

**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)**

# **Non-Hodgkin's Lymphomas**

Version 2.2015

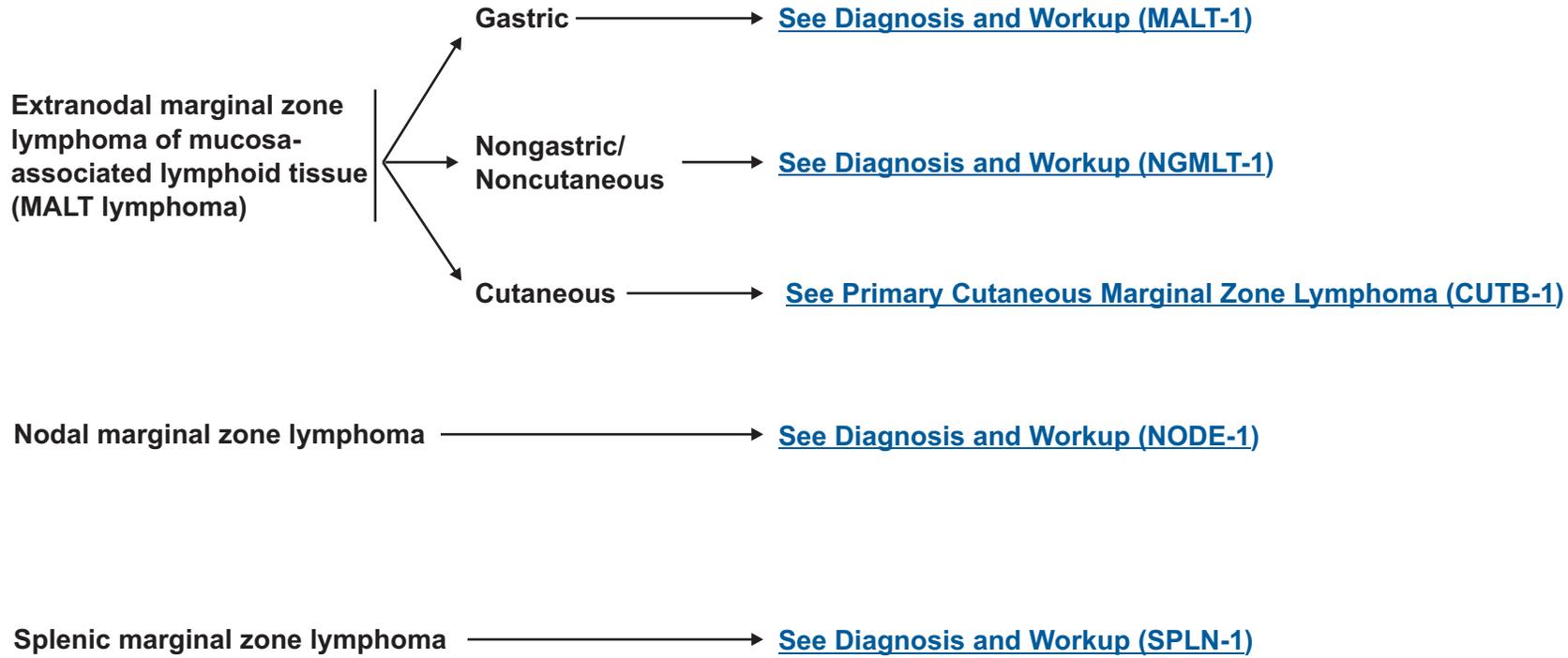
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# Marginal Zone Lymphomas



**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



#### DIAGNOSIS

##### ESSENTIAL:

- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.<sup>a,b</sup>
- Diagnosis of gastric MALT lymphoma requires an endoscopic biopsy and an FNA is never adequate.
- Adequate immunophenotyping to establish diagnosis<sup>c,d</sup>
  - ▶ IHC Panel: CD20, CD3, CD5, CD10, BCL2, kappa/lambda, CD21 or CD23, cyclin D1, BCL6 or
  - ▶ Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10
- *Helicobacter pylori* (*H. pylori*) stain (gastric), if positive, then PCR or FISH for t(11;18)<sup>e</sup>

##### USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Molecular analysis to detect: antigen receptor gene rearrangements; MYD88 mutation status to differentiate WM versus MZL if plasmacytic differentiation present
- Cytogenetics or FISH: t(1;14); t(3;14); t(11;14);<sup>f</sup> t(11;18)
- FISH or PCR: t(14;18)

#### WORKUP

##### ESSENTIAL:

- Physical exam with attention to nongastric sites (eyes, skin)
- Performance status
- CBC, differential, platelets
- Comprehensive metabolic panel
- LDH
- If *H. pylori* negative by histopathology, then use noninvasive *H. pylori* testing (stool antigen test, urea breath test, blood antibody test)
- Hepatitis B testing<sup>g</sup> if rituximab contemplated
- Hepatitis C testing
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

##### USEFUL IN SELECTED CASES:

- Bone marrow biopsy ± aspirate
- MUGA scan/echocardiogram if anthracycline or anthracenedione-based regimen is indicated
- Endoscopy with ultrasound (if available) with multiple biopsies of anatomical sites<sup>h</sup>
- Discussion of fertility issues and sperm banking
- SPEP

[See Initial Therapy \(MALT-2\)](#)

<sup>a</sup>Nondiagnostic atypical lymphoid infiltrates that are *H. pylori* positive should be rebiopsied to confirm or exclude lymphoma prior to treatment of *H. pylori*.

<sup>b</sup>Any area of DLBCL should be treated according to the [NCCN Guidelines for Diffuse Large B-Cell Lymphoma \(BCEL-1\)](#).

<sup>c</sup>Typical immunophenotype: CD10-, CD5-, CD20+, cyclin D1-, BCL2 follicles.

<sup>d</sup>[See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms \(NHODG-A\)](#).

<sup>e</sup>Locally advanced disease is more likely in patients with gastric MALT lymphoma with t(11;18), which is less likely to respond to antibiotics.

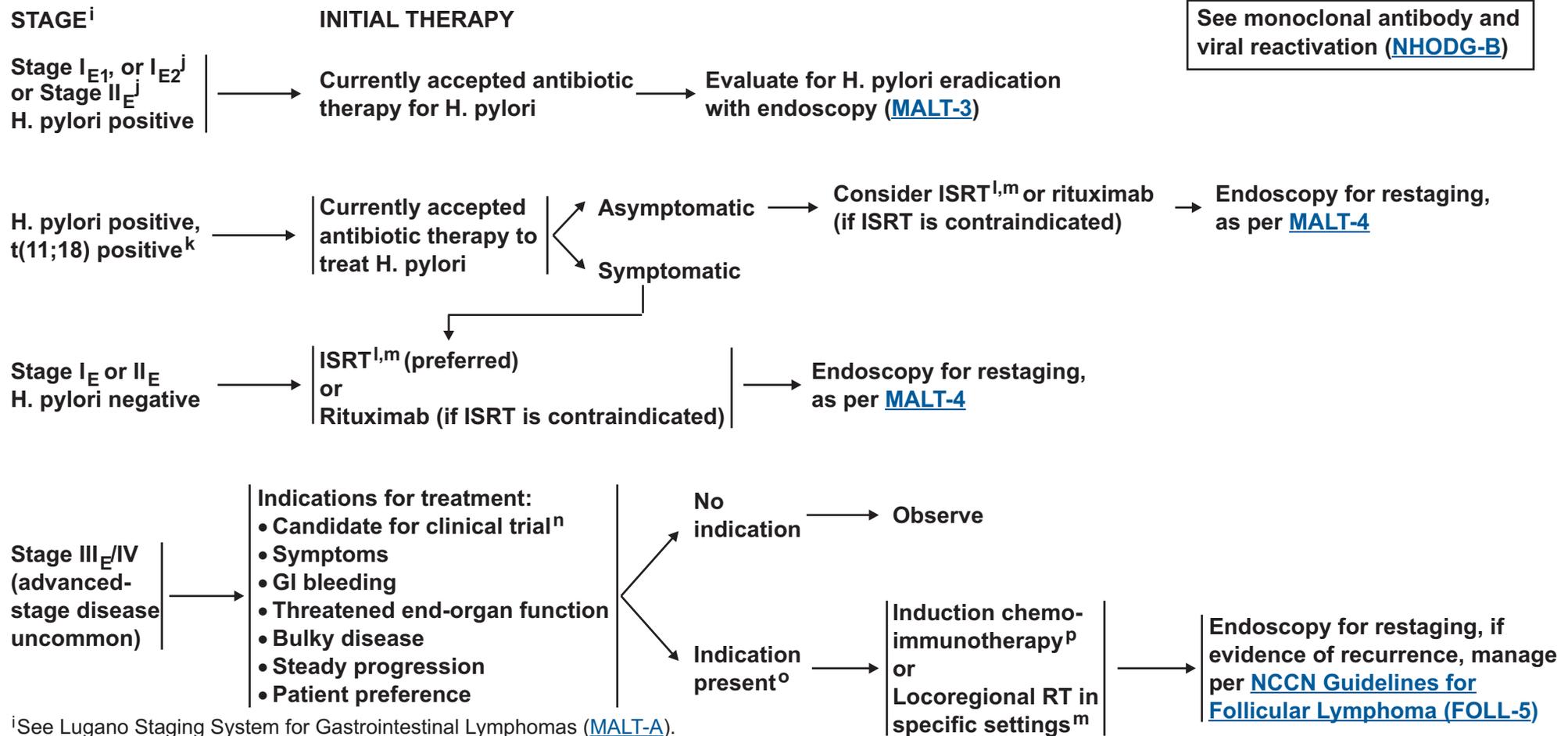
<sup>f</sup>If IHC for cyclin D1 is positive, FISH for t(11;14) is not necessary.

