}\)

\(^1\)Young *et al* 1999, \(^2\)Shankar *et al* 2006, \(^3\)Wahl *et al* 2009
Definition of the measures

Vanderhoek, ... Jeraj 2012, J Nucl Med 53: 4-11
Images are more than just one number!

- Size measures
  - Volume
  - 1D size (axial)

- Standardized Uptake Value (SUV) measures:
  - $\text{SUV}_{\text{mean}}$
  - $\text{SUV}_{\text{total}}$
  - $\text{SUV}_{\text{max}}$
  - $\text{SUV}_{\text{peak}}$

- Uptake Non-uniformity measure:
  - $\text{SUV}_{\text{sd}}$

- ...
But ambiguity of information
But ambiguity of information
Molecular imaging biomarkers in AML

Acute myeloid leukemia patients treated with anthracycline and cytarabine
Acute myeloid leukemia (AML)

Can molecular imaging do better?

Specificity = 43%
NPV = 64%

AML clinical trial

Chemotherapy

Week 0 1 2

FLT 1 FLT 2 FLT 2 FLT 2 FLT 2

PI: Jeraj, Juckett
Quantitative Total Bone Marrow Imaging

FLT PET $\times$ CT Mask $\rightarrow$ FLT PET

Bone Marrow
FLT PET as a biomarker

Pre-therapy

Post-therapy (2 wks)

CLINICAL OUTCOME (6 mo)

Complete remission

Resistant disease

Vanderhoek, … Jeraj 2011, Leuk Res 35: 310
### Early treatment response assessment

<table>
<thead>
<tr>
<th>Complete Remission (6 mo)</th>
<th>Post-therapy</th>
<th>Day 6</th>
<th>Day 5</th>
<th>Day 4</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistant Disease (6 mo)</td>
<td>Post-therapy</td>
<td>Day 2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>SUV(_{\text{mean}})</th>
<th>SUV(_{\text{max}})</th>
<th>Coefficient of Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Remission</td>
<td>0.81 ± 0.03</td>
<td>3.6 ± 0.4</td>
<td>0.33 ± 0.02</td>
</tr>
<tr>
<td>Resistant Disease</td>
<td>6.1 σ</td>
<td>6.5 σ</td>
<td>6.3 σ</td>
</tr>
</tbody>
</table>

\(\sigma\) indicates standard deviation.

**t-test:** \(p<0.001\) for SUV\(_{\text{mean}}\), SUV\(_{\text{max}}\), CV
Heterogeneity of the response

Pre-treatment FLT PET

Post-treatment FLT PET

Pre FLT PET/Pre FLT PET

Post FLT PET/Pre FLT PET

SUV Ratio

Post CT# 0 200 400

Pre CT# 0 200 400

SUV

SUV
Why so low NPV?

NPV = 64%

Vanderhoek, ... Jeraj 2011, Leuk Res 35: 310
Quantitative Total Bone Marrow imaging with FLT PET/CT is used for early assessment of treatment response in AML.

Treatment response is comprehensively characterized and quantified by the total bone marrow.

FLT PET/CT may be an imaging biomarker of response in AML but needs to be validated:
- NCTN U10 Integrated Translational Science Grant (Leukemia; Paietta PI)
- ECOG-ACRIN multicenter trial
Molecular Imaging Biomarkers mCRPC
Multicenter NaF PET/CT clinical trial linked with Quantitative Total Bone Imaging analysis
Drug development in mCRPC

- Osseous metastases are found in 85% of patients

- No standard tools available for assessment of response in bone metastases
  - PCWG2 definitions of PD

- What to do if a subpopulation of lesions keeps responding?

