Early Neoplasms of the Stomach

*Diagnosis and endoscopic therapy*

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University Medical Center Mainz, Germany
Case Presentation 1

• 32 year old patient with *dyspepsia*

• Outpatient gastroscopy in March 2012

• Macroscopic findings: inconspicuous

• But histology of *routine* biopsies from the *corpus*:
  "Detection of a signet ring cell carcinoma"
Case Presentation 1

• Presentation in our clinic on 26.3.2012

• Investigations carried out
  – Gastroscopy with Endomicroscopy
  – Endoscopic ultrasonography
  – Abdominal ultrasound
  – CT abdomen
Final histology of serial biopsies and resected EMR

- Inconspicuous gastric mucosa
- Immunohistology without pathological findings
Endomicroscopy and EMR 26.3.2012

Normal gastric mucosa

Suspected signet ring cell carcinoma

EMR

Final histology of serial biopsies and resected EMR
- Inconspicuous gastric mucosa
- Immunohistology without pathological findings

Genetic analysis of the positive sample and the new negative sampling:
identical genetic profile (exclusion of confusion)
Case Presentation 1

• Presentation in our clinic on 26.3.2012

• Investigations carried out
  – Gastroscopy with Endomicroscopy
  – Endoscopic ultrasonography (normal)
  – Abdominal ultrasound (normal)
  – CT abdomen (normal)
Question

What is your next procedure?

1. Surgery
   1. Subtotal gastrectomy
   2. Total gastrectomy
2. Endoscopic surveillance
3. Watch and Wait
Tumor-Board Presentation

• **Tumor-Board:**
  Recommendation for total gastrectomy

• **Expert gastroenterologist’s opinion:**
  Regular endoscopic surveillance with Mapping

• **Discussion with the patient**
  Decision for monitoring strategy
Literature for Biopsy Carcinoma

22 Patients – Treatment with photodynamic therapy

Diagnostic assessment of invisible gastric cancer
- Reference histology
- Two upper gastrointestinal endoscopies (HR-videoendoscopy and chromoendoscopy with indigo carmine)
- Endoscopic ultrasond (conventional EUS and 20 MHz miniprobe)

Invisible gastric cancer

ALA-PDT

Follow-up program after ALA-PDT
- HR-videoendoscopy and chromoendoscopy with indigo carmine
  - Year 1 to 2: every 3 months
  - Year 3 to 5: every 6 months
  - Year 6 to 10: every 12 months

- Endoscopic ultrasond (conventional EUS and 20 MHz miniprobe)
  - Year 1 to 5: every 6 months
  - Year 6 to 10: every 12 months

- CT-scan and sonography of the abdomen
  - Year 1 to 5: every 6 months
  - Year 6 to 10: every 12 months
Literature for Biopsy Carcinoma

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Invisible gastric cancer

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  - Year 3 to 5: every 6 months
  - Year 6 to 10: every 12 months
- Endoscopic ultrasonds (conventional EUS and 20 MHz miniprobe)
  - Year 1 to 5: every 6 months
  - Year 6 to 10: every 12 months
- CT-scan and sonography of the abdomen
  - Year 1 to 5: every 6 months
  - Year 6 to 10: every 12 months

Results: 18/22 (82%) without recurrence (Follow-up 56 months)
Endoscopic Mapping

Endoscopies
> 6 months

April 2012
June 2012
September 2012

all normal and inconspicuous
Renewed Gastroscopy on 6.11.12

• Macroscopically inconspicuous gastroscopy

• Histology in the antrum area with detection of individual glands with signet ring cell type differentiation
Renewed Gastroscopy on 6.11.12

Histology
Question

- What is your next procedure?
  1. Surgery
  2. Endoscopic surveillance
  3. Watch and Wait
Total Gastrectomy on 3.12.12

Total gastrectomy on 03.12.12

• No evidence of a signet ring cell carcinoma

Final histology including the endoscopic diagnosis

• \( pT1aNo \ (0/13) \) M0, R0
Summary  Case 1

• The biopsy carcinoma is a rare entity with good prognosis.

• The endoscopic surveillance using modern endoscopy techniques is an effective option.

• For renewed carcinoma detection in macroscopically inconspicuous mucosa or multifocal infections, gastrectomy is recommended (especially with signet ring cell type differentiation).
Early Neoplasms of the Stomach

*Diagnosis and endoscopic therapy*
4 open Questions

• Do we sufficiently recognize early gastric cancers?
• What is the best diagnostic strategy?
• What should be treated endoscopically (EMR versus ESD)?
• How good are the clinical results?
Do we recognize early gastric cancers?
What is the best diagnostic strategy?
What should be treated endoscopically?
(EMR versus ESD)
How good are the clinical results?

