Imaging in Clinical Trials
Streamline Regulatory Submissions through the Qualification, Diagnostic Review and Scientific Interpretation of Imaging Data
March 29-30, 2016
Wyndham, Philadelphia Historic District
Keosys brief overview

Diameters measurement optimization

CT Volume measurement optimization

Integrated platform for multimodality
Keosys overview

About Keosys

- Founded in 2001
- 1400 Reference Sites
- Locations: Europe | USA | Asia
- 60+ ongoing Clinical Trials including Phase III
- Over 100 Medical Experts

Business Areas

- Clinical Trial: imaging management
- Clinical Routine: image analysis solutions
Keosys overview

Clinical Trials

IT Expertise
- Software developer
- IT Platform for Clinical Trials
- Medical Imaging data management
- Worldwide Datacenters

Medical expertise
- Medical Directors
- Network of readers
- Network of technologists
- Project Management
- GCPs and 21 CFR part 11

Clinical Routine

Medical expertise

Medical Device
- Advance image analysis Software
- Workstation / Application Server
- IT Platform (telemedicine)
- FDA 510k clearance / CE MD Class IIa

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Diameters measurement optimization

CT Volume measurement optimization

Integrated platform for multimodality
• Therapeutic response evaluation using anatomical imaging (CT, MRI, RX, ...) and dimensional measurements is still common.

• From first World Health Organization WHO criteria (1981) other way to get information about therapeutic response has been published then used. They each take into account specificity: therapeutic agent, pathologies, ...

• Example of criteria:
  - WHO
  - RECIST (version 1.0 and 1.1)
  - CHESON
  - CHOI
  - mRECIST
  - PERCIST
  - EORTC
  - irRECIST
Diameter measurement optimization

Each criteria has its own way to assess the therapeutic response.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Complete Response</th>
<th>Partial Response (PR)</th>
<th>Stable Disease (SD)</th>
<th>Progressive Disease (PD)</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria based on conventional imaging biomarkers</td>
<td>- WHO: Disappearance of all lesions</td>
<td>≥ 50% decrease in the sum of the area (longest diameters multiplied by longest perpendicular diameters)</td>
<td>Neither PR nor PD</td>
<td>≥ 25% increase in the sum of the area</td>
<td>≥ 10% decrease in size or 15% decrease in density of GIST on contrast-enhanced CT</td>
</tr>
<tr>
<td></td>
<td>- RECIST, version 1.0: Disappearance of all lesions</td>
<td>≥ 30% decrease in the sum of the longest diameters</td>
<td>Neither PR nor PD</td>
<td>≥ 20% increase in the sum of the longest diameters</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- RECIST, version 1.1: Disappearance of all lesions and pathologic lymph nodes</td>
<td>≥ 30% decrease in the sum of the longest diameters</td>
<td>Neither PR nor PD</td>
<td>≥ 20% increase in the sum of the longest diameters and ≥ 5 mm absolute increase in the sum of the longest diameters</td>
<td></td>
</tr>
<tr>
<td>Criteria based on newer imaging biomarkers</td>
<td>- Choi: Disappearance of intratumoral arterial enhancement</td>
<td>≥ 50% decrease in the sum of the arterially enhancing areas (longest diameters multiplied by longest perpendicular diameters)</td>
<td>Neither PR nor PD</td>
<td>≥ 25% increase in the size of the arterially enhancing areas or development of a new lesion or lesions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- EASL: Disappearance of all lesions and pathologic lymph nodes</td>
<td>At least a 30% decrease in the sum of diameters of viable (enhancing) target lesions, taking as reference the baseline sum of the target lesions</td>
<td>Neither PR nor PD</td>
<td>≥ 20% in the sum of diameters of viable target lesions recorded since treatment started or development of a new lesion or lesions</td>
<td></td>
</tr>
</tbody>
</table>


Each criteria chose different number of target lesion, with different sizes:

<table>
<thead>
<tr>
<th>Criterion</th>
<th>RECIST Version 1.0</th>
<th>RECIST Version 1.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum size of target lesion</td>
<td>≥ 10 mm on helical CT; ≥ 20 mm on nonhelical CT and MRI</td>
<td>≥ 10 mm on helical CT or MRI; ≥ 20 mm on chest radiography</td>
</tr>
<tr>
<td>Overall tumor burden</td>
<td>Maximum of 10 target lesions total (maximum of 5 per organ)</td>
<td>Maximum of 5 target lesions total (maximum of 2 per organ)</td>
</tr>
<tr>
<td>Measurement</td>
<td>1D longest diameter of tumor</td>
<td>1D longest diameter of tumor; short axis of lymph nodes</td>
</tr>
<tr>
<td>New lesions</td>
<td>None</td>
<td>Clarified</td>
</tr>
<tr>
<td>Measurement of bone and cystic lesions</td>
<td></td>
<td>Clarified</td>
</tr>
<tr>
<td>Lymph node measurements</td>
<td>None</td>
<td>Lymph nodes ≥ 15 mm are target lesion; lymph nodes &lt; 10 mm are nonpathologic</td>
</tr>
<tr>
<td>Response criteria for target lesions (PD)</td>
<td>20% increase over smallest sum on study or new lesions</td>
<td>20% increase over smallest sum on study and at least 5 mm increase or new lesions</td>
</tr>
<tr>
<td>Response criteria for nontarget lesions (PD)</td>
<td>Unequivocal progression considered as PD</td>
<td>More detailed description of “unequivocal progression”</td>
</tr>
<tr>
<td>Confirmation of CR and PR</td>
<td>After at least 28 d</td>
<td>Only required if response is primary endpoint and not randomized</td>
</tr>
<tr>
<td>$^{18}$FDG PET</td>
<td>None</td>
<td>Used only to support CT if PD or to confirm CR</td>
</tr>
</tbody>
</table>

Note—CR = complete response, PR = partial response, PD = progressive disease.

Main sources of variabilities

There is a lot of sources of variabilities in imaging response assessment:
- Patient preparation
- Imaging procedure (vendor, acquisition protocol, modality capabilities,...)
- Imaging post processing (if applicable)
- Imaging diffusion workflow (from PACS)
- Reading software
- Reader training, experience
- Reporting procedures at each step

In a global multi-centric (i.e multi-cultural) study, all this leads to costly manual checks and correction.

=> Improvement is required.
Standardization and consensus about procedures to implement in order to get a given performance is one of the goal of QIBA Profiles. For more:
http://qibawiki.rsna.org

Profiles give indication on:
- Subject Handling
- Image Data Acquisition
- Image Data Reconstruction
- Image QA
- Image Analysis

But Image Analysis done in a central reading context may be cumbersome: need use of several software, platforms, paper forms, CD-Rom, ...

=> An integrated Image analysis platform may improve the process of Clinical Trials (CT)
How an integrated platform may improve CT

1 - Image analysis tool and eCRF in the same system

- One screen (web) for visit selection, and eCRF validation. Also display needed info: previous reviews, relevant clinical data

- One screen for imaging display, with all tools needed for CT or MR reading and lesion identification & documentation.
2 - Check image presentation rules in the image analysis system

Imaging example: Use case # 2102: Baseline CT reading - Cheson

Pathology: Follicular Lymphoma
Timepoint: T0 (Baseline)
Imaging acquisition: Optimal: IV CTAP + lung / Accepted: IV CTAP
Imaging review criteria: Cheson 99
Specifics: If appropriate, it is recommended to measure also 6 non target lesions that will be followed quantitatively.
Reading methodology:
   central reading with 2 different readers. Expert adjudication if no agreement. Agreement based on inter-reader CV
How an integrated platform may improve CT

Image presentation rules:

- Dedicated display layout, with MPR display (measurements only in axials)
- Cheson measurement tools: bi-dimensional measurement, flags.
- Cheson criteria rules enforcement: lesion size (target vs non target), type (node/non node), maximum number of targets,
- Easy access to measurement tools, localisation and optional comment by lesion
- Possible to save work even if validation rules are not ok.
- Imaging review automatically imported in eCRF, user may add information about relevant non measurable findings.
Use case # 2102 : Key points

CT reading dedicated view with:

- Native axial slice
- MPR software reconstruction (coronal & sagittal).
- Reconstructions support custom thickening, MIP, MinP, VRT, 3D real time rotations
- Slicing, pan, zoom & window adjustment from mouse actions
- Target measurement only on native axial.

Volatile measure with 1cm caliper under mouse cursor

MPR Triangulation cross hair

3D rotation handlers (colored axis)
3 – Lesion measurement and documentation rules

Use case #2102: Key points

The lesion monitoring:

- A click on a lesion line recall the lesion on CT images
- 2 way to identify lesion: measurement (target lesion) or a position flag.
- Rules are triggered by localisation. E.g: size requirement are ≠ for nodes & non nodal localisation.
- Note: Specific to RECIST criterion: SA will be automatically selected for lymph nodes.

