Original Article

Follicular gastritis associated with *Helicobacter pylori*

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In order to understand the pathogenesis of gastric lymphoma, we investigated the association of *H. pylori* infection with lymphoid follicular hyperplasia. Eighty-four gastric specimens removed for gastroduodenal ulcer were histologically examined. The distribution and prevalence of *H. pylori*, neutrophilic and lymphocytic infiltration, mucosal atrophy, intestinal metaplasia, and lymphoid follicles were scored. The lymphoid follicles were more frequently observed in *H. pylori* positive cases. They indicated a positive correlation with the score of *H. pylori*. When follicular gastritis (FG) was defined as a case in which the secondary lymphoid follicles (Lf,) numbered two or more per one centimeter of mucosa in the pyloric gland area of the lesser curvature, twenty specimens out of the 84 (24%) fit that definition. All of the FG cases were *H. pylori* positive, and they displayed high *H. pylori* scores. It was supposed that most FG cases would ultimately lead to atrophic gastritis, whereas *H. pylori* would gradually decrease or disappear in accordance with the aging and progression of intestinal metaplasia. The histological features of the FG cases, however, were similar to the background mucosal state of early-stage MALT-type gastric lymphoma. We may conclude that *H. pylori* infection is one cause of the FG, which may be a high-risk condition that gives rise to MALT-type gastric lymphoma.

Key words: *Helicobacter pylori*, lymphoid follicular hyperplasia, follicular gastritis, MALT lymphoma.

Introduction

Since Warren and Marshall published their observation that *Helicobacter pylori* (*H. pylori*) is associated with gastritis in 19831, it has become clear that *H. pylori* is a major etiologic agent of chronic active gastritis1-4. Recently, it has been recognized that *H. pylori* takes part in the induction of chronic atrophic gastritis14, gastroduodenal ulcer5, gastric cancer6-10 and gastric mucosa-associated lymphoid tissue (MALT) lymphoma11-13. A close relationship between MALT lymphoma and *H. pylori* infection was confirmed by several reports on high *H. pylori* infection ratios11 and regression of the lesion after eradication of *H. pylori*.14-16

The concept of reactive lymphoid hyperplasia (RLH) widely included borderline lesions characterized as being between reactive lymphoid tissue proliferation and malignant lymphoma17-20, whereas MALT lymphoma, which was introduced by Isaacson et al. in 198321, covered a major part of RLH. The borderline, however, between reactive lymphoid tissue proliferation and MALT lymphoma is still obscure.
To understand the pathogenesis of gastric lymphoma, it is important to clarify the association of *H. pylori* infection with lymphoid follicular hyperplasia. Although several studies on this issue have been done, those research objects were biopsy specimens. There was limitation associated with using biopsy specimens in the *H. pylori* study as Genta pointed out. Thus a study using surgical materials is required.

The aim of this study is to elucidate the contribution of *H. pylori* infection to the development of gastric MALT lymphoma, by histopathologically investigating the distribution and prevalence of *H. pylori* and lymphoid follicles.

**Materials and methods**

**Subjects**

From the pathological registry at our hospital for the years between 1950 and 1966, 84 gastrectomy cases with gastroduodenal ulcer were selected. They consisted of 75 males and 9 females with ages ranging from 18 to 79 years (mean, 52 years).

Routinely-processed formalin-fixed paraffin-embedded tissue blocks taken from the entire length of both the lesser and greater curvatures were examined. Both the curvatures from 67 cases and only the lesser curvature from 17 cases were available for this examination. Each tissue block was cut in sequential 4-μm sections, and stained by the hematoxylin-eosin (HE; Myer’s hematoxylin for 20 min) and Giemsa (10% Giemsa solution for 2 h) methods.

**Histopathological findings**

The stained preparations were histopathologically examined according to the Sydney System, which is a classification introduced for the histopathologic and endoscopic appearance of gastritis and *H. pylori* infection. As this system was designed for biopsy specimens, we modified it to fit the study using surgical materials.

