Imaging in Clinical Trials: An Overview

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NIH NATIONAL CANCER INSTITUTE

AAPM Beyond Clinical Imaging
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Outline

- *Introduction to Oncology Clinical Trials*
- *Role of Imaging in Oncology Clinical Trials (Onc, Rad Onc, Interventional)*
- *Quantitative measures and biomarkers*
- *NCI Clinical Trials Network*
- *Examples of imaging in clinical trials*

Introduction: Clinical Trials

- *Definition:* **A clinical Trial is a prospective study comparing the effect and value of interventions(s) against a control in human beings.**

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- **"Stretchy glue inspired by slugs could be the future of sutures"**

Washington Post, July 27, 2017

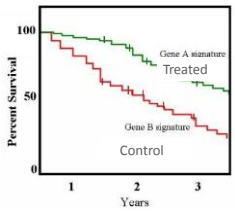
Introduction: Clinical Trials

- *Definition:* **A clinical Trial is a prospective study comparing the effect and value of interventions(s) against a control in human beings.***
- *Key Components*
  - **Primary and secondary questions**
  - **Study design**
  - **Study population and sample size**
  - **Data collection and quality control**
  - **Data analysis**
  - **Study monitoring**
  - **Close out and reporting**

* Friedman LM, Furberg CD, DeMets DL. Fundamentals of Clinical Trials. Springer-Verlag, New York Inc., 1998 (3rd Ed.)

Phases of Clinical Trials

- **Phase I**
  - Safety
  - Tx administration
  - n ~ 15-30
- **Phase II**
  - Efficacy
  - n ~ < 100
  - Randomized (some)
- **Phase III**
  - Comparison of new application with standard
  - n ~ 100 – thousands
  - All randomized



Oncology Clinical Trials

- Overall goal in an oncology trial is typically one of the following:
  - **Treat cancer**
  - **Diagnose cancer**
  - **Prevent cancer**
  - **Manage symptoms and side effects of treatment**

Oncology Therapy Trials

Designed to address questions on safety, efficacy, and advantage compared to current standard therapies

- Drugs
- Vaccines
- Interventional
- Combinations

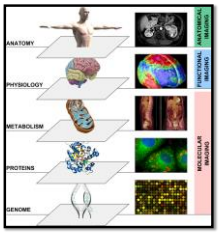
Oncology Clinical Trial Team Members

- Principal Investigator
- Research nurse
- Staff physician or nurse
- Data manager
- Statistician
- Physicist – imaging and/or RT

Imaging in Clinical Trials

- Imaging applications in clinical trials
  - Screen imaging → Early Detection & Prevention
  - Diagnostic imaging → Diagnosis & Management
  - Imaging to guide therapy & Monitor response → Therapy

Imaging Capabilities



Lambin P, et. al., EJC 2012

Quantitative Imaging

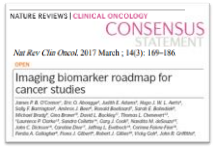
- *Definition* – **Quantitative Imaging:** Extraction of quantifiable features from medical images for the assessment of normal or the severity, degree of change, or status of a disease, injury, or chronic condition relative to normal.

Quantitative Imaging Biomarker Alliance (QIBA)

ww.rsna.org/QIBA/

Biomarkers

- Definition: Biomarker - defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention, including therapeutic interventions.



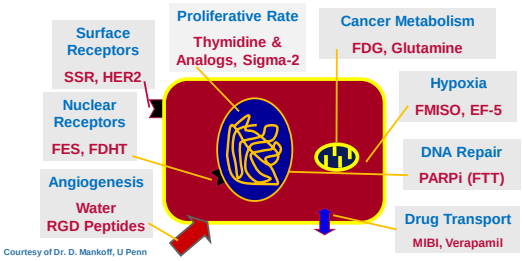
- FDA–NIH Biomarker Working Group: Molecular, histologic, radiographic or physiologic characteristics are examples of biomarkers.

