Imaging and Molecular Biomarkers of Lung Cancer Prognosis

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The Era of Precision Oncology

• Lung cancer is a heterogeneous disease.
• Molecularly targeted therapies exist according to the unique genetic makeup of each individual tumor.

Li T et al. J Clin Oncol 2013
Biomarkers as a Pillar of Precision Oncology

- Biomarkers can be used to inform diagnosis and prognosis, or to select appropriate therapy.
- PSA level, Oncotype Dx recurrence score, EGFR activating mutation.
- Conventional: biological molecules measured in tissue, serum, or circulation, at DNA, RNA, or protein level.

Tissue-based Molecular Biomarkers

- Mainstay of current oncology practice
  - NGS: rapid, high-throughput profiling at reduced cost
  - Genome, transcriptome, proteome, metabolome, etc
- Exquisite molecular detail, but...
- Invasive
  - Requires biopsy or surgery
- Biased
  - Samples a small portion of a tumor
- Incomplete
  - Does not characterize tumor anatomy or in vivo physiology (e.g., blood flow)

Imaging-based Biomarkers

- The current FDA-NIH Biomarker Working Group definition includes radiographic characteristics.
- Routine, noninvasive, repeatable, whole tumor & surrounding tissue
- Currently based on radiologist’s visual assessment
  - Subjective: inter-/intra-observer variations
  - Qualitative, not quantitative
  - Low-throughput (one or few: RECIST)
Radiomics: the Process

- Quantitative, high-throughput extraction of information from medical images
  - Converts pictures to ‘omic’ data
- Correlate with clinical outcomes: biomarkers
- Correlate with molecular data: potential driving biology

Prognostic Biomarkers in Early-Stage NSCLC

- Excellent local control after SABR.
- Distant metastasis occurs in a significant proportion of patients.
- Most patients do not receive adjuvant systemic therapy.
- Need to accurately identify patients at highest risk of recurrence, who might benefit from additional therapy.

Identifying Prognostic Imaging Biomarker

101 stage I NSCLC patients treated with SABR

Wu et al, Radiology, 2016
Radiomic Analysis of PET/CT

- Our radiomic feature set includes:
  - 6 statistical (mean, max, variance, skewness, etc)
  - 5 SUV histogram
  - 2 morphology (CT)
  - 24 Wavelet
  - 30 Laws
  - Total: 70 quantitative image features.

Wu et al, Radiology, 2016

Discovery of a Radiomic Signature

- The final radiomic signature was:
  - 2.1 x SUV<sub>peak_2cc</sub> + 3.6 x Gauss_ClusterShade

Wu et al, Radiology, 2016

Pre-SABR PET images

Distant metastasis free 34 mo after SABR
Distant metastasis 9 mo after SABR
Independent Validation

- Radiomic Signature
- SUV<sub>max</sub>
- Tumor Volume

Logrank $P = 0.0498$  
HR = 4.79  
C-index = 0.710

Logrank $P = 0.731$  
HR = 1.48  
C-index = 0.874

Logrank $P = 0.538$  
HR = 2.01  
C-index = 0.642

Wu et al, Radiology, 2016

Histology Adds to Imaging

- Histology type combined with radiomic signature
- Radiomic signature alone

Logrank $p = 0.0001$  
HR = 13.31  
C-index = 0.797

Logrank $p < 0.0001$  
HR = 13.31  
C-index = 0.797

Wu et al, Radiology, 2016

Prognostic Imaging Biomarker in Pancreatic Cancer

- A radiomic signature of FDG-PET improved upon SUV and tumor volume (C-index: 0.67 vs 0.58).

Cui et al, IJROBP, 2016  
Basic/Translational Science Abstract Award, ASTRO 2015
**Pre-SRRT PET images**

- Image 1: $SIR_{max} = 3.55$
  - Volume = 37.1cm³
  - Proposed Signature = -0.235
  - TS = 45.1 days
- Image 2: $SIR_{max} = 5.10$
  - Volume = 55.0cm³
  - Proposed Signature = 0.526
  - TS = 268 days

Cui et al. IJROBP, 2016

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**Beyond Radiomics: Multi-Region Analysis**

- Aggregate image features from the bulk tumor
  - Assuming tumor is well mixed
- Clonal evolution causes regional differences in a tumor.
- Habitat imaging to identify ‘high-risk’ subregions

Sottoriva, et al. PNAS, 2013

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**Intra-Tumor Partitioning of Lung Tumors**

1. Step 1: Intra-patient PET/CT alignment
2. Step 2: Patient-level over-segmentation of tumor into supervoxels
3. Step 3: Population-level clustering into tumor subregions

Consistent labels

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### 3 Distinct Intra-Tumor Subregions

The high-risk subregion represents the metabolically active & heterogeneous solid component of the tumor.

