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

Daniel L. Rubin, MD, MS

Assistant Professor of Radiology
Member, Stanford Cancer Center
Chair, ACRIN Informatics Committee
Department of Radiology
Stanford University

Acknowledgements

Collaborators and Funding

–Mia Levy

–Edward Graves

–Cesar Rodriguez

–George Fisher

–Sandy Napel

–Andrew Evens

- Annotation and Image Markup
  - –David Channin, Pattanasak Mongkolwat
- Funding Support
  - –NCI caBIG In-vivo Imaging Workspace
  - –NCI QIN U01CA142555-01
  - –GE Medical Systems

Outline

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

Outline

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

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

CLINICAL HISTORY: Protocol

COMMENT: CT scan of the chest, abdomen, and pelvis was performed with the use of oral but without the use of intravenous contrast. Multiple contiguous axial images were obtained from the lung apices through the pubic symphysis. This study is compared to a prior study dated October 25, 2006.

There is no evidence of mediastinal, hilar, or axillary lymphadenopathy. No pleural effusions are present. There are a few tiny subpleural nodules present in the right lung. These are not significantly changed in comparison to the prior study. These are most likely inflammatory in etiology.

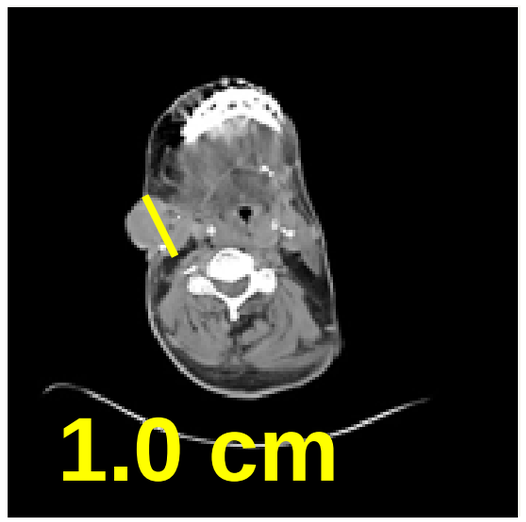
Multiple hypodense hepatic masses are present. These are well defined and fairly low in density. These most likely represent cystic metastatic lesions. Overall these are not significantly changed in size in comparison to the prior study. The spleen, pancreas, adrenal glands, and kidneys are within normal limits. There is a large juxtarenal fusiform infrarenal abdominal aortic aneurysm present. This measures 5.6 X 5.4 cm. on image 78 and is not significantly changed in comparison to the prior study. Note is also made of mild aneurysmal dilatation of the descending thoracic aorta.

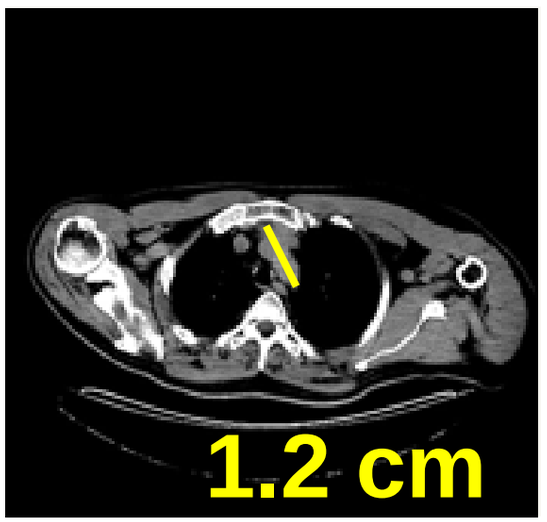
There is no retroperitoneal or pelvic lymphadenopathy. There is no free fluid in the abdomen or pelvis. The uterus and adnexal regions are within normal limits. The bladder is non-distended but grossly normal.

IMPRESSION:
1. Stable hepatic metastases.
2. Stable small subpleural pulmonary nodules on the right that most likely are inflammatory in nature.

Interpreting Radiologist: BARTON MILESTONE M.D. on Dec 20 2006 12:20P
Transcribed by: MEB on Dec 26 2006 8:32A
Approved Electronically by: BARTON MILESTONE RADIOLOGIST Dec 26 2006 8:54A
ATTENDING DR: BARBARA BURTNESS M.D.
ORDERING DR: BARBARA BURTNESS M.D

&





- 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

Lesion ID	Location/Description	Baseline	Follow-up
1	Right upper lung nodule	2.5 cm	1.2 cm
2	Liver nodule - segment 5	2.3 cm	1.4 cm
3	Liver nodule - segment 2	1.7 cm	1.0 cm
	Sum Longest Diameters	6.5 cm	3.6 cm
	Response Rate		-44%
	Response Category		Partial Response

Information Reported by Radiologist

ACCESSION #: 260649 FCT - CHEST/ABDOMEN/PELVIS W/O CONTRAS -
Dec 20 2006
10:49AM

CLINICAL HISTORY: Protocol

COMMENT: CT scan of the chest, abdomen, and pelvis was performed with the use of oral but without the use of intravenous contrast. Multiple contiguous axial images were obtained from the lung apices through the pubic symphysis. This study is compared to a prior study dated October 25, 2006.

There is no evidence of mediastinal, hilar, or axillary lymphadenopathy. No pleural effusions are present. There are a few tiny subpleural nodules present in the right lung. These are not significantly changed in comparison to the prior study. These are most likely inflammatory in etiology.

Multiple hypodense hepatic masses are present. These are well defined and fairly low in density. These most likely represent cystic metastatic lesions. Overall these are not significantly changed in size in comparison to the prior study. The spleen, pancreas, adrenal glands, and kidneys are within normal limits. There is a large juxtarenal fusiform infrarenal abdominal aortic aneurysm present. This measures 5.6 X 5.4 cm. on image 78 and is not significantly changed in comparison to the prior study. Note is also made of mild aneurysmal dilatation of the descending thoracic aorta.

There is no retroperitoneal or pelvic lymphadenopathy. There is no free fluid in the abdomen or pelvis. The uterus and adnexal regions are within normal limits. The bladder is non-distended but grossly normal.

IMPRESSION:
1. Stable hepatic metastases.
2. Stable small subpleural pulmonary nodules on the right that most likely are inflammatory in nature.

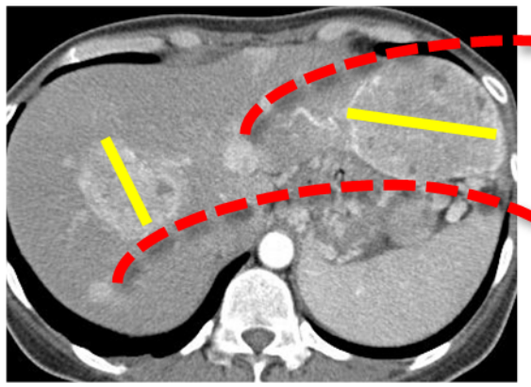
Interpreting Radiologist: BARTON MILESTONE M.D. on Dec 20 2006 12:20P
Transcribed by: MEB on Dec 26 2006 8:32A
Approved Electronically by: BARTON MILESTONE RADIOLOGIST Dec 26 2006 8:54A
ATTENDING DR: BARBARA BURTNESS M.D.
ORDERING DR: BARBARA BURTNESS M.D

