Informatics Infrastructure to Standardize and Optimize Quantitative Imaging in Clinical Trials and Drug Development

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Outline

1. Challenges in clinical cancer research
2. Informatics opportunities and approach
3. Planned deliverables and future work
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Clinical cancer research goals

• Evaluate cancer response to new treatments with great sensitivity so benefits of advances are not overlooked

• Leverage new technologies
  – Molecular medicine is producing new treatments
  – Can exploit quantitative image information (“biomarkers”) about tumor burden
  – Can determine better secondary endpoints based on quantitative imaging biomarkers
  – Can develop/validate better, more sensitive criteria for individual & cohort response
Challenges

• Poor *reproducibility of measurements* on images

• Lack of *coordination and effective communication* between *oncologists and radiologists* and *local vs. central sites* in making quantitative imaging assessments

• Little *integration of multiple quantitative measures* of tumor burden that, taken together, are more informative than individual indicators

• *Lack of tools* for recording quantitative image metadata to enable data sharing and data mining
Oncologist Response Assessment

- Oncologist reviews radiology report & images
- Defines certain lesions as “measurable disease” for tracking
- Applies criteria to assess treatment response

*Manual, labor-intensive, error-prone*
## RECIST Flowsheet

<table>
<thead>
<tr>
<th>Lesion ID</th>
<th>Location/Description</th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right upper lung nodule</td>
<td>2.5 cm</td>
<td>1.2 cm</td>
</tr>
<tr>
<td>2</td>
<td>Liver nodule - segment 5</td>
<td>2.3 cm</td>
<td>1.4 cm</td>
</tr>
<tr>
<td>3</td>
<td>Liver nodule - segment 2</td>
<td>1.7 cm</td>
<td>1.0 cm</td>
</tr>
<tr>
<td></td>
<td>Sum Longest Diameters</td>
<td>6.5 cm</td>
<td>3.6 cm</td>
</tr>
<tr>
<td></td>
<td>Response Rate</td>
<td></td>
<td>-44%</td>
</tr>
<tr>
<td></td>
<td>Response Category</td>
<td></td>
<td>Partial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Response</td>
</tr>
</tbody>
</table>
Information Reported by Radiologist

Markup Regions of Interest (ROI)

Text Report

– Lesion Location (anatomic region; image number)
– Lesion Dimension(s)
– Impression of disease status
– (not machine-accessible)

Usually unaware of lesion being tracked and measurement criteria
Challenges in recording, coordinating, and communicating quantitative imaging information in cancer research.
Need standardization in imaging for clinical trials

• To control variability and inconsistency in
  – Methods of acquisition
  – Analysis of images
  – Interpretation of images

• To improve data quality

• To streamline conduct and reduce cost of trials

• To identify earlier whether drugs are effective in individual patients and cohort studies
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Our goals

• **Informatics platform** to streamline and improve quality of data collection/analysis from imaging in clinical research

• **Reproducible measurement** of tumor burden and cancer treatment response

• **Coordination and effective communication** between oncologists and radiologists and local/central study sites

• **Integration of multiple quantitative measures** of tumor burden
  – Comparing quantitative imaging biomarkers
  – Pooling/analyzing aggregate quantitative imaging data
Our technological approach

1. **Ontologies** for standard descriptors of data
2. **Image metadata schemas** to capture semantic image content
3. **Image warehouses** integrated with clinical data compliant with standards for data sharing
4. **Tools** to analyze quantitative imaging data and provide decision support for assessing cancer treatment response.
1. Ontologies

- Provide standard names for the key entities in cancer imaging domain
  - Diseases
  - Anatomy
  - Imaging findings and measures
  - Imaging procedures
- Resolve synonyms to preferred terms
- Several for cancer research (RadLex, NCIt, SNOMED)
There is a hypodense mass measuring 4.5 x 3.5 cm in the right lobe of the liver, likely a metastasis.
2. Image metadata schemas: AIM

- **Annotation** and **Image Markup** standard to make image contents “computable”
- Reader records image observations via annotation tool
- Enables high-volume analysis of image observations and quantitative image biomarkers

“There is a hypodense mass measuring 4.5 x 3.5 cm in the right lobe of the liver, likely a metastasis.”

