Non-Hodgkin’s Lymphoma of Mucosa-Associated Lymphoid Tissue

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Key Words. Mucosa-associated lymphoid tissue • Non-Hodgkin’s lymphoma • Helicobacter pylori

Learning Objectives
After completing this course, the reader will be able to:
1. Outline the definition and classification of MALT lymphoma.
2. Summarize the current understanding of the pathogenesis of MALT lymphoma.
3. Articulate treatment options for patients with MALT lymphoma.

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Abstract
The concept of mucosa-associated lymphoid tissue (MALT) lymphomas was introduced by Isaacson and Wright in 1983. After more than 20 years of clinical research MALT lymphomas are now recognized as a distinct subtype of non-Hodgkin’s lymphoma (NHL) with unique pathogenic, histological, and clinical features. Although this subtype of NHL occurs frequently, optimal management remains elusive. This manuscript reviews features of the clinical presentation, diagnosis, pathology, molecular characteristics, and management of both gastric and non-gastric MALT lymphoma. The Oncologist 2006;11:1100–1117

Introduction
The concept of mucosa-associated lymphoid tissue (MALT) lymphomas was introduced by Isaacson and Wright in 1983. They described two cases of gastrointestinal (GI) lymphoma with histology resembling that of mucosa-associated lymphoid tissue rather than lymph nodes [1]. A year later, lymphomas of similar histology were identified in extraintestinal sites in these same patients [2]. After more than 20 years of clinical research, MALT lymphomas are now recognized as a distinct subtype of non-Hodgkin’s lymphoma (NHL) with unique pathogenic, histological, and clinical features. Although this subtype of NHL occurs frequently, optimal management remains elusive. This manuscript reviews features of the diagnosis, pathology, and management of MALT lymphoma.

Definition and Classification
MALT lymphomas constitute a group of low-grade extranodal B-cell neoplasms that share similar clinical, pathologic, immunologic, and molecular features and arise in the...
context of pre-existing prolonged lymphoid proliferation in mucosal sites. In the past, this disease was often misinterpreted as “pseudolymphoma,” but in recent years, it has been classified as a specific subtype of NHL.

The Revised European-American Lymphoma (REAL) classification first recognized MALT lymphoma as a discrete entity in 1994. MALT NHL was classified as a peripheral B-cell neoplasm, in the group of marginal zone B-cell lymphomas (MZLs) [3], with a marginal zone B cell being its normal counterpart. In the more recent World Health Organization (WHO) classification system, MZLs comprise three subtypes: nodal, extranodal (MALT type), and splenic.

The distinction between nodal and extranodal MZLs is clinically important. Despite overlapping morphologic features, they demonstrate distinct clinical behavior. Nodal MZL behaves as a conventional indolent and incurable low-grade lymphoma, often widely disseminated early in the disease course. Extranodal MALT lymphoma remains localized for an extended duration, lacks poor prognostic features, and has a superior 5-year overall survival rate (81% versus 56%) and failure-free survival rate (65% versus 28%) compared with its nodal counterpart [4].

The lymphoid tissue in which MALT lymphomas arise normally may be present at the site of origin (e.g., Waldeyer’s ring or intestinal Peyer’s patches) or may be acquired in the setting of chronic infection or autoimmune disorder. MALT lymphomas occur most commonly in the GI tract but have been described in a variety of extranodal sites including the ocular adnexa, salivary gland, thyroid, lung, thymus, and breast.

Histologic features of low-grade MALT lymphomas are similar regardless of the site of origin. This tumor is characterized by an infiltrate of “centrocyte-like” cells (small-to-medium-sized lymphocytes with abundant cytoplasm and irregularly shaped nuclei), but scattered transformed blasts (large cells) also are present. Nonmalignant reactive follicles are observed frequently. A pivotal feature is the presence of lymphoepithelial lesions, with invasion and partial destruction of mucosal glands and crypts by aggregates of tumor cells. The immunophenotype of a MALT lymphoma recapitulates that of the marginal zone B-cell. Typically, tumors express pan-B antigens (CD19, CD20, CD22, CD79a), but they lack CD5, CD10, CD23, and Bcl-1 expression. In rare cases, MALT lymphomas exhibit aberrant CD5 expression, which may be associated with a more aggressive clinical course [5]. Table 1 summarizes the immunophenotypic and genetic features of common small lymphocytic B-cell neoplasms included in the differential diagnosis of MALT lymphomas. Surface immunoglobulins that demonstrate light chain restriction are present on MALT lymphoma cells. In a prospective study by Wohrer and colleagues, 19 of 52 (36%) patients with newly diagnosed MALT lymphoma also were found to have a serum monoclonal gammopathy [6]. Plasmacytic differentiation is associated with the production of a paraprotein, correlating in turn with advanced disease, including involvement of lymph nodes and bone marrow [6, 7].

Molecular Characteristics

Subtypes of NHL have characteristic chromosomal alterations. Unique to MALT lymphomas are at least three reciprocal translocations: t(11;18)(q21;q21), t(1;14)(p22;q32), and t(14;18)(q32;q21). The translocation t(11;18)(q21;q21) is found in 18%–53% of cases in all anatomic MALT lymphoma sites [8, 9]. The translocation t(1;14)(p22;q32) is much less common, but more specific, and is found in gastric and pulmonary MALT lymphomas. The translocation t(14;18)(q21;q32), cytogenetically identical to the translocation involving BCL-2 in follicular lymphoma but affecting malt lymphoma translocation 1 gene (MALT1) in this case, has been described in approximately 20% of MALT lymphomas and involves rearrangement of the immunoglobulin heavy-chain locus (IGH) to the MALT1 gene [10]. It is more commonly found in lymphomas of the ocular adnexa, liver, and skin than of the GI tract or lung, and is frequently associated with other genetic abnormalities including trisomy 3 and 18. Trisomy 3 occurs in 60% of MALT lymphomas, but is not specific for this type of lymphoma [11].