- O'Connor JBP, et. al., Nature Reviews Clinical Oncology 2016
- FDA and NIH: BEST (Biomarkers, Endpoints, and other tools) resource. NCBI 2016

Molecular Imaging Biomarkers

Measure Factors Affecting Tumor Behavior

Variable Levels in Tumor

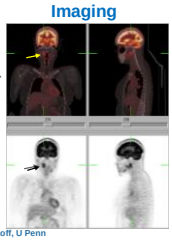


Courtesy of Dr. D. Mankoff, U Penn

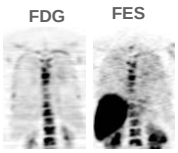
Imaging Requirement for Biomarker Imaging

Simultaneously Localize and Characterize Disease Sites

Functional/Anatomic Imaging



Functional Imaging Combinations



Courtesy of Dr. D. Mankoff, U Penn

Imaging and Cancer Therapy

Novel Approaches to Biomarker Imaging

- Choosing the right patients
  - Is the therapeutic target present?
- Choosing the right drug
  - Does the drug reach the target?
- Getting the right result
  - Is there a pharmacodynamic response?
- Predicting the outcome
  - Will response lead to better patient survival?

Courtesy of Dr. D. Mankoff, U Penn

Clinical Indications for Imaging in a Clinical Trial Setting

Role	Definition
Diagnosis and staging	To determine whether a lesion is positive or negative for malignancy
Prognostic marker	To determine the expected outcome under standard therapy for the patient's disease stage
Predictive biomarker assay	To differentiate between patients expected to benefit clinically on one treatment relative to another from those not expected to experience such a benefit
Pharmacokinetics marker	To confirm that the drug has reached the intended target
Pharmacodynamics marker	To measure the effects of the drug on the body
Early response indicator	To determine the expected ultimate outcome on a particular therapy regimen from changes in a tumor characteristic following a few cycles of treatment
Basis of a Phase II trial end point	A pre- to posttreatment change measurement used to determine whether to proceed to the subsequent Phase III investigation
Basis of a Phase III trial end point	A pre- to posttreatment change that serves as a surrogate for a definitive clinical end point

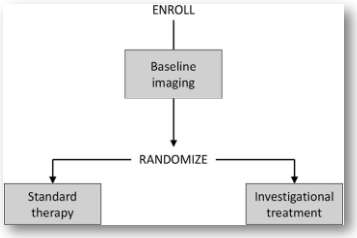
Lin F, et. al., Acad Radiol 24 (8), 2017

Statistical Tests in the Context of Clinical Trials

Test	Purpose
Log-rank test	To test whether the distributions of a time-to-event outcome between two groups are equal
Logistic regression	To model the probability of an event (e.g., pathologic complete response) occurring as a function of one or more explanatory variables
Cox regression	To model the rate at which an event (e.g., progression or death) occurs as a function of one or more explanatory variables
Fisher exact test	To test the association between two categorical variables
Mann-Whitney U test	To test whether the distributions of a quantitative variable between two groups are equal
Test for qualitative interaction	To test whether one treatment is more efficacious than another in one subset of patients but not in another subset
Kendall tau rank Correlation coeff.	A measure of the association between two quantitative or ordered categorical variables
Wilcoxon signed-rank test	To test whether repeat measurements on a particular patient differ

Huang EP, et. al., Acad Radiol 24 (8), 2017

Qualitative Interaction between Treatment & Biomarker



Marker by Treatment Interaction Design
without stratification
to test the value of an imaging-based predictive marker.

Huang EP, et. al., Acad Radiol 24 (8), 2017

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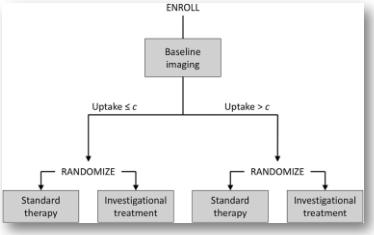

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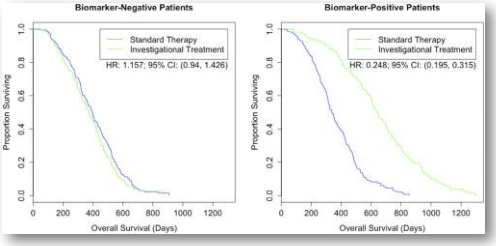
Huang EP, et. al., Acad Radiol 24 (8), 2017

A Predictive Marker



Huang EP, et. al., Acad Radiol 24 (8), 2017

Challenges and Approaches for Quantitative Imaging in Cancer Clinical Trials

1) Selection of the appropriate imaging endpoint and modality

2) Qualification of the QI capabilities of participating sites

3) Data collection and image analysis for imaging endpoint determination

4) Auditing and quality control for quantitative imaging data

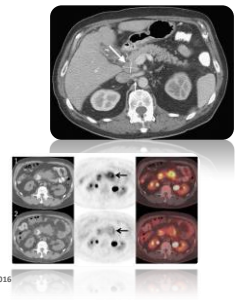
Yankeelov T., et. al., Clin Cancer Res. 2016 Jan 15; 22(2): 284–290.

