# Lymphoma Network of New Zealand

# MALT Lymphoma Protocol

## Summary of Recommendation

- **Diagnosis and Staging:**
  - Initial work up includes standard lymphoma and site specific investigations.
    - 
    - Wotherspoon Scoring System should be used to standardise diagnosis for gastric MALT lymphoma.
    - Endoscopic USS can be useful at time of biopsy but not critical (resource and logistic limitation)
  - Staging system
    - 3 staging systems used for gastric MALT lymphoma.
      - Lugano, TNM and Ann Arbor.
      - The staging system used should be clearly documented since stages can vary slightly between systems.
    - 1 for non-gastric MALT lymphoma.
      - Ann Arbor.
    - Molecular Studies:
      - Testing for t(11;18)(q21;q21):
        - Should be considered for **ALL** gastric MALT lymphoma given the prognostic utility.
        - Could be considered in lung, stomach, small intestine, conjunctival and orbital MALT lymphoma given the specificity.
      - Testing for other genetic aberration could be useful in selected cases but currently is not recommended for routine testing.

- **Treatment:**
  - All patients with gastric MALT lymphoma should be considered for antibiotic therapy regardless of their clinical stage and *H. pylori* status.
    - Proposed treatment for early stage gastric MALT lymphoma
  - Antibiotic therapy in non-gastric MALT lymphoma may be of limited value in NZ setting.
  - Radiation therapy is highly active in MALT lymphoma and could be favoured

approach in selected cases.
    - R-chemo gives promising results
    - In transformed disease treat as early stage DLBCL
        - Short course of R-CHOP + RT
        - Antibiotic therapy can be added in patient positive for *H. pylori*.

## Sub Topics

1. Introduction
    - Gastric MALT Lymphoma Overview
    - Non-Gastric MALT Lymphoma Overview
2. Diagnosis and Staging
    - Histology
    - Prognostic Marker
    - Staging
    - Molecular Genetics
3. Treatment
    - Antibiotic Therapy
        - Gastric MALT Lymphoma
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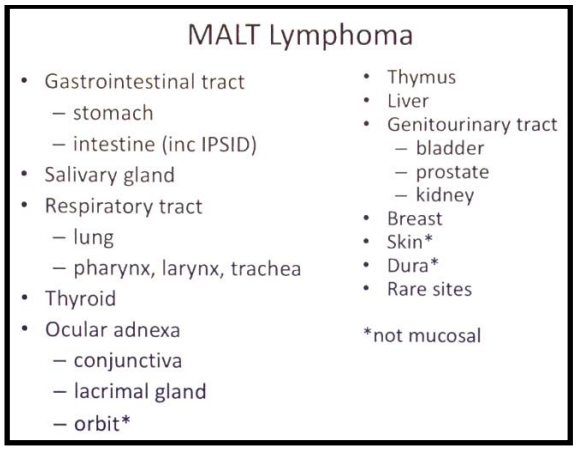
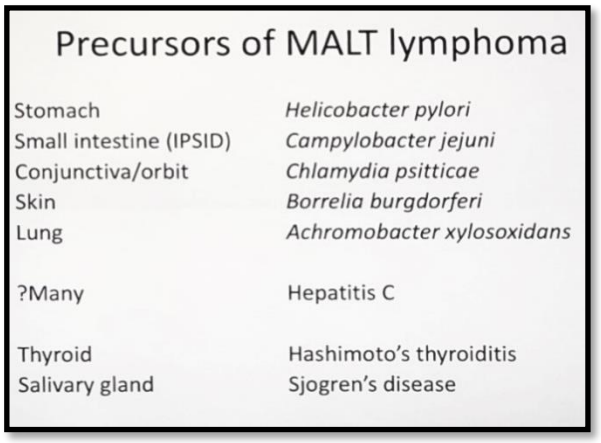
    - Flow Diagram for The Management of Early Stage Gastric MALT Lymphoma

# Introduction

Mucosa-Associated Lymphoid Tissue (MALT) lymphoma can be induced/expanded by chronic antigenic stimulation (infection, autoimmune disorders). MALT lymphoma account for ~8% of all NHL and is more common than splenic and nodal MZL (1% and 2% respectively).