#### Image features
- Super-voxels
- Clusters

#### Clusters
- A
- B
- C

#### Entropy
- PET
- CT

#### WVU, 2016

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### Two Patients with Stage IIIb NSCLC

<table>
<thead>
<tr>
<th>CT</th>
<th>PET</th>
<th>Local Entropy(CT)</th>
<th>Local Entropy(PET)</th>
<th>Over-Segmentation</th>
<th>Population-Level Clustering</th>
</tr>
</thead>
</table>

**Patient 1**
- Total volume: 41.3 ml
- SUV$_{max}$: 13.1
- MTV$_{50}$: 5.8 ml
- Tumor burden for cluster A: 8.9 ml
- Alive after 4 years, no out-of-field progression

**Patient 2**
- Total volume: 39.1 ml
- SUV$_{max}$: 8.7
- MTV$_{50}$: 2.1 ml
- Tumor burden for cluster A: 21.7 ml
- Deceased after 3 months

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### Prognostic Value in NSCLC (All Stage)

- CI: concordance index
- Logrank p

**Tumor burden associated with the high-risk subregion predicts metastasis and overall survival better than conventional imaging metrics.**

- CI = 0.56
- Logrank p = 0.82
- CI = 0.61
- Logrank p = 0.59
- CI = 0.55
- Logrank p = 0.63
- CI = 0.66
- Logrank p = 0.04

**Green:** < median
**Red:** $\geq$ median

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Wu et al. IJROBP, 2016
Stronger Prognostic Power in Stage III Patients

- Tumor burden associated with the high-risk subregion strongly predicts metastasis and overall survival in stage III patients.

Combine Radiomics with Multi-Region Analysis

- Intra-tumor partitioning based on multi-parametric MRI
- Extract radiomic features for each subregion and gross tumor.

Prognostic imaging signature in GBM

- A 5-feature radiomic signature predicted overall survival, independent of age, gender, extent of resection.
Initial Work on Radiogenomics

• Radiogenomics in HCC
  - First study to show that CT image features correlate with global gene expression.
  - 28 image features predicted the expression of 78% out of 6732 genes in 32 patients.

  Segal et al, Nat Biotechnol 2007

• Radiogenomics of GBM
  - Identified image features in brain MRI correlated with gene expression in 22 patients.
  - Tumor contrast enhancement and mass effect predicted hypoxia and proliferation gene expression programs.
  - Infiltrative imaging phenotype was correlated with clinical outcome.

  Diehn et al, PNAS, 2008

Initial Work on Lung Cancer Radiogenomics

• Gene expression and CT image data from 26 NSCLC patients
• Linear models predict metagenes by 180 image features, vice versa
  - Accuracy: 59%–83%, or 65%–86%
• Tumor size, edge shape, and sharpness ranked highest for prognostic significance

  Gevaert et al, Radiology, 2012
Limitations of Initial Work

- Proof of concept
- Small number of samples (~20-30)
- Large number of variables: false discovery
- Lack independent validation

Current Paradigms of Radiogenomics

1. Understand how a biological process is reflected at imaging.
2. Understand the biological basis behind an image feature

Depending on the endpoint of the study...

Type 1 Radiogenomic Association

- What imaging features are associated with a biological process?
  - EGFR, KRAS mutation, ALK rearrangement in NSCLC
- Can imaging be used to predict genomic alternations?
  - 385 patients from a single institution
  - 30 CT features to assess EGFR mutation
  - smaller size, homogeneous enhancement, and pleural retraction
  - Good accuracy
  - Clinical value uncertain

Liu et al, Radiology, 2016
Type 2 Radiogenomic Association

- What molecular pathways or biological processes are associated with a specific imaging phenotype?
  - Maximum SUV at FDG-PET prognostic of survival in NSCLC
  - 14 differentially expressed genes for SUV_{max} in 26 patients (FDR < 0.20)
  - Linked with survival and epithelial-mesenchymal transition.
  - Small, exploratory analysis
  - Additional validation required
  - No mechanistic evidence.


