Update: gastric MALT lymphoma

Brad S. Kahl

Purpose of review

Gastric MALT lymphoma is a model malignancy for examination of how neoplasia may arise from chronic inflammation. It is also exemplifies the translation of biologic knowledge of a disease towards improved clinical practice. Several recent publications have furthered the understanding of gastric MALT lymphoma pathogenesis, clinical behavior, and treatment.

Recent findings

A substantial fraction of cases will harbor a balanced translocation between chromosomes 11 and 18. This translocation results in the generation of a novel fusion protein, aberrant nuclear BCL10 expression, and activation of the NF-kB pathway. The result is *H. pylori*-independent growth and a unique clinical picture characterized by a more advanced presentation and unresponsiveness to *H. pylori* eradication therapy. While more likely to require cytotoxic therapy, this subtype is paradoxically less likely to undergo large-cell transformation. Finally, clinical trials are helping define the optimal role for *H. pylori* eradication therapy and are demonstrating that therapeutic approaches incorporating stomach conservation are preferable for those cases unresponsive to eradication therapy.

Summary

The pathogenesis of gastric MALT lymphoma has been elucidated to a large degree in recent years. Understanding the biology of this disease will most certainly translate into clinical practice.

Keywords

B-cell lymphoma, Helicobacter pylori, MALT

Curr Opin Oncol 15:347–352. © 2003 Lippincott Williams & Wilkins.

Hematology Section, Department of Medicine, University of Wisconsin, Madison Wisconsin, USA

Correspondence to Brad Kahl, MD, 600 Highland Avenue, H4/534 CSC, Madison, WI 53792, USA
E-mail: bsk@medicine.wisc.edu

Current Opinion in Oncology 2003, 15:347–352

Abbreviations

API2	inhibitor of apoptosis gene 2
CHOP	cyclophosphamide, hydroxyldaunorubicin, oncovin, prednisone
CR	complete response
DLBCL	diffuse large B-cell lymphoma
EFS	event free survival
FISH	fluorescence in situ hybridization
H. pylori	helicobactor pylori
MALT	mucosa associated lymphoid tissue
MLT	MALT 1 gene
NF-kB	nuclear factor kB
OS	overall survival
PR	partial response
RT-PCR	reverse transcriptase polymerase chain reaction

ISSN 1040–8746 © 2003 Lippincott Williams & Wilkins

Introduction

Lymphomas arising from mucosa associated lymphoid tissue (MALT) were first described as a distinct pathologic entity in 1983 [1]. Since then, they have been reclassified as extranodal marginal zone lymphomas MALT-type [2]. The marginal zone lymphomas are a discrete group of indolent B-cell lymphomas, including nodal, primary splenic, and MALT type. The MALT type are by definition extranodal lymphomas, arising in a background of mucosa associated lymphoid tissue, paradoxically in locations typically devoid of lymphoid tissue. The MALT develops as a result of chronic inflammation, which may be due to infection such as Helicobacter pylori gastritis, or due to an autoimmune process such as the myeloepithelial sialadenitis of Sjögren syndrome. MALT lymphomas comprised 7.6% of the cases in the nonHodgkin lymphoma classification project and had the best prognosis of all lymphoma subtypes [3]. MALT lymphomas can arise in a variety of anatomic locations including the salivary glands, respiratory tract, thyroid, orbit, conjunctiva, breast, prostate, bladder, small intestine, and most commonly, the stomach. This review will focus on gastric MALT lymphoma and recent advances in the biology and the management of this disorder.

Helicobacter pylori

The link that *H. pylori* gastritis predates MALT, which predates MALT lymphoma, is established. The microbe can be detected in approximately 90% of gastric MALT lymphoma cases. *In vitro* experiments have demonstrated that malignant B cells proliferate after T-cell activation in an *H. pylori* strain-specific fashion [4,5]. Perhaps the strongest evidence is the observation that in approximately two thirds of cases, the lymphoma will regress after treatment for *H. pylori* infection. It is assumed the initial proliferation of lymphoma cells occurs in an antigen-dependent fashion, explaining the tendency for these lymphomas to remain anatomically localized and to respond to antibacterial therapy. Given that most patients with *H. pylori* gastritis do not develop MALT lymphoma, it is clear that additional events (*eg*, environmental, microbial, immune, genetic) are important.

Biology

Improved understanding of the biology of gastric MALT lymphoma has occurred in the past few years. The most common structural cytogenetic abnormality is the t(11;18)(q21;q21), which is detected in 30 to 40% of cases. This translocation fuses the amino terminal of the

inhibitor of apoptosis (API2) gene to the carboxyl terminal of the MALT 1 (MLT) gene and generates a chimeric fusion protein [6]. The fusion protein appears to significantly increase nuclear factor-kB (NF-kB) activation, a molecular pathway important in a variety of tumor types. Several recent interesting biologic and clinical observations regarding the t(11;18) cases have been made.

First, cases harboring the t(11;18) are significantly less likely to respond to *H. pylori* eradication therapy [7–9••]. The largest series examining this question assessed 111 patients with *H. pylori*-positive gastric MALT lymphoma who were treated with antibiotics [9••]. Diagnostic tissue was analyzed for the API2-MLT transcript by reverse transcription polymerase chain reaction (RT-PCR). Of the stage IE cases, 46 of 63 t(11;18) negative cases experienced complete regression after antibiotic therapy, while only 1 of 27 t(11:18) positive cases experienced complete regression. Of 17 stage IIE t(11:18) positive cases, only one patient responded to antibiotic therapy. Both t(11;18) positive patients who responded to antibiotic therapy later relapsed, without evidence of recurrent *H. pylori* infection. Based upon this large series, it appears that t(11;18) positive cases are highly unlikely to respond to *H. pylori* eradication therapy, and are likely to recur if antibiotic treatment is initially successful.

Second, there appears to be a high incidence of t(11;18) in *H. pylori*-negative gastric MALT lymphoma [10]. In approximately 5 to 10% of gastric MALT lymphomas, evidence for *H. pylori* infection is absent. Ye *et al.* [10] evaluated 17 *H. pylori*- negative cases by RT-PCR and found the t(11:18) in 9 cases (53%).

Third, t(11:18) positive case are associated with aberrant expression of nuclear BCL10. In normal B-cell follicles, BCL10 is expressed in the cytoplasm of germinal center B cells and in marginal zone cells, while nuclear expression is not observed. Liu *et al.* [11•] found nuclear BCL10 staining by immunohistochemistry in 28 of 53 MALT lymphomas. Nuclear BCL10 was highly associated with the t(11;18) translocation and both features were more likely to be seen in advanced stage disease. Maes *et al.* [12•] demonstrated that the aberrant nuclear BCL10 expression is not due to mutations in the BCL10 gene. They showed aberrant nuclear expression in 10 of 10 cases harboring the t(11;18) translocation, compared with 4 of 25 cases without the translocation. The exact biochemical relation between the API2-MLT fusion product and the BCL10 protein is not entirely clear, but appears to result in altered subcellular localization of the latter. The end result is upregulation of the NF-κB pathway. Lucas *et al.* [13••] have shown the API2-MLT fusion protein can activate NF-kB. They also demonstrated that BCL10 can complex with MLT, resulting in NF-kB induction through the same pathway. This is an interesting finding since a less common translocation seen in some gastric MALT lymphoma cases, t(1;14), transfers the entire BCL10 gene to the Ig heavy chain promoter region, resulting in BCL10 overexpression. Thus, there may be two different pathways leading to NF-kB activation in both t(11;18) and t(1;14) gastric MALT lymphoma. NF-kB induction appears to drive antigen independent growth of the lymphoma cells, promoting disease dissemination and unresponsiveness to *H. pylori* eradication therapy.

Fourth, gastric MALT lymphomas harboring the t(11;18) are more likely to present with advanced stage disease [10,11•,12•]. In the large series by Liu *et al.*, there were 17 stage IIE t(11;18) positive cases but only 4 stage IIE t(11;18) negative cases [9••]. In the report by Liu *et al.* examining the presence of nuclear BCL10, t(11;18) was seen in 78% of cases disseminated outside the stomach, while nuclear BCL10 was seen in 93% of such cases [11•]. Cases confined to the gastric mucosa were found to harbor t(11;18) in 10% of cases, and nuclear BCL10 expression in just 38%.

Finally, t(11;18) cases appear unlikely to develop secondary chromosomal abnormalities and are unlikely to transform into diffuse large cell lymphoma. A plenary paper suggests that gastric MALT lymphomas develop along two distinct pathways [14••]. Microsatellite screening of 24 gastric MALT lymphomas was performed and the results were compared with a previous study on gastric diffuse large B-cell lymphoma (DLBCL) cases. Only 1 of 10 t(11;18) positive cases showed an additional clonal abnormality while numerous allelic imbalances were detected in the t(11;18) negative cases. Some of these imbalances were identical to aberrations seen in gastric DLBCL, suggesting this group may be the source of tumors that eventually transform.

In summary, the t(11;18) positive cases are less likely to respond to *H. pylori* eradication therapy, are more likely to be found in *H. pylori* negative cases, are likely to be associated with aberrant nuclear BCL10 expression, are more likely to present with advanced stage disease, and are less likely to transform to aggressive lymphomas.

Clinical features

The median age of presentation is 63 with an equal proportion of males and females. The most common presenting symptoms are nonspecific dyspepsia and epigastric pain. Rarely, patients will present with nausea and vomiting or bleeding. It is exceedingly rare for patients to present with classic B symptoms. At endoscopy, erythema, erosions, or ulcers are most commonly seen and masses are rare. The most common gastric location is the antrum, but multifocal disease is present in at least 1 in 3, and would probably be found more often if random biopsies of normal-appearing gastric mucosa were routinely obtained. Helicobacter organisms, if present, will typically be seen in the histologic sections. Other tests

that can document infection include biopsy urease testing, a urea breath test, serology, or a stool test. At a minimum, one invasive test and one noninvasive test should be negative before a patient is considered a *H. pylori*-negative case. The diagnosis of gastric MALT can usually be made with be routine histology but some cases are challenging. Immunohistochemistry or flow cytometry may be needed to differentiate from other lymphoma subtypes. The tumor cells may resemble follicular center cells, small lymphocytes, or monocytoid cells. Scattered transformed blasts are common and may cause concern for transformation. An important histologic clue is the presence of lymphoepithelial lesions formed by invasion of the tumor cells into individual glands. Evidence of a local immune response is noted by the presence of scattered transformed blasts and plasma cells. The immunophenotype is that of typical marginal zone B-cells (CD20+, CD21+, CD35+, IgM+, IgD-). Notably, the neoplastic cells should be CD5-, CD10-, and cyclin D1 negative. Given the unique biology and clinical characteristics of the t(11;18) positive cases, the search for this chromosomal aberration should become routine. The method for detecting this abnormality will vary from center to center depending upon molecular diagnostic capabilities. Reliance upon routine karyotyping should be avoided, since this method will fail to detect most cases. Rather, fresh tissue should be sent for RT-PCR or for fluorescence *in situ* hybridization (FISH). If all tissue has already been placed in paraffin, newer techniques should allow the performance of tissue-FISH [15•].

Staging should mimic that for other lymphomas and include CT scans of the chest, abdomen and pelvis, a bone marrow evaluation, and routine laboratory tests including LDH and B2M. Additional staging, unique to MALT lymphomas, should be considered. This is not standardized but could include an upper airway examination, upper GI with small bowel follow-through, colon examination, and endoscopic ultrasound of the stomach. With more intense staging, disseminated disease may be found in up to 1 in 3 cases [16]. In the report by Thieblemont *et al*. [16] (which included nongastric MALT), 54 of 158 patients were found to have disseminated disease at diagnosis. Of these 54 patients, 17 (30%) were found to have multiple involved mucosal sites, while 37 patients (70%) had only one mucosal site plus other sites of disease. Of the latter group, 23 had bone marrow involvement, 12 had multiple lymph node involvement, and 2 had nonmucosal site involvement. The optimal staging system for gastric MALT lymphomas is controversial. Either the Ann Arbor staging system or the Lugano staging system (Table 1) of gastrointestinal lymphomas can be used [17].

Table 1. Lugano staging of GI lymphomas

Stage I	Tumor confined to GI tract (single primary site or multiple noncontiguous site)
Stage II	Tumor extending into abdomen from primary GI site II_1 = local nodal involvement II_2 = distant nodal involvement
Stage II_E	Penetration of serosa to involve adjacent organs or tissues
Stage IV	Disseminated extranodal involvement, or supradiaphragmatic nodal involvement

Treatment

Mucosa associated lymphoid tissue lymphomas of all types are notoriously indolent diseases with the best 5- and 10-year survival of any NHL subtype [3]. Optimal treatment for gastric MALT lymphoma will vary from patient to patient depending upon *H. pylori* status, presence of t(11;18), disease stage, and evidence for large-cell transformation. Given that greater than 90% of cases are associated with *H. pylori*, it seems reasonable to treat all patients with a course of eradication therapy at the outset (Table 2), as this may be the only required lymphoma therapy [18–20]. Truly *H. pylori*-negative patients will not respond to this approach, but occasionally patients have false-negative testing. Given the indolent nature of MALT lymphomas, a course of antibiotics is unlikely to do harm and may spare some patients' chemotherapy, radiotherapy, or surgery. This recommendation is consistent with NCCN guidelines [21]. Patients with more advanced stage disease and patients with the t(11;18) are also unlikely to respond to *H. pylori* eradication. Again, a trial of eradication therapy may be worthwhile, as a minority of patients will have lymphoma regression and may be spared other treatments. Additionally, it seems prudent to eradicate the infection to lower the risk of peptic ulcer disease and gastric carcinoma, and to eliminate a source of antigenic stimulation that may contribute to lymphoma recurrence.

The subgroup of patients most likely to respond to eradication therapy will be the *H. pylori*-positive stage IE patients without t(11:18). In the report by Liu *et al*. [9••], 47 of 64 (73%) patients in this category responded to eradication therapy. If one analyzes the patients in this series only by stage, 47 of 90 (52%) stage IE patients responded to eradication therapy while only 1 of 21 (5%) stage IIE patients responded. If one analyzes the patients only by t(11;18) status, 46 of 67 (69%) translocation negative patients responded to eradication therapy while only 2 of 44 (5%) translocation positive patients responded. Thus both stage and translocation status are important predictors of response. It is important to note that lymphoma regression can be gradual, varying from a few weeks to 18 months [22]. It is reasonable to repeat endoscopy 2 months after the completion of eradication therapy to make the initial assessment. Patients with complete regression should be monitored yearly for recurrence. Patients with no response should be considered for alternative therapies (see below), while patients demonstrating partial regression should undergo continued monitoring with serial endoscopies until regression is complete, or until it is clear that complete regression will not occur. Therefore, prolonged follow-up with re-

Table 2. *H. Pylori* treatment

Regimen #1	Regimen #2	Regimen #3
Omeprazole (20 mg, twice a day)	Omeprazole (20 mg, twice a day)	Omeprazole (20 mg, twice a day)
Amoxicillin (1 gm, twice a day)	Metronidazole (500 mg, twice a day)	Tetracycline (500 mg, 4 times a day)
Clarithromycin (500 mg, twice a day)	Clarithromycin (500 mg, twice a day)	Metronidazole (500 mg, 4 times a day)
		Bismuth (525 mg, 4 times a day)

Treatment duration is 10–14 days. Regimen #1 is the regimen of choice. Regimen #2 is for penicillin-allergic patients. Other proton pump inhibitors may be substituted at equivalent dosages. Eradication rates exceed 85% with all three regimens.

peat endoscopies and biopsies are required for proper disease status monitoring.

There are now provocative reports suggesting gastric MALT lymphoma, which has undergone histologic transformation to large-cell lymphoma, can successfully be treated with *H. pylori* eradication therapy alone. The paper by Morgner *et al.* [23•] is a retrospective review of 8 patients with evidence of large-cell transformation who were treated with eradication therapy. Six patients were stage IE and two patients were IIE using the Lugano criteria. They observed 7 complete remissions (CR) and one partial remission (PR). One of the complete remission patients recurred outside the stomach and was subsequently treated with CHOP chemotherapy. The other 6 patients remained in CR with follow-up time ranging from 6 to 66 months. Chen *et al.* [24••] conducted a prospective study of eradication therapy in 16 patients with *H. pylori*-positive stage IE MALT lymphoma with convincing evidence of large-cell transformation. Patients underwent follow-up endoscopy 4 to 6 weeks after completion of eradication therapy and then every 6 to 12 weeks until complete remission was documented. Patients not improving or with any evidence of progression were immediately started on CHOP chemotherapy. Overall, 15 of 16 patients achieved *H. pylori* eradication. Ten patients achieved a complete histologic regression of their lymphoma. Most patients in this series underwent endoscopic ultrasound as part of their staging. Only 2 of 7 patients with tumor extension into or beyond the muscularis propria achieved a CR, suggesting these patients may be less likely to respond to eradication therapy as the sole treatment modality. All 10 of the complete responders remained disease free at the time of publication with median follow-up of 43.5 months (21–67 months). These two studies strongly suggest that patients with localized transformed gastric MALT lymphoma should receive *H. pylori* eradication therapy and that chemotherapy or radiation should be withheld from the initial treatment whenever feasible. Close monitoring is essential so that cytotoxic therapy can be rapidly instituted in those failing to respond to eradication therapy.