The gastric mucosal areas of both the curvatures were divided into 3 types according to the histological construction, that is: (1) the pyloric-gland area (P-f area) composed of the pyloric gland and intestinal metaplasia, (2) the fundic-gland area (F-C area) composed of only the fundic gland, and (3) the intermediate area (I-F area) with the mixed fundic gland and intestinal metaplasia.

Each specimen was observed at 100-fold magnification field by field through the curvatures. In each microscopic field, histological findings including *H. pylori* infection (H.p), neutrophil infiltration (N), lymphocytic infiltration (Ly), mucosal atrophy (A) and intestinal metaplasia (Im) were evaluated based upon the standard of the Sydney System as for biopsy specimens. A mild degree or higher of H.p or Im, and a moderate degree or higher of N, Ly, or A were defined as positive findings.

The proportion of the mucosal length exhibiting positive finding (a) to one field mucosal length (l) was recorded as a percentage \( x_\text{a} = (a/l) \times 100 \). Each histological finding was scored as a mean percentage of each field score \( X = (\Sigma x_\text{a}) / n \) over the total examined length (L) (Figure 1).

For the evaluation of *H. pylori* infection, we considered as *H.p* infection only "H.p in-epithelium" deeply embedded into the foveoli or lying between the

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**Figure 1.** Evaluation of histological findings. The proportion of the mucosal length exhibiting positive finding \( a_\text{a} \) to one field mucosal length \( l \) was recorded as a percentage \( x_\text{a} = (a_\text{a}/l) \times 100 \). Each histological finding was scored as a mean percentage of each field score \( X = (\Sigma x_\text{a}) / n \) in the total examined length \( L \).
epithelial cells, because “H.p in-mucus”, limited to mucus or surface epithelium, was likely not to represent the true distribution.

As for the lymphoid follicular hyperplasia, follicles were classified into primary ones (Lf₁) and secondary ones (Lf₂) by the presence or absence of a germinal center. The number of each type of follicles was counted, and scored per unit length (1cm) of mucosa.

Statistical analyses

The data were analyzed with statistical software (Stat View-J4.11, Abacus Concepts, Inc.) on a Power Macintosh 7100/80AV (Apple computer, Inc.). Statistics were evaluated using t-test, χ²-test, and correlation analysis. A value of P < 0.05 for each test was regarded as statistically significant.

Results

*H. pylori*

*Helicobacter* -like organisms observed in histological preparations with Giemsa stain were considered to be *H. pylori*⁵. The *H. pylori* was found in 65 cases out of total 84 cases (77.4%); it was evenly distributed all over the stomach (Tables 1, 2), the mean *H.p score* was 21.9%. As a representative of the whole stomach, histological findings in the P-f area of the lesser curva-

![Figure 2](https://via.placeholder.com/150)

*Figure 2. H.pylori* was clearly identified by Giemsa staining (a), although it is difficult to observe by HE staining (b) with operation material.

<table>
<thead>
<tr>
<th>Table 1. Comparison of histological findings between the lesser and greater curvatures (67 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>histological findings (mean ± SD)</td>
</tr>
<tr>
<td><strong>Helicobacter pylori</strong></td>
</tr>
<tr>
<td>neutrophil</td>
</tr>
<tr>
<td>lymphocyte</td>
</tr>
<tr>
<td>mucosal atrophy</td>
</tr>
<tr>
<td>intestinal metaplasia</td>
</tr>
<tr>
<td>primary follicle</td>
</tr>
<tr>
<td>secondary follicle</td>
</tr>
</tbody>
</table>

a. **p<0.05;  b. p<0.001;  c. p<0.0001**
Table 2. Comparison of histological findings between 3 histological areas (23 cases)

