Can We Predict the Natural History of Ulcerative Colitis?

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Overview

• Endpoints
  — Hospitalization
  — Surgery
  — Colorectal cancer
  — Death

• Risk Factors
  — Extent
  — Age at Diagnosis
  — PSC
Rochester Epidemiology Project

- Mayo Clinic and Olmsted Medical Group provide essentially all medical care
- Computer linkage for medical diagnoses, surgical procedures
- Access to records of all providers, including ambulatory care
- Identifies full spectrum of disease
- Over 1600 epidemiological reports on acute and chronic disease

## UC Cohort, Olmsted County, 1970-2004

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>155</td>
<td>42%</td>
</tr>
<tr>
<td>Male</td>
<td>210</td>
<td>58%</td>
</tr>
<tr>
<td>Age &lt; 40 years</td>
<td>216</td>
<td>59%</td>
</tr>
<tr>
<td>Age &gt; 40 years</td>
<td>146</td>
<td>41%</td>
</tr>
<tr>
<td>Diagnosed in the 1970’s</td>
<td>80</td>
<td>22%</td>
</tr>
<tr>
<td>1980’s</td>
<td>93</td>
<td>25%</td>
</tr>
<tr>
<td>1990’s</td>
<td>117</td>
<td>32%</td>
</tr>
<tr>
<td>2000-2004</td>
<td>75</td>
<td>21%</td>
</tr>
</tbody>
</table>

### UC Cohort, Olmsted County, 1970-2004

<table>
<thead>
<tr>
<th>Risk Factors (first 90 days)</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extent of Disease:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA/Normal</td>
<td>6</td>
<td>2%</td>
</tr>
<tr>
<td>Proctitis</td>
<td>108</td>
<td>30%</td>
</tr>
<tr>
<td>Left Sided</td>
<td>137</td>
<td>38%</td>
</tr>
<tr>
<td>Extensive</td>
<td>114</td>
<td>31%</td>
</tr>
<tr>
<td><strong>Early Hospitalization:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>298</td>
<td>82%</td>
</tr>
<tr>
<td>Yes</td>
<td>67</td>
<td>18%</td>
</tr>
<tr>
<td><strong>Early Corticosteroid Use:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>299</td>
<td>82%</td>
</tr>
<tr>
<td>Yes</td>
<td>66</td>
<td>18%</td>
</tr>
</tbody>
</table>

Cumulative Risk Of Hospitalization From UC Diagnosis

Cumulative Risk Of Hospitalization, Stratified By Decade Of UC Diagnosis

Cumulative Risk Of Hospitalization, Stratified By Initial UC Extent


P=0.0107
Cumulative Risk Of Hospitalization, Stratified By Initial Need For Corticosteroids


Cumulative Probability of Hospitalization

- No steroids 1st 90 days
- Steroids 1st 90 days

Years to Hospitalization

P<0.0001
Cumulative Risk Of Hospitalization, Stratified By Initial Need For Hospitalization


Cumulative Probability of Hospitalization

Years to Hospitalization

- No hospitalization 1st 90 days
- Hospitalization 1st 90 days

P<0.0001
## Risk Of Initial Hospitalization After First 90 Days: Cox proportional hazards regression

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive disease</td>
<td>1.58 (1.10-2.26)</td>
<td>0.0126</td>
</tr>
<tr>
<td>Early steroid use</td>
<td>1.85 (1.23-2.80)</td>
<td>0.0035</td>
</tr>
<tr>
<td>Early hospitalization</td>
<td>1.61 (1.08-2.40)</td>
<td>0.0182</td>
</tr>
</tbody>
</table>

UC Hospitalization - Conclusions

• 47% of UC patients were hospitalized at least once between 1970 and 2004
  — Mean length of stay of 9.6 days

• 5-year cumulative risk of hospitalization increased from 20.2% in the 1970's to 44.7% in 2000-2004.

• Extensive disease, early corticosteroid use and early hospitalization were associated with increased risk of hospitalization.