Recent work on the products of these seemingly unrelated translocations has enhanced our understanding of the biology of MALT lymphomas. The translocation t(11;18)(q21;q21) results in a fusion of the apoptosis inhibitor 2 (API2) gene on chromosome 11q21 with the MALT1 gene on chromosome 18q21 [12–14]. The product of the translocation, a novel fusion protein API2-MALT1, markedly increases nuclear activation of nuclear factor (NF)-

Table 1. Immunophenotypic and cytogenetic features of small lymphocytic B-cell neoplasms

<table>
<thead>
<tr>
<th>Lymphoma type</th>
<th>CD5</th>
<th>CD10</th>
<th>CD23</th>
<th>CD43</th>
<th>Cytogenetic abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marginal zone/MALT lymphoma</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−/+</td>
<td>t(11;18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>t(1;14)</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>t(14;18)</td>
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<td></td>
<td>(q32;q21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>t(3;14) Trisomy 3, 18</td>
</tr>
<tr>
<td>SLL</td>
<td>+</td>
<td>−/−</td>
<td>+</td>
<td>+</td>
<td>Del 13q14 Trisomy 12</td>
</tr>
<tr>
<td>Follicular</td>
<td>−</td>
<td>+/+</td>
<td>−/+</td>
<td>−</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Mantle</td>
<td>+</td>
<td>−/+</td>
<td>−</td>
<td>+</td>
<td>t(11;14)</td>
</tr>
</tbody>
</table>

Abbreviations: MALT, mucosa-associated lymphoid tissue; SLL, small lymphocytic lymphoma.
κB, which induces the transcription of a number of genes involved in immunity, inflammation, and apoptosis. Translocation t(1;14) results in the juxtaposition of the coding region of BCL-10 to chromosome 14 with resulting over-expression of the Bcl-10 protein. The overexpressed Bcl-10 increases nuclear NF-κB, thus affecting the same apoptotic signaling pathway as the API2-MALT1 protein. The net result of these translocations is inhibition of apoptosis, conferring a survival advantage on affected cells.

Recently, an Austrian group observed a novel translocation, t(3;14)(p14.1;q32), in a thyroid MALT lymphoma [15]. In a series of 91 patients with MALT lymphoma who did not demonstrate the three previously recognized translocations, 10% harbored this t(3;14) translocation, including three of six thyroid, 4 of 20 ocular adnexa, and 2 of 20 cutaneous primaries, but no gastric, lung, or salivary gland lesions.

Some MALT lymphomas transform into diffuse large B-cell lymphomas (DLBCLs). Starostik and coworkers [16, 17] evaluated genetic abnormalities in MALT lymphomas and DLBCL. The t(11;18)(q21;q21) translocation was not identified in DLBCL. MALT lymphomas expressing t(11;18)(q21;q21) rarely harbored additional clonal aberrations. In contrast, 67% of t(11;18)(q21;q21)-negative MALT lymphomas had allelic imbalances, the most common of which was amplification of 3q26.2-27 (which contains the BCL-6 gene). All allelic imbalances in t(11;18)(q21;q21)-negative MALT lymphomas were also identified in DLBCL. The authors proposed that t(11;18)(q21;q21)-positive MALT lymphomas are genetically stable and do not transform into DLBCL, while t(11;18)(q21;q21)-negative MALT lymphomas with clonal aberrations could transform into DLBCL [16, 17].

Gastric MALT lymphomas are associated with Helicobacter pylori infection in 85%–90% of cases. They are classified as H. pylori-dependent and H. pylori-independent according to the presence of H. pylori infection and response to H. pylori-directed therapy. The t(11;18)(q21;q21) translocation is more common in H. pylori-negative gastric MALT lymphoma (53% of cases) than in H. pylori-associated gastric MALT lymphoma (23.7%–50% of cases) [18]. H. pylori-dependent cases exhibit greater methylation of CpG islands than H. pylori-independent cases; CpG island methylation leads to inactivation of tumor suppressor genes [19]. Nuclear expression of Bcl-10 and of NF-κB, with or without t(11;18)(q21;q21), has been shown to correlate with H. pylori independence [20].

**Clinical Features**

MALT lymphoma is the third most common NHL subtype, after DLBCL and follicular lymphoma. In a survey conducted by the Non-Hodgkin’s Lymphoma Classification Project, MALT lymphomas represented 7.6% of the total number of cases [21]. MALT NHL also represents the most common type of primary extranodal lymphoma.

The median age at presentation is in the sixth decade of life and there is a slight female predominance. Patients often have a history of autoimmune disease or *H. pylori* gastritis. The signs and symptoms depend on the involved extranodal site. The clinical course usually is indolent. MALT lymphoma often remains localized for prolonged periods of time, without progression even in the absence of treatment. When dissemination occurs, it is frequently to other mucosal sites. After therapy, relapse rates approached 40% in one retrospective analysis with a median follow-up of 47 months (range, 14–307 months); gastric MALT lymphomas were less likely to relapse than nongastric lesions (22% versus 48%) [22]. Rarely, the disease undergoes transformation to a more aggressive lymphoma type.

**Gastric MALT Lymphoma**

Gastric MALT lymphoma, with its unique dependence on *H. pylori* infection, has become the model for MALT lymphomagenesis. Although the stomach is normally devoid of mucosal lymphoid tissue, acquired tissue of the MALT type can develop in the setting of chronic *H. pylori* infection [23–25]. Many studies have reported the almost universal presence of *H. pylori* in gastric biopsies from patients with chronic gastritis [25, 26]. Infection with *H. pylori*, a Gram-negative organism, is prevalent worldwide. The incidence of *H. pylori* infection in the general population in the U.S. is approximately 30%, and up to 50% in individuals over age 50 [27]. However, only a small proportion of the *H. pylori*-infected population will develop MALT, and an even smaller fraction will go on to develop a MALT lymphoma. Genetic and environmental factors and differences in the virulence of *H. pylori* strains must play an important role in gastric MALT lymphoma development.

Investigation of these associated factors is in its infancy, but a recent German publication suggests that polymorphisms in toll-like receptor 4 (TLR4), the main receptor for lipopolysaccharide on marginal zone B cells and part of the innate immune response, may play a role in the neoplastic process [28]. Data also are accumulating regarding the part that free radicals may play; antioxidant capacity, affected by polymorphisms in the *IL1RN* and *GSTT1* genes and the presence of cytotoxin-associated antigen A (CagA)-positive strains of *H. pylori*, seems to represent an important component of MALT lymphomagenesis [29, 30].

Data from epidemiological, laboratory, and clinical studies support the causative role of *H. pylori* in MALT lymphoma development. A strikingly high incidence of gastric lymphoma observed in Northeastern Italy is accom-
panned by a remarkably high prevalence of *H. pylori* infection [31]. In one case-controlled study, previous *H. pylori* infection was associated with subsequent development of gastric lymphoma [32]. The most compelling evidence that chronic *H. pylori*-induced gastritis is a trigger for the development of low-grade gastric MALT lymphomas is provided in clinical studies in which eradication of *H. pylori* infection with antibiotics led to complete histologic and endoscopic remission of lymphoma [33–37].