RECIST, irRECIST, & PERCIST

RECIST (Response Evaluation Criteria In Solid Tumors) is a set of published rules that define when cancer patients improve ("respond"), stay the same ("stable") or worsen ("progression") during treatments.

irRECIST (Immune-related Response Evaluation Criteria In Solid Tumors) is a set of published rules that provide better assessment of the effect of immunotherapeutic agents.

Positron Emission Tomography (PET) Response Criteria in Solid Tumors (PERCIST 1.0) - methods to ensure the comparability of PET FDG images from different time points to allow quantitative measurements of change and assessment of overall treatment response in PET studies.

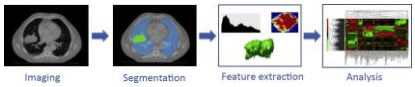


Eisenhauer EA, et. al., EJC 2009
Bohnsack O, et., al., ESMO 2014

Wahl R, et. al., JNM 2009
O JH, Lodge M, Whal R, Radiology 2016

Radiomics

Radiomics hypothesis: advanced image analysis on conventional and novel medical imaging could capture additional information not currently used, and more specifically, that genomic and proteomics patterns can be expressed in terms of macroscopic image-based features.



Lambin P, et. al., EJC 2012

NCI Quantitative Imaging Excellence (CQIE)

- initiated in 2010 in collaboration with ACRIN to establish a resource of clinical trial-ready sites within the National Cancer Institute (NCI)-designated Cancer Centers (NCI-CCs).
- The intent was to enable imaging centers in the NCI-CCs network capable of conducting treatment trials with advanced quantitative imaging end points.
- CQIE provided PET/CT and MRI phantoms and protocols for site qualification.

Rosen M, et. al., Acad Radiol 2017; 24:232–245

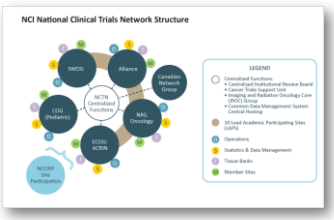
NCI Network Trials

- National Clinical Trials Network (NCTN)
- NCI Community Oncology Research Program (NCORP)
- Experimental Therapeutics Clinical Trials Network (ETCTN)

…and

- NCI-designated cancer centers
- NIH Clinical Center in Bethesda, Maryland

NCI National Clinical Trials Network Structure

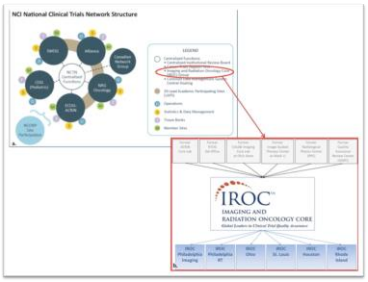


https://www.cancer.gov/research/areas/clinical-trials/nctn/nctn-clinical-trials-network

Phase II and III trials:

- **help establish new standards of care**
- **prepare for FDA approval**
- **new approaches to interventions**
- **validate new biomarkers**

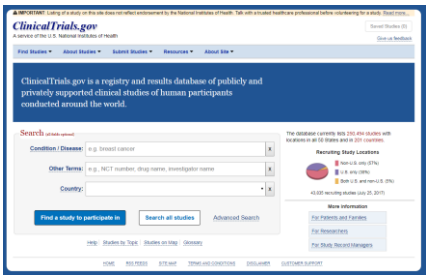
NCI NTCN Imaging and Radiation Oncology Core



- FitzGerald TJ, et. al., IJROBP 2016
- ASTRONews 2014

ClinicalTrials.gov

https://clinicaltrials.gov/



Some Examples of
Imaging in Clinical Trials in Cancer

Example 1 - Change in Relative Cerebral Blood Volume as a Biomarker for Early Response to Bevacizumab in Recurrent Glioblastoma [ECOG-ACRIN: EAF151]

- Imaging: **DSC-MRI**
- **Primary Outcome Measures:**
  - **Change in rCBV within enhancing tumor [Baseline to 2 weeks]**
  - **OS [Up to 5 years]**
- **Secondary Outcome Measures:**
  - CBF [Baseline]
  - Change in CBF [Baseline to 2 weeks]
  - PFS [Up to 5 years]
  - rCBV [Baseline]
- Estimated Enrollment: 165

https://clinicaltrials.gov/ct2/show/record/NCT03115333

Example 2 - FDG-PET/CT in Tumor Assessment and Surgical in Patients With Newly Diagnosed H&N Cancer (ACRIN 6685)

