Panel: Image Interpretation

Challenges and Approaches to Standardization

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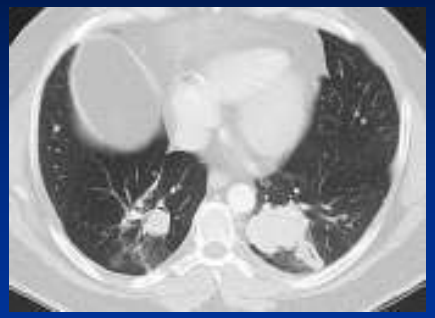
Imaging Committee Chair for CALGB

Wright Center of Innovation in Biomedical Imaging

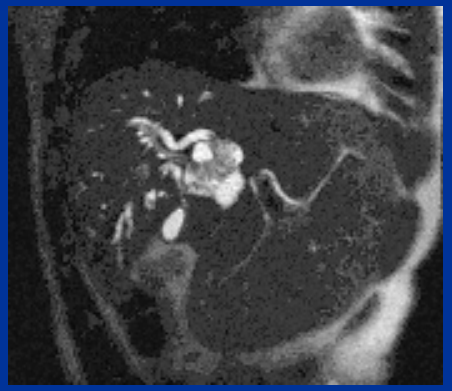
Imaging Modalities Used in Clinical Trials

Image Interpretation Standardization

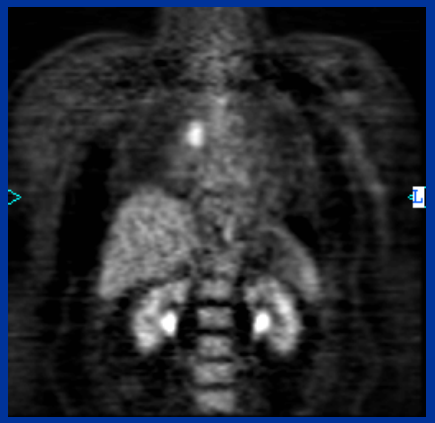
CT



MRI

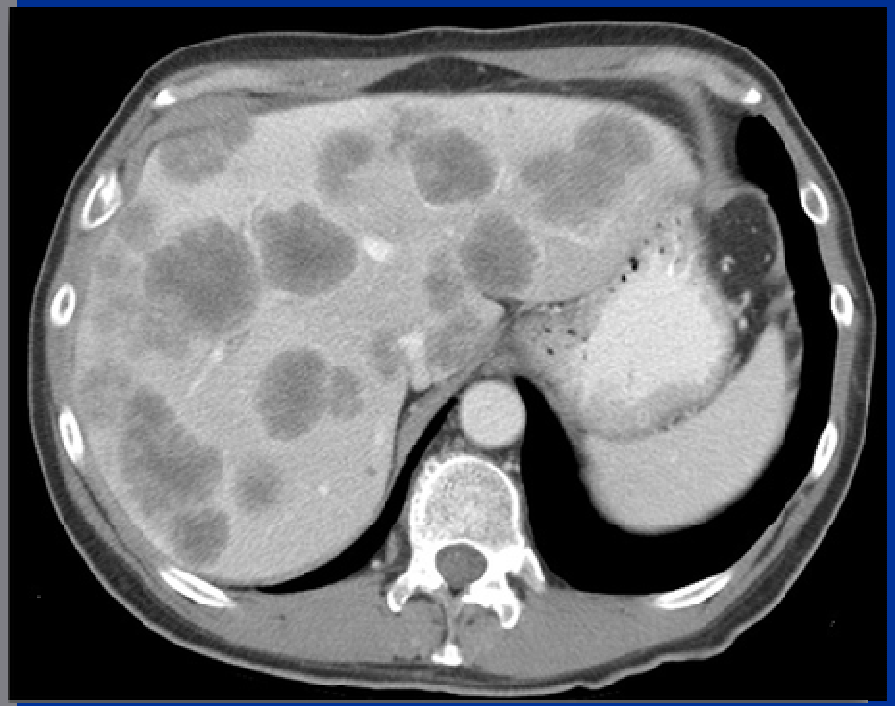


PET

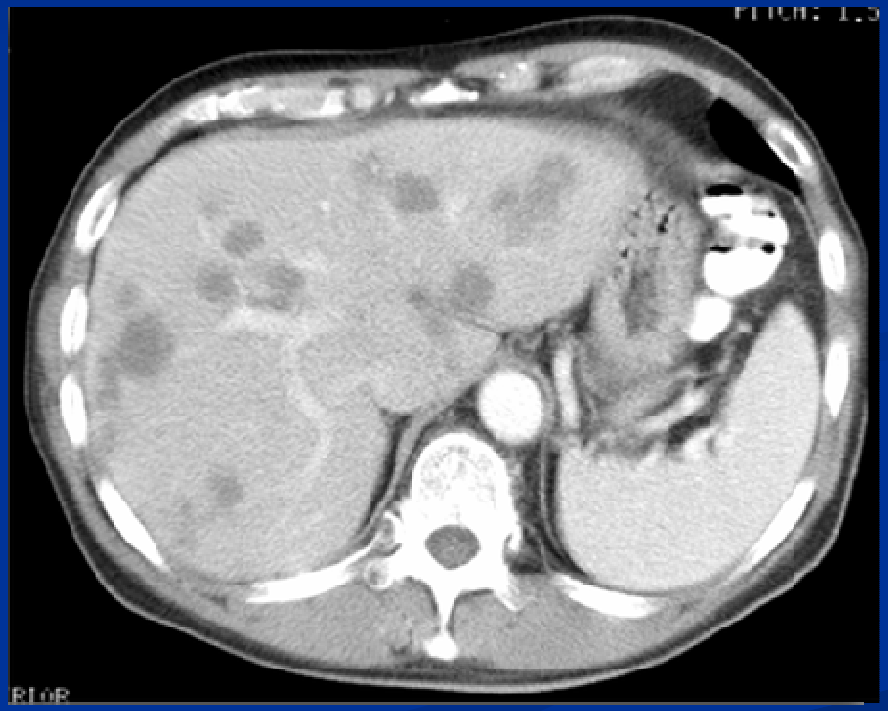


- The need for standardization varies by imaging modality, technique and potentially therapeutic option
- The need and degree of standardization is clearly related to the magnitude of the therapeutic effect which is to be measured