• 365 UC pts were followed for 5,260 person-years (median follow-up was 13.8 years; range, 1 month - 36 years).
• 23% (85/365) of pts had at least one surgery.
• 21% (75/365) of pts had a colectomy.
• 71% (60/85) of pts had more than one surgery.

Ingle SB et al. ACG 2007 and UEGW 2007 abstracts.
Ingle SB et al. ACG 2007 and UEGW 2007 abstracts.
Cumulative Risk Of Colectomy By UC Duration

Ingle SB et al. ACG 2007 and UEGW 2007 abstracts.
Cumulative Risk Of Colectomy
Stratified by Gender

$HR = 2.26 \ (1.3 - 3.8)$

$P = 0.0014$

Ingle SB et al. ACG 2007 and UEGW 2007 abstracts.
Cumulative Risk Of Colectomy
Stratified By Decade Of Diagnosis

HR=2.3
(1.2–2.6)

HR=3.9
(1.7–8.7)

HR=1.3
(0.6–2.7)

P=0.0028

Ingle SB et al. ACG 2007 and UEGW 2007 abstracts.
Among 365 UC patients diagnosed between 1970-2004, 20.5% required colectomy.

The cumulative incidence of colectomy increased to 19.4% at 10 years and almost 30% at 25 years from UC diagnosis.

Male gender and diagnosis after 1990 were associated with greater risk of colectomy.

Ingle SB et al. ACG 2007 and UEGW 2007 abstracts.
Risk of Colorectal Cancer in UC Meta-Analysis

Eaden: Gut 2001; 48:526
Risk Factors for IBD-Related Colorectal Cancer

- **Classic risk factors**
  - Increased extent (i.e., pancolitis vs. proctitis)
  - Increased duration

- **Newer risk factors**
  - Primary sclerosing cholangitis (PSC)
  - Family history of CRC
  - Backwash ileitis?
  - Severity of inflammation?
Cumulative Risk of Colorectal Cancer Among 376 Ulcerative Colitis Patients From Olmsted County, Minnesota

## Colorectal Cancer Risk in UC - Olmsted County, 1940-2001

<table>
<thead>
<tr>
<th></th>
<th>Patients (n)</th>
<th>Person-years</th>
<th>Obs</th>
<th>Exp</th>
<th>SMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>378</td>
<td>5567</td>
<td>6</td>
<td>5.38</td>
<td>1.1 (0.4 - 2.4)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>166</td>
<td>2618</td>
<td>2</td>
<td>2.56</td>
<td>0.8 (0.1 - 2.8)</td>
</tr>
<tr>
<td>Men</td>
<td>212</td>
<td>2949</td>
<td>4</td>
<td>2.82</td>
<td>1.4 (0.4 - 3.6)</td>
</tr>
<tr>
<td><strong>Age at diagnosis (yrs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-29</td>
<td>149</td>
<td>2273</td>
<td>1</td>
<td>0.43</td>
<td>2.3 (0.1 - 12.8)</td>
</tr>
<tr>
<td>30-49</td>
<td>144</td>
<td>2288</td>
<td>4</td>
<td>1.86</td>
<td>2.2 (0.6 - 5.5)</td>
</tr>
<tr>
<td>50+</td>
<td>85</td>
<td>1006</td>
<td>1</td>
<td>3.09</td>
<td>0.3 (0.01 - 1.8)</td>
</tr>
<tr>
<td><strong>Calendar year at diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1940-1959</td>
<td>34</td>
<td>874</td>
<td>1</td>
<td>1.20</td>
<td>0.8 (0.02 - 4.6)</td>
</tr>
<tr>
<td>1960-1979</td>
<td>143</td>
<td>2933</td>
<td>5</td>
<td>1.92</td>
<td>1.9 (0.6 - 4.5)</td>
</tr>
<tr>
<td>1980-1989</td>
<td>85</td>
<td>1084</td>
<td>0</td>
<td>0.00</td>
<td>0.0 (0.0 - 3.9)</td>
</tr>
<tr>
<td>1990-2002</td>
<td>116</td>
<td>676</td>
<td>0</td>
<td>0.00</td>
<td>0.0 (0.0 - 7.7)</td>
</tr>
</tbody>
</table>