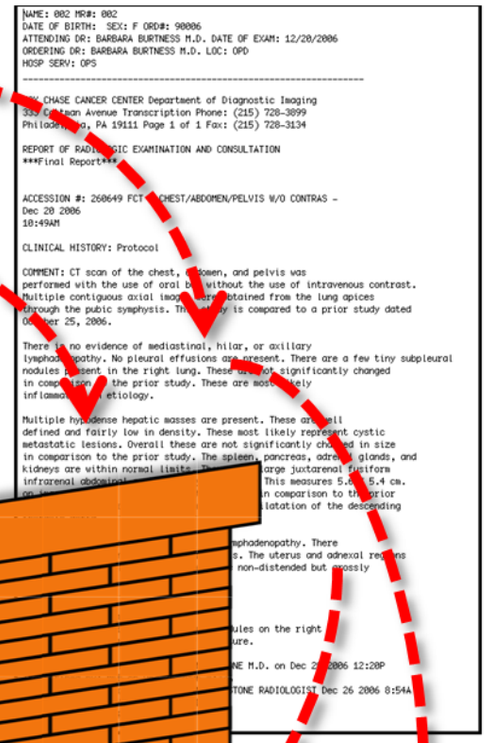
- Markup Regions of Interest (ROI)
- Text Report
  - Lesion Location (anatomic region; image number)
  - Lesion Dimension(s)
  - Impression of disease status
  - (not machine-accessible)

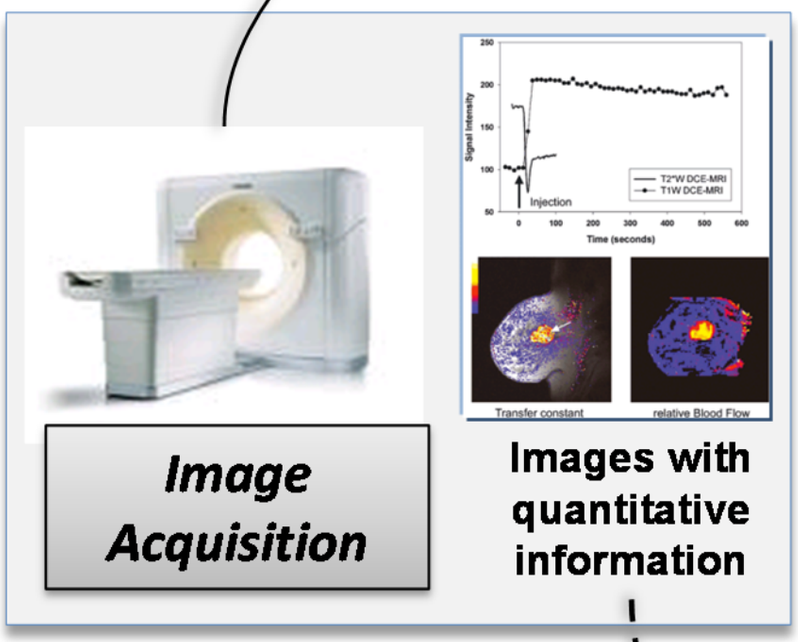
Usually unaware of lesion being tracked and measurement criteria

Challenges in recording, coordinating, and communicating quantitative imaging information in cancer research

Radiologist

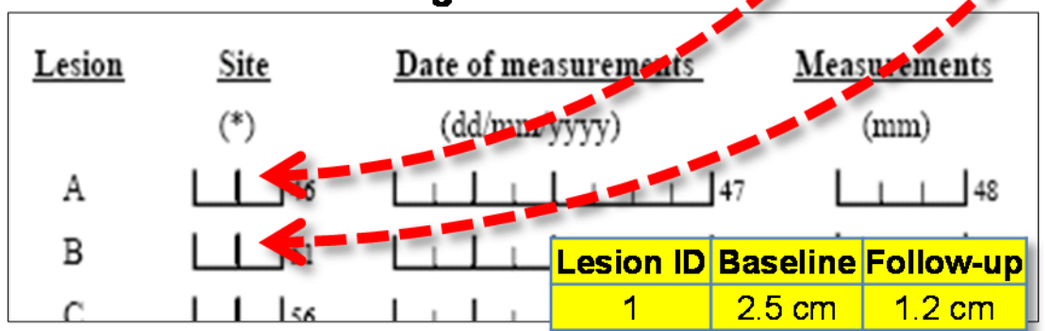






Oncologist

Measurements and description of target lesions



Response Assessment and Decision Making

Lesion ID	Baseline	Follow-up
1	2.5 cm	1.2 cm
2	2.3 cm	1.4 cm
3	1.7 cm	1.0 cm
SLD	6.5 cm	3.6 cm
RR		-44%
Response Category		PR

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

Outline

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

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)

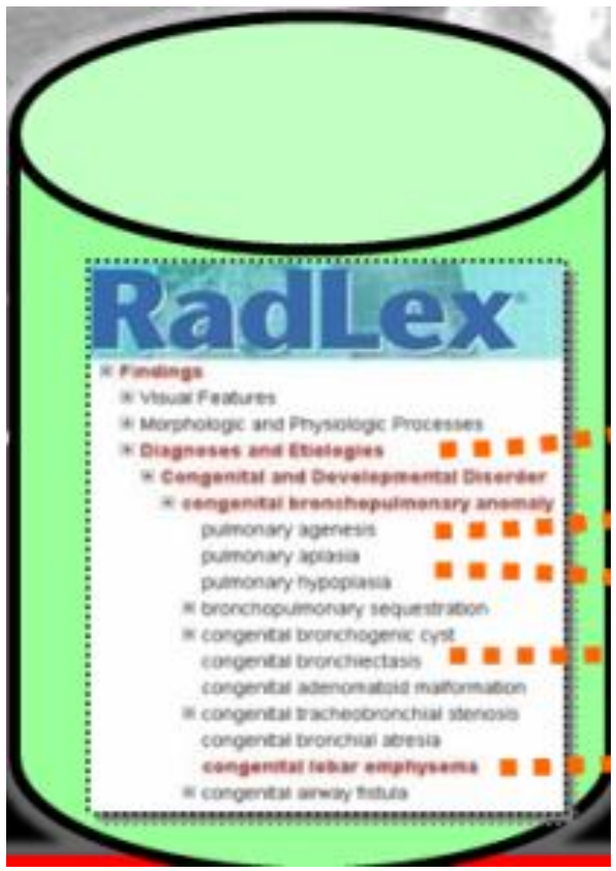
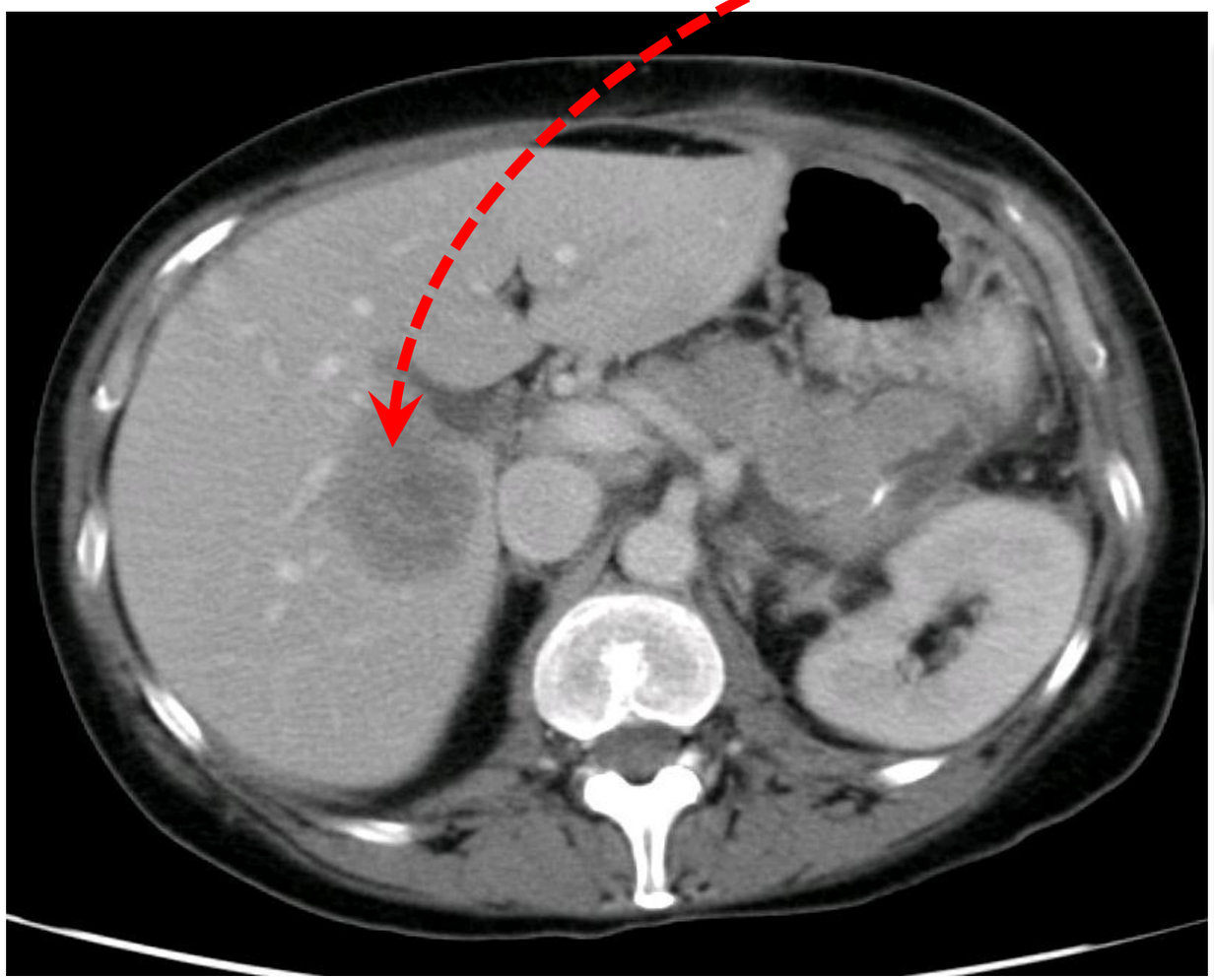