Can imaging be a biomarker of response?
1. **Individual validation (measurement)**
   Successfully measures a quantifiable characteristic both precisely and reproducibly

2. **Internal validation (study)**
   Correlates with clinical endpoint, adds accuracy to precision and reproducibility

3. **External validation**
   Demonstrates similar predictive power in other populations or in other related treatment studies

4. **Broad qualification**
   Can be used as a surrogate in evaluating other classes of disease
Clinical protocol

- NaF PET/CT repeatability, responsiveness, and response assessment in patients with metastatic castrate-resistant prostate cancer to bone treated with either docetaxel-based chemotherapy or androgen receptor (AR)-directed therapies
  - University of Wisconsin Carbone Cancer Center
  - Memorial Sloan Kettering Cancer Center
  - National Cancer Institute

- Total N = 96 evaluable patients (32/site)
  - 60 test-retest (20/site)
  - 48 docetaxel-based treatment (16/site)
  - 48 AR-directed therapies (16/site)

PI: Liu, Jeraj
Clinical protocol

**Docetaxel Therapy Cohort**

- **Docetaxel**
  - **Pre-Treatment**
    - 1
  - **On-Treatment**
    - 0, 3, 6, 9, 12 weeks
  - **Baseline:** BL 1, BL 2
  - **Week:** Wk 8

**AR-Directed Therapy Cohort**

- **Baseline:** BL
- **Week:** Wk
- **AR-Directed Therapy**
- **Pre-Treatment**
  - 1
- **On-Treatment**
  - 0, 3, 6, 9, 12 weeks
  - **Wk 6**, **Wk 12**
- **Baseline:** BL 1, BL 2
- **Week:** Wk 8

PI: Liu, Jeraj
Bone scintigraphy vs PET/CT

Tc-99m MDP Bone scan

NaF PET/CT

Imaging harmonization

- **Harmonization of acquisition**
  - Minimize limitations due to different scanner hardware and software

- **Harmonization of scanning protocols**
  - Creating harmonized imaging protocols, which need to be tuned to specific scanners

- **Harmonization of image analysis**
  - Unifying image analysis protocols, which often means centralized analysis

- **Harmonization of reporting**
  - Unified reporting, otherwise the data can
<table>
<thead>
<tr>
<th>Site</th>
<th>SUV&lt;sub&gt;max&lt;/sub&gt;</th>
<th>SUV&lt;sub&gt;mean&lt;/sub&gt;</th>
<th>SUV&lt;sub&gt;total&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>SD</td>
<td>mean</td>
</tr>
<tr>
<td>Site 1</td>
<td>1 %</td>
<td>9 %</td>
<td>-1 %</td>
</tr>
<tr>
<td>Site 2</td>
<td>-7 %</td>
<td>24 %</td>
<td>-2 %</td>
</tr>
<tr>
<td>Site 3*</td>
<td>6 %</td>
<td>2 %</td>
<td>3 %</td>
</tr>
</tbody>
</table>

* 3 patients only
Test/retest - lesions ($\text{SUV}_{\text{max}}$)

- **Site 1**: -0.5 +/- 15
- **Site 2**: -3 +/- 21
- **Site 3**: 8 +/- 20
Quantitative Total Bone Imaging (QTBI)

CT Mask \times NaF PET = \text{Skeletal NaF Uptake} \rightarrow \text{Total Bone Involvement (SUV Threshold)}
Quantitative total bone imaging

Articulated Registration

Lesion matching

Yip, ... Jeraj 2014, Phys Med Biol (in press)
Unique QTBI output

**Identification**
- All lesions

**Response Characterization**
- Responding lesion
- Non-responding lesion

**Response Quantification**
-50% to +50%
Inter-lesion response heterogeneity

Treatment Response

- Responding lesion
- Non-responding lesion

SUV\text{\ max} Response (%)
Abiraterone Tx

- 67 yo male Dx 1998 with PSA 9.2 ng/mL; Gleason 3+3
- Prior therapies: AS, ADT, steroid sulfatase inhibitor, XRT left shoulder, docetaxel + AZD2171
- Enrolled on NaF Trial 8/2/2012 with rising PSA
  - PSA 137.3 ng/mL
  - Bone scan: increased axial and appendicular mets
  - CT: increased LAN and bone sclerosis
- Therapy: Abiraterone with prednisone started 8/6/2012
  - PSA 38.6 (9/2012)
  - PSA 55 (10/2012)
  - PSA 132 (11/2012)
  - CT after cycle#3 with decreased LAN; increased size of sclerosis
  - Taken off study 12/26/2012 for increasing pain; increased sclerosis on bone scan; new liver mets and increasing LAN on CT
QTBI non-responder (Week 12)
Which imaging biomarkers?