## Subtype of MALT lymphoma:




In general MALT lymphoma is divided into 2 subgroups:

- Gastric MALT lymphoma (70%).
- Non-gastric MALT lymphoma (30%).

## Gastric MALT Lymphoma Overview

First described by Spencer et al in 1984 and arise in GI mucosa and 90% of gastric MALT lymphoma is associated with *H. pylori* infection. *H. pylori* is a Gram negative bacterium and colonises the gastric mucosa and it is transmitted within the family in childhood (likely faecal-oral transmission).

The prevalence is more than 50% of the human population however the true prevalence can be variable even within local community (associated with low social economic class and developing countries). Overall, the prevalence is likely increasing in NZ due to migration pattern.

Postulated Pathogenesis:

Gut is an immune privilege site due to the complex interplay between gut microbiome, gut luminal antigen and intestinal epithelial barrier host interaction. The process is designed to induce tolerance to microbiome and dietary antigen and prevent the development of inflammatory bowel disease or food allergy. The marginal zone B cell are clonally separate to the classical B cells in the gut and occupy a niche between germinal centre and follicle associated epithelium in GALT surrounded by classical memory B cells. The marginal zone B cells express high level of TACI (**T**ransmembrane **A**ctivator and **C**alcium-modulator and cyclophilin ligand **I**nteractor; a molecule involved in the generation of antigen-specific antibody secreting B cells, in host response) and FcRL4.

The two types of interactions are described for *H. pylori* and the host environment.

- Type 1
    - *H. pylori* escapes immune system and get nutrients from host tissue leading to asymptomatic gastritis.
- Type 2
    - Proinflammatory genetic background and certain strain of *H. pylori* can result in immune response leading to chronic inflammation.
        - Cag A mediated
    - The chronic inflammation lead to hypochlorhydria and development of malignancy
        - From acquisition of genetic abnormalities

It is beyond the scope of this guideline to delve deeply into the pathogenesis of MALT lymphoma. It is postulated that chronic abnormal interaction between *H. pylori* and host results in the development of **l**ympho**e**pitheal **l**esions (LELs) with invasive follicle centres cells and non-invasive plasma cells and tends to remain localised. These monoclonal B cells (MZL) express CD27+, IgM+ and predominantly IgD- on their surface membrane.

## Non-gastric MALT Lymphoma Overview

The association between non-gastric lymphoma and infection induced chronic stimulation is less well established. There are reported cases of association between ocular MALT lymphoma and *C. psittaci* and between skin MALT lymphoma and B. burgdorferi. However, these infections are rare in NZ setting and are unlikely to be the culprit driving the inflammatory process. The list for potential precursor to different type of MALT lymphoma was shown earlier.

# Diagnosis and Staging

In general, the initial investigations for MALT lymphoma are similar to routine lymphoma work up. However, due to the chronic antigen stimulation as the hallmark of the disease process certain condition should be tested depends on site of lymphoma. It is critical to invest significant time and resource to test for the potential cause of chronic stimulation as this can be an important consideration when it comes to treatment.

Below table summarised the recommended site-specific workup in MALT lymphoma.

**Table 2. Recommended site-specific workup in MALT lymphomas**

| MALT lymphoma site | Site-specific staging procedures |
|---|---|
| Stomach | Ear/nose/throat examination, EGD, endoscopic ultrasound to evaluate regional lymph nodes and gastric wall infiltration, search for *H pylori* (histochemistry, serology, breath test, fecal antigen), search for MALT1 translocation by FISH |
| Salivary glands | Ear/nose/throat examination and ultrasound. Anti-SSA or anti-SSB antibodies for possible association with Sjögren syndrome |
| Thyroid | Ultrasound ± CT scan of the neck and thyroid function tests |
| Lung | Bronchoscopy with bronchoalveolar lavage |
| Small intestine | Search for *C jejuni* in the tumor biopsy (PCR, immunohistochemistry or in situ hybridization) |
| Large intestine | Colonoscopy |
| Breast | Mammography and MRI |
| Ocular adnexa | MRI and ophthalmologic examination. Search for *C psittaci* in the tumor biopsy and blood mononuclear cells by PCR may be considered |
| Skin | Search for *B burgdorferi* in the tumor biopsy by PCR may be considered in areas where it is endemic |

EGD, esophagogastroduodenoscopy; FISH, fluorescence in situ hybridization; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; SSA, Sjögren syndrome A; SSB, Sjögren syndrome B.