The Need for Interpretation Standardization
CT in Colorectal Cancer

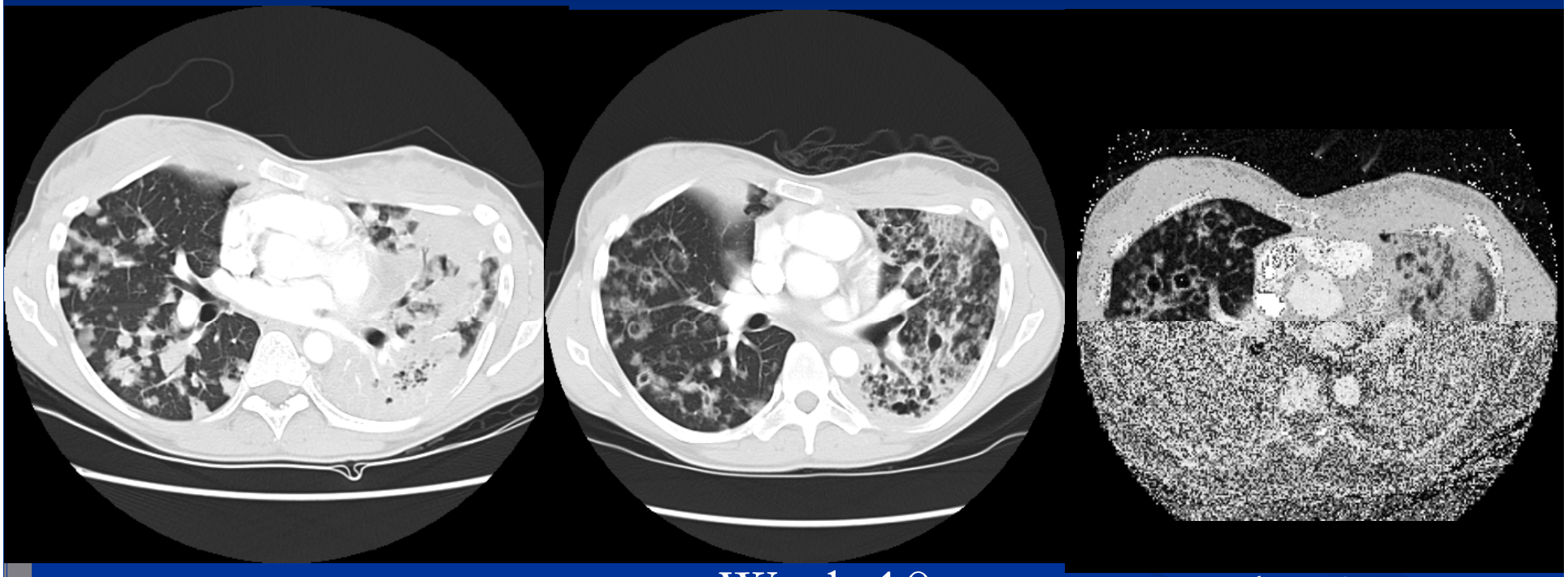


pre-Therapy



post-Therapy

The Need for Interpretation Standardization
CT in Lung Cancer

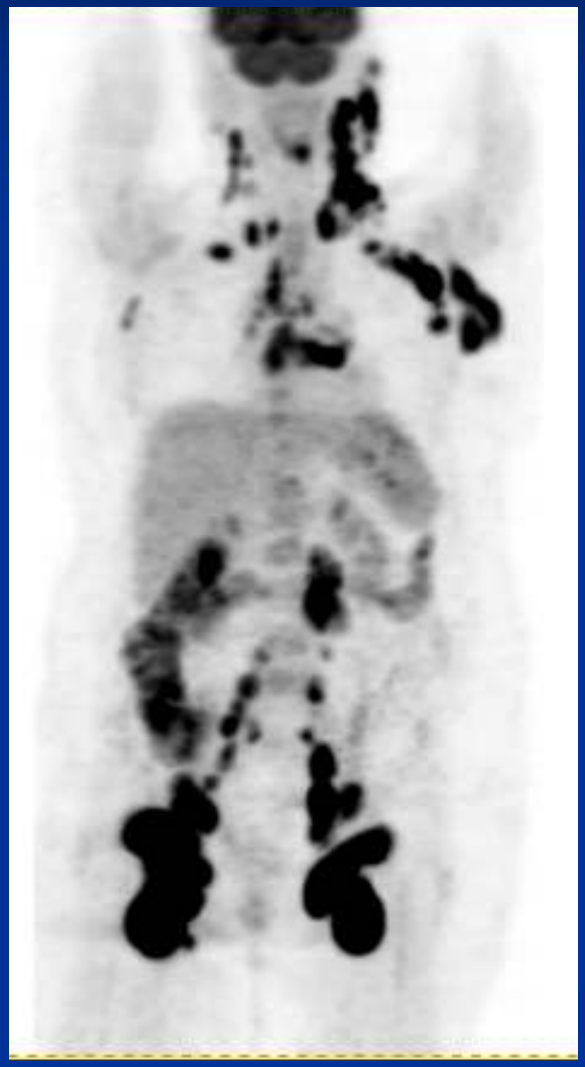


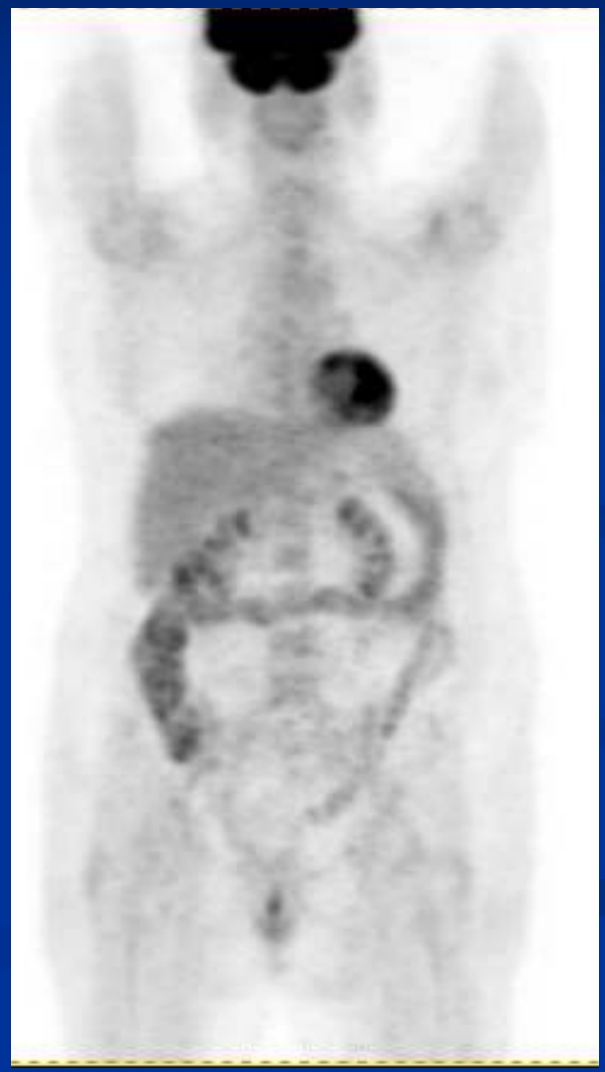
Baseline

Week 10

Month 10

The Need for Interpretation Standardization
PET in Lymphoma Cancer





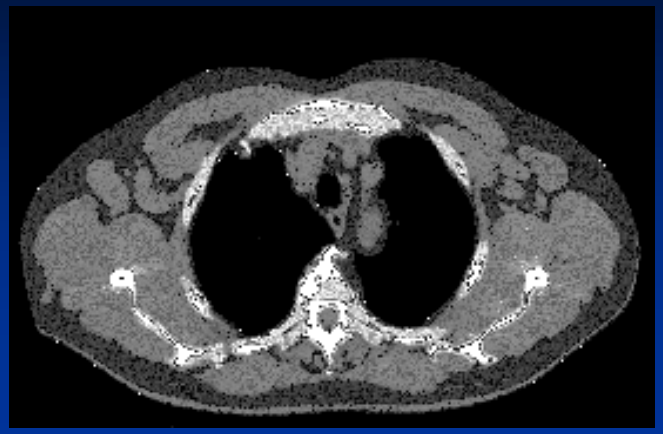
The Need for Interpretation Standardization

What are sources of variability ?

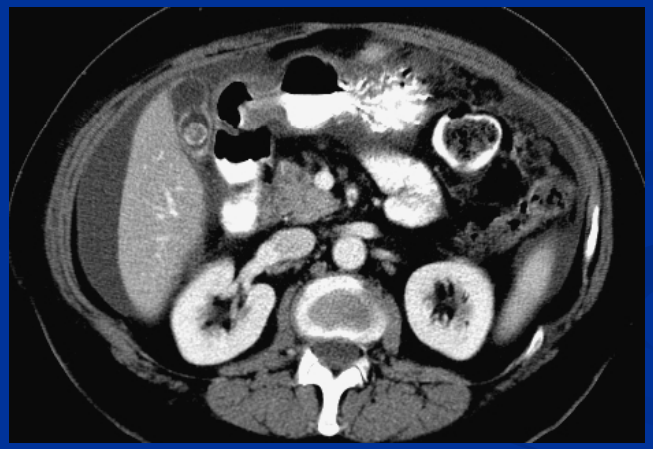
- Target lesion selection
- Image acquisition protocols
- Measurement of target lesions
- Interpretation of "clear unequivocal progression of non-target disease"
- Identification of new lesions
- Primary tumor type

Categories of Lesions in RECIST

- Target



- Non Target



- New Lesion

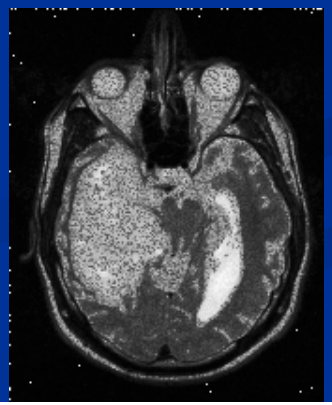


Table of Response Assessment RECIST

Overall responses for all possible combinations			
Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

The Need for Interpretation Standardization

Variability - Target Lesion Selection

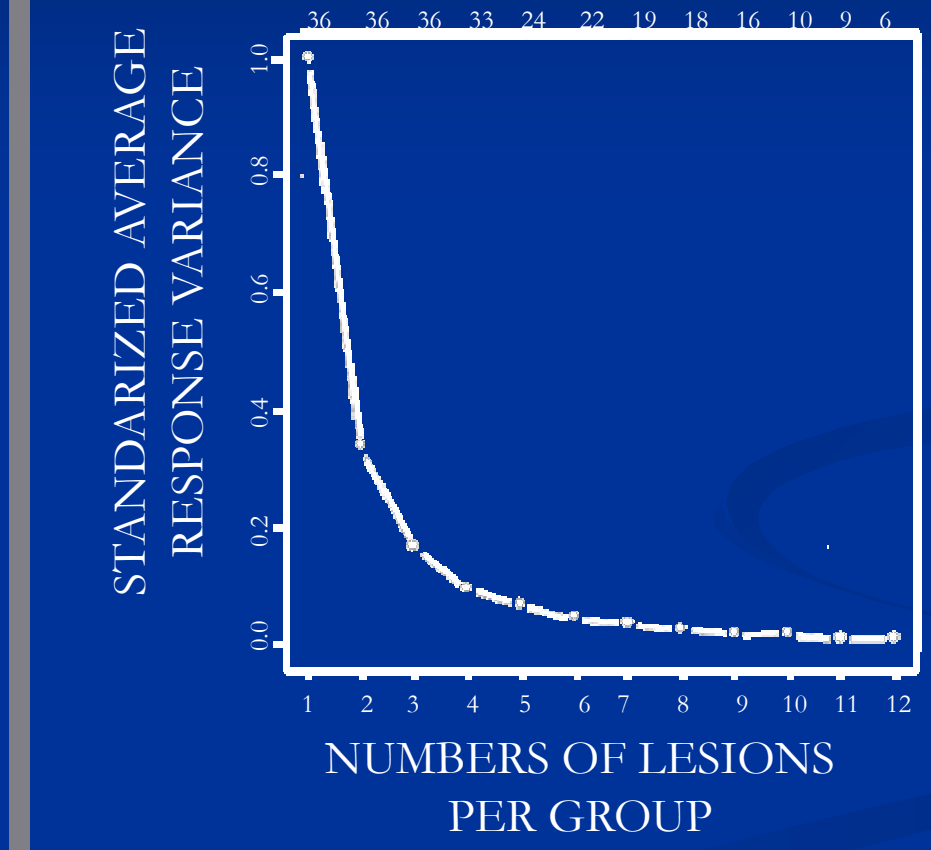
			Response assessment				Response Rank			
Patient No.	Total No . of lesions	No. of groupings	CR	PR	SD	PD	1	2	3	No. of response categories
1	7	21	0	0	0	21	1	0	0	1
2	16	4368	0	0	3697	671	0.85	0.15	0	2
3	10	252	0	100	152	0	0.6	0.4	0	2
4	10	252	1	232	19	0	0.98	0.08	0.004	3
5	12	792	0	0	31	761	0.96	0.04	0	2
6	15	3003	0	0	3003	0	1	0	0	1

Calculated tumor response assessments, response ranks, and response categories for one patient, analyzing 10 lesions with RECIST criteria

Clin Cancer Res. 2003 Oct 1;9(12):4318-23

The Need for Interpretation Standardization

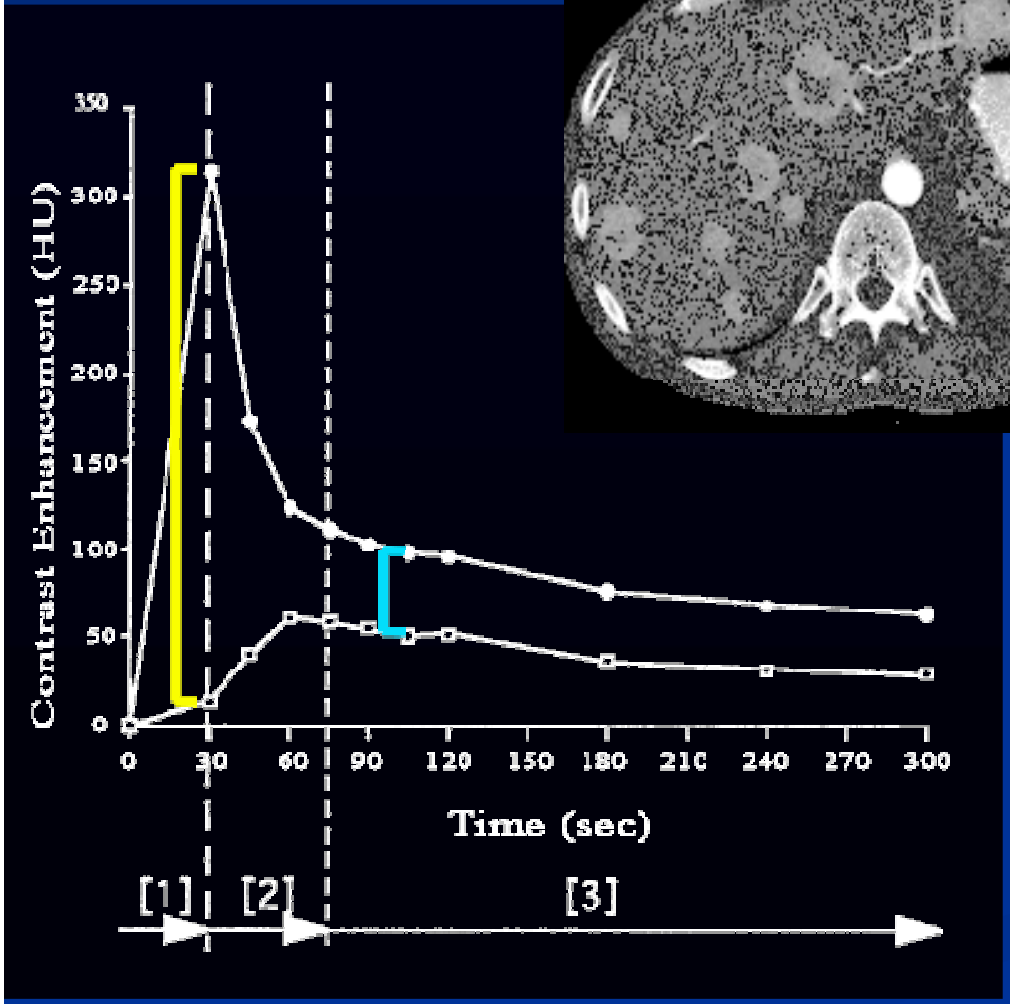
Target Lesion Selection

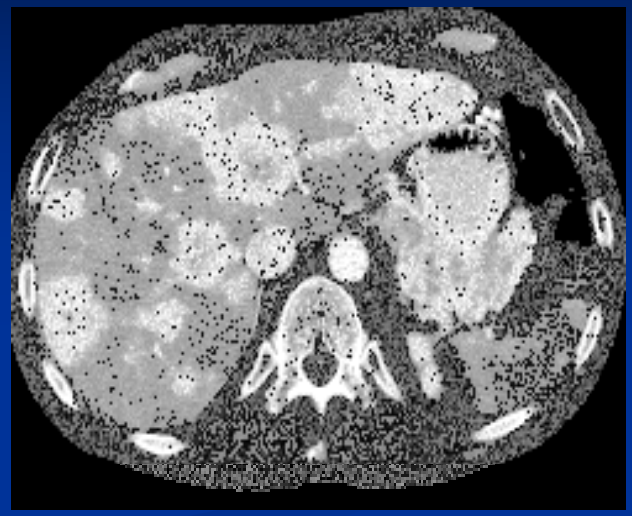


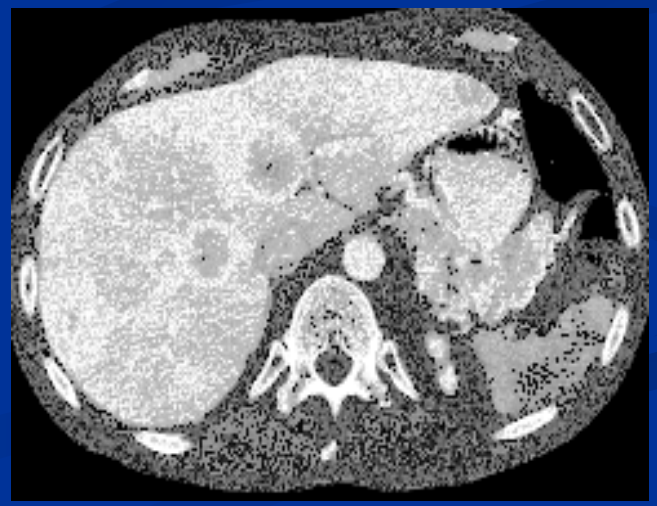
Clin Cancer Res. 2003 Oct 1;9(12):4318-23