There are a variety of therapeutic options for patients who do not respond to *H. pylori* eradication therapy. The approach must be individualized and will depend upon patient age and comorbidities, disease stage, and symptoms. It is clear that overall survival is usually excellent irrespective of the treatment chosen, although disease-free survival will vary. Given the long survival times, attention must be given to side effects of therapy and quality of life (QOL) issues. For patients with localized disease, opinions differ whether surgery, radiation, or chemotherapy is the least morbid, and there is considerable bias in the literature. No studies, either prospective or retrospective, have addressed these issues adequately. Surgical resection is an option and was historically the mainstay of therapy. More recent literature has demonstrated excellent outcomes with radiation therapy [25–28]. The group from Memorial Sloan Kettering published results in 17 patients who had persistent lymphoma after *H. pylori* therapy or who were *H. pylori*-negative [29]. The median radiation dose was 30 Gy. All patients achieved complete remission and the event-free survival (EFS) was 100% with a median follow-up of 27 months. A large prospective, nonrandomized study comparing surgery to a stomach-preserving approach has been reported by the German Multicenter Study Group [30••]. Decisions about treatment were left to individual institutions, as the study investigators feared patients or physicians would not accept a randomized study. Only patients with stage IE and IIE primary gastric lymphoma were eligible. Eligible histologies included gastric MALT without high-grade components, gastric MALT with high-grade components, and high- grade lymphoma without evidence of underlying MALT. A total of 277 patients enrolled. The surgically based approach did not appear to confer any EFS or overall survival (OS) advantage for the study population as a whole, nor in any subgroup analysis. Given the presumed improvement in QOL with stomach preservation, the authors concluded that the more conservative approach should be considered for patients with primary gastric lymphoma. Patients with advanced stage disease should be treated like other indolent lymphomas. Options therefore included watchful waiting, single agent chemotherapy, combina-

tion chemotherapy, and antibody-based approaches. Rituximab appears to have single agent activity comparable to that seen in follicular lymphoma [31•]. Radioimmuno therapy may also play a therapeutic role in the future but should only be tested in the settings of clinical trials, which include dosimetry designed for extranodal lymphomas [32].

Conclusions

Significant knowledge has been gained in the past few years regarding gastric MALT lymphoma biology and treatment. There are diagnostic and therapeutic implications for cases that are t(11;18) positive. Patients with this finding are more likely to present with advanced stage disease, are less likely to respond to *H. pylori* eradication therapy, are more likely to be found in *H. pylori*-negative cases and appear less likely to transform to aggressive lymphomas. The discovery that these cases result in activation of the NF-kB pathway suggests another target for novel therapeutics such as proteosome inhibition. Regarding treatment, *H. pylori* eradication is a worthy goal in all cases and will be the only required therapy in a majority. Reports indicating durable remission even in transformed cases suggest that many more patients than initially thought may be spared cytotoxic therapy. Finally, the weight of evidence suggests that surgical resection is not necessary in those cases unresponsive to *H. pylori* eradication, and stomach-preserving approaches should become the standard of care.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • Of special interest
- •• Of outstanding interest

1 Isaacson P, Wright DH: Malignant lymphoma of mucosa-associated lymphoid tissue. A distinctive type of B-cell lymphoma. Cancer 1983, 52:1410–1416.

2 Harris NL, Jaffe ES, Diebold J, et al.: World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol 1999, 17:3835–3849.

3 A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma: The Non-Hodgkin's Lymphoma Classification Project. Blood 1997, 89:3909–3918.

