EGILS consensus report. Gastric extranodal marginal zone B-cell lymphoma of MALT

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ABSTRACT
This consensus report of the EGILS (European Gastro-Intestinal Lymphoma Study) group includes recommendations on the management of gastric extranodal marginal zone B-cell lymphoma of MALT. They are based on data from the literature and on intensive discussions and votings of the experts during their annual meetings.

The EGILS (European Gastro-Intestinal Lymphoma Study) group is a group of clinicians and scientists with a special expertise in the field of gastrointestinal lymphomas. This report summarises consensual clinical evidence gathered by these experts during the collegial multidisciplinary discussions at EGILS’ group annual meetings in Paris 2007, Barcelona 2008 and London 2009. The panel consisted of gastroenterologists, medical and clinical haematologists, pathologists, molecular biologists and microbiologists.

The two persons responsible for the organisation and implementation (AR-F and WF) defined seven topic complexes: histopathology, molecular biology, diagnosis and staging, Helicobacter pylori (H pylori), radiotherapy, chemotherapy and follow-up. Every working group was headed by one or two experts (authors). A literature search was performed within the single groups using a non-systematic approach. Statements were prepared by the heads of the groups and discussed during the above-mentioned meetings. Voting took place and an agreement of >75% of the participants was accepted as consensus. Editorial revision of the task force manuscripts was done by the two first authors. The final draft of the manuscript was reviewed and approved by all participants.

Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is a rare disease. As a consequence of this, there are no prospective randomised trials available. Data included original publications and reviews. Abstracts were not considered. The recommendations outlined below do generally not fulfil the criteria for high evidence levels as the application of the GRADE (Grading of Recommendations Assessment, Development and Evaluation. Jaeschke R, BMJ 2008,337:a744) criteria was not possible. Therefore, this paper is a consensus report rather than a guideline.

DIAGNOSIS
Histopathology
Definition
Gastric extranodal marginal zone B-cell lymphoma of MALT is a B-cell non-Hodgkin lymphoma that arises in the stomach and has a perifollicular/marginal zone growth pattern. The lymphoma is derived from marginal zone B-cells and recapitulates the architecture and organisation of native MALT exemplified by the Peyers’ patches in the terminal ileum.1–3

Synonym
Gastric MALT lymphoma (this abbreviation will be used in the subsequent text).

Recommendation
The diagnosis of gastric MALT lymphoma is based on histomorphological criteria according to the WHO classification. A reference pathologist should confirm the diagnosis.

Comment
In the earliest stage, the neoplastic cells (sometimes known as centrocyte-like cells) adopt a perifollicular distribution, but with time the infiltrate extends into the lamina propria away from the follicles and this may be a helpful diagnostic feature. The neoplastic cells infiltrate into gastric gland epithelium causing eosinophilic change to the epithelial cells and destruction of the architecture (lymphoepithelial lesion).4–6

Lymphoid follicles are an ubiquitous finding in MALT lymphoma. The neoplastic cells infiltrate and may over-run these follicles. Sometimes specific colonisation of the germinal centres may occur.

The neoplastic cells have variable morphology including mature round lymphocyte cells resembling germinal centre centrocytes with irregular nuclei, cells with monocytoid/marginal zone B-cell appearance and cells with lymphoplasmacytic appearances. Plasma cell differentiation is a frequent finding, and in some cases may be very prominent. All cases have a variable number of large transformed cells, but these are usually...
distributed within the small cell infiltrate. When large neoplastic cells are present in sheets, the diagnosis of an associated diffuse large B-cell lymphoma (DLBCL) should be made.

Features that help to distinguish MALT lymphoma from reactive infiltrates include the presence of a dense infiltrate of monotonous B-cells (identified by staining for CD20 or another B-cell marker) extending away from lymphoid follicles with a poorly demarcated border, the presence of cytological atypia and the finding of Dutcher bodies. Lymphoepithelial lesions are characteristic of lymphoma and are not commonly seen in reactive infiltrates. Staining for CD45 may be helpful in determining the neoplastic nature of the infiltrate as normal B-cells are negative and the antigen is frequently expressed in MALT lymphoma, but is also present on cells of B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma and mantle cell lymphoma.

Immunohistochemistry is used to distinguish MALT lymphoma from other non-Hodgkin lymphomas. Staining for CD20 or another pan B-cell antigen confirms the B-cell nature of the infiltrate. Although a few gastric MALT lymphomas stain for CD5, positive staining is more characteristic for B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma, which also express CD25, and mantle cell lymphoma which co-express cyclin D1. A stain for cytookeratin may help to identify lymphoepithelial lesions and a stain for follicular dendritic cells (eg, anti-CD21) will identify indistinct lymphoid follicles.

Where large cells are present, immunohistochemistry to distinguish neoplastic cells from residual germinal centre centroblasts should be used (antibodies to CD10 and bcl-6). Staining for bcl-2 protein is helpful as reactive germinal centre centroblasts should be used (antibodies to CD10 and bcl-6).

Identification of light chain expression by immunohistochemistry or in situ hybridisation may help confirm the diagnosis of lymphoma but is frequently difficult to assess in small mucosal biopsies.

