ARTICLE TITLE: Clinicopathologic Characteristics and Treatment of Marginal Zone Lymphoma of Mucosa-Associated Lymphoid Tissue (MALT Lymphoma)

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1. Describe/discuss/review the role of chronic infections and autoimmunity in the pathogenesis of MALT lymphoma.
2. Summarize current recommendations for the diagnosis, staging, and treatment of patients with MALT lymphoma.

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Clinicopathologic Characteristics and Treatment of Marginal Zone Lymphoma of Mucosa-Associated Lymphoid Tissue (MALT Lymphoma)

Markus Raderer, MD1; Barbara Kiesewetter, MD2; Andrés J. M. Ferreri, MD3

Extranodal marginal zone lymphoma of the mucosa-associated lymphoid tissue (MALT lymphoma) accounts for 7% to 8% of newly diagnosed lymphomas. Because of its association with infectious causes, such as Helicobacter pylori (HP) or Chlamydia psittaci (CP), and autoimmune diseases, it has become the paradigm of an antigen-driven malignancy. MALT lymphoma usually displays an indolent course, and watch-and-wait strategies are justified initially in a certain percentage of patients. In patients with gastric MALT lymphoma or ocular adnexal MALT lymphoma, antibiotic therapy against HP or CP, respectively, is the first-line management of choice, resulting in lymphoma response rates from 75% to 80% after HP eradication and from 33% to 65% after antibiotic therapy for CP. In patients who have localized disease that is refractory to antibiotics, radiation is widely applied in various centers with excellent local control, whereas systemic therapies are increasingly being applied, at least in Europe, because of the potentially systemic nature of the disease. Therefore, the objective of this review is to briefly summarize the clinicopathologic characteristics of this distinct type of lymphoma along with current data on management strategies. CA Cancer J Clin 2016;66:152–171. © 2015 American Cancer Society.

Keywords: antigen-driven malignancy, Chlamydia psittaci, extranodal, non-Hodgkin lymphoma, Helicobacter pylori

Introduction

Extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT lymphoma), as defined in the recent World Health Organization classification of lymphoid malignancies,1 is a unique type of lymphoma with marked differences from other indolent B-cell lymphomas. MALT lymphoma was initially described by pathologists Peter Isaacson and Dennis Wright in 1983,2 when they noticed that certain gastric lymphomas did not resemble lymph node architecture but rather strikingly recapitulated the features of the Peyer patches, a physiologic aggregate of lymphoid cells in the terminal ileum. These observations could soon be extended to various other extranodal locations, forming the basis for the current definition of MALT lymphoma, which is a diagnosis based on pathologic features distinguishing it from other types of extranodal lymphomas, including diffuse large B-cell lymphoma, follicular lymphoma, and mantle cell lymphoma.

It is not without a certain irony that the same year also witnessed the (re)-discovery and definition of the stomach-dwelling, Gram-negative rod Helicobacter pylori (HP) by Warren and Marshall,3 which has subsequently been linked intimately with MALT lymphoma. It also took a decade of intense scientific commitment before MALT lymphoma finally was accepted in the 1994 version of the Revised European American Lymphoma classification,4 and it took an even longer time for some clinical communities to recognize the fascinating properties of this disease.

According to recent data, MALT lymphoma is among the more common lymphoma entities, accounting for 7% to 8% of newly diagnosed lymphomas; it is not as common as follicular and diffuse large B-cell lymphoma but is about equal in

1Programme Director for Extranodal Lymphomas, Department of Internal Medicine I, Division of Oncology, Medical University Vienna, Vienna, Austria; 2Resident-in-Training, Department of Internal Medicine I, Division of Oncology, Medical University Vienna, Vienna, Austria; 3Director, Unit of Lymphoid Malignancies, Division of Onco-Hematological Medicine, Department of Onco-Hematology, National Institute for Research and Treatment, San Raffaele Scientific Institute, Milano, Italy.

Corresponding author: Markus Raderer, MD, Internal Medicine I, Division of Oncology, Medical University Vienna, Waehringer Guertel 18-20, Vienna, Austria; markus.raderer@meduniwien.ac.at

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incidence to mantle cell lymphoma. According to the literature, there is a slight female preponderance in MALT lymphoma patients, and the median age at diagnosis is about 65 years.\(^5\)

Although it initially was described as a subtype of gastric lymphoma, it has subsequently been shown that it may arise in almost all organs of the human body, including unusual sites, such as the dura. Although the World Health Organization classification published in 2008 still defines the stomach as the most common organ of origin (accounting for roughly 50% of MALT lymphomas), recent data have suggested a decline in the percentage of gastric MALT lymphomas. In our own patients, including a total of 320 MALT lymphomas, we found 116 patients (36%) who had gastric MALT lymphoma; whereas the majority had extragastric MALT lymphomas located predominately in the ocular adnexa, the parotid, and the lung.\(^6,7\)

However, it has to be emphasized that, although they are lumped under one common diagnosis based on histopathology, there appear to be clinically relevant differences between gastric and nongastric MALT lymphomas and most probably even within these according to the site of origin. In addition to pathophysiologic and genetic differences, which are covered below, the clinical presentation and course also vary. While initially thought to be localized to a single organ in most cases,\(^8\) subsequent investigations applying a strict staging routine have shown that gastric MALT lymphoma is a multiorgan disease in up to 25% of patients, whereas extragastric MALT lymphomas present with multiorgan involvement in up to 50% of patients.\(^7,9\)

Thus, staging procedures, as discussed below, are mandatory in the pretherapeutic workup of patients with MALT lymphoma; and, because of the potential life-long risk of recurrence, long-term follow-up is also recommended.

In addition to the more disseminated presentation of extragastric MALT lymphomas, the rate of recurrence after successful therapy also appears to be significantly higher compared with their gastric counterparts.\(^7,9\) A difference between the clinical presentation of gastric versus nongastric MALT lymphoma was also emphasized by a Dutch analysis of 72 patients with extragastric MALT lymphomas who showed a high rate of multiorgan involvement (32%) and dissemination (26% had stage IV disease) at diagnosis.\(^10\)

Pathogenesis, Risk Factors, and Related Disorders

Native and Acquired MALT

The finding that most MALT lymphomas were diagnosed in the stomach was puzzling, as the stomach is usually a priori devoid of lymphoid tissue. Compared with the gut, which is thought to contain the largest accumulation of lymphoid tissue in the human body, gastric lymphoid structures are not present at birth but, rather, develop in individuals subject to chronic antigenic stimulation. It has been shown that this acquired gastric MALT is more prone to the development of lymphoma as opposed to predefined/physiologic intestinal MALT, which hardly ever gives rise to MALT lymphoma. Reflecting an association with various chronic conditions, ie, infection and inflammation, MALT follicles have been described in various organs; and, in the past, different abbreviations, including BALT (bronchus-associated lymphoid tissue) and SALT (skin-associated lymphoid tissue), have been coined.\(^11\) It has been noted that different types of MALT may show specialized immunologic trafficking with predominate homing to corresponding mucosal structures, which appear to be different for gastrointestinal (GI) MALT versus non-GI MALT.\(^11\) Thus, it is not surprising that different dissemination patterns have been seen in patients with MALT lymphomas of various gastric and extragastric sites.\(^7,9,12,13\) More recently, a pattern of subcutaneous MALT lymphoma dissemination was observed almost exclusively in MALT lymphoma of the breast and the ocular adnexa;\(^14\) this crosstalk between mucosal structures might mimic embryogenetically primed tissue relationships, ie, organ systems generated within the ectodermal layer.

The homing properties of MALT lymphoma cells initially were described for gastric MALT lymphoma and were associated with adhesion molecules and mucosal homing receptors, including MAdCAM-1 (mucosal vascular addressin cell adhesion molecule 1) and \(\alpha 4\beta 7\)-integrins, interacting with high endothelial venules.\(^15-17\) In addition, chemokine receptors, including chemokine C-X-C motif receptor 4 (CXCR4) and CXCR7, have been implicated in homing and dissemination and also in potential transformation, especially of gastric MALT lymphomas.\(^18\)

Autoimmune Disorders

The close association between autoimmune diseases (ADs), especially Sjögren syndrome (SS) with salivary gland lymphoma and chronic autoimmune thyroiditis (CAT) (Hashimoto disease) with thyroid MALT lymphoma, has repeatedly been published, and it is thought that the risk of developing lymphoma is as high as 70-fold for individuals with ADs compared with the risk for healthy control populations. This suggestion that chronic antigenic stimulation of the target organ may give rise to acquired MALT with subsequent transformation to lymphoma is in line with the MALT lymphoma concept.\(^5,8,19\)

In the largest series so far on this topic,\(^20\) 158 patients with MALT lymphoma were systematically analyzed, and 61 (39%) of them were found to have an AD. These patients were significantly younger at diagnosis (56 years vs 67 years), had a higher rate of extragastric lymphomas, and were more likely to be female (79%) than patients without AD.
The most common ADs were SS (70%), followed by CAT (13%), and rheumatoid arthritis (3%). Interestingly, a lower rate of response of gastric MALT lymphoma after HP eradication has been seen in patients with AD, a finding that was subsequently verified in another study showing a higher than expected presence of CAT (16%) in patients with gastric lymphoma. These findings suggest that AD negatively influences the response to antibiotic therapy in gastric MALT lymphoma, but it does not appear to modify long-term outcomes after other therapies; indeed, no significant differences in relapse rates or in the time to relapse after successful treatment between AD-related and AD-unrelated subgroups were found after a median follow-up of 47 months, which has been confirmed for both gastric and nongastric MALT lymphomas.