HD Endoscopy
Virtual Chromo endoscopy

Endomicroscopy or endosonography (EUS)

EMR/ESD

Final Histology;
Moderately differentiated adeno carcinoma
(Mucosal cancer – complete resection)

Recognize
In vivo diagnosis
Targeted intervention
4 open Questions

• Do we sufficiently recognize early gastric cancers?
• What is the best diagnostic strategy?
• What should be treated endoscopically (EMR versus ESD)?
• How good are the clinical results?
4 open Questions

• Do we sufficiently recognize early gastric cancers?
• What is the best diagnostic strategy?
• What should be treated endoscopically (EMR versus ESD)?
• How good are the clinical results?
INCIDENCE OF GASTRIC CARCINOMA
Early Gastric Cancer
Proportion of early gastric cancer

Early Gastric Cancer in Japan: 40-50%, 10,000 ca/year

Kojima 1998

Early gastric cancers account for only 5-10% in Europe

Sandler 2000
Overlooked carcinomas

Evaluation of 36,577 endoscopy findings, UK
Overlooked carcinomas (up to 5 years after gastroscopy)
Overlooked carcinomas

Evaluation of 36,577 endoscopy findings, UK

Overlooked carcinomas (up to 5 years after gastroscopy)

- 524 cancers, 20% overlooked:
  - 37% esophageal carcinoma, 63% gastric carcinoma
  - 40% gastroscopy 3-12 months ago, 31% 1-3 years ago, 29% 3-5 years ago

Cheung et al. DDW 2013, Abstract Tu1268
Overlooked carcinomas

Evaluation of 36,577 endoscopy findings, UK

Overlooked carcinomas (up to 5 years after gastroscopy)

- 524 cancers, 20% overlooked:
  - 37% esophageal carcinoma, 63% gastric carcinoma
  - 40% gastroscopy 3-12 months ago, 31% 1-3 years ago, 29% 3-5 years ago

In 30% of the most overlooked carcinomas:

  Abnormalities at the site seen before,
  but not biopsied or no tumor suspicious histology.

Cheung et al. DDW 2013, Abstract Tu1268
4 open Questions

• Do we sufficiently recognize early gastric cancers?
• What is the best diagnostic strategy?
• What should be treated endoscopically (EMR versus ESD)?
• How good are the clinical results?
ADVANCED ENDOSCOPIC DIAGNOSIS
Endoscopic Diagnosis

chromo endoscopy
Endoscopic Diagnosis

chromo endoscopy
Endoscopic Diagnosis

(virtual)
chromo endoscopy

<table>
<thead>
<tr>
<th>Type</th>
<th>Macroscopic appearance</th>
<th>Rate of submucosal invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protruded type</td>
<td>Ip</td>
<td>Pedunculated</td>
</tr>
<tr>
<td></td>
<td>Ips</td>
<td>Subpedunculated</td>
</tr>
<tr>
<td></td>
<td>Is</td>
<td>Sessile</td>
</tr>
<tr>
<td>Flat type</td>
<td>Ib</td>
<td>Flat</td>
</tr>
<tr>
<td></td>
<td>IIb</td>
<td>Flat-elevated</td>
</tr>
<tr>
<td></td>
<td>IIa + IIc</td>
<td>Flat-elevated with depression</td>
</tr>
<tr>
<td>Depressed type</td>
<td>IIc</td>
<td>Slightly depressed</td>
</tr>
<tr>
<td></td>
<td>IIc + IIa</td>
<td>Low risk of submucosal invasion</td>
</tr>
</tbody>
</table>

Lambert et al, Endoscopy 2002
Early Gastric Cancer: Narrow-band imaging (NBI)

- Conventional white light
  - White light is composed of an equal mixture of RGB wavelengths
  - Degree of light intensity vs. Wavelength (nm)

- Narrow band imaging
  - The narrow band light is composed of two specific bands that are strongly absorbed by hemoglobin
  - Degree of light absorption vs. Wavelength (nm)

- Short wavelengths have shallow penetration characteristics, whereas long wavelengths penetrate deeper into the mucosa
- 415 nm light: Short wavelengths penetrate only the superficial layers of the mucosa
- 540 nm light: Longer wavelengths penetrate deeper compared with 415 nm light

Absorbed by capillary vessels in the surface layer of mucosa

Moehler ESMO 2015
Early Gastric Cancer: Narrow-band imaging (NBI)

