Gastrointestinal Lymphoma

W. Fischbach
Gastrointestinal Lymphoma

- Classification
- Aetiology and pathogenesis
- Diagnosis and staging
- Therapy
- Specifics of intestinal lymphoma
## Gastrointestinal Lymphoma

### WHO-classification 2002

<table>
<thead>
<tr>
<th>B-cell-lymphoma</th>
<th>T-cell-lymphoma</th>
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</thead>
<tbody>
<tr>
<td><em>marginalzone-B-cell-lymphoma of MALT-type</em></td>
<td>enteropathy-associated T-cell-lymphoma (EATCL)</td>
</tr>
<tr>
<td>follicular lymphoma (grade I-III)</td>
<td>peripheral T-cell-lymphoma (previously: non-EATCL)</td>
</tr>
<tr>
<td>mantle cell lymphoma (lymphomatous polyposis)</td>
<td></td>
</tr>
<tr>
<td><strong>diffuse large B-cell-lymphoma with/without MALT components</strong></td>
<td></td>
</tr>
<tr>
<td>Burkitt-lymphoma</td>
<td></td>
</tr>
<tr>
<td><em>immunodeficiency associated lymphoma</em></td>
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Gastrointestinal Lymphoma

• Classification
• **Aetiology and pathogenesis**
• Diagnosis and staging
• Therapy
• **Specifics of intestinal lymphoma**
Helicobacter pylori and MALT lymphoma

Aetiopathogenetic role of Hp for MALT-lymphoma

Morphological data

Epidemiological data

Animal studies

Molecular biological findings
Helicobacter pylori and gastric MALT lymphoma

Hp induces acquisition of lymphoid tissue in the gastric mucosa: **Condition** for the development of gastric MALT lymphoma.

Hp represents an antigenic stimulus for the lymphoma growth: **Progression** of gastric MALT lymphoma.
**Hp associated gastritis**

- Hp induces and sustains an active proliferating B-cell population
- Hp attracts and activates neutrophils
- Release

**Marginal zone B cell lymphoma of MALT**

- t(1;14) $\leq 5\%$
- Apoptose regulierendes BCL10

- **t(11;18)** + (mostly single clonal abnormality)
- **t(11;18)** - (numerous genetic changes)

**Hp eradication**

- Responsive
- Failure (definition?)

**DLBCL**

- t(11;18) -

**De novo**
Helicobacter pylori and MALT Lymphoma

- > 90% of MALT-Lymphoma are Hp +
- ≤ 1% of Hp infected individuals develop a MALT-Lymphoma

➢ virulence factors ?: No!
Helicobacter pylori und MALT Lymphom

Genetic host factors

- **HLA-B35: protective role**
  (Reimer P et al., Ann Hematol 2004)

- **TNF-α promoter polymorphisms**
  (Hellmig S et al., Am J Gastroenterol 2005)

- **Mutation of NOD2/CARD15-gene**
  (Rosenstiel et al., DDW 2006)

- **MALT1-gene: somatic alterations and germ line variations**

- **CDH1-Gen**
Aetiology and pathogenesis of gastric MALT Lymphoma

- Helicobacter pylori
- Genetic host factors
- other ????
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Gastrointestinal Lymphoma

**histology** (low grade – high grade) and **stage** (I1, I2, II-IV) are the decisive prognostic factors and therapeutic determinants.

Cogliatti et al., Gastroenterology 1991
Radaszkiewicz et al., Gastroenterology 1992
How can we reliably diagnose gastric lymphoma?