## Histology:

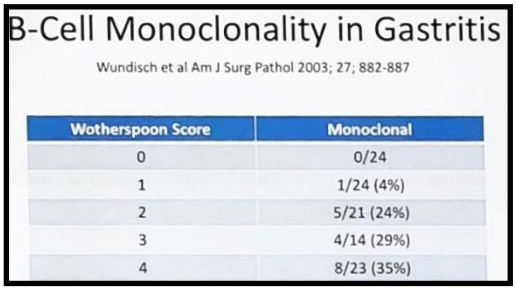
The diagnosis of gastric MALT lymphoma can be difficult based on histology alone. The proposed diagnostic scoring system is the Wotherspoon Scoring System.

### Wotherspoon Scoring System for Diagnosis of Gastric MALT Lymphoma

| *Score* | *Diagnosis* | *Histological features* |
|---|---|---|
| 0 | Normal | Scattered plasma cells in lamina propria<br>No lymphoid follicles |
| 1 | Chronic active gastritis | Small clusters of lymphocytes in lamina propria<br>No lymphoid follicles<br>No lymphoepithelial lesions |
| 2 | Chronic active gastritis with florid lymphoid follicle formation | Prominent lymphoid follicles with surrounding mantle zone and plasma cells No lymphoepithelial lesions |
| 3 | Suspicious lymphoid infiltrate, probably reactive | Lymphoid follicles surrounded by small lymphocytes that infiltrate diffusely in lamina propria and occasionally into epithelium |
| 4 | Suspicious lymphoid infiltrate, probably lymphoma | Lymphoid follicles surrounded by marginal zone cells that infiltrate diffusely in lamina propria and into epithelium in small groups |
| 5 | MALT lymphoma | Presence of dense diffuse infiltrate of marginal zone cells in lamina propria with prominent lymphoepithelial lesions |

The positive predictive value is low and don't significantly improves even when the Wotherspoon Score increased from 2 to 4.

The key is to have multiple/generous biopsies so additional tests can be performed.



## Prognostic Markers:

In gastric MALT lymphoma the prognostic factors are:

- *H. pylori* negativity
- Depth of gastric lesions
- Number of lesions
- t(11;18)(q21;q21)
- Nodal involvement
- IgM paraprotein level

Therefore, it is critical to establish the presence of *H. pylori* by combining various diagnostic methods (IHC of tissue, urea breath tests, serology and stool antigen test). Endoscopic USS should be used at time of biopsy which can identify the depth of lesions but logistically this is often not possible (scare resource and often at the time of biopsy the diagnosis isn't clear).

In non-gastric MALT lymphoma depends on the site of involvement specific test can be considered to look for the possible cause of chronic antigen stimulation.

- ANA/ENA to look for Sjogren syndrome in salivary gland
- *C. jejuni* in small intestine
- *C. psittaci* in ocular adnexa
- *B. burgdorferi* in skin

## Staging:

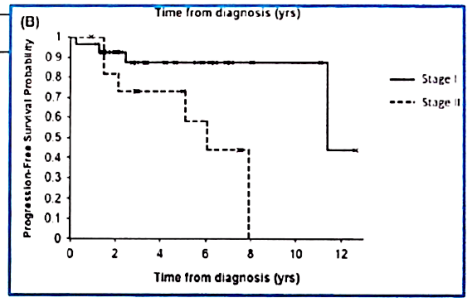
For gastric MALT lymphoma there are 3 staging systems. For non-gastric MALT lymphoma Ann Arbor staging system are frequently used. TNM staging system is less commonly used in NZ setting due to the requirement of endoscopic USS (depth of the lesions). Regardless, of what staging system is used it is important that it is clearly stated given the variation in stage depending on the system used (i.e. invasion of adjacent structures is staged as IIE in Lugano and IE in Ann Arbor staging system).