The presence of *Helicobacter pylori* should be assessed using an appropriate stain (see *Helicobacter pylori* section). A confident diagnosis of gastric MALT lymphoma can be expressed using the Wotherspoon score.7

### Molecular investigations

#### Recommendations

- Demonstration of monoclonality by PCR analysis of the rearranged immunoglobulin genes using the BIOMED-2 protocols is not a prerequisite for the diagnosis of gastric MALT lymphoma.
- Testing for translocation t(11;18) should be considered at diagnosis. During post-treatment follow-up routine clonality analysis is not recommended.

#### Comment

For diagnostic biopsies, clonality analysis of the rearranged immunoglobulin genes by PCR may help in a diagnosis of MALT lymphoma when histological and immunophenotypic features induce suspicious but not diagnostic.8 For follow-up biopsies after treatment, the tumour clone may be detectable by PCR in ~50% of cases in the absence of any macroscopic and histological evidence of lymphoma.9–14 Although the monoclonality disappears with time in some cases, it is persistently present in a high proportion (~40%) of cases, and the basal lymphoid aggregates are the source of the clonal B-cells.9 11–14 Independent studies of large cohorts with long follow-up show that cases with persistent monoclonality were associated with only a slightly higher risk of lymphoma relapse than those without persistent monoclonality.11–16 Thus, beyond clinical trials or a research setting, the current evidence does not support a significant role for clonality analysis in routine post-treatment follow-up of gastric MALT lymphoma. For clonality analysis, use of the standardised BIOMED-2 PCR protocols and a modified strategy as proposed by Liu et al are highly recommended.17 18

Translocation t(11;18)(q21;q21) fuses the N-terminus of the API2 gene to the C-terminus of the MALT1 gene and generates a functional API2–MALT1 fusion product19 20, which develops the ability to activate the nuclear factor-κB (NF-κB) pathway.21 The translocation is specifically associated with the MALT lymphoma entity, but occurs at remarkably variable incidences in different anatomical sites.22 In gastric MALT lymphoma, t(11;18)(q21;q21) is found in 25% of cases, more frequent in cases at stage IIIE or above than those at stage IE.23 24 Independent retrospective studies from several centres demonstrate that t(11;18)(q21;q21) is seen in 47% and 68% of gastric MALT lymphomas at stage IE and stage IIIE or above, respectively, which do not respond to *H pylori* eradication.12 13 20–22 In contrast, the translocation is only observed in 5% of gastric MALT lymphomas that respond to *H pylori* eradication, and these translocation-positive cases often show a late response and/or lymphoma relapse during follow-up.25 Thus, t(11;18)(q21;q21) is a strong predictor of the response of gastric MALT lymphoma to *H pylori* eradication. In addition, t(11;18)(q21;q21) was significantly associated with treatment failure of single oral alkylating agents (chlorambucil or cyclophosphamide),26 but did not predict the response to treatment with the nucleotide analogue cladribine (2CdA)27 or the anti-CD20 antibody rituximab.28 Despite its strong association with adverse clinical features, t(11;18)(q21;q21) is only rarely seen in transformed MALT lymphoma or DLBCL in patients from Western countries,29 30 suggesting that the translocation-positive MALT lymphomas rarely undergo high-grade transformation. For the reasons discussed above, testing for t(11;18)(q21;q21) at diagnosis would be valuable in guiding treatment choice. Nevertheless, *H pylori* eradication will be initiated as the first step of treatment in *H pylori*-positive cases irrespective of the t(11;18)(q21;q21) status. There is, however, no clear evidence to suggest that monitoring t(11;18)(q21;q21) during follow-up is useful in guiding clinical management.

Translocation t(11;18)(q21;q21) can be detected fairly simply by interphase fluorescence in situ hybridisation (FISH) with a commercial MALT1 dual-colour break-apart probe and a API2-MALT1 dual-colour dual-fusion probe, or reverse transcription–PCR (RT–PCR) of the API2–MALT1 fusion mRNA transcripts. Both methods can be applied to routine formalin-fixed paraffin-embedded tissue biopsies and showed highly concordant results when appropriately performed. Interphase FISH requires small amounts of tissue (only 1–2 tissue sections), allows easy correlation with histological features and has no or a minimal risk of a false-positive result, while the RT–PCR-based detection method is highly sensitive, but requires larger amounts of tissue (≥5 tissue sections depending on the size of the tissue biopsy) than FISH and does not permit accurate morphological correlation. Currently, there are no immunophenotypic markers
that are sensitive and specific enough to be used as a reliable surrogate marker for t(11;18)(q21;q21) and gastric MALT lymphomas that do not respond to H pylori eradication. The above molecular and genetic methods should be used for the translocation detection. Translocations t(1;14)(p22;q32)/BCL10-IGH, t(14;18)(q21;q21)/IGH-MALT1 and t(8;14)(p14;q32)/FOXP1-IGH are only rarely found in gastric MALT lymphomas, and the clinical significance of these translocations remains to be investigated. Chromosomal trisomies 3, 12 and 18 are frequently seen in t (11;18)(q21;q21)-negative MALT lymphomas. Currently, there is no clear evidence to suggest that detection of these chromosomal numerical changes is valuable in guiding clinical management.

