Radiomics in Oncology: Future Prospects

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Disclosure

- Research grant: Bayer
Precision Medicine

- Better understanding of the molecular drivers of cancer
- Stratify patients based on pathophysiological pathways
- Tailor of medical treatment to the individual characteristics of each patient
Cancer targets

Hanahan. Cell 2011
Cancer immunotherapy revolution

- Monoclonal antibodies
- Cancer vaccines (against tumor antigens, peptides, proteins…)
- Injection of Ag-specific T-cells
- Non-specific immunotherapies
Nobel prize in physiology or medicine 2018

- Allison: Discovery of CTLA4 T-cell protein
- Honjo: Discovery of PD-1 T-cell protein
- Both act as brakes on T cells
Immune function of anti-PD1 mAb

Tumor Killing

No killing

Tumor

Dendritic cells
Macrophages

Courtesy Miriam Merad, Immunology Institute, Mount Sinai
Cancer genomics

- Genome sequencing of cancer cells: characterization and identification of the DNA or RNA sequences of cancer cells, based on tumor tissue and adjacent tissue and microenvironment
- Genomic (copy number and mutation status of DNA), transcriptomic (coding and non-coding RNA), epigenetic (DNA) and proteomic
- Understanding the complexity of oncogenic processes
- New treatment targets (druggable pathways, “basket” trials based on molecular aberrations)
- Prognostication
Targeted therapy based on molecular profiles

- Organ based treatment challenged
- Basket trials: designed to improve outcomes for cancers harboring specific molecular tumor types (e.g., NCI-MATCH trial, ASCO TAPUR trial)
- CRC: KRAS, BRAF, PIK3CA, and PTEN loss mutations: can predict non-response to EGFR monoclonal antibodies (cetuximab and panitumumab) in mCRC
- NSCLC: EGFR-tyrosine kinase inhibitors (EGFR-TKIs) efficient in EGFR-mutated tumors (10-15% cases)
- Breast cancer: ER+ (70%), HER 2+ (15%), Triple Negative (15%)

Intra-Tumor Heterogeneity

- Intra-patient and between patients
- Distinct morphological/phenotypic and molecular profiles
- Significant challenges in designing effective treatment strategies
- Sampling error with biopsy
- Metastatic lesions can acquire new mutations and evolve independently
- Imaging can assess whole tumor

Burell. Nature 2013
Phenotypic heterogeneity in HCC

Substantial intra-tumor heterogeneity

Regions of high flow associated with low $R_2^*$ and vice versa

Hectors. Sc Reports 2017
Radiomics

- Extraction of quantitative imaging features from standard medical images using high throughput methods generates mineable databases that can be used to build predictive models relating imaging features to clinical outcomes and genomics
- Assessment of intra- and intertumoral heterogeneity
- Identification of sub-regions, or ‘habitats’, within tumors
Radiomics

- Semantic: size, shape, location, vascularity, spiculation, necrosis, et cetera
- Agnostic
  - First order: histogram features (mean, median, maximum, minimum, kurtosis, skewness)
  - Second order: texture features (descriptors of the relationships between image voxels (e.g. gray-level cooccurrence matrix (GLCM), run length matrix (RLM), size zone matrix (SZM), and neighborhood gray tone difference matrix (NGTDM) derived textures)
  - Higher order: wavelet, fractal analysis, Laplacian transforms

Gillies et al. Radiology 2016
Gray Level Co-occurrence Matrix (GLCM) features: probability that pixel with signal intensity $i$ has neighbor with signal intensity $j$.

Haralick RM. IEEE Trans Syst Man Cybern 1973
Radiomic workflow

Radiomic feature extraction

- $N$ lesions
- $M$ features per sequence
- 4 first-order statistics per lesion

Anant Madabhushi. Case Western University
Potential applications of radiomics

- Virtual biopsy: features can be surrogate markers of histopathological, genomics and clinical parameters
- Enabling diagnosis
- Estimating prognosis
- Patient-specific treatment stratification
CT radiomics in lung and H&N cancers

- Aerts. Nature Commun 2014:
  - CT radiomics analysis of tumor phenotypes in 1019 patients with lung and head/neck cancers
  - 440 features (among image intensity, shape, and texture) with potential prognostic value

- Coroller. Radiother Oncol 2016: 7 features predictive of pathologic gross residual disease, and one of pathologic complete response in lung Ca
Radiogenomics

- Correlate imaging features (typically radiomics) with gene expression, molecular signatures and immune infiltrate

- **Rationale:** avoid tissue sampling, especially after treatment

- **Imaging:** noninvasive, repeatable, assess whole tumor and surrounding tissue/metastatic foci, quantifiable, assesses ITH

- Develop a non invasive monitoring tool that predict cancer outcome and response to treatment
Radiogenomics studies in HCC