Image Semantics:
"Image meaning"



Radiology Image

*** Final Report ***

CT ABDOMEN AND PELVIS WITH CONTRAST

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

Organ = **liver**
Location = **right lobe**
Measurement = **4.5 x 3.5 cm**
Diagnosis = **metastasis**
Probability = **likely**

*** Final Report ***

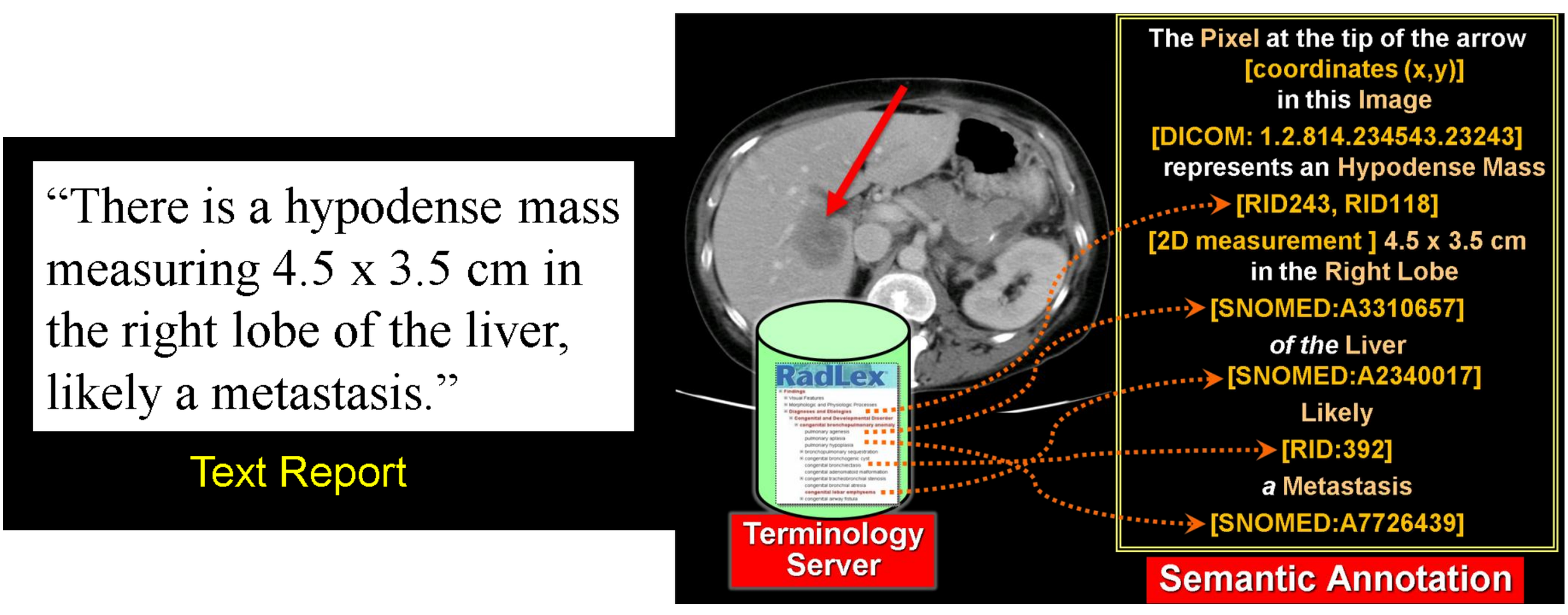
4. Diverticulosis without radiographic evidence of diverticulitis.

Thank you for the courtesy of this referral.

