Calibration of computed tomography (CT) volumetric measurements for assessing tumour response to drug therapy in a randomised multicentre oncology study

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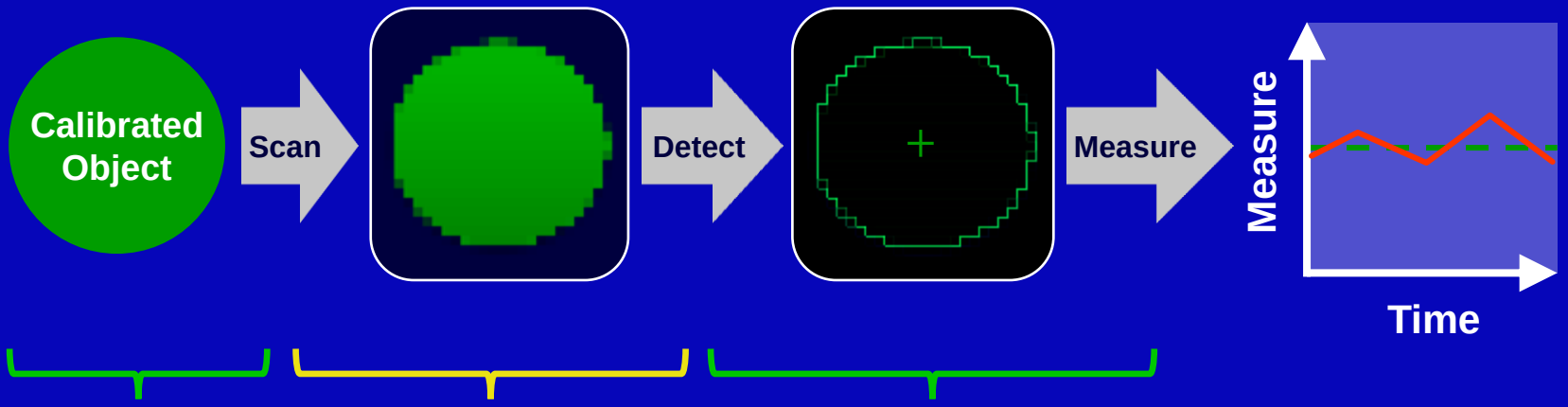
Disclosures

- Ricardo Avila
  - Kitware, Inc. shareholder
  - Kitware has a business interest in pocket phantom technology
- David Yankelevitz
  - Dr David Yankelevitz is a named inventor on a number of patents and patent applications relating to the evaluation of diseases of the chest including measurement of nodules. Some of these, which are owned by Cornell Research Foundation (CRF) are non-exclusively licensed to General Electric. As an inventor of these patents, Dr Yankelevitz is entitled to a share of any compensation which CRF may receive from its commercialisation of these patents
- Venice Archer
  - employed by Roche Products Ltd, UK
- Gudrun Zahlmann
  - employed by F. Hoffmann-La Roche Ltd, Switzerland

Goal

- To quantify tumour diameter and volumetric measurement variability, due to CT acquisition properties, for patients participating in a clinical NSCLC trial



Same phantom

Multicentre clinical trial
- Patient variation
- HR CT protocol
- Scanner variation

Same Automated software

How much variation is due to image acquisition?