The Need for Interpretation Standardization

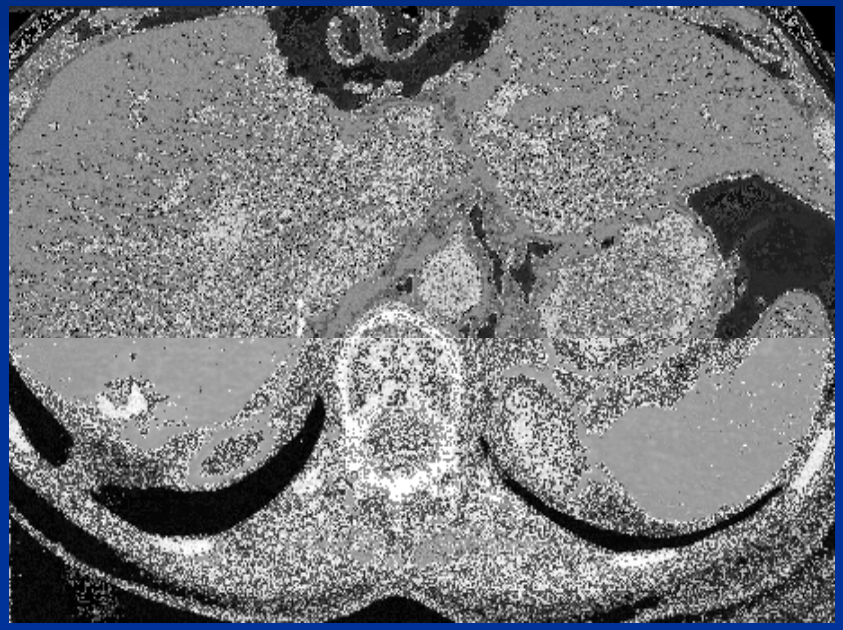
Image Acquisition - Contrast Administration

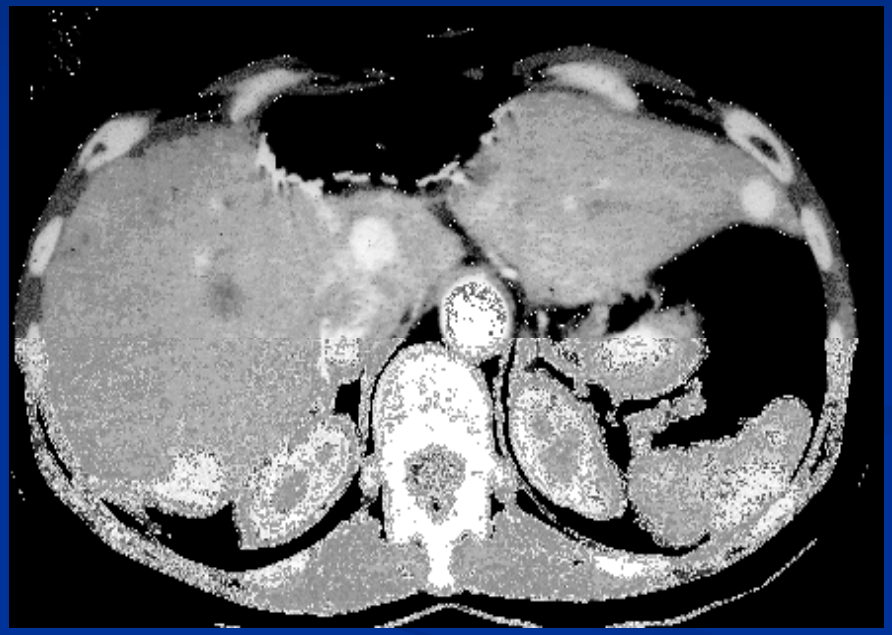






The Need for Interpretation Standardization
CT Contrast Administration





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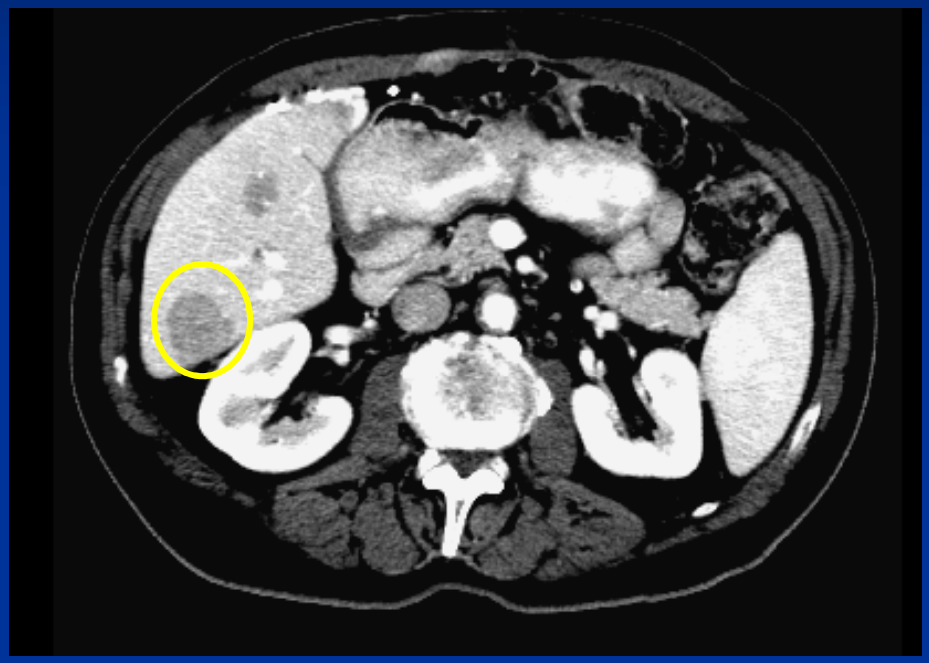
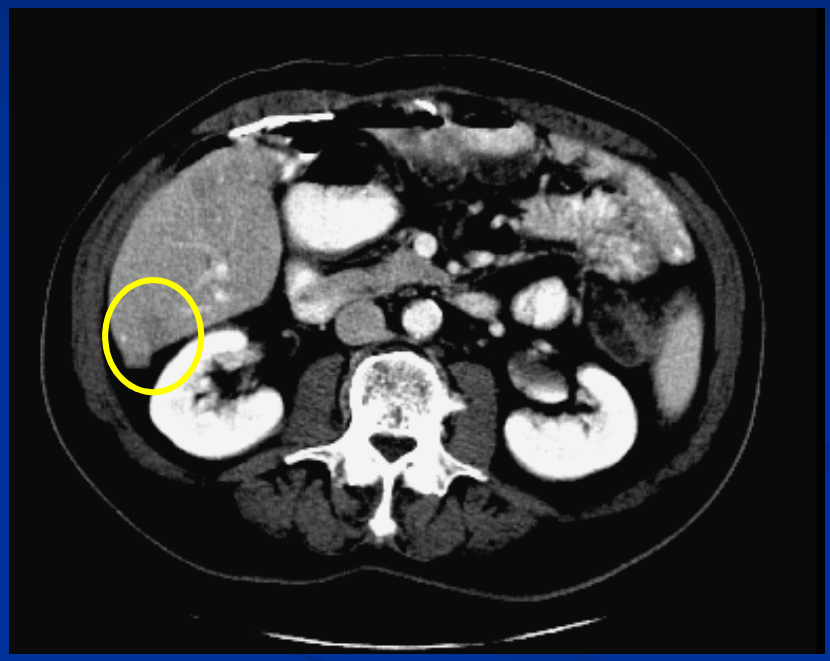
CT Contrast Administration

