Quantifying Responses to Treatment with CT Volumetry

Quantitative Imaging Biomarkers Alliance — RSNA

Establish 3D CT Volumetry as Surrogate Endpoint Biomarker for Tumor Response

Specific Aims
To develop methods and processes for accurate and reproducible measurements of anatomic structures and masses.

Stakeholders
FDA, NIST, NCI, FNIH, ACRIN, manufacturers and developers, CROs, PIG, and academic centers.

Progress during past year
- Charter studies have reported or are reporting results.
- Expanded studies to characterize technical performance under an increasing range of settings and to establish clinical performance.
- Written and refined Profile and Protocol documents through Public Comment and Field Test processes.

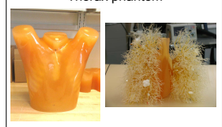
Clinician Sizing of Synthetic Spherical and Non-Spherical Lung Nodules

Aim
To estimate bias/variance of radiologists estimating the size of synthetic nodules

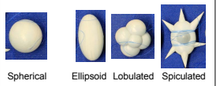
Sizing Techniques
- Manual 1-D size
- Manual 2-D size
- Semi-automated 3-D volume

Reader Study Design
- 6 radiologists measured each of the 40 nodules using each sizing technique in each of 2 reading sessions

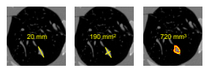
Anthropomorphic Phantom
Thorax phantom



Synthetic Nodules

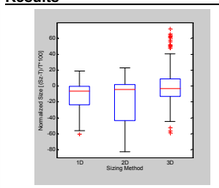


- Densities: -10HU, +100HU
- Shapes:
  Spherical: 10, 20 mm diameters
  Ellipsoid: Volume of 20 mm sphere
  Lobulated: Volume of 10 mm sphere
  Spiculated: Volume of 10 mm sphere



1D Sizing 2D Sizing 3D In-slice Sizing

Results



- Box and whisker plot of reader size estimates for the 1D, 2D and 3D sizing methods (all phantom nodules included).

Sizing Method	Relative Bias	Relative Std. Deviation
1D (length)	-14.6%	20.4%
2D (area)	-18.8%	28.3%
3D (volume)	-1.3%	21.9%

- Table of reader size estimates [bias (±std)] for the 1D, 2D and 3D methods (all phantom nodules included).

Size Method	Spherical Nodules		Non-spherical Nodules	
	0.8 mm	5.0 mm	0.8 mm	5.0 mm
1D	2% (±5)	0% (±4)	-23% (± 20)	-27% (±21)
2D	4% (±10)	0% (±11)	-33% (±26)	-33% (±29)
3D	1% (±12)	5% (±23)	0% (±14)	-2% (±30)

- Table of reader size estimates [bias (±std)] as a function of sphericity and slice thickness.

Summary
- Overall, 3D method provided low bias estimates of nodule volumes
- 3D method applied to thin slice data provided low bias & low variance estimates

Determining Minimum Detectable Change and Comparing Sizing Methods in Patient Datasets

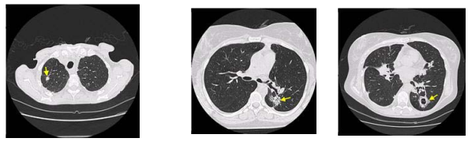
Aims
1. Investigate the **minimum detectable level of change** in patient datasets (acquired under a "No Change" condition)
2. Investigate measurement **variance** for volumes, diameters and bi-dim diameters (Using algorithm assisted readers)

Methods
Patient Datasets - MSKCC RIDER Coffee Break ("No Change") Experiment
- 32 NSCLC Patients; Scanned twice over a period < 15 minutes (i.e. No Change)
- Low dose, thin slice (1.25 mm) acquisition for both scans; I lesion per patient
- These datasets are PUBLICLY AVAILABLE (https://imaging.nci.nih.gov/ncia/)

Measurements (6 total) on both Scan 1 and Scan 2
- **5 radiologists** measured each of the **32 lesions** using **each sizing technique**:
- Manual 1-D length
- Manual 2-D area (and derive 1-D length)
- Semi-automated 3-D volume (and derive 1-D length and 2-D area)