**Clinical diagnosis and staging**

**Endoscopic diagnosis**

**Recommendation**

- A gastric mapping procedure with a sufficient number of biopsies from macroscopic lesions and normal mucosa should be performed in the case of suspected or diagnosed gastric MALT lymphoma to allow an accurate diagnosis and typing of the lymphoma.

**Comment**

A minimum of 10 biopsy samples should be taken from visible lesions. In addition, biopsies should also be taken from macroscopically normal mucosa. In cases where gastric MALT lymphoma is suspected but insufficient or inadequate initial biopsy materials have been received, a second endoscopy could be necessary. H pylori eradication therapy should not be started until the results of the reference pathologist are available.

A gastric mapping procedure should also be performed to assess subsequent treatment response (regarding lymphoma regression) to H pylori eradication, radiation or chemotherapy.

**Staging**

**Recommendation**

- Staging classification should be based on the Ann Arbor staging system with its modifications by Musshoff and Radaszkiewicz. In addition, staging can be done according to the Paris staging system (TNMB).

**Comment**

Over time, the staging of extranodal lymphomas based on the Ann Arbor classification has been modified many times to make its application to lymphomas of the gastrointestinal tract possible. Musshoff introduced the first modification in 1977 that differentiated stage IIE lymphomas with involvement of neighbouring lymph nodes (IIE) and distant lymph nodes (IIE). In 1992, differentiation of stage IE was introduced: mucosa and submucosa (IIE) versus muscularis propria to serosa (IIE) involvement. The Blackledge staging system known as the ‘Lugano staging system’ proposed in 1994 was mainly based on radiological findings. Many systems have been proposed before introduction of endoscopic ultrasound in clinical routine. These systems do not describe the depth of infiltration of the gastric wall that is highly predictive for the MALT lymphoma response to anti-Helicobacter treatment. For the specific diagnostic requirements of gastrointestinal lymphomas, a modification of the existing TNM system was implemented by the EGILS group (table 1). This Paris staging system (TNMB) adequately describes the three most important characteristics of gastrointestinal lymphomas: (1) depth of lymphoma infiltration, (2) lymph node infiltration and (3) lymphoma spread. However, this system has not been validated by prospective studies yet.

**Recommendations**

- If a diagnosis of gastric MALT lymphoma is established, a staging procedure to assess the dissemination of the lymphoma (clinical stage) is mandatory.

- Initial staging examinations must include: physical examination (including peripheral lymph nodes and Waldeyer’s ring), routine laboratory parameters (complete blood count, lactate dehydrogenase (LDH) and β-2-microglobulin levels, serum protein immunofixation, HIV, hepatitis C virus (HCV) and hepatitis B virus (HBV) serology) and abdominal, pelvic and thoracic CT scan.

- Endoscopic ultrasound should be performed in initial staging. Bone marrow biopsy should be done in the case of failure of lymphoma regression after H pylori eradication and before initiating oncological treatment. Ileocolonoscopy should be considered.

**Comment**

As the stage of disease is one of the two most important prognostic factors and therapeutically determinant, an adequate staging procedure has to be performed in every case. Ultrasound of the abdomen and lymph nodes seems unnecessary with the use of corresponding CT scans. Endoscopic ultrasound (EUS) is the only technique that visualises the different layers of the gastric wall and perigastric lymph node involvement. Therefore, it has the potential to differentiate stages IIE, IIE and IIE and T1–4, N0/1, respectively (table 1). This differentiation is of clear prognostic value.

<table>
<thead>
<tr>
<th>Table 1 Staging systems for gastrointestinal lymphomas</th>
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<tr>
<td>Ann Arbor system, modified*</td>
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<tr>
<td>IIE</td>
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*Modified by Musshoff and Radaszkiewicz et al.
†Ruskone-Fourmestraux et al. 2009.
A bone marrow biopsy is recommended when no lymphoma regression is seen after an adequate interval, following H pylori eradication. Before initiating locoregional treatment (ie, radiation), disseminated disease needing systemic chemotherapy has to be excluded.59

In patients with gastric MALT lymphoma, multifocal involvement of the gastrointestinal tract may occur occasionally.50 59–61 There are very few systematic data on the involvement of the small intestine and colon.62 Therefore, a general recommendation on small intestine diagnostics and ileocolonoscopy cannot be given, although we tend to favour the latter.

HELCOBACTER PYLORI

Recommendation

► H pylori infection causes most cases of gastric MALT lymphoma. Therefore, diagnosis and treatment of H pylori infection is the first step in the management of gastric MALT lymphoma independent of the stage of disease.