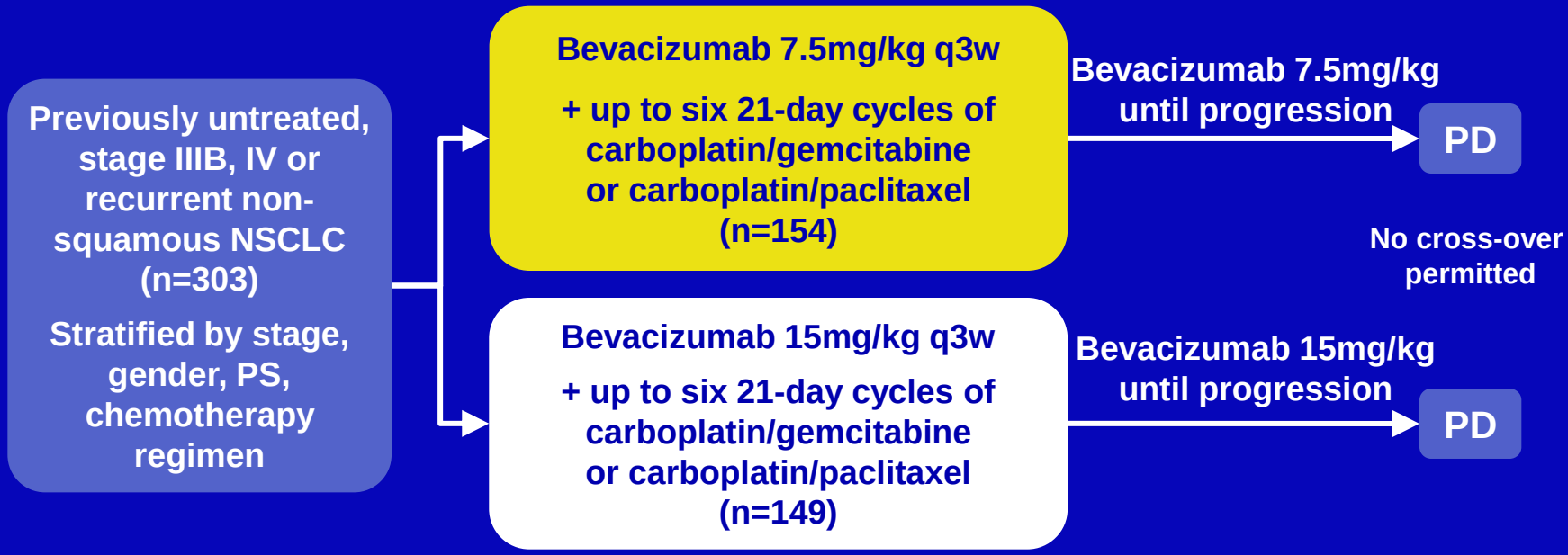
ABIGAIL Study

Avastin Biomarkers In LunG And 3D Innovative anaLysis

Roche study BO21015

A randomised, multicentre phase II study to explore whether biomarkers correlate with treatment outcome in chemo-naïve patients with advanced or recurrent non-squamous NSCLC, who receive treatment with bevacizumab (at a dose of either 7.5mg/kg or 15mg/kg) in addition to carboplatin-based chemotherapy (gemcitabine or paclitaxel)

BO21015 (ABIGAIL) study design and endpoints



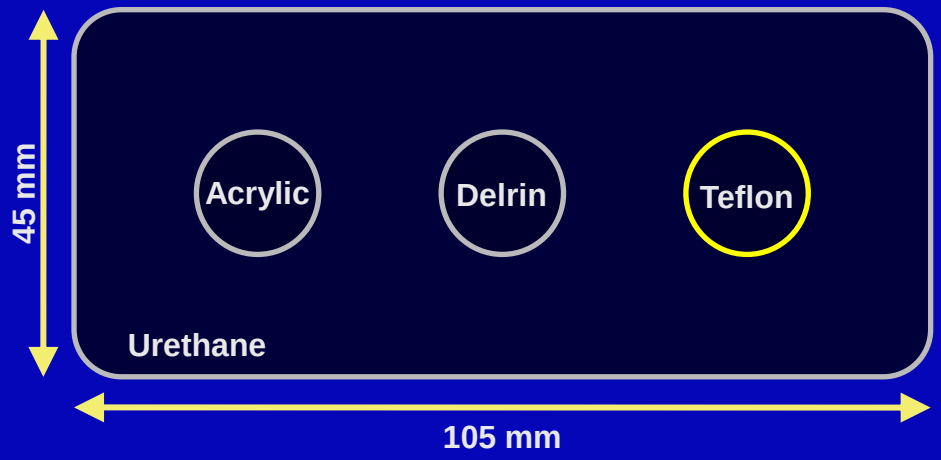
- Primary endpoint: to explore correlation between candidate biomarkers and ORR to chemotherapy + bevacizumab

- **Key exploratory endpoints include:** Correlation of response rate according to RECIST with tumour volume changes

