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

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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

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**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
  - Diagnostic imaging
  - Imaging to guide therapy & Monitor response

Imaging Capabilities

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.

Molecular Imaging Biomarkers

Measure Factors Affecting Tumor Behavior

![Diagram of Molecular Imaging Biomarkers](image)

- Surface Receptors
  - SSR, HER2
- Nuclear Receptors
  - FES, FDHT
- Angiogenesis
- Water
- RGD Peptides
- Proliferative Rate
  - Thymidine & Analogs, Sigma-2
- Cancer Metabolism
  - FDG, Glutamine
- Hypoxia
  - FMISO, EF-5
- DNA Repair
  - PARPI (FTT)
- Drug Transport
  - MIBI, Verapamil

Imaging Requirement for Biomarker Imaging

Simultaneously Localize and Characterize Disease Sites

- Functional/Anatomic Imaging
  - PET/CT Fusion
  - FDG PET
- Functional Imaging Combinations
  - FDG
  - FES
  - Glucose Metabolism
  - Estradiol Binding

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?

Clinical Indications for Imaging in a Clinical Trial Setting

<table>
<thead>
<tr>
<th>Role</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis and staging</td>
<td>To determine whether a lesion is positive or negative for malignancy</td>
</tr>
<tr>
<td>Prognostic marker</td>
<td>To determine the expected outcomes under standard therapy for the patient's disease stage</td>
</tr>
<tr>
<td>Predictive biomarker assay</td>
<td>To determine patients experiencing benefit clinically no one treatment relative to another from those not expected to experience such benefit</td>
</tr>
<tr>
<td>Pharmacokinetics marker</td>
<td>To confirm the drug has reached the intended target</td>
</tr>
<tr>
<td>Pharmacodynamics marker</td>
<td>To measure the effects of the drug on the body</td>
</tr>
<tr>
<td>Early response indicator</td>
<td>To determine the expected ultimate outcomes on a particular therapy regimen from changes in a tumor characteristic following a few cycles of treatment</td>
</tr>
<tr>
<td>Basis of a Phase II trial end point</td>
<td>A pre- to posttreatment change measurement used to determine whether to proceed to the subsequent Phase III investigation</td>
</tr>
<tr>
<td>Basis of a Phase III trial end point</td>
<td>A pre- to posttreatment change that serves as a surrogate for a definitive clinical end point</td>
</tr>
</tbody>
</table>

Statistical Tests in the Context of Clinical Trials

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

Marker by Treatment Interaction Design with stratification to test the value of an imaging-based predictive marker.

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


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.

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.
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

Phase II and III trials:
- help establish new standards of care
- prepare for FDA approval
- new approaches to interventions
- validate new biomarkers

https://www.cancer.gov/research/areas/clinical-trials/nctn/nctn-clinical-trials-network
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:
  - rCBV [Baseline]
  - Change in CBF [Baseline to 2 weeks]
  - PFS [Up to 5 years]
  - cCBV [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 metastases in the clinically N0 neck (both by neck and lymph node regions) and 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 forgo 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]
- Target Enrollment: A total of 250 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/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-MRI and DBT on both the initial and 1 year follow up studies.
- To estimate and compare the sensitivity and specificity of AB-MRI 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-MRI 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

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)
Acknowledgment

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