Barrett‘s Esophagus and Early Neoplasia – Management in 2019

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St. John of God Hospital Regensburg, Germany
Conflict of interests

Speaker honorarium from Olympus, Fujifilm, Medtronic, Norgine, BMS, Boston Scientific, Cook

Advisory Board
Cook, Boston Scientific
Detection of Early Lesions in Barrett‘s esophagus

- Early neoplastic lesions in Barrett‘s esophagus are often very subtle and hard to detect

- In daily practice most endoscopist hardly see patients with early Barrett‘s neoplasia and
Basic principles of endoscopic detection of early lesions

1. Take your time
2. Take your best endoscope
3. Inspect carefully
4. Look for subtle abnormalities
5. Biopsy even subtle abnormalities
6. If in doubt take it out
Improving detection of neoplasia in Barrett’s esophagus – The BORN Project

CLINICAL—ALIMENTARY TRACT

An Interactive Web-Based Educational Tool Improves Detection and Delineation of Barrett’s Esophagus–Related Neoplasia


http://best-academia.eu/imaging
Improving detection of neoplasia in Barrett’s esophagus – The BORN Project

- Multi-step validation in >200 endoscopists in 5 countries
- 25 videos in 4 batches; mandatory feedback after each batch
  - Was your biopsy correct?
  - How much of the lesion did you delineate?
  - How close were you to being an expert?

<table>
<thead>
<tr>
<th></th>
<th>Batch 1</th>
<th>Batch 2</th>
<th>Batch 3</th>
<th>Batch 4</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection score (%)</td>
<td>70%</td>
<td>85%</td>
<td>88%</td>
<td>88%</td>
<td>P&lt;.0001</td>
</tr>
<tr>
<td>Delineation score (%)</td>
<td>44%</td>
<td>69%</td>
<td>73%</td>
<td>78%</td>
<td>P&lt;.0001</td>
</tr>
<tr>
<td>Expert agreement score (%)</td>
<td>49%</td>
<td>73%</td>
<td>76%</td>
<td>82%</td>
<td>P&lt;.0001</td>
</tr>
</tbody>
</table>
Diagnosis of Barrett's neoplasia

Gupta et al, Gastrointestinal Endoscopy 2013
## Performance measures for upper gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy (ESGE) Quality Improvement Initiative

### Authors
Raf Bisschops¹, Miguel Areia²,³, Emmanuel Coron⁴, Daniela Dobru⁵, Bernd Kaskas⁶, Roman Kuvaev⁷, Oliver Pech⁸, Krish Ragunath⁹, Bas Weusten¹⁰, Pietro Familiari¹¹, Dirk Domagk¹², Roland Valori¹³, Michal F. Kaminski¹⁴,¹⁵, Cristiano Spada¹¹, Michael Bretthauer¹⁴,¹⁶, Cathy Bennett¹⁷, Carlo Senore¹⁸, Mário Dinis-Ribeiro³,¹⁹, Matthew D. Rutter²⁰,²¹

<table>
<thead>
<tr>
<th>Key performance measures</th>
<th>Minor performance measures</th>
</tr>
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<tbody>
<tr>
<td>Fasting instructions prior to UGI endoscopy</td>
<td>Minimum 7-minute procedure time for first diagnostic UGI endoscopy and follow-up of gastric intestinal metaplasia</td>
</tr>
<tr>
<td>Documentation of procedure duration</td>
<td>Minimum 1-minute inspection time per cm circumferential Barrett’s epithelium</td>
</tr>
<tr>
<td>Accurate photodocumentation of anatomical landmarks and abnormal findings</td>
<td>Use of Lugol chromoendoscopy in patients with a curatively treated ENT or lung cancer to exclude a second primary esophageal cancer</td>
</tr>
<tr>
<td>Accurate application of standardized disease-related terminology</td>
<td>Application of validated biopsy protocol to detect gastric intestinal metaplasia (MAPS guidelines)</td>
</tr>
<tr>
<td>Application of Seattle protocol in Barrett’s surveillance</td>
<td>Prospective registration of Barrett’s patients</td>
</tr>
<tr>
<td>Accurate registration of complications after therapeutic UGI endoscopy</td>
<td></td>
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</tbody>
</table>
Where to look in Barrett’s esophagus?