| | Lugano Staging System for gastrointestinal lymphomas[113] | TNM Staging System adapted for gastric lymphoma[44] | Ann Arbor stage | Tumor extension |
|---|---|---|---|---|
| Stage I | Confined to GI tract (single primary or multiple, noncontiguous) | T1 N0 M0 | $I_E$ | Mucosa, submucosa |
| | | T2 N0 M0 | $I_E$ | Muscularis propria |
| | | T3 N0 M0 | $I_E$ | Serosa |
| Stage II | Extending into abdomen | | | |
| | $II_1$ = local nodal involvement | T1-3 N1 M0 | $II_E$ | Perigastric lymph nodes |
| | $II_2$ = distant nodal involvement | T1-3 N2 M0 | $II_E$ | More distant regional lymph nodes |
| Stage $II_E$ | Penetration of serosa to involve adjacent organs or tissues | T4 N0 M0 | $I_E$ | Invasion of adjacent structures |
| Stage IV | Disseminated extranodal involvement or concomitant supra-diaphragmatic nodal involvement | T1-4 N3 M0 | $III_E$ | Lymph nodes on both sides of the diaphragm/distant metastases (eg, bone marrow or additional extranodal sites) |
| | | T1-4 N0-3 M1 | $IV_E$ | |

# Lugano GI-NHL Staging System

**Table 1.** Staging of gastrointestinal non-Hodgkin's lymphoma (GI-NHL) according to the International Workshop[1]

| Stage | Criteria |
|---|---|
| I | Tumor confined to the gastrointestinal (GI) tract |
| | Single primary site or multiple non-contiguous lesions |
| II | Tumor extending in abdomen from primary GI site |
| | Nodal involvement |
| II1 | Local (paragastric or paraintestinal) |
| II2 | Distant (mesenteric, para-aortic, paracaval, pelvic, inguinal) |
| IIE | Penetration of serosa to involve adjacent organs or tissues |
| IV | Disseminated extranodal involvement or a GI tract lesion with supradiaphragmatic nodal involvement |




Rohatiner A et al. Ann Oncol 1994; 5:397
Keiss AP et al Leuk Lymph 2013;54:177-80

Currently the staging requires CT and bone marrow biopsy. MRI can be used depend on site of the primary disease.

## Molecular Genetics:

MALT lymphoma has somatically mutated *IGHV* genes in all cases with *IGHV* sequence analysis showed somatic hypermutation & rearrangement patterns suggesting Ag selection in GCs. Presence of ongoing mutations & biased usage of *IGHV* segments (e.g., 1-69 in salivary glands) indicate expansion of lymphoma cells is Ag-driven.

Common genetic aberrations detected in MALT lymphomas:



**Table 1. Most common genetic aberrations detected in MALT lymphomas**

| Genetic lesion[3-22] | Involved genes | Deregulated pathway | Prevalence, % | Anatomical sites | Clinical relevance |
|---|---|---|---|---|---|
| t(11;18)(q21;q21) | BIRC3-MALT1 | NF-κB | 15-40 | Stomach, lung | Antibiotic resistance alkylating agents resistance? |
| t(14;18)(q32;q21) | IGHV-MALT1 | NF-κB | 20 | Lung, salivary gland, skin, ocular adnexa | Antibiotic resistance? |
| t(1;14)(p22;q32) | IGHV-BCL10 | NF-κB | <5 | Stomach, lung | Antibiotic resistance |
| t(3;14)(p13;q32) | IGHV-FOXP1 | Wnt* | <5 | Unclear | Transformation risk? |
| t(9;14)(p24;q32) | *IGHV-JMJD2C* | Chromatin remodeling† | <5 | Unclear | |
| t(X;14)(p11;q32) | *IGHV-GPR34* | NF-κB ? | <5 | Unclear | |
| t(5;14)(q34;q32) | *IGHV- TENM2* | Unclear | <5 | Unclear | |
| Trisomy 3 | Unclear | Unclear | 20-40 | Equal distribution | Inferior outcome? |
| Trisomy 18 | Unclear | Unclear | 20-40 | Equal distribution | |
| del(6q23) | *TNFAIP3* | NF-κB | 15-30 | Equal distribution | |

