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8th Gastro Foundation Weekend for Fellows; Spier Hotel & Conference Centre, Stellenbosch

Diagnostic techniques for surveillance of dysplasia

Gerhard Rogler, Department of Gastroenterology and Hepatology, University Hospital Zürich
Case: R.B., ♂, born 1977

- **2001** first diagnosed with left sided ulcerative colitis (age 24)
- Insufficient response to 5-ASA
- Steroid dependent disease course
- **03/2003** ACT 2 clinical trial: Remicade® for UC;
- **2006**: good clinical condition under Remicade®, 3-4 bowel movements/day; 2-3 times per month abdominal pain; increasing symptoms 6 weeks after infusion;
  
  medication: Prednisolone 10 mg/day
  Imurek 150 mg
  Pentasa 3g
Case: R.B., ♂, born 1977

- **01/2007** stable clinical situation
- **07/2008** colonoscopy: histologically moderate – severe chronic inflammation, pancolitis
- **2/2009** aggravation of clinical symptoms; 10 bloody bowel movements/day → steroids
- **11/2009** ongoing clinical symptoms; evaluation for Millenium study (vedolizumab in UC)
Case: R.B., ♂, born 1977

- 11/2009

70 cm ab ano

60 cm ab ano

50 cm ab ano
Case: R.B., ♂, born 1977

- 11/2009
Case: R.B., ♂, born 1977

- **26/11/2009** start study medication; 5 bowel movements
- **12/2009** 6 – 7 bowel movements; sometimes blood; sometimes pain left upper quadrant
- **2/2010**
Case: R.B., ♂, born 1977

- **03/2010** 2-3 bowel movements; no blood
- **07/2010** worsening of condition; 5-8 bowel movements
- **08/2010** again abdominal pain, bloody diarrhea
- **10/2010**
Case: R.B., ♂, born 1977

- **03/2010**: 2-3 bowel movements; no blood
- **07/2010**: worsening of condition; 5-8 bowel movements
- **08/2010**: again abdominal pain, bloody diarrhea
- **10/2010**: endoscopy and biopsies: histology: moderately differentiated invasive CRC
- **CT scan**: liver metastases, lung metastases, bone metastases
- **11/2010**: colectomy: positive lymphnodes (21 of 29)
Increased Risk of Colorectal Cancer in UC Patients

Meta-analysis of 116 worldwide studies assessing the risk of CRC in UC patients

Cumulative risk of developing CRC:
- 2% at 10 yrs,
- 8% at 20 yrs and
- 18% at 30 yrs

Is the Risk Still The Same?

- 600 patients with extensive UC at St. Mark’s in London followed for 5932 person-years

- 30 CRCs detected (annual risk: 0.5% or 1/200)

- Cumulative probability of CRC was
  - 2.5% at 20 years,
  - 7.6% at 30 years and
  - 10.8% at 40 years

- Linear regression suggested that CRC risk declined over the course of the study.

Is the Risk Still The Same?

Eaden et al., 2001

Rutter et al., 2006

Jess et al., 2006

Rogler G.
Chronic ulcerative colitis and colorectal cancer.
## The declining risk of CRC in ulcerative colitis

Risk of developing CRC in UC stratified by decade of publication of studies

<table>
<thead>
<tr>
<th>Decade</th>
<th>N. of studies</th>
<th>Patient-yrs</th>
<th>Number of cases of CRC</th>
<th>Cumulative incidence per 1000 py (95% CI)</th>
<th>Incidence rate per 1000 py (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950s</td>
<td>3</td>
<td>4.759</td>
<td>22</td>
<td>33.15 (0.58-65.73)</td>
<td>4.29 (0.95-7.64)</td>
</tr>
<tr>
<td>1960s</td>
<td>7</td>
<td>19.304</td>
<td>80</td>
<td>31.43 (20.21-42.65)</td>
<td>4.18 (2.67-5.68)</td>
</tr>
<tr>
<td>1970s</td>
<td>4</td>
<td>12.909</td>
<td>40</td>
<td>29.47 (2.47-56.37)</td>
<td>3.22 (0.67-5.77)</td>
</tr>
<tr>
<td>1980s</td>
<td>14</td>
<td>123.866</td>
<td>310</td>
<td>31.37 (20.36-42.38)</td>
<td>2.58 (1.81-3.34)</td>
</tr>
<tr>
<td>1990s</td>
<td>12</td>
<td>87.499</td>
<td>132</td>
<td>15.59 (9.6-21.57)</td>
<td>1.53 (1.06-2)</td>
</tr>
<tr>
<td>2000s</td>
<td>23</td>
<td>369.829</td>
<td>525</td>
<td>14.26 (10.47-18.05)</td>
<td>1.29 (1-1.58)</td>
</tr>
<tr>
<td>2010-2013</td>
<td>18</td>
<td>861.478</td>
<td>1180</td>
<td>9.05 (6.8-11.3)</td>
<td>1.21 (0.95-1.48)</td>
</tr>
</tbody>
</table>