*Jess T et al, Gastroenterology 2006*
Overall Survival From Diagnosis of 378 Ulcerative Colitis Patients From Olmsted County, Minnesota, 1940-2001

62 deaths total
12 deaths (19%) due to GI causes or GI cancers

Jess T et al, Gut 2006
<table>
<thead>
<tr>
<th>Causes</th>
<th>Obs</th>
<th>Exp</th>
<th>SMR (95% CI)</th>
<th>Men</th>
<th>Obs</th>
<th>Exp</th>
<th>SMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>0</td>
<td>0.5</td>
<td>0.0 (0.0-7.4)</td>
<td>0</td>
<td>0.9</td>
<td>0.0 (0.0-4.0)</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>5</td>
<td>8.2</td>
<td>0.6 (0.2-1.4)</td>
<td>10</td>
<td>11.0</td>
<td>0.9 (0.4-1.7)</td>
<td></td>
</tr>
<tr>
<td>Intestinal</td>
<td>1</td>
<td>1.0</td>
<td>1.0 (&lt;0.1-5.3)</td>
<td>4</td>
<td>1.2</td>
<td>3.3 (0.9-8.4)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>0</td>
<td>1.6</td>
<td>0.0 (0.0-2.4)</td>
<td>2</td>
<td>3.9</td>
<td>0.5 (0.1-1.9)</td>
<td></td>
</tr>
<tr>
<td>Heme</td>
<td>0</td>
<td>0.1</td>
<td>0.0 (0.0-26)</td>
<td>1</td>
<td>0.1</td>
<td>7.1 (0.2-39)</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>2</td>
<td>0.7</td>
<td>3.1 (0.4-11)</td>
<td>1</td>
<td>0.7</td>
<td>1.5 (&lt;0.1-8.3)</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>8</td>
<td>18.1</td>
<td>0.4 (0.2-0.9*)</td>
<td>15</td>
<td>18.9</td>
<td>0.8 (0.4-1.3)</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>4</td>
<td>2.9</td>
<td>1.4 (0.4-3.5)</td>
<td>2</td>
<td>3.6</td>
<td>0.6 (0.1-2.0)</td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td>2</td>
<td>1.3</td>
<td>1.5 (0.2-5.5)</td>
<td>4</td>
<td>1.7</td>
<td>2.4 (0.7-6.2)</td>
<td></td>
</tr>
<tr>
<td>GU</td>
<td>2</td>
<td>0.7</td>
<td>2.7 (0.3-10)</td>
<td>0</td>
<td>0.6</td>
<td>0.0 (0.0-6.1)</td>
<td></td>
</tr>
<tr>
<td>Suicide</td>
<td>0</td>
<td>0.2</td>
<td>0.0 (0.0-16)</td>
<td>1</td>
<td>1.0</td>
<td>1.0 (&lt;0.1-5.6)</td>
<td></td>
</tr>
<tr>
<td>Accidents</td>
<td>1</td>
<td>0.9</td>
<td>1.2 (&lt;0.1-6.5)</td>
<td>1</td>
<td>2.0</td>
<td>0.5 (&lt;0.1-2.8)</td>
<td></td>
</tr>
<tr>
<td>All other</td>
<td>2</td>
<td>2.2</td>
<td>0.9 (0.1-3.4)</td>
<td>1</td>
<td>2.3</td>
<td>0.4 (0.1-2.4)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>36.3</td>
<td>0.7 (0.5-1.1)</td>
<td>36</td>
<td>42.9</td>
<td>0.8 (0.6-1.2)</td>
<td></td>
</tr>
</tbody>
</table>

Jess T et al, Gut 2006
Multivariate Analysis of Survival: Ulcerative Colitis

• Independent predictors of mortality
  — Male gender
  — Older age
  — Diagnosis after 1980 was protective