- Clinical symptoms are unspecific
- The endoscopic appearance of gastric lymphoma varies widely
- Up to 20% reveal low and high grade components
- Diagnosis of gastric lymphoma is an incidental findings in most cases

Kolve M, Fischbach W, Greiner A, Gastrointest Endosc 1999
ENDOSCOPIC-BIOOPTIC TECHNIQUE

Gastric mapping

in special case use of giant forcep or snare

1 biopsy from corpus and antrum resp for urease test

4 biopsies from unsuspicious areas
in antrum und corpus (each quadrant)
as well as 2 biopsies from fundus

10 biopsies from suspicious areas
in formalin (and native)
for histological (molecular) work-up.
Staging of gastric lymphoma

When gastric lymphoma is diagnosed and confirmed by a reference pathology

- a staging procedure including
  - abdominal and cervical ultrasound
  - abdominal and thoracic CT scan
  - bone marrow puncture
  - ileocolonoscopy
  - endoscopic ultrasound (EUS)
  - MR-Sellink or capsule endoscopy or enteroscopy?

- is necessary!
EUS in the locoregional staging

EI1
Mucosa
submucosa

EI2
M. propria
serosa

EII1
lymph
nodes

EUS is an obligatory diagnostic procedure!

Fischbach et al., Gastrointestinal Endoscopy 2002;56:696-700
### Paris Staging System

**Ann Arbor/Musshoff/Radaszkiewicz**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Lymphoma extent not specified</td>
</tr>
<tr>
<td>TO</td>
<td>No evidence of lymphoma</td>
</tr>
<tr>
<td>T1</td>
<td>Lymphoma confined to the mucosa/submucosa</td>
</tr>
<tr>
<td>T1m</td>
<td>Lymphoma confined to mucosa (I1)</td>
</tr>
<tr>
<td>T1sm</td>
<td>Lymphoma confined to submucosa (I1)</td>
</tr>
<tr>
<td>T2</td>
<td>Lymphoma infiltrates muscularis propria or subserosa (I2)</td>
</tr>
<tr>
<td>T3</td>
<td>Lymphoma penetrates serosa (visceral peritoneum) without invasion of adjacent structures (I2)</td>
</tr>
<tr>
<td>T4</td>
<td>Lymphoma invades adjacent structures or organs (I2)</td>
</tr>
</tbody>
</table>

Ruskone-Fourmestraux A et al., Gut 2003;52:912
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Involvement of lymph nodes not assessed</td>
</tr>
<tr>
<td>NO</td>
<td>No evidence of lymph node involvement</td>
</tr>
<tr>
<td>N1</td>
<td>Involvement of regional lymph nodes (II1)</td>
</tr>
<tr>
<td>N2</td>
<td>Involvement of intra-abdominal lymph nodes beyond the regional area (II2)</td>
</tr>
<tr>
<td>N3</td>
<td>Spread to extra-abdominal lymph nodes (III)</td>
</tr>
<tr>
<td>MX</td>
<td>Dissemination of lymphoma not assessed</td>
</tr>
<tr>
<td>MO</td>
<td>No evidence of extranodal dissemination</td>
</tr>
<tr>
<td>M1</td>
<td>Non-continuous involvement of separate sites in gastrointestinal tract</td>
</tr>
<tr>
<td>M2</td>
<td>Non-continuous involvement of other tissues (peritoneum, pleura) or organs (IV)</td>
</tr>
<tr>
<td>BX</td>
<td>Involvement of bone marrow not assessed</td>
</tr>
<tr>
<td>B0</td>
<td>No evidence of bone marrow involvement</td>
</tr>
<tr>
<td>B1</td>
<td>Lymphomatous infiltration of BM (IV)</td>
</tr>
</tbody>
</table>
Small bowel diagnostics in gastrointestinal lymphomas

Rationale

multifocal spread of gastric lymphoma within the GI tract occurs in 6.5% (Koch et al., J Clin Oncol 2001;19:3861-3873)
Capsule endoscopy

follicular lymphoma ?: Yes
Follicular lymphoma grade I
duodenum, ileum, colon
Double-Balloon-Enteroscopy

60 - 70 cm proximal of the valvula
Diffuse large B-cell-lymphoma
Diagnosis and staging of gastric lymphoma

Endoscopic biopsies and staging are of utmost importance for diagnosis and typing of gastric lymphoma and the appropriate treatment.
# Therapeutic strategies in gastric lymphoma