- Cheson bidimensional measures are show, along with PPD
- Reader can add a textual comment at lesion level.
- Global SPD is shown
- Cheson rules are checked and errors are displayed at bottom. Here: for lesion #5 no choice made between target/non Target, and lesion #2 is too small to be target (10x14mm)
- Even if there remain errors the user can save the results of his reading. Submiting the review is not allowed.
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How an integrated platform may improve CT

4 – Automatic eCRF filling from image analysis

Use case # 2102 : Key points

- Aditional radiological observations and comments
- Automatic import of CT measurements
- Automatic quantized measurement lesion response assessment
- Validation button (e.g. eCRF signature)
- Access to relevant clinical information
How an integrated platform may improve CT

Use case # 2104 : Follow-up reading key points : Dedicated display layouts, presentation rules

Image display requirements :

- Allows a global view of CT Acquisition and pathologic involvement
- Native axials: measurement available
- Slicing synchronization per FOV
- Image transformations not allowed : rotation, MIP reconstructions ...
Use case # 2104: Key points: Lesion splitting management

Each previously assessed lesion must be assessed by the reader.

Assessment may be a measurement, a flag or the disappearance.

Lesion split and coalesce is managed.

A sample of a splitted lesion is shown.
How an integrated platform may improve CT

Use case # 2104: Key points: Reading conclusion

Imaging electronic case report form:

- Additional radiological observations and comments
- Automatic import of CT measurements
- Automatic calculation of target lesion progression
- Manual non-target lesion assessment
- Access to relevant clinical information
- Validation button (e.g., eCRF signature)
How an integrated platform may improve CT

Use case # 2102: Adjudication lesions display: lesion measurement version management

CT Adjudication global view

- Comparative layout per FOV. Current visit on the left, previous visit on the right.
- Display of lesion measured by reader 1 and reader 2
- Lesions measurement may be temporary hidden

Reader_2 lesion measurement (green)       Reader_1 lesion measurement (blue)
Use case # 2102 (cont’d) : Key points

The lesion adjudication toolbox:

- This is a moveable toolbox to be positioned conveniently.
- Results of reading 1 in blue row, reading 2 in the green row. Lesions are sorted by localization and z axis position to allow quick association between readers.
- A click on a lesion cell recall the lesion on CT images: click on the blue cell for reading 1 and on the green cell for reader 2.
- Expert take is own measurements with same rules enforcement than for reading.
- RECIST rules are checked and errors are displayed at bottom.
- Even if there remain errors the user can save the results of his reading. Submitting the review is not allowed.

Nota: two dimension measurement of LD first and then SA is preferred in order to improve reproducibility of SA measure.
How an integrated platform may improve CT

Improving quality management through the entire workflow
Keosys brief overview

Diameters measurement optimization

CT Volume measurement optimization

Integrated platform for multimodality
Automatic lesion segmentation
In partnership with Columbia University
(Pr L. Scwhartz)

- Lung lesions
  - All kind of lesions: ground glass, small attached, chest wall attached, spiculated.
  - Qiba 3C Challenge participation
- Liver lesions
- Lymph nodes lesions
CT Volume measurement optimization

- Chest wall attached lesion
- Spiculated lesion
- GGO lesion
- Liver lesion
CT Volumetric analysis improves:

- Reads consistency
- Automated diameters calculation in addition to volume analysis
- Quick and reputable assessment
- Must provide ergonomic way of drawing/edit boundaries

Variability in Assessing Treatment Response: Metastatic Colorectal Cancer as a Paradigm

Binosong Zhao, Shing M. Lee, Hyun-Ju Lee, Yongqiang Tan, Jing Qi, Thorsten Perseghl, David P. Mozley, and Lawrence H. Schwartz

Abstract

Purpose: The cutoff values currently used to categorize tumor response to therapy are neither biologically based nor tailored for measurement reproducibility with contemporary imaging modalities. Sources and magnitudes of discordance in response assessment in metastatic colorectal cancer (mCRC) are unknown.
Keosys brief overview

Diameters measurement optimization

CT Volume measurement optimization

Integrated platform for multimodality
Integrated platform for multi modality

• Reduce risk of combined modality criteria use ex: RECIST/PERCIST

Combined specialty reads:
• Radiology physician
• Nuclear medicine physician
Integrated platform for multi modality

- Reduce risk of combined modality criteria ex: RECIST/PERCIST: dedicated QC
Integrated platform for multi modality

- Benefit from a companion diagnostic for RECIST target selection

Selected target on CT must be visible on NM Images (uptake > background) => Contribution from radiology and nuclear medicine
Take home messages

Integrated IT platform can improve database quality and reduce delays by:

- An automation of consistency checks along the imaging workflow
- Improving coding consistency along the workflow (ex. Localization)
- Improving adherence to imaging reading criteria and its customizations
- Allows to use and control complex imaging reading workflow
Questions?

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