Patch-based Carcinoma Detection on Confocal Laser Endomicroscopy Images - A Cross-Site Robustness Assessment

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Squamous Cell Carcinoma (SCC)

- Common kind of cancer of the epithelium
- Approx. 1.2M cases each year
  (Forastiere et al., 2001; Ferlay et al., 2014)
- Head and Neck SCC occurs e.g. in:
  - Oral Cavity
  - Vocal Cords
- Often diagnosed at late stage
  - Reduced treatment outcomes
  - Increased mortality (Muto et al., 2004)
Diagnosis of Head and Neck Squamous Cell Carcinoma

- Diagnosis (gold standard) is performed using histopathology

- Invasive, carries risks of infections and bleeding

- Problematic for intra-operative use
  - Limited sample size (Nathan et al., 2014)
  - Frozen samples —> Reduced quality
  - Associated with high stress level and effort (Agaimy et al., 2012)
Confocal Laser Endomicroscopy

- X-scanner
- Y-scanner
- Laser
- Dichroic filter
- Fiber bundle
- Photodetector

[Laemmel et al 2004]
[Cellvizio, Mauna Kea Technologies]
Impairments and Artifacts

- Motion Artifacts
- Noisy Images
- Optical Artifacts

→ Not all image parts should be used for classification.
Our data set

- Oral Cavity (OC) data set:
  - N=12 patients, all with squamous cell carcinoma
  - Recorded 3 defined locations plus lesion site.

[Aubreville et al., 2017]
CLE images of epithelial tissue of the oral cavity

Clinically normal oral cavity images

- Labial
- Hard palate
- Alveolar ridge

Verified carcinoma
Preprocessing [Aubreville et al., 2017]

- Patch extraction:
  - Coverage of large parts of the overall image
  - Reduction of network capacity to reduce overfitting

- Downscaling
  - Reduction of computational complexity
  - Reduction of noise

All code available: www5.cs.fau.de/~aubreville
Patch Classification [Aubreville et al., 2017]

- Used image labels as patch labels
- NN trained from scratch, optimized with cross-entropy / ADAM optimizer
Patch Probability Fusion  [Aubreville et al., 2017]

\[
A_{x,y}(P_i) = \begin{cases} 
1 & \text{if } (x, y) \in [c_1, c_2] \times [c_3, c_4] \\
0 & \text{else}
\end{cases}
\]

\[
PA_{x,y} = \left( \sum_i A_{x,y}(P_i) \right) \geq 1
\]

\[
PC_{x,y} = \max\left(1, \sum_i A_{x,y}(P_i) \right)
\]

\[
PM_{x,y} = PA_{x,y} \cdot PC_{x,y}^{-1} \cdot \sum A_{x,y}(P_i) \cdot p(P_i)
\]

\[
p(I) = \left( \sum_{x,y} PA_{x,y} \right)^{-1} \sum_{x,y} PM_{x,y}
\]
Transfer Learning Approach

- Backpropagation only on dense layers
- Approach is discarding image information
LOPO Cross-Validation Results

![Graph showing LOPO Cross-Validation Results with different models and their AUC values]

[Aubreville et al., 2017]
Generalization

Does the method work well on other similar data?

Does the classifier trained on our data set work on other data sets?

Test on:
Different data set, from different clinic, from different anatomy.
Squamous Cell Carcinoma (SCC) of the vocal folds

- SCC is the most prevalent form of cancer of the vocal tract (Parkin et al., 2015)

- Bright light endoscopy insufficient (high range of benign alterations) (Goncalves et al., 2017)

- Tiny structures, yet biopsies require sufficient amount of material.

- Extensive biopsy causes functional problems (Cikojevic et al., 2008)
  - chronic hoarseness
  - other voice modifications

Non-invasive diagnostic tool would significantly increase life quality
CLE images of epithelial tissue of the vocal folds

clinically normal vocal fold

verified carcinoma
Our two data sets and the respective sites

<table>
<thead>
<tr>
<th>Oral Cavity</th>
<th>Vocal Cords</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 patients</td>
<td>5 patients</td>
</tr>
<tr>
<td>116 sequences</td>
<td>73 sequences</td>
</tr>
<tr>
<td>7,879 images</td>
<td>4,425 images</td>
</tr>
</tbody>
</table>

- Epithelium similar in the vocal cords as in the oral cavity
- Different clinical crew
- Different hospital
Results (Leave 1 patient out X-Validation)

Oral Cavity

Vocal Folds

- Train: OC, Test: OC (LOPO x-val), AUC=0.9550
- Train: VC, Test: VC (LOPO x-val), AUC=0.9485
- Train: OC, Test: VC, AUC=0.9548
- Train: VC, Test: OC, AUC=0.8484
- Train: OC+VC, Test: OC+VC, AUC=0.9697
Why doesn’t generalization from VC to OC work?

- **Cornification** prevalent only in parts of OC data set

- not cornified:
  Vocal folds, inner lip, alveolar ridge \textsuperscript{(Rohen, 1994)}

- cornified:
  hard palate, outer lip \textsuperscript{(Luellmann-Rauch, 2015)}
Cornification leads to worsened SNR

- Raw pixel values are inductive of optical response
- Lower optical response leads to lower SNR
- Vocal folds data set shows generally higher median pixel values
- Restricted data set variance of VC data set hinders generalization to OC
Detection Examples
Discussion

● Questionable, if CLE alone is sufficient for assessment. (Goncalves et al., 2017, Oetter et al., 2016)
  ● Potential to overlook tumors in greater depth
  ● Combination with other optical techniques

● More CLE image data required for:
  ● clinically acceptable sensitivity/specificity rates
  ● proving generalization in a broader sense
  ● especially histo-pathologically proven healthy images required
Outlook

- Robust artifact detection in CLE images
- Acquisition of more patient data in our group
- Whole sequence analysis
Conclusions

- Sometimes optimization of preprocessing yields much higher gains than network architecture.

- Proposed method generalized well from one anatomical location to another and profited from joined data set.

- Classifiers learnt from Oral Cavity CLE data generalize well on Vocal Fold CLE data.
Thank you for listening!

Agaimy et al. (2012). Intraoperative frozen section diagnosis of head and neck tumors. DOI: 10.1007/s00292-012-1598-4

Aubreville et al. (2017). Automatic Classification of Cancerous Tissue in Laserendomicroscopy Images of the Oral Cavity using Deep Learning. DOI: 10.1038/s41598-017-12320-8

Cikojevic et al. (2008). Comparison of contact endoscopy and frozen section histopathology in the intra-operative diagnosis of laryngeal pathology. DOI: 10.1017/S0022215107000539

Ferlay et al. (2014). Cancer incidence and mortality worldwide, DOI:10.1002/ijc.29210


Muto et al. (2004). Squamous cell carcinoma in situ at oropharyngeal and hypopharyngeal mucosal sites. DOI: 10.1002/cncr.20482


Parkin et al. (2002). Global cancer statistics. PMID: 15761078
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in cooperation with: