41811 - The Translation of Quantitative Imaging to Clinical Research and Precision Medicine: Goals and Challenges

Importance of Quantitative Imaging in Medical Oncology

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Quantitative Imaging for Medical Oncologist

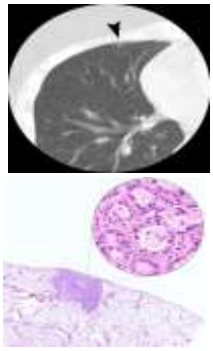
Context

Qualitative **vs.** **Quantitative Imaging**
Metastatic Disease (Y/N) Change Analysis (Early Disease)

Change Analysis
Manual (RECIST) **vs.** **Automated** (semi-automated)

Clinically QI is Essential for the setting of Early Stage Disease Management

Impact of CT on Lung Cancer Management



- **CT resolution doubling every two yrs for > decades**
- **Improved microprocessor speed drives rapidly increasing image processing capabilities**
- **Image database expanding to accelerate quantitative software development (LIDC & RIDER Databases)**
- **Finding smaller CAs drives changes in clinical care**

Mulshine JL, Sullivan D, NEJM, 352, 2005

US Leading Causes of Death

Disease	Rank 1990	Rank 2016	% Change	Deaths 2016*
Isch.Hrt.Dis	1	1	-19.5	544.8
Lung CA	2	2	13.6	191.5
COPD	4	3	69.8	163.8
Alzheimer	7	4	78.7	105.3
Colon CA	6	5	15.7	79.3

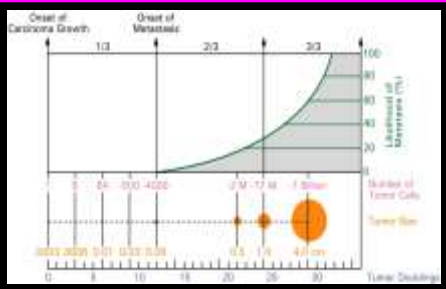
State of US Health,1990-2016, JAMA 319:1444-7, 2018

** #s in thousands*

NLST Trial Result

N Engl J Med 2011;365:395-409.

Relationships: Tumor Growth and Likelihood of Metastasis



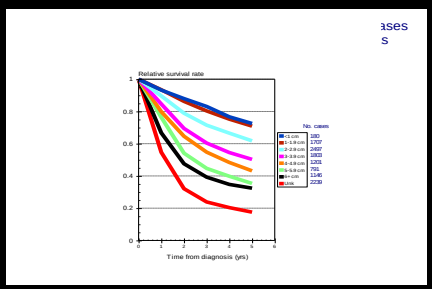
Modified Krokowski, 1964

Estimating Sojourn Time

- **Analysis of 6 prospective CT screening studies with a 3-state Markov model with a Bayesian approach**
- **Projected results over a 10-year time horizon of follow-up based on an approach used by the NELSON screening trial.**
- **Spiral CT had median sensitivity of 97%**
- **Advanced lung Ca DX 1 year earlier than CXR**
- **Annual CT screening, there would be an estimated 23% mortality reduction with a relative risk of 0.77 (95%, CI: 0.43-0.98**).

Chen and Chien, Intl J of Cancer,122: 2594, 2008

Relative Survival Rates Based on Primary Size: SEER Data (1988-92)



Wisnivesky JP et al, Chest 126:761, 2004

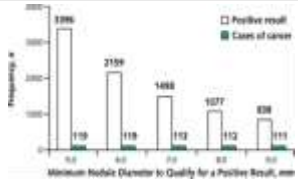
Response Evaluation Criteria in Solids Tumors (RECIST)

- Objective endpoint of biological drug activity or inactivity
- Precision of endpoint depends on frequency and timing of imaging assessment
- Measures longest diameter in axial plane
- Dynamic range of CT evaluation is 10mm (when slice thickness is ≤ 5mm, or 2-fold slice thickness when slice thickness is >5mm)
- PR is ≥30% decrease in the sum of the longest diameter of target lesions
- PD is 20% increase in the sum of the longest diameter of the target lesion and an absolute increase of >5mm

Litiere S et al. Nature Reviews Clin Oncol 14:187-92, 2017

Annals of Internal Medicine

Definition of a Positive Test Result in Computed Tomography Screening for Lung Cancer: A Cohort Study