PS = performance status;
PD = progressive disease;
ORR = overall response rate

Mok T et al, 2011

CT pocket phantom



Teflon Sphere

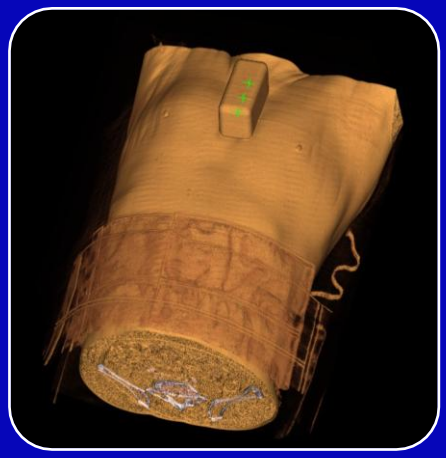
Diameter:
15.88 ± 0.05 mm

Volume:
2094.8 ±19.8 mm^3

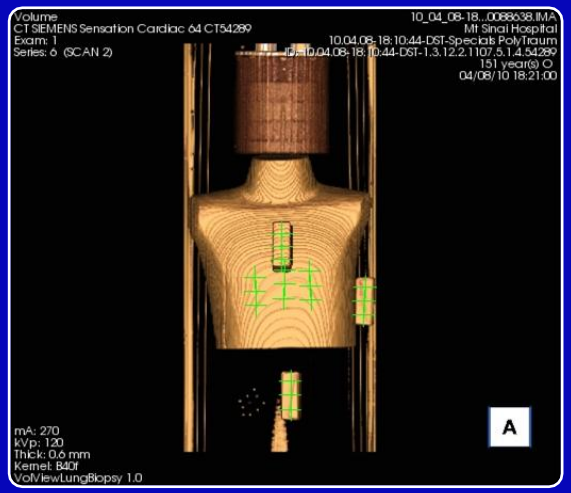
- **Designed to estimate fundamental properties of CT acquisitions**
  - **3D resolution and sampling rate**
  - **X-ray attenuation performance**
  - **noise characteristics**
- **Also provides direct metrics of image measurements**
  - **2D linear measurement**
  - **3D volume measurement**

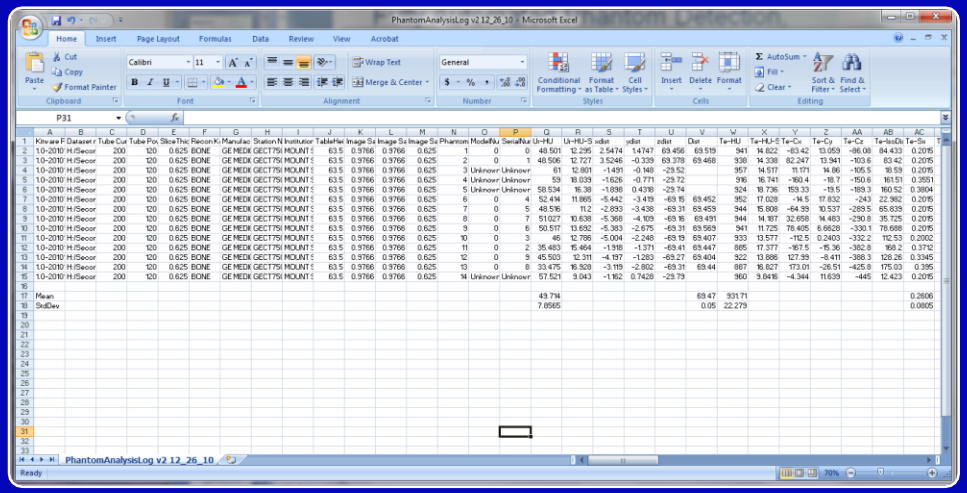
ABIGAIL high-resolution CT imaging

- All patients scanned with a high-resolution CT protocol
  - before starting therapy
  - every 6 weeks during the course of the trial until PD
- All scans performed on multi-slice scanners
- All efforts to scan in a single breath-hold
- Scans obtained from thoracic inlet through the liver at full inspiration
- Intravenous contrast used, scanning of liver in the portal venous phase
- A single acquisition was acquired at standard dose
- Acquisitions obtained with 120–140 kVp
- Reconstruction field of view (FOV) fit to patient
- Acquired data was reconstructed into 2 separate series
  - 5mm contiguous images (for RECIST)
  - ≤1.25 mm contiguous images (for volume)
- 20 clinical trial sites were provided with a CT pocket phantom