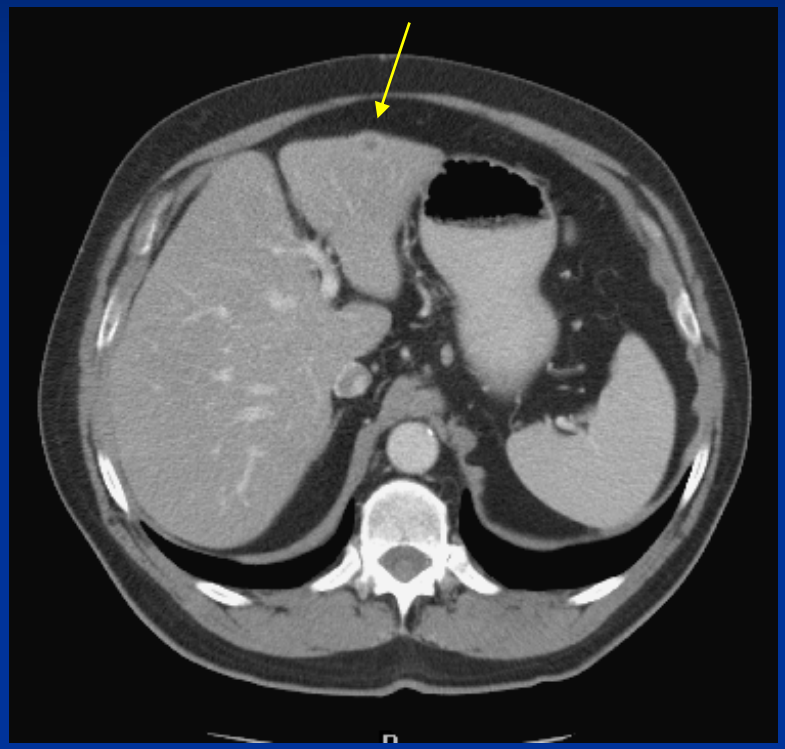


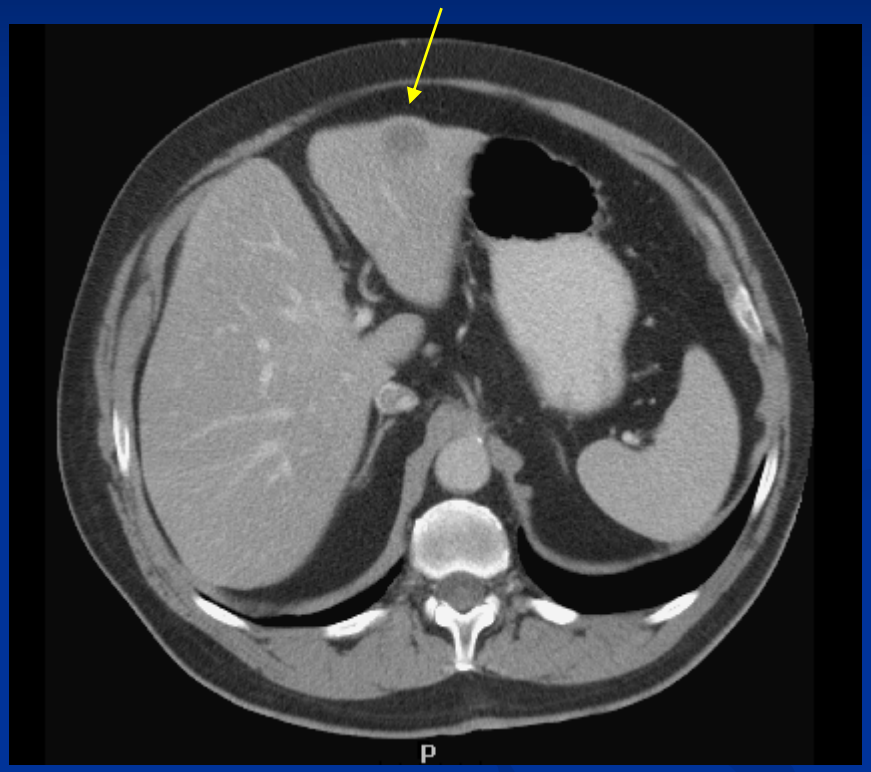


Response = PR

The Need for Interpretation Standardization

CT Contrast Administration

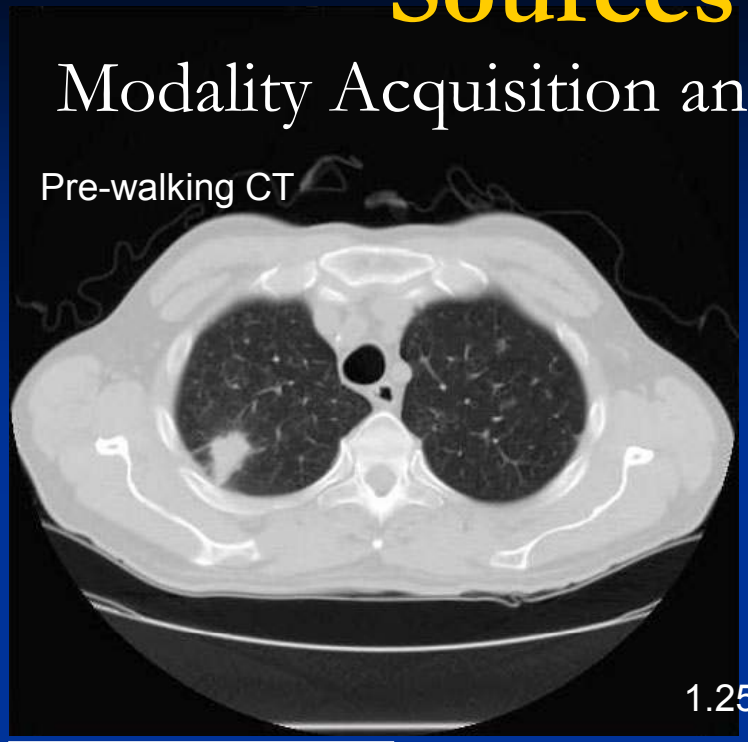


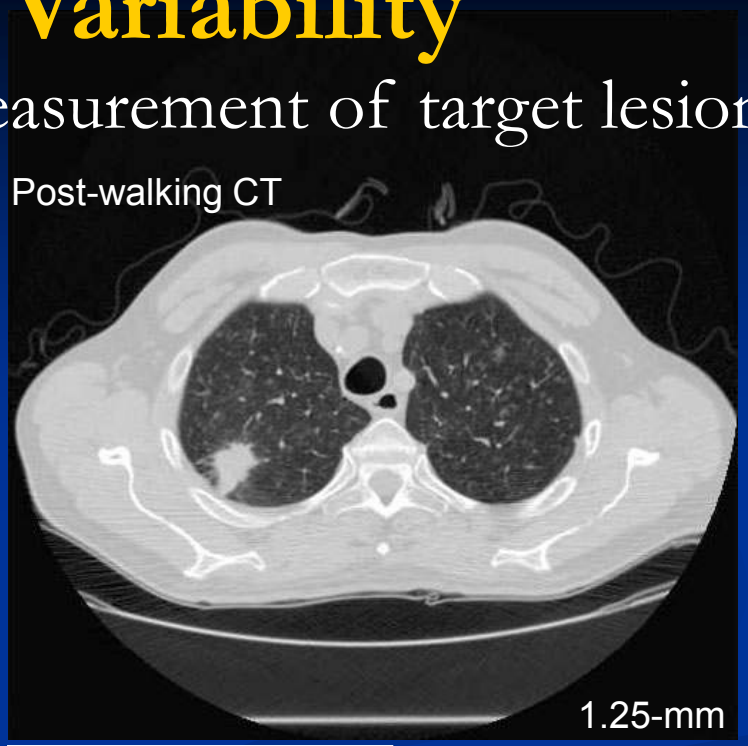


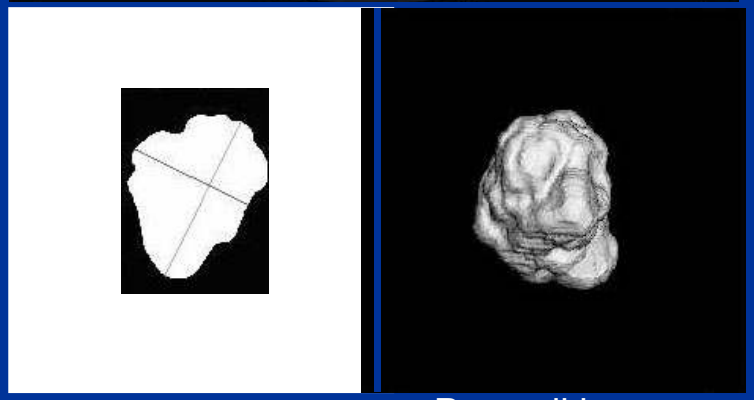
Response = PD

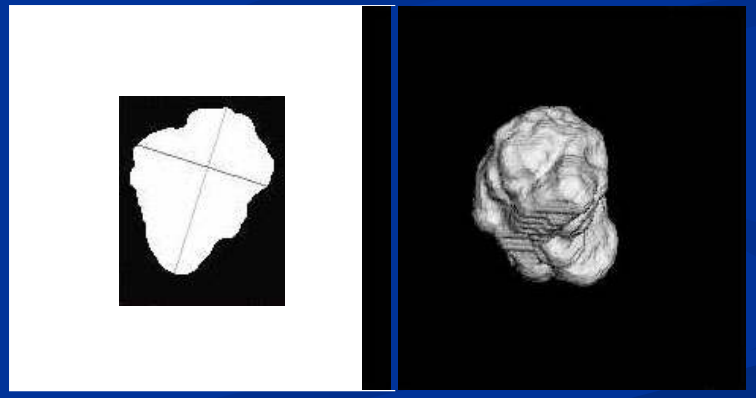
Sources of Variability

Modality Acquisition and Measurement of target lesions









	Pre-walking	Post-walking	Variation
Uni-dimension (mm):	27.6	27.8	0.7%
Bi-dimension (mm^2):	552	597.7	7.9%
Volume (mm^3):	4957.1	4852.3	2.1%

Zhao Radiolo

Sources of Variability

Modality Acquisition and Measurement of target lesions

	Concordance correlation coefficient		Mean % relative difference	95% Limits of agreement
	ρ_c	95% CI		
Uni-dimensional	1.00	(1.00, 1.00)	-0.6%	-7.3 %, 6.2 %
Bi-dimensional	1.00	(0.99, 1.00)	1.1%	-17.6 %, 19.8 %
Volume	1.00	(1.00, 1.00)	0.7%	-12.1 %, 13.4 %

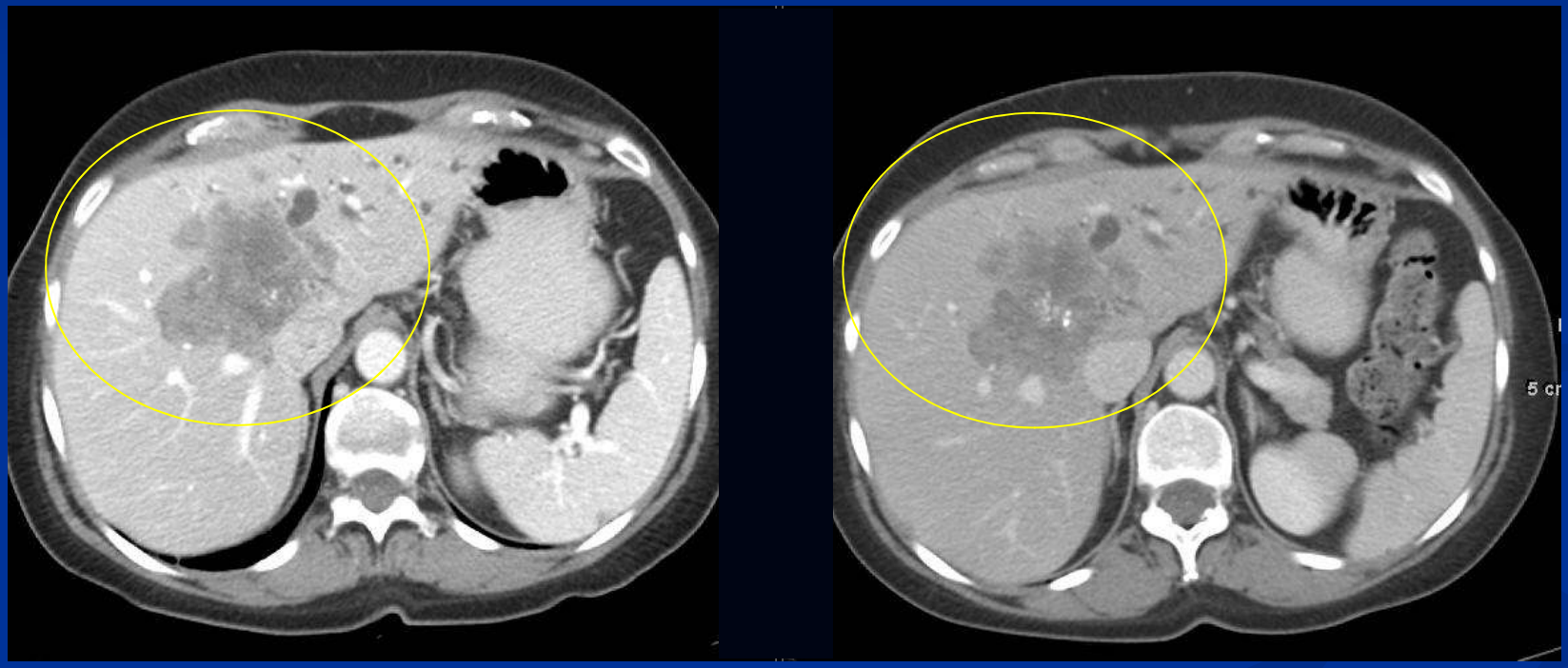
Sources of Variability

Interpretation of "clear unequivocal progression of non-target disease"

- There is no clear definition or interpretation of "clear unequivocal progression of non-target disease" in RECIST
  - This may result in variable interpretations impacting TTP image analysis especially in diseases with more extensive non target component

