Grading Dysplasia in Barrett’s Oesophagus
Virtual Pathology Slides

AFZAN ADAM [afzan@ukm.edu.my]
MEDICAL & HEALTHCARE INFORMATICS LAB
CENTER FOR ARTIFICIAL INTELLIGENCE TECHNOLOGY
THE NATIONAL UNIVERSITY OF MALAYSIA
Dysplasia in Barrett’s Oesophagus

Illustration of dysplasia staging in Oesophagus [1]

Dysplasia in Barrett’s Oesophagus

- Pre-malignant but treatable condition where ‘any portion of the normal squamous lining has been replaced by a metaplastic columnar epithelium that is visible microscopically’[1].

- 30-50 times greater chance to develop into oesophagus adenocarcinoma, 10 times to oesophagus cancer[2].

- Continuous changes of tissue structure and architecture during transition from Barrett’s->Low Grade Dysplasia (LGD)->High Grade Dysplasia (HGD)->IntraMucosal Carcinoma(IMC)

The need for a diagnosis tool

Lack of universally accepted definition of Barrett’s Oesophagus[2]

Variations of observation results.
  ◦ Overall agreement: 57%[3]

Continuous transitions of tissue structure and pattern:
  ◦ Poor kappa score (k=0.32) for LGD [4]
  ◦ Good kappa score (k=0.65) for HGD alone[4]
  ◦ Fair kappa score (k=0.42) to compare HGD to ICM[5]

The tissue’s cytological and architectural features characterise the level of dysplasia severity [6] and these changes may be too subtle for humans to measure.

[3] TREANOR D ET AL. TRACKING WITH VIRTUAL SLIDES: A TOOL TO STUDY DIAGNOSIS ERROR IN HISTOPATHOLOGY. HISTOPATHOLOGY, 2009
Some of the challenges:

1. Lack of literature review focuses on finding texture of dysplasia in BO
Some of the challenges:

2. GROUND TRUTH:
annotated regions contain ambiguity.
Using consensus diagnosis.

Virtual slide no: 11013  consensus diagnosis: 4

<table>
<thead>
<tr>
<th>Grade 4</th>
<th>Grade 2</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade dysplasia</td>
<td>indefinite-probably negative</td>
<td>low grade dysplasia</td>
</tr>
</tbody>
</table>
Grading scale

<table>
<thead>
<tr>
<th>Transition direction</th>
<th>Modified classification (2 groups)</th>
<th>Modified classification: 3 groups</th>
<th>Vienna Classification of Dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-dysplasia</td>
<td>G1</td>
<td>1- Barrett’s only</td>
</tr>
<tr>
<td></td>
<td>Dysplasia</td>
<td>G3</td>
<td>2- Atypia, probably negative for dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>G5</td>
<td>3- Atypia, probably positive for dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4- Low grade dysplasia (LGD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5- High grade dysplasia (HGD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6- Intramucosal carcinoma (IMC)</td>
</tr>
</tbody>
</table>

*Table 1. Range of dysplasia grading which could be used.*
Our Ground Truth

140 Virtual slides

- Graded by 6 consultant GI pathologist
  - Vienna classification
    - 57% agreement
    - 0.41 KV
  - Simplified 3 grades
    - G1: 0.73 KV
    - G3: 0.37 KV
    - G5: 0.73 KV

- Graded by 2 consultant GI pathologist
  - Vienna classifications: 0.68 KV
  - Simplified 3 grades: 0.77 KV
  - Produces 438 annotated regions
  - Different magnification levels
  - Different sizes
  - Location: different and partly overlapped
The whole scenario

VIRTUAL SLIDE DIS-INTEGRATION

Tissue detection from VS (thumbnail-sized) → Region creation (10X) → Patch creation (40X)

VIRTUAL SLIDE RE-INTEGRATION

VS diagnosis suggestion with cf and heatmap → Tissue re-modelling & grading → Region grading