Radiology Report

2. Image metadata schemas: AIM

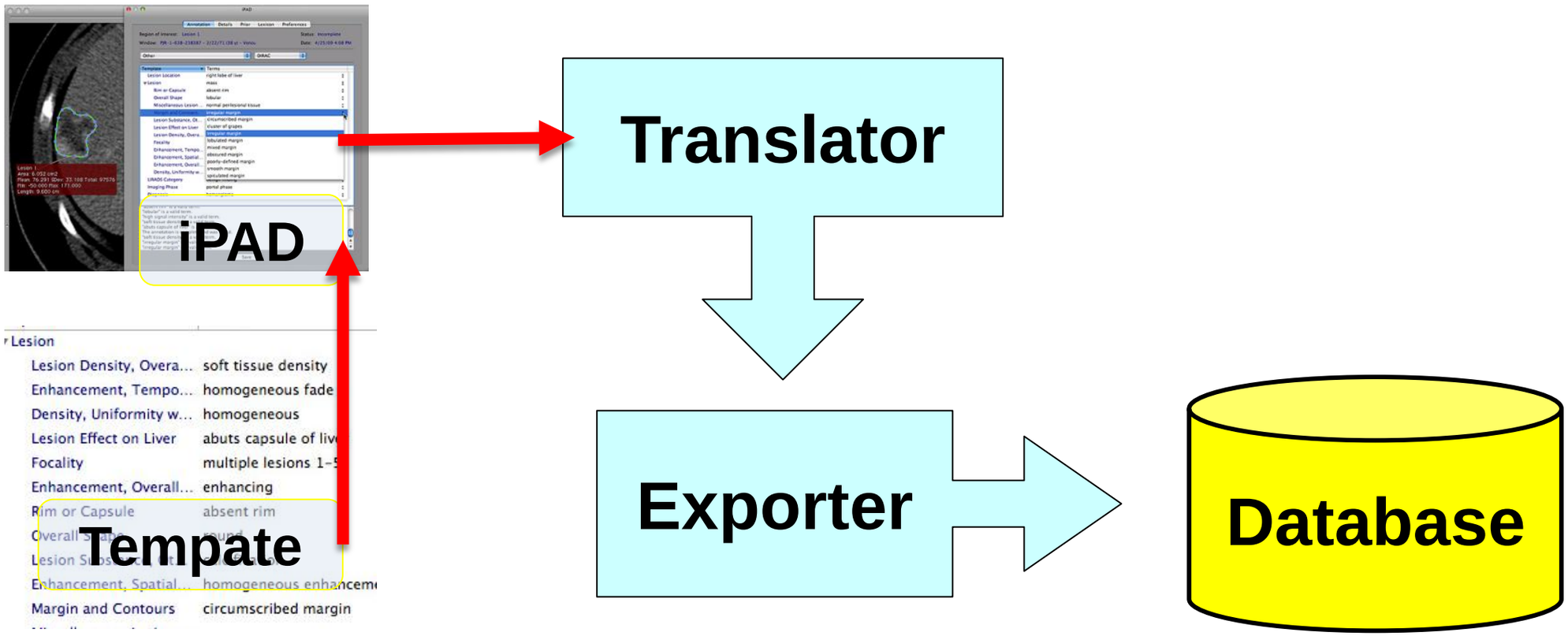
- **A**nnotation and **I**mage **M**arkup standard to make image contents "computable"
- Reader records image observations via annotation tool
- Enables high-volume analysis of image observations and quantitative image biomarkers



iPAD (imaging Physician Annotation Device)

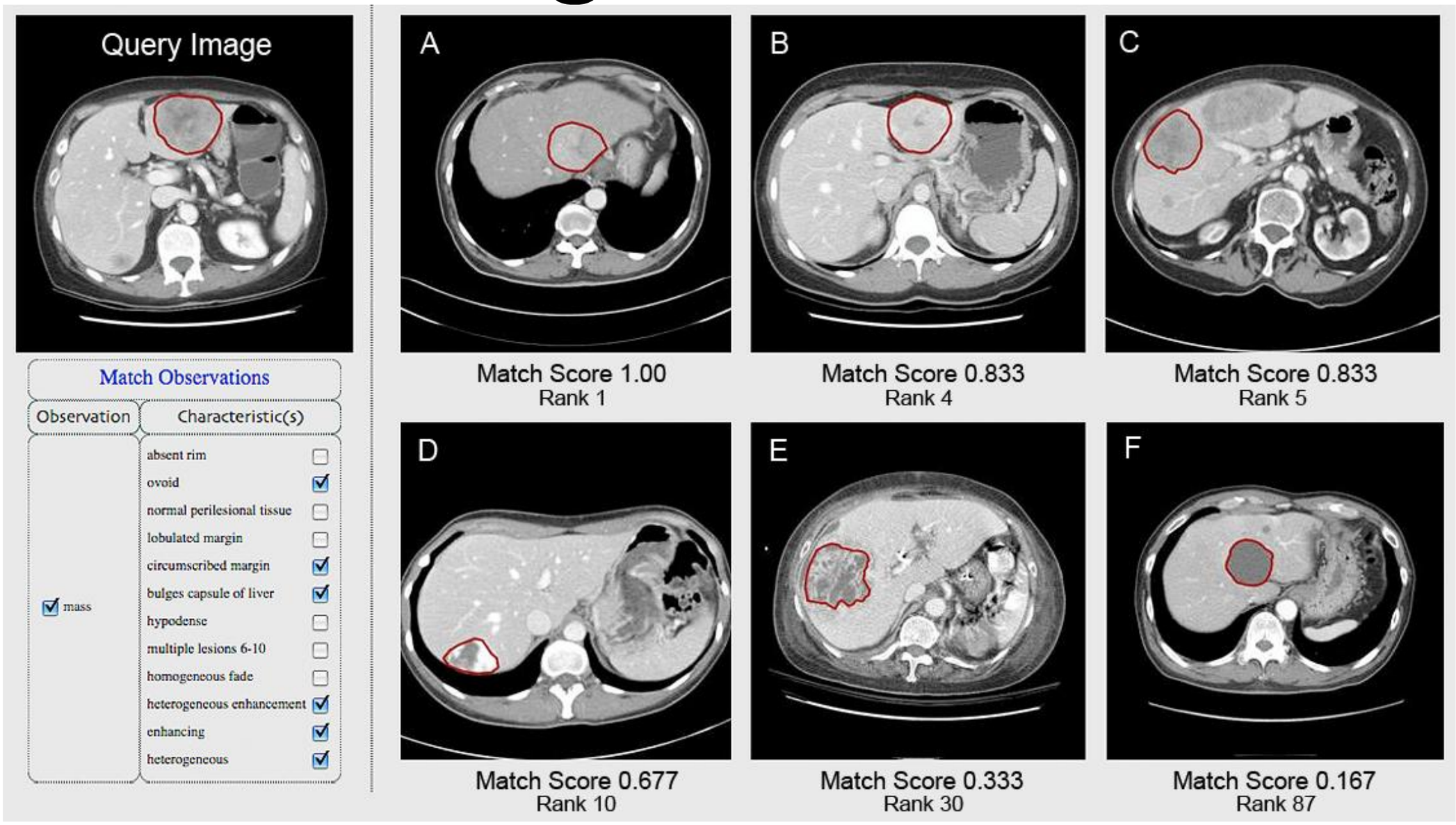
- Plug-in to OsiriX open source workstation
- OsiriX provides
  - Tools for visualizing and annotating images
  - Plug-ins for image analysis
- iPAD provides
  - Template for collecting AIM-compliant annotations
  - Features for identifying and tracking lesions
  - Automated assessment of treatment response

