Tissue diagnosis – is the gold standard challenged?

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Endomicroscopy

It’s not about predicting histology
It is about seeing histology
Case report
Case report
Case report
Case report
Case report
**Case report**

**Final histology:**
Moderate differentiated adenocarcinoma (Mucosal cancer – complete resected)
New clinical algorithm

Detection
In vivo diagnosis using **Endomicroscopy**
Targeted intervention

Questions
- What is the evidence of **Endomicroscopy**?
- Can we rely on in vivo histology?
- Can we avoid random biopsies?
- Can we ensure complete resection?
New imaging possibilities

Functional imaging

Molecular imaging

Local barrier dysfunction in IBD  VEGF receptors in vivo

Questions: Where are we going and what will be clinically relevant?
Endomicroscopy
Barrett’s esophagus
Barrett‘s esophagus
Key endomicroscopic features

Goblet Cell

Malignant Cell

Barrett Esophagus Multicenter trial

- 192 patients (62.2 years, Barrett length 1-10cm)
- Randomization
  High Definition (HD) WLE versus HD-WLE + Endomicroscopy

<table>
<thead>
<tr>
<th>Per patient analysis</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endomicroscopy</td>
<td>100%</td>
<td>93%</td>
<td>81%</td>
<td>100%</td>
</tr>
<tr>
<td>WLE</td>
<td>40%</td>
<td>98%</td>
<td>75%</td>
<td>90%</td>
</tr>
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Endomicroscopy: 4.8 fold reduction of biopsies
Rate of endomicroscopic guided biopsies with neoplasia: 81%
No patient with neoplasia was missed using endomicroscopy

Canto et al. DDW 2012
Gastritis and gastric cancer

**Type E**

**Sensitivity and specificity**

**Gastric atrophy**
83.6%; 99.6%

**Gastric cancer**
90.0%; 99.4%

**Type F**

Zhang et al., Gastrointest Endosc 2008
Landmark study: Gastric Cancer

Comparison of white light endoscopy and endomicroscopy (eCLE) for the diagnosis of gastric neoplasia (LGIN, HGIN, Cancer)

Li et al, Gut 2011
Landmark study

Diagnostic value of WLE and eCLE for gastric neoplasia in phase II

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Sensitivity (%,(CI))</th>
<th>Specificity (%,(CI))</th>
<th>Accuracy (%,(CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td>WLE</td>
<td>72.2 (61.9 to 82.6)</td>
<td>95.1 (94.0 to 96.2)</td>
<td>94.1 (92.9 to 95.3)</td>
</tr>
<tr>
<td>iCLE</td>
<td>88.9 (81.6 to 96.1)</td>
<td>99.3 (98.8 to 99.7)</td>
<td>98.8 (98.3 to 99.3)</td>
</tr>
<tr>
<td>p Value</td>
<td>0.012</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

eCLE can be used to identify gastric superficial cancer/HGIN lesions with high validity and reliability.

Li et al, Gut 2011

Additional study by the same group
Accuracy of eCLE for **predicting incomplete resection** was 91.7%

Ji et al, Surg Endosc 2010
Colonic Lesions: Mainz Classification

In vivo diagnosis (eCLE) of colonic neoplasia

Sensitivity: 97.4%; Specificity: 99.4%; Accuracy: 99.2%

Kiesslich et al., Gastroenterology 2004
Endomicroscopy of colorectal lesions

Endomicroscopic (eCLE) Adenoma Dysplasia Score (ADS) reliably discriminated high-grade dysplasia from low-grade dysplasia - accuracy, 96.7%.

Sanduleanu et al., Clin Gastroenterol Hepatol 2009
Endomicroscopy – in vivo Histology
Xie XJ et al. Endoscopy 2011; 43: 87–93

- Modified Mainz Classification based on 150 colonic lesions (vascular and tissue pattern)
- Accuracy: 95%
- Sensitivity: 94%
- Specificity: 96%
- Kappa: 0.93

Conclusions:
Endomicroscopy is as accurate as standard histology after mucosal biopsies (differentiation between neoplastic and non-neoplastic tissue)
Endomicroscopy versus virtual chromoendoscopy

- 75 patients with 119 polyps
- Characterization with FICE or NBI, followed by Endomicroscopy (pCLE)

<table>
<thead>
<tr>
<th></th>
<th>pCLE</th>
<th>NBI &amp; FICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>91%</td>
<td>77%</td>
</tr>
<tr>
<td>Specificity</td>
<td>76%</td>
<td>71%</td>
</tr>
</tbody>
</table>

Conclusions:
Endomicroscopy can judge colorectal lesions more accurate than virtual chromoendoscopy
Optical and dynamic imaging