Comment

There is now overwhelming evidence that H pylori infection causes gastric MALT lymphoma, and a systematic review of published series has shown H pylori infection in 88.8% of 2000 patients with gastric MALT lymphoma.63 Hill’s criteria of causality have been fulfilled, including the healing of the lesions after H pylori eradication, even if double-blind randomised clinical trials have not been carried out for ethical reasons.8

A minority of gastric MALT lymphomas are caused by a different Helicobacter species named ‘H heilmannii’. This is not a validated species and corresponds to a group of different microorganisms which are very fastidious to grow and, consequently, difficult to differentiate: H felis, H bizzozeroni, H salomonis, H suis and H bovis.64 65 A small minority of gastric MALT lymphomas appears to be unrelated to any of these microorganisms and are probably due to as yet unidentified causes.

There is evidence that H pylori eradication cures gastric MALT lymphoma only in stage IE and, to a much lesser percentage, in stage IIIE. Nevertheless it is preferable to eradicate H pylori in all cases as it is a trigger of the immune response.

In gastric MALT lymphoma diagnosis, these limitations do not exist. In order to obtain an accurate diagnosis of lymphoma, a large number of biopsies are examined and, in many cases, the slides are reviewed by a group of expert pathologists who devote time to reach a consensus. It was shown that the sensitivity of histology for H pylori diagnosis increased with the number of biopsies, up to 95% with five biopsies.68 Histology is at its optimum in this context.

For histological assessment of H pylori, biopsies from the gastric antrum and body have to be taken from an area away from mucosal lesions. Proton pump inhibitor (PPI) treatment has to be withdrawn at least 2 weeks before endoscopy because it may give a false-negative result with all the H pylori diagnostic tests except serology.59 70 Besides H pylori, histological examination also allows the detection of H heilmannii.

These organisms are usually detectable on H&E-stained sections. Special stains such as Giemsa, immunohistochemistry or FISH increase the sensitivity of H pylori detection. These are advised, particularly in the case of a scanty bacterial load or an apparent absence of infection on routinely stained slides.71

In the case of positive histology, culture is recommended as the second diagnostic test, if another endoscopy is needed for diagnosis or gastric mapping. In gastric MALT lymphoma, culture has a lower sensitivity than histology even if performed under good conditions,72 but gives information on the antimicrobial susceptibility especially for the key antibiotic—clarithromycin.

In the case of negative histology, serology is recommended.72 73 Consumption of PPIs or antibiotics can suppress the infection but does not lead to eradication,69 70 74 75 and serology will be the only diagnostic test to be positive in such cases. After H pylori eradication, the antibodies remain present for weeks and often months. Serology, therefore, also allows detection of a recently cured infection.

Recommendation

► PPI+clarithromycin-based triple therapy with either amoxicillin or metronidazole is the first choice for H pylori eradication. In case of failure, bismuth-based quadruple therapy is recommended.

Comment

Most of the consensus conferences held around the world in recent years have recommended the use of a PPI+clarithromycin-based triple therapy composed of a double dose of a PPI plus two antibiotics: clarithromycin and amoxicillin or metronidazole.76

However, because of an increasing clarithromycin resistance, an important drop in efficacy has been observed leading to the recommendation either to avoid this drug or to test its susceptibility before using it in the areas where the incidence of clarithromycin resistance is >15%.76 77

The length of treatment is debatable. However, the data from meta-analyses show better results if the treatment is given for 14 days compared with 7 days, while the difference is not significant between 7 and 10 days.76 A recent pooled data analysis of 1271 patients with gastric MALT lymphoma from 34 studies has shown a successful eradication rate of 91% after first-line treatment which was extended to 98% after more attempts.78

A meta-analysis of bismuth-based quadruple therapy containing a PPI, bismuth, tetracycline and metronidazole
shows that the best results are obtained when the four drugs are given for 10–14 days. Even in areas with a high prevalence of metronidazole resistance, the quadruple regimen eradicated >85% of *H pylori* strains. Other treatments comprising PPI–tetracycline–metronidazole or PPI–amoxicillin–rifabutin have been proposed, but the latter has toxic effects and should be considered as the last option. It should be mentioned, however, that in some countries bismuth compounds are currently not available.

**Recommendation**

- The outcome of *H pylori* eradication therapy should be checked by urea breath test at least 6 weeks after eradication therapy and at least 2 weeks after withdrawal of PPI medication.

**Comment**

To assess the effective *H pylori* eradication the method universally accepted is the urea breath test. To assess MALT lymphoma remission, a first endoscopy is performed 3–6 months after completion of antibacterial treatment, thus allowing for checking of the *H pylori* status histologically at the same time. Culture and susceptibility testing are particularly recommended to guide further treatment in the case of a resistant strain indicated by a persistent positive breath test.

**Recommendation**

- *H pylori*-negative patients with gastric MALT lymphoma can also undergo anti-*H pylori* treatment.

**Comment**

Prescription of an eradication treatment has also been advised in cases of *H pylori*-negative gastric MALT lymphoma. The arguments to support this are that *H pylori* may have been missed by the diagnostic tests, or that another *Helicobacter, H heilmannii*, may be the cause. Some *H pylori*-negative gastric MALT lymphomas have been reported to respond with complete lymphoma remission after exclusive anti-*H pylori* treatment, but these were only anecdotal cases. A recent review of the published cases shows that out of 72 patients, 14 (19%) responded to the treatment.

**TREATMENT**

**Recommendation**

- The first-line treatment of all gastric MALT lymphomas is *H. pylori* eradication therapy independent of the stage. Nevertheless, the staging procedure has to be performed before starting eradication therapy. Patients who respond to eradication therapy (lymphoma regression) should not receive any other treatment.

**Comment**

In patients with localised disease *H pylori* eradication leads to complete lymphoma remission in some 60–90% of cases. In a recent systematic review of the literature analysing data from 52 studies including 1408 patients, the gastric MALT lymphoma remission rate was 77.5%. It was significantly higher in patients with stage IE than stage IIIE lymphoma (78.4% vs 55.6%). Neoplasia confined to the mucosa regressed more frequently (82.2% of cases) than those with a deeper invasion of the gastric wall (54%). This complete remission is maintained for years in most cases, and offers a chance of cure. Relapses have been described in 10% of patients (7.2% in the review of Zullo et al) and may be occasionally associated with *H pylori* recrudescence/reinfection. Should the presence of *H pylori* be found again with or without relapsing lymphoma, further eradication therapy is indicated.

Some patients show histologically identified residual circum-scribed lymphoid aggregates after successful *H pylori* eradication and normalisation of the endoscopic findings. The histological changes regress during the second year of follow-up in 32% of cases and remain stable in another 62%. They do not need additional treatment and can be managed by a ‘watch and wait’ strategy unless progression or recurrence of endoscopic lesions can be demonstrated.

In patients responding to *H pylori* eradication (either complete or partial remission), treatment with chlorambucil did not result in a superior disease control when compared with a ‘watch and wait’ strategy in a recently reported randomised trial.

There are specific situations in which treatment with antibiotics will probably not result in a good response of the lymphoma. *H pylori*-negative lymphomas and *t(11;18)*-positive lymphomas and those with lymph node involvement will hardly respond to antibiotics. Patients with gastric MALT lymphoma refractory to *H pylori* eradication and persistent endoscopic lesions as well as those with disseminated or bulky disease will require further local or systemic treatment.

**Recommendation**

- Surgery nowadays is restricted to the treatment of rare complications such as perforation or bleeding that cannot be controlled endoscopically.

**Comment**

In the ‘pre-*Helicobacter pylori* era’, surgery has been the main therapeutic intervention. It has provided very good results for localised disease, with long-term survival for between 75% and 97% of patients. Despite these excellent data, the major limitation of total gastrectomy to control this multifocal disease is that it has life-long nutritional and metabolic consequences. In recent years a few prospective studies reported no disadvantage with the organ-preserving treatment. For these reasons, surgery nowadays is restricted to the treatment of rare complications such as perforation or bleeding that cannot be controlled endoscopically.

**Recommendation**

- Both radiotherapy and chemotherapy have a curative potential in localised gastric MALT lymphoma. There is no recommendation in favour of one of these two modalities. If clinical trials are available, patients should be included.
Comment
The curative potential of radiation and chemotherapy as well as of diverse combined treatment modalities in gastric MALT lymphoma was shown in retrospective studies. There is no doubt that disseminated disease needs systemic chemotherapy. A pooled data analysis assessing the efficacy of different oncological therapeutic approaches to treat limited disease gastric MALT lymphoma unresponsive to *H pylori* eradication showed a slightly higher remission rate following radiotherapy as compared with chemotherapy (97.3% vs 85.5%; *p*<0.007), being similar to surgery (97.3% vs 92.5%; *p*=0.2). However, in the case of localised disease, there is only one study which compared surgery, radiotherapy and chemotherapy, CHOP/COP, suggesting a higher event-free survival with chemotherapy but no significant difference in overall survival after a median follow-up of 7.5 years (table 2). No data are available directly comparing radiation and chemotherapy. With respect to the high response rate of gastric MALT lymphoma to *H pylori* eradication and its indolent course, it is difficult to conduct such studies. Nevertheless, a study on radiation versus chemotherapy following failure of *H pylori* eradication would offer important information for treating such patients.

Radiotherapy

**Recommendation**

- Radiation is effective for patients with localised gastric MALT lymphoma of stage IE–IIIE (T1–4, N0/1M0B0) that failed to respond to *H pylori* eradication.

Comment
Concepts concerning radiotherapy in gastric MALT lymphoma have changed significantly over time. Knowledge concerning the pattern of spread of gastric MALT lymphoma has increased through surgical series and the use of modern radiological examinations. Low-grade MALT lymphoma tends to be confined to the gastric wall. In contrast to MALT lymphomas of other origin, distant relapses of gastric MALT lymphoma rarely occur (0–5%). Lymph node involvement may be observed, but in the vast majority only restricted to the perigastric nodes (stage IIIE or T1–4, N+). Therefore, the target volume for radiotherapy should be limited to the stomach and the perigastric nodes. In parallel, radiation doses have been reduced over decades.

MALT lymphomas have been reported to be highly sensitive to radiation, and treatment is potentially curative in localised stage IE and IIIE (5-year event-free survival rates ~80–90%). These studies used relatively high doses of 36 Gy up to 45 Gy (mostly 40 Gy) or a multimodality treatment approach. However, in several small series using lower radiation doses of ≤30 Gy, response rates between 95% and 100% and overall survival rates between 96% and 100% based on a median follow-up of 3.3–7.2 years were reported.