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

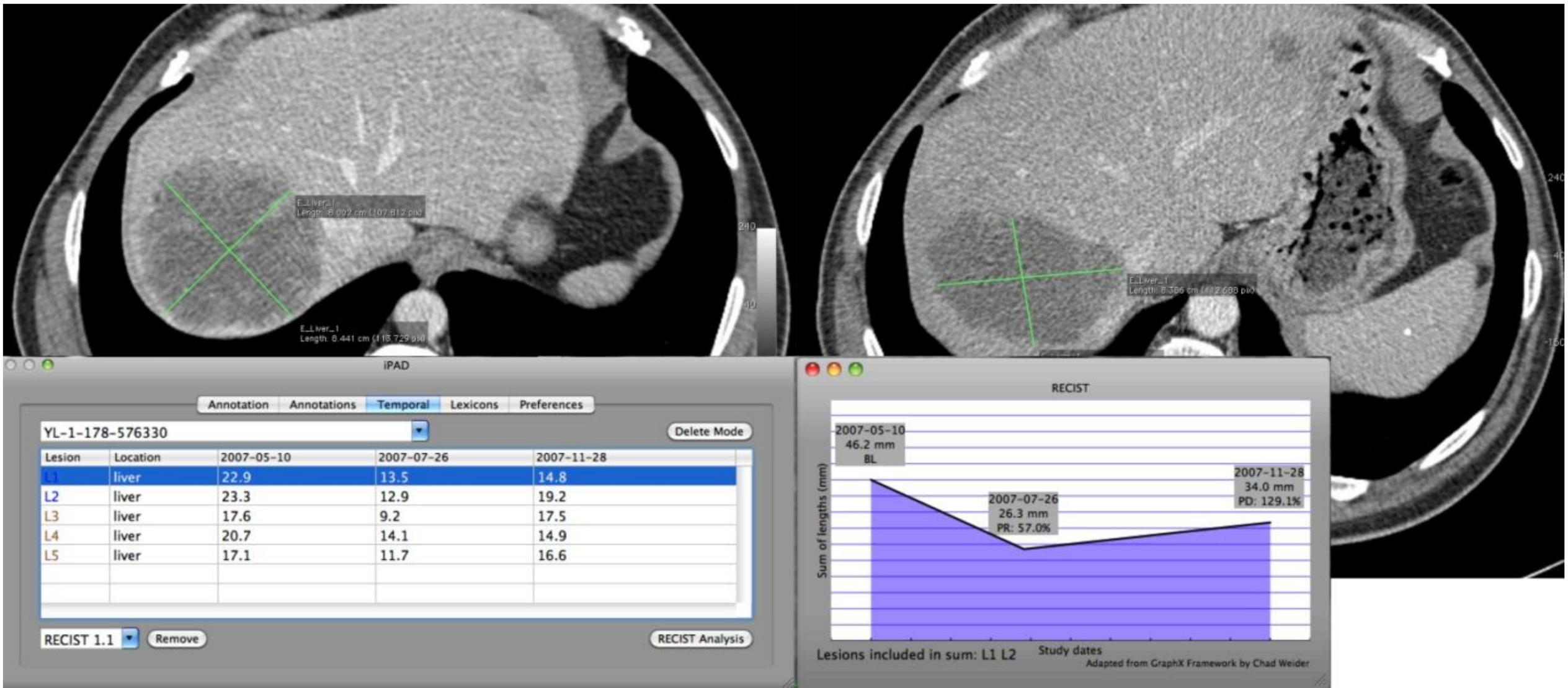
3. Image warehouse



- 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



Outline

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

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

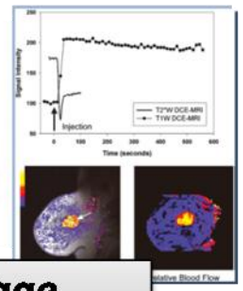
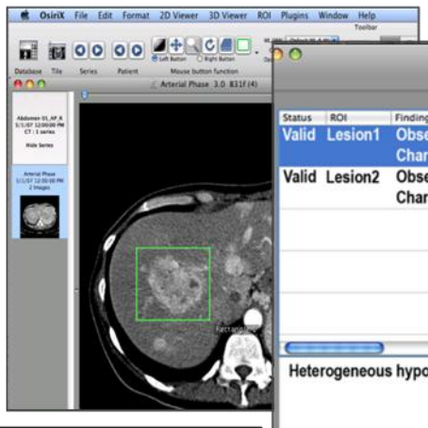
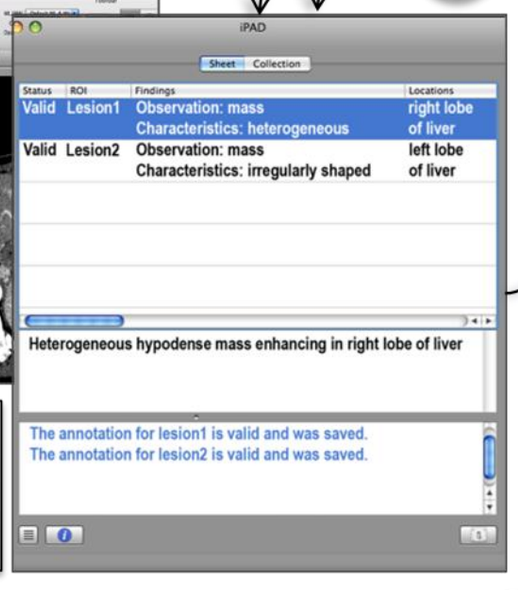


Image Acquisition





Semantic Annotation (iPad or PACS)