<sup>g</sup>Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

<sup>h</sup>This is particularly useful for *H. pylori*-positive cases because the likelihood of tumor response is related to depth of tumor invasion.

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See monoclonal antibody and viral reactivation ([NHODG-B](#))

<sup>i</sup>See Lugano Staging System for Gastrointestinal Lymphomas ([MALT-A](#)).

<sup>j</sup>Involvement of submucosa or regional lymph nodes are much less likely to respond to antibiotic therapy. If there is persistent disease after evaluation, RT may be considered earlier in the course.

<sup>k</sup>t(11;18) is a predictor for lack of tumor response (<5%) to antibiotics. Antibiotics are used in these patients to eradicate the H. pylori infection. These patients should be considered for alternative therapy of the lymphoma. Liu H, Ye H, Ruskone-Fourmestreaux 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.

<sup>l</sup>If negative by both histology and serum antibodies, RT is recommended.

<sup>m</sup>See [Principles of Radiation Therapy \(NHODG-D\)](#).

<sup>n</sup>Given incurability with conventional therapy, consider investigational therapy as first line of treatment.

<sup>o</sup>Surgical resection is generally limited to specific clinical situations (ie, life-threatening hemorrhage).

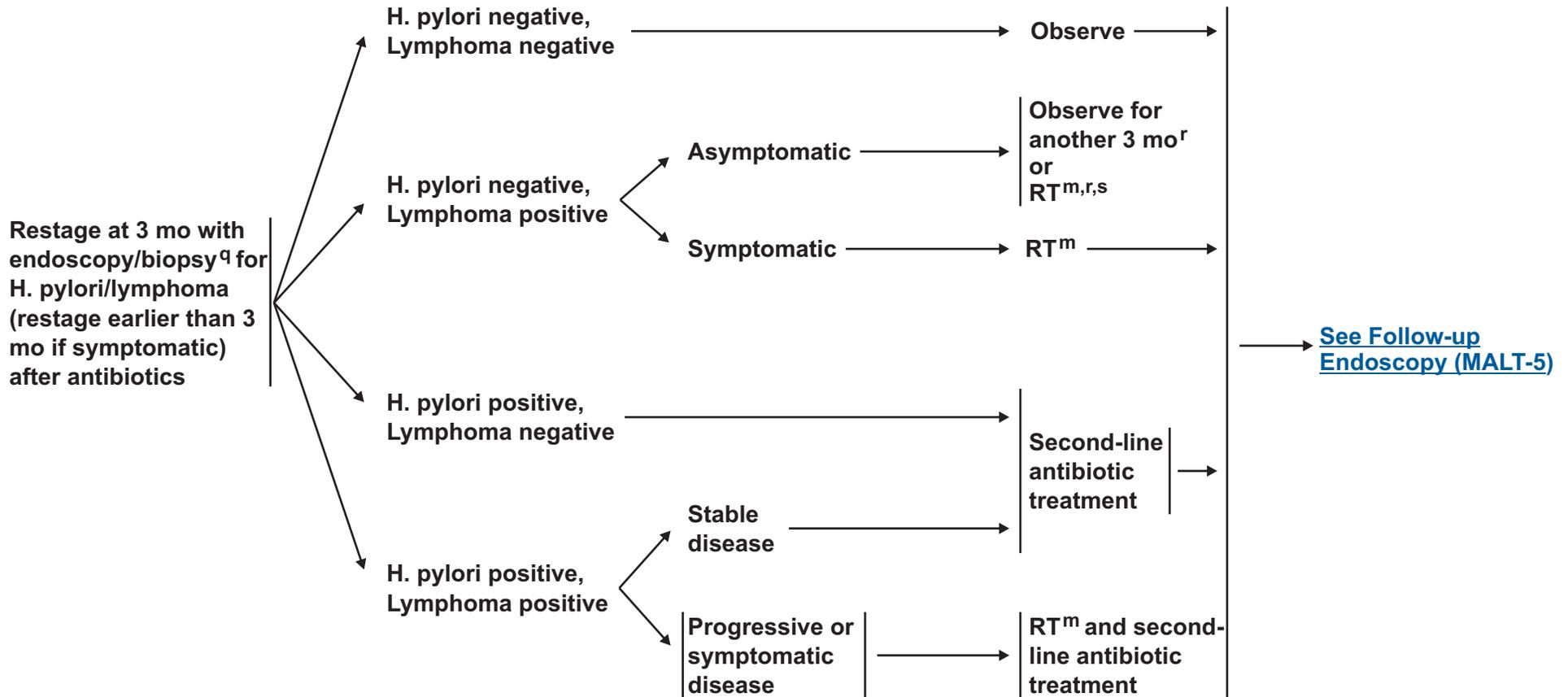
<sup>p</sup>See [Suggested Treatment Regimens \(FOLL-B\)](#).

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### 3-MONTH RESTAGING AND FOLLOW-UP ENDOSCOPY

#### AFTER ANTIBIOTICS



<sup>m</sup>See Principles of Radiation Therapy (NHODG-D).

<sup>q</sup>Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated according to the [NCCN Guidelines for Diffuse Large B-Cell Lymphoma \(BCEL-1\)](#).

<sup>r</sup>If re-evaluation suggests slowly responding disease or asymptomatic nonprogression, continued observation may be warranted. RT can be considered as early as 3 mo after observation but can be prolonged to 18 mo (category 2B).

<sup>s</sup>If patient originally had clinical Stage I<sub>E2</sub> or Stage II<sub>E</sub>, early RT should be considered if there is no response to antibiotics.