In in vitro experiments, T cells activated by *H. pylori* in a strain-specific response stimulate proliferation of lymphoma cells [38]. In addition, gastric lymphoma cells show a pattern of somatic hypermutation, indicating that tumor cells are positively selected during a secondary immune response [39, 40]. Therefore, it is likely that the development of lymphoma is antigen driven in its early phase. This antigen dependency might explain the propensity of gastric lymphoma to remain localized for long periods of time. Interestingly, tumor-derived immunoglobulins frequently do not recognize *H. pylori*; rather they recognize autoantigens [41]. In fact, a Dutch group recently reported that, among B-cell lymphomas, MALT lymphomas possess a unique antibody repertoire: 18% of gastric and 41% of salivary lesions express B-cell antigen receptors with strong IgVH-CDR3 homology to rheumatoid factors [42]. It seems that a complex cascade of events, beginning with the interaction of antigen-presenting cells and T cells with bacterial antigens ultimately leads to the autonomous clonal proliferation of B cells and development of a MALT lymphoma.

### Clinical Presentation

Gastric MALT lymphoma affects patients of a wide range of ages, with a median age at presentation of 57 years. The incidence in both sexes is similar [43]. The majority of patients have localized disease at diagnosis. In a European series reporting on 93 patients with low-grade gastric MALT lymphoma, 88% of patients had disease confined to the stomach, either primarily in the antrum (41%) or multifocal (33%) [44]. t(11;18)(q21;q21)-positive lymphomas may present with more advanced features than their t(11;18)(q21;q21)-negative counterparts [17]. Dyspepsia and epigastric discomfort are the commonest presenting symptoms, but gastric bleeding is rare. Systemic B symptoms and bone marrow involvement are present in only 1%–8% of patients [44, 45]. Rarely, patients may have elevated lactate dehydrogenase or β2-microglobulin levels. A majority of patients have no abnormal findings on physical examination [46]. The endoscopic appearance of gastric low-grade lymphoma often mimics that of benign diseases such as chronic gastritis or a peptic ulcer [47].

### Diagnosis

Historically, the diagnosis and staging of GI tract lymphomas required an invasive surgical approach with laparotomy and resection. Progress in endoscopic and immunopathologic techniques now permits accurate diagnosis by endoscopic biopsy in over 90% of patients. Diagnostic gastric biopsies should be taken from multiple areas of endoscopically abnormal tissue, and histological gastric mapping should be completed with random sampling from macroscopically uninvolved mucosa. Biopsies from gastric low-grade MALT lymphoma usually display the characteristic histological features, including lymphoepithelial lesions and a diffuse infiltrate of marginal-zone “centrocyte-like” B cells (Figs. 1–3).

Often, it can be difficult to differentiate between a reactive lymphoid infiltrate and a low-grade MALT lymphoma. In such instances, demonstration of monoclonality can be helpful. Monoclonality is established either by light chain restriction or by assessment of immunoglobulin heavy chain gene rearrangements by the polymerase chain reaction (PCR). However, monoclonality also can be detected in uncomplicated chronic gastritis and has been shown to precede the histological evidence of malignant transformation [48, 49]. Therefore, gastric MALT lymphoma should not be diagnosed in the absence of supportive histological evidence.

### Staging

The Ann Arbor classification system developed for nodal lymphomas has limited value in staging primary extranodal tumors. An alternative staging system for GI tract lymphomas was proposed by Blackledge et al. [50] and later modified by Musshoff [51] and by the International Workshop in Lugano, Switzerland [52] (Table 2). Stage I is subclassified into I1 and I2 on the basis of tumor size (<5 cm) and depth of invasion (with or without penetration into serosa). Subscript “E” is reserved for GI tract lesions extending from the GI primary site to involve adjacent organs (e.g., pancreas, posterior abdominal wall). Ann Arbor stage III was deleted and supradiaphragmatic nodal disease was included within stage IV.

With the advent of endoscopic ultrasound (EUS), the depth of infiltration of the gastric wall by lymphoma was found to correlate strongly with the extent of lymph node involvement. Thus, it became possible to apply the tumor–node–metastasis (TNM) staging system, in which the depth of lymphoma infiltration measured by EUS corresponds to the T stage of gastric cancer [36]. This system correlates well with gastric lymphoma’s pattern of spread and has relevant prognostic implications.
In one study, non-contiguous lesions were shown to originate from the same malignant clone, which may explain reported recurrences of MALT lymphomas at the gastric stump following partial gastrectomy with negative margins.

Gastric MALT lymphomas tend to disseminate to other parts of the GI tract and to the splenic marginal zone. Overexpression of mucosal-homing receptor \( \alpha_4\beta_7 \) integrin, induced in gastric lymphoma cells by \( H. pylori \)-activated T cells, is most likely responsible for this phenomenon. The ligand for \( \alpha_4\beta_7 \) integrin, the mucosal addressin cell adhesion molecule (MAdCAM-1), is expressed in the intestinal mucosa and splenic marginal zone. Gastric lymphoma cells with secondarily overexpressed homing receptors are attracted to environments with high concentrations of their ligands. MALT lymphomas that present in nongastric sites develop gastric involvement in one third of cases.

In clinical practice, the staging evaluation includes all procedures routinely done in NHLs and, in addition, examination of Waldeyer’s ring and EUS (Table 3). The presence of \( H. pylori \) infection also needs to be documented. Occasionally, patients may require a small bowel series or barium enema for evaluation of the intestinal mucosa.

**Table 2. Staging of gastrointestinal (GI) tract lymphomas**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor confined to GI tract</td>
</tr>
<tr>
<td>I1</td>
<td>Infiltration limited to mucosa with or without submucosa</td>
</tr>
<tr>
<td>I2</td>
<td>Infiltration into muscularis propria, subserosa, or serosa, or both</td>
</tr>
<tr>
<td>II</td>
<td>Tumor extending into abdomen from primary GI site</td>
</tr>
<tr>
<td>II1</td>
<td>Local (paragastric in gastric lymphoma)</td>
</tr>
<tr>
<td>II2</td>
<td>Distant (para-aortic, para-caval, pelvic, inguinal)</td>
</tr>
<tr>
<td>II E</td>
<td>Penetration of serosa to involve adjacent organs or tissues</td>
</tr>
<tr>
<td>IV</td>
<td>Disseminated extranodal, or a GI tract lesion with supradiaphragmatic involvement</td>
</tr>
</tbody>
</table>

Although commonly described as a long-standing localized malignancy, gastric MALT lymphomas disseminate both locally and systemically more frequently than originally believed. Histological examination of gastrectomy specimens frequently reveals multiple tumor foci distributed throughout the gastric mucosa, including macroscopically normal regions. In one study, non-contiguous lesions were shown to originate from the same malignant clone, which may explain reported recurrences of MALT lymphomas at the gastric stump following partial gastrectomy with negative margins.

Gastric MALT lymphomas tend to disseminate to other parts of the GI tract and to the splenic marginal zone. Overexpression of mucosal-homing receptor \( \alpha_4\beta_7 \) integrin, induced in gastric lymphoma cells by \( H. pylori \)-activated T cells, is most likely responsible for this phenomenon. The ligand for \( \alpha_4\beta_7 \) integrin, the mucosal addressin cell adhesion molecule (MAdCAM-1), is expressed in the intestinal mucosa and splenic marginal zone. Gastric lymphoma cells with secondarily overexpressed homing receptors are attracted to environments with high concentrations of their ligands. MALT lymphomas that present in nongastric sites develop gastric involvement in one third of cases.

In clinical practice, the staging evaluation includes all procedures routinely done in NHLs and, in addition, examination of Waldeyer’s ring and EUS (Table 3). The presence of \( H. pylori \) infection also needs to be documented. Occasionally, patients may require a small bowel series or barium enema for evaluation of the intestinal mucosa. The role of positron emission tomography scanning is controversial; some groups find it useful for initial staging and follow-up, while others do not.

**Treatment**

Despite abundant literature on the histopathologic and biologic features of MALT lymphomas, treatment data remain limited. No publications of randomized, controlled trials have appeared to date and the results of older studies need to
be interpreted with caution. Variations in diagnostic criteria and staging procedures often preclude meaningful comparison of published series [63].

Gastric low-grade MALT lymphoma, in contrast to other low-grade lymphomas, is localized in over 80% of patients at presentation. The prognosis is very favorable, regardless of the type of treatment, with 5-year survival rates better than 80% [44]. The clinical course is usually indolent; in fact, some patients remain free of progression for several years without treatment [64]. The curative potential of treatment remains unclear as very long follow-up is needed with relapses reported many years after the initial diagnosis [65].

Eradication of H. pylori

Based on the close association between gastric MALT lymphoma and the presence of H. pylori infection, Isaacson and coworkers first examined the hypothesis that eradication of H. pylori would remove the “driving stimulus” for lymphoma growth and result in lymphoma regression [33]. Six patients with H. pylori infection and MALT lymphoma were treated with antibiotics. H. pylori infection was eradicated in all six patients and histological complete regression of lymphoma was observed in five of those patients. These results have been confirmed by several independent investigators (Table 4), and antibiotic treatment is now the standard first-line therapy for localized low-grade gastric MALT lymphoma. Using this strategy, complete remission (CR) can be expected in over 70% of patients presenting with localized disease [66].

A variety of regimens can be used to eradicate H. pylori infection. Each includes a combination of two or three antibiotics, such as amoxicillin, clarithromycin, tetracycline, and metronidazole, with a proton pump inhibitor or H2-receptor antagonist, with or without bismuth salicylate [67]. The time interval between eradication of H. pylori and lymphoma regression can vary from 6 to 14 months [68].

Unfortunately, 20%–30% of gastric MALT lymphomas associated with H. pylori do not regress after antibiotic therapy. In a study of 34 endosonographically staged patients, antibiotics induced CR in 70% of patients with tumor confined to the mucosa and submucosa, but in only 42% of patients with lymphoma involving the muscularis, subserosa, or perigastric lymph nodes [36]. French investigators achieved a CR rate of 43% in a series of 46 patients treated with antibiotics [69]. In their study, the only predictive factor for regression was the absence of nodal involvement (p < .0001), with CR rates of 79% in patients with negative lymph nodes by EUS and 56% in patients with positive nodes. The investigators also noted a difference between the response of superficial tumors and that of more deeply penetrating, mass lesions, although depth of invasion was not predictive in a multivariate analysis. Furthermore, none of the H. pylori-negative patients in that study responded to antibiotics. The molecular features of lymphoma cells also can be associated with resistance to antibiotics. Gastric lymphomas harboring translocation t(11;18)(q21;q21), including those at stage IE, do not respond to H. pylori eradication [70, 71].

An area of active investigation includes the search for factors associated with tumor recurrence. Neubauer and coworkers reported 2-year follow-up data for 40 patients who achieved a histologic CR after H. pylori eradication [35]. Of these patients, five relapsed, one distally and four locally. In three of these patients, no H. pylori could be detected. Fischbach et al. [37] reported on 56 patients with
H. pylori of 24 patients with stage I low-grade disease treated with recently published 10-year follow-up of a Spanish cohort reported by the International Extranodal Lymphoma Study logic evidence of MALT lymphoma. Similar findings were B-cell monoclonality, despite the disappearance of histologic cure after antibiotic treatment [73]. During a median follow-up of 33 months, 45% of those patients had persistent B-cell monoclonality on presentation and achieved histologic CR after antibiotic treatment [73]. During a median follow-up of 33 months, 45% of those patients had persistent B-cell monoclonality, despite the disappearance of histologic evidence of MALT lymphoma. Similar findings were reported by the International Extranodal Lymphoma Study Group and the United Kingdom Lymphoma Group [74]. A recently published 10-year follow-up of a Spanish cohort of 24 patients with stage I low-grade disease treated with H. pylori eradication therapy revealed persistent IgVH gene rearrangements in 82% of the histologically cured patients [75]. Only one of the 19 patients with continued monoclonality relapsed, however. Notably, the t(11;18) translocation was not present in any of the patients with persistent monoclonality. Persistent monoclonality after radiation-induced histologic cure also has been documented [76].

That PCR-detectable monoclonality may persist after histological disappearance of MALT lymphoma suggests that H. pylori eradication suppresses but does not eliminate lymphoma clones. A recent analysis of IgVH sequences in patients with gastric MALT lymphoma revealed clonal instability, ongoing somatic hypermutation, and antigen selection after the eradication of H. pylori [77]. Whether there are as yet unknown antigens that drive proliferation of gastric MALT lymphomas and whether low-grade MALT lymphoma can be cured solely by eradication of H. pylori remain unanswered questions. It also remains to be seen whether long-lasting molecular remissions will translate into a higher cure fraction.

In clinical practice, close endoscopic follow-up of patients treated with antibiotics is of utmost importance (Fig. 4). Eradication of H. pylori should be documented. Patients should undergo endoscopy with multiple biopsies 3 months after completion of treatment. If histological CR is achieved, endoscopy should be repeated every 6 months for 2 years, and then yearly. If only a partial response (PR) is seen, endoscopy should be repeated every 3 months to monitor histologic regression of lymphoma. If there is no histologic response after 3 months or only a PR after 6 months, the patient should be treated with alternative modalities (e.g., chemotherapy, antibody therapy, radiation therapy, or surgery).

**Surgery**

Historically, gastrectomy was the treatment of choice for patients with localized gastric lymphoma [78, 79]. In a German series, 69 patients with low-grade gastric MALT lymphoma, 48 stage I patients had additional radiation, 12 received adjuvant chemotherapy, and one patient received both radiation and chemotherapy postoperatively [80]. The 5-year survival rate was 91% (95% for stage IE and 82% for IIE), with no statistically significant differences between those patients who had surgery only and those who received additional treatments. Surgical treatment has several important drawbacks. Negative resection margins do not prevent local recurrence because MALT lymphoma is a multifocal disease [81]. Although total gastrectomy offers a greater chance for cure than partial resection, it is associated with significant morbidity and the potential for an impaired quality of life. Mortality directly related to total gastrectomy can be as high as 4% [81]. Favorable experiences with local radiotherapy, chemotherapy, and antibody therapy, allowing for gastric preservation, have limited the role of surgery even in patients failing primary therapy, although surgery may still be required for complications [82].

**Radiation Therapy**

Adjuvant radiation occasionally has been added for bulky, locally advanced, or incompletely resected tumors after primary surgical excision. Radiation therapy as an organ-preserving approach became an attractive alternative to gastrectomy for treatment of localized gastric lymphomas with the development of endoscopic and radiologic procedures that allowed physicians to be less dependent on surgery for diagnosis and staging.

Schechter and coworkers treated 17 patients with stage I–II, low-grade gastric MALT lymphoma, either resistant to antibiotics or H. pylori-negative [46]. Eighty-two percent of patients had identifiable tumor on EUS, and 36% had perigastric lymph node involvement. Patients were treated with a median total radiation dose of 30 Gy, delivered in 1.5-Gy fractions over 4 weeks, to the stomach and adjacent lymph nodes, and were followed with serial endoscopies and biopsies. All patients achieved a complete pathologic response, and at a median follow-up of 27 months, the event-free-survival rate was 100%. Treatment was well tolerated. All patients experienced mild fatigue, and 50% had grade 1 or 2 nausea. None of the patients developed diarrhea, GI...
bleeding, or gastric perforation. Park and coworkers treated six patients with stage IE low-grade gastric MALT lymphoma, including one patient with an ulcerative lesion, with a median total radiation dose of 30.6 Gy. All patients had a CR, with no evidence of tumor recurrence at a median follow-up of 12 months [83].

**Figure 4.** Gastric mucosa-associated lymphoid tissue (MALT) lymphoma treatment algorithm. Abbreviations: CR, complete response; EGD, esophagogastroduodenoscopy; NR, no response; PR, partial response.
Radiation therapy seems to be feasible and effective, allowing stomach preservation. Longer follow-up is needed, however, to determine its long-term efficacy and to quantify the risk for late side effects. Although the risk for second malignancies is low [84], this cannot be neglected, especially in patients who may already have an increased incidence of gastric cancer, because of the link between H. pylori infection and the development of gastric adenocarcinoma [85, 86]. Remission with chemotherapy has been described in a patient who relapsed following partial gastrectomy and postoperative radiation [87].

Because MALT lymphomas are radiosensitive and express the CD20 antigen, delivery of targeted radiation using an anti-CD20 radioimmunoconjugate may be an intriguing option for patients with disseminated disease. Witzig and coworkers treated four patients with stage IV MALT lymphomas of various primary sites with Zevalin® (Biogen Inc, Cambridge, MA) (the anti-CD20 antibody ibritumomab conjugated to 90Y). Zevalin demonstrated significant activity in these patients, who were previously treated with both chemotherapy and radiation therapy. Three patients achieved a CR and one achieved a PR. Hematological toxicity was tolerable [88].

**Chemioimmunotherapy**

Data on the use of chemotherapy in gastric MALT lymphoma are limited. Chemotherapy usually is reserved for patients who fail antibiotic treatment, as well as for patients with locally advanced disease or simultaneous extragastric involvement. Regimens include alkylating agents (chlorambucil or cyclophosphamide), which are commonly used in low-grade lymphomas, purine analogs, rituximab, and occasionally anthracycline-based chemotherapy for younger patients with more aggressive disease. French investigators used continuous oral administration of a single alkylating agent [89]. Twenty-four patients were treated with cyclophosphamide or chlorambucil for 12–24 months. A CR was documented in 75% of the patients, and partial remission occurred in the remaining 25%. The time to achieve a CR was significantly longer in more advanced disease (9 months in stage I versus 15 months in stage IV). Five patients (21%) relapsed 1–8 years after chemotherapy was discontinued. Of note, the presence of the t(11;18) translocation was associated with alkylator resistance in this cohort [90]. A Japanese group has found no difference in outcome between oral monoclonal antibody and radiation as second-line therapy in patients who do not respond to eradication therapy [91].

An ongoing international prospective trial is comparing chlorambucil with observation after H. pylori eradication in primary gastric MALT lymphoma [74, 92]. Preliminary results of the molecular follow-up were reported, with less than half of the patients achieving continuous molecular remission after antibiotics. The addition of chlorambucil as maintenance did not significantly improve molecular response. These results are not encouraging, but the median follow-up was only 2 years. Longer observation is needed to adequately evaluate treatment strategies for this indolent lymphoma.

Jager and coworkers reported a phase II study of the purine analog cladribine in 19 patients with gastric MALT lymphoma. All patients achieved CR. The median time to response was 2 months. Three patients relapsed at a median follow-up of 32 months [93]. Importantly, in applying these strategies, one must remember that prolonged exposure to alkylating agents may be associated with a risk for secondary myelodysplasia or leukemia, and that treatment with purine analogs can be profoundly immunosuppressive.

Anti-CD20 monoclonal antibody therapy with rituximab shows promising efficacy in relapsing or H. pylori-negative MALT lymphomas. Raderer and colleagues retrospectively evaluated response to rituximab in nine patients. Three achieved a CR and two achieved a PR for 6 and 14 months [94]. A phase II study of 35 patients by the International Extranodal Lymphoma Study Group documented a 73% response rate, with a median time to best response of 2.2 months. The response rate was higher (87%) in chemotherapy-naïve patients relative to previously treated patients (45%, p = .03). The median response duration was 10.5 months. The median time to treatment failure was 22 months in the chemotherapy-naïve patients versus 12 months in the previously treated patients (p = .001). Thirty-six percent of responders ultimately relapsed [95]. Martinelli et al. [96] evaluated weekly rituximab in 27 patients with relapsed or refractory MALT lymphoma, and in those not otherwise eligible for H. pylori eradication. Seventy-seven percent achieved an objective response, including 12 (46%) who had complete pathological and clinical remissions. With a median follow-up of 33 months, only two patients had relapsed (14 and 26 months). Fluorescence in situ hybridization analysis for the translocation t(11;18)(q21;q21) was not found to be predictive of either response or relapse in this cohort. In light of synergy between rituximab and chemotherapy in high-grade lymphomas [97], a randomized trial to evaluate the combination of rituximab and chlorambucil in MALT lymphoma has been initiated [95].

**Treatment Recommendations**

For patients with early-stage gastric MALT lymphoma, the use of antibiotics as first-line treatment is recommended. Careful follow-up with endoscopy and biopsy is necessary to monitor the regression of lymphoma. In patients with
locally advanced disease (bulky masses, deep infiltration of gastric wall, regional nodal involvement) or with high-grade tumors, antibiotics should be combined with chemotherapy, antibody therapy, or radiation therapy. There are no clear guidelines for the treatment of relapsed or H. pylori-negative disease. Chemotherapy, antibody therapy, or radiation can be used, either alone or in combination, with surgery reserved for those patients with persistent and refractory symptomatic disease. It is important to remember that some patients with persistent disease may be managed expectantly without active therapy, and they may go on to live a normal lifespan with an intact stomach.

High-Grade Gastric MALT Lymphoma

Although MALT lymphoma is by definition a low-grade neoplasm, cases have been reported in which a low-grade MALT component is mixed with variable numbers of large, transformed cells. Clinically, these patients demonstrate a less favorable course, with resistance to antibiotic therapy and more rapid progression [98]. Bayerdorffer and coworkers examined gastrectomy specimens from five patients whose lymphoma did not respond to H. pylori eradication. They found “unmasked” histologically high-grade disease in all patients [99]. Immunohistochemical studies, as well as PCR of immunoglobulin heavy chain gene rearrangements, demonstrated that the low- and high-grade components derive from the same clone [100].

In an effort to stratify patients with respect to histologic grade, de Jong and coworkers proposed a grading system for gastric MALT lymphoma [101]. Category A applies to classic low-grade MALT lymphoma, with <5% blasts, in clusters of up to 10 cells. Category B includes tumors with >10%–20% blasts or blast clusters of up to 20 cells. Category C is consistent with typical high-grade transformation, in which sheets of blasts and only small foci of low-grade tumor can be seen. Category D corresponds to large B-cell lymphoma, without a low-grade component. The clinical relevance of this grading system remains controversial. Within the spectrum of low-grade lymphomas, a greater presence of blasts has been associated with inferior outcome in some studies [101, 102], but not in others [103]. Among cases of gastric DLBCL, the clinical behavior and outcome seem to be similar regardless of the presence or absence of a low-grade MALT component [80].

In a retrospective analysis, Cogliatti and coworkers reported a 5-year survival rate of 73% in surgically treated patients with stages IE and IIE low-grade lymphoma in transformation to high-grade lymphoma (lymphomas with both high- and low-grade components). Postoperative chemotherapy and/or radiotherapy did not improve survival [80]. Ranaldi and coworkers reported a 74.1% 5-year survival rate in patients with both low-grade and high-grade components. Adjuvant chemotherapy improved survival in the subset of patients with tumor infiltration of the subserosal fat tissue [104].

High-grade gastric MALT lymphomas generally are considered to be H. pylori independent. This view was recently challenged by the results of a study in which 10 of 15 patients with stage IE high-grade MALT lymphoma achieved complete histologic remission after anti-H. pylori therapy [105]. In an effort to identify which patients might respond to antibiotic therapy, Kuo et al. [106] retrospectively evaluated the expression of CD86 (costimulatory molecule B7.2) and the infiltration by CD56+ natural killer cells in tumors from a cohort of patients with high-grade gastric MALT lymphomas. Both factors were found to correlate with H. pylori dependence and may help direct therapy in this group of patients. Nevertheless, a treating clinician should be reluctant to use antibiotic therapy alone in patients with high-grade gastric MALT lymphoma who are otherwise appropriate candidates for chemotherapy.

Nongastric MALT Lymphoma

MALT can develop in nearly every organ in response to persistent stimuli such as chronic infection or an autoimmune process. In the setting of prolonged lymphoid proliferation, a malignant clone may emerge, followed by the development of a MALT lymphoma. While gastric lymphoma is the most common and the most extensively studied, lymphomas with similar pathology have been found in a variety of primary sites. The role of infectious agents other than H. pylori in MALT lymphomagenesis is certainly less well established, but the list of possible infectious etiologic agents is growing. A group from Italy has documented the frequent presence of Chlamydia psittaci in tumor tissue and peripheral blood mononuclear cells (PBMCs) from patients with ocular adnexal lymphomas, although it is important to mention that other data do not support a causative role [107–109]. Borrelia burgdorferi infection has been identified in some skin lymphomas, MALT and otherwise [110, 111]. A few observational and epidemiologic studies suggest a possible link between hepatitis C virus infection and the development of MALT lymphoma [112–114]. Work by Lecuit et al. [115] suggests that Campylobacter jejuni may play a role in the development of small bowel MALT lymphomas. A patient with HIV disease who developed a MALT lymphoma with lung, conjunctival, and laryngeal involvement was effectively treated with antiretroviral therapy alone, suggesting a possible role for HIV in lymphomagenesis as well, although there are certainly other explanations for this response, such as immune reconstitution or the treatment of another undiagnosed infection [116]. Autoimmunity
also seems to be implicated in the pathogenesis of non-GI lesions. In the salivary gland and the thyroid, the development of lymphoma is preceded by autoimmune processes such as myoepithelial sialadenitis [117] and Hashimoto’s thyroiditis [118], respectively.

Several large series describe the characteristic features and outcome of nongastric MALT lymphomas [102, 119–121]. Patients present with localized, indolent disease, and rarely have adverse prognostic factors. They respond well to treatment (CR rate, 76%) and have a 10-year expected survival rate >75% [102]. Although survival data are not significantly different from those of gastric MALT lymphoma, non-GI MALT lymphoma patients tend to relapse more frequently and late relapses are not uncommon. Up to 25% of patients may have stage IV disease on presentation, including bone marrow involvement. In one study, a high International Prognostic Index score and lymph node involvement predicted poorer outcomes, but multiple mucosal sites of involvement did not seem to adversely impact prognosis [102, 120].

In a series published by the International Extranodal Lymphoma Study Group, the most common nongastric primary sites were the salivary glands and the ocular adnexa (25% of cases each), the lung (14%), and the skin (12%) [120]. Localization of the primary site is important when planning treatment strategies. All modalities, including surgery, radiation therapy, and chemotherapy, have been used, in a patient- and site-tailored fashion. The thyroid and lacrimal gland sites have the longest response duration, whereas skin lymphomas have had poorer outcomes in at least one series [119].

**Salivary Glands**

MALT lymphoma of the salivary gland arises in a background of myoepithelial sialadenitis (MESA), usually in association with Sjögren’s syndrome. The distinction between benign MESA and early lymphoma can be difficult using histological criteria alone. There is unresolved controversy regarding the significance of B-cell monoclonality; some authors believe that demonstration of B-cell clonality in the lymphoepithelial lesion is diagnostic of lymphoma [122]. Others argue that clonality does not predict progression to clinically overt lymphoma [123]. MALT lymphomas can arise in any of the salivary glands, but the parotid gland is most frequently involved [124]. Salivary MALT lymphomas demonstrate a very indolent course with a long time to progression (3–18 years), even in the absence of treatment [117]. Some patients develop disseminated disease, usually to other MALT sites (ocular adnexa, stomach) or to lymph nodes [124]. The optimal therapeutic strategy is not yet defined. In one retrospective analysis, Ambrosetti et al. [125] reported no significant differences in outcomes among patients undergoing a variety of treatment modalities, including surgery, radiotherapy, and chemotherapy. As in gastric and other nongastric MALT lymphomas, there is evidence for the safety and activity of rituximab [95].

**Ocular Adnexa and Lacrimal Gland**

Historically diagnosed as small lymphocytic lymphoma of the ocular adnexa, this low-grade B-cell lymphoma is frequently of MALT origin [126]. The clinical course is indolent and the risk for dissemination is low. Patients present with painless conjunctival injection and photophobia, mimicking allergic conjunctivitis. Examination reveals orange- or salmon-pink masses in the fornices, which are frequently multifocal or bilateral [127–129]. Radiation therapy comprises standard treatment; Uno and coworkers [130] treated 50 patients with radiation in one series. The CR and PR rates were 52% and 40%, respectively, and the 5-year overall survival rate was 91% [130]. Cataracts developed in six patients, with two patients undergoing cataract extraction 2–3 years after radiotherapy. Retinal complications attributed to radiotherapy developed in two patients, including radiation retinopathy 72 months after receiving 40 Gy at 2 Gy per fraction and mild retinal bleeding accompanied by decreased visual acuity 10 years after 40 Gy. One patient who underwent an initial excisional biopsy for a tumor in the orbital soft tissue developed a corneal ulcer after receiving 40 Gy. There were no severe, late, lacrimal complications attributable to radiotherapy.

In cases of lacrimal gland involvement, low-dose radiotherapy provides excellent local control and is the treatment of choice [131]. Subconjunctival intralosomal injections of interferon-α were tried in a small group of patients, with promising results [119, 132]. Recently, a pilot study of *C. psittaci*-eradicating therapy in patients with ocular MALT lymphoma was undertaken by the Italian group that initially published data on the association between the two entities [133]. Nine patients (five with relapsed or refractory disease) were treated with oral doxycycline (100 mg orally twice a day for 3 weeks). An objective overall response rate of 44.4% was seen, with two complete responses, two partial responses, and three minor responses (<50% regression). Of note, *C. psittaci* DNA was found in the PBMCs of four of seven patients upfront, but was undetectable in all four patients following treatment.

**Lung**

Low-grade MALT lymphoma is the most common form of primary lymphoma of the lung, accounting for 70%–78% of cases [134, 135], and arises from bronchus-associated lymphoid tissue (BALT), the pulmonary counterpart of MALT.
Some patients with lymphocytic interstitial pneumonia (LIP), an entity encountered in some autoimmune diseases, were found to harbor low-grade MALT lymphoma, but the risk for progression to MALT lymphoma from chronic bronchiolitis or LIP is small [136]. In pathology specimens, lymphoepithelial lesions with invasion of bronchial epithelium and alveolar lining are commonly seen. The tumors are composed of nodules that form a confluent central mass with a peripheral lymphangitic pattern [135]. The disease occurs most commonly in elderly men aged 60–80 [134, 135]. Some of the patients have a history of autoimmune disorders (Sjogren’s disease, rheumatoid arthritis) [137, 138]. About 40% of patients are asymptomatic and present with a solitary pulmonary nodule on chest x-ray. Symptomatic patients may have fever, weight loss, and pulmonary symptoms such as cough, dyspnea, and hemoptysis, and have radiological evidence of bilateral diffuse interstitial infiltrates [139]. The prognosis is significantly worse when systemic symptoms are present. The disease has a tendency to become multifocal, spreading to other parts of the lung and to distant mucosal sites such as the stomach or salivary glands [134, 140].

Treatment comprises limited resection, sometimes with chemotherapy or low-dose radiation therapy, when the disease is localized, and chemotherapy when multifocal [135, 141–143]. In a case series of 48 patients from the Mayo Clinic who underwent surgery for NHL of the lung, 35 patients had MALT lymphoma. Complete surgical resection could be performed in 40% of the patients. Survival rates at 5 and 10 years were 68% and 53%, respectively. Postoperative chemotherapy did not improve survival. No prognostic factors could be identified [144]. Zinzani and coworkers reported a 100% 6-year survival rate in patients with stage I disease treated with chemotherapy (n = 8), surgery (n = 2), or both (n = 2) [145]. Chemotherapy regimens comprised of alkylating agents, anthracyclines, or purine analogs have been employed, either as single agents or in combination, with high response rates [146]. Chong et al. [147] reported on a patient with recurrent disease 4 years following primary chemotherapy who responded to rituximab, and an Austrian group reported a response to low-dose thalidomide in a patient refusing other modalities of therapy [148].

Thyroid

Primary thyroid lymphomas arise in the setting of chronic autoimmune thyroiditis. Most lymphomas are of the large-cell type, arising as a transformation from a low-grade component. Pure low-grade MALT lymphomas of the thyroid are rare, but the risk for thyroid lymphoma in patients with Hashimoto’s thyroiditis is 67 times higher than in the general population [149]. Clinical features of thyroid MALT lymphoma may be difficult to distinguish from Hashimoto’s thyroiditis. Most commonly, MALT lymphoma presents as a growing mass in the thyroid gland sometimes associated with obstructive symptoms. Although fine-needle aspiration is a commonly used procedure for initial pathologic evaluation of a thyroid nodule, it is not diagnostic in half of the patients with thyroid lymphoma. Differentiating low-grade lymphoma from Hashimoto’s thyroiditis by cytology can be difficult, and open biopsy may be necessary [150]. Interestingly, clonal B-cell populations can be found in samples of thyroid tissue in patients with Hashimoto’s thyroiditis, in the absence of lymphoma [151]. In one series, none of the three such patients developed lymphoma over a follow-up of 10–13 years.

In a Cleveland Clinic report describing 53 patients with NHL of the thyroid, only three patients had low-grade MALT-type lymphoma [152]. Among 45 patients with DLBCL, 18 were classified as high-grade MALT type, defined by the presence of a low-grade component or large-cell lymphoepithelial lesions. All patients with low-grade MALT-type lymphoma were alive and free of disease at a mean of 26 months. Patients with high-grade MALT lymphoma had worse outcomes than those with classic DLBCL (5-year survival rates of 25% versus 65%, respectively), primarily as a result of a more advanced clinical stage at diagnosis. In general, surgery, radiation, or both is offered for local disease; supplemental chemotherapy is offered for advanced disease [153]. Interestingly, Arima and Tsudo [154] reported a case of thyroid MALT lymphoma that regressed following anti- H. pylori therapy, even though H. pylori organisms were not detected in the lymphoma [154].

Skin

Skin MALT lymphomas usually develop in middle-aged patients. They present as single or multiple brown or red-brown papulonodular lesions or plaques, predominantly found on the extremities or the back [155, 156]. They can be treated by surgical excision, radiation therapy, or observation (especially in the case of multiple lesions). Nodules can recur at the same or a new cutaneous site, although there is usually no extracutaneous dissemination [156]. The clinical course is indolent, with a 5-year survival rate >95%. A recent report described a skin MALT lymphoma associated with Borrelia burgdorferi infection that nearly completely regressed after eradication of the organism, suggesting that B. burgdorferi infection may play a role in the pathogenesis of skin lymphoma [110].

Breast

Primary breast lymphomas are uncommon and tend to be high grade: large B-cell or Burkitt’s type. In a large population-based registry, they comprised 0.14% (20 of 14,046
cases) of primary breast malignancies [157]. Low-grade MALT lymphomas occur in only 10%–35% of cases [157, 158]. Most patients are middle-aged women (median age, 57 years) [158]. They usually present with a painless, enlarging unilateral breast mass detected during physical examination or on mammogram. Infiltrating breast carcinoma is often suspected and can be misdiagnosed on frozen section. The role of “lymphocytic mastopathy,” a form of autoimmune breast disease, as a precursor to breast lymphoma is controversial [159, 160]. Published data about treatment are limited. Local excision and/or radiation therapy have been associated with an excellent prognosis in small series of patients [161].

Dura
Although the central nervous system contains no MALT tissue, it has been hypothesized that meningotheial cells of the arachnoid system are analogous to epithelial cells from sites where MALTs do arise [162]. In a retrospective review, several tumors originally diagnosed as small lymphocytic lymphomas and plasmacytomas of the dura were later reclassified as lymphomas of the MALT subtype. All patients presented with focal neurologic deficits and had a well-localized dural mass on x-ray, suggesting a preoperative diagnosis of meningioma. No recurrences were reported after surgical removal either with or without radiation therapy or chemotherapy [163–166]. Although the first 10 patients reported in the literature were women, a case in a man was recently described [162].

Urinary Tract
Primary bladder lymphoma represents 0.2% of all bladder neoplasms, and is primarily of the low-grade MALT subtype. The prognosis is excellent with local treatment [167], although transformation into a high-grade large B-cell lymphoma has been described [168]. Rarely, primary MALT lymphomas of the kidney have been reported as well [169].

CONCLUSIONS
With improved recognition of the immunologic and histologic features of MALT NHL, this pathologic entity has been diagnosed with increased frequency. Although most clinicians associate this subtype of NHL with gastric involvement, the frequency of involvement of other extranodal sites is striking. At most extranodal sites, the etiology of the MALT lymphoma is uncertain. H. pylori, B. borgdorferi, and C. psittaci have been associated with the disease. Fortunately, this is a highly treatable type of lymphoma, with excellent anticipated 5-year survival rates.

Because of the relative rarity of MALT NHL at any given extranodal site, management has been guided by retrospective clinical series. It is unlikely that prospective clinical trials will be conducted for most of the disease subtypes beyond gastric MALT NHL, but the development of appropriate registries should be encouraged to permit pooled data from single institutions. MALT lymphoma is well treated by local therapy. Radiation is highly effective and major surgery can be avoided in most cases. Although systemic chemotherapy is active, it should be reserved as a palliative treatment for advanced stage disease. The role of rituximab remains undefined, but this treatment has high response rates with low toxicity in MALT lymphoma.

Disclosure of Potential Conflicts of Interest
The authors indicate no potential conflicts of interest.

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