*DLBCLs bearing the same chromosomal translocation show deregulated Wnt signaling.[21]
†*JMJD2C* is amplified and overexpressed in other lymphoma subtypes in which its genetic silencing leads to decreased levels of H3K9me3, a marker of transcriptional repression.[22]

- t(11;18)(q21;q21) [BIRC3-MALT1 fusion]
    - Specific for MALT lymphoma
        - Negative in EMZL and NMZL
    - Incidence various from 15-40% but depends on site
    - In gastric MALT lymphoma, it predicts
        - Lack of response to *H. pylori* eradication
        - Lower risk of transformation to DLBCL

Incidence of t(11;18) in MALT Lymphomas of Different Sites

| Sites | No of Cases (unselected) | t(11;18) (%) |
|---|---|---|
| Lung | 47 | 38 |
| Stomach | 135 | 24 |
| Small intestine | 8 | 63 |
| Conjunctiva | 27 | 18 |
| Orbital | 28 | 14 |
| Salivary gland | 72 | 1 |
| Thyroid | 18 | 0 |
| IPSID | 22 | 0 |
| Skin | 19 | 0 |

- t(1;14) & *BCL-10*
    - t(1;14) juxtaposes *BCL-10* gene next to the immunoglobulin heave chain gene
    - *BCL-10* induces apoptosis and activates NF-kB

- t(14;18)(q32;q21)
    - Identical to t(14;18)(q32;q21) involving *BCL2* in FL or DLBCL
    - It juxtaposes *MALT1* gene to promoter region of *IGHV* genes
    - Leading to subsequent *MALT1* deregulation

t(14;18)(q32;q21) in MALT lymphomas [IgH-MALT1]

| | |
|---|---|
| Stomach | 0/10 |
| Intestine | 0/9 |
| Lung | 0/7 |
| Liver | 4/4 |
| Skin | 3/11 |
| Ocular adnexae | 3/8 |
| Salivary gland | 2/11 |

All negative for t(11;18)
Trisomy 3 in 4/12 cases

Streubel et al

# Treatment

The treatment for MALT lymphoma differ slightly from the usual treatment of low grade lymphoma due to the unique pathophysiology of chronic antigen stimulation. As mentioned under the diagnosis and staging section that significant time and resouces should be spent identifying the underlying cause of the chronic antigen stimulatin.

The general principles are:

- MALT lymphoma can regress if the underlying cause of chronic stimulation can be adequately treated.
- Radiotherapy is very active in MALT lymphoma.
- R-chemo is effective in advanced stage MALT lymphoma.

## Antibiotic Therapy In Gastric MALT Lymphoma:

In patient with *H. pylori* positive gastric MALT lymphoma, *H. pylori* eradication with strict follow-up is associated with complete response (CR) rate of 70-80%. This is similar overall survival (OS) to chemotherapy, surgery, surgery + chemo and radiation therapy. In patient with *H. pylori negative* gastric MALT lymphoma the response rate relatively modest 28%. However, **all newly diagnosed patients with gastric MALT Lymphoma should be considered to have an indication for antibiotic therapy regardless of their clinical stage and *H. pylori* status**.

- Standard Antibiotic Therapy
  - Omeprazole 20mg/PO BD Day 1 to 7
  - Amoxicillin 1000mg/PO BD Day 1 to 7
  - Clarithromycin 500mg/PO BD Day 1 to 7

- Response based on Histological Feature

| GELA category | Morphological features | Recommendation |
|---|---|---|
| CR-complete histological response | Empty appearance of LP with fibrosis,few glands,small lymphocytes and plasma cells; no LELs | No need of additional therapy |
| pMRD-probable Minimal Residual Disease | Base of lamina propria and/or submucosa with small lymphoid nodules and fibrosis;no LELs | No need of additional therapy |
| rRD-responding residual diseas | Presence of lymphomatous infiltrate in a diffuse or nodular pattern, some degree of stromal changes; focal or no LELs | Evaluation of clinincal progression should delineate additional therapy |
| NC-no change | Dense lymphomatous infiltrate similar to diagnostic biopsy;LEL present | Oncological treatment should be proposed if infiltrate persists over sequential examinations |

