Lung CT as a Marker for Pulmonary Sarcoidosis

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Outline

• Background supporting the development of a radiographic biomarker
• GRADS study as a basis for CT study
• Radiomic analysis
• Deformation-based morphometry
• Future directions
Pulmonary Sarcoidosis

- Primary cause of death
- Impacts individuals in the prime of their lives (mean age at death= 55 years)
- Response to therapy variable
- No definitive prognosticicators
- Designing treatment and longitudinal studies is problematic

Swigris  AJRCCM 2011
Scadding Staging

- Prognostic value for remission
- Easy to use

- Not linear
- Interobserver variability
- Low sensitivity/specificity for fibrosis
- Correlation with lung function variable
Variable Manifestations of Sarcoidosis on HRCT
Can information from HRCT better inform disease classification and prognosis?

- **Radiomics** – A quantitative method that extracts large quantities of texture and related measures from medical images
  - Good for detecting differences in CT patterns; lung cancer COPD

- **Deformation-based morphometry** – A quantitative method that detects structural changes
  - Good for detecting differences in lung size and structure
Hypothesis: Detailed radiomic analysis of lung CT images in sarcoidosis will identify new more refined subtypes of pulmonary disease

Combined with clinical and genomic information radiomics will identify novel integrative disease phenotypes that can predict resolution or progression of sarcoidosis.

Study Design:
• Exploratory case-control study using NJH GRADS sarcoidosis cases (N=73) and COPD Non-smoking healthy controls (N=78)
• Classification study using only GRADS sarcoidosis cases (N=330)
GRADS Research Study

• Case-comparison Study

• N = 330 participants enrolled from 7 sites, n=73 from NJH

• Clinically well-defined Cases
  • Demographics, Past Medical History, Treatment, Exposures etc
  • CXR Scadding Stage
  • Lung function: at least Spiro +DLCO
  • Blood and BAL samples from most

• Research Chest HRCT –
  • Based on COPD gene
  • TLC Inspiration and RV Expiration
  • Visual Scoring
Description of Radiomic Analyses

A quantitative method that extracts large quantities of texture and related measures from medical images

- First-order: Mean HU, SD, skew, kurtosis, etc.

Normal lung - left skewed

Normal lung - peaked kurtosis
Spatial and Textural Radiomic Features

- Grey-level co-occurrence matrix (GLCM): How similar adjacent voxels (2, 4, 8, 16 and 32 voxels) apart in any direction
  - Energy, entropy, contrast, correlation
- Spatial summaries: Moran’s I and Geary’s C
- Complexity of pattern: Fractal dimension

Grey-level co-occurrence matrix (GLCM):
Differences in Radiomic Measures between Sarcoidosis & Controls and Scadding Stage

<table>
<thead>
<tr>
<th>Radiomic Feature</th>
<th>Control (N = 78)</th>
<th>Sarcoidosis (N = 73)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skewness</td>
<td>3.615 (0.037)</td>
<td>3.252 (0.064)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>16.12 (0.299)</td>
<td>13.0 (0.451)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fractal D</td>
<td>2.269 (0.005)</td>
<td>2.236 (0.005)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moran's I</td>
<td>0.815 (0.002)</td>
<td>0.838 (0.003)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Geary's C</td>
<td>0.135 (0.002)</td>
<td>0.120 (0.002)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*adj for age, gender, BMI
### Differences in Radiomic Measures by Scadding Stage

* vs Stage IV; † vs Stage III

<table>
<thead>
<tr>
<th>Radiomic Feature</th>
<th>Stage 0 (N = 9)</th>
<th>Stage I (N = 8)</th>
<th>Stage II (N = 28)</th>
<th>Stage III (N = 11)</th>
<th>Stage IV (N = 17)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skewness</td>
<td>3.356 (0.099)*</td>
<td>3.631 (0.072)*</td>
<td>3.301 (0.103)*</td>
<td>3.479 (0.095)*</td>
<td>2.791 (0.150)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>13.71 (0.785)*</td>
<td>16.06 (0.521)*</td>
<td>13.33 (0.769)*</td>
<td>14.65 (0.850)*</td>
<td>9.57 (0.793)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fractal D</td>
<td>2.259 (0.011)*</td>
<td>2.246 (0.008)*</td>
<td>2.234 (0.006)*</td>
<td>2.254 (0.015)*</td>
<td>2.210 (0.010)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moran's I</td>
<td>0.827 (0.008)*</td>
<td>0.816 (0.003)*</td>
<td>0.840 (0.005)*</td>
<td>0.819 (0.007)*</td>
<td>0.863 (0.007)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Geary's C</td>
<td>0.131 (0.005)*</td>
<td>0.126 (0.004)*</td>
<td>0.117 (0.003)**†</td>
<td>0.136 (0.007)*</td>
<td>0.105 (0.005)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Differences in Spatial Radiomic Measures Between Sarcoidosis and Controls

Slice Percentage (%)
Spirometry is Associated with Radiomic Measures

- Associations stronger and statistically associated with sarcoidosis compared to controls
Radiomic Measures are Significantly Associated with Visual Scoring