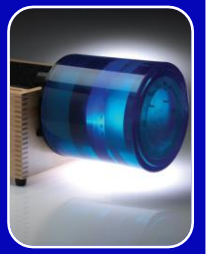


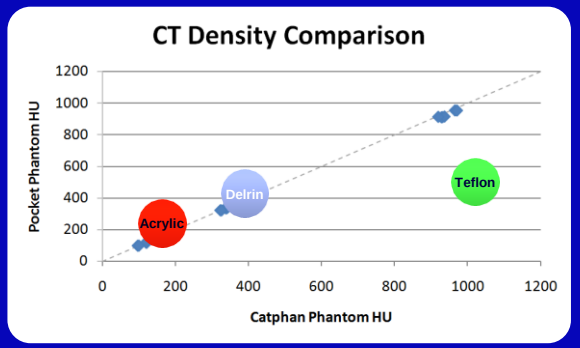
Fully automated phantom analysis





Catphan phantom comparison

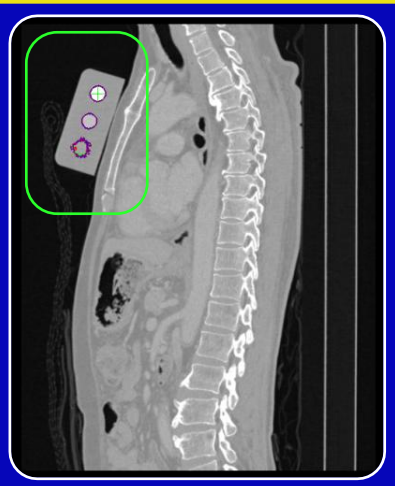


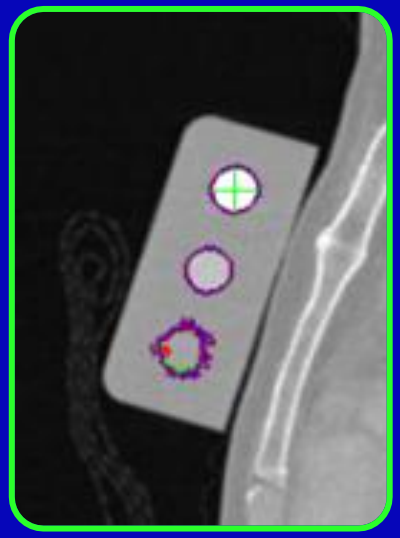


Avila R et al. 2010

Fully automated measurements

- Phantom(s) were detected within each CT scan
- The outer boundary of each sphere was calculated using constant thresholding
- For this analysis, the boundary of the Teflon sphere was used to measure:
  - maximum diameter along the x axis
  - maximum diameter along the y axis
  - maximum diameter along the z axis
  - ‘RECIST’ axial diameter
  - volume



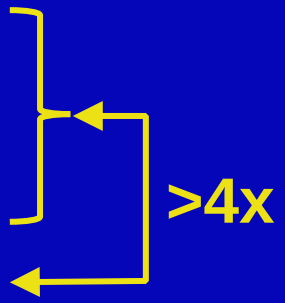


Phantom study entrance criteria and subjects

- Patient data entrance criteria
  - one or more 3D CT scans
    - whole CT pocket phantom imaged
    - CT slice thickness ≤2.0 mm
    - CT trans-axial (z-axis) sampling rate of ≤3.0 mm
- This resulted in a total of
  - 77 patients
  - scanned at 20 different clinical sites
  - 245 individual 3D CT series
  - scanned on 13 different scanner models
  - manufactured by 3 different scanner companies

Teflon sphere diameter and volume measurements

Measurement	Mean (μ)	Standard deviation (δ)	Coefficient of variation (δ/μ) (%)
Diameter x axis	15.7 mm	0.13 mm	0.8
Diameter y axis	15.6 mm	0.15 mm	1.0
Diameter z axis	15.8 mm	0.71 mm	4.5
Diameter ‘RECIST’	15.6 mm	0.15 mm	1.0
Volume	1,989 mm^3	99 mm^3	5.0

