Panel: Image Interpretation

Challenges and Approaches to Standardization

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Imaging Committee Chair for CALGB
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**

<table>
<thead>
<tr>
<th>Overall responses for all possible combinations</th>
<th>Target lesions</th>
<th>Nontarget lesions</th>
<th>New lesions</th>
<th>Overall response</th>
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</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>Incomplete response/SD</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>Non-PD</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>Non-PD</td>
<td>No</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or No</td>
<td>PD</td>
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<tr>
<td>Any</td>
<td>PD</td>
<td>Yes or No</td>
<td>PD</td>
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</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
<td></td>
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</table>
### The Need for Interpretation Standardization Variability - Target Lesion Selection

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Total No. of lesions</th>
<th>No. of groupings</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>No. of response categories</th>
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<tr>
<td>1</td>
<td>7</td>
<td>21</td>
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<td>0</td>
<td>1</td>
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<tr>
<td>2</td>
<td>16</td>
<td>4368</td>
<td>0</td>
<td>0</td>
<td>3697</td>
<td>671</td>
<td>0.85</td>
<td>0.15</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>252</td>
<td>0</td>
<td>100</td>
<td>152</td>
<td>0</td>
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<td>0.4</td>
<td>0</td>
<td>2</td>
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<tr>
<td>4</td>
<td>10</td>
<td>252</td>
<td>1</td>
<td>232</td>
<td>19</td>
<td>0</td>
<td>0.98</td>
<td>0.08</td>
<td>0.004</td>
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<tr>
<td>5</td>
<td>12</td>
<td>792</td>
<td>0</td>
<td>0</td>
<td>31</td>
<td>761</td>
<td>0.96</td>
<td>0.04</td>
<td>0</td>
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<td>6</td>
<td>15</td>
<td>5003</td>
<td>0</td>
<td>0</td>
<td>3003</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
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</table>

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
The Need for Interpretation Standardization

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

<table>
<thead>
<tr>
<th>Source</th>
<th>Pre-walking</th>
<th>Post-walking</th>
<th>Variation</th>
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<tbody>
<tr>
<td>Uni-dimension (mm)</td>
<td>27.6</td>
<td>27.8</td>
<td>0.7%</td>
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<tr>
<td>Bi-dimension (mm²)</td>
<td>552</td>
<td>597.7</td>
<td>7.9%</td>
</tr>
<tr>
<td>Volume (mm³)</td>
<td>4957.1</td>
<td>4852.3</td>
<td>2.1%</td>
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</table>

**Pre-walking CT**

**Post-walking CT**

1.25-mm
## Sources of Variability

Modality Acquisition and Measurement of target lesions

<table>
<thead>
<tr>
<th></th>
<th>Concordance correlation coefficient</th>
<th>Mean % relative difference</th>
<th>95% Limits of agreement</th>
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<tr>
<td></td>
<td>( \rho_c )</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uni-dimensional</td>
<td>1.00 ( (1.00, 1.00) )</td>
<td>-0.6%</td>
<td>-7.3 %, 6.2 %</td>
</tr>
<tr>
<td>Bi-dimensional</td>
<td>1.00 ( (0.99, 1.00) )</td>
<td>1.1%</td>
<td>-17.6 %, 19.8 %</td>
</tr>
<tr>
<td>Volume</td>
<td>1.00 ( (1.00, 1.00) )</td>
<td>0.7%</td>
<td>-12.1 %, 13.4 %</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>No. of Nodules</th>
<th>Observer A</th>
<th></th>
<th>Observer B</th>
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<tr>
<td></td>
<td>1.25 mm</td>
<td>5 mm</td>
<td>1.25 mm</td>
<td>5 mm</td>
</tr>
<tr>
<td>2-5 mm</td>
<td>28</td>
<td>13</td>
<td>36</td>
<td>22</td>
</tr>
<tr>
<td>6-10 mm</td>
<td>18</td>
<td>14</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>11-30 mm</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
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<tr>
<td>Total</td>
<td>55</td>
<td>36</td>
<td>65</td>
<td>49</td>
</tr>
</tbody>
</table>

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

Reader 1
0 1 2 3 4 5 6 7 8
SD SD PR PR PR PR PR PD

Reader 2
0 1 2 3 4 5 6 7 8
SD SD PR PD PD PD PD PD PD

Case 2

Reader 1
0 1 2 3 4 5 6 7 8
SD SD PR PR PR PR PR PR PD

Reader 2
0 1 2 3 4 5 6 7 8
SD SD PR PR PR PR PR PD PD
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