If radiotherapy is indicated for limited stage low-grade gastric MALT lymphoma, radiation doses of 30–40 Gy in 15–20 fractions are actually proposed. Currently, studies are being performed evaluating the possibility of lowering the radiation dose to ~30 Gy. It is recommended to treat patients with such protocols. Using 3D conformal radiotherapy and intensity-modulated radiation therapy (IMRT) enables the kidney dose to be decreased compared with parallel opposed beams. In addition, stomach distension can be minimised by treating the patient in a fasting state. As always the dose to normal tissues should be kept as low as reasonably achievable; the dose to the kidneys should be limited to <20 Gy (for at least two-thirds of one kidney) and to <30 Gy mean liver dose.

The side effects of irradiation strongly depend on the radiation field and dose. Acute side effects of radiation to the stomach consist mainly of transient anorexia, nausea and vomiting. These complaints can usually be adequately treated with anti-emetics and a PPI. Late effects of radiotherapy to the stomach and perigastric nodes of 30–40 Gy in 15–20 fractions using modern radiation techniques are expected to be minimal.

Hence radiotherapy is effective and safe.

Chemotherapy and immunotherapy

**Comment**
Different types of chemotherapy and immunotherapy are effective in the treatment of gastric (and non-gastric) MALT lymphoma with both limited and advanced stages of disease. However, the available data come from only a few phase II studies with a limited number of patients and relatively short duration of follow-up (table 2). Therefore, they cannot provide consistent evidence, and no standard chemotherapy has been defined so far.

Alkylation agents as a sole treatment are well tolerated and effective, with 75% of patients showing a complete remission and 28% showing relapsing disease, but they seem to lack activity in t(11;18)(q21;q21)-positive lymphomas. In t(11;18)-positive patients, chlorambucil might be used, while 2CdA exerts activity irrespective of t(11;18) status and is the drug with the best documented long-term activity in gastric MALT lymphoma, albeit in a small number of patients. However, there is concern regarding the risk of developing myelodysplasia. Outside of clinical trials, cyclophosphamide, vincristine and prednisolone might also be used. Other drugs such as oxaliplatin, bortezomib or various combinations including mitoxantrone, chlorambucil and dexamethasone have suggested activity, but the number of patients tested so far is simply too small to justify the use outside of clinical trials.

The use of rituximab has not been clearly defined in MALT lymphoma, but despite its potential palliative activity the rate of complete remissions is relatively low (29–46%). Combination with CHOP is relatively toxic, and should be discouraged in this indolent disease. Combination with fludarabine or 2CdA has been tested, but has not been shown to be more effective than the nucleosides alone. Rituximab and chlorambucil produced 100% responses in 13 patients with t(11;18)-positive gastric lymphomas. The combination of rituximab and flexible doses of fludarabine has provided sustained responses in 100% of 10 patients, with acceptable toxicity. The treatment response occurred in both positive and negative t(11;18) lymphomas.
<table>
<thead>
<tr>
<th>First author and year</th>
<th>No. of patients</th>
<th>Treatments</th>
<th>Response</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hammel, 1995</td>
<td>24</td>
<td>Continuous alkylating agents cyclophosphamide or chlorambucil</td>
<td>75% CR</td>
<td>Median FU 14 months, 28% relapses</td>
<td>All stages I–IV. Non-treated. ‘Prominent’ gastric involvement</td>
</tr>
<tr>
<td>Levy, 2005</td>
<td>21</td>
<td>Continuous alkylating agents 12 cases t(11;18) + 9 cases t(11;18)−</td>
<td>(+) 42% CR (−) 89% CR</td>
<td>(+) 8% persistent CR at 7 years (−) 89% persistent CR at 7 years</td>
<td>All stages I–IV. Non-treated. Alkylating agents not active in t(11;18)+ Early stages IE–IE. Non-treated, no H pylori eradication</td>
</tr>
<tr>
<td>Aviles, 2005</td>
<td>83</td>
<td>Alternating CHOP21/CVP</td>
<td>4 (80%) CR 1 (20%) PR</td>
<td>Median FU 7.5 years, 87% EFS, 87% OS at 10 years</td>
<td>Stages I–II. Chemotherapy-naive.</td>
</tr>
<tr>
<td>Wohrer, 2005</td>
<td>5*</td>
<td>Mitoxantrone/chlorambucil and prednisone (MCP)</td>
<td>4 (80%) CR 1 (20%) PR</td>
<td>Median FU 7.5 years, 87% EFS, 87% OS at 10 years</td>
<td>Stages I–II. Chemotherapy-naive. Prior H pylori eradication</td>
</tr>
<tr>
<td>Jager, 2002/2006</td>
<td>19*</td>
<td>2CdA</td>
<td>100% CR</td>
<td>FU 80 months 3/19 (15%) relapses 78.5% DFS</td>
<td>All stages I–IV. Chemotherapy-naive. Active in t(11;18)+. Risk of myelodysplasia?</td>
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<tr>
<td>Raderer, 2005</td>
<td>4*</td>
<td>Oxaliplatin</td>
<td>2 (50%) CR 1 (25%) PR</td>
<td>No relapses at time of publication</td>
<td>All stages I–IV. Treated and non-treated. Active in t(11;18)+</td>
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<tr>
<td>Raderer, 2003</td>
<td>7 gastric*</td>
<td>Rituximab</td>
<td>3 (33%) CR 2 (22%) PR†</td>
<td>FU 8–14 months. No relapses after CR</td>
<td>All stages I–IV. Treated and non-treated. Still CD20 cells in LEL(+)</td>
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<tr>
<td>Conconi, 2003</td>
<td>14*</td>
<td>Rituximab</td>
<td>9 (64%) OR 4 (29%) CRS (35%) PR</td>
<td>Median FU 14.2 months</td>
<td>All stages I–IV. Treated and non-treated. Better in non-treated</td>
</tr>
<tr>
<td>Martinelli, 2005</td>
<td>26</td>
<td>Rituximab</td>
<td>20 (77%) OR 12 (46%) CR 8 (31%) PR</td>
<td>Median FU 33 months, 2/20 relapses</td>
<td>All stages I–IV. Treated and non-treated. Active in t(11;18)+</td>
</tr>
<tr>
<td>Wohrer, 2007</td>
<td>7*</td>
<td>R-CHOP/R-CNOPP</td>
<td>7 (100%) OR 5 (71%) CR 2 (29%) PR</td>
<td>FU 10–23 months. No relapses after CR. PR stable</td>
<td>All stages I–IV. Treated and non-treated. Active in t(11;18)+. Haematological toxicity</td>
</tr>
<tr>
<td>Salar, 2009</td>
<td>10*</td>
<td>Rituximab+fludarabin</td>
<td>100% CR 91% CR after 3 cycles</td>
<td>FU 24 months. No relapses after CR. 100% PFS at 24 months</td>
<td>All stages I–IV. Chemotherapy-naive.</td>
</tr>
<tr>
<td>Levy, 2010</td>
<td>13</td>
<td>Rituximab+clorambucil</td>
<td>100% CR</td>
<td>Median FU 24 months. No relapse, 2 adenocarcinoma operated on</td>
<td>All stages I–IV all t(11;18)+. Treated and non-treated</td>
</tr>
</tbody>
</table>