Texture Feature

Lesion
How can we understand this?

Harmon, … Jeraj 2013 (AAPM)
Is 'big data' the new 'big oil'?

As big data surpasses oil production and economic value, stricter global standards and steep fines may not be far off. FULL STORY |
Conclusions – Imaging in mCRPC

- **Quantitative Total Bone Imaging with NaF PET/CT developed as an imaging response biomarker**

- Complete *imaging harmonization*:
  - Acquisition
  - Scanning protocol
  - Image analysis
  - Reporting

- Treatment response is *comprehensively quantified* for all AND each lesion:
  - Total disease burden appears a potential biomarker candidate
  - Individual lesion response can indicate drug efficacy beyond clinical progression
TIRWG website goes live today!
Example: Consultation service

Translational Imaging Research Working Group

Consultation Services

Centralized imaging consultation services are provided by the UWCCC Image Response Assessment Team (IRAT) and are accessed through the completion of an IRAT Questionnaire and electronically submitted to the TIRC Administrative Coordinator. IRAT consulting team members provide expertise and recommendations on all imaging modalities, imaging biomarkers and the development of clinical protocols with imaging endpoints.

IRAT Consulting Team

<table>
<thead>
<tr>
<th>CT</th>
<th>MRI</th>
<th>PET/CT</th>
<th>US</th>
<th>Imaging Analysis</th>
<th>Oncology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meghan Lubner, MD</td>
<td>Fred Kelcz, MD, PhD</td>
<td>Scott Perlman, MD</td>
<td>Meghan Lubner, MD</td>
<td>Sean Fain, PhD</td>
<td>Glenn Liu, MD</td>
</tr>
<tr>
<td>Frank Ranallo, PhD</td>
<td>Frank Korosec, PhD</td>
<td>Robert Jeraj, PhD</td>
<td>Timothy Hall, PhD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ALL clinical protocols that include imaging components require **TIRWG review**
  - Average time is 5 days (all during PRMC 7 day window)

**DOWGs utilizing TIRWG:**
  - GU
  - GI
  - Breast
  - Lung
  - Surgery
  - Radiation/Oncology
  - CTD2
  - Melanoma
  - GYN
  - Heme/Lymphoma
TIRWG meetings

Translational Imaging Research Working Group

Meetings, Collaborations and Presentations

The TIRWG meets the first Friday of every month, to discuss UWCCC imaging clinical trials, case presentations of patients actively imaged on clinical trials and protocol-related issues and reviews. Additionally, the TIRWG meetings provide a venue for basic, translational and clinical researchers to share research findings, new imaging agents and technologies and changes in clinical imaging standards. By sharing developments in the laboratory and clinical worlds, ongoing collaborations are strengthened, new hypothesis generated and better studies designed.

2014 TIRWG Meetings

Dates: March 7, April 4, May 2, June 6, July 11, August 1, September 5, October 3, November 7, December 5

Time: 8-9am

Location: 7001A, Wisconsin Institutes for Medical Research
Wisconsin Oncology Network of Imaging Excellence (WONIX)

GOVERNOR SCOTT WALKER ANNOUNCES INVESTMENT IN THE UW CARBONE CANCER CENTER (THURSDAY, FEBRUARY 14, 2013)

February 14, 2013
For Immediate Release

Governor Scott Walker Announces Investment in the UW Carbone Cancer Center

Madison—Today, Governor announced a $3.75 million state taxpayer investment in the UW Carbone Cancer Center Investment to accelerate the development of and access to cutting-edge molecular imaging technology developed by the Center.

