Oncology - Evolution of imaging
From ‘helpful’ to ‘essential’

Imaging 2016: Essential at Every Step of Ca Care
### 2000 – 2014 Trends in Utilization of CT

<table>
<thead>
<tr>
<th>National Trends*</th>
<th>MSKCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>96%</td>
<td>147%</td>
</tr>
<tr>
<td>2009-2010</td>
<td>2009-2010</td>
</tr>
<tr>
<td>-1.7%</td>
<td>-0.9%</td>
</tr>
<tr>
<td>2010-2015</td>
<td>2010-2015</td>
</tr>
<tr>
<td>NA</td>
<td>27.1%</td>
</tr>
</tbody>
</table>

*J Am Coll Radiol 2012
Precision Medicine

Conundrum & Understanding Tumor Heterogeneity

18FDG PET/CT
Breast Ca - Metastasis
Bx: HER2 positive

64Cu Trastuzumab PET/CT

HER2 Amplified Gene Copies

HER2 Normal Gene Copy

Investigational: MSKCC
Prostate Cancer
Heterogeneous Biology of Tumor Metastasis

CT

$^{18}$F-FDG PET/CT Glycolysis

Zr-89 J591 PSMA mAb*

Radiomics: From Machine Data to Image Data, from Image Data to Big Data

**Technology**
- CT
- MRI
- PET

**Processing**
- Digital geometry processing
  - Filtered back projection
  - Maximum likelihood expectation maximization
- Radiofrequency signal encoding
  - Spatial
  - Phase
  - Frequency
  - Fourier transformation
- Localization of positron annihilation
  - Coincidence statistics

**Images**

Radiomics in clinical decision making
- Conversion of Images into Mineable Data
- Implications for diagnosis, intratumoral heterogeneity, precision Bx, predictive biomarkers, Tx decisions, Tx planning & monitoring
Images are more than Pictures

Images are Data

Computer Aided Diagnosis - CAD (FDA approved) to either detect (CADe) or diagnose (CADx)*

Radiomics – development of new software - processes for high-throughput extraction of quantitative features of a large number of imaging data (Big Data) including intensity, shape, size, texture etc. and offers information on tumor phenotype and micro-environment (or habitat imaging) Radiomic data are most powerful when used in combination with other metrics, such as clinical history & demographics histopathology, genomics - to improve classifier models

*Effectiveness of Computer-Aided Detection in Community Mammography Practice – JNCI 2011
Big data correlations do not prove cause and effect!
US spending on science, space, and technology correlates with Suicides by hanging, strangulation and suffocation

Correlation: 99.79% ($r=0.99789126$)

Data sources: U.S. Office of Management and Budget and Centers for Disease Control & Prevention
Age of Miss America correlates with Murders by steam, hot vapours and hot objects

Correlation: 87%  Sources: Wikipedia & CDC  tylervigen.com
Total number of Political Action Committees (US) correlates with People who died by falling out of their wheelchair
**Radiomics**

OMICS - Lessons Learned & Path Forward*

- Discovery *(Let Chaos Reign)*
- Clinical relevance *(Rein in Chaos)*
- Validation *(Exercise Discipline)*
- Re-Validate on defined pt. population in multi-center studies *(Confirm Clinical Utility)*
- Disseminate *(Share, New Clinical Paradigms)*

*IOM Report – Evolution of Translational Omics; 2011*
Radiomics Entering the Clinical Realm

Emerging Applications

• Reducing Uncertainty in Diagnosis
  o Facilitates dissemination of “Best Practice”

• Improving Visualization of Intra/Inter-tumoral Heterogeneity
  o Improves tumor characterization
  o Facilitates precision biopsy (phenotypic heterogeneity)

• Integrated Diagnostics - Predictive Biomarker Consortium
  o Assesses treatment response
  o Predicts drug resistance
  o Guides adaptive therapy

*R. J. Gillies, P. E. Kinahan, H. Hricak: Radiomics: Images are data: Radiology 2016
Radiomics: Prostate Ca Tumor Characterization

Texture Analysis*
Compared to T2WI & DWI there is improvement in visualization of intra-tumoral heterogeneity**


*Harlick: Structural Approach 1979
Automatic Classification of Prostate Cancer Aggressiveness from mpMRI ($N=147$)

Fehr, et al: PNAS 2015
Bladder Cancer: Interrogating Tumor Heterogeneity
Bladder Cancer: Correlating between Radiomics and Gene Expression Signatures - Radiogenomics

Correlations were extracted through cross-validation based learning RFE-SVM* method with 22 texture and shape features.