**Functional imaging**

*Enteric nervous system in vivo*

**Molecular imaging**

*Local barrier dysfunction in IBD*

*VEGF and EGFR receptors in vivo*
Bacteria can induce colon cancer

Colon with exposition of Bacteroides fragilis

Colon without exposition of Bacteroides fragilis

Bacteroides fragilis toxin leads to inflammatory diarrhea and cancer

Wu et al, Nature Medicine 2009
**Egfp E. coli – Animal Study**

Single and cluster of bacteria can be identified with endomicroscopy

*Moussata et al. Gut 2011*
Mucosal Bacteria - Humans

Intramucosal bacteria can be identified in humans

Moussata et al. Gut 2011
Macrophages and processed bacteria

Patients with IBD showed more intramucosal bacteria than normal controls

Moussata et al. Gut 2011
Functional Imaging
Cell Shedding

Cell shedding is a physiologic process, which is essential to regenerate tissue.
Gaps in the gut: Acriflavine

Transient epithelial gaps occur after shedding and can be differentiated from goblet cells

Kiesslich et al. Gastroenterology 2007
Endomicroscopy – functional imaging

Endomicroscopy allows to define local barrier dysfunction in patients with IBD

Kiesslich et al. Gut 2011
Endomicroscopy can predict flares in patients with IBD

58 patients with IBD and mucosal healing based on white light endoscopy

Watson I

with

Watson II/III

without

local barrier dysfunction

Kiesslich et al. Gut 2011
Bacteria can induce barrier dysfunction

Affected epithelial cell layer (% per visible circumference)
Before and after bacterial application

Control (12)  UC (6)  CD (7)

Moussata et al. Plenary Session DDW 2010
IBD - pathogenesis

Normal villi
Normal Cell shedding

Genetic disposition in IBD
Increased Cell shedding
Bacterial translocation

Local barrier dysfunction
Micro erosions
Immunological process

Bacterial exposition

FLARE
Dual Band Endomicroscopy

Mouse Colon
Translocation of bacteria
Gut – Liver axis

Enteral enema in mouse with egfp E. coli

Kiesslich et al. unpublished data
Endomicroscopy of the liver

Hepatocytes

Small bile ducts

Goetz et al. Endoscopy 2008 & J Hepatol 2010
Endomicroscopy of the liver (mouse)

Acriflavine

Fluorescein

Goetz et al. Am J Physiol Gastrointest Liver Physiol 2011
Needle-based confocal laser endomicroscopy to assess liver histology in vivo

Rat liver
Surface and parenchyma analysis through 19G needle

Mennone, Nathanson GI Endoscopy 2012
Access to muscularis propria
Enteric nervous system

Sumiyama et al. DDW 2012
Sumiyama, Kiesslich et al. Gastroenterology 2012
Enteric nervous system
in vivo – in humans
Enteric nervous system - ganglia
Molecular Imaging
Molecular imaging

- Phase I study: Adalimumab labeled with Fluorescein
  - Topical application of marked labeled antibody in 15 patients with Crohn’s disease and indication for therapy with adalimumab
- End points: Safety and prediction of response (Decrease of CDAI of more than 100 points)
- Endomicroscopy: Identification of membranous TNF-receptor

Atreya et al. Endoscopy 2012, Gut Abstract 313
mTNF EXPRESSION IN THE LAMINA PROPRIA

ADALIMUMAB

FITC

FITC

FLUORESCENT ANTI-TNF ANTIBODY
IN VIVO MOLECULAR IMAGING IN CROHN’S DISEASE PATIENTS WITH FLUORESCENT ANTI-TNF ANTIBODIES

Field of view: 500x500µm
Invasion depth: 0-250µm
Lateral resolution: <1µm

Adapted from Prof. Ralf Kiesslich
MOLECULAR IMAGING OF mTNF+ CELLS IN VIVO
MOLECULAR IMAGING OF mTNF+ CELLS IN VIVO

High definition endoscopy

Molecular imaging in vivo

High mTNF

Low mTNF

High definition endoscopy

Molecular imaging in vivo
RESULTS OF THE STUDY

Mean CDAI score vs. Visit:

- Low mTNF group:
  - Visit 3 (0 weeks): n=13
  - Visit 4 (4 weeks): n=13
  - Visit 5 (12 weeks): n=13
  - Visit 6 (52 weeks): n=13

- High mTNF group:
  - Visit 3 (0 weeks): n=12
  - Visit 4 (4 weeks): n=12
  - Visit 5 (12 weeks): n=12
  - Visit 6 (52 weeks): n=12
Conclusions

Endomicroscopy – optical sectioning

- *Endomicroscopy provides in vivo histology* which is comparable to conventional histology of mucosal biopsies.

- *Endomicroscopy provides functional and molecular imaging.* These are new and unique features for gastrointestinal endoscopy.

- Functional imaging can be used to predict flares in IBD and it will help us to further clarify the pathophysiologic changes of IBD.

- Motility disorders will be better characterized.

- Molecular imaging using in vivo endomicroscopy can differentiate gastrointestinal cancers based on their molecular signatures. These information might be used in the future to better detect early malignant changes, to define new treatment algorithms and to better refine follow-up intervals.
Thank you for your kind attention