

# Antibiotic Treatment of Gastric Lymphoma of Mucosa-Associated Lymphoid Tissue

## An Uncontrolled Trial

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**Background:** Gastric lymphoma of mucosa-associated lymphoid tissue (MALT) is related to *Helicobacter pylori* infection and may depend on this infection for growth.

**Objective:** To determine the response of gastric MALT lymphoma to antibiotic treatment.

**Design:** Prospective, uncontrolled treatment trial.

**Setting:** University hospital referral center and three collaborating university and community hospitals.

**Patients:** 34 patients with stage I or stage II N1 gastric MALT lymphoma.

**Intervention:** Two of three oral antibiotic regimens—1) amoxicillin, 750 mg three times daily, and clarithromycin, 500 mg three times daily; 2) tetracycline, 500 mg four times daily, and clarithromycin, 500 mg three times daily; or 3) tetracycline, 500 mg four times daily, and metronidazole, 500 mg three times daily—were administered sequentially (usually in the order written) for 21 days at baseline and at 8 weeks, along with a proton-pump inhibitor (lansoprazole or omeprazole) and bismuth subsalicylate.

**Measurements:** Complete remission was defined as the absence of histopathologic evidence of lymphoma on endoscopic biopsy. Partial remission was defined as a reduction in endoscopic tumor stage or 50% reduction in the size of large tumors.

**Results:** 34 patients were followed for a mean ( $\pm$ SD) of  $41 \pm 16$  months (range, 18 to 70 months) after antibiotic treatment. Of 28 *H. pylori*-positive patients, 14 (50% [95% CI, 31% to 69%]) achieved complete remission, 8 (29%) achieved partial remission (treatment eventually failed in 4 of the 8), and 10 (36% [CI, 19% to 56%]) did not respond to treatment. Treatment failed in all 6 (100% [CI, 54% to 100%]) *H. pylori*-negative patients. Patients with endoscopic appearance of gastritis (stage I T1 disease) were most likely to achieve complete remission within 18 months. Tumors in the distal stomach were associated with more favorable response than tumors in the proximal stomach.

**Conclusions:** A subset of *H. pylori*-positive gastric MALT lymphomas, including infiltrative tumors, may respond to antibiotics. The likelihood of early complete remission seems to be greatest for superficial and distal tumors.

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Gastric low-grade B-cell lymphoma is related to *Helicobacter pylori* infection according to histopathologic, epidemiologic, and clinical characteristics. Although normal gastric mucosa does not contain organized lymphoid tissue, lymphoid follicles develop with *H. pylori* infection (1) and with autoimmune diseases, such as the Sjögren syndrome (2). Low-grade B-cell lymphoma has been postulated to arise within this mucosa-associated lymphoid tissue (MALT) and is often called low-grade MALT lymphoma (3, 4).

The incidence of gastric low- and high-grade MALT lymphoma is increased in populations with a high prevalence of *H. pylori* infection, and *H. pylori* infection has been reported in up to 90% of patients with low-grade MALT lymphoma (4–6). In addition, investigators have shown that growth of this tumor may depend on antigenic stimulation by *H. pylori*: They demonstrated that the proliferation of lymphoma B cells in cell culture can be stimulated by *H. pylori*-specific T cells and related cytokines in the presence of *H. pylori* (7). On the basis of these findings, trials of antibiotic treatment of gastric low-grade MALT lymphoma have been initiated, and the regression of lymphoma after cure of *H. pylori* infection has been reported in a high proportion of patients with low tumor burden (8–13). Data on patients with significant tumor infiltration are still forthcoming (13, 14).

Because MALT lymphoma has only recently been approached as a distinct clinicopathologic entity (15, 16), its natural history and clinical course are not fully defined. Current data suggest that it is often an indolent tumor with long periods of mild activity and confinement to the stomach. Patients often present with nonspecific upper intestinal discomfort, ulcer-associated symptoms, or gastric bleeding. The endoscopic appearance may suggest benign gastritis, and extensive biopsies may be required for diagnosis. Progression to significant tumor mass, dissemination, or transformation to high-grade, aggressive lymphoma occur in an undefined subset of pa-

tients, who may present with early satiety or weight loss. Spontaneous remissions are rare (17–20).

Because low-grade MALT lymphoma is an uncommon, often indolent form of cancer with few clinical findings and because the risk for progression to high-grade MALT lymphoma is still unknown (15, 16), definitive data on cure require long-term follow-up of large cohorts from standardized clinical trials. This report presents an interim analysis of an ongoing trial designed to determine the long-term response of low-grade gastric MALT lymphoma to antibiotic treatment and to define criteria for treatment and follow-up.

## Methods

### Patients

Patients with gastric MALT lymphoma restricted to the stomach and perigastric lymph nodes (modified Ann Arbor stage I and II N1) were eligible for the study. The University of Texas, M.D. Anderson Cancer Center (MDACC), Internal Review Board approved the study, and all patients provided written informed consent. The National Cancer Institute and the institutional review boards of participating institutions approved the multi-institutional protocol. To enable a follow-up period of at least 18 months, only patients treated before May 1997 were included in this analysis.

### Study Design and Treatment

The interim data are derived from an ongoing, prospective, uncontrolled treatment trial with third-party patient registry. Patients were studied at four participating centers. Pathologic diagnosis and resolution of MALT lymphoma were confirmed at MDACC, and all but one patient were examined endoscopically at MDACC.

Study design included 1) tumor staging with bilateral bone marrow biopsies and aspirates and computed tomography of the abdomen and pelvis done at baseline and yearly; 2) endoscopy at baseline, at weeks 6 to 8, at 3- to 4-month intervals thereafter until resolution of MALT lymphoma was seen on two consecutive endoscopies, at 6-month intervals thereafter for 2 years, and then yearly thereafter; and 3) endoscopic ultrasonography at baseline and at each endoscopy until resolution of masses or infiltration of the muscularis propria, if present (defined as thickness > 2 mm or obliteration of wall architecture), and then at 6- to 12-month intervals.

The treatment protocol consisted of two of the following three oral antibiotic regimens—1) amoxicillin, 750 mg three times daily, and clarithromycin, 500 mg three times daily; 2) tetracycline, 500 mg

four times daily, and clarithromycin, 500 mg three times daily; or 3) tetracycline, 500 mg four times daily, and metronidazole, 500 mg three times daily—administered sequentially for 21 days at baseline and at 8 weeks along with a proton-pump inhibitor (lansoprazole, 30 mg twice daily [ $n = 29$ ], or omeprazole, 20 mg twice daily [ $n = 5$ ]), and bismuth subsalicylate, two tablets four times daily. Patients who were allergic to penicillin received the tetracycline-based regimens.

### Tumor Staging

Tumors were staged endoscopically to separate superficial gastritis from significant ulcers and infiltration and from mass lesions. A modified Ann Arbor staging system that incorporated changes proposed by Blackledge, Musshoff, and Rohatiner and their coworkers was used initially (21–23). The TNM (tumor, node, metastasis) classification of the American Joint Committee on Cancer and Union Internationale Contre le Cancer (24, 25), which corresponds to the modified Ann Arbor staging, was subsequently adapted and applied (Table 1). The extent of tumor (T) infiltration through the stomach wall and to adjacent organs corresponds to T staging of gastric cancer. Modified Ann Arbor stage I corresponds to stage I T1–4 N0 M0. Modified Ann Arbor stage II<sub>1</sub> (22) (involvement of perigastric lymph nodes) corresponds to stage II T1–4 N1 M0. Modified Ann Arbor stage II<sub>2</sub> (22) (involvement of distant lymph nodes caudal to the diaphragm, including para-aortic and retroperitoneal lymph nodes) corresponds to stage II T1–4 N2 M0. Ann Arbor stage III (lymph node involvement on both sides of the diaphragm) is designated by stage III T1–4 N3 M0. Ann Arbor stage IV (organ metastasis or involvement of a second extranodal site) is designated by stage IV T1–4 N0–3 M1.

### Criteria for Response

Response to treatment was evaluated at 3- to 4-month intervals beginning with the fifth month after treatment. Treatment was considered to have failed if patients did not meet criteria for improvement; these patients were removed from the study. In stage I T2, I T3, and II N1 tumors, improvement was defined as regression to a lower stage, 30% reduction in abnormal wall thickness, or 30% reduction in the size of the tumor mass (product of the greatest diameters). These patients remained in the study if sequential improvement was evident at each 3-month interval. Patients with persistent mucosal disease (stage I T1) documented by histopathology were formally reviewed at 12-month intervals; a consensus on withdrawal from or continuation in the study was based on clinical considerations, current knowledge, and patient preference. Initially,

**Table 1. Staging of Gastric Lymphoma of Mucosa-Associated Lymphoid Tissue**

Ann Arbor Stage*	TNM Stage	Endoscopic Appearance	Extent of Involvement
I	T1 N0 M0	Normal appearance, erythema, erosions, nodules < 3 mm, ulcers < 1 cm†	Normal appearance, mucosa, submucosa
I	T2 N0 M0	Ulcers ≥ 1 cm, nodules ≥ 3 mm, mass < 5 cm; induration	Muscularis propria
I	T3 N0 M0	Mass ≥ 5 cm	Serosa
I	T4 N0 M0	Mass ≥ 5 cm	Invasion of adjacent organs
II	T1-4 N1 M0‡	Any of the above	Perigastric lymph nodes
II	T1-4 N2 M0§	Any of the above	Regional lymph nodes more distant than in N1 disease, including retroperitoneal, mesenteric, and para-aortic lymph nodes
III	T1-4 N3 M0	Any of the above	Lymph nodes on both sides of the diaphragm
IV	T1-4 N0-3 M1	Any of the above	Visceral metastases (e.g., bone marrow) or second extranodal site (e.g., parotid)

\* Stage corresponds to the Ann Arbor classification based on histopathologic diagnosis of gastric biopsy specimens and staging by endoscopic ultrasonography or computed tomography and bone marrow biopsy. Tumor (T) depth and involvement of lymph node (N) and metastases (M) correspond to the American Joint Committee on Cancer and Union Internationale contre le Cancer TNM classification adapted for gastric lymphoma.

† Sizes indicate the greatest dimension.

‡ Equivalent to modified (Mushoff) Ann Arbor stage II<sub>1</sub>.

§ Equivalent to modified Ann Arbor stage II<sub>2</sub>.

patients with persistent stage I T1 disease were withdrawn from the study at 12 months ( $n = 2$ ). Subsequently, patients with persistent stage I T1 disease were observed for more than 36 months if improvement was documented at 12-month intervals. Criteria for improvement in stage I T1 disease included reduction in the number of affected gastric sites or affected biopsy specimens or improved histologic score (8), endoscopic appearance of progressive atrophy and scarring, or resolution of abnormal wall thickness on endoscopic ultrasonography.

Complete remission was defined as the absence of histopathologic evidence of lymphoma and an endoscopic appearance of gastritis or better. Partial remission was defined as a reduction in endoscopic stage in stage I T2 disease or at least 50% reduction in the size of the mass lesions in stage I T3 or II T3 N1 disease. In stage I T1 disease, partial remission was defined as at least 75% reduction in the number of gastric sites or biopsy specimens showing lymphoma. Treatment was considered to have failed in patients who met criteria for failure or who were withdrawn from the study before complete remission occurred.

### Endoscopy and Biopsies

The gastric mapping protocol included 2 or more maximum-capacity biopsies from each of 7 to 12 areas of the gastric map (26) and at least 6 biopsies from 2 or more of the most abnormal areas. The more extensive mapping was done at baseline and at clinically relevant time points. Studies, done at defined intervals, included routine histopathology, *H. pylori* testing by Genta stain, rapid urease test (CLO-test, Delta West, Bentley, Australia) or serology, Southern blot or polymerase chain reaction (PCR) for immunoglobulin gene rearrangement analysis, and immunoglobulin light-chain immunocytochemistry.

### Diagnostic Criteria

Low-grade B-cell MALT lymphoma was diagnosed by established histologic criteria (15, 27), including 1) a dense diffuse infiltrate of marginal-zone centrocyte-like B cells with round to slightly irregular nuclear contours, often with abundant pale cytoplasm; 2) presence of lymphoepithelial lesions, characterized by infiltration and disruption of gastric glands or crypts by groups of neoplastic lymphoid cells; and 3) absence of any areas where large cells predominate. Minor criteria supporting but not essential for diagnosis included presence of immunoglobulin light-chain restriction; presence of residual secondary follicle centers with or without intact mantles; and presence of follicular colonization, defined as replacement of follicle centers by neoplastic lymphoid cells. Immunophenotypic expression of pan-B-cell antigens, such as CD20, and lack of expression of CD5 or CD10 supported the diagnosis. Patients with foci of large-cell transformation were excluded from the study.

### Southern Blot and Polymerase Chain Reaction

High-molecular-weight DNA was isolated from frozen tissue by conventional proteinase K and organic extraction procedures. Aliquots of purified DNA were individually digested to completion with restriction enzymes Hind III, EcoR I, and BamH I, were size-fractionated on 0.7% agarose gels, were vacuum-transferred to Sure blot membranes, were hybridized with <sup>32</sup>P-labeled probes for the immunoglobulin heavy-chain joining region (*JH*) gene (Oncor, Gaithersburg, Maryland), and were subjected to autoradiography for 96 hours at 70 °C.

Polymerase chain reaction amplification was performed in an automated DNA Thermal Cycler (Perkin-Elmer Cetus, Norwalk, Connecticut) by using primers directed to framework 3 of the vari-

able region (5'-CTGTTCGACACGGCCGTGTATT-ACTG-3') and to the conserved 3' region of *JH* segments (5'-AACTGCAGAGGAGACGGTGACC-3'). The reaction mix containing 0.5  $\mu$ g of DNA was subjected to 30 cycles of PCR. Eighteen microliters of PCR product was resolved by electrophoresis on 5% polyacrylamide gel, was stained with ethidium bromide, and was visualized under ultraviolet light. The size-fractionated PCR products were transferred to Sure blot membranes (Oncor, Gaithersburg, Maryland), were hybridized with a <sup>32</sup>P-labeled *JH*-specific internal oligo probe, and were autoradiographed as described elsewhere (28).

### Statistical Analysis

The initial analysis compared responses in *H. pylori*-positive patients with responses in *H. pylori*-negative patients by using the Fisher exact test. Because *H. pylori*-positive MALT lymphomas are considered a distinct biological and clinical entity (3, 4, 8), all subsequent analyses were performed and reported separately in *H. pylori*-positive patients. A two-tailed Fisher exact test was used to test for an association between response to treatment and tumor stage or anatomic location. Associations with a *P* value less than 0.05 were considered worthy of further study. The proportions of patients achieving complete remission of MALT lymphoma in different groups and the differences in these proportions are reported with their exact 95% CIs. The statistical analysis was performed by using StatXact software, version 3.0 (Cytel Software Corp., Cambridge, Massachusetts). Continuous variables are expressed as the mean  $\pm$ SD.

## Results

Thirty-seven patients with gastric low-grade MALT lymphoma were eligible. Two of these patients were

withdrawn from the study after the baseline evaluation: One had severe cardiovascular disease and one had alcoholism. One *H. pylori*-positive patient who had been responding was withdrawn at 6 months to receive chemotherapy. Thirty-four patients (19 women and 15 men) were followed for more than 18 months and are included in the analysis. The mean duration of follow-up was 41 months (range, 18 to 70 months). The patients' mean age was 57 years (range, 26 to 77). Twenty-eight patients had newly diagnosed lymphoma, and 6 had recurrent lymphoma 2 to 240 months after surgery (*n* = 3), chemotherapy (*n* = 4), or both.

### Cure of *Helicobacter pylori* Infection

Twenty-eight of the 34 patients had evidence of *H. pylori* infection according to serology and histopathology (*n* = 23), serology and rapid urease test (*n* = 1), serology alone (*n* = 3), or histology alone (*n* = 1). Histologic evidence of *H. pylori* infection persisted in 1 patient after the first course of antibiotic treatment but in no patients after the second course. Drug-related side effects were clinically minor and were consistent with those described in previous reports (29).

### Remission of Lymphoma

Fourteen (41% [95% CI, 25% to 59%]) of 34 patients achieved complete remission of MALT lymphoma, and treatment failed in 16 patients (47% [CI, 30% to 65%]). Eight patients (24%) achieved partial remission: Four of these patients continued to meet criteria for improvement and remain in partial remission, and treatment eventually failed in the other 4 (Table 2). The latter 4 patients are included among the 16 patients with treatment failure. Of 28 *H. pylori*-positive patients, 14 (50% [CI, 31% to 69%]) achieved complete remission and 8 (29%) achieved partial remission (Table 2). None of the 34 patients showed disease progression on

**Table 2. Response of Gastric Lymphoma of Mucosa-Associated Lymphoid Tissue to Antibiotic Treatment in 34 Patients According to *Helicobacter pylori* Status and Endoscopic Stage**

Variable	Patients	Patients in Whom Therapy Failed	Patients with Partial Remission	Patients with Complete Remission [95% CI]	Mean Time to Complete Remission (Range)
Positive for <i>H. pylori</i>					
Stage I T1 N0	10*	2	1	7 (70 [35-93])	6 (3-13)
Stage I T2 N0	12†	4	5‡	5 (42 [15-72])	19 (5-45)
Stage I T3 N0	1	0	0	1	6
Stage II T3 N1	5§	4	2‡	1 (20)	46
Negative for <i>H. pylori</i>					
Stage I	6¶	6	0	0**	

\* Includes one patient with recurrent tumor after chemotherapy who achieved complete remission.

† Includes one patient with recurrent tumor after chemotherapy in whom therapy failed.

‡ Therapy subsequently failed in two patients. These patients are also included among the patients in whom therapy failed.

§ Includes one patient with recurrent tumor after chemotherapy who achieved partial response.

|| Two patients with stage T1 disease, two with T2 disease, and two with T3 disease.

¶ Includes three patients with recurrent tumors.

\*\* *P* < 0.001 for association between response and *H. pylori* status by the Fisher exact test.

**Table 3. Predominant Tumor Location in 34 Patients with Gastric Lymphoma of Mucosa-Associated Lymphoid Tissue Stages I and II N1 According to *Helicobacter pylori* Status, Response to Antibiotics, and Tumor Stage**

Variable	Patients	Patients with Tumor in Proximal Stomach*	Patients with Tumor in Distal Stomach†	Patients with Tumor in Diffuse Locations
	←----- n ----->			
Positive for <i>H. pylori</i>				
Complete remission‡	14	4	5§	5
Failure	10	6	0	4
All				
Stage I T1 N0	10	2	4	4
Stage I T2 N0	12	7	1	4
Stages I T3 N0 and II T3 N1	6	4	0	2
Negative for <i>H. pylori</i>				
All stages¶	6	5	0	1

\* Includes the cardia, fundus, and body proximal to the antrum and incisura.

† Includes the antrum and incisura.

‡ Complete remission differed among proximal, distal, and diffuse tumors ( $P = 0.012$ ; Fisher exact test).

§ 73% difference (95% CI, 21% to 97%;  $P = 0.006$ ) compared with proximal stomach.

|| Excludes four active patients who achieved partial response.

¶ Two patients with stage I T1 disease, two with stage I T2 disease, and two with stage I T3 disease.

restaging with bone marrow biopsies and computed tomography during the study period, and none progressed to high-grade lymphoma. In two *H. pylori*-negative patients, however (stage I T2 and I T3 disease, respectively), tumor size increased according to endoscopic criteria at 12 and 5 months, respectively. No relapses occurred in patients who achieved complete remission, and no patients died.

*Helicobacter pylori*-positive patients with stage I T1 lymphomas ( $n = 10$ ) responded most readily (within 18 months) to antibiotic treatment. Seven of these patients (70% [CI, 35% to 93%]) achieved complete remission within 18 months of treatment (mean, 6.4 months [range, 3 to 13]; difference compared with combined stage I T2, I T3, and II N1, 48% [CI, 8% to 83%];  $P = 0.02$ ). One patient improved and is still in the study at 18 months of follow-up. Treatment failed in 2 patients, who subsequently declined chemotherapy or radiation but have not progressed at 54 to 60 months of follow-up. Among *H. pylori*-positive patients with stage I T2 lymphomas ( $n = 12$ ), only 5 (42% [CI, 15% to 72%]) achieved complete remission at a mean of 19.4 months (range, 5 to 45 months). Five patients with stage I T2 lymphomas achieved partial remission; 3 of these showed full regression according to endosonographic criteria at 12 to 20 months, but lymphoma was still seen on histopathology. Of note, in the subset of *H. pylori*-positive patients with newly diagnosed (nonrecurrent) stage I T2 lymphomas ( $n = 11$ ), 10 (91% [CI, 59% to 100%]) achieved partial remission or complete remission.

Of the 6 *H. pylori*-positive patients with stage I T3 or stage II T3 N1 lymphomas, 2 (stages I T3 and II T3 N1) achieved complete remission and 2 (stage II T3 N1) achieved partial remission. In *H. pylori*-positive patients, tumors that did not fully respond to treatment ( $n = 4$ ) were considerably larger (greater than semi-circumferential and greater than

150 cm<sup>2</sup>) than those that achieved complete remission (less than semi-circumferential and less than 75 cm<sup>2</sup>). Of interest, 1 patient with a stage II T3 N1 circumferential tumor with two perigastric lymph nodes achieved apparently complete remission at 12 months but had relapse with a 6-mm lesion at 16 months.

Among *H. pylori*-positive patients with newly diagnosed MALT lymphoma in whom infiltration was documented at baseline, infiltration of the muscularis propria fully resolved in 4 of 5 patients with stage I T2 disease and in 2 of 4 patients with stage II T3 N1 disease.

Lymphomas not associated with *H. pylori* infection responded poorly to antibiotic treatment ( $P < 0.001$ ). This treatment failed in all 6 *H. pylori*-negative patients with lymphomas. Anatomic location in the stomach also influenced the tumor response to treatment (Table 3). The complete remission rate differed among patients with proximal, distal, and diffuse tumors ( $P = 0.012$ ). Patients with distal tumors had a higher complete remission rate (100%) than patients with proximal tumors (27%) (difference, 73 percentage points [CI, 21 to 97 percentage points];  $P = 0.006$ ).

Tumor clonality was shown by restriction fragment analysis or PCR in 30 tumors and by immunoglobulin light-chain immunochemistry in 2 additional tumors. Ten of 14 tumors that achieved complete remission were clonal by Southern blot or PCR analysis. Thus far, the clonal bands have resolved in 5 of these 10 tumors.

Of the 16 patients in whom antibiotic therapy failed, 6 did not receive further radiation or chemotherapy because of patient preference ( $n = 5$ ) or serious concurrent illness ( $n = 1$ ). Tumors progressed in only 1 of these patients, at 24 months after failure of antibiotic treatment. Ten patients were treated with radiation ( $n = 1$ ), chemotherapy ( $n = 1$ ), or

both ( $n = 8$ ). Thus far, 9 of these patients have achieved complete remission and 1 has achieved partial remission.

## Discussion

Gastric low-grade MALT lymphoma is related to an infectious or autoimmune inflammatory process that may sustain tumor growth. Clinical studies have shown that a subset of these tumors is dependent on *H. pylori* antigen, as judged by the response to antibiotic treatment; other subsets are independent of *H. pylori* antigen, as judged by the lack of response to antibiotic treatment; and still others constitute a mixture of the two preceding types, as judged by partial response or relapse after apparently complete remission (8–14). In the clinical management of lymphoma, it is important to make this distinction early on. Doing so presents a challenge to define the clinical and biological characteristics of responding and unresponding tumors. The present study has elucidated several clinical variables related to response.

Systematic staging and long follow-up revealed that at all endoscopic stages, lymphomas confined to the stomach and perigastric lymph nodes can respond to antibiotic treatment, although the time to complete remission of infiltrative lesions may be considerable. Only superficial lesions were highly responsive. Seventy percent of *H. pylori*-positive patients with endoscopic stage I T1 disease attained complete remission within approximately 1 year (range, 3 to 13 months). Similarly, 100% complete remission occurred in Wotherspoon and colleagues' initial cohort of 6 patients with endoscopic appearance of gastritis (8), and an 86% complete remission was observed in Sackmann and colleagues' patients with mucosal disease in the German MALT Lymphoma Study Group (13). Roggero and colleagues (9) reported a 60% rapid complete remission rate in a group with a high proportion of mucosal-appearing tumors. These data, together with the clinical characteristics of stage I T1 disease, support the use of antibiotics as initial therapy in stage I T1 MALT lymphoma, provided that methodical staging and follow-up are done and endoscopic evidence for staging is unambiguous. The appropriate duration of observation before diagnosis of treatment failure remains to be defined. We define treatment failure in T1 disease as lack of histopathologic improvement at 12-month intervals.

Patients with infiltrative lesions were less likely to achieve complete remission within 18 months of follow-up, although a high partial remission rate was seen in stage I T2 tumors. Whether a clinically significant proportion of stage I T2 to II N1 lymphomas can achieve complete remission with anti-

biotic treatment and whether long-term observation of these patients is safe must be determined by studies with larger sample sizes. The main concern with antibiotic treatment of invasive lymphomas is the potential presence of an undiagnosed high-grade component and the potential transformation to high-grade lymphoma. This is of particular concern in large T3 tumors, the bulk of which remain inaccessible to endoscopic biopsies during long observation periods. Responding stage I T2 tumors, on the other hand, were found to become superficial within 20 months and were thus easily accessible to extensive biopsies and to sensitive ultrasonographic monitoring. In light of these considerations, the current data support observation of patients with stage I T2 disease under a strict staging and follow-up protocol similar to that described in the Methods section. The one exception is that endoscopic staging at 4-month rather than 3-month intervals is considered adequate. Enrollment of such patients in clinical trials is recommended.

The current data do not support the routine use of antibiotics as the sole therapy in patients with stage I T3–4 or stage II N1 tumors. These patients should be offered the option of chemotherapy or radiation therapy, which promises a complete remission rate greater than 90%, in addition to antibiotic treatment (18, 30). A cautious approach is supported by a recent report of treatment failure at short-term follow-up of tumors that involve the muscularis propria or serosa and of stage II N1 lymphomas and by reports of high-grade lymphoma in nonresponding patients who had surgical evaluation (13). In the current study, unresponding stage I T3 and stage II T3 N1 tumors were associated with large masses. Whether tumors that focally involve the serosa but lack significant masses behave like stage I T2 tumors remains to be studied.

Our findings underscore the clinical importance of endoscopic and endosonographic staging to differentiate gastritis or mucosal disease from significant ulceration or infiltration and advanced mass lesions. The TNM staging system, which is the current standard for the staging of solid tumors, was found to be well suited to the endoscopic staging of gastric MALT lymphoma (Table 1). The "T" designation is identical to that used for gastric cancer. The numerical designations of "N" stage correspond to stage II subscripts 1 and 2—designating perigastric (N1) and distant regional (N2) lymph nodes, respectively—in the Musshoff modification of the Ann Arbor staging and correspond to Ann Arbor stage III—designating lymph nodes on both sides of the diaphragm (N3). The TNM staging defines stage I T1 (tumor involving the mucosa or submucosa with endoscopic appearance of gastritis), which is

not defined by the Ann Arbor staging. Stage I T1 distinguishes a common presentation of gastric MALT lymphoma in the community setting and the clinical subset of patients with high and rapid response to *H. pylori* treatment, for whom antibiotics should be initially offered as a single therapy.

The importance of adequate biopsy sampling, gastric mapping, and histologic examination of the submucosa must be stressed because gastric MALT lymphoma is often multifocal and because of the high rate of falsely negative biopsy findings (data not shown). For example, all three of the *H. pylori*-positive patients with stage I T1 disease who did not achieve complete remission had one or more falsely negative endoscopy results.

In addition to advanced tumor stage, factors that adversely affected response were lack of *H. pylori* infection and location of the tumor primarily in the proximal stomach. The significance of anatomic location is probably related to the differing clinical course and pathology of distal, antral-predominant *H. pylori* gastritis and of proximal, corpus-predominant *H. pylori* gastritis. The former is associated with reversible active gastritis and peptic ulcer disease in developed countries; the latter is associated with multifocal atrophic gastritis, gastric cancer, and loss of *H. pylori* antibody titer after chronic infection, which are more common in technologically underdeveloped regions. Although both subsets of MALT lymphoma may be related to *H. pylori* infection, their biology and infiltrative potential may differ. Some of these differences may also be secondary to host factors. Proximal lymphoma might also be associated with *H. pylori* infection or may be *H. pylori*-independent autoimmune gastritis, which is generally proximal in distribution (31). Recent studies indicate that autoimmune gastritis may derive from *H. pylori* infection and suggest that antibiotic resistant tumors or slowly responding tumors may be sustained by autoantigen-responsive T cells (32, 33). Hence, the subset of *H. pylori*-negative MALT lymphomas probably includes autoimmune-related or autonomous tumors in patients with previous *H. pylori* gastritis.

The entity of stage I T1 MALT lymphoma (which includes mildly symptomatic or asymptomatic tumors with the benign endoscopic appearance of acute or chronic gastritis), as well as the emerging entity of monoclonal gastritis without histologic evidence of MALT lymphoma, poses challenges in the clinical evaluation and treatment of patients with *H. pylori* gastritis. On the basis of current knowledge, one could recommend inclusion of MALT lymphoma in the differential diagnosis during endoscopic examinations and inclusion of adequate biopsies for significant or atypical gastritis. We include biopsies of the antrum, incisura, mid-lesser and great-

er curvatures, and anterior and posterior portions of the proximal body. The increasing practice of empirical, nonendoscopic treatment of *H. pylori* may be expected to reduce the incidence and mortality rates of *H. pylori*-related high- and low-grade MALT lymphoma. The inherent risk that early lesions may remain undiagnosed in antibiotic-treated patients does not yet warrant changes in current indications for endoscopy. Studies of the incidence and natural history of asymptomatic or incidental MALT lymphoma in the setting of *H. pylori* gastritis should serve as a basis for further clinical practice guidelines.

Although low-grade MALT lymphoma is considered an indolent disease, an undefined subset of patients is probably at significant risk for progression (18). Supporting this idea are the observations that most patients in the current study presented with infiltrative lymphomas and that most gastric MALT lymphomas are high grade or combined low and high grade at presentation (19, 20). Reports of the regression of gastric low-grade MALT lymphoma in response to antibiotic treatment have raised the question of whether antibiotics should be the sole initial treatment for this tumor. In the current series, less than one third of the patients were highly likely to respond fully to antibiotic treatment by clinical criteria: *H. pylori* positivity and stage I T1 distal or diffuse tumors. The lower rate of complete remission in this study may be related to the rigorous biopsy and study protocol and the U.S. patient population. Until the clinical and cellular characteristics of *H. pylori*-dependent and *H. pylori*-independent tumors are better defined, it would be prudent to pursue a cautious approach to the treatment and follow-up of these patients.

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