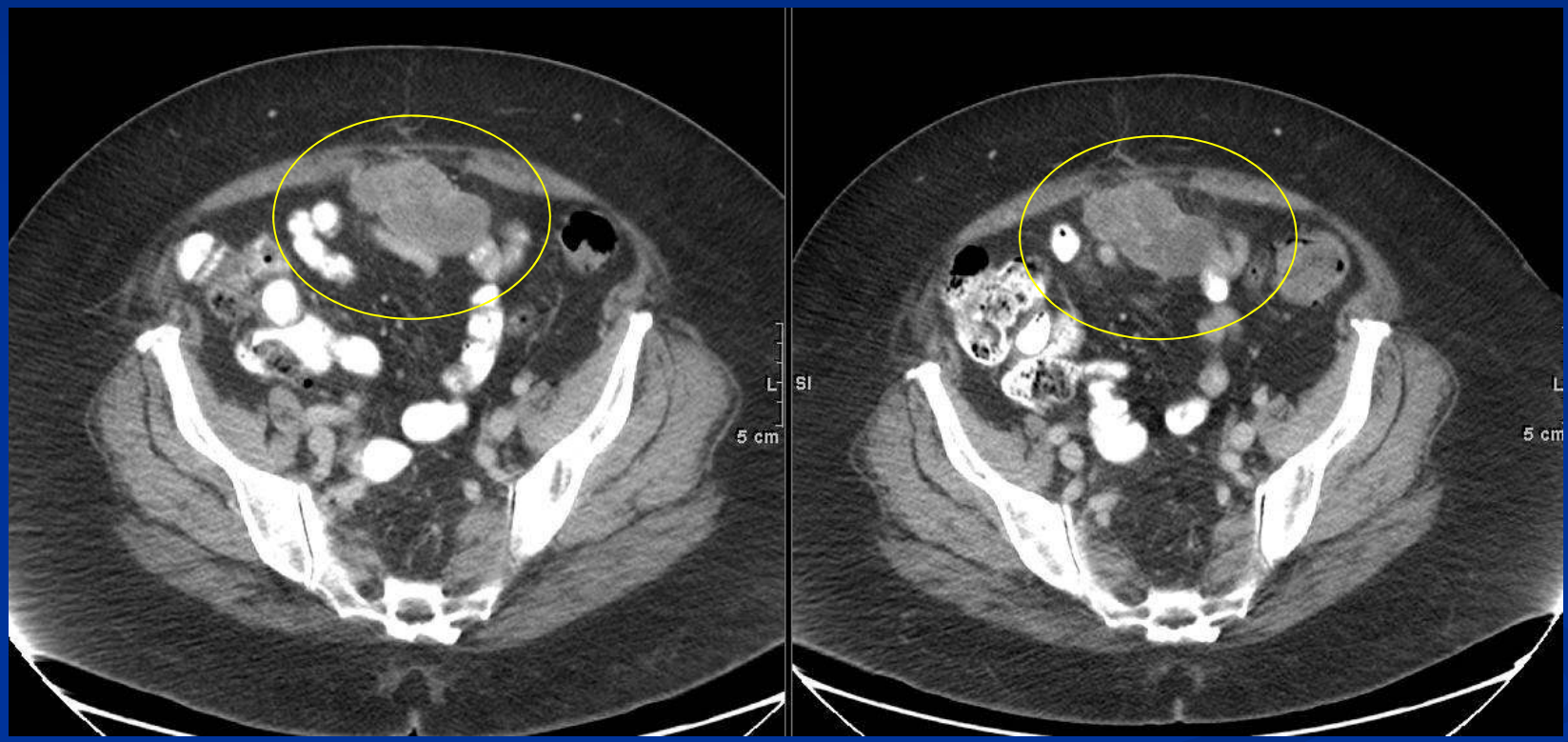
Sources of Variability

Interpretation of "clear unequivocal progression of non-target disease"



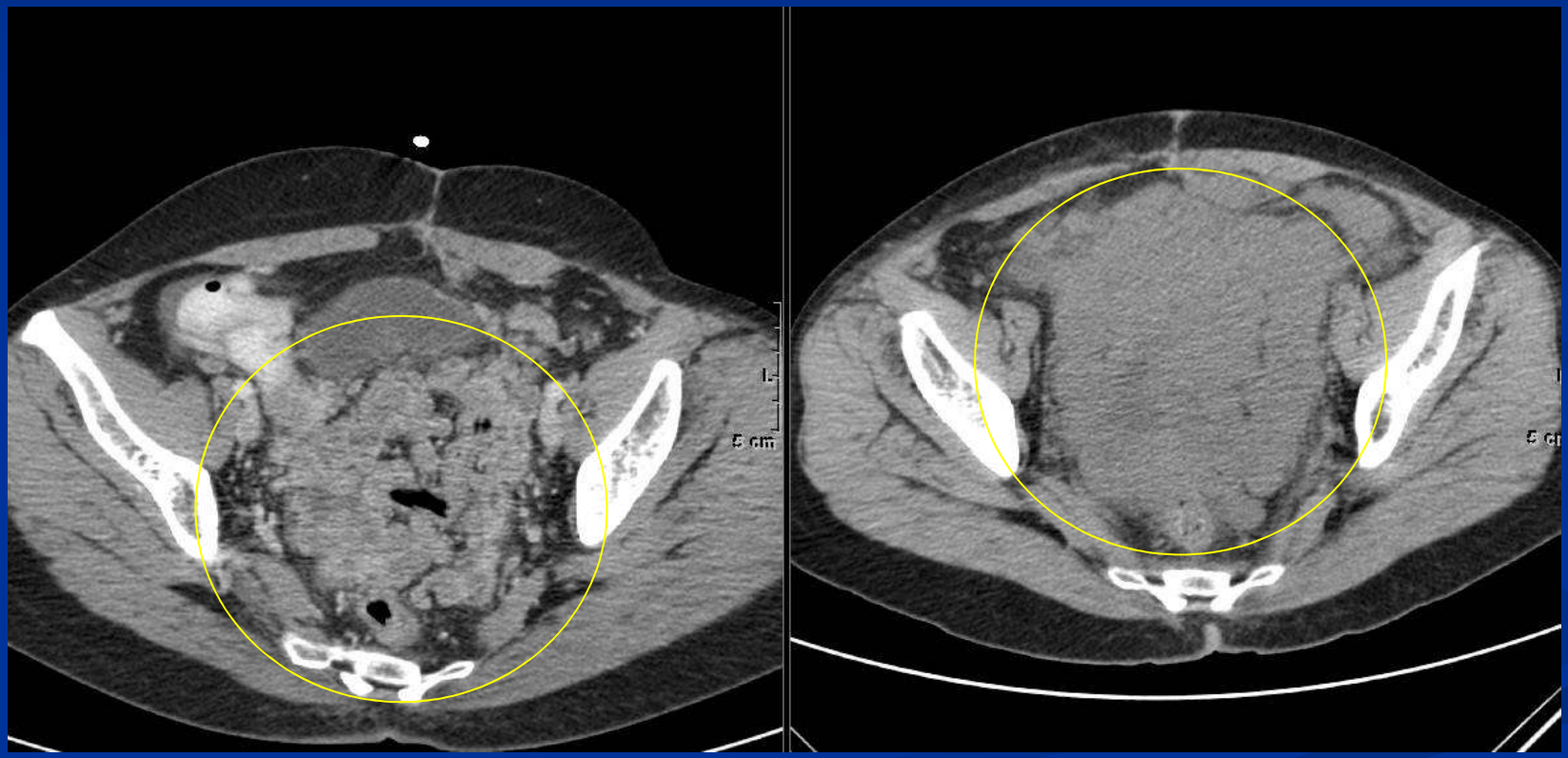
Sources of Variability

Interpretation of "clear unequivocal progression of non-target disease"



Sources of Variability

Interpretation of "clear unequivocal progression of non-target disease"



Sources of Variability

Identification of new lesions

Frequency of pulmonary nodules detection

No. of Nodules	Observer A		Observer B	
	1.25 mm	5 mm	1.25 mm	5 mm
2-5 mm	28	13	36	22
6-10 mm	18	14	20	18
11-30 mm	9	9	9	9
Total	55	36	65	49

Impact on lung lesion detection for time to progression analysis

What is an "optimal" or "acceptable" Agreement among observers?

- Consideration of the Primary Tumor and type of metastatic disease

- Mesothelioma
- Ovarian
- Pancreas
- Gastric
- Colorectal
- Renal
- Breast

- Others – Prostate, lymphoma

A single, standard agreement/adjudication rate would not reflect the variability in assessments across clinical trials

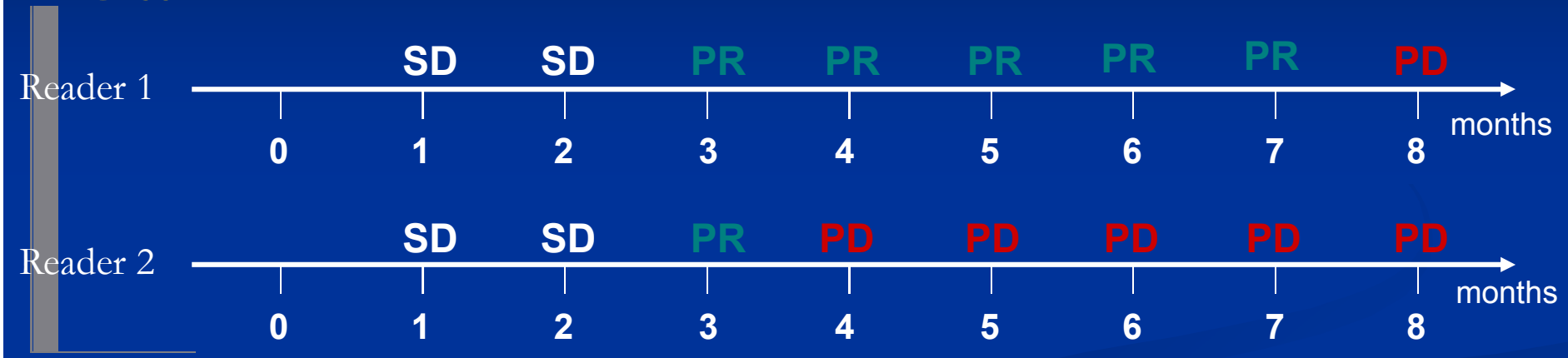
Acceptable Adjudication Rate?
Number of Modalities Assessed

- Case Study 1
  - Nonsmall Cell Lung Cancer
    - CT – Chest /Abdomen
- Case Study 2
  - Ovarian Cancer
    - CT – Chest / Abdomen / Pelvis
    - FDG-PET
    - CA-125
    - QOL assessment
    - Paracentesis for ascites

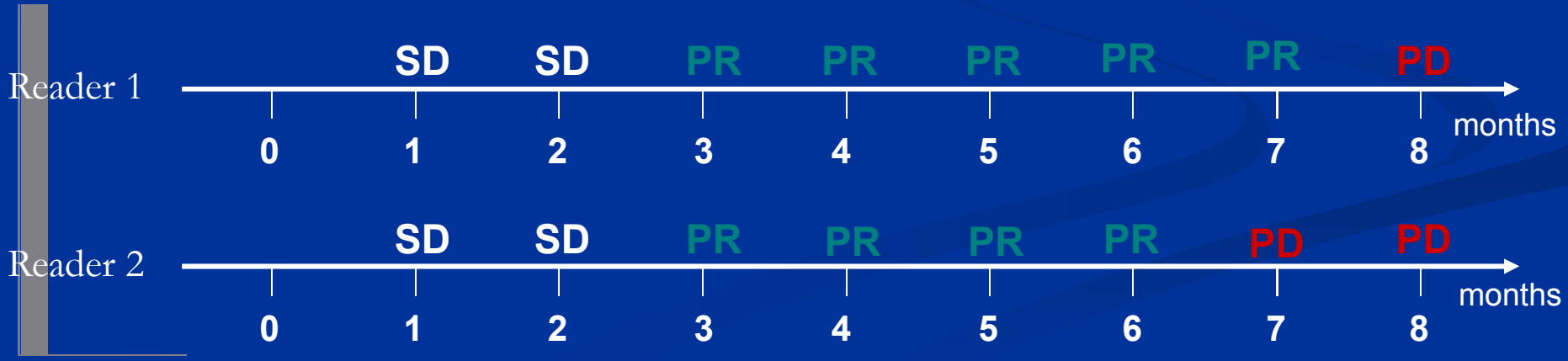
A single, standard agreement/adjudication rate would not reflect the variability in assessments across clinical trials