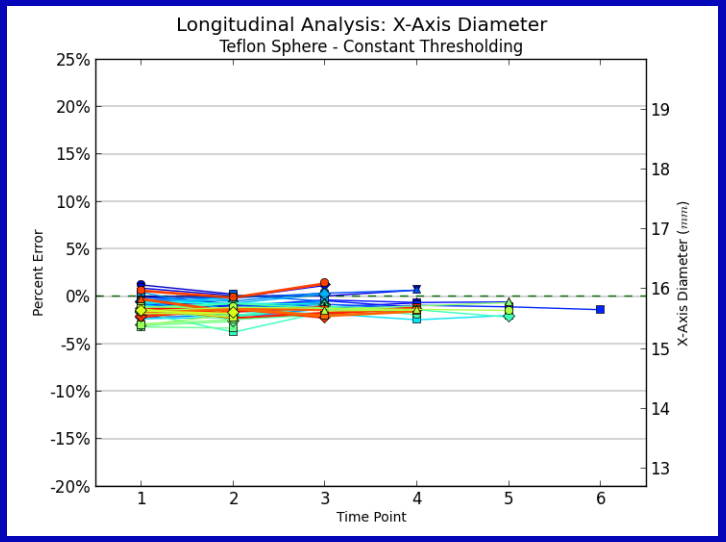


Longitudinal analysis

- Cases were analysed for longitudinal analysis if:
  - two or more consecutive scans with the same reconstruction kernel, slice thickness, and slice spacing were available
- This resulted in the selection of
  - 45 of the 77 total patient cases
  - a total of 59 longitudinal datasets with ≥2 time points
    - some patient datasets contained additional reconstructions, resulting in additional longitudinal datasets

Longitudinal diameter measurements

X



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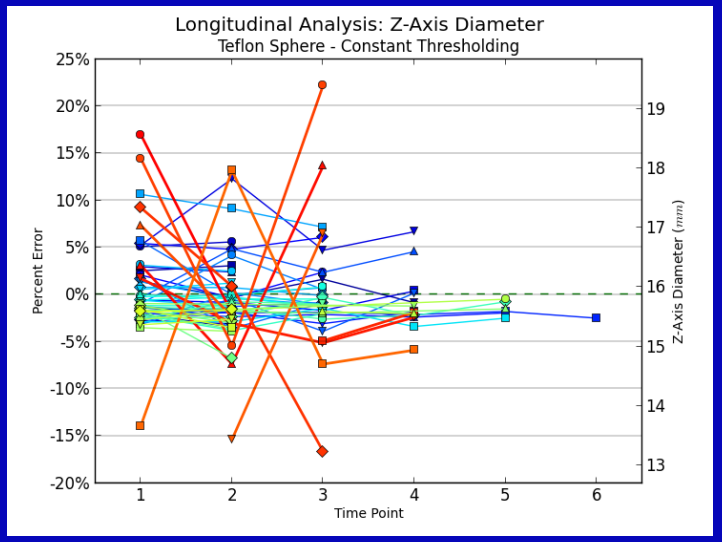