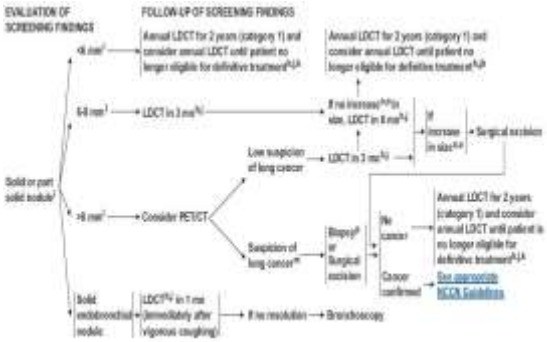


Frequency of a positive result and cases of lung cancer diagnosed within 12 mo of baseline enrollment

I-ELCAP: 73 Institutions; 60,869 Participants & 131,942 CT scans

Ann Intern Med. 2013;158(4):246-252. doi:10.7326/0003-4819-158-4-201302190-04

NCCN Screening Management



Challenge of QIBA: Routinely Measuring Small Lung Nodules

Precision Engineered 6 mm Ellipsoid courtesy of Accumetra

QIBA Small Lung Nodule Profile Claims

Claim 1: Nodule Volume

For a measured nodule volume of Y, and a CV as specified in table 1, the 95% confidence interval for the true nodule volume is Y ± (1.96 x Y x CV).

Claim 2: Nodule Volume Change

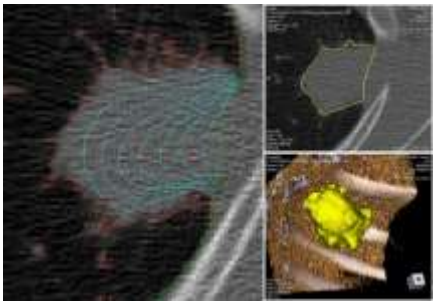
A measured nodule volume percentage change of X indicates that a true change in nodule volume has occurred if X > (2.77 x CV1 x 100), with 95% confidence.

If Y1 and Y2 are the volume measurements at the two time points, and CV1 and CV2 are the corresponding values from Table 1, then the 95% confidence interval for the nodule volume change $Z = (Y_2 - Y_1) \pm 1.96 \times \sqrt{([Y_1 \times CV1]^2 + [Y_2 \times CV2]^2)}$.

These Claims Hold When:

- **the nodule is completely solid**
- **the nodule longest dimension in the transverse (axial) plane is between 6 mm (volume 113 mm3) and 10 mm (volume 905 mm3) at the first time point**
- **the nodule's shortest diameter in any dimension is at least 60% of the nodule's longest diameter in any dimension (i.e., the nodule shape does not deviate excessively from spherical)**
- **the nodule is measurable at both time points (i.e., margins are distinct from surrounding structures of similar attenuation and geometrically simple enough to be segmented using automated software without manual editing)**
- **Interpolation is used to arrive at CV values between provided table values.**

Other Application of Lung Volumetrics



Karthik Krishnan, Optic Express Suppl, 2010

CDER's Annual Novel Drug Approvals 2008 - 2017

- From 2008- 16, CDER has averaged about 31 novel drug approvals/yr. (range: 21-46)
- In 2017, CDER approved 46 novel drugs
- CDER identified 15 of the 46 novel drugs approved in 2017 (33%) as first in-class
- First in-class drugs work through mechanisms of action different from existing therapies
- May indicate drug's potential for strong positive impact on health

https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ReportsBudgets/UCM591976.pdf

Cancer Drugs Approved by FDA on the Basis of a Surrogate End Point

- From 2008-12, 36 of 54 contemporary cancer drug approvals (67%) were made on the basis of a surrogate end point (RR, DFS, PFS)
- With >4 year follow-up, 31 (86%) of these approvals (57% of the 54 drugs approved) have unknown effects on overall survival or fail to show gains in survival.
- Our results show that most cancer drug approvals have not been shown to, or do not, improve clinically relevant end points.