Feature extraction
Clustering
Grading
Stages

**Stage 1**
- No of high curvature features in whole tissue + distance ⇒ ROIs
- [BMVA tech. meeting 2010](#)

**Stage 2**
- Unsupervised classification of patches in whole region
- Created cluster coded images (CCI) for each region
- Extract the cluster coded co-occurrence matrices (CCM) for the CCI and freq of clusters (F1)
- Decision Tree to grade region into G1, G3 and G5
- [MiUA 2011](#)

**Stage 3**
- Textural features along ROI's epithelial membrane (F2)
- Distance of each cluster relative to tissue surface is calculated (close, middle, far) (F3)
- Grade region with F1, F2 and F3 using DT

**Stage 4**
- Detect tissue and eliminate artefacts
- Create regions & patches, extract features and grade region
- Highlight regions with grading probability represented as RGB value (severe[G3], safe[G1] and medium[G3])
- Tissue spatial features as well to grade region
- Tissue reintegration
Virtual slides: Tissue detection

Preprocess: eliminates tear-off
Region creation

For each detected tissue:

1800pix*1800pix

@40X

Rejected regions highlighted

Region selection process
Region selection processes

ARTEFACTS ELIMINATIONS

1. candidate regions (cr) are indexed
2. $1800 \text{ pix}^2 > cr > 800 \text{ pix}^2$
3. Reject cr if
   1. Background $> 65$
   2. Average greylevel $< 0.75$
   3. Not in accepted region
      *around the bounding box

Filtered out:
Region analysis and grading

For each accepted regions:

- Boundary detection
  - Epithelial layer analysis
  - Lamina analysis
  - Spatial analysis
Epithelial layer analysis

Figure 4.5: (a) shows the creation of rotated patches along the detected epithelial layer while (b) shows the unrotated patches. \( R \) represents the height and \( \theta \) represents the angle for rotation.

<table>
<thead>
<tr>
<th>Reference line</th>
<th>train-test</th>
<th>10-fold</th>
<th>8-fold</th>
<th>6-fold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclei lining</td>
<td>65.0%</td>
<td>47.5%</td>
<td>45.0%</td>
<td>55.0%</td>
</tr>
<tr>
<td>Tissue boundary</td>
<td>83.5%</td>
<td>82.5%</td>
<td>82.0%</td>
<td>80.0%</td>
</tr>
</tbody>
</table>

Table 4.3: Result comparison of grading annotated regions into dysplasia and non-dysplasia [20:20] between tissue texture along nuclei lining and along tissue boundary
Stage (2): feature extraction on region

CCM: Cluster co-occurrence matrices
GLCM: Gray level co-occurrence matrices
Lamina analysis

<table>
<thead>
<tr>
<th>Clusters</th>
<th>Sample Images</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td><img src="image1" alt="Clustered patches" /></td>
</tr>
<tr>
<td>C2</td>
<td><img src="image2" alt="Clustered patches" /></td>
</tr>
<tr>
<td>C3</td>
<td><img src="image3" alt="Clustered patches" /></td>
</tr>
<tr>
<td>C4</td>
<td><img src="image4" alt="Clustered patches" /></td>
</tr>
<tr>
<td>C5</td>
<td><img src="image5" alt="Clustered patches" /></td>
</tr>
</tbody>
</table>

- CCI from EXP1 and EXP2

Published in MIUA '11
Lamina analysis

Upgrade result from MIUA with 7 sets of features, binary decision tree, and colour not normalised

Published in HIMA workshop, (MICCAI '12)
Stage (2): feature extraction on region

Single tree (3 grades)

<table>
<thead>
<tr>
<th>features</th>
<th>Best Result (Accuracy %)</th>
<th>Confusion matrix</th>
</tr>
</thead>
<tbody>
<tr>
<td>FREQUENCY OF CLUSTER5</td>
<td>66.7 0.17 [0.24]</td>
<td>G1  G3  G5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>G1  5  2  1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>G3  2  3  3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>G5  0  1  7</td>
</tr>
</tbody>
</table>