1

AIM annotations linked to images

3

Clinical Research PACS

Biomedical Image Metadata Manager

Quantitative Imaging Data Resource

Data Sharing on caGrid

Decision Support Tools

Queries and Analysis

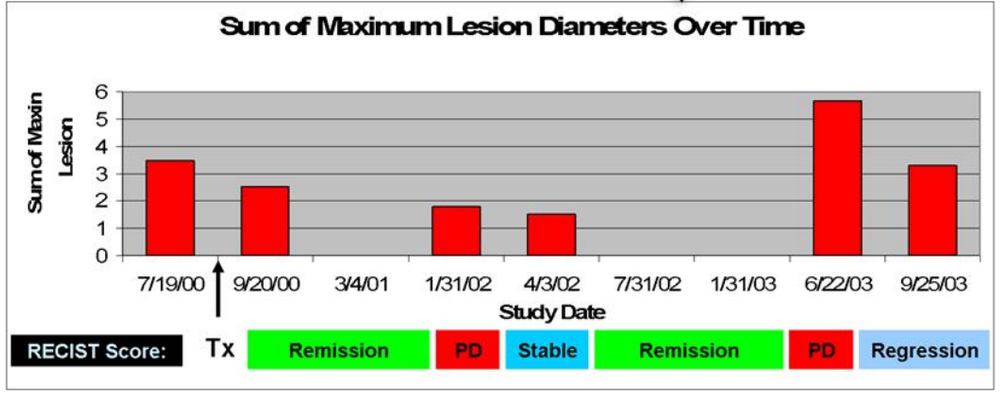
4

TUMOR BURBEN ASSESSMENT 2

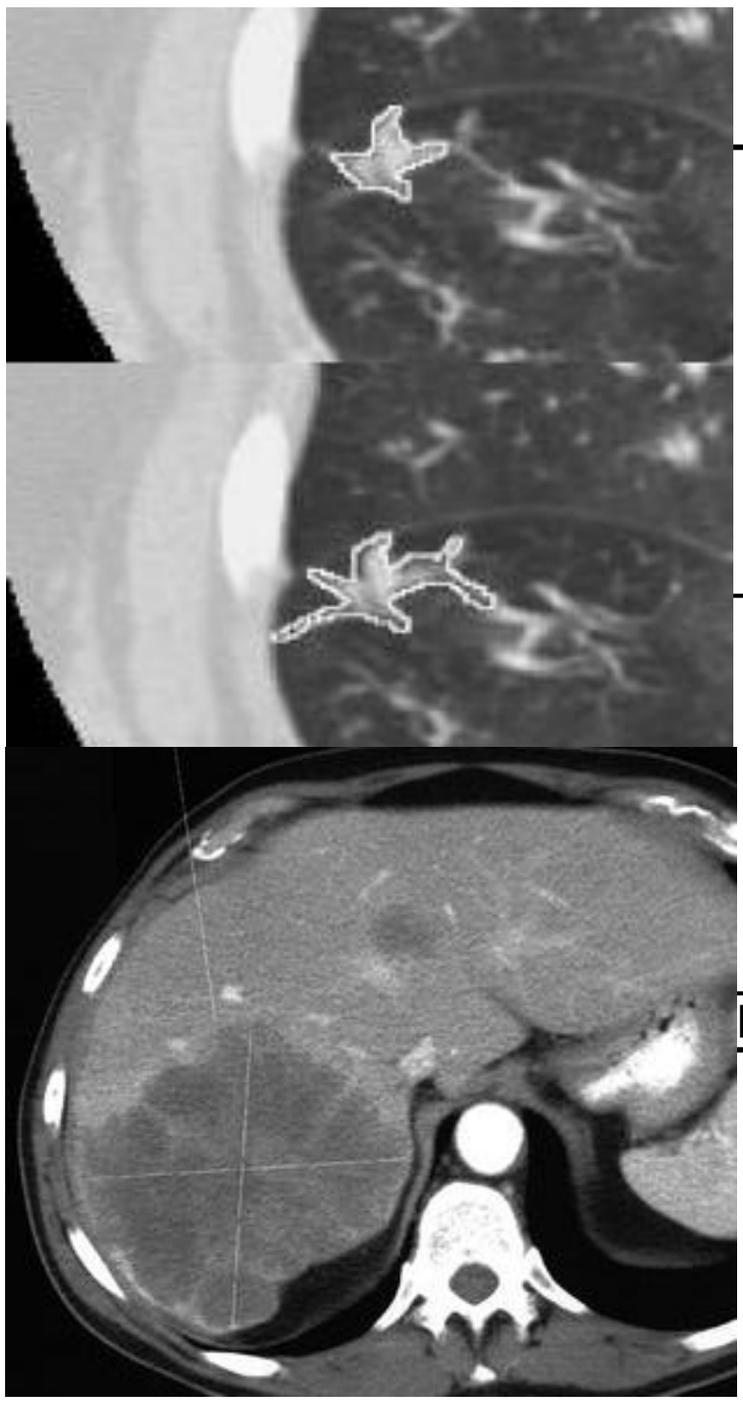
Radiologist

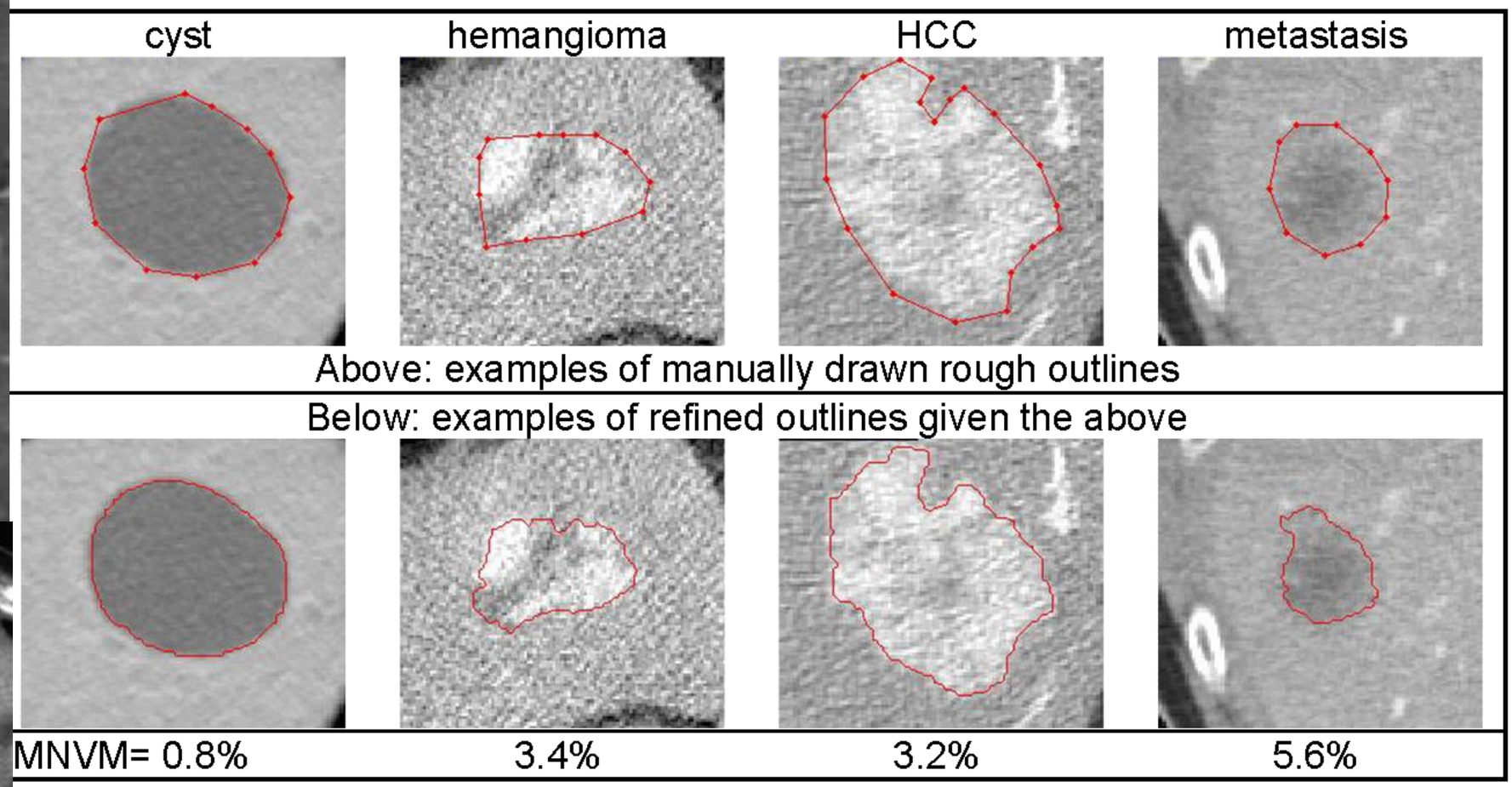
Lesion characteristics:
- **Unique identifier**
- **Quantitative measures**
- **Calculations**
- **Anatomic location**
- **Visual features**