• No association
  — Extent (trend with extensive UC)

Jess T et al, Gut 2006
Classification by Extent

• **Proctitis**
  — Limited to rectum
  — Within 15-20 cm of anal verge

• **Left-sided colitis**
  — Distal to splenic flexure
  — Within 60 cm of anal verge

• **Extensive colitis**
  — Proximal to splenic flexure
## UC Disease Extent Predicts Severity

<table>
<thead>
<tr>
<th>Setting</th>
<th>Colectomy Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proctitis</td>
</tr>
<tr>
<td>St Mark’s</td>
<td>2%</td>
</tr>
<tr>
<td>Cleveland Clinic</td>
<td>14%</td>
</tr>
<tr>
<td>Copenhagen</td>
<td>9%</td>
</tr>
<tr>
<td>IBSEN</td>
<td>2%</td>
</tr>
</tbody>
</table>

Lennard-Jones, Scand J Gastroenterol Suppl 1983  
Farmer, Dig Dis Sci 1993  
Langholz, Gastroenterol 1992  
Moum, Scand J Gastroenterol 1997
UC Disease Extent Influences Colorectal Cancer Risk

• Uppsala, Sweden: relative risk of CRC
  — Proctitis, 1.7
  — Left-sided, 2.8
  — Extensive, 14.8

• Cleveland Clinic: cumulative risk of CRC after 30 years of disease
  — Left-sided, 4%
  — Extensive, 25%

Mir-Madjlessi, Cancer 1986
UC Disease Extent May Influence Mortality

- Copenhagen County
  - Subgroup with extensive colitis had standardized mortality ratio (observed/expected) of 1.68
  - Other SMRs not significantly elevated
- Extended follow-up in this cohort
  - Again showed elevated SMR in extensive
  - Also showed a significantly lower SMR for proctitis

Langholz, Gastroenterology 1992
Winther, Gastroenterology 2003
Is Age of Diagnosis a Prognosis Indicator?

- Some studies suggest that childhood-onset UC has higher rate of complications, is more severe, has higher risk of CRC, etc
  - Data are conflicting
  - Colectomy rates similar
- Likewise, older studies suggest that late-onset UC is milder
  - Data again conflicting
- Insufficient evidence for age as a risk factor

IBD Associated with Primary Sclerosing Cholangitis (‘PSC-IBD’)

- PSC and IBD are closely linked
  - 5% of UC has PSC
  - 70-80% of PSC has IBD (usually UC)
- PSC-IBD is typically extensive
  - High rate of rectal sparing
  - High rate of backwash ileitis
- PSC-IBD associated with dysplasia and CRC
- PSC-IBD more likely to develop pouchitis
- Is PSC-IBD a special phenotype of IBD?

Is Natural History of UC Different in Asia?

- Similar rates of relapse and proximal progression
- Perhaps a lower risk of CRC
- Lower prevalence of PSC
- Perhaps lower colectomy rates
  - Less severe disease?
  - Greater reluctance to accept surgery?
- Need more natural history cohorts with longer durations of follow-up

Conclusions

• In our population-based inception cohort:
  — Extensive disease, early steroids, early hospitalization were associated with subsequent hospitalization
  — Male gender and diagnosis after 1980 were associated with increased risk of colectomy
  — No risk factors for CRC were observed, although no CRC were observed in patients diagnosed after 1980
Conclusions (2)

• In our population-based cohort:
  — Male gender and older age were risk factors for mortality but diagnosis after 1980 was protective
  — A nonsignificant trend of increased mortality with increased extent was noted

• In other cohorts:
  — Increased extent has been associated with increased colectomy rates, cancer risk and mortality
  — Data on age at diagnosis conflicting
  — PSC increases cancer risk and mortality
Conclusions (3)

• We need more natural history studies incorporating all of these endpoints as well as other markers
  — Serologies?
  — Genetic polymorphisms?
  — Inflammatory biomarkers?
    • CRP
    • Fecal stool markers