C. Cordon-Cardo: p53 MUTATIONS IN HUMAN BLADDER CANCER GENOTYPIC VERSUS PHENOTYPIC PATTERNS; Int. J. Cancer 1994
Radiogenomics - Radiation Therapy
The link between Germ line genetic variations and normal tissue response to radiation therapy, with the long term goal to identify patient at risk for radiation toxicity based on genetic variations

Radiogenomics - Imaging
An association between Imaging features and genetic & epigenetic signatures; a link between diagnostic imaging & molecular diagnostics
Radiogenomics in Imaging

- Radiogenomics - defines relationships, association maps, between image features (including Radiomics) and molecular markers (OMICS)
- A Radiogenomic correlation does not imply causation!!!
- Pilot studies include both big data (radiomics analysis and descriptive findings can be correlated with genome or gene cluster/candidate genes: GBM, HCC, Breast Ca, Lung Ca & Kidney Ca


Clear Cell RCC: Phenotypic Heterogeneity

Contrast enhanced CT
Radiogenomics

Association between CT features (8 descriptive & 5 quantitative) & Clear-Cell RCC genetic mutations

Cluster mutations in clear-cell RCC

(N=232)*

**CT Parameter**

<table>
<thead>
<tr>
<th></th>
<th>VHL</th>
<th>PBRM1</th>
<th>BAP1</th>
<th>SETD2</th>
<th>KDM5C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Vein Invasion</td>
<td>0.194</td>
<td>1.000</td>
<td>0.030</td>
<td>0.391</td>
<td>0.030</td>
</tr>
<tr>
<td>Lobulated Tumor Enhancement Pattern</td>
<td>0.166</td>
<td>0.010</td>
<td>1.000</td>
<td>0.743</td>
<td>0.747</td>
</tr>
<tr>
<td>Low Nephrographic Phase Enhancement</td>
<td>0.737</td>
<td>0.394</td>
<td>0.101</td>
<td>0.023</td>
<td>0.445</td>
</tr>
<tr>
<td>Collecting System Invasion</td>
<td>0.031</td>
<td>1.000</td>
<td>0.059</td>
<td>0.168</td>
<td>0.209</td>
</tr>
</tbody>
</table>

*C. A. Karlo et al: Radiogenomics of clear-cell renal cell carcinoma: Associations between CT imaging features and mutations; Radiology 2014*
Ovarian Cancer: Radiogenomics

Frontiers in Science and Education

Is there association between CT imaging findings and prognostically relevant gene signatures (TCGA) in HGSOC?

Radiogenomics – Ovarian Cancer

Inter-Site Entropy: 1.72
Inter-Site Prominence: 541
Inter-Site Shade: 67

MSKCC Investigational: Sala, Veeraraghavan et al
Mesenchymal CLOVAR HGSOC

Affinity matrix showing similarity of metastatic sites

Tree-Based Representation of similarities
Radiomics: Mesenchymal CLOVAR HGSOC

Spatial Tumor Texture Heterogeneity May Predict Outcome

Mesenchymal CLOVAR HGSOC (69 months OS)

Mesenchymal CLOVAR HGSOC (10 months OS)

MSKCC Investigational:
Sala & Veeraraghavan et al
Convergent Evolution

Genotype

Phenotype

INTEGRATED DIAGNOSTICS
Convergence of “Omics,” Molecular Pathology, Laboratory Medicine & Imaging
NEXT GENERATION SEQUENCING IMAGING

Patient

Tumor

Treatment selection

Real time monitoring

Biopsy

Genotyping

Targeted drugs

PET scanning

Tumor

Pathway analysis

Tumor match

Circulating tumor cells

*D. Haber, N. Gray, J. Baselga: The Evolving War on Cancer; Cell 2011
Thank you!

Harini Veeraraghavan

Evis Sala

Wolfgang Weber

Yousef Mazaheri

Yulia Lakhman

Andreas Wibmer

Jo Deasy

Alberto Vargas