Early Gastric Cancer: NBI

- 1,353 patients after endoscopic therapy of early gastric cancer has taken place - Follow-up
- Randomized trial: NBI with magnification (M-NBI) versus white light endoscopy (C-WLI)

<table>
<thead>
<tr>
<th>Group</th>
<th>Test method</th>
<th>Accuracy [95% C.I.]</th>
<th>Sensitivity [95% C.I.]</th>
<th>Specificity [95% C.I.]</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-NBI</td>
<td>M-NBI</td>
<td>0.90 [0.85-0.94]*</td>
<td>0.60 [0.36-0.81]</td>
<td>0.94 [0.89-0.97]*</td>
</tr>
<tr>
<td>C-WLI</td>
<td>C-WLI</td>
<td>0.65 [0.57-0.72]</td>
<td>0.40 [0.19-0.64]</td>
<td>0.68 [0.60-0.75]</td>
</tr>
<tr>
<td>C-WLI+M-NBI</td>
<td>C-WLI+M-NBI</td>
<td>0.97 [0.94-0.99]**</td>
<td>0.95 [0.93-0.99]**</td>
<td>0.97 [0.93-0.99]**</td>
</tr>
</tbody>
</table>

Rating: NBI is now according to this study established standard in Japan for the detection and characterization of early gastric cancer
Endomicroscopy

Confocal laser endomicroscopy and endocytoscopy permit high-resolution assessment of gastrointestinal mucosal histology at a cellular and sub-cellular levels.
...based upon **illuminating a tissue with a low-power laser** and then **detecting fluorescent light reflected from the tissue**.

The laser is **focused at a specific depth** and only light reflected back from that plane is refocused and able to pass through the pinhole confocal aperture.

The area is scanned in the horizontal and vertical planes and an image is reconstructed.
Endomicroscopy

...expands the imaging capabilities of flexible endoscopy by their ability to obtain "optical biopsies" of accessible endoluminal surfaces.

The examinations are carried out in vivo with real-time image display.
Intestinal metaplasia
83.6%; 99.6%

Neoplasia
90.0%; 99.4%

Zhang et al., Gastrointest Endosc 2008
4 open Questions

• Do we sufficiently recognize early gastric cancers?
• What is the best diagnostic strategy?
• What should be treated endoscopically (EMR versus ESD)?
• How good are the clinical results?
CLASSIFICATION OF EARLY CARCINOMA
TNM: Early Carcinoma

Soetinko R et al, J Clin Oncol 2000
Risk of Metastasis

Early gastric cancer:

Limited to the mucosa and submucosa, regardless of the lymph node involvement or areal extent (stage IA/B UICC)

Lymph node metastasis in mucosal type: 0-3%
Lymph node metastasis in submucosal type: 4-20%
Risk of Metastasis

Lymph node regions

Kompartiment I
Perigastric LN (1-6)

Kompartiment II
Truncus coeliacus (7-12)

Kompartiment III
Paraaortal LN (>12)
retropancreatic,
mesenterial LN
Endosono EUS

1. Radial Scanner
2. Longitudinal Scanner (+FNA)
Endosono EUS
Endosono EUS

Eintrittsreflex
Mukosa
Submukosa
Muskularis
Serosa

5-7,5 MHz
Endosono EUS

EUS is complementary to CTscan for patient selection before *perioperative therapy*.

Moehler et al. Gastric Cancer 2014
CRITERIA OF ENDOSCOOPIC THERAPY
Endoscopic Mucosal Resection (EMR)

Classical criteria

- Mucosal carcinomas
- Sublime, flat and slightly sunken tumors
- Paris Type II A-B, tumor size <2 cm,
- Paris Type IIc <1 cm
- Histologically well (G1) or moderately differentiated (G2) carcinomas
- No invasion of vessels (lymphatics N0, veins V0)
Endoscopic Mucosal Resection (EMR)
Endoscopic Mucosal Resection (EMR)

R0 Resection

horizontal

vertical
Endoscopic Mucosal Resection (EMR)

Paris Klassifikation Type 0 (superficial)

Low risk: Barrett’s Typ I und II
Endoscopic Mucosal Resection (EMR)
Endoscopic Mucosal Resection (EMR)

Peace-meal Resektion
Endoscopic Mucosal Resection (EMR)

1. Overtreatment!

2. Undertreatment!
Endoscopic Mucosal Resection (EMR)
Endoscopic Submucosa Dissection (ESD)
Endoscopic Submucosa Dissection (ESD)

Advanced Criteria

Differentiated adenocarcinoma

- Yes
  - ulcer
    - Yes
      - $\leq 2\text{cm}$
        - Yes: AI
        - No: EI
    - No: Surg
  - No: Surg

