Detection of dysplasia in ulcerative colitis

Markus Neurath
Ulcerative colitis

Risk factors for cancer: duration of disease, flares, PSC
- High frequency of steroid-dependent or refractory cases
- Complications of UC:
  Bleedings, intraepithelial Neoplasia (IN), Cancer

Neurath et al. Chirurg 2000
Clinical situation

2% CaC after 10 years of disease
9% after 20 years
19% after 30 years
32% after 45 years

Intraepithelial neoplasia

Cancer

Eaden et al. Gastroenterology 1999
The problem of flat lesions in endoscopy

Murine model of colitis associated cancer (AOM/DSS)

Improvements in endoscopy: Magnification

Hyperplasia  Adenoma
Crypt Architecture Analysis

Non-Neoplastic

Neoplastic (Targeted biopsies)

Kudo et al. Gastrointest Endosc 1996
High-grade IN
Detection of the margins of lesions
Colitis associated cancer
Methylene blue aided chromoendoscopy for the detection of intraepithelial neoplasia in ulcerative colitis

<table>
<thead>
<tr>
<th></th>
<th>Chromo</th>
<th>Conv. Colonoscopy</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>84</td>
<td>81</td>
</tr>
<tr>
<td>Patients with IN</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td><strong>Number of IN</strong>*</td>
<td>32</td>
<td>10</td>
</tr>
<tr>
<td>LGI N</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td>HGI N</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Cancer</td>
<td>3</td>
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</tr>
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<td>Polypoid IN</td>
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<td><strong>IN in „flat mucosa“</strong>*</td>
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*significant; Fisher’s exact test

*Methylene blue aided chromoendoscopy for the detection of intraepithelial neoplasia in ulcerative colitis*

Kiesslich et al. Gastroentrology 2003
# Chromoendoscopy in UC

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*Kiesslich et al. Gastroenterology 2003*

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<tbody>
<tr>
<td>N</td>
<td>162</td>
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</tr>
<tr>
<td>Number of IN</td>
<td>42</td>
<td>11</td>
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</table>

*Hurlstone et al. Gastroenterology 2004*

**Back to back colonoscopy (n=100)**

Chromo versus conventional colonoscopy

2 IN versus 9 IN  (4.5 fold increase)  

*Rutter et al. Gut 2004*
Chromoendoscopy dangerous?

Lancet 2003

Chromoendoscopy with methylene blue and associated DNA damage in Barrett’s oesophagus
J R Olliver, C P Wild, P Sahay, S Dexter, L J Hardie
RESEARCH LETTERS

However, concerns about the safety of methylene blue staining have been raised recently suggesting that this dye may cause genotoxic effects driving carcinogenesis.

Problems:
- High dose of methylene blue
- No control group
- Upper and not lower GI
# Safety of methylene blue

**Initial Study:** Kiesslich et al. Gastroenterology 2003

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**Current Study**

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<tbody>
<tr>
<td>Expected</td>
<td>75</td>
<td>71</td>
</tr>
<tr>
<td>Lost in follow-up</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Final Analyzed</td>
<td>71</td>
<td>68</td>
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</table>
## Results

**Median Follow-up: 29 months**

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<tr>
<td>Total No. of INs</td>
<td>16*</td>
<td>2</td>
</tr>
<tr>
<td>Low-grade INs</td>
<td>11*</td>
<td>2</td>
</tr>
<tr>
<td>High-grade INs</td>
<td>5*</td>
<td>0</td>
</tr>
<tr>
<td>Polypoide INs</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Flat INs</td>
<td>12*</td>
<td>1</td>
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*significant; Fisher's exact test
Results

- **Total time for colonoscopy:**
  - Chromoendoscopy: 29.7 min.
  - Conventional Endoscopy: 26.4 min
  \[ p \geq 0.05 \]

- **Biopsies:**
  - Chromoendoscopy: 21.4 per pat.
  - Conventional Endoscopy: 39.1 per pat.
  \[ p = 0.039 \]

*Kiesslich et al., DDW 2004*
How should chromoendoscopy be done?
SURFACE-Guidelines

- Strict patients selection
- Unmask the mucosal surface
- Reduce peristaltic waves
- Full length staining of the colon
- Augmented detection with dyes
- Crypt architecture analysis
- Endoscopic targeted biopsies

Kiesslich, Neurath Gut 2004
Pit Pattern Classification

Surface pattern as a prediction of dysplasia:

- Sensitivity: 93%
- Specificity: 93%
- Pos. pred. value: 83%
- Neg. pred. value: 98%
Recent studies indicate that chromoendoscopy can greatly enhance the endoscopic detection of dysplastic lesions in colitic colons.