Quantitative Pleural Contact Index in NSCLC

- Explicitly quantify relation of tumor and surrounding pleura
- PCI has a high degree of reproducibility for multiple contours (ICC = 0.87).


Prognostic Value of Pleural Contact in Stage I NSCLC

- PCI was significantly associated with overall survival in both discovery and validation imaging cohorts.
- PCI also stratified patients for distant metastasis.
- Pleural attachment was not prognostic.
Complementary Value PCI to Clinical Features

- PCI further stratified patients within clinical stage IA, IB subgroups.
- PCI was independently associated with survival beyond age, gender, tumor size, and histology.

Molecular Correlates of Pleural Contact in NSCLC

- In 89 patients, extracellular matrix (ECM) remodeling was enriched among genes correlated with PCI (FDR=0.005).
- Role of ECM remodeling in cancer invasion and metastasis
- Built a genomic classifier for PCI (10-fold CV accuracy: 78%).

Validation of Prognostic Value of PCI in Stage I NSCLC

The genomic surrogate of PCI:
- stratified patients for overall survival in 4 cohorts (775 patients).
- remained a strong, independent prognostic factor adjusting for age, gender, and tumor stage.
Radiogenomics of Breast Cancer Parenchyma

• Breast parenchyma enhances to various extents on DCE MRI.
• Background enhancement has been linked to breast cancer risk, but molecular mechanisms are poorly understood.
• Goal: determine biological underpinnings and assess prognostic relevance of parenchymal enhancement.

BI-RADS 2015

Discovery of Prognostic Parenchymal Image Features

<table>
<thead>
<tr>
<th>Imaging features</th>
<th>Wald P*</th>
<th>FDR</th>
<th>Concordance Index (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>dissimilarity</td>
<td>0.14</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>energy</td>
<td>0.56</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>entropy</td>
<td>0.41</td>
<td>0.52</td>
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</tr>
<tr>
<td>homogeneity</td>
<td>0.07</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>correlation*</td>
<td>0.001</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>PpPrecon-1 s</td>
<td>0.02</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>PrePost-1 s</td>
<td>0.049</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>PreRADS-1 s</td>
<td>0.037</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>SDE (iso)</td>
<td>0.34</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>SDE (iso)</td>
<td>0.37</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Includes statistical significance adjusted for multiple testing (FDR 0.05)
* Value from linear Où regression index

Prognostic value independent of tumor imaging features

Wu et al. Radiology, 2017. in press

Radiogenomic Map

Parenchymal heterogeneity on DCE MRI was associated with the TNF signaling pathway (hypergeometric test, P = 0.0001)
Independent Validation on Two Cohorts

73-Gene Signature on TCGA

Wu et al. Radiology, 2017. in press

Breast Cancer Intrinsic Imaging Subtypes

The imaging subtypes were not correlated with intrinsic molecular subtypes such as luminal A, luminal B, basal-like, HER2-enriched (Person's Chi-square test P = 0.87)

Wu et al. Clin Cancer Res 2017

Clustering of Image Features Revealed Three Subtypes

Reproducibility
Cluster IGF
1 82%
2 92%
3 60%

Wu et al. Clin Cancer Res 2017
Imaging Subtypes Associated with Distinct Prognosis

The imaging subtypes were independent predictors of RFS adjusting for clinical and pathological factors.

Imaging Subtypes Associated with Distinct Molecular Pathways

PARADIGM analysis

Wu et al. Clin Cancer Res 2017

Challenges of Radiomics

- Reproducibility and robustness
  - Multi-center validation
- Statistical pitfalls
  - False discovery or over-fitting due to multiple testing
- Biological interpretation difficult
  - Radiogenomics could help, with careful use.
Conclusion

• Radiomics is a useful tool to discover new imaging biomarkers.
  – Gross tumor, intratumoral, peritumoral
• Integrating imaging with molecular data may improve biological understanding.
• Prospective validation is essential to truly establish the value of imaging in precision medicine.

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