- No: EI

AI: Accepted Indication; EI: Extended Indication

Baptista et al. Curr Opin Gastroenterol 2012
4 open Questions

• Do we sufficiently recognize early gastric cancers?
• What is the best diagnostic strategy?
• What should be treated endoscopically (EMR versus ESD)?
• How good are the clinical results?
Case Presentation 2

• 74 year old patient
• Physically healthy - wished a check-up
• When asked – reported sometimes acid reflux

• Indication for gastroscopy and colonoscopy
Gastroscopy
Histology of the Biopsies

- Well differentiated adenocarcinoma
- Endosonography:
  No evidence of transmural involvement, submucosal involvement unclear
Question

What is your next procedure?

1. Surgery
2. Endoscopic therapy
   1. EMR
   2. ESD
3. Endoscopic surveillance
Final Histology

• Surgery

Early gastric cancer type I, Lauren pT1b, pN0 (0/29), G1, cM0

Conclusion II: depressions and size of the lesion are important features that should have a direct influence on the therapy.
Case Presentation 3

- 85 year-old male from Ludwigshafen
- Increased bloating

- Gastroscopy:
  - Circular growing tumor in the region of the pylorus
  - Histology of biopsies: adenocarcinoma
Gastroscopy
Question

What is your presumption diagnosis?

1. peptic ulcer
2. early cancer
3. advanced cancer
Circular ESD of the Stomach
1. Endopatho-Workshop

Endoskopie und Pathologie live und interaktiv erleben

Themenfocus: (Prä) Maligne Läsionen des Magens

N. Yahagi
Endoscopy on the following day
Histology: pT1(m3), G1, R0, V0, L0
Follow-up

- 2x dilatation of the pylorus

The patient (85 years) is currently symptom-free and there is no evidence of recurrence or secondary neoplasia

Conclusion: The ESD is a new and effective treatment for mucosal carcinoma
ESD of the Stomach

ESD versus Gastrectomy – Prince of Wales University Hongkong

- No difference in survival and other oncologic criteria
- ESD patients had significantly fewer perioperative complications

ESD should be preferably carried out at existing expertise in the stomach.

Chiu et al. Sa1650; DDW 2011
## Meta-Analysis ESD versus EMR

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ESD</th>
<th>EMR</th>
<th>Odds Ratio M-H. Random. 95% CI</th>
<th>Odds Ratio M-H. Random. 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>1.1.1 primary cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oka, 2006</td>
<td>162</td>
<td>195</td>
<td>347</td>
<td>825</td>
</tr>
<tr>
<td>Oda, 2006</td>
<td>281</td>
<td>303</td>
<td>230</td>
<td>411</td>
</tr>
<tr>
<td>Watanabe, 2006</td>
<td>110</td>
<td>120</td>
<td>105</td>
<td>125</td>
</tr>
<tr>
<td>Choi, 2006</td>
<td>33</td>
<td>33</td>
<td>25</td>
<td>33</td>
</tr>
<tr>
<td>Shimura, 2007</td>
<td>52</td>
<td>59</td>
<td>15</td>
<td>48</td>
</tr>
<tr>
<td>Catalano, 2009</td>
<td>11</td>
<td>12</td>
<td>26</td>
<td>36</td>
</tr>
<tr>
<td>Min, 2009</td>
<td>233</td>
<td>243</td>
<td>80</td>
<td>103</td>
</tr>
<tr>
<td>Nakamoto, 2009</td>
<td>115</td>
<td>122</td>
<td>43</td>
<td>80</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1087</td>
<td>1661</td>
<td>95.3%</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>997</td>
<td>871</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.20; Chi² = 16.59, df = 7 (P = 0.02); I² = 58%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 8.90 (P &lt; 0.00001)</td>
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<table>
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<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>1.1.2 recurrent cancer</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yokoi, 2006</td>
<td>41</td>
<td>46</td>
<td>0</td>
<td>18</td>
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<tr>
<td>Hirasaki, 2008</td>
<td>17</td>
<td>17</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>63</td>
<td>33</td>
<td>4.7%</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>58</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 2.23; Chi² = 1.97, df = 1 (P = 0.16); I² = 49%</td>
<td></td>
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<td></td>
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<tr>
<td>Test for overall effect: Z = 2.75 (P = 0.006)</td>
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<td></td>
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</tr>
<tr>
<td>Total (95% CI)</td>
<td>1150</td>
<td>1694</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>1055</td>
<td>882</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.28; Chi² = 22.55, df = 9 (P = 0.007); I² = 60%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 8.64 (P &lt; 0.00001)</td>
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</tr>
</tbody>
</table>