Acceptable Agreement Rate?
Each Adjudicated Case may not be Equal

Case 1

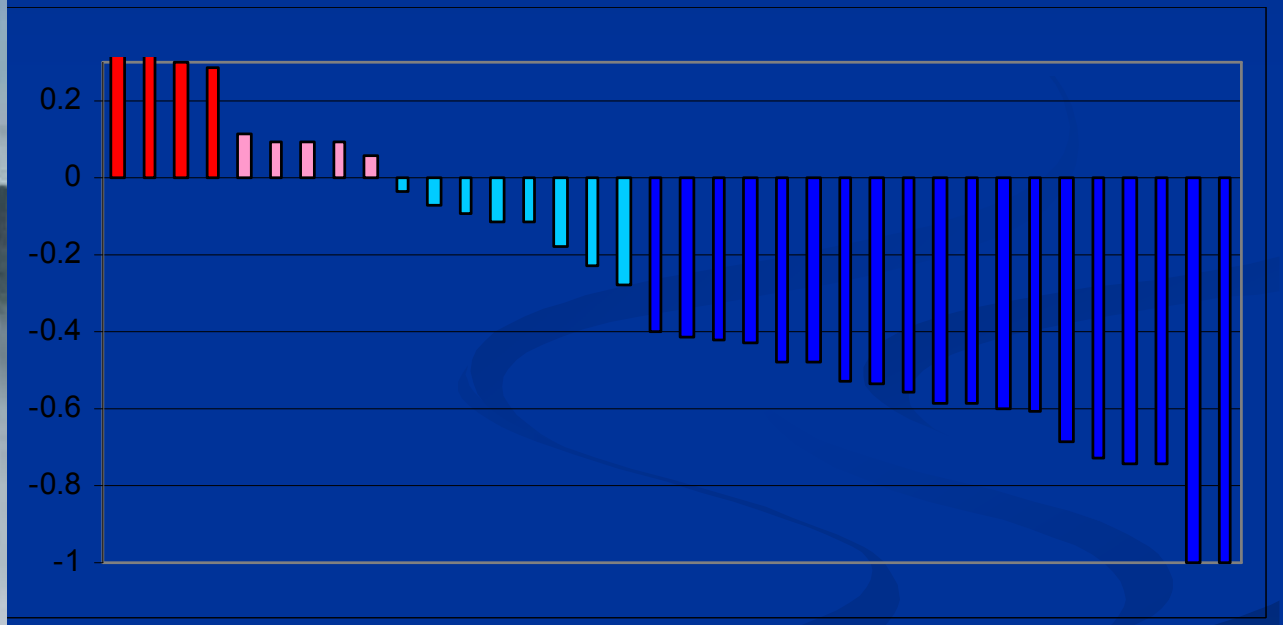


Case 2



Waterfall Plot / Analysis

May mandate even greater agreement….



CALGB
US Cooperative Groups

- Cooperative groups are consortia of institutions that conduct research in cancer treatment, prevention, biology and health outcomes

- Founded 1956
- The unit of membership is the institution; 28 main members, 14 CCOPs, 225 affiliates
- (Headquarters): University of Chicago; Statistical Center: Duke University

Treatment (Intervention) Trials @ CALGB

- Breast
- Lymphoma
- GI
  - Colorectal, esophagus, rectal
- GU
  - Kidney, bladder, prostate
- Pathology
- Imaging

- Phase I or limited access n = 3
- Phase II n = 22
- Phase III n = 18

- Registration directed (prospective) n = 4
- Several retrospective registration directed trials

Setting Standards of Care

- FDA approvals based on cooperative group data:
  -cisplatin for NSCLC
  -paclitaxel for ovarian and NSCLC
  -paclitaxel as adjuvant therapy for breast cancer
  -tamoxifen for breast cancer prevention
  -interferon for high risk melanoma
  -5-azacytidine for MDS
  -oxaliplatin for met. CRC
  -bevacizumab in 2nd line therapy for mCRC

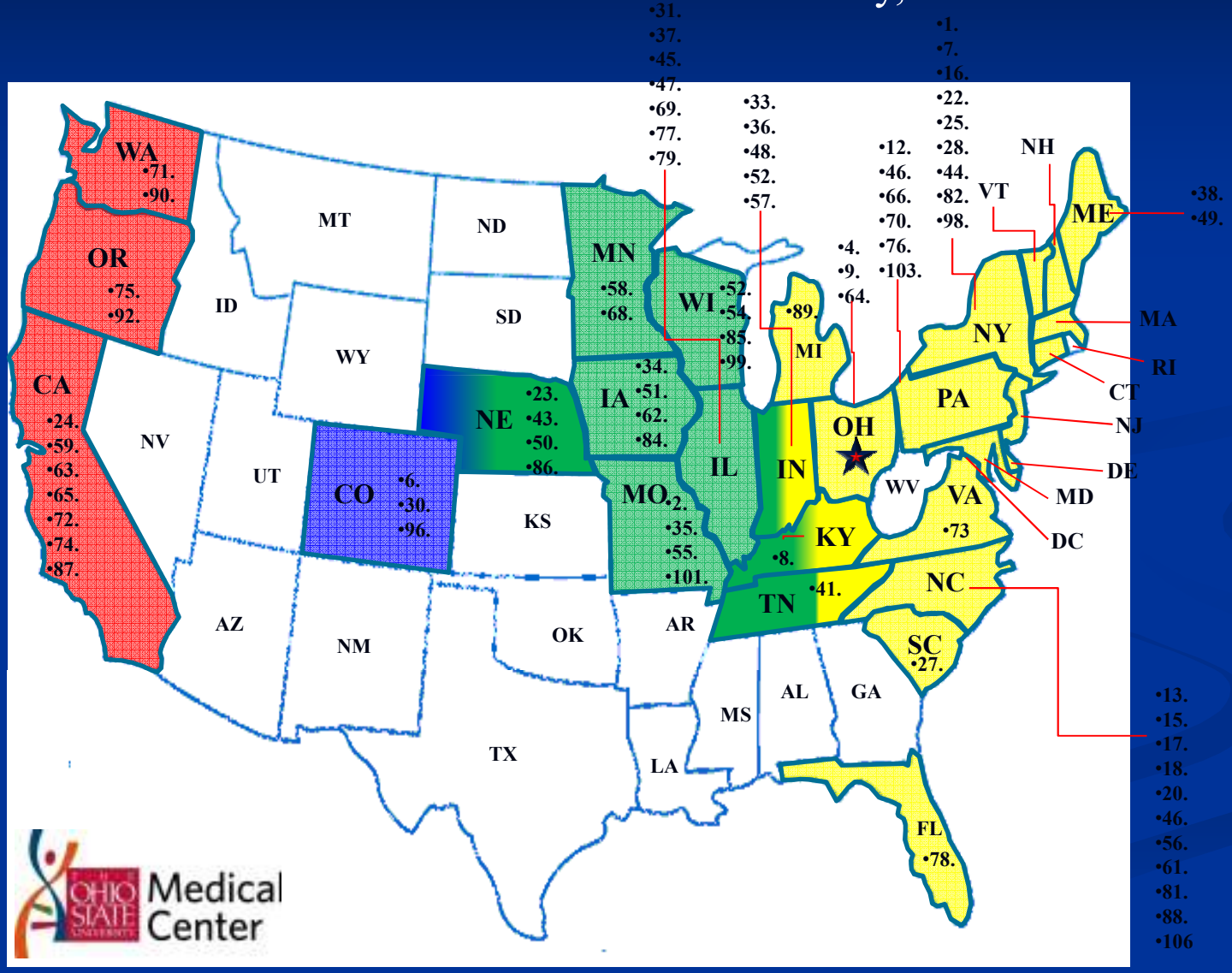
New CALGB Trials Utilizing Imaging

Protocol	Study Chair	Imaging Co-Chair
CALGB40502	Hope Rugo, M.D.	Deanna L. Kroetz, Ph.D.
CALGB40503	Maura Dickler, M.D.	Federico Innocenti, M.D.
CALGB50303	Wyndham H. Wilson, M.D., Ph.D. Andrew D. Zelentz, M.D., Ph.D.	Heiko Schoder, M.D.
CALGB50701	Barbara Grant, M.D.	Lale Kostakoglu, M.D.
CALGB80302	David H. Ilson, M.D., Ph.D.	Nathan Hall, M.D., Ph.D.
CALGB140503	Nasser Altorki, M.D.	Ernest Scalzetti, M.D.
CALGB80802	Ghassan Abou-Alfa, M.D.	Lawrence Schwartz, M.D.
SWOG0816	Oliver W. Press, M.D., Ph.D.,	Heiko Schoder, M.D.
CALGB30803	Sarita Dubey, M.D.	Ernest Scalzetti, M.D
CALGB50604	David J. Straus, M.D.	Lale Kostakoglu, M.D.
CALGB50801	Ann S. LaCasce, M.D.	Lale Kostakoglu, M.D.
CALGB30901	Arkadiusz Z. Dudek M.D., Ph.D.	Ernest Scalzetti, M.D
CALGB50602	Sonali M. Smith, M.D.	Heiko Schoder, M.D.
CALGB50201	Thomas Shea, M.D.	Lawrence Schwartz, M.D.
CALGB50203	David J. Straus, M.D.	Malik Juweid, M.D.
CALGB50404	Barbara Grant, M.D.	Malik Juweid, M.D.

Study Number	Study Name	pts accural	Total Studies Received
CALGB140503	A Phase III Randomized Trial of Lobectomy versus Sublobar Resection for Small (</= 2 cm) Peripheral Non-small Cell Lung Cancer	99	241
CALGB80302	A Phase II Trial of Preoperative Irinotecan, Cisplatin and Radiation in Esophageal Cancer	45	137
CALGB50701	A Phase II Trial of Extended Induction Epratuzumab (Anti-CD22 Monoclonal Antibody) (CALGB IND #101241) Plus Rituximab in Previously Untreated Follicular Non-Hodgkin's Lymphoma (NHL)	61	104
CALGB50602	A Phase II Study of Galiximab (Anti-CD80) for Patients with Relapsed/Refractory Hodgkin Lymphoma	14	25
CALGB50303	Phase III Randomized Study of R-CHOP v. Dose-Adjusted EPOCH-R with Molecular Profiling in Untreated De Novo Diffuse Large B-Cell Lymphomas	53	151
CALGB50203	Phase II Trial of Doxorubicin, Vinblastine and Gemcitabine (AVG) Chemotherapy for Non-Bulky Stage I and II Hodgkin Lymphoma	105	409
CALGB40503	Endocrine Therapy in Combination with Anti-VEGF Therapy: A Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Endocrine Therapy Alone or Endocrine Therapy Plus Bevacizumab (NSC 704865: IND 7921) for Women with Hormone Receptor Positve Advanced Breast Cancer	57	133
CALGB40502	A Randomized Phase III Trial of Weekly Paclitaxel Compared to Weekly Nanoparticle Albumin Bound NAB-Paclitaxel or Ixabepelone Combined with Bevacizumab as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer	112	285
CALGB50201	A Phase II Study to Evalutae the Safety and Efficacy of Zevalin (IND # BB IND 11023) Theraputic Regimen in Patients with Transformed CD20+ B-cell Non-Hodgkin's Lymphoma	7	24
SWOG0816	A PHASE II TRIAL OF RESPONSE-ADAPTED THERAPY OF STAGE III-IV HODGKIN LYMPHOMA USING EARLY INTERIMPDG-PET IMAGING	30	42