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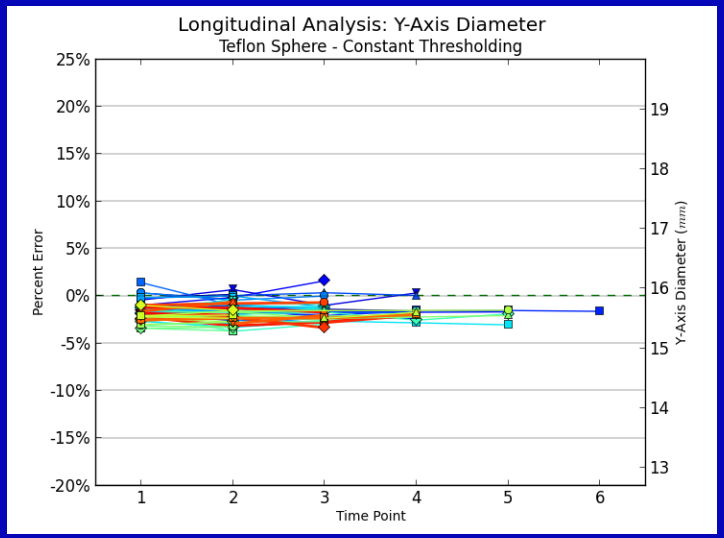
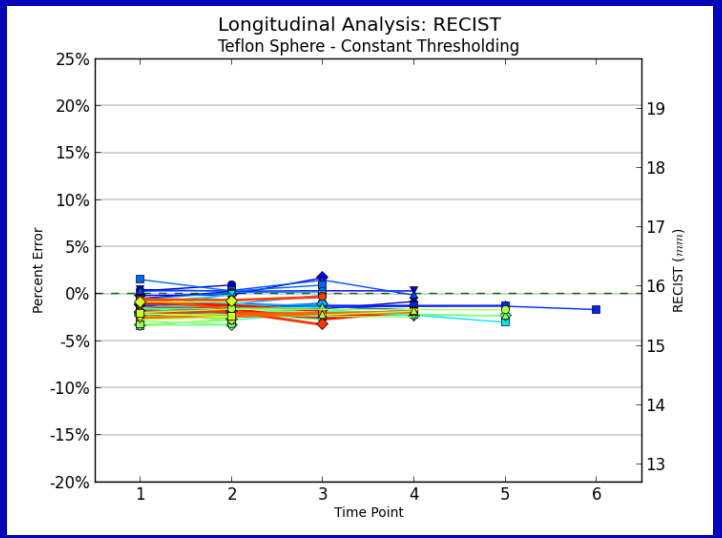
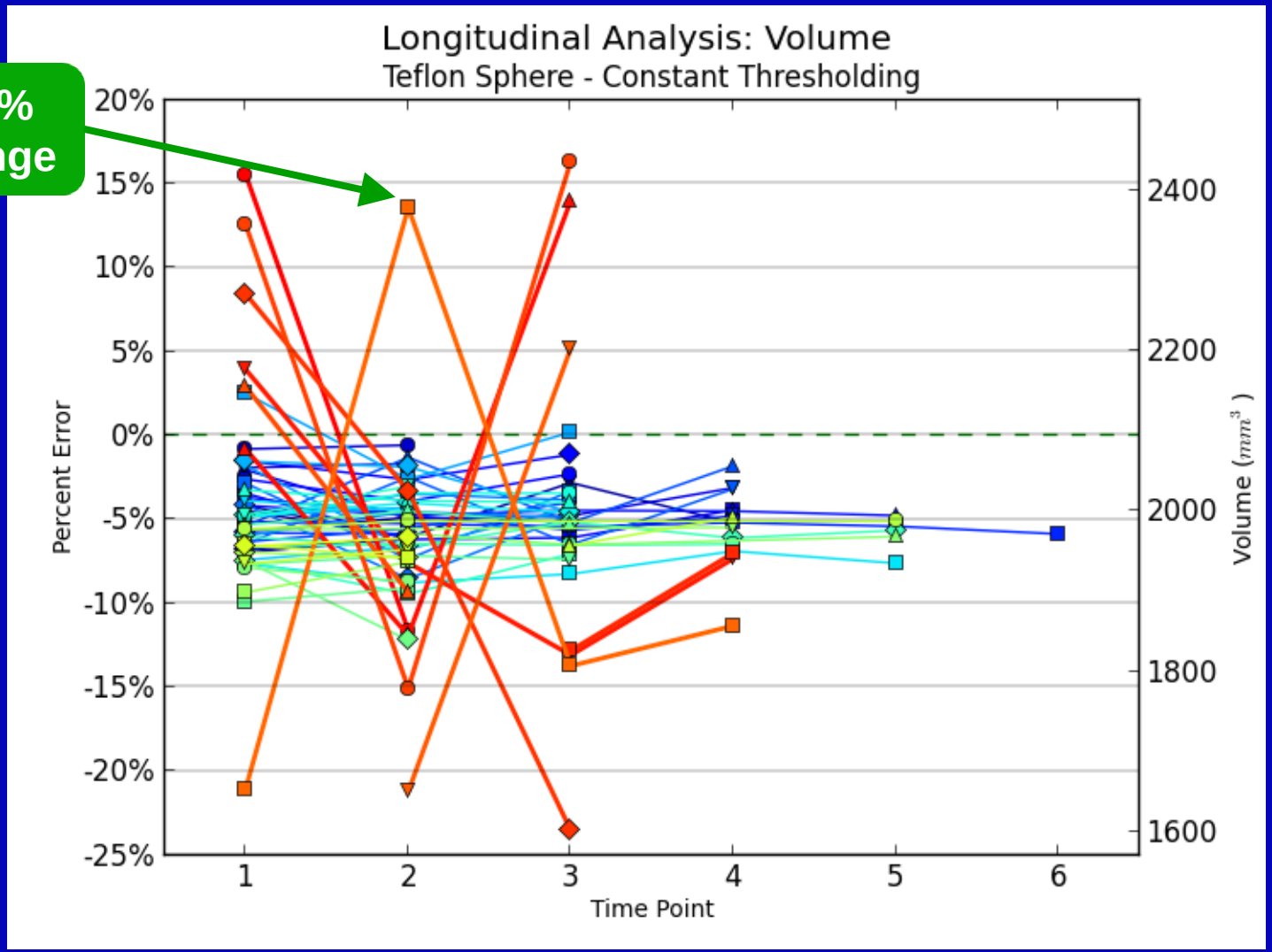