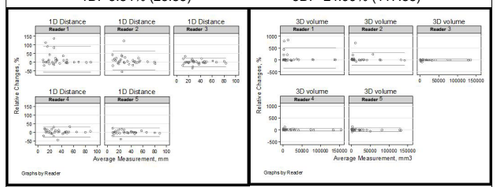
Analyses
- Variability between different measures (e.g. Volume vs. Diameter) and readers
- Minimum detectable difference

Sample Images of Lesions to be Measured
- Size range is from 8 to 88 mm
- Shapes range from simple and isolated to complex and cavitated



small, isolated, cavitated — complex composition

Results: Variability, Pooled Analysis - All readers, All lesions
% Difference between scans 1 & 2 (Mean (SD))
1D: 5.84% (23.83) 3D: 24.99% (117.88)



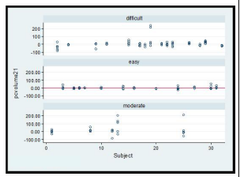
1D results by reader 3D results by reader

(NOTE: Different y-axis scales for 1D and 3D; note differences between readers)

Results: Variability in Sub-Group Analyses
Subjectively assessed lesions and categorized into easy, moderate, difficult

Method	1D	2D	3D
Easy	0.99 (.06)	2.58 (15.6)	2.85 (13.5)
Moderate	9.42 (28.6)	17.99 (61.8)	42.82 (107)
Difficult	8.52 (29.5)	24.40 (91.8)	36.76 (159)

Percent difference between repeat scans: "Easy" category has much lower differences



Next Steps
- Repeat Portion of Reader Study: follow more clinical conditions by allowing readers to see previous annotation when they perform the next timepoint read
- Use Variance Estimates to determine minimum detectable change

Clinician Sizing of Synthetic Nodules to Evaluate Inter-scanner Effects

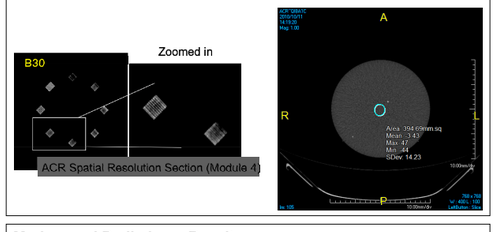
Aims
1. Characterize the level of variation associated with multiple scanners in reader measurements of volumes of phantom nodules.
2. Investigate volume variation in CT imaging protocol with two arms: an industry-standard protocol arm and a quality-based arm applicable to any scanner.

Methods
1. Develop and apply the two arms of the Imaging Protocol
   - ACRIN Study 6678
   - Quality-based arm targeting constant noise and resolution across scanners
2. Image anthropomorphic phantom (see first column) at six imaging sites
   - 6 sites, 6 MDCT scanners, 4 manufacturers
   - Thorax phantom has 6 spherical and 6 spiculated nodules, 6 in each 'lung'. The sizes are 5 mm, 10 mm and 20 mm (volume of an equivalent sphere.)
3. Readers measure semi-automated 3-D volume. 1-D & 2-D sizings are derived
4. Analysis - primary: variance and bias between scanners and protocol arms; - secondary: factors such as reader & nodule size and shape

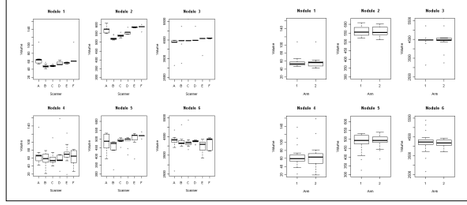
Imaging Protocol has 2 arms:
Arm 1: ACRIN 6678 (*FDG-PET/CT as Predictive Marker of Tumor Response…*)
Quality Control Parameters for CT Scan Tumor Volume Measurement