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<tr>
<th>Stage</th>
<th>MALT</th>
<th>DLBCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>I 1/2</td>
<td>Hp eradication if progression, relapse or refractory to Hp eradication: RTx (surgery)</td>
<td>R-CTx + RTx (surgery + CTx) (Hp eradication)</td>
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<td>II 1/2</td>
<td>hMRD: Watch-and-wait</td>
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HELICOBACTER PYLORI ERADICATION IN LOW GRADE GASTRIC MALT-LYMPHOMA

Wotherspoon et al., Lancet 1993

6 patients with low grade gastric B-cell-lymphoma of MALT-type

Hp eradication

regression of lymphoma: 5/6 cases

“Hp eradication should be the first choice of treatment“
Helicobacter pylori eradication in low grade gastric MALT-lymphoma of stage I

lymphoma regression in 70 - 80%

(summary of literature)
What is the long-term outcome after exclusive Hp eradication therapy?

Are lymphoma regressions long lasting?

Does it offer a real chance of cure?

How often do relapse, progression or high grade transformation occur?
Long-term outcome of patients with gastric marginal zone B-cell lymphoma of MALT following exclusive H. pylori eradication therapy

Experience from a large prospective series

Fischbach W. et al., Gut 2004
n = 95

Hp eradication

Follow-up 49.5 (12-89 mo)

Fischbach et al., Gut 2004;53:34-37
Long-term outcome after Helicobacter pylori eradication therapy

Conclusions

The majority of patients have a favourable long-term outcome.

Hp eradication offers a real chance of cure

Fischbach W. et al., Gut 2004
Wündisch Th. et al. J Clin Oncol 2005
Minimal residual low-grade gastric MALT-type lymphoma after eradication of Helicobacter pylori

Fischbach W, Goebeler-Kolve ME, Starostik P, Greiner A, Müller-Hermelink HK

Lancet 2002; 360:547-548
No relapse
No lymphoma dissemination
No high grade transformation

<table>
<thead>
<tr>
<th>case</th>
<th>age *</th>
<th>sex</th>
<th>number of endoscopies during 12 months following Hp eradication therapy/thereafter</th>
<th>t(11;18)</th>
<th>JH-PCR</th>
<th>Observation time ** (months)</th>
<th>Specifics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43</td>
<td>female</td>
<td>4/4</td>
<td>+</td>
<td>+</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>male</td>
<td>4/10</td>
<td>+</td>
<td>+</td>
<td>44</td>
<td>***</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>male</td>
<td>4/5</td>
<td>n.a.</td>
<td>n.a.</td>
<td>34</td>
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<tr>
<td>4</td>
<td>57</td>
<td>male</td>
<td>4/8</td>
<td>-</td>
<td>+</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>male</td>
<td>4/7</td>
<td>n.a.</td>
<td>n.a.</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>female</td>
<td>4/3</td>
<td>+</td>
<td>-</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>49</td>
<td>male</td>
<td>4/3</td>
<td>+</td>
<td>+</td>
<td>22</td>
<td></td>
</tr>
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</table>
Most patients with minimal histological residuals of MALT lymphoma after successful eradication of Hp reveal a favourable course of disease without any oncological treatment.

A watch-and-wait strategy appears to be safe and may become the approach of choice

(Fischbach W et al., Gut Online First 16 July 2007, in press)
mhRD after successful eradication of *H. pylori*
Experience from a clinical series of the EGILS group (Fischbach W. et al., Gut 2007)

Low grade gastric MALT lymphoma stage I
n = 108

Hp eradication after 12 months:

mhRD

Follow-up
42.2 (2–144 months)

CR n = 35 (32%)

mhRD n = 67 (62%)

PD n = 6 (6%)

local progression: n=5
high grade lymphoma n=1

Favourable natural course of disease in 95%
HELICOBACTER PYLORI ERADICATION in DLBCL

8 patients (26-85 years)
high malignant = 6; high/low malignant = 2
stage I = 6; stage II = 2
CR 7/8 patients; PR 1/8
abdominal lymph node relapse = 1