*Series include lymphomas from other MALT sites. Data in the table refer only to gastric MALT lymphomas.
†Percentage results refer to 7 gastric and 2 non-gastric lymphomas.
Non-treated, no previous treatment, except H pylori eradication; chemotherapy-naive, no previous treatment with chemotherapy. Other treatments eventually used.
2CdA, cladribine; CR, complete response; DFS, disease-free survival; EFS, event-free survival; FU, follow-up; (+) LEL lymphoepithelial lesions in gastric mucosa; MALT, mucosa-associated lymphoid tissue; OR, overall response; OS, overall survival; PR, partial response; R-CHOP/R-CNOPP, rituximab plus cyclophosphamide, vincristine, prednisone with either doxorubicin or mitoxantrone.
RESPONSE AND FOLLOW-UP

Post-treatment evaluation

Response is defined according to the well-accepted multidisciplinary oncological criteria. Histological evaluation of post-treatment biopsies should be performed in the context of reviewing previous biopsies and requires assessment of the cellular infiltrate, lymphoepithelial lesions and stromal changes. Wotherspoon’s score7 is recommended for initial diagnosis, is no longer considered adequate for response assessment during follow-up. The system proposed by GELA (Groupe d’Etude des Lymphomes de l’Adult), which has good interobserver concordance, is recommended as it provides information on the evolving type and change in an individual case.132 In this system, four morphological categories are identified: complete histological response (CR), probable minimal residual disease (pMRD), responding residual disease (rRD) and no change (NC) (Table 3).

Treatment response

Complete remission (CR) is defined as no macroscopic findings of lymphoma and negative histology (CR or pMRD) in two subsequent follow-up investigations.

Partial remission (PR) is defined as normalisation or reduction of macroscopic findings, histological signs of lymphoma regression (rRD) and no signs of progressive disease.

Stable disease (SD) is characterised by unmodified macroscopy and/or unmodified histology (NC).

Progressive disease (PD) is defined by worsening of macroscopic findings or dissemination of gastric MALT lymphoma, or transformation into DLBCL.

Relapse is defined as persistent histologically confirmed lymphoma after a complete remission was documented.