**Patch features**

<table>
<thead>
<tr>
<th></th>
<th>GLCM with correlation</th>
<th>GLCM without correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>G1 vs non</td>
<td>G3 vs non</td>
</tr>
<tr>
<td></td>
<td>G1 vs non</td>
<td>G3 vs non</td>
</tr>
<tr>
<td></td>
<td>G1 vs non</td>
<td>G3 vs non</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Full CCM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CCM without correlation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(CCMWC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Full CCM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cluster frequency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Average full CCM features</td>
</tr>
<tr>
<td></td>
<td></td>
<td>over each direction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Average CCMWC over each</td>
</tr>
<tr>
<td></td>
<td></td>
<td>direction</td>
</tr>
</tbody>
</table>

**AP/KAPPA VALUE (KV)**

|                      | 75.0 0.5 [0.33]       | 75.0 [72%] 0.5          | 81.25 0.63 [0.6]        | 87.5 0.75 [0.33]  |
|                      | 75.0 0.5 [0.33]       | 75.0 [72%] 0.5          | 81.25 0.63 [0.6]        | 87.5 0.75 [0.33]  |
|                      | 75.0 0.5 [0.33]       | 75.0 [72%] 0.5          | 81.25 0.63 [0.6]        | 87.5 0.75 [0.33]  |
|                      | 75.0 0.5 [0.33]       | 75.0 [72%] 0.5          | 81.25 0.63 [0.6]        | 87.5 0.75 [0.33]  |

**Confusion matrix**

|                      | 7  1  3  5            | 6  2  2  6            | 6  2  1  7            | 8  0  2  6            | 4  4  0  8            | 7  1  3  5            |
Stage (3): extract spatial features
### Region analysis and grading

<table>
<thead>
<tr>
<th></th>
<th>Epithelial</th>
<th>Lamina</th>
<th>Spatial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selected method</strong></td>
<td>Clusters co-occurence on boundary-based line</td>
<td>Unsupervised clustering of patches, CCM &amp; freq</td>
<td>Clusters relative to boundary (3 bins)</td>
</tr>
<tr>
<td><strong>Selected parameter</strong></td>
<td>Unrotated patches, k=5, R=150, j=100, n=10, zoom=10X</td>
<td>k=5, pz=100, n=10, zoom=20X</td>
<td>Surface(&lt;200pix), far(&gt;500pix), middle</td>
</tr>
<tr>
<td><strong>Output</strong></td>
<td>classification</td>
<td>3 BDT models</td>
<td>3 BDT models</td>
</tr>
<tr>
<td><strong>Performance</strong></td>
<td>82.5% AP [Dyp vs non]</td>
<td>A7² 0.75 [0.33] A4¹ 75% [72%] A1¹ 0.63 [0.60]</td>
<td>EXP2 0.50 EXP1 68.8% EXP1 0.37</td>
</tr>
</tbody>
</table>
Stage(4): module merging

Virtual slides preprocesses & tissue detection

Region creation & feature extraction

Region grading

TreeG1

TreeG3

TreeG5
Conclusions

CONTRIBUTIONS

1. Solution for boundary effect for BO virtual slides.
   * separate method to analyse tissue around boundary

2. Texture mapping method (CCI)
   * translate regions into map of different tissue texture

3. Understand the spatial arrangement of tissue texture with reference to the epithelial layer.

OBJECTIVE ACHIEVED?

- Help identify and measure dysplasia conditions with textural and spatial features.
- High agreement score with 0.80 KV with our pathologist
Thanks to:

Dr Andrew J Bulpitt @ School of Computing, University of Leeds
Dr Darren Treanor, Consultant Pathologist @ St James’s Hospital, Leeds
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Pattern Recognition Group @ Faculty of Information Science & Technology, UKM
Center for Artificial intelligence Technology@ Universiti Kebangsaan Malaysia