Py, patient-years; CI, confidence interval

Survival in UC associated CRC versus sporadic

Overall Survival (OS) in Sporadic, UC and CD colorectal cancer

HC – HR: 1.12 (95% CI 1.04-1.20, p=0.003)
CD – HR: 1.32 (95% CI 1.20-1.45, p<0.001)

Hospital Episode Statistics (HES)

All admission in England 1997-2012
Total of 286,591 patients underwent surgical resection for CRC
UC: 1,546 (0.5%)
CD: 776 (0.3%)
Age at CRC diagnosis:
- IBD-CRC: median 64 years
- Sporadic CRC: median 71 years
Dysplasia has specific genetic signatures


Transcriptional analysis of left-sided colitis, pancolitis, and ulcerative colitis-associated dysplasia.
Who is at increased risk for colorectal cancer?

ECCO Statement 9 B + C

- Risk is highest in patients with extensive colitis, intermediate in patients with left-sided colitis, and not increased in proctitis [EL2].
- Patients with early onset of disease (age < 20 years at onset of disease) and patients with UC-associated primary sclerosing cholangitis (PSC) may have a particularly increased risk [EL2].
- Persistent inflammation and family history of CRC may contribute to the risk of CRC in patients with UC [EL3]

Factors influencing CRC risk

- Disease duration,
- more extensive disease,
- primary sclerosing cholangitis,
- and a positive family history of sporadic CRC

- Colonic strictures in patients with UC and/or
- a shortened colon, and/or
- multiple post-inflammatory pseudopolyps

- Inflammation is a risk factor for progression to colorectal neoplasia.

How to perform surveillance colonoscopy in UC?

ECCO Statement 9H

- Random biopsies (4 every 10 cm) and targeted biopsies of any visible lesion should be performed during surveillance colonoscopy [EL2b, RGB].

- Methylene blue or indigo carmine chromoendoscopy is an alternative to random biopsies for appropriately trained endoscopists and is superior to random biopsies in the detection rate of neoplastic lesions [EL1b, RG B]

Chromoendoscopy

318 patients

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Patients with at least one dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional colonoscopy</td>
<td>10/154 (6.5%)</td>
</tr>
<tr>
<td>+ 0.1% methylene blue</td>
<td>24/164 (14.6%)</td>
</tr>
</tbody>
</table>

$\rightarrow$ 2.2x detection rate with chromoendoscopy with methylene blue


## Impact of NBI – so far not better than WL

### 42 Patients

<table>
<thead>
<tr>
<th>Grade</th>
<th>NBI missed</th>
<th>WL missed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade n=9</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>High grade n=5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Karzinom n=3</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

### 48 Patients

<table>
<thead>
<tr>
<th>Grade</th>
<th>NBI targeted</th>
<th>WL targeted</th>
<th>random</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade n=16</td>
<td>11 (69%)</td>
<td>13 (82%)</td>
<td>3</td>
</tr>
<tr>
<td>High grade n=0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karzinom n=0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
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*Dekker E, van den Broek FJ, Reitsma JB, Hardwick JC, Offerhaus GJ, van Deventer SJ, Hommes DW, Fockens P.*

Narrow-band imaging compared with conventional colonoscopy for the detection of dysplasia in patients with longstanding ulcerative colitis.


Is surveillance in colitis effective?

![Graph showing survival probability over time with and without surveillance.

Number at risk:
- Non-surveillance group: 124, 44, 11, 5, 1
- Surveillance group: 21, 9, 3, 1, 0

Lutgens et al, Br J Cancer 2009]
Summary

- The pathomechanism of CRC in IBD is different from sporadic CRC; already dysplasia have a unique expression pattern.

- Severity of inflammation, extend of disease, disease duration, presence of pseudopolyps, family history and PSC are risk factors.

- CRC in UC patients usually is more aggressive and has a worse prognosis.

- The magnitude of CRC risk in IBD is uncertain: not all studies report an increased risk: Decreasing incidence of CRC in IBD over the last 50 years.

- Surveillance is effective and strongly recommended but should be stratified to the risk profile. *But what to do with the increasing prevalence of dysplasia???
Thank you for your attention