Table 3  GELA grading system for post-treatment evaluation of gastric MALT lymphoma (Copie-Bergman et al132 with comments by the authors)

<table>
<thead>
<tr>
<th>GELA category</th>
<th>Histology</th>
<th>Clinical significance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete histological response (CR)</td>
<td>Total disappearance of the lymphoid infiltrate with only scattered small lymphocytes and plasma cells. Regressive stromal changes with fibrosis and separation of glands can be seen.</td>
<td>Complete remission</td>
<td>Identification of CR may be subject to sampling ‘artefact’ and the designation of complete regression needs sustained absence of histological disease in the context of remission as assessed by all other means. No need for additional treatment.</td>
</tr>
<tr>
<td>Probable minimal residual disease (pMRD)</td>
<td>Small lymphoid aggregates present, usually at the base of the lamina propria. Associated stromal regressive changes are usually present.</td>
<td>Complete remission</td>
<td>The significance of the lymphoid aggregates is impossible to determine by morphology or immunocytochemistry, but it has been established that these nodules frequently, but not always, harbour cells with the same clonal gene rearrangement as the original lymphoma cells, consistent with the presence of a small number of residual neoplastic cells. However, no adverse prognostic significance has been demonstrated associated with this histology which is detected in early follow-up biopsies after Helicobacter pylori eradication of most cases undergoing subsequent complete remission. No need for additional treatment.</td>
</tr>
<tr>
<td>Responding residual disease (rRD)</td>
<td>Overt residual lymphoma with a nodular or diffuse infiltrate of neoplastic E-cells but with clear evidence of regressive stromal changes characterised by fine fibrosis and an ‘empty lamina propria’.</td>
<td>Partial remission</td>
<td>Comparison with the diagnostic biopsy is helpful in this context. These features are considered to indicate a partial and ongoing response. In the absence of unfavourable endoscopic results or clinical features of progressive disease, a decision about additional treatment can be postponed until after the following endoscopic assessment. Management should be individually tailored.</td>
</tr>
<tr>
<td>No change (NC)</td>
<td>Persistence of overt lymphoma identical to that seen at diagnosis with no morphological features to suggest response to treatment (such as stromal fibrosis).</td>
<td>Stable disease or progressive disease</td>
<td>In the case of persisting macroscopic lesions or evidence of dissemination of the disease, oncological treatment should be proposed. If only microscopic infiltration is present, oncological treatment can be postponed up to 24 months after achievement of Helicobacter pylori eradication, after which management should be individually tailored.</td>
</tr>
</tbody>
</table>

GELA, Groupe d’Etude des Lymphomes de l’Adult; MALT, mucosa-associated lymphoid tissue.

Recommendations

- A first evaluation of lymphoma regression should be performed 3–6 months after completion of treatment. Further follow-up should be performed every 4–6 months thereafter until complete remission of lymphoma (clinical and histological (GELA: CR or pMRD) is documented.
- Gastroscopy with multiple biopsies (mapping—see Diagnosis section) has to be performed. Additionally, the initial sites of lymphoma involvement should be checked by appropriate methods.

Comment

Once eradication is documented (see Helicobacter pylori eradication section), the follow-up of gastric MALT lymphoma is usually restricted to endoscopy with biopsy mapping (see Endoscopic diagnosis section). Whatever the mapping procedure adopted at initial staging, it is important to keep the same protocol during the follow-up endoscopy, in order to allow a proper histological comparison. EUS is, therefore, not generally recommended in this context.133–136

Comment

The importance of evaluating the lymphoma response after effective H pylori eradication (see Helicobacter pylori section) has to be emphasised again. Complete remission is obtained usually within 6–12 months from eradication. In some cases, however, it may be delayed up to 24–72 months.90

Two sequential follow-up gastroscopies without lymphoma are mandatory to assume complete remission regarding the possibility of a sampling error of endoscopic biopsies.
Patients with persistent histological lymphoma (rRD and NC) can be managed up to 24 months by a ‘watch and wait’ strategy unless progression or recurrent endoscopic lesions can be demonstrated. The detection of rRD might encourage continuation of this strategy beyond 24 months before considering alternative oncological treatment. However, the ‘watch and wait’ duration might be shorter in patients with more advanced disease stage, involvement of perigastric lymph nodes, suspected high-grade transformation lymphoma, H pylori-negative status and t(11;18)(q21;q21) positivity as these cases are more frequently unresponsive to anti-Helicobacter therapy alone.

The decision to continue a ‘watch and wait’ follow-up or to start oncological treatment should be an individually tailored multidisciplinary decision, based on clinical, histological and molecular features, the patient’s preferences and data emerging from ongoing trials. An extended ‘watch and wait’ period is an acceptable option as high-grade transformation is extremely rare, with a reported frequency of <1%.63 93

Patients with progressive disease or clinically/endoscopically evident relapse with positive biopsies should be offered oncological treatment.

Follow-up after complete remission

**Recommendation**

- If complete remission of gastric MALT lymphoma is achieved, follow-up gastroscopies with biopsies seem advisable.

**Comment**

The rationale for follow-up gastroscopies is based on two aspects. First, local relapses may arise. In the systematic review of published series by Zullo et al including 1408 patients, 7.2% of cases experienced lymphoma relapse, with a yearly recurrence rate of 2.2%.65 93 Secondly, an elevated risk for gastric carcinoma has been reported in patients with MALT lymphoma, especially when intestinal metaplasia or dysplasia are found.139 Optimal intervals between check-ups and duration of surveillance are not yet known.

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EGILS consensus report. Gastric extranodal marginal zone B-cell lymphoma of MALT

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