Pech et al., Endoscopy 2007
(Virtual) Chromoendoscopy
Acetic Acid Staining
Diagnosis of Barrett’s neoplasia

Acetic Acid 1.5%
Acetic Acid Chromoendoscopy

Coletta et al, Gastrointestinal Endoscopy 2016
Meta-Analysis of 13 prospective studies with 1690 patients

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Unit of analysis</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
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<tbody>
<tr>
<td>Mayinger 2006</td>
<td>11</td>
<td>12</td>
<td>4</td>
<td>171</td>
<td>Area</td>
<td>0.73 [0.45, 0.92]</td>
<td>0.93 [0.89, 0.97]</td>
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<td>Reaud 2006</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>65</td>
<td>Area</td>
<td>0.50 [0.12, 0.88]</td>
<td>0.98 [0.92, 1.00]</td>
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<tr>
<td>Yagi 2006</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>110</td>
<td>Area</td>
<td>1.00 [0.48, 1.00]</td>
<td>1.00 [0.97, 1.00]</td>
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<td></td>
</tr>
<tr>
<td>Fortun 2006</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>60</td>
<td>Area</td>
<td>1.00 [0.40, 1.00]</td>
<td>1.00 [0.94, 1.00]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pohl 2007</td>
<td>21</td>
<td>0</td>
<td>3</td>
<td>33</td>
<td>Patient</td>
<td>0.88 [0.68, 0.97]</td>
<td>1.00 [0.89, 1.00]</td>
<td></td>
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</tr>
<tr>
<td>Pohl 2010</td>
<td>89</td>
<td>204</td>
<td>3</td>
<td>405</td>
<td>Patient</td>
<td>0.97 [0.91, 0.99]</td>
<td>0.67 [0.63, 0.70]</td>
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<tr>
<td>Vasquez-Iglesias 2007</td>
<td>13</td>
<td>2</td>
<td>0</td>
<td>85</td>
<td>Patient</td>
<td>1.00 [0.75, 1.00]</td>
<td>0.98 [0.92, 1.00]</td>
<td></td>
<td></td>
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<tr>
<td>Bhandari 2012</td>
<td>161</td>
<td>24</td>
<td>5</td>
<td>73</td>
<td>Procedure</td>
<td>0.97 [0.93, 0.99]</td>
<td>0.75 [0.65, 0.83]</td>
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<tr>
<td>Longcroft-Wheaton 2010</td>
<td>70</td>
<td>34</td>
<td>2</td>
<td>84</td>
<td>Procedure</td>
<td>0.97 [0.90, 1.00]</td>
<td>0.71 [0.62, 0.79]</td>
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</table>

Sensitivity 92%, Specificity 96% for HGD/IMC
# The new PREDICT Classification

<table>
<thead>
<tr>
<th>Morphological Features</th>
<th>Classification</th>
<th>Barrett’s diagnosis</th>
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</thead>
<tbody>
<tr>
<td><strong>Acetowhiteness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No focal loss of acetowhiteness</td>
<td>Absent</td>
<td>Non-neoplastic</td>
</tr>
<tr>
<td>Focal loss of acetowhiteness</td>
<td>Present</td>
<td>Neoplastic</td>
</tr>
<tr>
<td><strong>Surface Pattern</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uniform evenly spaced pits with normal pit density</td>
<td>Normal</td>
<td>Non-neoplastic</td>
</tr>
<tr>
<td>Compactly packed small pits with increased pit density</td>
<td>Abnormal</td>
<td>Neoplastic</td>
</tr>
<tr>
<td>Focal irregularity or disorganized pits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent pit pattern</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Kadiah K, … Pech O, Bhandari P. Gut 2018
### The new PREDICT Classification