Chul K, Vinay P. JAMA Intern Med 175:1992-4, 2015

Early Lung Ca Drug Trial Using QI CT

- Neoadjuvant window of opportunity trial performed in resectable NSCLC patients
- Drug (Pazopanib) given daily for 2-3 weeks
- QCT done before & after drug exposure prior to lung CA resection
- Endpoint frequency of tumor shrinkage determined by QCT
- Image results compared to molecular/pathological outcomes

Altorki N et al. J Clin Oncol. 2010; 28:3131-7. PMID: 20516450

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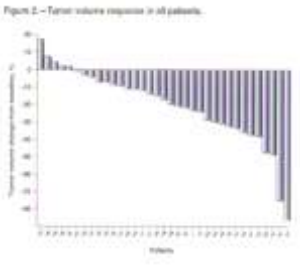
Neoadjuvant Treatment with Pazopanib

- dual kinase, VEGF inhibitor with Phase I activity in lung CA
- Effect on primary tumor volume measured in 35 patients
- **Waterfall plot showing tumor volume growth (upward bar)/shrinkage (downward bar) from serial CT scans**



Altorki N et al. J Clin Oncol. 2010; 28:3131-7. PMID: 20516450

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End Point Validation Criteria

- **Sound biological rationale**
- **Standardized protocol for interpreting measurements**
- **Understanding of the limitation associated with end point**
- **Evidence of correlation with a true patient-benefit end point**

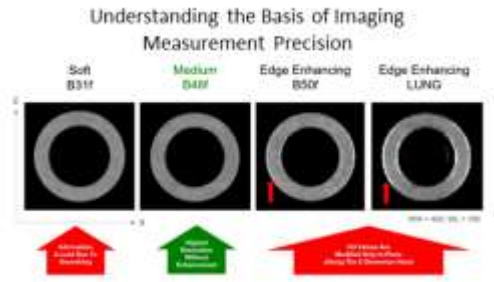
Litiere S et al. Nature Reviews Clin Oncol 14:187-92, 2017

Clinical Conformance Process

1. **CT Scanner and Lung Nodule Analysis Software**
   Verify CT scanner model is QIBA approved.
   Verify ACR CT accreditation is being followed.
   Verify lung nodule analysis software is QIBA approved. (QIBA vendor approvals are pending)
2. **Lung Screening Protocol**
   Establish and save a CT Lung Screening Protocol.
   CT scan a QIBA lung nodule phantom with the saved Protocol.
   Upload phantom DICOM data and obtain a passing Protocol report.
   Perform Step 2 Once Per Year and if Protocol or CT Scanner changes.
3. **Lung Nodule, Protocol, & Segmentation**
   Visually verify that nodule is solid, not attached to structures, has a diameter 6 - 10mm, and that the saved Protocol was used on the same scanner at all time points to be volume measured.
   Visually verify artifacts (e.g. motion, streaking) absent and image noise is not excessive.
   Visually verify measurement of nodule is free of segmentation issues.
4. **Obtain Volumetric Nodule Measurement Guidance**
   Use online QIBA calculator to obtain the latest measurement guidance.

QIBA Dedicated LDCT Conformance Phantom

- Lost Cost- $200 shipped
- Integrated with automated software for rapid data acquisition (<5 min)
- Output is a structured report that evaluates fundamental imaging properties using machine vision via web (< 30 min)



Courtesy of R Avila, 2015

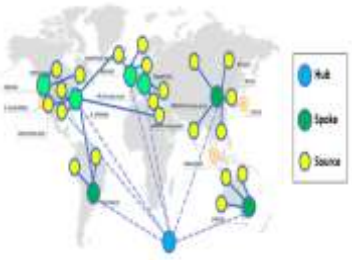
The Early Lung Image Confederation

1. Develop an IASLC hub and spoke system.

- ELIC Software System
- ELIC Governance

2. Provision of Global high-quality screening services.

- CT Image Quality Improvement Pilot Project
- Education and Training Pilot Project



Conclusions

Medical Oncologists think about disease status progression, stability or regression)
i.e. Disease Monitoring = QI = Clinical Decision Support

The precision and consistency required for quantitative imaging integration either for routine care/or trials is vastly more demanding than for routine qualitative imaging

To responsibly disseminated QI, workflow friendly profiles, economical QI tools, such as simple phantoms, cloud-based integrated software analysis and structured reports are crucial to enable QI quality across the array of imaging sites

Collaboration of imaging scientists, radiation physicists and clinicians are critical to defining tailored biomarker settings that leverage the utility of precise quantitative analysis