Text Report

Semantic Annotation
iPAD (imaging Physician Annotation Device)

• Plug-in to OsiriX open source workstation

• OsiriX provides
  – Tools for visualizing and annotating images
  – Plug-ins for image analysis

• iPAD provides
  – Template for collecting AIM-compliant annotations
  – Features for identifying and tracking lesions
  – Automated assessment of treatment response
iPAD architecture

- **GUI**: plug-in to OsiriX platform (www.osirix-viewer.com)
- **Template**: Structured data entry; Enforces annotation requirements
- **Translator**: Image annotations → AIM
- **Exporter**: Transmits AIM XML to local database or federated storage (caGrid)
- **Database**: Saves/queries AIM annotations
3. Image warehouse

- Biomedical metadata manager (BIMM)
- Resource for recording and storing quantitative image data compliant with caBIG standards (AIM)
- Enables query/analysis of image data
4. Tools for decision support and treatment response

- iPAD automatically processes image annotations and evaluates response criteria
- Can provide decision support and alerts
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Planned deliverables

1. **Tools to measure lesions on images comprehensively and reproducibly**

2. **Tools to estimate tumor burden according to imaging biomarkers**

3. **Resource for recording and storing quantitative image data** compliant with caBIG standards

4. **Tools for mining the image data for decision support** in clinical trials and research
Software framework for quantitative imaging assessment of tumor burden

1. Image Acquisition
2. Tumor Burden Assessment
   - Lesion characteristics:
     - Unique identifier
     - Quantitative measures
     - Calculations
     - Anatomic location
     - Visual features
3. Clinical Research PACS
4. Data Sharing on caGrid

Semantic Annotation (iPad or PACS)

Queries and Analysis

Biomedical Image Metadata Manager

Quantitative Imaging Data Resource

Decision Support Tools

Sum of Maximum Lesion Diameters Over Time

Radiologist

Oncologist

Recist Score: Tx | Remission | PD | Stable | Remission | PD | Regression
1. Measuring lesions reproducibly: Automated lesion segmentation

## Automated segmentation

<table>
<thead>
<tr>
<th>Cyst</th>
<th>Hemangioma</th>
<th>HCC</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Cyst" /></td>
<td><img src="image2" alt="Hemangioma" /></td>
<td><img src="image3" alt="HCC" /></td>
<td><img src="image4" alt="Metastasis" /></td>
</tr>
</tbody>
</table>

Above: examples of manually drawn rough outlines

Below: examples of refined outlines given the above

| MNVM= 0.8% | 3.4% | 3.2% | 5.6% |

## Manual segmentation
2. Tools to estimate tumor burden: Image Reporting

- Objective image assessments at each time point
- Alerts to missing data; required assessments
3. Recording and sharing quantitative image data

- Link quantitative and semantic data to images
- Sharing on caGrid
- Input to decision support tools and reporting applications
4. Tools for decision support: Patient response

Sum of Maximum Lesion Diameters Over Time

- Automated lesion tracking
- Classification of lesions (measurable/non-measurable)
- Calculation of quantitative imaging biomarkers
- Temporal analysis of biomarkers response assessment
Decision support: Cohort response

- Automated summary of cohort response data
Exploratory data mining for discovery
e.g., “*which image biomarker is best in cancer*?”

<table>
<thead>
<tr>
<th>Disease</th>
<th>WHO &amp; RECIST</th>
<th>Tumor Volume</th>
<th>PET SUV</th>
<th>DCE-MRI</th>
<th>DI-WI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHL</td>
<td>??</td>
<td>??</td>
<td>XX</td>
<td>??</td>
<td>??</td>
</tr>
<tr>
<td>Panc CA</td>
<td>XX</td>
<td>??</td>
<td>??</td>
<td>??</td>
<td>??</td>
</tr>
<tr>
<td>Br CA</td>
<td>XX</td>
<td>??</td>
<td>??</td>
<td>XX</td>
<td>??</td>
</tr>
<tr>
<td>GIST</td>
<td>??</td>
<td>??</td>
<td>XX</td>
<td>??</td>
<td>??</td>
</tr>
<tr>
<td>...</td>
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<td>??</td>
</tr>
</tbody>
</table>
Evaluation studies

• Evaluation of infrastructure in mock clinical trial

• Evaluation in two active clinical trials
  – Completeness of information on tumor burden
  – Reproducibility of measurement of tumor burden
  – Tool usability study
  – Assessment of treatment response in cohort studies
What we hope to gain

• Accommodate *all quantitative imaging metadata* into our infrastructure

• Determine value of *full spectrum of quantitative imaging biomarkers* of cancer

• *Widespread adoption* of image annotation tools for collecting structured image metadata

• *Demonstrate value* of pooled quantitative imaging data for discovery and decision support
Thank you.

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Software framework for quantitative imaging assessment of tumor burden

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2. Tumor Burden Assessment
   - Lesion characteristics:
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     - Calculations
     - Anatomic location
     - Visual features
3. Biomedical Image Metadata Manager
4. Decision Support Tools
   - Data Sharing on caGrid

AIM annotations linked to images

Clinical Research PACS

Quantitative Imaging Data Resource

Queries and Analysis

Radiologist

Oncologist

Sum of Maximum Lesion Diameters Over Time

RECIST Score: Tx Remission PD Stable Remission PD Regression