<table>
<thead>
<tr>
<th>Images &amp; Videos</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
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<tbody>
<tr>
<td><strong>Endoscopists</strong></td>
<td><img src="#" alt="Table" /></td>
<td><img src="#" alt="Table" /></td>
<td><img src="#" alt="Table" /></td>
<td><img src="#" alt="Table" /></td>
<td><img src="#" alt="Table" /></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>79.3% (299/377)</td>
<td>78.4% (316/403)</td>
<td>77.5% (299/386)</td>
<td>80.2% (316/394)</td>
<td>78.9% (615/780)</td>
</tr>
<tr>
<td>Specificity</td>
<td>98.1% (370/377)</td>
<td>65.5% (264/403)</td>
<td>72.7% (370/509)</td>
<td>97.4% (264/271)</td>
<td>81.3% (634/780)</td>
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<tr>
<td>PPV</td>
<td>18.8% (14.7%, 23.0%)</td>
<td>-12.9% (-19.0%, -6.8%)</td>
<td>-4.8% (-10.4%, 0.9%)</td>
<td>17.2% (12.8%, 21.6%)</td>
<td>2.4% (-1.7%, 6.5%)</td>
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<tr>
<td>NPV</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.10</td>
<td>&lt;0.001</td>
<td>0.25</td>
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<tr>
<td><strong>Nurses</strong></td>
<td><img src="#" alt="Table" /></td>
<td><img src="#" alt="Table" /></td>
<td><img src="#" alt="Table" /></td>
<td><img src="#" alt="Table" /></td>
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</tr>
<tr>
<td>Sensitivity</td>
<td>69.6% (119/171)</td>
<td>84.7% (160/189)</td>
<td>80.4% (119/148)</td>
<td>75.5% (160/212)</td>
<td>77.5% (279/360)</td>
</tr>
<tr>
<td>Specificity</td>
<td>95.9% (164/171)</td>
<td>88.9% (168/189)</td>
<td>88.7% (164/185)</td>
<td>96.0% (168/175)</td>
<td>92.2% (332/360)</td>
</tr>
<tr>
<td>PPV</td>
<td>26.3% (18.9%, 33.8%)</td>
<td>4.2% (-2.5%, 11.0%)</td>
<td>8.2% (0.7%, 15.8%)</td>
<td>20.5% (14.3%, 26.8%)</td>
<td>14.7% (9.5%, 19.9%)</td>
</tr>
<tr>
<td>NPV</td>
<td>&lt;0.001</td>
<td>0.22</td>
<td>0.03</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Accuracy</td>
<td>&lt;0.001</td>
<td>0.03</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Kadiah K,…Pech O, Bhandari P. Gut 2018
Other sampling methods will be available using AI

- Computer Analysis presents to the pathologist a 3D Image Synthesized from Multiple 1μ Optical Slices.
- 100 areas/sample in the 3D display image are highlighted for the pathologist by the neural network.
WATS3D : Randomized prospective trial

- The addition of WATS to biopsy yielded an additional 23 cases of HGD/EAC in comparison to Seattle protocol (absolute increase, 14.4%; 95% CI, 7.5%-21.2%).

- Among these 23 patients, 11 were classified by biopsy as NDBE, 12 as LGD/IND

- WATS added average of 4.5 minutes to the procedure.

Vennalaganti et al GIE. 2018 Feb;87(2):348-355
Low grade dysplasia – a difficult diagnosis

293 patients with LGD referred to the Dutch Barrett’s Advisory Committee

- Review BAC expert pathologists
- Confirmation in 27%
- Downstaging in 73%
  (40 to IND and 174 to no dysplasia)

Median follow-up 39 months

LGD: 27% progression rate
IND/no dysplasia: 2% progression rate

Incidence rate 9.1% per patient year

Duits et al, Gut 2015
SURF-Study– Prospective, randomized European multicenter study
RFA vs Surveillance

136 patients with LGD

RFA

CR LGD 98%

Progression to HGD/mAC 1.5%

Randomization

Follow-up

CR LGD 37%

Progression to HGD/mAC 25%

Follow-up 21 months

Phoa et al, JAMA 2014
Indication for Endoscopic Treatment of Barrett's neoplasia

Barrett's adenocarcinoma

<table>
<thead>
<tr>
<th>T1m1-4</th>
<th>T1sm1</th>
<th>T1sm2-3</th>
</tr>
</thead>
</table>

LN-Risk: <1%  0-10%  20-50%

Further Risk Factors for lymph node metastasis:
- lymph vessel infiltration (L1), Odds Ratio 3.83 – 7.00 ¹-³
- blood vessel infiltration (V1), Odds Ratio 3.02 ¹,²
- poorly differentiated carcinoma (G3) Odds Ratio 3.19 ¹,²
- high tumor cell dissociation (TCD3) Odds Ratio 1.07 ⁴
- Tumor size (>20mm) Odds Ratio 4.47 ³