More recently, the role of B-cell–activating ADs in the development of MALT lymphoma was also reemphasized by results from the InterLymph Non–Hodgkin Lymphoma Project. In that pooled analysis of 1052 cases with marginal zone lymphomas (MZLs) (633 MALT lymphomas, 140 splenic MZLs, and 157 nodal MZLs), an increased risk was found for all subtypes of MZL. In the analysis, however, additional risk factors for MALT lymphoma were defined, including seropositivity for hepatitis C, a family history of a hematologic malignancy, and peptic ulcers. Interestingly, a lower risk for MALT lymphoma was reported in individuals who consumed alcohol and in teachers. Of note is the finding that the defined risk factors differed markedly between MALT lymphoma, nodal MZL, and splenic MZL, again emphasizing these diseases as distinct entities.

**Infectious Agents**

After the initial definition of MALT lymphoma, the pathogenetic link between gastric MALT lymphoma and infection with the Gram-negative rod HP was soon discovered. In addition to epidemiologic data showing a high rate of gastric lymphoma after HP infection, the presence of HP was demonstrated in greater than 90% of patients with gastric MALT lymphoma. Interestingly, microscopic detection of HP becomes increasingly difficult with progression from gastritis to lymphoma, suggesting that not only light microscopic assessment should be used to ascertain the presence of HP, but additional methods, including breath test or ultimately serology, should also be applied.

The discovery and exact definition of a clear causative role of HP in gastric MALT lymphoma has revolutionized and redefined treatment of this disease (see below). In vitro experiments have clearly demonstrated that attempts to culture unsorted cells from cases of gastric MALT lymphoma under standard conditions usually result in cell death within 5 days, but the addition of heat-killed, whole-cell preparations of HP results in a positive effect on the proliferation of lymphoma cells. This effect is specific for the particular strain of HP used and is associated with the expression of interleukin 2 (IL-2) receptors and the release of tumor cell–derived immunoglobulin (Ig) and IL-2 into supernatant. By contrast, cells cultured from indolent nodal B–cell lymphomas did not respond to HP. An important role of HP-specific T cells has been suggested by the finding that the removal of T cells from cell suspensions of MALT lymphomas before culturing did not result in any growth stimulus when adding HP. Apparently, immunologic specificity for HP is defined by intratumoral T cells acting via the cluster of differentiation 40 (CD40) (a B-cell surface antigen) ligand system and, thus, stimulating the growth of MALT lymphoma cells.

HP infection is a common, worldwide phenomenon, but only a small minority of patients will develop gastric MALT lymphoma. This is mostly because, apart from HP-related factors, such as expression of cytotoxin-associated gene A (CagA), which have been implicated not only in the general virulence of the strains but also in their ability to induce lymphomagenesis and solid cancers, host-related factors may also play a role, such as the presence of an AD, as discussed above. In this setting, however, it is not clear whether HP and AD synergistically interact in generating MALT lymphoma or if HP infection might be a bystander phenomenon in this setting, which has been speculated in view of the finding of lower response rates to antibiotics in such patients.

The role of CagA in lymphomagenesis has been discovered to be also operative at a more complex molecular level. In vitro data published by Zhu and colleagues in 2007 have shown that transfection of CagA into B1 lymphocytes resulted in protection against apoptosis and in an increase of phosphorylation of endoplasmic reticulum kinase 1 and 2 (Erk1/2). More recent data specifically focusing on gastric MALT lymphoma have demonstrated that CagA might translocate into MALT lymphoma cells of HP-dependent cases. This was further underscored by an analysis of samples from 47 patients with localized gastric MALT lymphoma. Of those 47 patients, 25 were rated as HP-dependent; immunohistochemical studies for CagA and various signal-transduction pathways (phosphorylated Src homology-2 domain containing protein tyrosine phosphatase-2 [pSHP-2], protein kinase R-like ERK [pERK], as well as phosphorylated p38 mitogen-activated protein [MAP] kinase, B-cell lymphoma-2 [bcl-2], and B–cell lymphoma-extra large [bcl-x]) were performed, revealing a significant association with HP dependence and also with the transduction molecules studied. These fascinating data suggest that the role of CagA is more complex than that of a mere marker/inducer of a more pronounced immune reaction to a more aggressive HP strain.
HP is still thought to be the most common cause of gastric MALT lymphoma; it is present in up to 90% of patients, and HP-negative patients are still regarded as a curiosity. However, some studies show an increasing proportion of HP-negative patients of up to 30% to 50% of gastric MALT lymphomas. The reason for this trend remains unclear, but the liberal use of antibiotics in patients with suspected HP infection/symptoms might be a potential explanation for this shift in MALT lymphoma characteristics.

Because of the specialized gastric environment colonized by HP, the association with MALT lymphoma was easily discovered in the absence of other bacterial agents in the stomach. The regression of MALT lymphoma after the eradication of Helicobacter heilmannii infection with antibiotics in 5 patients has demonstrated that other Helicobacter species also are able to induce MALT and lymphoma development. Although it has been validated in various animal models, the induction of gastric MALT lymphoma appears to be a rare event in humans.

Campylobacter jejuni has been implicated in the development of a rare form of intestinal MALT lymphoma also termed immunoproliferative small intestinal disease (IPSID) (or “x-heavy-chain disease”), which is especially prevalent in the Middle East as opposed to other regions of the world. So far, no clear role for HP infection has been detected in extragastric lymphomas, and routine attempts at HP eradication are not recommended. In general, data on bacterial causes for nongastric MALT lymphoma are relatively rare, and especially the association between infection with Campylobacter pylori and cutaneous MALT lymphoma has not been uniformly accepted compared with the association between HP and gastric MALT lymphoma. In pulmonary lymphomas, recent data have suggested a possible association with Achromobacter xylosoxidans infection, and a high rate of infection with Chlamyphilia psittaci (CP) also has been detected using paraffin-embedded specimens from patients with pulmonary MALT lymphoma.

In the last 2 decades, evidence supporting a pathogenic role of CP in patients with ocular adnexal MALT lymphomas has progressively increased. Various factors, including the observation that the risk for ocular adnexal lymphomas was markedly increased (overall increase by 7.69 compared with control subjects who had nodal lymphoma) by contact with household animals and the detection of chlamydial DNA in samples of ocular adnexal MALT lymphomas, have argued for an association with CP infection. The presence of CP antigens and nucleic acids has been demonstrated by immunohistochemistry, double immunofluorescence, and polymerase chain reaction (PCR) techniques on laser-captured cells. The combined use of these techniques and electronic microscopy has demonstrated the presence of CP elementary bodies and reticulate bodies in the cytoplasm of CD68-positive cells infiltrating MALT lymphomas. Moreover, viable and infectious CP has been isolated and grown in vitro cultures from samples of conjunctival swabs and peripheral blood from patients with ocular adnexal MALT lymphomas. Consequently, a role for antibiotic therapy targeting CP was established in various trials of doxycycline in patients with relapsing and newly diagnosed ocular adnexal MALT lymphoma. The high rate of infection with CP, as published in Italian series, nevertheless could not be reproduced in other countries, and a pronounced geographic variation has been suggested. Whether this is indeed a geographic difference or, rather, reflects methodological differences is an ongoing debate, as is the necessity of testing for CP before the application of doxycycline, because it has been reported that patients without evidence of CP infection also respond to doxycycline (see section on antibiotic therapy).

These data, however, have mostly been reported from populations within Southern Europe. As opposed to this, reports from various other regions of the world could not find an association between ocular adnexal MALT lymphomas and CP infection. Rosado and coworkers failed to detect CP-DNA in 57 MALT lymphoma specimens from South Florida, and an additional analysis performed in Miami of 49 samples (including 34 from the study by Rosado et al) from patients with ocular adnexal MALT lymphomas for bacterial DNA again could not demonstrate any evidence for bacterial DNA using PCR. As part of a study on morphology, phenotype, and genetic characteristics of ocular MALT lymphomas, Ruiz et al also performed PCR for CP, but the results were negative for all 30 patients assessed.

In view of this, the role CP in ocular adnexal MALT lymphoma has not been unequivocally accepted, and various crucial points for discussion remain. A meta-analysis that included 11 studies in a total of 458 patients from 10 countries found striking geographic variation and a relatively low percentage of CP infection overall (23%). In that analysis, the authors discussed various relevant factors, including various rates of infection, methodological differences, or a bystander effect of CP infection, even in patients who had positive CP test results.

**Pathology**

**Morphology**

The diagnosis of MALT lymphoma is established by histopathologic assessment of tissue samples according to standardized criteria. Although the diagnosis may not be straightforward from biopsy samples, current guidelines do not recommend the application of molecular methods; for example, monoclonality (which may be transient) has also been documented in patients with HP-associated
gastritis without lymphoma. In view of this, repeat biopsies might be necessary for definitive histopathologic diagnosis.

This is especially important, as other types of extranodal lymphoma, such as mantle cell lymphoma of the intestine, or extramedullary plasmacytoma, or small lymphocytic lymphoma, should be ruled out by immunohistochemistry or molecular methods, as they require a different therapeutic approach and have a different clinical course.¹

Although the group of MZLs is currently split into splenic, nodal and extranodal marginal zone B-cell lymphomas of the mucosa-associated lymphoid tissue,¹⁻² MALT lymphoma is also distinct from these 2 types of lymphoma.

MALT lymphoma is characterized by cellular heterogeneity of neoplastic cells, including centrocyte-like cells, monocytoid B-cells, small lymphocytes, and plasma cells. Occasional large cells are present in most cases. An increased number of large cells may be of prognostic importance, and tumor grading according to the number of large cells has been suggested. Some degree of plasma cell differentiation is often seen, sometimes to an extent that an erroneous diagnosis of extramyeloid myeloma/plasmacytoma is made. Reactive follicles are usually present, with the neoplastic cells occupying the marginal zone and the interfollicular region. Occasional follicles may contain an excess of marginal zone or monocytoid cells, giving them a neoplastic appearance (follicular colonization). In extranodal sites, mainly mucosal tissues, the marginal zone cells typically infiltrate the epithelium, forming lymphoepithelial lesions. Although it is believed that lymphoepithelial lesions are a hallmark of MALT lymphoma, they are not a prerequisite for diagnosis.⁵

**Immunophenotype**

As typified by immunohistochemistry, MALT lymphoma cells express monotypic surface Ig, are more frequently IgM-positive (IgM+) than IgG+ or IgA+, but not IgD+, and express cytoplasmic Igs in 40% of cases. Tumor cells express B-cell–associated antigens, such as CD19, CD20, CD22, CD79a, and CD79b, and are CD5-negative (CD5−), CD43−/CD43+, CD3−, CD23−, CD11c−/CD11c+, and CD10−. CD5 immunoreactivity has been reported in a small proportion of cases arising in some extranodal sites, particularly in the ocular adnexa.⁵

**Genetic Features**

Compared with some other forms of lymphoma, MALT lymphomas are not characterized by a diagnostic genetic aberration, with the exception (to some extent) of the t(11;18)(q21;q21) translocation (discussed below) but, rather, display a variety of genetic features.

Usually, MALT lymphoma is not associated with bcl-1, bcl-2, bcl-3, or bcl-6 rearrangements.⁴⁹ However, 3q27 translocations involving the BCL6 gene have been detected in less than 2% of cases assessed by interphase fluorescence in situ hybridization.⁵⁰ Trisomy 3 and t(11;18)(q21;q21) have been reported in a variable proportion of cases according to the involved extranodal organ,⁵¹ with 24% to 48% of gastric MALT lymphomas being positive for t(11;18) (q21;q21).⁵² In addition, numerical aberrations, ie, trisomy 7, 12, and 18, have been reported, as have structural changes located on chromosome 1.⁵³⁻⁵⁴

In cases transforming to diffuse large B-cell lymphoma, c-myc rearrangements and complete or partial inactivation of p53 have been reported.⁵⁵ Other common karyotypic alterations characteristic of MALT lymphomas include the translocations t(11;18)(q21;q21), t(1;14)(p22;q32), t(14;18) (q32;q21), t(3;14)(q27;q32), and t(3;14)(p14.1;q32). Of clinical interest is the finding that at least 3 of these aberrations result in the constitutive activation of the nuclear factor-κB (NF-κB) pathway.

The t(11;18)(q21;q21) translocation is the most common aberration in MALT lymphomas (13%-35% of cases)⁵⁶ and occurs in gastric, pulmonary, intestinal, and cutaneous MALT lymphomas. It is exclusively found in MALT lymphoma, but not in nodal or splenic MZLs. The t(11;18)(q21;q21) translocation fuses the apoptosis inhibitor-2 (API2) gene on chromosome 11 and the MALT lymphoma-associated translocation (MALT1) gene on chromosome 18.

T(11;18)(q21;q21) is usually the only chromosomal aberration, but it has been detected in rare cases of diffuse large B-cell lymphomas developing at mucosal sites. It is thought to be associated with lymph node and systemically disseminated disease and has been associated with disease that is unresponsive to HP eradication.⁵⁷⁻⁵⁹ In fact, t(11;18) (q21;q21) was identified in 70% of gastric MALT lymphomas that were unresponsive to antibiotic therapy, whereas it was not detected in responding patients. However, it is not associated with resistance to systemic therapies, including rituximab or cladribine.

In gastric MALT lymphoma, the t(11;18)(q21;q21) translocation has been significantly associated with infection of CagA-positive HP strains, which are more likely to be associated with inflammatory responses and potent neutrophil activation.⁵⁷

The t(1;14)(p22;q32) and variant t(1;2)(p22;p12) translocations occur in 1% to 2% of MALT lymphomas in the stomach, lung, and skin.⁶⁰⁻⁶² The t(1;14)(p22;q32) results in overexpression of nuclear BCL10 protein. BCL10 is an intracellular protein that is essential for both the development and function of mature B cells and T cells, linking antigen-receptor signaling to the NF-κB pathway. The deregulated expression of wild-type BCL10 resulting from
translocation is important in MALT lymphomagenesis. The t(1;14)(p22;q32) and t(1;2)(p22;p12) translocations have been reported exclusively in MALT lymphoma, and these tumors typically display additional genomic abnormalities. Similar to cases with t(11;18)(q21;q21), MALT lymphomas exhibiting these translocations are usually associated with advanced stage and antibiotic refractoriness.

The t(14;18)(q32;q21) translocation occurs in 15% to 20% of MALT lymphomas, bringing the MALT1 gene under the control of the Ig heavy-chain (IGH) enhancer on chromosome 14, resulting in deregulated expression of MALT1 and downstream activation of the NF-κB pathway. This translocation occurs more frequently in non-gastrointestinal MALT lymphomas (liver, lung, and ocular adnexa). MALT lymphomas with t(14;18)(q32;q21) frequently harbor additional genetic aberrations, including trisomies 3 and/or 12 and 18.

The t(3;14)(p14.1;q32) translocation brings the FOXP1 (forkhead box protein P1) gene at 3p14.1 under the control of the IGH gene enhancer and deregulates its expression. FOXP1 is a member of the FOXP subfamily (FOXPI-4) of forkhead transcription factors, which are characterized by a common DNA binding winged-helix or forkhead domain together with N-terminal zinc finger and leucine zipper domains. This translocation results in FOXP1 protein overexpression and is detected in MALT lymphomas arising in the thyroid (50%), ocular adnexa (20%), and skin (10%); its presence excludes t(11;18)(q21;q21). FOXP1 protein is also overexpressed in MALT lymphomas with trisomy 3, suggesting that increased gene copy number may be another mechanism of deregulated gene expression. Overexpression of FOXP1 seems to be associated with a poorer prognosis in other lymphomas, but its prognostic role in MALT lymphoma is still unclear.

Genetic Profiling

In the recent literature, assessment of genomic profiling of MALT lymphomas has also been published. In a pilot study of 130 MALT lymphomas of various localizations, Kwee and coworkers analyzed genetic profiles using high-density arrays. Because testing was done on fresh-frozen tissues, those authors admitted to a certain bias, as the predominant group in this analysis was ocular adnexal MALT lymphoma (41%), followed by gastric (21%) and parotid/salivary gland (9%) MALT lymphoma. In that analysis, trisomies 3 and 18 as well as loss at 6q23 could be found in gastric, orbital, salivary, thyroid, and pulmonary MALT lymphomas with similar frequency, suggesting a role in the pathogenesis of MALT lymphoma. In contrast, gains at 6p and 8q were most often found in MALT lymphomas suggested to have an infectious background, ie, gastric and ocular adnexal MALT lymphoma.

Diagnosis

Clinical Presentations

The clinical presentation of MALT lymphoma is variable, mostly because of differences in signs and symptoms associated with the different extranodal organs. Most patients present with localized disease (stage I-II), small tumor burden, excellent performance status, and normal lactate dehydrogenase and β2-microglobulin levels.

The GI tract is the most frequently involved site (66% of all MALT lymphomas). MALT lymphomas represent 40% to 50% of primary gastric lymphomas. The symptoms are usually dyspepsia with or without signs of chronic bleeding and, less frequently, abdominal pain and weight loss. “B” symptoms are exceedingly uncommon.

The endoscopic findings of gastric MALT lymphoma vary from a flat gastritis appearance to one or more ulcers. Stage of disease in gastric forms is stage IE in 70% to 80% of patients, stage IIE in 10% to 20%, and stage IVE in 5% to 10%. Gastric MALT lymphoma is usually multifocal, and this may explain the report of relapses in the gastric stump after surgical excision.

Ocular adnexa (conjunctival and lacrimal gland), lung, salivary glands, thyroid gland, and skin are the most commonly involved extra-GI organs. Patients with pulmonary MALT lymphoma usually complain of cough, dyspnea, hemoptysis, and chest pain. Atelectasis and pleural effusion are rare. In many cases, diagnosis requires surgical lung biopsy because of insufficient material for definitive diagnosis obtained by bronchoscopy or needle biopsy.

The clinical picture of ocular adnexal MALT lymphoma is related to the involved structures, with 25% showing conjunctival involvement, intraorbital lesions in 75% of cases, and bilateral (mostly conjunctival) involvement reported in 10% to 15% of cases. On clinical grounds alone, MALT lymphoma may be undistinguishable from other orbital diseases. As different lymphomas occur in the ocular adnexa, histologic diagnosis is mandatory for correct treatment. Ocular adnexal MALT lymphoma is a disease usually affecting elderly patients (median age, 65 years), with a higher prevalence among females. The interval between initial symptoms and diagnosis is variable (median, 6 or 7 months; range, 1–135 months). Clinical presentation of conjunctival lymphoma may consist of a classic “salmon red patch” with conjunctival swelling. Patients with intraorbital lymphoma may develop exopthalmos (27% of cases), palpable masses (19%), ptosis (6%), diplopia (2%), orbital edema or nodules, epiphora, and potentially impaired ocular motility. Extracocular muscle imbalance and limitation of the excursion of the eye are usually indicators of an expansive effect of the lesion rather than muscle damage. Visual acuity and field defects or choroidal folds are observed only in tumors with rapid growth, and only a few...
cases of ocular adnexal MALT lymphoma with infiltration and destruction of the eye have been published.74

MALT lymphoma usually remains localized for a prolonged period within the tissue of origin, but dissemination is not uncommon, occurring in up to one-fourth of non-GI MALT lymphomas.75 Bone marrow involvement is very rare (ie, <2% of cases) in recent series.6,7,9 Lymph node spread is reported with varied prevalence, mostly in gastric and pulmonary MALT lymphomas; this feature is associated with a poorer prognosis.

Diagnostic Procedures in Gastric MALT Lymphoma

Diagnosis of gastric MALT lymphoma is usually obtained by histopathologic examination of endoscopic biopsies. An accurate diagnosis requires a gastric mapping procedure with a sufficient number of biopsies from macroscopic lesions and normal mucosa to avoid a sampling bias because of insufficient material.48 According to recent guidelines, a minimum of 10 biopsy samples should be taken from visible lesions. Additional biopsies should be taken from macroscopically normal mucosa. In case of insufficient or inadequate initial biopsy material, a second endoscopy is necessary. Treatment should not be started until histopathologic diagnosis performed by a reference pathologist is available. Gastric mapping is also important to monitor treatment response. HP assessment on biopsies taken from an area distant from mucosal lesions is mandatory. Proton pump inhibitor treatment has to be withdrawn at least 2 weeks before endoscopy, because it may cause false-negative results with all HP diagnostic tests except serology.76,77 Special stains, such as Giemsa, immunohistochemistry, or fluorescence in situ hybridization, are recommended in case of a scanty bacterial load or an apparent absence of infection on routinely stained slides.78 Culture has lower sensitivity than histology even if performed under good conditions,79 but it does provide information on antimicrobial susceptibility, especially for the key antibiotic, which is clarithromycin.

Diagnostic Procedures in Extragastric MALT Lymphomas

Extragastric MALT lymphomas constitute a heterogeneous group of clinical entities; consequently, diagnostic procedures are varied, depending on the involved organ. Magnetic resonance imaging (MRI) and orbit ultrasonographic features are important for imaging ocular MALT lymphoma, particularly MALT lymphomas of the orbital structures, whereas suspicion of conjunctival MALT lymphoma is based on macroscopic aspects of the lesion (see above), and sample collection is performed by direct biopsy or resection. Neuroimaging techniques are fundamental for distinguishing MALT lymphoma from other orbital masses and for accurate staging and therapeutic response definition, because they allow precise volumetric measurements.

Routine chest x-rays are often able to detect pulmonary MALT lymphomas that have an alveolar aspect with badly defined margins and air bronchogram. Contrast-enhanced computed tomography (CT) scan of the thorax is the first-choice procedure to define the extension of pulmonary MALT lymphoma. The most common radiologic presentation is a nodule or mass measuring from 2 to 8 cm, most commonly located in the lower lobes, with air bronchograms in half of cases; nodules are multiple in less than 10% of cases. Interstitial infiltrate and pleural effusion are detected in 10% and 12%, respectively. Diagnostic samples may be achieved by bronchoscopy, fine-needle biopsy, or tumor resection for histologic assessment according to standard histopathologic criteria based on site of disease and lesion diameter.

Ultrasonography is used to assess nodules or masses located in the salivary glands or thyroid gland (with the potential for needle biopsy in case of thyroid lymphoma, whereas open biopsy to preserve the facial nerve is preferred in parotid masses), and MRI is more useful for distinguishing tumor border and extension.

Staging

Staging Procedures

The proportion of patients with disseminated disease at diagnosis varies among reported series, but there is a consensus that management and prognosis of these patients are different. Thus, sufficient staging workup is mandatory before initiating therapy.

Various recommendations have been published in recent guidelines, especially for patients with gastric MALT lymphoma.48,80 A list of staging procedures recommended in gastric and extragastric MALT lymphomas is reported in Table 1. Of note is the finding that 2-deoxy-2-[fluorine-18]fluorodeoxyglucose–positron emission tomography/CT is not recommended in these guidelines and, thus, should not be routinely applied in patients with MALT lymphoma, as there is a highly variable number of false-negative results, amounting to up to 50% of patients and probably depending on histologic characteristics, such as plasmacytic differentiation.81

Staging System

The optimal staging system in MALT lymphomas is matter of debate. This is especially important because MALT lymphoma might sometimes be multifocal in paired organs, such as the orbit,13 the parotid,12 and the lungs,82 but may also be disseminated within the GI tract without spread to other sites. Whether there is a clinical difference between “real” stage IV disease and dissemination within one organ...
system has been debated, and various staging systems have been applied for diverse situations. The Ann Arbor staging, which is based on the presence and localization of additional nonnodal lesions and the extent of lymph node involvement, is the most widely used system for extragastric MALT lymphomas, and several staging systems have been proposed for GI MALT lymphomas to take into account the nature of GI MALT lymphoma. The Ann Arbor staging system modified according to Musshoff and Radaszkiewicz is one of the most commonly used. This staging system differentiates between the extent of dissemination (ie, the involvement of neighboring [II1E] and distant [II2E] lymph nodes) and the depth of infiltration into the gastric wall (involving only the mucosa and submucosa [I1E] vs also extending beyond the submucosa [I2E]). In addition, the Lugano staging system has been widely applied in patients with MALT lymphomas. This system differs from others insofar as it recognizes stage I as a single lesion or multiple lesions confined to the GI tract, stage II as local lymph node involvement, II2 as distant lymph node involvement, and stage IIIE as direct extension through the serosa. There is no stage III, because disseminated extranodal involvement as well as the involvement of lymph nodes in supradiaphragmatic regions both are classified as stage IV disease. The most recent addition is the so-called Paris staging system, which has not been clearly validated to date. For a comparison between the Ann Arbor, Paris, and Lugano staging systems for GI lymphomas, see Table 2.

### Prognosis

#### Natural History

MALT lymphoma is an indolent malignancy that often presents with limited stage of disease. Some anecdotal cases of spontaneous tumor remission, mostly in Japanese patients with conjunctival MALT lymphoma, have been reported. However, the real rate of this phenomenon warrants further investigation, because some of these patients have been treated with topical steroids or antibiotics, which could have affected results. Both GI and non-GI MALT lymphomas have an excellent prognosis, with 5-year overall survival (OS) rates higher than 90% and a 10-year survival rate of 75% to 80%. Recurrences can occur several years after treatment, with a median of 5 years, involving the same organ (60% of cases) or other extranodal sites.

### Table 2. Comparison Between the Ann Arbor, Paris, and Lugano Staging Systems

| Lymphoma Extent                        | Ann Arbor Stage | Paris Staging* | Lugano Staging |
|----------------------------------------|-----------------|----------------|----------------|
| Mucosa and submucosal layer            | I1E             | T1N0M0         | I              |
| Muscularis propria, serosal layer      | I2E             | T2N0M0         | I              |
| Penetration beyond serosa              | I2E             | T3N0M0         | I              |
| Direct infiltration of adjacent organs | I2E             | T4N0M0         | II             |
| Locoregional lymph nodes               | I1E             | T1-T4N1M0      | II1            |
| Abdominal lymph nodes (beyond local)   | I2E             | T1-T4N2M0      | II2            |
| Extra-abdominal lymph node spread      | IIIE            | T1-T4N3M0      | IV             |
| Dissemination to distant/non-GI organs | IV              | T1-T4N0-N3M1   | IV             |

GI indicates gastrointestinal. *Bone marrow involvement is rated “B1” in the Paris staging system.*

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**TABLE 1. Recommended Staging Procedures in Mucosa-Associated Lymphoid Tissue Lymphoma**

| Gastric MALT lymphoma                  |                            |                            |
|----------------------------------------|-----------------|-----------------|
| Gastroscopy plus mapping biopsies      |                 |                 |
| Endosonography of the upper GI tract   |                 |                 |
| CT scan of thorax/abdomen/pelvis      |                 |                 |
| Colonoscopy                           |                 |                 |
| Ear, nose, and throat examination, including imaging of salivary glands |                 |                 |
| Imaging of ocular adnexa               |                 |                 |
| Bone marrow biopsy (not mandatory, to be considered before oncological therapy) |                 |                 |

| Nongastric MALT lymphoma               |                            |                            |
| CT scan of thorax/abdomen/pelvis      |                 |                 |
| Imaging of salivary glands and ocular adnexa (MRI or sonography) |                 |                 |
| Gastroscopy with multiple biopsies (recommended in case of pulmonary MALT lymphoma) |                 |                 |
| Colonoscopy (mandatory for primary nongastric-GI MALT lymphoma) |                 |                 |
| Dermatologic assessment for ocular adnexal/mammary MALT lymphomas |                 |                 |
| Bone marrow biopsy (not mandatory but to be considered before oncologic therapy) |                 |                 |

**TABLE 2. Comparison Between the Ann Arbor, Paris, and Lugano Staging Systems**

| Lymphoma Extent                        | Ann Arbor Stage | Paris Staging* | Lugano Staging |
|----------------------------------------|-----------------|----------------|----------------|
| Mucosa and submucosal layer            | I1E             | T1N0M0         | I              |
| Muscularis propria, serosal layer      | I2E             | T2N0M0         | I              |
| Penetration beyond serosa              | I2E             | T3N0M0         | I              |
| Direct infiltration of adjacent organs | I2E             | T4N0M0         | II             |
| Locoregional lymph nodes               | I1E             | T1-T4N1M0      | II1            |
| Abdominal lymph nodes (beyond local)   | I2E             | T1-T4N2M0      | II2            |
| Extra-abdominal lymph node spread      | IIIE            | T1-T4N3M0      | IV             |
| Dissemination to distant/non-GI organs | IV              | T1-T4N0-N3M1   | IV             |

GI indicates gastrointestinal. *Bone marrow involvement is rated “B1” in the Paris staging system.*
Dissemination occurs after a long disease-free interval in 30% to 50% of cases, often to other mucosal sites, without peripheral blood or bone marrow involvement. Transformation to large-cell aggressive lymphomas can occur in the first or later relapses. The precise frequency—although thought to be rare in our own cohort—and related mechanisms of histologic transformation are unclear. Several genetic alterations have been associated with histologic transformation, including p53 allelic loss and mutation, hypermethylation of p15 and p16, and p16 deletions. 

Prognostic Factors
Commonly reported indicators of a poorer outcome in MALT lymphoma are advanced age, impaired performance status, systemic symptoms, splenomegaly, elevated lactate dehydrogenase serum levels and/or β2-microglobulin levels, stage of disease, and, for primary gastric MALT lymphoma, the depth of infiltration of the gastric wall. Chromosomal translocations are related to lower responsibility to different therapies (see below).

Treatment
Therapeutic management of MALT lymphomas is extremely heterogeneous, and universally accepted therapeutic guidelines do not exist. Therapeutic choice depends on two main aspects: the primary involved organ and the extension of disease. The former is an important issue, because the involved extranodal organ is sometimes related to a particular ethiopathogenic association with an infectious agent; is linked to a certain dissemination pattern; and is an important treatment-determining factor, because some organs cannot be easily resected, whereas other organs cannot be safely irradiated. Stage of disease is the other relevant parameter, because patients with limited-stage MALT lymphoma can achieve long-term complete remission, and probably a cure, with local treatments (ie, surgery, radiotherapy), whereas patients with advanced disease require systemic treatments.

Watchful Waiting
Efficacy and the kinetics of response are two important parameters for therapeutic choice, mostly in “less indolent” MALT lymphomas that could rapidly impair organ function. Nevertheless, a variable proportion of MALT lymphoma patients can be managed with “watchful waiting” without compromising survival rates and quality of life. This is of particular importance for patients who have gastric MALT lymphoma and microscopic residual disease after HP eradication (see below). Sometimes, this condition is wrongly considered as a treatment failure, and affected patients are unnecessarily referred to second-line treatment; 94% of these patients will not actually experience progressive disease at a median watchful waiting period of 42 months. It is noteworthy that criteria to define “active disease” that needs immediate treatment remain to be recognized in MALT lymphomas, whereas some international guidelines suggest using the same criteria used for follicular lymphomas. Although the use of these criteria in MALT lymphomas is debatable, their application to prospective trials and routine practice may demonstrate that a relevant proportion of patients do not need immediate treatment. The “wait-and-watch” strategy after surgical resection or biopsy in patients with stage I ocular adnexal MALT lymphoma produces results similar to those reported with immediate radiotherapy in terms of time to progression, systemic dissemination, high-grade transformation, and lymphoma-related mortality, with a 10-year OS rate of 94%. This strategy could be safely proposed for selected patients, like elderly patients or patients with severe comorbidity, completely resected lesions, and/or indolent and asymptomatic disease. The “wait-and-watch” strategy is also associated with excellent disease control rates in pulmonary MALT lymphomas.

Treatment of Limited Disease (Stage I-II)
Patients with limited-stage disease constitute the vast majority of cases of MALT lymphoma. Patients requiring immediate intervention can be managed with local treatments, which include surgical resection or radiotherapy, with a curative intent; or systemic therapies, which could be ethiopathogenic, using a microorganism as the therapeutic target; or conventional chemotherapy or immunotherapy.

Local Treatments
Although surgical resection of tumors may be curative in many patients with MALT lymphoma, the use of this strategy is progressively decreasing. This is because postsurgical sequel and organ dysfunction are more injurious than the lymphoma itself. Therefore, surgery is mostly limited to diagnostic procedures for histopathologic diagnosis, management of therapeutic complications, or treatment of relapsing disease in patients who are not candidates for other treatments. Gastrectomy, for example, is currently being used as a salvage or palliative approach to bleeding or perforation, both of which are extremely rare in gastric MALT lymphoma.

It is noteworthy that some cases of pulmonary MALT lymphoma are completely resected, because radiologic assessment initially suspected a diagnosis other than lymphoma (ie, lung carcinoma). Complete excision can be performed in many conjunctival and lacrimal gland MALT lymphomas, especially in pseudoencapsulated lesions. However, additional efforts to completely resect lymphomatous lesions should be avoided considering that the extent
of surgical resection does not influence survival.\textsuperscript{95} No data support the use of adjuvant chemotherapy and/or immunotherapy in MALT lymphoma patients managed with primary complete surgical resection; similarly, complementary radiotherapy is not needed after complete resection.

Radiotherapy is the most extensively studied treatment in patients with MALT lymphoma. Radiotherapy is used as salvage therapy in patients with gastric MALT lymphoma who do not respond to or who relapse after HP eradication and is the standard primary treatment in many cases of extragastric MALT lymphoma. The best disease control is attained in lymphomas arising in the thyroid gland, whereas up to 40% of patients with ocular adnexal MALT lymphoma experience contralateral or distant relapse. MALT lymphomas of the lung and salivary glands exhibit intermediate survival rates. A universally accepted radiation schedule for MALT lymphomas does not exist, but doses from 25 to 30 grays in 10 to 15 fractions (minimal target dose, 25 grays) have been suggested.\textsuperscript{97} Four 9-megavolt photon beams are advisable in most MALT lymphomas, with the exception of conjunctival and cutaneous forms, in which electron beams (4-12 megavolts) are equally effective and less toxic. Most irradiated patients with stage I MALT lymphoma achieve an objective response that is slow and gradual. In-field relapses are uncommon; the 5-year failure-free survival rate varies from 60% to 65% for ocular adnexal MALT lymphoma and is up to 100% for thyroid MALT lymphoma.\textsuperscript{98}

With the above-suggested schedule, radiotherapy is usually well tolerated, and no serious acute toxicity is observed. Patients with ocular adnexal MALT lymphoma often develop a cataract 2 to 5 years after treatment. Irradiated patients with gastric MALT lymphoma develop transient anorexia and malaise and occasional nausea or dyspepsia. Radiotherapy is associated with significant residual xerostomia in patients with SS and MALT lymphoma of the salivary glands; this complication is often symptomatic and requires permanent dietary modifications. Radiation pneumonitis, presenting as permanent but nonprogressive fibrosis, occurs in patients with lung MALT lymphoma, even when low doses are used; this event is usually asymptomatic. Rare cases of in-field second cancers have been reported.\textsuperscript{95}

**Ethiopathogenetic therapies**

Some MALT lymphoma entities are associated with chronic persistent infections; these microorganisms can be used as therapeutic targets (see above). HP and gastric MALT lymphoma, CP and ocular adnexal MALT lymphoma, and *Borrelia* strains and cutaneous MALT lymphoma are the best-studied bacteria-lymphoma associations.

HP eradication with specific antibiotics is the standard treatment for patients with gastric MALT lymphoma.\textsuperscript{48,80} Triple combinations with clarithromycin as the backbone, combined with either metronidazole or amoxicillin plus a proton-pump inhibitor given for 10 to 14 days, are most commonly recommended in such patients.\textsuperscript{48} However, some have suggested avoiding clarithromycin or testing the susceptibility of HP before application in regions where clarithromycin resistance is greater than 15%. Meta-analyses data have suggested better outcomes when treatment is given for 14 days instead of 7 days, but there was no significant difference between 7 and 10 days.\textsuperscript{99} With this strategy, a first-line HP eradication rate of 91% can be expected in gastric MALT lymphoma; whereas 98% of patients will have a successful eradication after more lines of antibiotics.\textsuperscript{100} HP eradication should be checked by urea breath test and should be confirmed on gastric biopsies. In case of HP persistence, second-line antibiotics should be based on the results of culture and susceptibility testing of respective strains. HP eradication will result in lymphoma regression in approximately 65% of patients, with the time to best response being variable and in the range from 3 to 28 months.\textsuperscript{101} Tumor response should be defined histologically following the recently reviewed Groupe d’Étude des Lymphomes de l’Adulte (GELA) score.\textsuperscript{102} distinguishing between complete remission, no change, responding residual disease, and probable minimal residual disease based on cytology and the presence/absence of an “empty” lamina propria; and 2 sequential follow-up gastroscopies without lymphoma are mandatory to assume complete remission.\textsuperscript{63} The involvement of perigastric lymph nodes, involvement of the gastric wall beyond the mucosal muscle layer, and positivity for t(11;18)(q21;q21)/(API2-MALT1) are thought to be negative response predictors. However, there is no clear evidence to suggest that assessing and monitoring t(11;18)(q21;q21) during follow-up is useful in guiding management.\textsuperscript{48} There is a consensus that HP eradication should be performed in all cases of gastric MALT lymphoma, regardless of stage of disease and prognostic factors.\textsuperscript{48} Overall, greater than 60% of patients treated with HP eradication have residual monoclonality, or persistence of t(11;18(q21;q21), or histologic residual disease; however, only approximately 6% of them experience progressive disease.\textsuperscript{93} Accordingly, the addition of chemotherapy does not improve results in patients with gastric MALT lymphoma who are responsive to HP eradication.\textsuperscript{101} Interestingly, HP eradication has proved efficient also in cases of HP-negative gastric MALT lymphoma,\textsuperscript{103} which could be explained either by a low and undetectable bacterial load or by the involvement of other related bacteria (ie, *H. helmannii*).

The eradication of CP infection with doxycycline (100 mg administered orally, twice a day, for 3 weeks) is a fast, safe, cost-effective, and active therapeutic strategy for patients with ocular adnexal MALT lymphoma who do not require acute and aggressive therapy.\textsuperscript{104,105} The overall
response rate to doxycycline ranges up to 48%; lymphoma regression is slow and gradual and has been reported in patients with both CP-positive (65%) and CP-negative (38%) lymphomas, with a 3-year progression-free survival (PFS) rate of 68% and a median time to progression of >31 months. Responses are observed even in patients who did not respond to previous treatments and in patients with previously irradiated areas or regional lymphadenopathies.104,105 As upfront treatment, doxycycline has been associated with a chlamydial eradication rate of 48%, an overall response rate of 65%, and a 5-year PFS rate of 55% in patients with stage IE ocular adnexal MALT lymphoma.106 Better overall response (86% vs 47%; P = .02) and 5-year PFS (68% vs 47%; P = .11) rates have been recorded in patients who achieved successful CP eradication. A few patients with advanced-stage ocular adnexal MALT lymphoma have been treated with doxycycline and achieved responses that varied among the different tumors, which might be attributed to the heterogeneous distribution of tumor clones that depend on antigenic stimulation.107 Moreover, response to doxycycline might be influenced by other factors, such as reinfection because of prolonged contact with infected pets.108 See Table 3 for a selection of studies on antibacterial treatment for ocular adnexal MALT lymphoma.

While patients in immediate need of therapy because of lymphoma compromising the optic nerve need more aggressive forms of therapy, the results of antibiotic therapy suggest doxycycline as a potential first-line therapy even outside of a clinical trial in patients with asymptomatic lymphoma. Cutaneous MALT lymphoma is characterized by repeated relapses that usually are confined to the skin; thus, aggressive therapies should initially be avoided. Although lesions termed “borrelial lymphocytoma” are responsive to antibiotic treatment,111 the efficacy of Borrelia eradication in MALT lymphoma of the skin is less clear-cut and may vary. First-line antibiotic therapy with cephalosporins and tetracyclines, however, may be reasonably considered in Borrelia-positive patients.112 Treatment for patients who are unresponsive to antibiotics varies according to the extent of involvement: single lesions can be successfully resected, can be treated with intralesional interferon α (IFN-α) or rituximab, or may be irradiated using an electron beam. Patients with disseminated disease should be managed like those with other disseminated MZLs (see below).

Hepatitis C virus (HCV) is the only virus currently used as a therapeutic target, mostly in indolent lymphomas, including MZLs.113 Antiviral therapy is successfully used in different non-Hodgkin lymphoma subtypes but is more frequently being applied in MZLs. Treatment with pegylated IFN, with or without ribavirin, results in remission rates of 75% in patients with MZL114 and mixed cryoglobulinemia.115 The 5-year PFS and OS rates for patients treated with upfront antiviral therapy were 78% and 92%, respectively, and antiviral therapy was not significantly better when pegylated IFN is used.113 Until recently, antiviral therapy with IFN or ribavirin, or may be treated using an electron beam. Patients with disseminated disease should be managed like those with other disseminated MZLs (see below).

**Systemic treatments**

Chemotherapeutic and immunomodulatory agents were rarely used as part of first-line treatment for patients with limited-stage MALT lymphoma. This was based on the assumption that local therapies can lead to long-term local control in these patients. Accordingly, systemic agents had been used in selected patients who, because of disease site or extension of disease, could not be managed with local treatments and were affected by MALT lymphomas unrelated to a known etiologic microorganism. Unsectable, symptomatic, pulmonary MALT lymphoma and symptomatic, HP-negative, gastric MALT lymphoma are the most common examples of patients being given upfront systemic treatments. Agents and modalities are similar to

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**TABLE 3. Selection of Studies on Antibiotic Therapy for Ocular Adnexal Mucosa-Associated Lymphoid Tissue Lymphoma**

| FIRST AUTHOR | STUDY DESIGN | NO. OF PATIENTS | STAGE | Cp-POSITIVITY, % | THERAPY | RESPONSE RATE, % |
|--------------|--------------|----------------|-------|-----------------|---------|-----------------|
| Ferreri 2005 | Phase 2      | 9              | I-IVE | 100             | Doxycycline 100 mg BID × 21 d | ORR, 44 (CRR, 22) |
| Ferreri 2006 | Phase 2      | 27             | I-IVE | 41              | Doxycycline 100 mg BID × 21 d | ORR, 48 (CRR, 22) |
| Ferreri 2012 | Phase 2      | 34             | IE    | 85              | Doxycycline 100 mg BID × 21 d | ORR, 65 (CRR, 18) |
| Ferreri 2008 | Retrospective| 6              | IVE   | 100             | Doxycycline 100 mg BID × 21 d | ORR, 33 (CRR, 0) |
| Han 2015     | Retrospective| 90             | I-IVE | Not evaluated    | Doxycycline 100 mg BID × 21 d | ORR, 27 (CRR, 7) |
| Kim 2010     | Retrospective| 38             | I-IVE | 39              | Doxycycline 100 mg BID × 21 d | ORR, 47 (CRR, 18) |

BID indicates twice daily; Cp, Chlamydia psittaci; CRR, complete remission rate; ORR, overall response rate.
those used for patients with advanced-stage and/or relapsing MALT lymphomas (see below).

However, there has been a philosophical shift, at least in certain oncologic communities, also integrating systemic approaches into the front-line management of localized disease based on the clinicopathologic properties of the disease. Thus, the recent European Gastro-Intestinal Lymphoma Study consensus has stated that there is equally curative potential for systemic therapies and for radiation in localized gastric MALT lymphoma, and

### TABLE 4. Selection of Studies on Chemotherapy-Containing Treatment for Mucosa-Associated Lymphoid Tissue Lymphoma

| FIRST AUTHOR | STUDY DESIGN | NO. OF PATIENTS | GASTRIC/EXTRAGASTRIC, % | STAGE | THERAPY | RESPONSE RATE, % |
|--------------|--------------|----------------|-------------------------|-------|---------|-----------------|
| Hammel 1995176 | Retrospective | 24 | Gastric | I, IVE | Alkylating agents (po) continuously for 12-24 mo (cyclophosphamide 100 mg/d or chlorambucil) | ORR, 100 (CRR, 75) |
| Zucca 201317,18 | Randomized | 231 | 37/63 | I-IVE | Chlorambucil (po) vs R-chlorambucil (chlorambucil 6 mg/m² daily d1-42 in a 4-wk cycle × 4 followed by d1-14 in a 4-wk cycle × 4; R 375 mg/m² d1, 8, 15, and 22, then every 4 wk in absence of progression) | ORR, 87 vs 94 (CRR, 65 vs 78) |
| Hancock 2009102 | Randomized | 110 | Gastric | I, IIE | Chlorambucil (po) vs observation after HP eradication (chlorambucil maintenance: 6 mg/m² daily d1-14 in a 4-wk cycle × 6 after successful HP eradication) | 5-y recurrence rate, 21 vs 11 (P = 0.15, NS) |
| Lévy 201319 | Retrospective | 49 | Gastric | I-IVE | R-chlorambucil vs R monotherapy (R 375 mg/m² d1, 8, 15, and 22, then every 4 wk; chlorambucil 6 mg/m² daily d1-42 followed by d1-14 in a 4-wk cycle for 4 mo) | ORR, 93 vs 81 |
| Salar 2014120 | Phase 2 | 60 | 33/66 | I-IVE | R-bendamustine (R 375 mg/m² d1; bendamustine 90 mg/m² d1 + 2 in a 4-wk cycle × 4-6, depending on response) | ORR, 100 (CRR, 98) |
| Kiesewetter 2013121 | Retrospective | 14 | Extragastric | I-IVE | R-bendamustine (R 375 mg/m² d1; bendamustine 90 mg/m² d1 + 2 in a 3-wk cycle × 6) | ORR, 92 (CRR, 71) |
| Raderer 2006122 | Retrospective | 26 | 27/73 | I-IVE | R-CHOP/R-CNOP (R 375 mg/m² d1; cyclophosphamide 750 mg/m² d2, doxorubicin 50 mg/m² d2 or mitoxantrone 8 mg/m² d2, vincristine 1.4 mg/m², prednisone d1-5 every 3 wk × 6-8) | ORR, 100 (CRR, 77) |
| Jäger 2002123 | Phase 2 | 26 | 73/27 | I-IVE | Cladribine (iv) (0.12 mg/kg d1-5 every 4 wk × 6) | ORR, 100 (CRR, 84) |
| Troch 2013124 | Phase 2 | 40 | 53/48 | I-IVE | R-cladribine (sc) (R 375 mg/m² d1; cladribine 0.1 mg/kg d1-4 every 3 wk × 6) | ORR, 81 (CRR, 58) |
| Zinzani 2004125 | Phase 2 | 31 | Extragastric | IE | FM or CVP (iv) (fludarabine 25 mg/m² d1-3 and mitoxantrone 10 mg/m² d1; or cyclophosphamide 400 mg/m² d1-5, vincristine 1.4 mg/m² d1, and prednisone every 3 wk × 6) | ORR, 100 (CRR, 100) |
| Salar 2009126 | Phase 2 | 22 | 55/46 | I-IVE | R-fludarabine (iv/po; R 375 mg/m² d1; fludarabine 25 mg/m² iv or 40 mg po d1-5 every 4 wk × 4-6) | ORR, 100 (CRR, 90) |

CRR indicates complete remission rate; CVP, cyclophosphamide, vincristine, and prednisone; FM, fludarabine and mitoxantrone; HP, Helicobacter pylori; iv, intravenously; NS, nonsignificant; ORR, overall response rate; po, orally; R, rituximab; R-CHOP/CNOP, rituximab, cyclophosphamide, doxorubicin/mitoxantrone, vincristine, and prednisone; sc, subcutaneously.
recent data obtained in 185 patients with extragastric MALT lymphoma who were followed for a median of 49 months have also shown no difference in outcome between various therapeutic approaches in localized nongastric lymphomas in terms of response rates and PFS.7

Chemoinmunotherapies

According to the notion that MALT lymphoma was “just another” type of indolent lymphoma, patients with (mostly advanced) MALT lymphoma had been and still are included in trials mostly encompassing follicular lymphomas. The first paper to single out MALT lymphoma patients treated with the oral alkylating agents chlorambucil and cyclophosphamide was published in 1995,516 showing a 75% complete response rate (CRR) after a median duration of therapy of 12 months. Since then, several mostly small, uncontrolled trials using various agents and combinations in MALT lymphoma have been published, although few randomized data currently exist. The interested reader is referred to Table 4102,116-126 and to a recently published paper on the details of systemic therapies.127 Two randomized trials exist, including the International Extranodal Lymphoma Study Group (IELSG)-19 study on chlorambucil versus rituximab plus chlorambucil117 and a randomized study on wait and see versus chlorambucil in patients with gastric MALT lymphoma after HP eradication. Interestingly, the latter study, which randomized 110 patients,122 could not establish a benefit for chlorambucil monotherapy after HP eradication. The 5-year recurrence rate was 21% in the “wait-and-see” arm versus 11% in the chlorambucil arm (P = .15), and it is also interesting that no benefit was seen with chlorambucil in patients who had residual lymphoma after antibiotics. To date, the randomized, multicenter IELSG-19 trial117 is the largest prospectively randomized trial in MALT lymphoma, including a total of 231 patients, comparing chlorambucil versus rituximab-chlorambucil. Chlorambucil was given orally at 6 mg/m² for 42 consecutive days (weeks 1-6), followed by chlorambucil for 2 weeks every 28 days up to 4 cycles. The response rate was 87% for the chlorambucil arm and 94% for the combination arm (P = 0.069), whereas both the CRR and the 5-year event-free survival rate were significantly higher with the combination (78% vs 65% [P = .025] and 68% vs 50%, respectively) in both gastric and extragastric MALT lymphoma. However, the long-term outcome was not significantly improved, questioning the need for combining chlorambucil and rituximab in asymptomatic patients. As a consequence, the study was extended to include a rituximab-monotherapy arm to allow for further comparison of activity between rituximab and chlorambucil monotherapy.

In addition, it might be argued that chlorambucil per se may not currently be the most active chemotherapy available for patients with MALT lymphoma. Although it has to be noted that, especially in patients with MALT lymphoma (which is characterized by an indolent clinical course and with life expectancies measured in years to decades), toxicities should be important in the choice of treatment, excellent results have been published with more intensive regimens. The combination of rituximab plus bendamustine (R-Benda) has become standard for the treatment of various types of indolent lymphoma after publication of a randomized phase 3 trial of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) versus R-Benda.126 In keeping with the initial phase 2 study of the same regimen,129 which included 6 patients with MZL (without further specification of MALT vs non-MALT), such patients were also treated within the phase 3 Study Group Indolent Lymphomas study.128 In total, 37 patients with MZL were included in the R-Benda arm, and 30 were included in the R-CHOP arm, but the PFS was not significantly different for the subgroup of patients with MZL (57.2 vs 47.2 months, respectively; P = .32). However, the missing information on the exact nature of the MZL subtypes makes extrapolation of the findings to MALT lymphoma in general difficult.

The Spanish Lymphoma/Autologous Marrow Transplant Study Group (GELTAMO) has included 60 patients with treatment-naive MALT lymphoma in a trial of rituximab 375 mg/m² intravenously on day 1 and bendamustine 90 mg/m² on days 1 and 2.120 The protocol was designed to expose patients to minimal necessary therapy; thus, patients in complete remission after 3 courses were given only 4 cycles, whereas other patients underwent 6 cycles. In this study, a 100% response rate was seen, with no relapses occurring after a median follow-up of 14 months. In addition, an Austrian retrospective series has also shown responses in heavily pretreated patients with extragastric MALT lymphoma, underlining the high potential of R-Benda.121 In view of these findings, the combination of R-Benda appears to be attractive for use outside of clinical trials.

Treatment of Relapsed or Refractory Disease

Late recurrences and distant relapses have repeatedly been reported in patients with MALT lymphoma even after a prolonged follow-up time.130,131 In routine practice, salvage treatment depends on the primary site of disease and previous therapies. In case of (localized) gastric relapse, reinfestation with HP has to be considered as a potential trigger; and, if detected, reeradication is an appropriate treatment approach. Increasing primary drug resistance against formerly effective antimicrobial treatments has to be taken in account, and resistance profiles for local bacteria strains to assess appropriate measures may become increasingly important.132
However, the HP reinfection rate appears to be rather low, with an estimated rate of 0.7% per year.\textsuperscript{133}

In the case of dissemination or refractory disease, systemic treatment options with chemoimmunotherapy are seen as the treatment of choice, whereas local treatment should be restricted to the management of distinct complications (ie, radiotherapy for potential involvement of the optic nerve in ocular adnexal lymphoma). In the past, several cytostatic substances and regimens—mostly adapted from other indolent lymphoma entities—have been successfully tested in this setting, achieving CRRs of 80% to 100%; regimens that include anthracyclines,\textsuperscript{122} alkylating agents,\textsuperscript{102,116-121} and purine analogues,\textsuperscript{123-126} combined or not with rituximab, have been associated with high response rates. However, many of these combinations are quite toxic; thus, anthracycline-containing regimens in particular should be restricted to patients in need of rapid response or to those with transformation to diffuse large B-cell lymphoma.