4 Hussell T, Isaacson PG, Crabtree JE, et al.: The response of cells from low-grade B-cell gastric lymphomas of mucosa-associated lymphoid tissue to Helicobacter pylori. Lancet 1993, 342:571–574.

5 Hussell T, Isaacson PG, Crabtree JE, et al.: Helicobacter pylori-specific tumour-infiltrating T cells provide contact dependent help for the growth of malignant B cells in low-grade gastric lymphoma of mucosa-associated lymphoid tissue. J Pathol 1996, 178:122–127.

6 Dierlamm J, Baens M, Wlodarska I, et al.: The apoptosis inhibitor gene API2 and a novel 18q gene, MLT, are recurrently rearranged in the t(11;18)(q21;q21)p6ssociated with mucosa-associated lymphoid tissue lymphomas. Blood 1999, 93:3601–3609.

7 Alpen B, Neubauer A, Dierlamm J, et al.: Translocation t(11;18) absent in early gastric marginal zone B-cell lymphoma of MALT type responding to eradication of Helicobacter pylori infection. Blood 2000, 95:4014–4015.

8 Liu H, Ruskon-Fourmestraux A, Lavergne-Slove A, et al.: Resistance of t(11;18) positive gastric mucosa-associated lymphoid tissue lymphoma to Helicobacter pylori eradication therapy. Lancet 2001, 357:39–40.

9 •• Liu H, Ye H, Ruskone-Fourmestraux A, et al.: T(11;18) is a marker for all stage gastric MALT lymphomas that will not respond to H. pylori eradication. Gastroenterology 2002, 122:1286–1294.
This is a large retrospective series of 111 H. pylori-positive gastric MALT lymphoma patients who were treated with H. pylori eradication therapy. The study is sufficiently large to warrant examination of factors that may predict success or failure. It clearly shows that t(11;18) patients are unlikely to respond to eradication therapy.

10 Ye H, Liu H, Raderer M, et al.: High incidence of t(11;18)(q21;q21) in Helicobacter pylori-negative gastric MALT lymphoma. Blood 2003, 101:2547–2550.

11 • Liu H, Ye H, Dogan A, et al.: T(11;18)(q21;q21) is associated with advanced mucosa-associated lymphoid tissue lymphoma that expresses nuclear BCL10. Blood 2001, 98:1182–1187.
This is the first study to show t(11;18) is highly associated with nuclear BCL10 expression and this combination is associated with advanced MALT lymphoma cases.

12 • Maes B, Demunter A, Peeters B, et al.: BCL10 mutation does not represent an important pathogenic mechanism in gastric MALT-type lymphoma, and the presence of the API2-MLT fusion is associated with aberrant nuclear BCL10 expression. Blood 2002, 99:1398–1404.
Using a combination of RT-PCR and immunohistochemistry, this study confirmed that the API2-MLT fusion protein is associated with aberrant expression of nuclear BCL10.

13 •• Lucas PC, Yonezumi M, Inohara N, et al.: Bcl10 and MALT1, independent targets of chromosomal translocation in malt lymphoma, cooperate in a novel NF-kappa B signaling pathway. J Biol Chem 2001, 276:19012–19019.
This group was able to show that BCL10 and MLT form a strong complex within the cell and that these proteins synergize in the activation of NK-κB. Additionally, the API2-MLT fusion protein also strongly activates NF-κB and shows dependence upon the same downstream signaling factors.

14 •• Starostik P, Patzner J, Greiner A, et al.: Gastric marginal zone B-cell lymphomas of MALT type develop along 2 distinct pathogenetic pathways. Blood 2002, 99:3–9.
This plenary paper utilized microsatellite screening to show that t(11;18) positive cases of gastric MALT lymphoma are less to acquire secondary chromosomal abnormalities than t(11;18) negative cases, and this latter population is the group more prone to large-cell transformation.

15 • Nomura K, Sekoguchi S, Ueda K, et al.: Differentiation of follicular from mucosa-associated lymphoid tissue lymphoma by detection of t(14;18) on single-cell preparations and paraffin-embedded sections. Genes Chromosomes Cancer 2002, 33:213–216.
This case report details methods for performing FISH in single cell preparations and in paraffin-embedded tissue, permitting distinction between follicular center cell lymphoma and MALT lymphoma.

16 Thieblemont C, Berger F, Dumontet C, et al.: Mucosa-associated lymphoid tissue lymphoma is a disseminated disease in one third of 158 patients analyzed. Blood 2000, 95:802–806.

17 Rohatiner A, d'Amore F, Coiffier B, et al.: Report on a workshop convened to discuss the pathological and staging classifications of gastrointestinal tract lymphoma. Ann Oncol 1994, 5:397–400.

18 Wotherspoon AC, Doglioni C, Diss TC, et al.: Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of Helicobacter pylori. Lancet 1993, 342:575–577.

19 Roggero E, Zucca E, Pinotti G, et al.: Eradication of Helicobacter pylori infection in primary low-grade gastric lymphoma of mucosa-associated lymphoid tissue. Ann Intern Med 1995, 122:767–769.

20 Steinbach G, Ford R, Glober G, et al.: Antibiotic treatment of gastric lymphoma of mucosa-associated lymphoid tissue. An uncontrolled trial. Ann Intern Med 1999, 131:88–95.

21 NCCN preliminary non-Hodgkin's lymphoma practice guidelines. Oncology (Huntingt) 1997, 11:281–246.

22 Pinotti G, Zucca E, Roggero E, et al.: Clinical features, treatment and outcome in a series of 93 patients with low-grade gastric MALT lymphoma. Leuk Lymphoma 1997, 26:527–537.

23 • Morgner A, Miehlke S, Fischbach W, et al.: Complete remission of primary high-grade B-cell gastric lymphoma after cure of Helicobacter pylori infection. J Clin Oncol 2001, 19:2041–2048.
This is a retrospective case series detailing successful treatment in six of eight patients with transformed gastric MALT lymphoma using H. pylori eradication therapy.

24 •• Chen LT, Lin JT, Shyu RY, et al.: Prospective study of Helicobacter pylori eradication therapy in stage I(E) high-grade mucosa-associated lymphoid tissue lymphoma of the stomach. J Clin Oncol 2001, 19:4245–4251.
This is a prospective study suggests that H. pylori eradication therapy can be attempted prior to cytotoxic therapy in transformed gastric MALT lymphoma. Utilizing this strategy, cytotoxic therapy was able to be avoided in a majority of the cohort.

25 Willich NA, Reinartz G, Horst EJ, et al.: Operative and conservative management of primary gastric lymphoma: interim results of a German multicenter study. Int J Radiat Oncol Biol Phys 2000, 46:895–901.

26 Willich NA, Reinartz G, Reers B, et al.: Radiotherapy in early stage gastrointestinal lymphoma: results of the German GIT-NHL group. Ann Hematol 2001, 80(Suppl 3):B97–B99.

27 Schechter NR, Yahalom J: Low-grade MALT lymphoma of the stomach: a review of treatment options. Int J Radiat Oncol Biol Phys 2000, 46:1093–1103.

28 Yahalom J: MALT lymphomas: a radiation oncology viewpoint. Ann Hematol 2001, 80(Suppl 3):B100–B105.

29 Schechter NR, Portlock CS, Yahalom J: Treatment of mucosa-associated lymphoid tissue lymphoma of the stomach with radiation alone. J Clin Oncol 1998, 16:1916–1921.

30 •• Koch P, del Valle F, Berdel WE, et al.: Primary gastrointestinal non-Hodgkin's lymphoma: II. Combined surgical and conservative or conservative management only in localized gastric lymphoma–results of the prospective German Multicenter Study GIT NHL 01/92. J Clin Oncol 2001, 19:3874–3883.
This large prospective German study compared results between surgical- and non-surgical- based treatments for primary gastric lymphoma. The group is to be commended for executing a logistically difficult study.

31 • Conconi A TC, Martinelli G, Ferreri AJM, et al.: IELSG phase II study of rituximab in MALT lymphoma: final results. Proc of ASCO 2002, 21:267a.
This ASCO abstract gives results from a multicenter European trial testing rituximab in either untreated or relapsed MALT lymphoma. A total of 35 patients were treated with four weekly doses, yielding an overall response rate of 71%.

32 Witzig TE GL, Emmanouilides C, Wiseman GA, et al.: Safety and efficacy of Zevalin in four patients with mucosa associated lymphoid tissue (MALT) lymphoma. Blood 2001, 98:254b.