<table>
<thead>
<tr>
<th>histological findings (mean ± SD)</th>
<th>histological areas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P-f</td>
</tr>
<tr>
<td>Helicobacter pylori (Hp) (%)</td>
<td>22.0±23.4</td>
</tr>
<tr>
<td>neutrophil (N) (%)</td>
<td>27.2±27.1</td>
</tr>
<tr>
<td>lymphocyte (Ly) (%)</td>
<td>37.0±19.9</td>
</tr>
<tr>
<td>mucosal atrophy (A) (%)</td>
<td>72.7±20.3</td>
</tr>
<tr>
<td>intestinal metaplasia (Im) (%)</td>
<td>18.4±26.0</td>
</tr>
<tr>
<td>primary follicle (Lf1) (cm)</td>
<td>1.46±1.47</td>
</tr>
<tr>
<td>secondary follicle (Lf2) (cm)</td>
<td>1.24±1.02</td>
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</tbody>
</table>

Table 3. Histological findings in P-f area of the lesser curvature by H. pylori positivity

<table>
<thead>
<tr>
<th>histological findings (mean)</th>
<th>FG (n=20)</th>
<th>non-FG (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H. p (+)</td>
<td>H. p (-)</td>
</tr>
<tr>
<td>patient's age (y/o)</td>
<td>(n=20)</td>
<td>(n=9)</td>
</tr>
<tr>
<td>Helicobacter pylori (Hp) (%)</td>
<td>41.6</td>
<td>47.8</td>
</tr>
<tr>
<td>neutrophil (N) (%)</td>
<td>41.2</td>
<td>35.6</td>
</tr>
<tr>
<td>lymphocyte (Ly) (%)</td>
<td>29.3</td>
<td>24.6</td>
</tr>
<tr>
<td>mucosal atrophy (A) (%)</td>
<td>50.4</td>
<td>38.6</td>
</tr>
<tr>
<td>intestinal metaplasia (Im) (%)</td>
<td>64.0</td>
<td>48.3</td>
</tr>
<tr>
<td>primary follicle (Lf1) (cm)</td>
<td>10.7</td>
<td>12.6</td>
</tr>
<tr>
<td>secondary follicle (Lf2) (cm)</td>
<td>1.98</td>
<td>1.86</td>
</tr>
</tbody>
</table>

A in L.C. < 40% (n=9)         | 54.9      | 17.5          |
A in L.C. > 40% (n=36)        | 31.7      | 17.5          |
A in L.C. > 40% (n=16)        | 7.6       | 0             |
A in L.C. < 40% (n=3)         | 21.4      | 0             |

A = in L.C.: the value of mucosal atrophy in the entire lesser curvature.

Lymphoid follicular hyperplasia

Lymphoid follicles (Lf1, Lf2) were more frequently observed in the greater curvature than in the lesser curvature (Lf1; p < 0.05; Lf2; p < 0.001) (Table 1), and more frequently observed in the P-f or f-F areas than in the F-C area (p < 0.05) (Table 2). A statistically significant difference in H. pylori positivity between the two types of lymphoid follicles was observed (Table 3); the score of the secondary lymphoid follicle (Lf2) demonstrated a more obvious association to H. pylori positivity than did the score of the primary one (Lf1) (Figure 3). Both Lf1 and Lf2 scores had positive statistical correlation with the H.p score in the P-f area of the lesser curvature (Lf1; r = 0.40, p < 0.0001; Lf2; r = 0.45, p < 0.0001).

Neutrophilic and lymphocytic infiltration

The scores of neutrophilic (N) and lymphocytic infiltration (Ly) were significantly higher in H. pylori positive cases (p < 0.0001) (Table 3). A positive correlation with the H.p score was seen in N (r = 0.30, p < 0.005), but was unclear in Ly. The score of lymphocytic infiltration presented a positive correlation with the score of lymphoid follicles (Lf1; r = 0.46, p < 0.0001; Lf2; r = 0.58, p < 0.0001).

Patient's age, mucosal atrophy, and intestinal metaplasia

The scores of H.p and lymphoid follicles (Lf1 and Lf2) had inverse correlation to patient's age (H.p; r = -0.42, p < 0.05).
**Follicular gastritis**

A case in which the score of secondary lymphoid follicle (L\(_f\)\(_2\)) was 2.0/cm or more in the P-\(_f\) area of the lesser curvature was defined as follicular gastritis (FG) (Figure 4), and that in which the score of L\(_f\)\(_2\) was less than 2.0/cm, as non-follicular gastritis (non-FG). Twenty out of the 84 cases fit the criteria for FG (24%), and sixty-four cases were classified as non-FG (76%).

The positive ratio of \(H.\text{pylori}\) infection in the FG cases (20/20, 100%) was higher than that in the non-FG cases (45/64, 70.3%) (\(\chi^2 = 7.7, p < 0.01\)). The \(H.\text{pylori}\) score of FG (41.2 \(\pm\) 28.6%) was higher than that of non-FG (14.9 \(\pm\) 22.0%) (\(p < 0.0001\)). Between the FG and the non-FG cases, there was a significant difference in L\(_f\)\(_2\) (\(p < 0.0001\)) and Ly (\(p < 0.0001\)), but not in L\(_f\)\(_1\) and N. The mean age of the FG cases (41.6 \(\pm\) 11.6y) was significantly younger than that of the non-FG cases (54.7 \(\pm\) 13.7y) (\(p < 0.001\)). The scores of mucosal atrophy and intestinal metaplasia were less in FG cases than in non-FG cases (A: \(p < 0.05\); Im: \(p < 0.001\)) (Table 4-1).

As the scores of \(H.\text{pylori}\) and lymphoid follicles showed an inverse correlation with the patient’s age, we examined what phase the FG would fall under in the chronology of \(H.\text{pylori}\)-associated mucosal changes. In a dispersion map of \(H.\text{pylori}\) scores by age, the FG cases overlapped a part of the \(H.\text{pylori}\) positive cases of the non-FG (Figure 5). Therefore, by \(H.\text{pylori}\) positivity and the degree of mucosal atrophy (atrophy) in the lesser
Table 4-1. Comparison of histological findings between the follicular gastritis (FG) and the non-FG (in P-I area of lesser curvature)

<table>
<thead>
<tr>
<th>histological findings (mean ± SD)</th>
<th>FG (n=20)</th>
<th>non-FG (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>patient’s age (y/o)</td>
<td>41.6±11.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>54.7±13.7&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Helicobacter pylori (Hp) (%)</td>
<td>41.21±28.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>14.90±22.6&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>neutrophil (N) (%)</td>
<td>29.3±22.6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>23.20±24.1&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>lymphocyte (Ly) (%)</td>
<td>50.4±23.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>28.5±16.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>mucosal atrophy (A) (%)</td>
<td>64.0±20.0&lt;sup&gt;d&lt;/sup&gt;</td>
<td>78.0±24.4&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>intestinal metaplasia (Im) (%)</td>
<td>10.7±17.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>42.9±36.8&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>primary follicle (Lf&lt;sub&gt;p&lt;/sub&gt;) (cm)</td>
<td>1.98±1.15</td>
<td>1.48±1.25</td>
</tr>
<tr>
<td>secondary follicle (Lf&lt;sub&gt;s&lt;/sub&gt;) (cm)</td>
<td>4.01±1.44&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.68±0.65&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a, b, c, d, e</sup> p<0.001; <sup>;</sup> p<0.0001; <sup>c</sup> p<0.05

Table 4-2. Comparison of histological findings between the follicular gastritis (FG) and the non-FG (in P-I area of lesser curvature)

<table>
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<tr>
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<tr>
<td>secondary follicle (Lf&lt;sub&gt;s&lt;/sub&gt;) (cm)</td>
<td>4.01</td>
<td>0.86</td>
</tr>
</tbody>
</table>

<sup>A in L.C.<40% | A in L.C.<40% | A in L.C.<40% | A in L.C.<40%</sup> | (n=9) | (n=36) | (n=16) | (n=3) |

A in L.C.: the value of mucosal atrophy in the entire lesser curvature.

curvature, which was thought to better reflect chronological mucosal changes, the non-FG cases (64 cases) were sub-classified into 4 groups: group A (n = 9, Lf<sub>p</sub> < 2.0/cm, Hp+, atrophy < 40%), group B (n = 36, Lf<sub>p</sub> < 2.0/cm, Hp+, atrophy ≥ 40%), group C (n = 16, Lf<sub>p</sub> < 2.0/cm, Hp+, atrophy ≥ 40%), and group D (n = 3, Lf<sub>p</sub> < 2.0/cm, Hp−, atrophy < 40%) (Table 4-2).

The mean patient’s age and the score of intestinal metaplasia (Im) increased from group A to group C; conversely, the Hp score decreased. Although the scores of lymphocytic infiltration (Ly) and lymphoid follicles (Lf<sub>p</sub>, Lf<sub>s</sub>) also decreased, that of neutrophilic infiltration (N) maintained a high level in group A and group B. In group D, with slight mucosal atrophy, neither inflammation nor intestinal metaplasia was seen. The FG cases exhibited a scoring pattern close to that of group A (Table 4–2).

Discussion

Because no lymphoid follicle exists in the natural gastric mucosa, it is thought that the lymphoid follicles are raised by an immune reaction against daily foods and drinks or specific microorganisms<sup>26</sup>. In this study, it was clarified that the secondary lymphoid follicles had resulted from a specific reaction to H.pylori, and that H.pylori infection was a major cause of lymphoid follicular hyperplasia.

Similarly to several reports<sup>22,23,29</sup>, the distribution of lymphoid follicles depended on differences in the histological mucosal structure. That is, there were more
lymphoid follicles in the pyloric-gland or its intermediate area than in the fundic-gland area, and more in the lesser curvature than in the greater curvature.

Dragosics et al. (1985)\textsuperscript{30}, and Mohri (1987)\textsuperscript{31} reported that 26.5 to 32.2% of gastric malignant lymphomas were found in the antrum or pyloric gland area (corresponding to the P–F area of this study), 54.2 to 67.6% in the body or intermediate zone (F–F area), and 5.9 to 13.6% in the cardiofundic region or fundic glandic area (F–C area). Although it is difficult to compare or contrast the histological division of the stomach with the anatomical one, the distribution of malignant lymphomas was similar to that of lymphoid follicles.

The distribution of lymphoid follicles, however, did not always coincide with the diffuse distribution of \textit{H.pylori}. There are two reasons for this. The first, ammonia produced by the \textit{H.pylori} urease enzyme is a main factor causing injury to the gastric mucosa. As the ammonia flows towards the distal part of the stomach together with gastric mucus, more severe inflammation will be raised in the anulus and antrum.\textsuperscript{32,33} The second, different from neutrophilic infiltration that means a direct inflammatory response, lymphocytic infiltration as well as lymphoid follicular hyperplasia is thought to be an indirect and a secondary immune response to \textit{H.pylori} infection. Recently, it is suggested that MALT-type lymphoma may be derived from autoreactive B cells provoked on the background of \textit{H.pylori}-induced inflammation.\textsuperscript{34–36}

Aging and its ensuing mucosal atrophy or intestinal metaplasia affects \textit{H.pylori} infection or its resultant mucosal inflammation. In this study, grouping of the cases by mucosal state enabled us to infer somewhat the age-dependent histological changes of the gastric mucosa (Table 4–2, Figure 6).

The FG group was seen mainly in patients in the fifth decade of life. It not only had a lot of secondary lymphoid follicles but also had a high \textit{H.p} score, a large amount of neutrophilic infiltration, and a little intestinal metaplasia. On the other hand, patients in group A of the non-FG, which could be called active non-atrophic gastritis, presented histological findings similar to those of the FG group, except for the number of secondary lymphoid follicles and the degree of mucosal atrophy. The difference of lymphoid follicular hyperplasia between the FG group and group A, may be caused by individual differences in the immunological reactivity to \textit{H.pylori}. That is, the FG group might represent a special type of active non-atrophic gastritis (group A).