En bloc resection: ESD 8.4 times better

Park et al. Surg Endosc 2011
**Meta-Analysis ESD versus EMR**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ESD Events</th>
<th>ESD Total</th>
<th>EMR Events</th>
<th>EMR Total</th>
<th>Risk Ratio (M-H Random)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1.1 &lt; 1 year</td>
<td>0</td>
<td>572</td>
<td>13</td>
<td>328</td>
<td>0.02 [0.00, 0.36]</td>
<td></td>
</tr>
<tr>
<td>Hoteya, 2009</td>
<td>9</td>
<td>243</td>
<td>0</td>
<td>103</td>
<td>8.10 [0.48, 137.85]</td>
<td></td>
</tr>
<tr>
<td>Min, 2009</td>
<td>0</td>
<td>40</td>
<td>2</td>
<td>22</td>
<td>0.11 [0.01, 2.24]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>855</td>
<td>453</td>
<td></td>
<td></td>
<td>0.27 [0.01, 9.19]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>9</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 7.56; Chi² = 9.00, df = 2 (P = 0.01); I² = 78%</td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 0.73 (P = 0.47)</td>
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<td></td>
</tr>
</tbody>
</table>

| 4.1.2 2-4 year    | 0          | 192       | 31         | 825       | 0.07 [0.00, 1.11]       |        |
| Oka, 2006         | 3          | 303       | 12         | 411       | 0.34 [0.10, 1.19]       |        |
| Oda, 2006         | 0          | 46        | 3          | 18        | 0.06 [0.00, 1.07]       |        |
| Yokoi, 2006       | 1          | 59        | 17         | 48        | 0.05 [0.01, 0.35]       |        |
| Shimura, 2007     | 1          | 59        | 17         | 48        |                         |        |
| Subtotal (95% CI) | 600        | 1302      |            |           | 0.13 [0.04, 0.40]       |        |
| Total events      | 4          | 63        |            |           |                         |        |
| Heterogeneity: Tau² = 0.33; Chi² = 3.88, df = 3 (P = 0.28); I² = 23% |
| Test for overall effect: Z = 3.51 (P = 0.0005) |

| 4.1.3 ≥5 year     | 0          | 15        | 1          | 15        | 0.33 [0.01, 7.58]       |        |
| Hirasaki, 2006    | 0          | 122       | 14         | 80        | 0.02 [0.00, 0.38]       |        |
| Nakamoto, 2009    | 137        | 95        |            |           | 0.08 [0.00, 1.30]       |        |
| Subtotal (95% CI) | 1592       | 1850      |            |           | 0.13 [0.04, 0.41]       |        |
| Total events      | 0          | 15        |            |           |                         |        |
| Heterogeneity: Tau² = 1.75; Chi² = 1.76, df = 1 (P = 0.18); I² = 43% |
| Test for overall effect: Z = 1.78 (P = 0.08) |

**Recurrence rates: ESD 7x less**

---

Park et al. Surg Endosc 2011
4 open Questions

• Do we sufficiently recognize early gastric cancers?
• What is the best diagnostic strategy?
• What should be treated endoscopically (EMR versus ESD)?
• How good are the clinical results?
Answers

• Do we recognize sufficient early gastric carcinomas?
  (Unfortunately) No, not yet

• What is the best diagnostic strategy?
  HD endoscopy + NBI + EMR

• What should be treated endoscopically (EMR versus ESD)?
  ESD is better than EMR
  ..... but time-consuming and technically challenging

• How good are the clinical results?
  ESD is better than EMR (En-bloc rates and recurrences) -
  yet unproven reduction in mortality
Gastroskopie → Diagnose

Wenn möglich mit
• Färbung, Vergrößerung
Optional:
• In-vivo-Mikroskopie

Endosonographie
mit/ohne Minisonde

Wenn möglich mit
• Färbung, Vergrößerung

Mukosales T1

Mukosektomie

histologisch
bestätigt R0

RI oder RII

Chirurgie
(Ziel: erweiterte D1-
Lymphadenektomie)

bei Magenkarzinomen
Perioperative
Chemotherapie
Alternativ bei AEG I-III
Tumoren
neoadjuvante
Radiochemotherapie

distale positive
Lymphknoten oder
Metastasen

palliative
Chemotherapie
mit HER2-Bestimmung

BEOBACHTUNG:
Endosonographie
Follow-up

T1 (> sm1)
od T2 N0 M0

T3 oder T4
+/- regional
positive
Lymphknoten

Moehler ESMO 2015
Thank you!