CALGB Imaging Core Lab Overview Procedures and Services

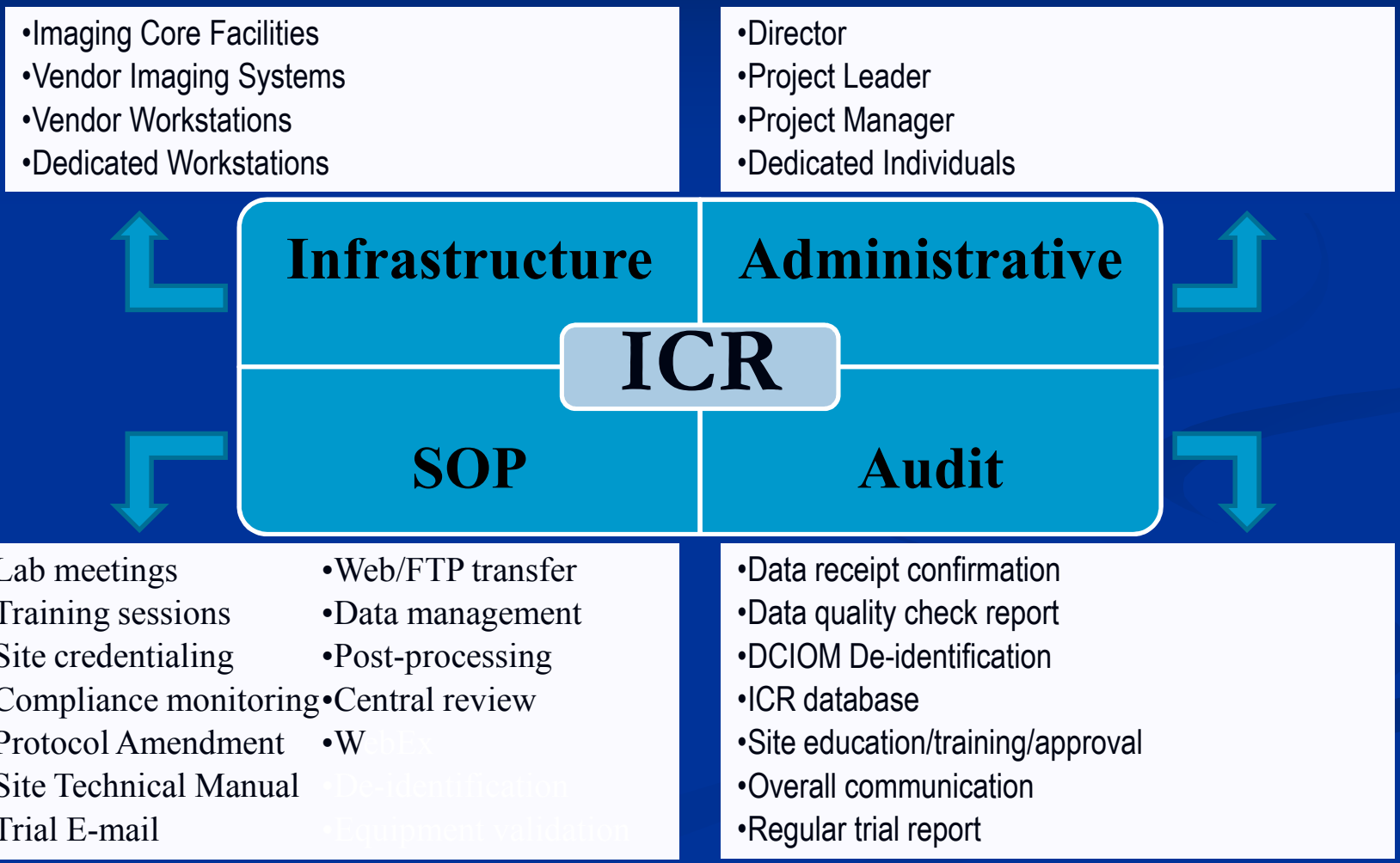
Jun Zhang, PhD; Nathan C. Hall, MD, PhD; Michael V. Knopp, MD, PhD
The Ohio State University, Columbus



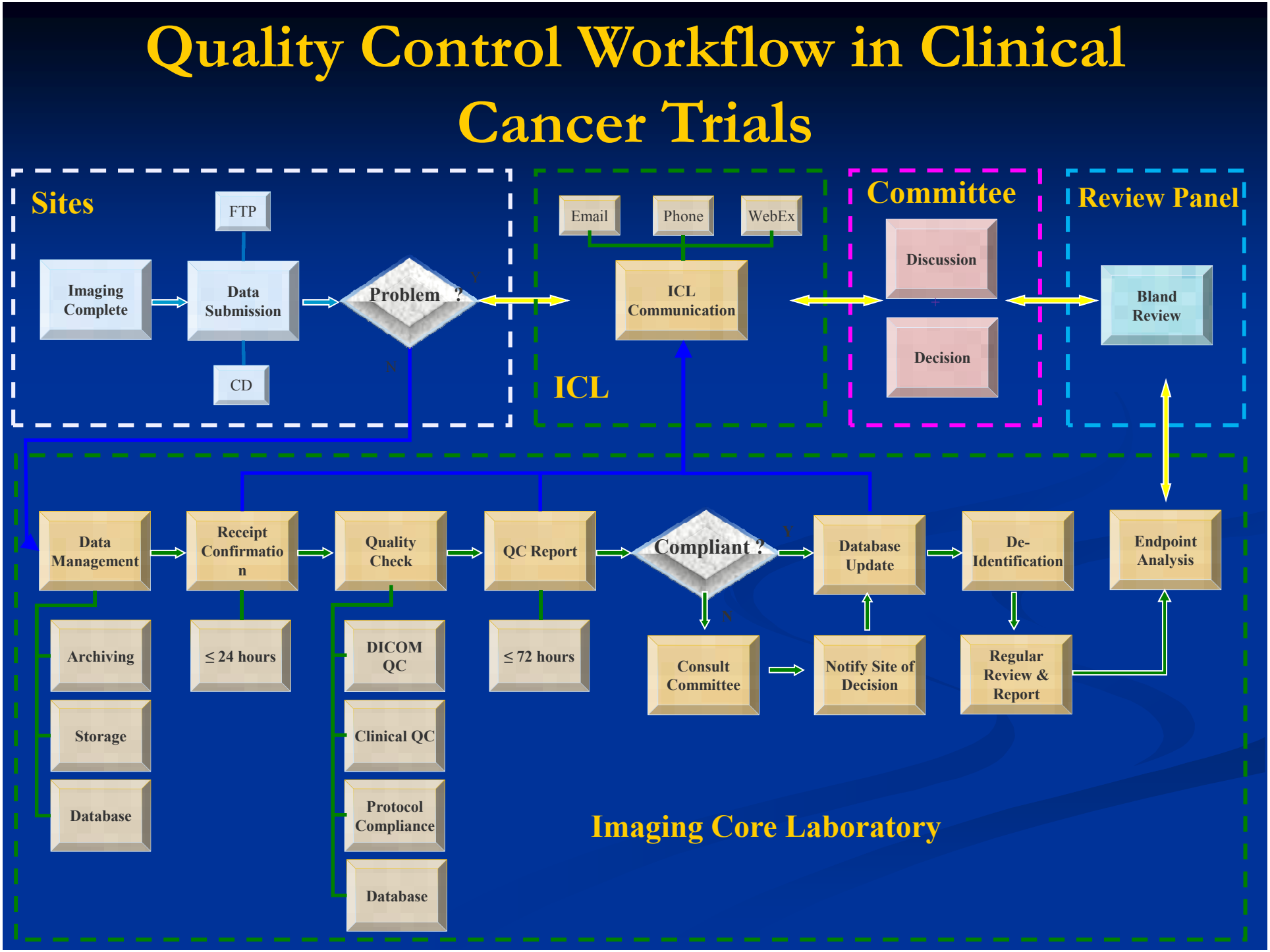
ICL

VT	•10. •30. •105.
NH	•21. •39. •40. •53.
MA	•14. •26. •42. •60.
CT	•80. •83. •95.
RI	
NJ	•67. •102
DE	•11. •19.
MD	•32. •91. •104.
DC	•5. •29.

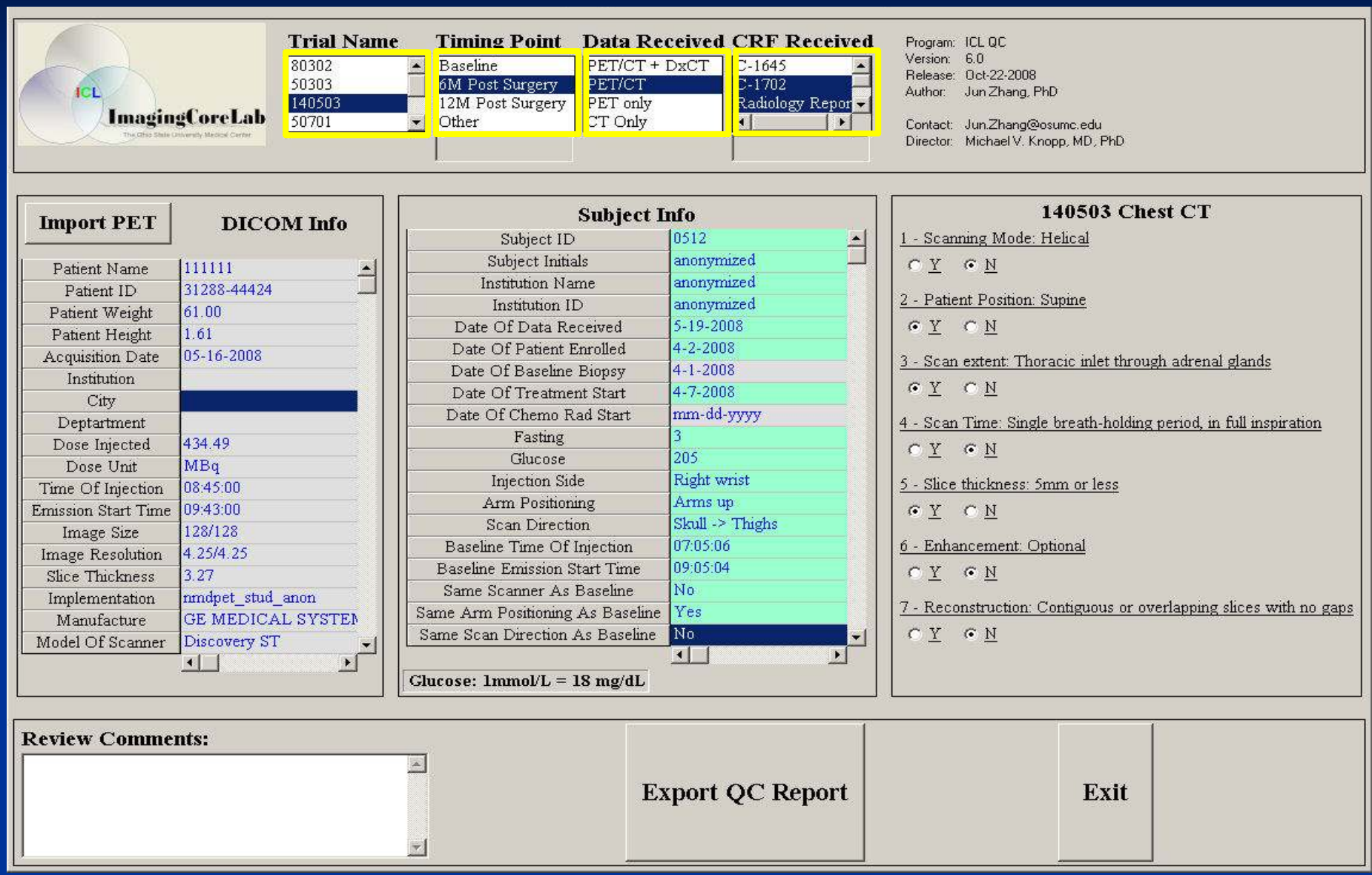
Imaging Core Service
Clinical Trials Quality Control