“Cancer is one of Wisconsin’s deadliest health problems,” said Governor Walker. “This investment will leverage investment in the private sector to help the Wisconsin Oncology Network of Imaging Excellence, which will provide better access to diagnostics and treatment in rural areas. I am hopeful by making targeted investments the state can partner with the private sector to ensure Wisconsin remains on the cutting edge of healthcare systems.”

According to the Wisconsin Department of Health Services, in Wisconsin, 11,268 Wisconsinites were killed by cancer in 2010, more than one person every hour and nearly a quarter of all deaths in the state that year. A recent study found that the cost of cancer treatment in Wisconsin is expected to grow to $4 billion by the end of 2015. According to the American Cancer Society, nearly 30,000 Wisconsinites were diagnosed with cancer in 2010 or 81 people every day.

Governor Walker’s budget proposal supports the creation of the Wisconsin Oncology Network of Imaging Excellence, along with funding imaging research related equipment and expansion of the Wisconsin Oncology Network. State funding is contingent on DOA approval of a plan to obtain a fundraising match.
- **Enhance Wisconsin Oncology Network (WON)** to be able to conduct advanced molecular imaging clinical trials

- **Supplement imaging expertise of WON members** by the unique imaging resources at UWCCC and UW SMPH:
  - Patient accrual and imaging performed through the WON network
  - Imaging clinical trial design, coordination, analysis and quality assurance performed at UWCCC

- **Reorganize and expand the existing UWCCC Translational Imaging Research (TIRWG) resources** to enable:
  - Consultation
  - Coordination
  - Imaging QA
  through the WONIX network
WONIX working groups

- WONIX Working Groups:
  - Informatics WG
  - Molecular imaging agent WG
  - Imaging QA WG
  - Imaging clinical trial WG

- WG strategic plans:
  - Immediate plans (now)
  - Short-term plans (2 yrs)
  - Long-term plans (5 yrs)
Next steps

- **WONIX Working Group meetings** (Q4 2013)
  - Refining strategic plans (Immediate/Short-term/Long-term)
  - Identifying key personnel
  - Identifying challenges and opportunities

- **WONIX launch** (Q1-Q2 2014)
  - Formal approval process (Board of Regents and DoA/Joint Finance Committee)
  - MOA between UWCCC and WONIX sites

- **WONIX site qualification** (Q2-Q3 2014)
  - Initial assessment of the sites
  - Gradual “roll-out”

- **WONIX clinical trial initiation** (Q3-Q4 2014)
  - MITOS trial already in Q2 2014
Summary

- Imaging is getting a **new role in the era of precision medicine:**
  - Assessment of tumor heterogeneity
  - Assessment of total disease burden

- Imaging is an **indispensable tool** for effective drug development and clinical management:
  - Optimization of treatment schedules, dosing, treatment combinations

- Imaging is still facing **issues:**
  - Quantification
  - Imaging assay validation
  - Imaging biomarker qualification
Thanks to:

- **Image-guided therapy group**
  - Vikram Adhikarla
  - Tyler Bradshaw
  - Enrique Cuna
  - Ngoneh Jallow
  - Matt La Fontaine
  - Stephanie Harmon
  - Christie Lin
  - Surendra Prajapati
  - Matt Scarpelli
  - Urban Simoncic
  - Peter Scully
  - Damijan Valentinuzzi
  - Natalie Weisse
  - Stephen Yip
  - Former students…

- **Funding**
  - NIH, PCF, UWCCC, Pfizer, Medivation, AstraZeneca, Amgen, State of Wisconsin

- **TIRWG/TIRC**
  - Scott Perlman
  - Dona Alberti
  - Katie Kovacich

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

- **Radiology**
  - Tom Grist
  - Chris Jaskowiak

- **Human Oncology**
  - Søren Bentzen
  - Bert van der Kogel
  - Paul Harari
  - Mark Ritter

- **Veterinary School**
  - Lisa Forrest
  - David Vail

- **Medical Physics**
  - Rock Mackie
  - Sean Fain
  - Ed Jackson

- **Phase I Office**