The Committee endorses the incorporation of chromoendoscopy into surveillance colonoscopy for appropriately trained endoscopists.

We hope that the development of newer techniques will further refine our current surveillance recommendations and our understanding of the natural history of dysplasia.
Endomicroscope: in vivo histology

Joint venture: Pentax, Japan & Optiscan, Australia
Confocal Laser Endomicroscopy

Normal Endoscopy
- ~ 30X
- No microscopic details

Zoom Endoscopy
- ~100X
- Crypts visible, but no details

Confocal Endoscopy
- ~1000X
- Cellular resolution of crypts
Technique

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

Fluorescein 5ml; 10%; i.v.
Image Acquisition
Instrument ID: 225501
Software Version No.: 1.9.0

Depth
Set Depth Datum

Gamma Control
Low Light
High Light
1.00

Min ▼ Mid ► Max

Brightness Control
Min ▼ Mid ► Max

0.51

Laser Control
Laser Beam
497μW

Off ▼ Mid ► Max

Subject:
Current Procedure: Fluorescent imaging
Total # Images: 0
# Images for this Site: 0

Acquisition Control
Acquisition Mode: Single

Pause Change Mode Capture

Site Control
30cm

<< Previous Next ► Modify Site List

Scan Mode Control
1024x1024 500x500 um

<< Slower Faster ►

Back Next Exit
Analysis of single cells
In vivo versus ex vivo histology

Kiesslich et al., Gastroenterology 2004
Inflammation in UC
Ulcerative colitis
Hypervascularization
Severe inflammation in UC
Aberrant Crypt Foci
Intraepithelial Neoplasia
Intraepithelial neoplasia
Hyperplastic lesion
Colon Cancer
Confocal Pattern Classification

Vessels

Crypts

Normal

Regeneration

Neoplasia

Prediction of Neoplasia
Sensitivity: 97.4%; Specificity: 99.4%; Accuracy: 99.2%

Kiesslich et. al Gastroenterology 2004
Chromo & Confocal Endoscopy

Does *chromoendoscopy* in conjunction with *confocal endomicroscopy* facilitate early detection and in vivo diagnosis of *neoplasias in ulcerative colitis*?
## Results

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<td>73</td>
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Results

134 circumscript lesions (outside from severe inflammatory changes); 5580 confocal images compared with 311 biopsies.

Correlation between confocal imaging and histology

<table>
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<tr>
<th>Confocal</th>
<th>Histology</th>
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<tbody>
<tr>
<td>sites</td>
<td>Non-Neoplastic</td>
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<td>Neoplastic</td>
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Sensitivity: 94.7%; Specificity: 98.3%; Accuracy: 97.8%

Kiesslich et al., DDW 2005, Plenary Session
Results

Examination time:
- Conventional Endoscopy: 31 minutes [range 18-48]
- Confocal laser endomicroscopy: 42 minutes [range 29-64]

Number of biopsies:
- Conventional endoscopy with random biopsies:
  - 42.2 Bx per patient
- Confocal laser endomicroscopy with targeted biopsies:
  - 21.2* Bx per patient (total)
  - 3.9* Bx per patient (with suspicious in vivo architecture)

*significant; Fisher’s exact test

Kiesslich et al., DDW 2005, Plenary Session
Conclusions

• Chromoendoscopy unmasks circumscribed lesions in UC and helps to recognize dysplastic areas.
• The newly discovered diagnostic tool of high-resolution endomicroscopy enables *in vivo* histology.
• Confocal laser microscopy in ulcerative colitis detects intraepithelial neoplasias with high accuracy.
• “Smart” biopsies can be restricted to relevant lesions.
• These newly combined techniques may lead to significant improvements in cancer surveillance of patients with ulcerative colitis.
REvolution in Endoscopy