Yellow values p<0.05
Radiomic Measures Explain More Variability in Lung Function than Visual Scoring

<table>
<thead>
<tr>
<th>Lung Function</th>
<th>Base</th>
<th>Base + Visual</th>
<th>Base + Radiomics</th>
<th>Base + Visual + Radiomics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-BD FVC</td>
<td>0.54</td>
<td>0.61</td>
<td>0.69</td>
<td>0.69</td>
</tr>
<tr>
<td>Pre-BD DLCo</td>
<td>0.46</td>
<td>0.58</td>
<td>0.61</td>
<td>0.63</td>
</tr>
<tr>
<td>Pre-BD FEV1</td>
<td>0.44</td>
<td>0.60</td>
<td>0.62</td>
<td>0.64</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>0.044</td>
<td>0.25</td>
<td>0.20</td>
<td>0.30</td>
</tr>
</tbody>
</table>

The addition of the visual scoring and radiomic measures to the base model (age, gender, BMI, race/ethnicity) increases the adjusted $R^2$, with the radiomics measures outperforming the visual scoring for FVC, DLCO, and FEV1.
Radiomic Measures can be used to Classify Sarcoidosis Subtypes

<table>
<thead>
<tr>
<th>Scadding Stage</th>
<th>Cluster 1 (N=22) (N(%))</th>
<th>Cluster 2 (N=94) (N(%))</th>
<th>Cluster 3 (N=35) (N(%))</th>
<th>Cluster 4 (N=55) (N(%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 ((N=30))</td>
<td>4 (13)</td>
<td>18 (19.1)</td>
<td>2 (5.7)</td>
<td>6 (10.9)</td>
</tr>
<tr>
<td>1 ((N=39))</td>
<td>9 (40.9)</td>
<td>21 (22.3)</td>
<td>3 (8.6)</td>
<td>6 (10.9)</td>
</tr>
<tr>
<td>2 ((N=62))</td>
<td>6 (27.3)</td>
<td>33 (35.1)</td>
<td>6 (17.1)</td>
<td>17 (30.9)</td>
</tr>
<tr>
<td>3 ((N=26))</td>
<td>2 (9.1)</td>
<td>14 (14.9)</td>
<td>5 (14.3)</td>
<td>5 (9.1)</td>
</tr>
<tr>
<td>4 ((N=49))</td>
<td>1 (4.5)</td>
<td>8 (8.5)</td>
<td>19 (54.3)</td>
<td>21 (38.2)</td>
</tr>
</tbody>
</table>

We found 4 radiomic subtypes – they don’t mimic Scadding stages.
Deformation-Based Morphometry

**Description** – A quantitative method that detects structural changes in the lungs by transforming the original CT scan to a common lung atlas

- Standard lung created using N=62 healthy controls from COPDGene

**Our Research Questions**

1. Are there differences in lung structure between sarcoidosis and controls?
2. Which CT patterns in sarcoidosis result in lung structure differences? TBD
Lung Size Differs between Sarcoidosis and Controls

Results adjusted for age, gender, height and race.
Lung Structure Differs between Sarcoidosis and Control

Colored regions indicate significant volume loss in sarcoidosis compared to control, with green indicating the most significant regions. Results adjusted for age, gender, height and race.
Processing Chest CTs

Software: `lungct` R package
[https://github.com/ryansar/lungct](https://github.com/ryansar/lungct)

**Functionality**
1. Convert DICOM to NIfTI
2. Resample to 1x1x1 mm\(^3\)
3. Segment the left and right lungs
4. Calculate radiomic features on 2D slice or 3D lung
5. Register lungs to the standard lung template
6. Create study-specific templates
7. Calculate the amount of lung shrinkage
8. And more!
Future Directions

• Integrated Biomarker of Sarcoidosis based on Radiomics
• Using GRADS subjects as discovery cohort
• Clinical data, Visual Scores, BAL transcriptome, GWAS data
• Validation cohort NJH and CCF
Summary

• Radiomic analyses of Sarcoidosis Chest CT:
  • Differentiate cases and controls
  • Associate with lung function
  • Classify sarcoidosis subtypes and may be useful as a biomarker

• Preliminary results from deformation-based morphometry show promising results – more work to be done

• There is now publicly-available, open-source software to perform many of these analyses for your own data
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UL 1TR002535
ADD GRADS NUMBERS
• Our patients!
Questions
## Risk factors for advanced pulmonary sarcoidosis unclear

### Risk Factors for Disease Persistence
- Scadding Stage at presentation
  - Absence of lymphadenopathy
  - Ascending Scadding Stage
- Architectural distortion of the airways or cystic changes
- Multiple organ involvement
- Splenomegaly
- Need for systemic therapy
- Older age
- Female gender
- Black race

### Risk Factors for Clinically Bothersome Disease
- Ascending Scadding stage
- Dyspnea at time of diagnosis
- Need for treatment in 1st 6 months
- Multiple organ involvement
- Lower socioeconomic status
- Black race