DICOM Tag#	Parameter	GE VCT 64	Philips Brilliance 16	Philips Brilliance 64	Siemens Sensation 64	Toshiba Aquilion
0018,0050	Slice width	0.75 – 1.25 mm	0.75 – 1.25 mm	0.75 – 1.25 mm	0.75 – 1.25 mm	0.75 – 1.25 mm
0020,1041	reconstruction interval	0 – 20 % overlap	0 – 20 % overlap	0 – 20 % overlap	0 – 20 % overlap	0 – 20 % overlap
0028,0030	voxel size	0.55 – 0.75 mm	0.55 – 0.75 mm	0.55 – 0.75 mm	0.55 – 0.75 mm	0.55 – 0.75 mm
	motion/ breathing artifact	none	none	none	none	none
scanner dependent	mAs	X-ray Tube Current * Exposure time 95 - 245	Exposure 120-310	Exposure 120-310	Exposure 120-310	X-ray Tube Current * Exposure time 120-310
0018,0060	kVp	120	120	120	120	120
0018,1210	reconstruction algorithm	STD	B	B	B30	FC10

Arm 2: Image quality performance arm
Aim – determine control parameters to achieve constant image quality across scanners. Image ACR CT Accreditation Phantom, set quality level by varying:
- recon kernel for resolution: target of 6 lp/cm (< 7 lp/cm) is achieved on left.
- mAs for noise: target 17 +/- 1 HU in module 3. Target is missed on right.



Markup and Preliminary Results
1. Determine volume with semi-automated segmentation. 1-D and 2-D size measurements are computed from the segmentation.
2. 7 readers size 6 nodules in 11 CT scans.
3. Analysis of preliminary data suggests, for larger nodules, variability in volumes is within 15% of the nodule means (box plots on left). The data also suggests the protocol-arm effect (box plots on right) is less than 15%.



Development of Assessment and Predictive Metrics for Quantitative Imaging in Chest CT

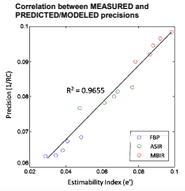
Aims
Develop and evaluate a metric (estimability index, e') capable of modeling/ predicting the performance of chest CT volume quantification.

Methods
1. Measure protocol-specific precision
- Simulated embedded nodules
- Repeated acquisitions with various protocols (dose and recon)
- Volume quantified using software
- Volumetry precision calculated in terms of **repeatability coefficient (RC)**

$$RC = 1.96\sqrt{2\sigma_w^2} = 2.77\sqrt{\sum_{i=1}^{n}\sum_{k=1}^{K}\frac{(V_{ik}-\bar{V}_i)^2}{n(K-1)}}$$

2. Model protocol-specific precision
- System characteristic in terms of Task Transfer Function and noise
- Ascertain volumetry task function W_{task}
- Volumetry precision estimated in terms of **estimability index (e')**

$$e'^2 = \iint \frac{|W_{task}(u,v)|^2\, TTF(u,v)^2}{NPS(u,v)}\,du\,dv$$



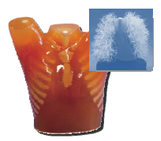
Preliminary Results
e' strongly correlates with 1/RC (R^2 = 0.9655) across all dose levels and recons

Current Status
- Expanding TTF/NPS measurement to 3D
- Expected Completion 4th Qtr 2012

Quantifying Volumes of Part-Solid Nodules

Aim
Extend characterization of nodule measurement performance to the part-solid case in low-dose and standard dose CT acquisitions. The primary endpoints include bias and variability relative to known nodule volume, with covariates including nodule shape, size, measurement algorithm, mean CT density and slice thickness.

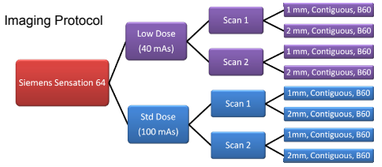
Methods
Phantom – LUNGMAN



Part-Solid Nodules (CIRS)*	
Outer Size, Shape, Density	Inner Size, Shape, Density
10mm, Spherical, -630 HU	5mm, Spherical, -10 HU
10mm, Spherical, -630 HU	5mm, Spherical, 100 HU
20mm, Spherical, -630 HU	10mm, Spherical, -10 HU
20mm, Spherical, -630 HU	10mm, Spherical, 100 HU
10mm, Lobulated, -630 HU	5mm, Lobulated, -10 HU
10mm, Lobulated, -630 HU	5mm, Lobulated, 100 HU
20mm, Lobulated, -630 HU	10mm, Lobulated, -10 HU
20mm, Lobulated, -630 HU	10mm, Lobulated, 100 HU