Although historical data are mostly derived from small case series or retrospective studies, recently, increasing numbers of prospective trials were performed, hence leading to the implementation of new standards. The above-mentioned trials (see Systemic treatments, above), called IELSG-19 and MALT2008-01, have produced excellent results with combinations of chlorambucil or bendamustine plus rituximab in patients with newly diagnosed MALT lymphoma\textsuperscript{117,120}; however, these encouraging experiences provide the rationale to also use these combinations in patients with MALT lymphoma that has relapsed after or is refractory to local therapies or ethiopathogenic therapies.

With the implementation of rituximab into the treatment plan of nearly all B-cell malignancies, this monoclonal antibody was also studied in MALT lymphoma. Although it is a strong partner for combination with some substances like bendamustine,\textsuperscript{120,121} its benefit might be questionable for other regimens, including cladribine or chlorambucil.\textsuperscript{117,124} Single-agent rituximab has been tested in several small studies, including 3 prospective trials for localized/disseminated and gastric/extragastric lymphoma, respectively; but, with CRRs from 15% to 45% and overall response rates from 65% to 75%, this treatment appears to be inferior to chemo-containing regimens.\textsuperscript{134-136} However, there is evidence that rituximab monotherapy might be more effective for some primary sites than for others,\textsuperscript{137} and it remains a reasonable approach for elderly and frail patients because of a favorable toxicity profile.

A retrospective analysis of the Surveillance, Epidemiology, and End Results–Medicare database that extracted patients with gastric MALT lymphomas who were treated between 1997 and 2007 has reported on 347 patients with disease localized to the stomach, suggesting a benefit for treatment with rituximab. With all the caveats of such a retrospective series, where certain data, such as the need for therapy, comorbidities, and potential parallel use of antibiotics against HP, cannot be extracted, the authors nevertheless found that regimens including rituximab resulted in a better survival ($P = .017$), and no benefit of combined chemoimmunotherapy was found after adjusting for confounding factors.\textsuperscript{138} Median OS, however, was relatively short for MALT lymphoma at 6.7 years, and the analysis included only patients who were being treated with either cyclophosphamide-containing regimens (cyclophosphamide, vincristine, and prednisone and CHOP) or fludarabine. For an overview on immunotherapy for MALT lymphoma, see Table 5.\textsuperscript{134-137,139-144}

### New Active Drugs and Therapeutic Options

Because of the indolent clinical course of MALT lymphoma and the high remission rates achieved by conventional chemotherapy, modern treatment strategies concentrate on “chemo-free” approaches to minimize toxicities, maintaining efficacy.

Multiple myeloma and MALT lymphoma share common features, such as their close relationship to the plasma cell; consequently, established therapeutic options for myeloma have also been assessed in small prospective trials of patients with MALT lymphoma. Bortezomib, a proteasome inhibitor, was active but showed a high rate of polyneuropathy and diarrhea, resulting in dose reductions in 15 of 16 patients with relapsed MALT lymphoma.\textsuperscript{139} Thalidomide monotherapy showed a lack of efficacy in a small pilot series,\textsuperscript{141} whereas recent data on the second-generation immunomodulator lenalidomide are more encouraging, with an ORR of 70% in a phase 2 trial addressing the activity and feasibility of lenalidomide 25 mg/day in 16 patients with newly diagnosed or relapsing MALT lymphoma.\textsuperscript{142} A phase 2 trial of combined rituximab and lenalidomide (at a dose of 375 mg/m\textsuperscript{2} intravenously on day 1 and 20 mg daily for 21 days, respectively, every 28 days) is currently being finalized, and preliminary results suggest a high activity.\textsuperscript{145}

A further interesting approach is the macrolide antibiotic clarithromycin, which apparently not only has antimicrobial but also has immunomodulatory and antitumoral effects. These are most likely mediated through the inhibition of vascular endothelial growth factor and tumor necrosis factor-$\alpha$, enhancement of natural killer cells and CD8- cytotoxic T-cells, and interaction with several other immune mediators. Single-drug clarithromycin has been associated with a 38% ORR in a small pilot study of patients with relapsed or refractory MALT lymphoma.\textsuperscript{143} To further confirm the role of clarithromycin, a multicenter trial that included only patients with refractory disease who had no evidence of active HP infection or chlamydia infection was
performed and recently reported. Taking in account a putative dose-dependent effect, clarithromycin was applied at an increased dose of 2 g/day. In 23 patients at first or greater relapse, the response rate was 52% (95% confidence interval, 32%-72%) with a 2-year PFS rate of 56%.

With increasing use of targeted therapies, MALT lymphoma also might become a focus of interest for such agents such as idelalisib. In fact, the pivotal study leading to the approval of idelalisib in follicular lymphoma has also included 15 patients with MZL, showing a promising response rate in this—albeit rather small—subset. In addition, from the data, it cannot be extrapolated whether there had indeed been any MALT lymphomas among these patients; nevertheless, the mode of action makes idelalisib an interesting agent for MALT lymphoma.

**Follow-Up**

Current guidelines recommend follow-up strategies in line with those used for other indolent B-cell malignancies, proposing to perform physical examination, performance status assessment, hematologic and biochemical examinations, and instrumental examinations that were positive at the baseline assessment (parameters of disease). The selection of examinations depends on the primary extranodal site of disease: ocular adnexal MALT lymphoma should be assessed with gadolinium-enhanced MRI, ophthalmologic examination, and photography of conjunctival lesions; MALT lymphoma of the salivary glands and thyroid gland should be assessed with neck ultrasonography; gastric MALT lymphoma should be assessed with contrasted CT scans; MALT lymphoma of the breast should be assessed with mammography and/or ultrasonography; colorectal MALT lymphoma should be assessed with colonoscopy and endoscopic biopsies; and MALT lymphomas of the skin and oral cavity should be assessed with physical examination and photography. Multigorgan MALT lymphomas should be assessed with combinations of the above-mentioned procedures. Given the indolent nature of disease, excessively short intervals between visits should be avoided.

### Table 5: Selection of Studies on Immunomodulatory Treatment for Mucosa-Associated Lymphoid Tissue Lymphoma

| First Author | Study Design | No. of Patients | Gastrointestinal, % | Stage | Therapy | Response Rate, % |
|--------------|--------------|----------------|---------------------|-------|---------|-----------------|
| Conconi 2003 | Phase 2      | 35             | 43/57               | I-IVE | Rituximab 375 mg/m² iv weekly × 4 | ORR, 73 (CRR, 44) |
| Martinelli 2005 | Phase 2   | 27             | Gastric             | I-IVE | Rituximab 375 mg/m² iv weekly × 4 | ORR, 77 (CRR, 46) |
| Lossos 2007  | Phase 2      | 12             | 25/75               | I-IVE | Rituximab 375 mg/m² iv weekly × 4 | ORR, 67 (CRR, 17) |
| Valencak 2008 | Retrospective | 5              | Skin                | ---   | Rituximab 375 mg/m² iv weekly × 4 | ORR, 100 (CRR, 80) |
| Troch 2009   | Phase 2      | 16             | 25/75               | I-IVE | Bortezomib 1.5 mg/m² iv d1, 4, 8, and 11 every 3 wk × 8 | ORR, 80 (CRR, 43) |
| Conconi 2011 | Phase 2      | 32             | 44/56               | I-IVE | Bortezomib 1.3 mg/m² iv d1, 4, 8, and 11 every 3 wk × 6 | ORR, 48 (CRR, 31) |
| Troch 2009   | Phase 2      | 8              | 63/37               | I-2E  | Thalidomide 100–400 mg/d po, escalated | ORR, 0 |
| Kiesewetter 2013 | Phase 2 | 18             | 28/72               | I-IVE | Lenalidomide 25 mg po d1-21 in a 4-wk cycle × 6 | ORR, 61 (CRR, 33) |
| Govi 2010    | Phase 2      | 13             | 8/92                | I-IVE | Clarithromycin 1000 mg/d po for 6 mo | ORR, 38 (CRR, 15) |
| Ferreri 2015 | Phase 2      | 23             | 17/83               | I-IVE | High-dose clarithromycin (2000 mg po d1-14) in a 3-wk cycle × 4 | ORR, 52 (CRR, 26) |

CRR indicates complete remission rate; iv, intravenously; ORR, overall response rate; po, orally.
after 10 years have been observed, justifying lifelong clinical follow-up. In addition, the common risk factor HP also may predispose individuals to the development of gastric adenocarcinoma, arguing for endoscopic surveillance of patients after treatment for HP-positive gastric MALT lymphoma.

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