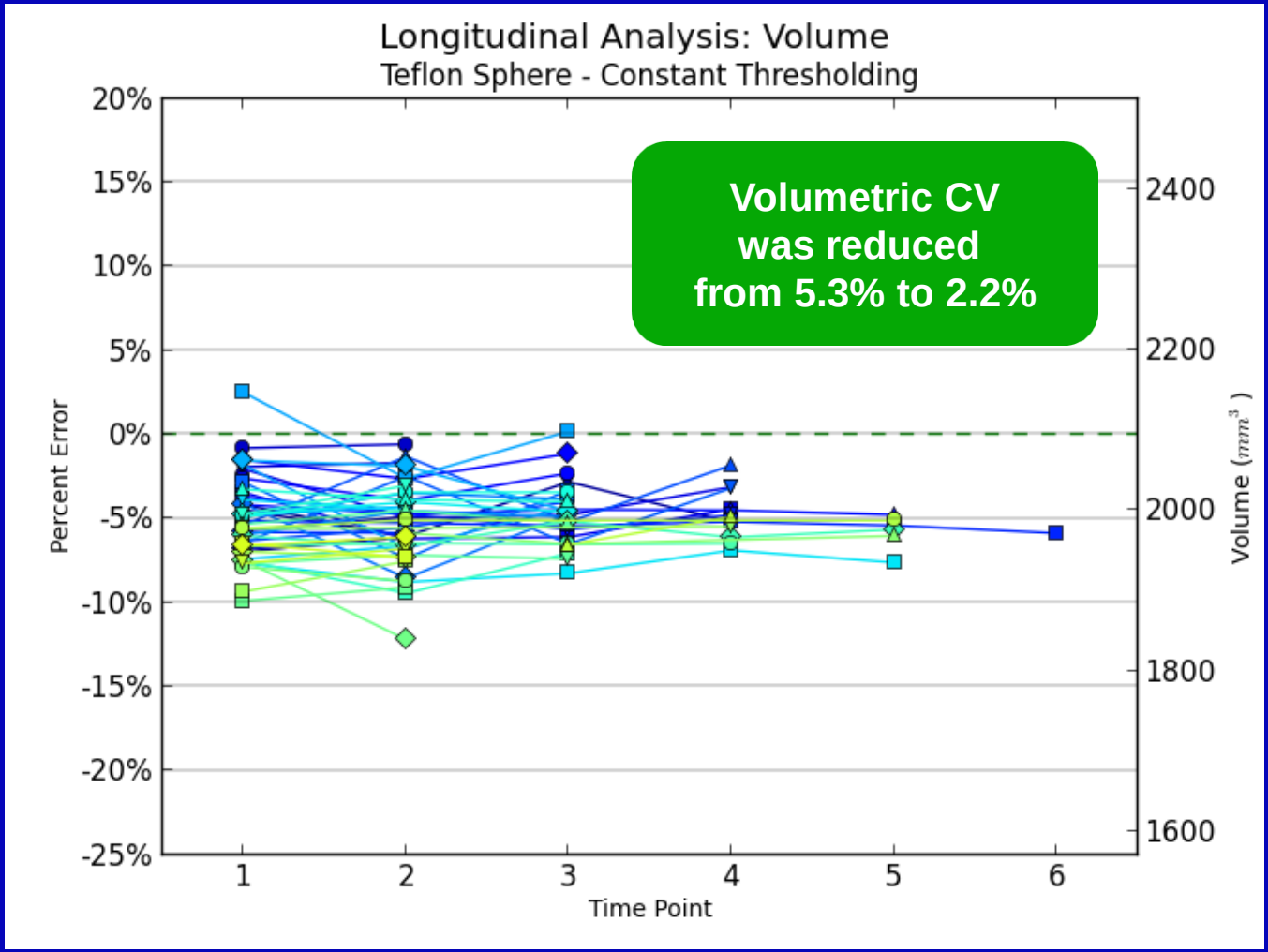
RECIST



Longitudinal volume measurements



Longitudinal volume measurements after removing the six highest varying patient cases