Oncologist



1. Measuring lesions reproducibly: Automated lesion segmentation

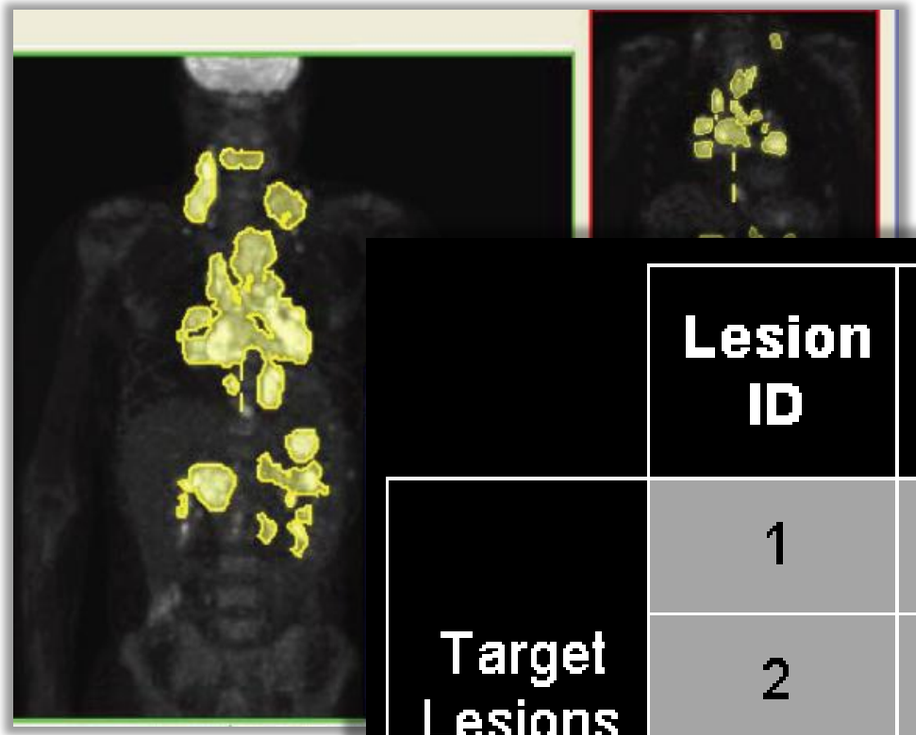




Automated segmentation

Manual segmentation

2. Tools to estimate tumor burden:
Image Reporting

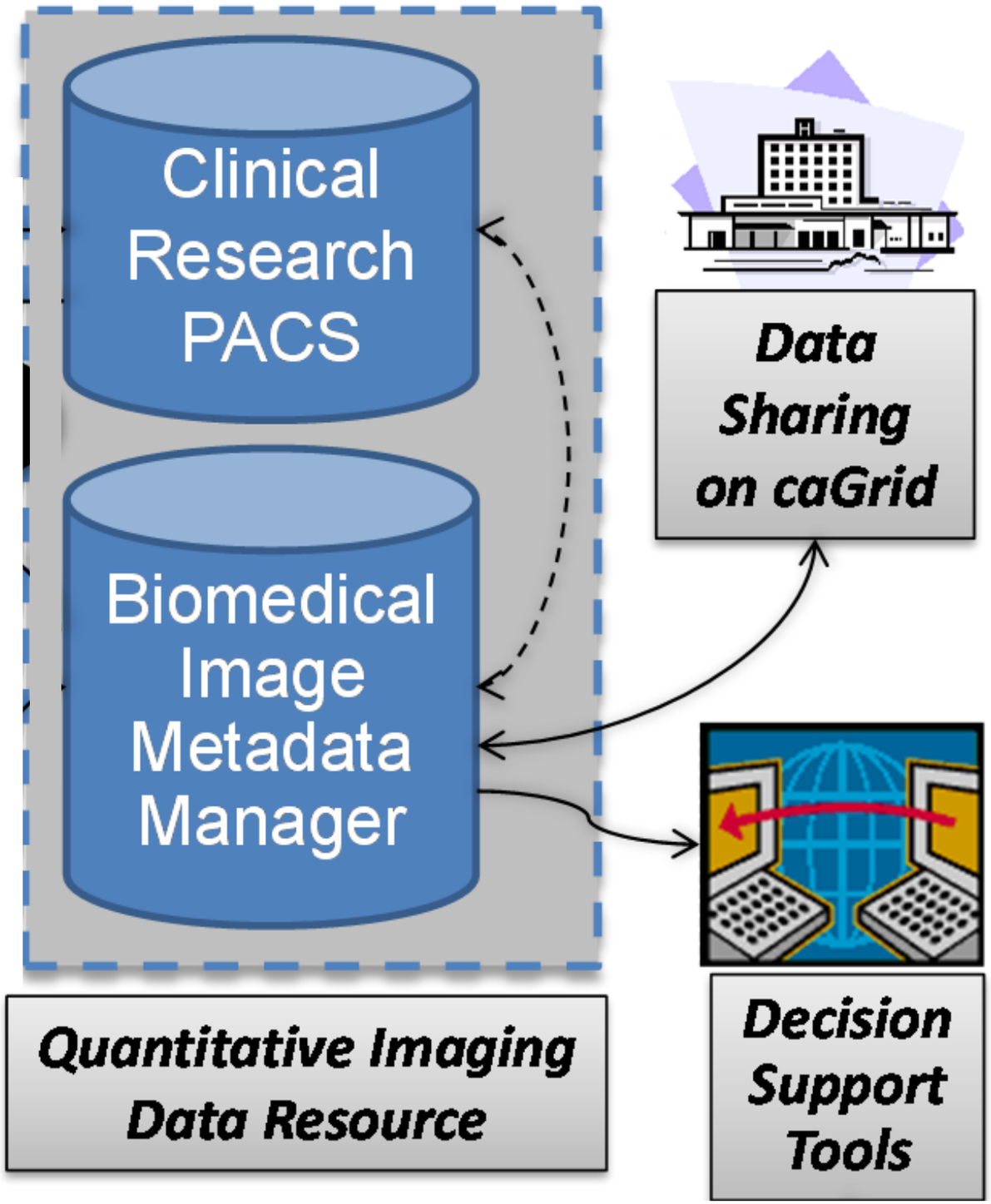


	Lesion ID	Imaging Finding	Finding Location	Objective Image Assessments		
				Baseline: 6/10/2007	Follow-up: 9/12/2007	Follow-up: 12/1/2007
Target Lesions	1	Lung Nodule	Left Lower Lobe	2.3	??	1.6
	2	Liver Mass	Couinaud Segment 4b	2.0	1.6	1.2
	3	Lymph Node	Pre-tracheal	2.4	2.0	??
Non-Target Lesions	7	Pleural Effusion	Right pleural space	+++	+	-
	8	Bone Lesion	C4 vertebral body	+	+	+

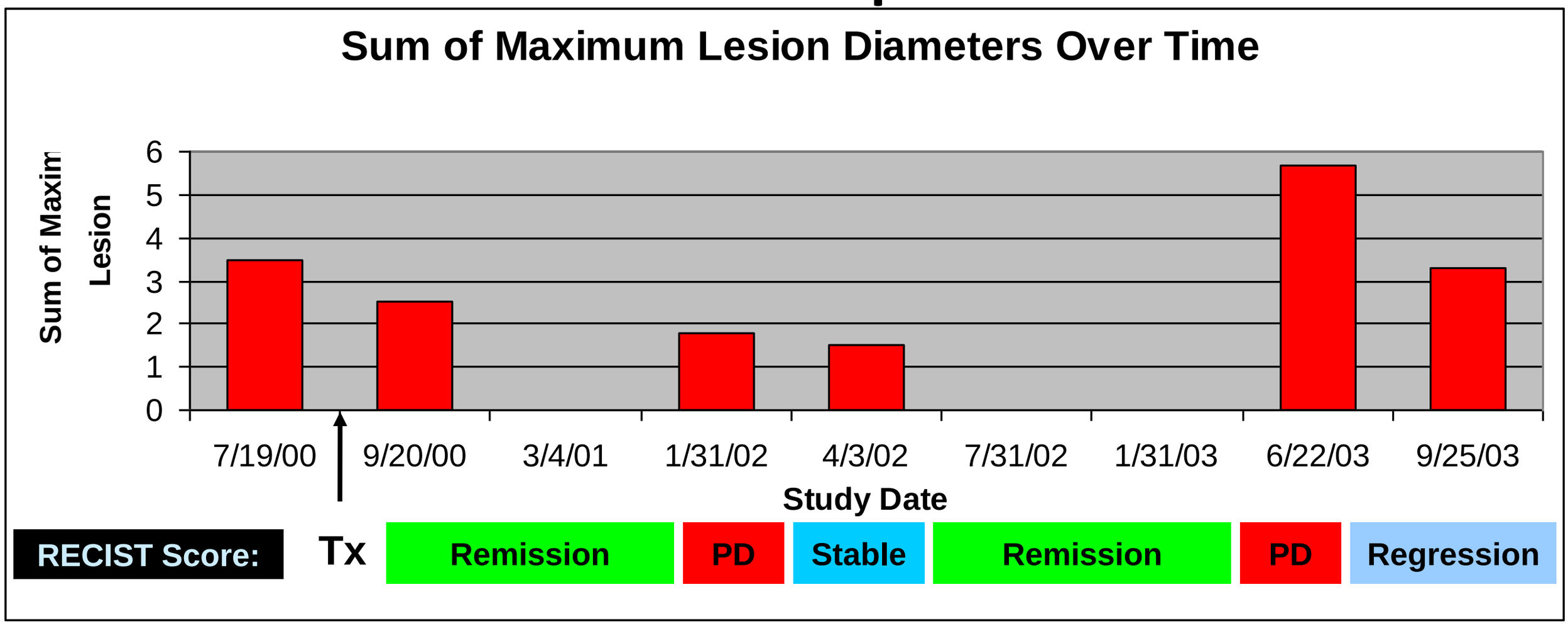
- Objective image assessments at each time point
- Alerts to missing data; required assessments