*2 Solid, 5 mm and 10 mm, 100 HU nodules included

Imaging Protocol

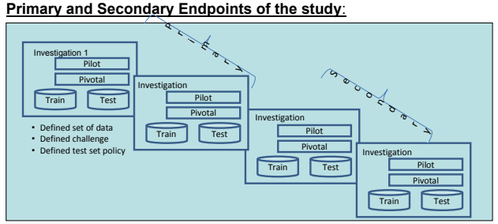


Reading Protocol
- 4 Radiologists
- 80 datasets (1 scanner * 2 doses * 2 thicknesses * 2 scans * 10 nodules)
- 2 reading sessions per dataset
- Nodule Metrics
  - McKesson PACS (1D), Vitrea (3D), Siemens Oncology (3D)
  - Mean CT density from 3D segmentation
  - Degree of manual intervention in semiautomatic measures

Inter- and Intra-algorithm Variability by Estimating the Volume of Synthetic Lung Nodules

Aim
To estimate **inter- and intra-algorithm variability** by the volume estimation of **synthetic nodules from CT scans of anthropomorphic phantoms** (according to the work of the QIBA 1A Group). The study is connected to the analysis section of QIBA Profile.
Website for the study design: http://qibawiki.rsna.org/images/9/99/3A_study_design_0.7.pdf).
Participants include *academic* and *commercial* algorithm developers.
Study realization due a ***Challenge*** in Cooperation of **QIBA, RSNA and NIST**.

Primary and Secondary Endpoints of the study:



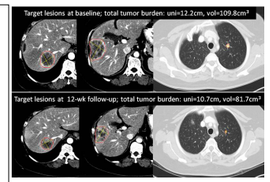
Investigation 1 is started: 3A (current focus):
- Investigation (scope of participant agreement)
  - Challenge Definition: estimate absolute volumes in phantom data
  - Explicitly indicate experimental factors (primary: analysis software model. Secondary is acquisitions settings)
  - Explicitly indicate descriptive statistics: bias, variance
  - Null hypothesis: analysis software model does not have a significant effect on the bias and variance
- Policy regarding test data: participants see test data but may not to use it in algorithm optimization
- Defined set of data (cases same as was used in QIBA 1A Group Study):
  - **Pilot:** for sandbox practice, no power study
    - **Training:** 16 cases, one lesion per case
    - **Test:** same 16 cases, all lesions
  - **Pivotal:** for published results
    - **Training:** participants may use all of the 16 pilot cases for algorithm optimization
    - **Test:** 40 cases, all lesions

Validation of volumetric CT as biomarker for predicting patient survival

Aim
To validate the use of volumetric CT in predicting patient survival using a retrospective dataset of 451 patients from a multicenter phase II/III clinical trial in advanced colorectal cancer treated with target therapy

Deliverables
1. Knowledge about intra- and inter-reader variability in measuring tumor 1D, 2D, volume and their changes with help of computer-aided algorithms
2. Values of the volumetric response assessment in predicting patient survival

Experiment
Part 1: Studying intra- and inter- reader variability using a subset of the patients' data
- Radiologists: 3 (inter) & 1 (intra)
- 30 patients; baseline, 6-week & 12-week follow-ups
- RECIST 1.0 guidelines
- In-house segmentation algorithms for lung, liver and lymph nodes metastases to obtain tumor sizes
- Total tumor burden at each scan and changes at 6 weeks and 12 weeks from baseline



Computer-delineated tumor contours supervised by radiologist. 1D, 2D and vol were derived from the segmented tumor volume.

Profiles: technical specification documents

Profile for advanced neoplastic disease
- Drafted by the QIBA Technical Committee on Quantifying Volumes
- **Goal**
  - Measure volume of 10mm+ lesions with a technical variation below 15% (so measured changes of >30% will be greater than measurement variability, and therefore associated with true biological change)

Content
- Details considered to impact measurement quality and reproducibility.
- Covers patient positioning, contrast use, characteristics of acquisition and reconstruction protocols and provides parameter values for some models.

Status
- Profile published for Public Comment during Aug-Sept 2011.
- After resolving comments, it will be published for Trial Implementation by vendors and sites.
  http://qibawiki.rsna.org/index.php?title=Volumetric-CT_tech_cte