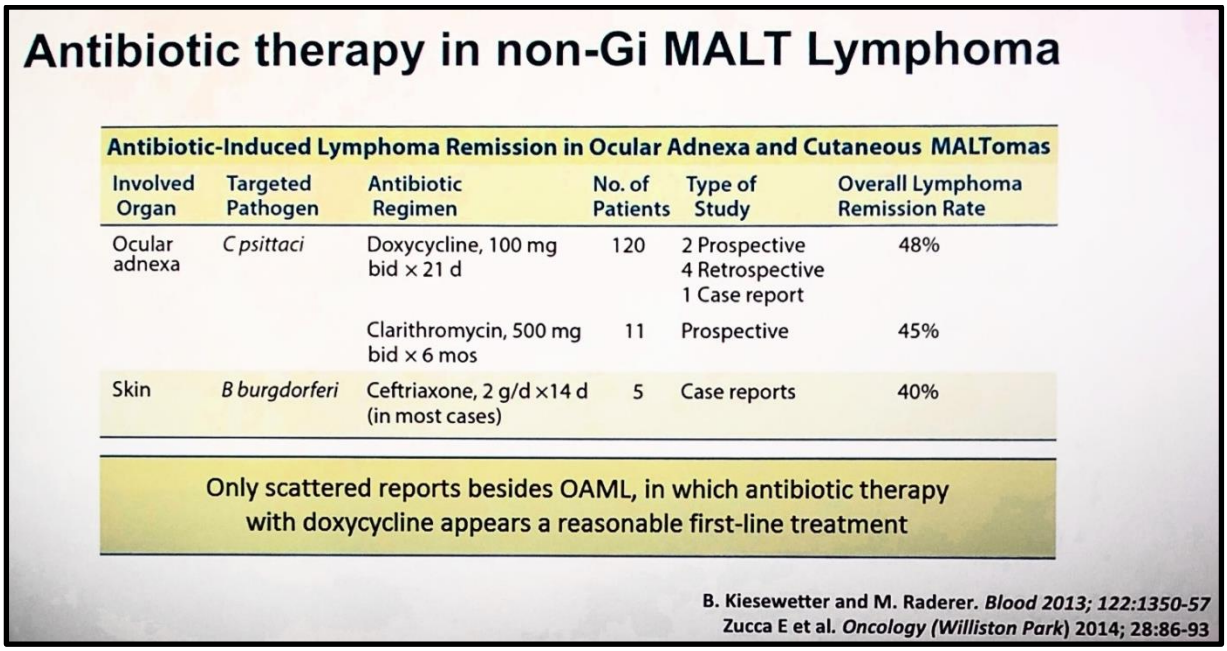
LP-lamina propria; LEL-lymphoepithelial lesion

- Predictors of Response to *H. pylori* Eradication
    - H. pylori status
    - Gastric Lesions status
        - Lesions in both proximal & distal parts of stomach
        - Depth of invasion of gastric wall
        - Number of lesions
    - Immunocytochemistry
        - Nuclear BCL-10
        - Nuclear NF-kB
        - Presence/absence of large cell component
    - Molecular
        - BIRC-3/MALT-1 t(11;18)
        - t(1;14)
        - Trisomy 3

- Non-responders:
    - Paper published by Nakamura et al. showed that patients who are "non-responders" to antibiotics therapy can still do very well.
        - 97 "non-responders"
            - 27 progressive disease, 10 relapse disease and 37 treatment failure.
        - 17/37 had watch and wait strategy
        - Large cell transformation in 9 patients (2.8%)
        - Altogether 90 patient had second line therapy with 10 year
            - Event free survival 86%
            - Free from treatment failure 90%
            - Overall survival 95%

- **Other Important Considerations:**
    - Due to increasing drug resistance of H. pylori, second line treatment is recommended if initial eradiation fails
        - Metronidazole can be used instead of clarithromycin
        - Best to discuss with local gastroenterologist regarding 2$^{nd}$ line therapy
    - An explanation of possible "non-antibiotic responsiveness" is insufficient time span between treatment and reassessment
        - Median time to reach CR is 6 months and in can take up to 24 months or longer in some cases to reach remission.
    - Rate of H. pylori negative MALT lymphoma is rising