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

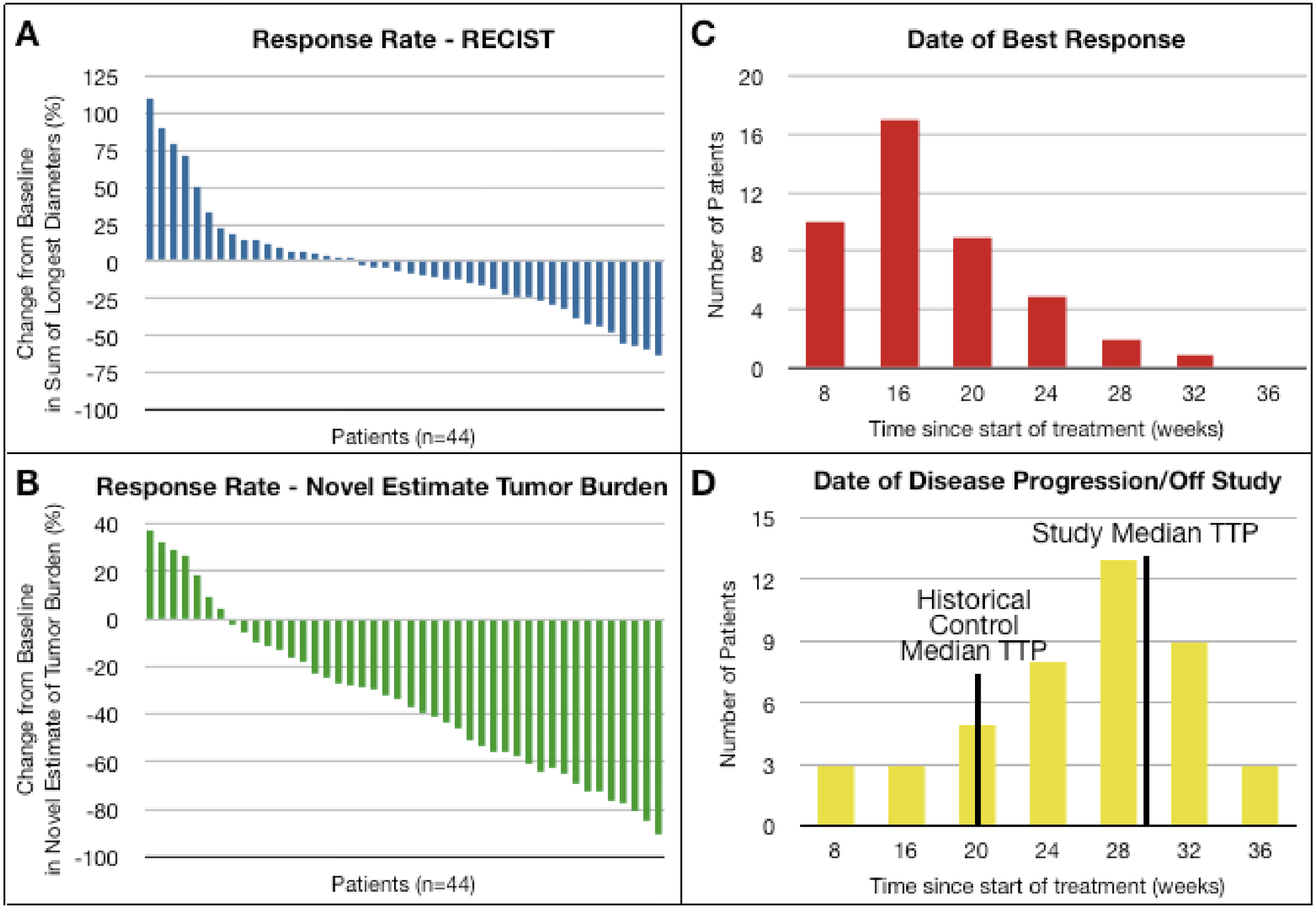


4. Tools for decision support:
Patient response



- 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?*"

IMAGE BIOMARKER →

DISEASE →	WHO & RECIST	Tumor Volume	PET SUV		DCE-MRI			DI-WI	…
Disease			Mean	25-75% max	Ktrans	RKtrans	Upstroke		
NHL	??	??	XX	??	??	??	??	??	??
Panc CA	XX	??	??	??	??	??	??	??	??
Br CA	XX	??	??	??	XX	XX	??	??	??
GIST	??	??	XX	??	??	??	??	??	??
…	??	??	??	??	??	??	??	??	??

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.

Contact info:
rubin@med.stanford.edu

Software framework for quantitative imaging assessment of tumor burden

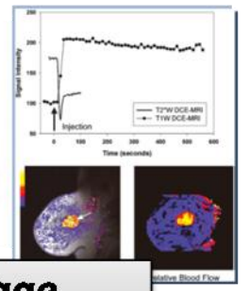
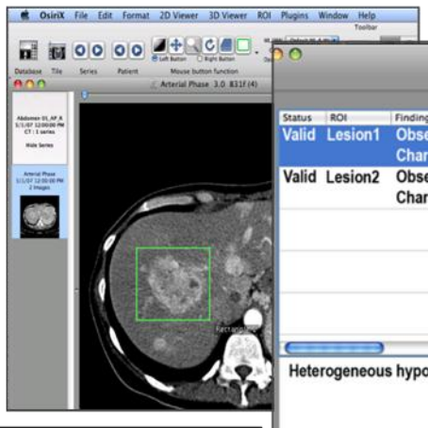
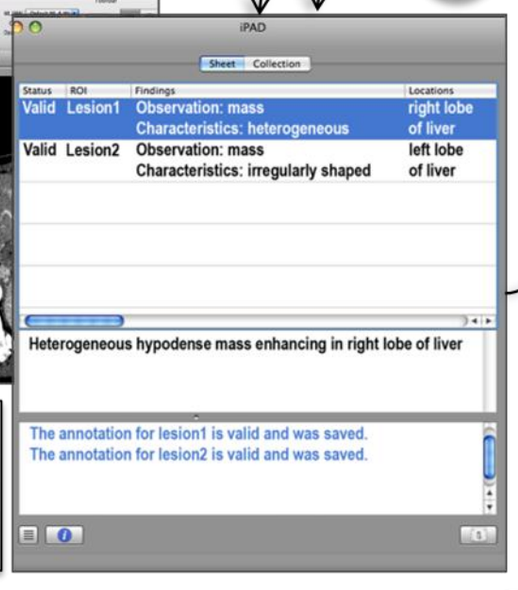


Image Acquisition





Semantic Annotation (iPad or PACS)

1

AIM annotations linked to images

3

Clinical Research PACS

Biomedical Image Metadata Manager

Quantitative Imaging Data Resource

Data Sharing on caGrid

Decision Support Tools

Queries and Analysis

4

TUMOR BURBEN ASSESSMENT 2

Radiologist

Lesion characteristics:
- **Unique identifier**
- **Quantitative measures**
- **Calculations**
- **Anatomic location**
- **Visual features**

Oncologist