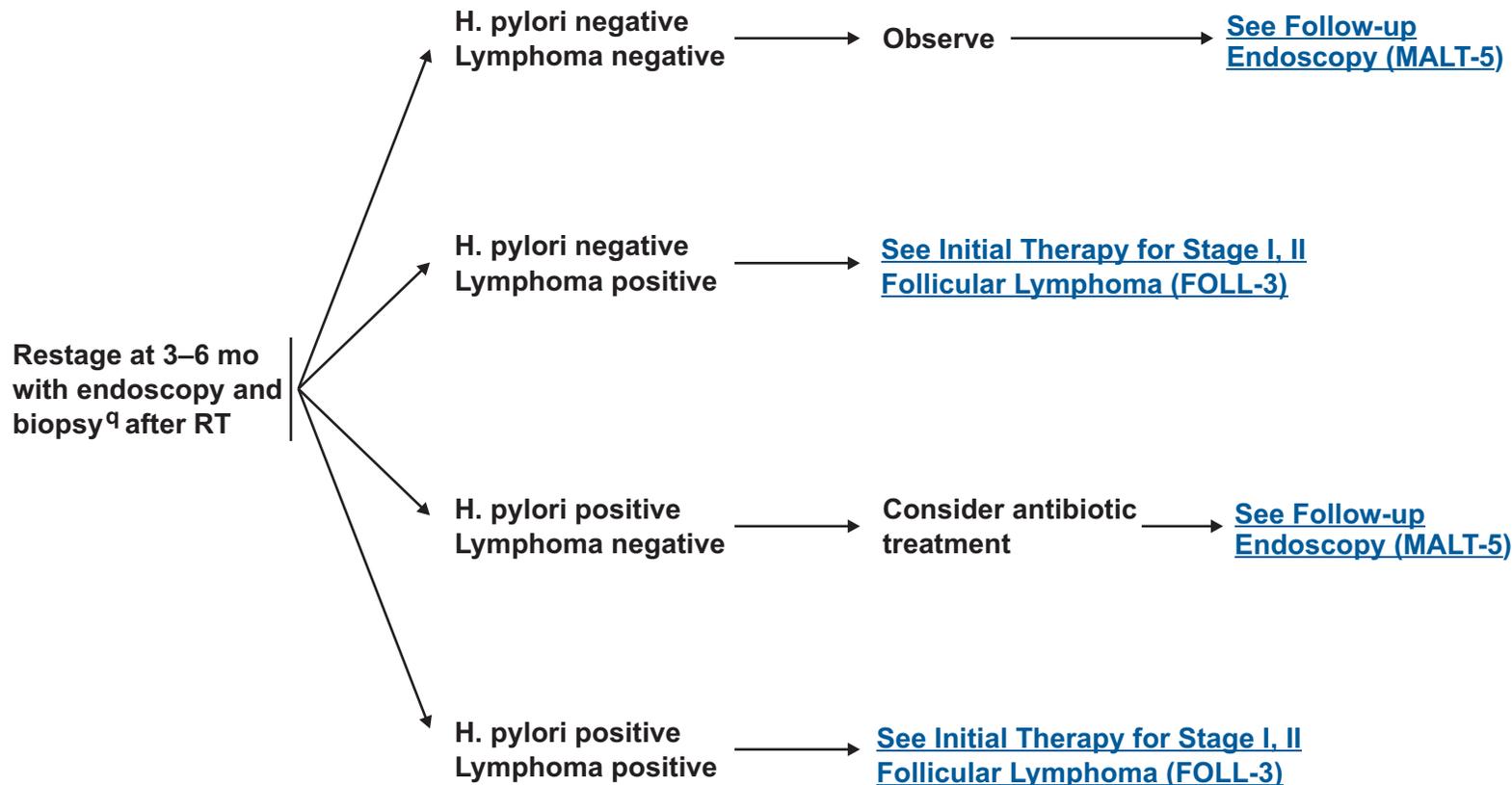
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#### 3- to 6-MONTH RESTAGING AND FOLLOW-UP ENDOSCOPY