The group B patients were mostly seen in the sixth decade. Although this group exhibited advanced mucosal atrophy and marked intestinal metaplasia, a low \textit{H.p} and high level of neutrophilic infiltration was maintained. Thus the group B patients could be identified as active atrophic gastritis. The members of group C presented in the seventh decade, free from \textit{H.pylori} infection, with little neutrophilic infiltration, and further advanced intestinal metaplasia. They suited the class of non-active atrophic gastritis. The group D patients, who had neither inflammatory findings nor intestinal metaplasia, could be regarded as almost normal cases. The relationship between age and \textit{H.p} score of the FG group and the groups A to D of non-FG were shown in Figure 6.

Genta et al. have presented the hypothesis that intestinal metaplasia is a progressive and irreversible phenomenon, and that \textit{H.pylori} infection may play a role as its promoter.\textsuperscript{10} They described that after the eradication of \textit{H.pylori}, the number of lymphoid follicles decreased in accordance with the disappearance of

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure6.png}
\caption{Eighty-four cases were classified into follicular gastritis (FG: L1 $\geq$ 2.0/cm) and non-follicular gastritis (non-FG: L1<2.0/cm) depending on the number of secondary lymphoid follicle (L1). Further, depending on the positivity of \textit{H.pylori} (\textit{H.p}) and the degree of mucosal atrophy (atrophy) in the lesser curvature, the non-FG cases were sub-classified into 4 groups. A (\textit{H.p+}, atrophy–40%); active non-atrophic gastritis; B (\textit{H.p+}, atrophy 40%): active atrophic gastritis; C (\textit{H.p+}, atrophy 40%): non-active atrophic gastritis; and D (\textit{H.p+}, atrophy–40%): almost normal cases. Each oval circle is drawn to indicate the mean score by the center of the circle, and SD by the horizontal and vertical diameters.}
\end{figure}
inflammatory cells, although the mucosal atrophy and intestinal metaplasia did not change. It is still unclear, whether group C in this study, which included cases with severe intestinal metaplasia and no H. pylori infection, really means the disappearance of H. pylori or not; however, inflammatory cells and lymphoid follicles decreased with the progression of intestinal metaplasia and the decreased amount of H.p. It could be inferred that the FG or active non-atrophic gastritis (group A) may transform to non-active atrophic gastritis (group C) through active atrophic gastritis (group B) (Figure 6).

In gastric lymphoma, the background gastric mucosa is atrophic in most cases, and the frequency of H.pylori infection or seropositivity is higher in low-grade malignant lymphoma than in high-grade. This may mean that H.pylori colonization decreases in amount or disappears in accordance with the progression of the lymphoma. Therefore, it is supposed that there is large amount of H.pylori and advanced mucosal atrophy when lymphoma is first appearing.

In this study, the FG cases, which were thought to be caused by large amounts of H.pylori, exhibited a lot of lymphoid follicles and advanced mucosal atrophy, compared with non-follicular active non-atrophic gastritis seen in patients of the same generation. These observations that the characteristics of the FG cases are similar to those of the low-grade gastric lymphoma, may suggest that gastric lymphoma will arise from the FG caused by rampant H.pylori infection.

Eidt et al. examined 162 cases of gastric lymphoma. They reported that lymphoid follicular hyperplasia existed also in areas distant from tumors and suggested that the lymphoid follicular hyperplasia was a background phenomenon of the tumor development, rather than a response to tumors. Although it remains unclear whether lymphoid hyperplasia is a necessary condition or not, it is thought that a background mucosal state such as would facilitate lymphoid hyperplasia or B-cell activation is required to give rise to malignant lymphoma.

In the stage of FG, the proliferation of B-cells is activated by continuous antigen stimulation of H.pylori. If the transformation from FG to non-active atrophic gastritis is not going well, and if the term of active H.pylori inflammation is prolonged, the patients will be in a high-risk condition for the occurrence of gastric lymphoma.

The combined findings from several reports show that the mean age of low-grade gastric lymphoma patients was 55–57 years, and of high grade 64–67 years. The mean for the FG patients in our study was 41.6 years, which was higher than that reported by Zeribb et al. (36.4y). If MALT lymphoma occurs on the background of the FG, 10 to 20 years would be needed from the initiation of follicular gastritis to the development of MALT-type gastric lymphoma.

References