- **Primary Outcome Measures:**
- **Negative predictive value of PET/CT imaging for staging the N0 neck based upon pathologic sampling of the neck lymph nodes [Within 2 Weeks Before Surgery]**
- **Potential of PET/CT imaging to change treatment of the N0 neck [Within 2 Weeks Before Surgery]**
- **Secondary Outcome Measures: (Partial list)**
- Sensitivity and diagnostic yield of PET/CT imaging for detecting occult metastasis in the clinically N0 neck (both by neck and lymph node regions) or other local sites [Within 2 Weeks Before Surgery]
- Effect of other factors (e.g., tumor size, location, second primary tumors, or intensity of FDG uptake) that can lead to identification of subsets of patients that could potentially forego neck dissection or …[Within 2 Weeks Before Surgery]
- Cost-effectiveness and cost-benefit of using PET/CT imaging for staging of head and neck cancer vs current good clinical practices [Time Frame: Within 2 Weeks Before Surgery]
- Correlation of PET/CT imaging findings with CT/MRI findings and biomarker results [Within 2 Weeks Before Surgery]
- **Target Enrollment:** A total of 292 participants will be enrolled.

https://clinicaltrials.gov/ct2/show/NCT00983697?term=NCT00983697&rank=1

Example 3 - Randomized Phase II Trial of Individualized Adaptive RT Using During-Treatment FDG-PET/CT in Locally Advanced NSCLC [RTOG 1106/ACRIN 6697]

- **Primary Outcome Measures:**
- **Local-regional, progression-free (LRPF) rate (NRG) [2 years]**
- **Relative change in SUV peak from the baseline to the during-treatment FDG-PET/CT to LRPF (ECOG-ACRIN) [Baseline to 2 years]**
- **Secondary Outcome Measures: (partial list)**
- Baseline FMISO uptake (tumor-to-blood pool ratio) association with LRPF (i.e. the assessment of using baseline FMISO-PET uptake as a prognostic marker) (ECOG-ACRIN) [Baseline]
- Change in metabolic tumor volume (ECOG-ACRIN) [Baseline to 5 years]
- Change of peak SUVs for FDG from pre- to during-treatment (ECOG-ACRIN) [Baseline to 5 years]
- FMISO total hypoxic volume (ECOG-ACRIN) [Up to 5 years]
- FMISO tumor-to-blood pool ratio (ECOG-ACRIN) [Time Frame: Up to 5 years]

https://clinicaltrials.gov/ct2/show/record/NCT01507428?term=NCT01507428&rank=1

Example 4 - Abbreviated Breast MRI and Digital Tomosynthesis Mammography in Screening Women With Dense Breasts

A Randomized Phase II trial

PRIMARY OBJECTIVES:

- **To compare the rates of detection of invasive cancers with abbreviated breast (AB)-MRI and digital tomosynthesis mammography (DBT).**

SECONDARY OBJECTIVES: (partial list)

- To compare the positive predictive value (PPV) of biopsies, call back rates, and short-term follow up rates after AB-MR and DBT on both the initial and 1 year follow up studies.
- To estimate and compare the sensitivity and specificity of AB-MR and DBT, using the 1 year follow up to define a reference standard.
- To compare patient-reported short-term quality of life related to diagnostic testing with AB-MR and DBT using the Testing Morbidities Index.
- To compare willingness to return for testing with AB-MRI versus (vs) DBT within the recommended screening interval and explore factors associated with willingness to return for screening.

https://clinicaltrials.gov/ct2/show/NCT02933489?term=ea+1141&recrs=a&rank=1

A Funding Opportunity for Early Phase Imaging Trials

8/2/2017

Early Phase Clinical Trials in Imaging & IGI (R01) [PAR-17-167]

- **3 year clinical trials in novel imaging or IGI**
- **Intended to accelerate the development of imaging and IGI modalities, methodologies, and agents through the early stages of clinical development -such as trials evaluating safety and preliminary efficacy**
- **Phase I & II studies to establish treatment parameters and early therapeutic efficacy**
- **SEP Review (CSR)**
  - https://grants.nih.gov/grants/guide/pa-files/PAR-17-167.html

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Acknowledgment

- Lalitha Shankar, MD, PhD

Cancer Imaging Program, NCI