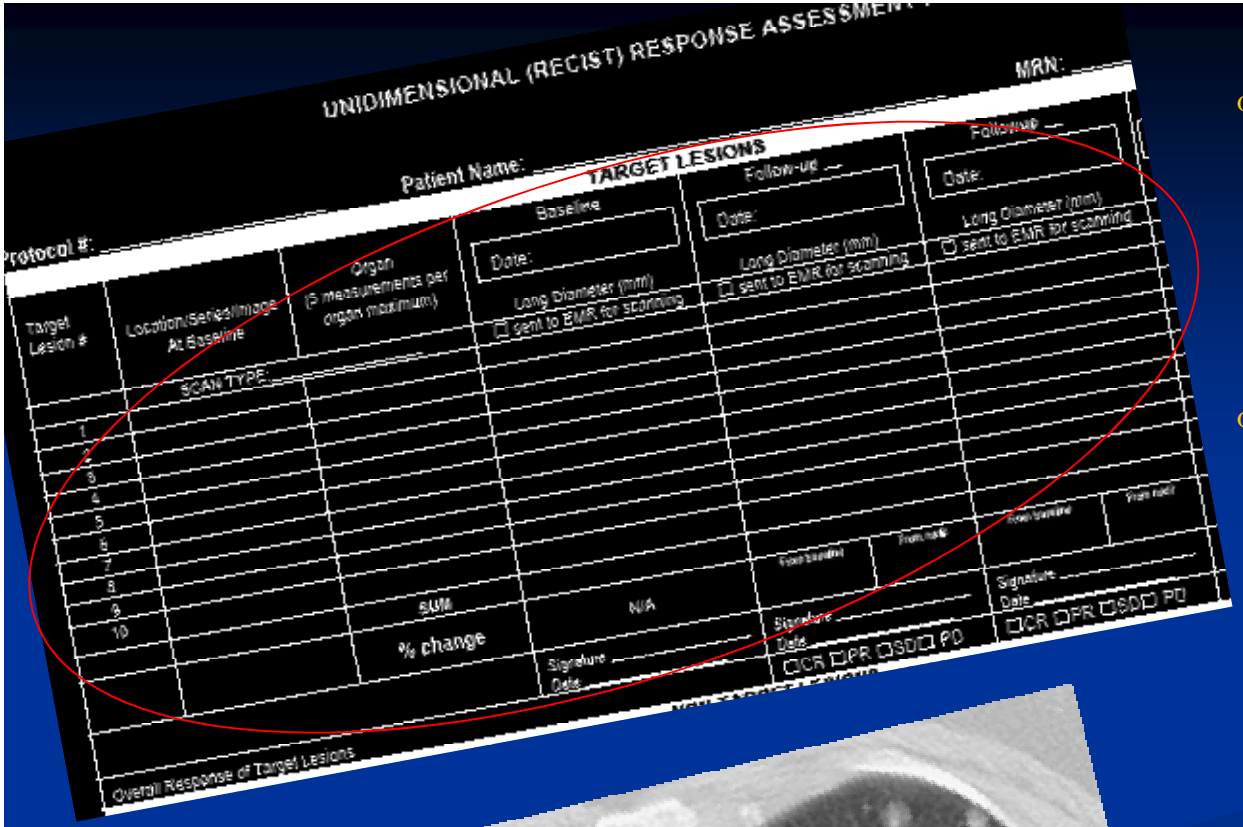


Quality Control Workflow in Clinical Cancer Trials



Semi-automatic PET/CT Image QC Program





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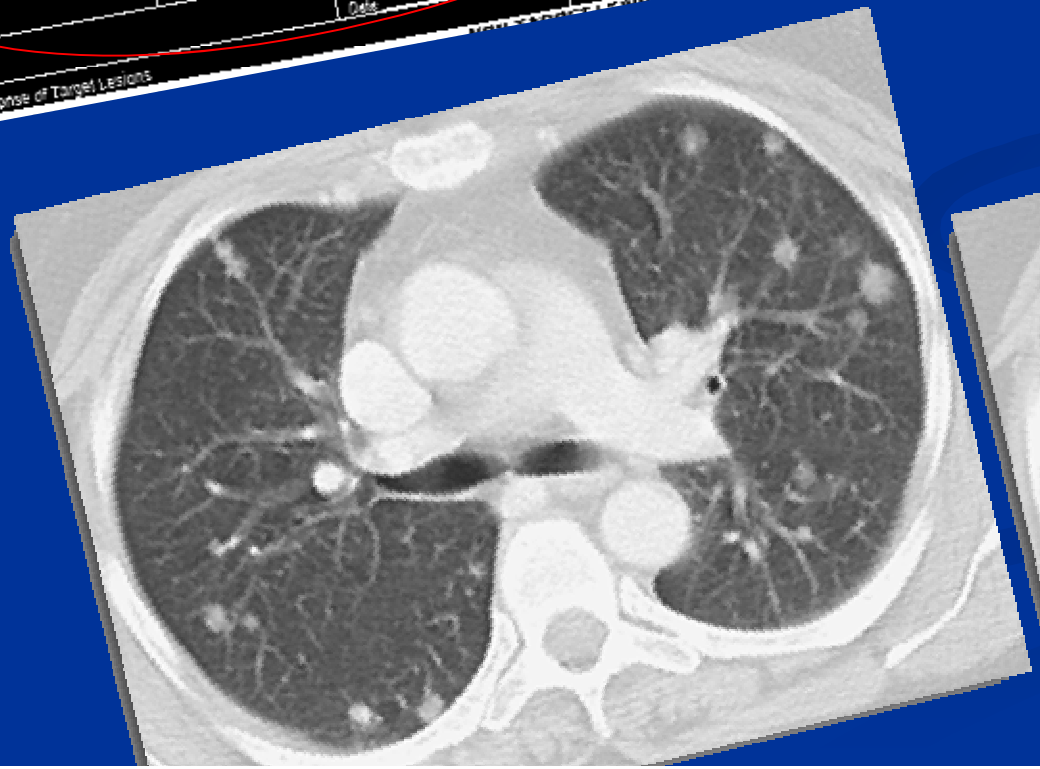
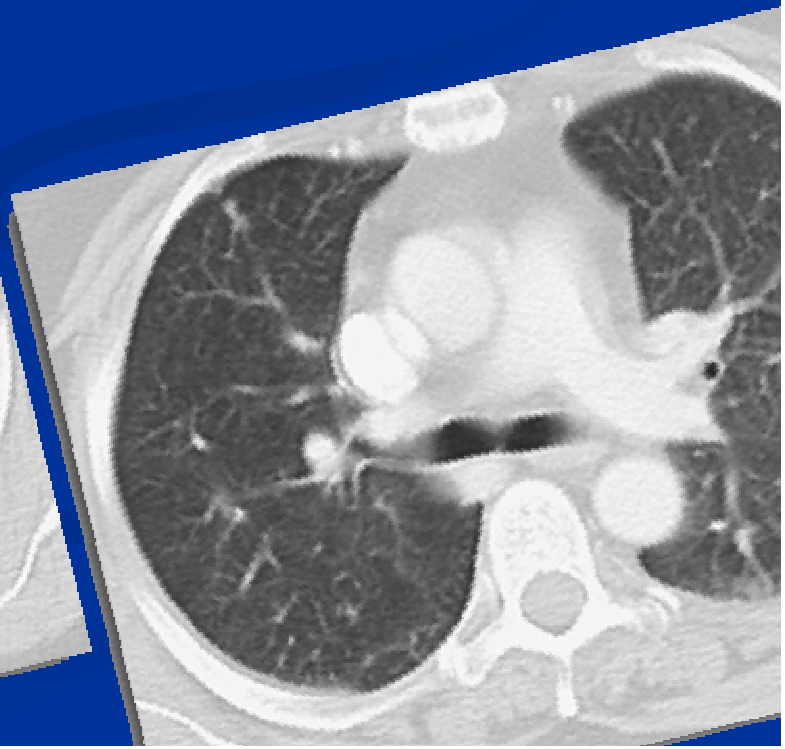


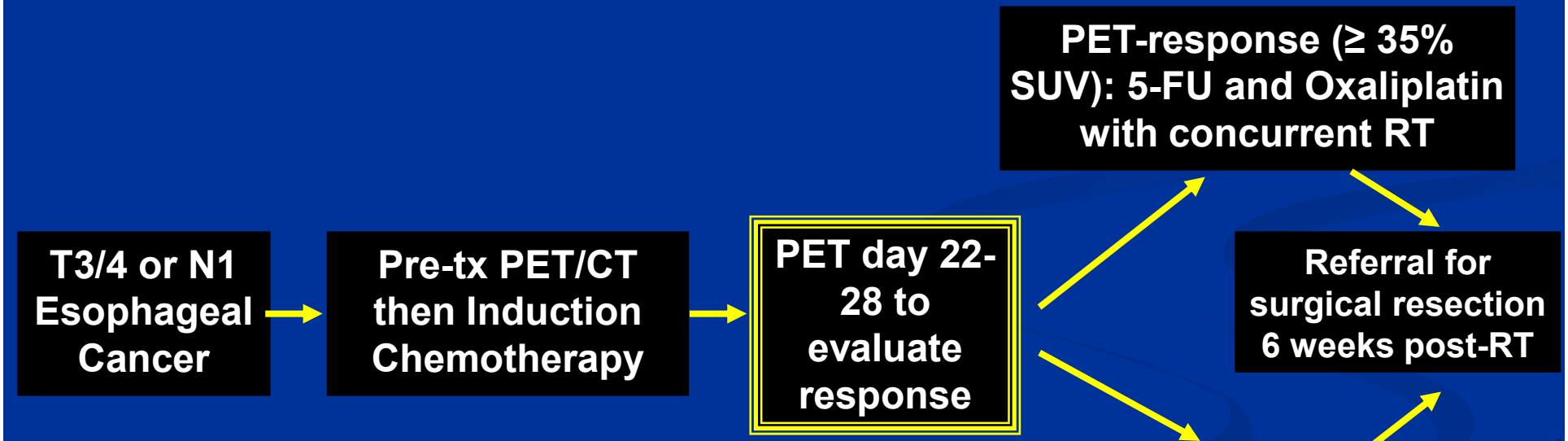


Centralized Data with Remote Review

- Vendor Advanced Workstation based
- Extended Brilliance Workspace
- Multi-Modality Workplace
- Centralized Data Review
- Data in one system
- Multiple reviewers
- Easy and Real-Time Access – Internet

Imaging Adaptive Trials

FDG PET/CT after induction chemo can identify patients who benefit from changing chemo resulting in improved response rates and PFS



CALGB
Tomorrow's Cancer Treatments Today

Intense need for real-time standardization of Acquisition and INTERPRETATION

Real-time Adaptive Trial Support -

1. New studies received? - Monitor trial Email and Workstation for the Review
2. New Pt registration? – Monitor trial email and remind sites of data submission
3. Data Receipt Confirmation within 24 hours upon data receipt
4. Quality Check Report notification within 48 hours for 'baseline' and 'final', 24 hours for 'interim'
5. For 'non-compliant' studies, contact imaging committee for a final decision.
6. DICOM image De-identification
7. Remote Review Scheduling with Central Readers
8. Prepare the review form for readers
9. Real-time Data Review with reader(s)
10. Request for review results from readers
11. Notification of central review results to sites and Central Office

ACADEMIC EXPERT PANEL REVIEW
72 HOUR TURN AROUND FROM ACQUISITION TO INTERPRETATION

Panel: Image Interpretation

Challenges and Approaches to Standardization

- Interpretation by its nature is both quantitative as well qualitative
  - Critical is standardization of acquisition, analysis and results reporting
  - Expert interpretation
- Training, education, experience – imaging and therapeutic specific
- The need for standardization varies by imaging modality and potentially therapeutic option
- The need and degree of standardization is clearly related to the magnitude of the therapeutic effect which is to be measured