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Study Chair</th>
<th>Imaging Co-Chair</th>
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</thead>
<tbody>
<tr>
<td>CALGB40502</td>
<td>Hope Rugo, M.D.</td>
<td>Deanna L. Kroetz, Ph.D.</td>
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<tr>
<td>CALGB40503</td>
<td>Maura Dickler, M.D.</td>
<td>Federico Innocenti, M.D.</td>
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<tr>
<td>CALGB50303</td>
<td>Wyndham H. Wilson, M.D., Ph.D.</td>
<td>Heiko Schoder, M.D.</td>
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<td>CALGB50701</td>
<td>Barbara Grant, M.D.</td>
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<td>CALGB80302</td>
<td>David H. Ilson, M.D., Ph.D.</td>
<td>Nathan Hall, M.D., Ph.D.</td>
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<td>CALGB140503</td>
<td>Nasser Altorki, M.D.</td>
<td>Ernest Scalzetti, M.D.</td>
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<tr>
<td>CALGB80802</td>
<td>Ghassan Abou-Alfa, M.D.</td>
<td>Lawrence Schwartz, M.D.</td>
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<tr>
<td>SWOG0816</td>
<td>Oliver W. Press, M.D., Ph.D.</td>
<td>Heiko Schoder, M.D.</td>
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<td>CALGB30803</td>
<td>Sarita Dubey, M.D.</td>
<td>Ernest Scalzetti, M.D.</td>
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<td>CALGB50604</td>
<td>David J. Straus, M.D.</td>
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<td>CALGB50801</td>
<td>Ann S. LaCasce, M.D.</td>
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<td>Arkadiusz Z. Dudek M.D., Ph.D.</td>
<td>Ernest Scalzetti, M.D.</td>
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<td>CALGB50602</td>
<td>Sonali M. Smith, M.D.</td>
<td>Heiko Schoder, M.D.</td>
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<td>CALGB50201</td>
<td>Thomas Shea, M.D.</td>
<td>Lawrence Schwartz, M.D.</td>
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<td>CALGB50203</td>
<td>David J. Straus, M.D.</td>
<td>Malik Juweid, M.D.</td>
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<td>Malik Juweid, M.D.</td>
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<tr>
<td>CALGB140503</td>
<td>A Phase III Randomized Trial of Lobectomy versus Sublobar Resection for Small (≤2 cm) Peripheral Non-small Cell Lung Cancer</td>
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<td>CALGB80302</td>
<td>A Phase II Trial of Preoperative Irinotecan, Cisplatin and Radiation in Esophageal Cancer</td>
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<td>CALGB50701</td>
<td>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)</td>
<td>61</td>
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<td>CALGB50602</td>
<td>A Phase II Study of Galiximab (Anti-CD80) for Patients with Relapsed/Refractory Hodgkin Lymphoma</td>
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<td>CALGB50303</td>
<td>Phase III Randomized Study of R-CHOP v. Dose-Adjusted EPOCH-R with Molecular Profiling in Untreated De Novo Diffuse Large B-Cell Lymphomas</td>
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<td>CALGB50203</td>
<td>Phase II Trial of Doxorubicin, Vinblastine and Gemcitabine (AVG) Chemotherapy for Non-Bulky Stage I and II Hodgkin Lymphoma</td>
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<td>CALGB40503</td>
<td>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 Positive Advanced Breast Cancer</td>
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<td>CALGB40502</td>
<td>A Randomized Phase III Trial of Weekly Paclitaxel Compared to Weekly Nanoparticle Albumin Bound NAB-Paclitaxel or Ixabepolone Combined with Bevacizumab as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer</td>
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<td>CALGB50201</td>
<td>A Phase II Study to Evaluate the Safety and Efficacy of Zevalin (IND # BB IND 11023) Therapeutic Regimen in Patients with Transformed CD20+ B-cell Non-Hodgkin's Lymphoma</td>
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<td>SWOG0816</td>
<td>A PHASE II TRIAL OF RESPONSE-ADAPTED THERAPY OF STAGE III-IV HODGKIN LYMPHOMA USING EARLY INTERIMPDG-PET IMAGING</td>
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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
Imaging Core Service
Clinical Trials Quality Control

**Infrastructure**
- Imaging Core Facilities
- Vendor Imaging Systems
- Vendor Workstations
- Dedicated Workstations

**Administrative**
- Director
- Project Leader
- Project Manager
- Dedicated Individuals

**SOP**
- Lab meetings
- Training sessions
- Site credentialing
- Compliance monitoring
- Protocol Amendment
- Site Technical Manual
- Trial E-mail

**Audit**
- Data receipt confirmation
- Data quality check report
- DCIOM De-identification
- ICR database
- Site education/training/approval
- Overall communication
- Regular trial report

**ICR**
- Web/FTP transfer
- Data management
- Post-processing
- WebEx
- DS-identification
- Equipment validation
## Semi-automatic PET/CT Image QC Program

<table>
<thead>
<tr>
<th>Patient Name</th>
<th>Patient ID</th>
<th>Patient Weight</th>
<th>Patient Height</th>
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### Subject Info

- **ID**: 0212
- **Anonymized**: anonymized
- **Institution Name**: anonymized
- **Date of Data Received**: 5-15-2008
- **Date of Baseline Bmp**: 4-1-2008
- **Date of Treatment Start**: 4-7-2008
- **Date of Chemotherapy Start**: random-yy-yy
- **Chemotherapy**: 3
- **Glucose**: 205
- **Injection Side**: right wrist
- **Arm Positioning**: arms up
- **Scan Direction**: Skull to Thighs
- **Baseline Time of Injection**: 07:05:05
- **Baseline Emission Start Time**: 09:05:04
- **Same Scanner As Baseline**: no
- **Same Arm Positioning As Baseline**: yes
- **Same Scan Direction As Baseline**: no

### 140503 Chest CT

1. **Scanning Mode**: Helical
   - y
   - n
2. **Patient Position**: Supine
   - y
   - n
3. **Scan Extent**: Thoracic inlet through adrenal glands
   - y
   - n
4. **Scan Time**: Single breath-holding period in full inspiration
   - y
   - n
5. **Slice Thickness**: 3 or less
   - y
   - n
6. **Enhancement**: Optional
   - y
   - n
7. **Reconstruction**: Continuous or overlapping slices with no gaps
   - y
   - n

### Review Comments:

- [ ]

### Export QC Report

- [ ]

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