- Taouli, Eur Radiology 2017:
  - Positive associations between certain imaging traits and gene signatures of aggressive HCC (G3-Boyault, Proliferation-Chiang profiles, CK19-Villanueva, S1/S2-Hoshida) (ORs 4.44–12.73, p<0.045)
  - Infiltrative pattern associated with signatures of microvascular invasion and aggressive phenotype
Heatmap

- Graphical representation of data where individual values contained in a matrix represented as colors
- Each row represents a gene and each column represents a sample
- May also be combined with clustering methods which group genes and/or samples together based on the similarity of their gene expression pattern
- Color and intensity of the boxes represent changes of gene expression (red represents up-regulated genes and blue represents down-regulated genes, white represents unchanged expression)

Radiogenomics correlations in HCC.
Taouli. Eur Radiology 2017
HCC ITH is associated with gene expression of immune checkpoints

Expression levels of liver-specific target GLUL, stemness markers (EPCAM, KRT19), early HCC markers (BIRC5, HSP70, LYVE1, EZH2), pharmacological target (FGFR4), angiogenesis marker (VEGFA) and immunotherapy targets (CD274=PD-L1, PDCD1, CTLA4)

Hectors. Sc Reports 2017
Correlation with Multiplex IHC staining

T-cells (CD3), endothelial cells (CD31), macrophages (CD68) and hypoxia (HIF1α)

Remark. Science Immunology 2016
Radiomics in HCC

71M with 6.4 cm HCC in right lobe. Texture analysis on T1 HBP image showed homogeneity of 0.293. Histopathology revealed a G2 tumor with MVI, and low expression of stemness marker EPCAM (expression level 0.471).
RCC

- Mutations of VHL associated with well-defined tumor margins, nodular tumor enhancement, and gross appearance of intratumoral vascularity; mutations of KDM5C and BAP1 associated with renal vein invasion (Karlo, Radiology 2014)
- BAP1 mutation associated with ill-defined tumor margins and presence of calcification; MUC4 mutation associated with exophytic growth (Shinagare, Abd Imaging 2015)
- No radiomics/genomics studies published
Prostate cancer

- Molecular analysis of 333 PCa TCGA: substantial heterogeneity in the spectrum of molecular abnormalities and variable clinical course (7 subtypes defined by ETS fusions or mutations).
- Correlation between ADC and certain gene expression levels (Buerki. Oncotarget 2016), not confirmed (Renard-Penna. J Urol 2015).
- Weak correlation of PTEN expression and DCE-MRI parameter (McCann. AJR 2016).

TCGA. Cell 2015
Prostate cancer

Association between PI-RADS score, adverse pathology features and 21 prognostic genomic signatures showing significant enrichment of PI-RADS 5 in patients with high risk prognosis

Tuna Beksac. J Urology 2018
Prostate cancer

Hectors et al. J Urol (in press)
Radiogenomics in prostate cancer

Correlation of MRI radiomics features with gene expression levels (311 significant positive and negative correlations observed involving 40 DWI radiomics features and 132 genes)

Hectors et al. J Urol (in press)
Radiomics in RCC

Said et al. SAR 2019
Combination of radiomics features

- ccRCC vs. other subtypes
  - AP SD
  - DP Variance
  - T2 HASTE Sum Variance

- ccRCC vs. pRCC
  - DP Skewness

AUC 0.87 (p < 0.001)
AUC 0.84 (p < 0.001)
Radiomics assessment in HCC treated with neoadjuvant nivolumab before resection
Challenges

▶ Scientific challenges:
  – Overestimation of statistical associations
  – Associations need to be confirmed in validation sets
  – Radiomics dependent on image quality and acquisition parameters/need QC/QI

▶ Operational and legal/ethical issues:
  – Massive amounts of computing data
  – Patient privacy/PHI
Repeatability of radiomics features

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<th>Pre-contrast T1</th>
<th>Post-contrast T1</th>
<th>ADC</th>
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<td>1&lt;sup&gt;st&lt;/sup&gt; order</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; order</td>
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<td>CV&lt;20%</td>
<td>3/5 (60%)</td>
<td>10/14 (71%)</td>
<td>4/5 (80%)</td>
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Inter-platform variability is needed
Take home messages

- Tumor profiling (genomic transcriptomic and phenotypic levels) will help dissect tumor heterogeneity and identify novel disease targets
- Radiomics has the potential to identify phenotypes that correlate with tumor molecular subclasses
- Radiomics: Biomarker of tumor outcome that help tailor treatment to tumor molecular defects and enhance the Precision Medicine mission
- More work needed
Personalized medicine in Oncology

- Imaging will play an essential role in screening, diagnosis, treatment and patient selection.
Taouli Lab (Translational and Molecular Imaging Institute/ISMMS)

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Representative expression pattern of vascular invasion signature genes (Affymetrix DNA microarray platform)

Taouli, Eur Radiology 2017