## Antibiotic Therapy In Non-gastric MALT Lymphoma:



**Antibiotic therapy in non-Gi MALT Lymphoma**

**Antibiotic-Induced Lymphoma Remission in Ocular Adnexa and Cutaneous MALTomas**

| Involved Organ | Targeted Pathogen | Antibiotic Regimen | No. of Patients | Type of Study | Overall Lymphoma Remission Rate |
|---|---|---|---|---|---|
| Ocular adnexa | *C psittaci* | Doxycycline, 100 mg bid × 21 d | 120 | 2 Prospective<br>4 Retrospective<br>1 Case report | 48% |
| | | Clarithromycin, 500 mg bid × 6 mos | 11 | Prospective | 45% |
| Skin | *B burgdorferi* | Ceftriaxone, 2 g/d ×14 d (in most cases) | 5 | Case reports | 40% |

Only scattered reports besides OAML, in which antibiotic therapy with doxycycline appears a reasonable first-line treatment

B. Kiesewetter and M. Raderer. *Blood 2013; 122:1350-57*
Zucca E et al. *Oncology (Williston Park)* 2014; 28:86-93

- These infections are rare in NZ setting and it is difficult to test for these infections.
    - The treatment response is modest 40-50%.
- **Given the effective treatment with radiation therapy (see below), we recommend these infection does not need to be routinely tested.**
- **We recommend involved field radiotherapy, as first line treatment for non-gastric extra-nodal localised and limited stage MALT- Lymphomas.**

## Radiation Therapy (RT):

MALT lymphomas are highly sensitive to RT and may be the favourable approach with:

- Symptomatic *H. pylori* negative localised disease
- Localised and low bulk extra gastric nodal involvement at diagnosis
- Patients who do not achieve lymphoma regression following antibiotic therapy
- Patients with risk factors that confers resistant to response to *H. pylori* eradication (see treatment section)

RT to the stomach and perigastric lymph nodes has shown excellent disease control.

Radiotherapy Results in MALT Lymphoma

| Author | No. of Patients | Site | RT dose (Gy) | Freedom from Treatment Failure |
|---|---|---|---|---|
| Yahalom, 2002 | 51 | Gastric | 22.5-43.59 | 89% at 4 years |
| Goda, 2010 | 192 | Gastric and non-gastric | 17.5-35 | 95% at 10 years for thyroid<br>92% for stomach<br>68% for salivary glands<br>67% for orbit |
| Wirth, 2013 | 102 | Gastric | 26-46 | 88% at 10 years |
| Ohga, 2013 | 53 | Orbit | 24-30 | 91% at 5 years |
| Kim, 2013 | 64 | Gastric | 30-44 | 89% at 5 years |
| Nam, 2014 | 48 | Gastric | 30-45 | 84% at 5 years |
| Harada, 2014 | 86 | Orbit | 30-46 | 88% at 10 years |

Bertoni & Zucca. *Lymphomas: Essentials for Clinicians* 2015

- Involved Field Radiation Therapy (IFRT) evidence supports low and moderate dose XRT
    - Moderate dose 24 to 30Gy over a period of 3 to 4 weeks

## Systemic Chemotherapy:

This is not discussed in detail in the protocol meeting. In general, any R-Chemo gives promising results.

## Transformed Disease:

- Treat as early stage DLBCL
    - Short course of R-CHOP + RT
    - Consider addition of antibiotic therapy in patient positive for *H. pylori*

Reports of disease regression with antibiotics therapy in this group of patients emerged few years ago, however, in view of lack of randomised data; we cannot recommend this approach at this stage.