¹ Eguchi et al, Mod Pathol 2006
² Chibana et al, J Gastro Hepatol 2005
³ Kim et al, J Gastroenterol Hepatol 2008
⁴ Tajima et al, Cancer 2000
Endoscopic Resection of Intramucosal Adenocarcinoma

Inclusion October 1996 to December 2010

1000 patients with intramucosal adenocarcinoma

2687 EMR  2.5 resections/patient

Complete remission 96.3%

Recurrence 14.5%

Re-Treatment

Long-term complete remission 93.8%

FU 55 months

Pech et al., Gastroenterology 2014
Endoscopic Resection of Intramucosal Adenocarcinoma

Inclusion October 1996 to December 2010

1000 patients with intramucosal adenocarcinoma

2687 EMR → 2.5 resections/patient

Complete remission 96.3%

Recurrence 14.5%

Re-Treatment

Long-term complete remission 93.8%

Long-Segment-BE 52%

Last 5 years: Recurrence rate 4.3%

FU 55 months

Pech et al., Gastroenterology 2014
2-Step-Strategy (EURO II-Study)

132
patients with HGD and early BC (C3M6)

Step 1: ER of all visible lesions

Step 2: RFA of remaining BE

Complete remission (per protocol)
Neoplasia: 98%
Barrett’s esophagus: 93%

5 treatment failures

13 European Centers

5 recurrences of HGIN/BC
→ Successful endoscopic treatment

25 months FU

3.8%

Phoa, Pouw, Bisschops, Pech et al, Gut 2015
ESD or not ESD – That is the question
## ESD in early Barrett’s cancer?

<table>
<thead>
<tr>
<th></th>
<th>Düsseldorf</th>
<th>Augsburg</th>
<th>Brussels</th>
<th>Hamburg</th>
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<tbody>
<tr>
<td>Patients (N)</td>
<td>30</td>
<td>87</td>
<td>75</td>
<td>22</td>
</tr>
<tr>
<td>Histology</td>
<td>6 HGIN/24 MC</td>
<td>73 MC/14 SMC</td>
<td>68 MC/7 SMC</td>
<td>20 MC/2 SMC</td>
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<tr>
<td>Barrett length</td>
<td>C0 M2</td>
<td>C2.3 M3.8</td>
<td>C2.5 M6</td>
<td>--</td>
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<tr>
<td>R0</td>
<td>38.5%</td>
<td>73.6%</td>
<td>56%</td>
<td>77.3%</td>
</tr>
<tr>
<td>CR-Neo</td>
<td>96.4%</td>
<td>76.7%</td>
<td>92%</td>
<td>94.6%</td>
</tr>
<tr>
<td>Follow-up</td>
<td>17 months</td>
<td>24.3 months</td>
<td>20 months</td>
<td>19 months</td>
</tr>
<tr>
<td>Recurrence</td>
<td>0%</td>
<td>5%</td>
<td>10%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Strictures</td>
<td>0%</td>
<td>9.1%</td>
<td>60%</td>
<td>13.6%</td>
</tr>
</tbody>
</table>

ESD in early Barrett’s cancer?

40 patients with HGIN and early Barrett’s cancer

EMR (n=20)  
R0-resection  
3/20  
CR neoplasia  
16/17

Randomisierung

ESD (n=20)  
R0 resection  
20/20  
CR nepoplasia  
16/16

Tergeggen et al, Gut 2016
ESD

Patienten-ID: 
Patientenname:

Geschlecht: Alter: 
Geburtsdatum: 
27/11/2018 
12:59:21 

CVP:273 

■■■/---(0/1) 
Eh:A3 Cm:1 

Kommentar:
Conclusions

• Thorough inspection of the Barrett’s segment with (virtual) chromoendoscopy is mandatory

• Acetic acid is the ideal „red flag“-technique and should be used

• In case of LGD 2nd opinion by an experienced GI pathologist should be obtained

• ER followed by radiofrequency ablation is the treatment of choice

• ESD should be performed in patients with large bulky lesions and suspicion for submucosal invasion
Thank You!

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