Comparison of two prospective studies dealing with Hp Eradication in MALT-Lymphoma of stage I

<table>
<thead>
<tr>
<th></th>
<th>MALT-Lym</th>
<th>DLBCL - MALT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>low grade predominant</td>
</tr>
<tr>
<td>n</td>
<td>34</td>
<td>13</td>
</tr>
<tr>
<td>Hp positive</td>
<td>94%</td>
<td>100%</td>
</tr>
<tr>
<td>Eradication</td>
<td>97%</td>
<td>85%</td>
</tr>
<tr>
<td>CR</td>
<td>80%</td>
<td>64%</td>
</tr>
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Hp associated gastritis

- Hp induces and sustains an active proliferating B-cell population
- Hp attracts and activates neutrophils

Marginal zone B cell lymphoma of MALT

- t(1;14) < 5%
- Apoptose regulierendes BCL10

- t(11;18)
  - Mostly single clonal abnormality
  - Hp eradication failure (definition?)
  - High grade transformation
  - De novo

DLBCL

- t(11;18) -

HP eradication

- Responsive
- Failure
Lymphoma regression after antibiotic therapy of Hp negative MALT-Lymphoma
Raderer M et al., Gut 2006

6 patients with gastric MALT-Lymphoma

extensive staging

Hp: histology, breath test, stool test, serology

stage I, H. pylori negative

Eradication (Italian triple)

4 CR
1 PR
1 SD
Immunohistochemical detection of Okadaella gastrococcus, an intracellular Gram negative bacterium, in the mucosa and lymphoma cells of 3 patients with MALT lymphoma.

Cases of Gastric MALT lymphoma and Diffuse large B-cell lymphoma associated with Okadaella gastrococcus-like organism.

Okada T, et al. (Australien, Japan)

DDW 2007  S2075

Conclusion:

A probatory eradication therapy can also be initiated in Hp negative patients with gastric MALT lymphoma.
Therapeutic strategies in gastric lymphoma

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Experience from a prospective Multicenter study (Münster, D)
Koch et al., J Clin Oncol 2001 und 2005

Results

No difference between conservatively or surgically treated patients with respect to relapse and survival
Radiotherapy
Schechter et al., J Clin Oncol 1998

- 17 patients with low grade gastric MALT lymphoma
  stage I = 12,  II1 = 4,  II2 = 1

- Hp positive: 5/17

- involved field  30 Gy

- 27 (11-68) months: disease free survival 100%

radiotherapy offers cure!
Radiation of MALT Lymphoma of stage I/II
Tsang RW et al., Int J Radiation Oncology 2001

- n = 70 (IE: 62; IIE: 8)
- 1989 - 1998
- RT: n=62
  - Allein: 52; + CT: 7; + Hp Era: 3

Stomach, thyroid gland
Other

Disease free survival

Fig. 2. Disease-free survival for patients with stomach and thyroid mucosa-associated lymphoid tissue (MALT) lymphoma (22 patients) vs. other sites (47 patients).
## Chemotherapy

### 1st line

- **prior:** CHOP–21
- **nowadays:** Rituximab-CHOP-14

➤ curative intention (MALT, stage III/IV ?)
## Chemotherapy

### alternatives – 2nd line

<table>
<thead>
<tr>
<th>2CdA – Oxaliplatin – MCP - DHAP</th>
</tr>
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<tr>
<td>Streubel B et al., Oncology 2004; Raderer M et al., J Clin Oncol 2005; Wöhrer S et al., Ann Oncol 200</td>
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Specifics of intestinal lymphoma

- are rare
- have a bad prognosis
- can be better diagnosed nowadays
- only very few therapeutic studies
Treatment of intestinal lymphoma

- No generally accepted standard (except DLBCL: R-CHOP)

- T-cell lymphoma (EATCL; Non-EATCL): Budesonid, prednisone, basiliximab, CHOP, Campath, Fludarabin, HD-BEAM+stem cell tx

- within clinical trials