## Flow Diagram for the Management of Early Stage Gastric MALT Lymphoma

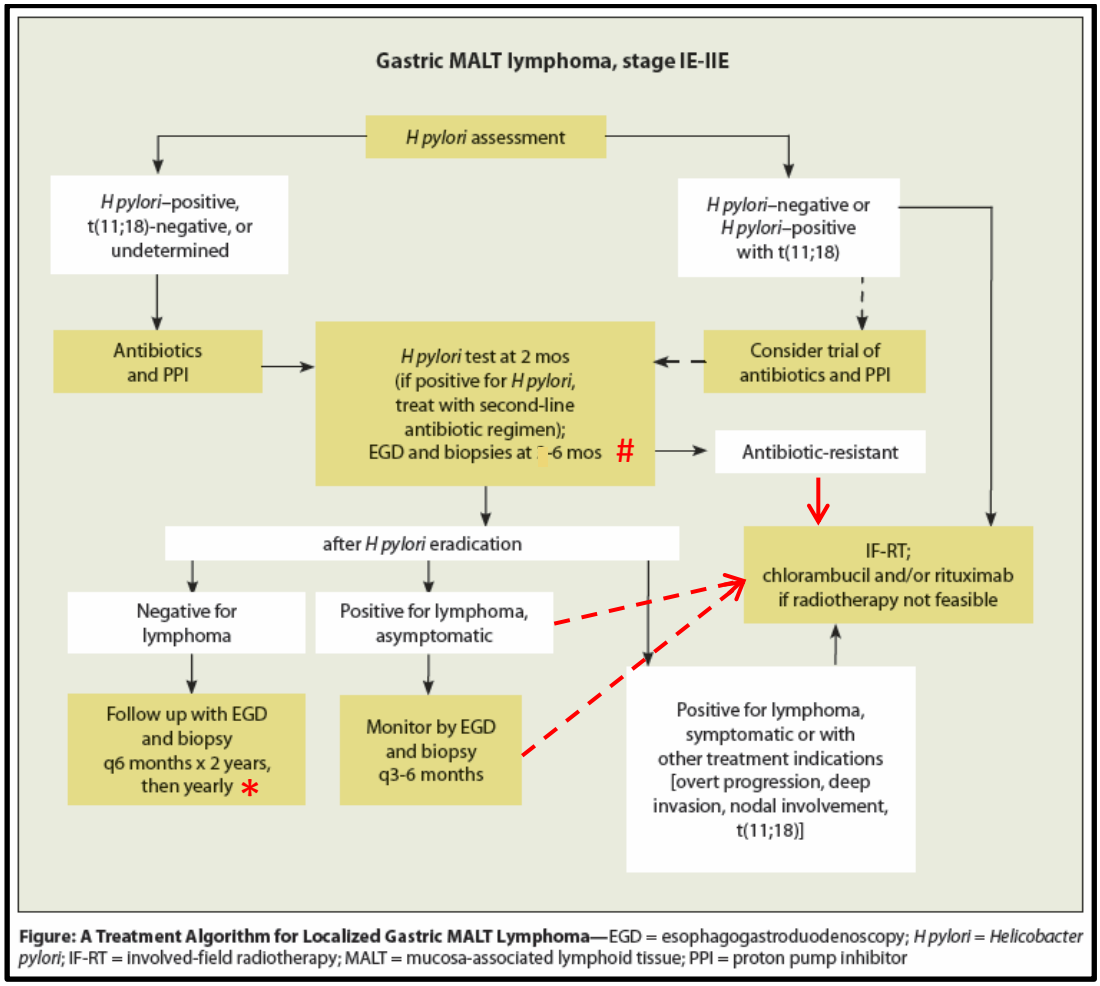



**Figure: A Treatment Algorithm for Localized Gastric MALT Lymphoma**—EGD = esophagogastroduodenoscopy; *H pylori* = *Helicobacter pylori*; IF-RT = involved-field radiotherapy; MALT = mucosa-associated lymphoid tissue; PPI = proton pump inhibitor

- Recommendation is for faecal antigen testing at 2 months and repeat gastroscopy and biopsy at 6 months (#).
- Given other effective therapies, those with antibiotic-resistant disease should proceed with further treatment (solid red line).
- Given the resource limitation in certain regions (requirement of on-going gastroscopy surveillance)
    - In patient with asymptomatic lymphoma after *H. pylori* eradication it is reasonable to proceed with other effective therapy (dashed red line).
    - In patients with CR after antibiotic therapy
        - Consensus was not reached regarding the duration of yearly gastroscopy surveillance after the first 2 years (*)

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