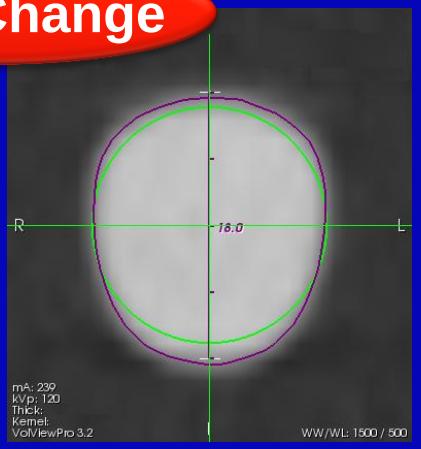
CV = coefficient of variation

Trans-axial spatial warping examples – coronal images

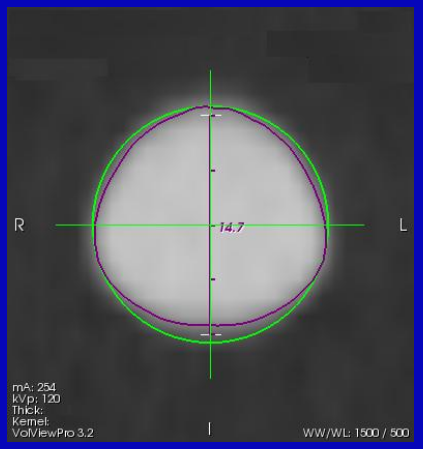
Model A Site 1

+44% Change

1654 mm^3



2379 mm^3

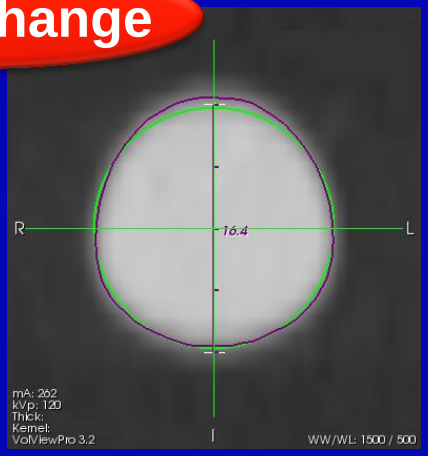


1807 mm^3

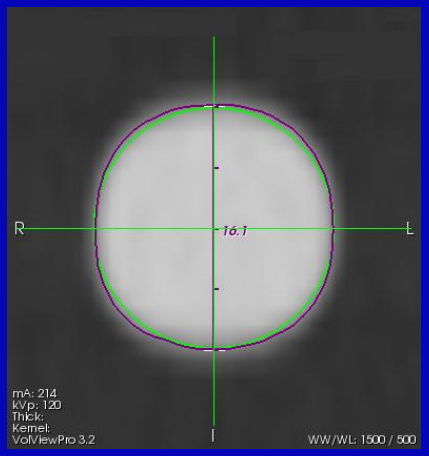
Model A Site 2

+33% Change

1601 mm^3



2127 mm^3



2177 mm^3

CT quality assurance

- Issue: >10 dimensional CT scan acquisition space
  1. # Slice scanner
  2. Tube current (mA)
  3. Tube voltage (kVp)
  4. Rotation time
  5. Table speed
  6. Table position
  7. Reconstruction kernel
  8. Reconstruction FOV
  9. Slice thickness
  10. Slice spacing
  11. Iterative reconstruction parameters
  12. Dual energy…

The only way to truly understand CT image quality is to independently measure it within individual patient scans

Future studies could define a general set of acquisition parameters and then verify that measurement error metrics are within specifications

Summary

- A new ‘pocket phantom’ approach has been developed for assessing intra-patient CT image measurement variation
- In a phase II clinical trial utilising a high-resolution CT protocol:
  - axial linear measurements were found to have consistently low variability (≤1% CV)
  - high variability was observed for:
    - linear measurement along the z axis (4.5% CV, >4x axial)
    - volumetric measurements (5.0% CV)
    - volumetric change in some individual cases (e.g. 44%)

Conclusions

- The ABIGAIL trial is, to our knowledge, the only clinical study investigating the use of an ‘in-patient’ CT calibration device
- The ABIGAIL trial demonstrates that the use of in-patient CT calibration devices is feasible in the context of a multinational, multicentre study
- Further investigation of scan-to-scan variation should be validated in future trials of tumour volumetry in order to move the field forward and to add to the body of knowledge

Questions?