Objectives

- Describe the motivation underlying analyses of tumor heterogeneity
- Describe the role of Image ‘omics in Oncology
- List the different levels of biomarker qualification

The bad news

Despite advances in cancer genetics,
We are not “curing” cancer

Even when we know target and have a great drug, benefit is measured in months

One of the problems...

- Erlotinib: the $12 BB drug
- Treats 7-10% NSCLC (those with activating EGFR mutation)
- Over 12 known resistance mechanisms
- Resistance mechanisms can be pre-existing or can result from adaptive responses

Cancer is not being “cured”
Cancers are Heterogeneous (RCC).

Genetic heterogeneity in 1930

Genetic heterogeneity in 1930

Evolutionary Dynamics of Carcinogenesis
Robert J. Gillies, Daniel Verduzco and Robert A. Gatenby
Nature Reviews | cancer online 14 June, 2012

Evolutionary game theory

Evolutionary Dynamics in Therapy

Size (RECIST) does not matter!
Size (RECIST) does not matter!

How can Molecular Imaging inform oncology decision making?
- (Quantification of Heterogeneity, σ)
- (Large Databases)

Lung tumor heterogeneity

Opportunity 1: Image Analysis

Quantitatively Characterize Phenotypic Heterogeneity, σ, using advanced analyses of tumor “textures”

Multiparametric MRI – Hs766t PanCan

Tumor Perfusion Heterogeneity (DCE MRI)

Opportunity 1: Image Analysis

Quantitatively Characterize Phenotypic Heterogeneity, σ, using advanced analyses of tumor “textures”
Texture in NSCLC

Coarse texture features correlated with SUV of FDG uptake ($p<0.003$).

Fine texture features predicted tumour stage with 100% sensitivity and 87.5% specificity.

Can Imaging Features predict gene expression (and therapy response)?

Convert Images to mineable data in high throughput (radiomics)

Rationale for Radiomics

Radiomics


Radiomics

N = 30 (training) + 32 (test)

Radiomics

N = 22 (training) + 110 (test)

Radiomics

N = 25 (training) + 63 (test)
Shape and Texture CT Features

Texture based features:
- Sphericity:
- Compactness:
- Skewness:
- Kurtosis:
- Entropy:

In our analyses, we have 211 3-D and 114 2-D texture and shape features.

Radiomics: workflow & challenges

"Convert Images to mineable data"

- Image
- Segment
- Report
- Analyze

Optimize acquisition & recon
Automate & Validate
Qualify Features
Databases

Kumar et al., MRI (in press) 2012

Context-dependent Automated Segmentation and Classification of organ systems

Feature Selection

Total # of 2D and 3D features is 324

CT Image Texture Features of NSCLC

Unsupervised Hierarchical Clustering

Recurrence 22% of those who recur, the median survival (months) = 10
Recurrence 44% of those who recur, the median survival (months) = 17
Recurrence 30% of those who recur, the median survival (months) = 15

Kumar et al., (in preparation)
Reducing Dimensionality

- 324 features are too many. Increased probability of over-fitting data.
- Useful features can be identified by sequentially determining:
  - Their reproducibility in test-retest
  - Their uniqueness from correlation matrices
  - Their dynamic range
- Goal is to reduce 324 features to ~40 that may be more useful.
- We have recently done this to identify 39 features that are non-redundant, robust and have high D.R. (*submitted*).

Clinical Imaging biomarkers

- PAST: anatomy (RECIST)
- PRESENT: DCE-MRI, FdG-PET, volumes.
- FUTURE:
  - Functional imaging endpoints:
    - Doppler US - Diffusion MRI
    - Magn Trans MRI - Macromolecule contrast (CT, MR)
  - Molecular imaging endpoints:
    - Receptor PET - Metabolic PET (FDG, FLT, cho)
    - Targeted nanoparticles - Magn. Reson. Spectroscopy
    - pH imaging - Hypoxia (PET, BOLD MRI)
    - CEST MRI - Hyperpolarized (e.g. 13C pyruvate)

Biomarkers

- Biomarkers are characteristics that are objectively and quantitatively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.
- In therapeutic applications:
  - Prognostic biomarkers predict response regardless of therapy
  - Predictive biomarkers predict response to specific therapies
  - Response biomarkers measure change in response to therapy and may be related to clinical outcome
- Biomarkers are not surrogates! Surrogate markers can substitute for clinical endpoint.

(clinical) Uses of Cancer Biomarkers*

- Prognosis – predict the probable outcome regardless of therapy
- Prediction – predict response to particular therapies
- Therapy monitoring – determine if therapy is having intended effect
- Screening – Detect and treat early-stage cancers in asymptomatic populations
- Risk stratification – assess likelihood that cancer will occur or recur
- Diagnosis – Definitively establish presence of cancer
- Classification – classify by disease subset
- Risk management – identify probability of adverse effects
- Surveillance – detect and treat recurrent disease

What does it take to be a ‘biomarker’?

One biomarker validated for >1,000 literature mentions of the word “biomarker”. To validate and qualify, 5 levels must be met.
- Correlative observation in cells or animals
- Retrospective analysis with human samples
- Inter-lab cross validation
- Prospective Study
- Multi-center Prospective Study

Linking and Mining Image, Medical and Genomic Data

*Cancer Biomarkers, IOM, 2007

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*Courtesy Daniel Rubin, Stanford*
Cancer Research is in a state of crisis at the moment because targeted therapies are not curing cancer.
A major factor in the ineffectiveness of targeted therapy is emergence of resistance.
This is predictable with Evolutionary Game Theory, give tumor heterogeneity.
Imaging is the best-equipped technology to assess tumor heterogeneity in all patients.
This requires advanced image analysis.
This requires high-throughput feature extraction.
This requires large data bases from multiple centers.

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