AFTER RT

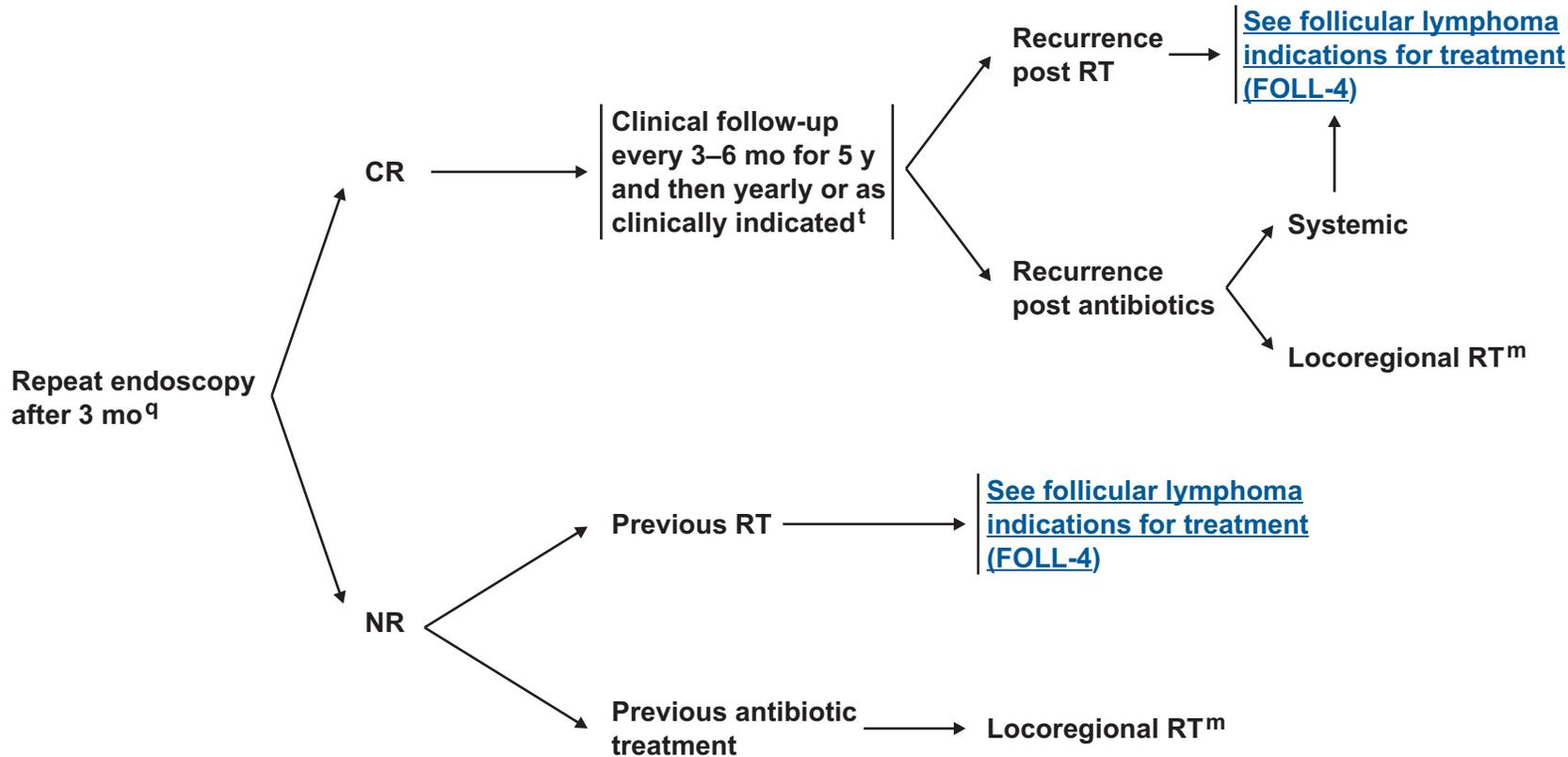
ADDITIONAL THERAPY



<sup>q</sup>Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated according to the [NCCN Guidelines for Diffuse Large B-Cell Lymphoma \(BCEL-1\)](#).

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#### FOLLOW-UP ENDOSCOPY



<sup>m</sup>See [Principles of Radiation Therapy \(NHODG-D\)](#).

<sup>q</sup>Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated according to the [NCCN Guidelines for Diffuse Large B-Cell Lymphoma \(BCEL-1\)](#).

<sup>t</sup>Optimal interval for follow-up endoscopy and imaging is not known. Follow-up endoscopy and imaging at NCCN Member Institutions is driven by symptoms.

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#### STAGING OF GASTRIC MALT LYMPHOMA: COMPARISON OF DIFFERENT SYSTEMS

Lugano Staging System for Gastrointestinal Lymphomas	Ann Arbor Stage	TNM Staging System Adapted for Gastric Lymphoma	Tumor Extension	
Stage I <sub>E</sub>	Confined to GI tract <sup>a</sup>			
	I <sub>E1</sub> = mucosa, submucosa	I <sub>E</sub>	T1 N0 M0	Mucosa, submucosa
	I <sub>E2</sub> = muscularis propria, serosa	I <sub>E</sub>	T2 N0 M0	Muscularis propria
		I <sub>E</sub>	T3 N0 M0	Serosa
Stage II <sub>E</sub>	Extending into abdomen			
	II <sub>E1</sub> = local nodal involvement	II <sub>E</sub>	T1-3 N1 M0	Perigastric lymph nodes
	II <sub>E2</sub> = distant nodal involvement	II <sub>E</sub>	T1-3 N2 M0	More distant regional lymph nodes
Stage II <sub>E</sub>	Penetration of serosa to involve adjacent organs or tissues	II <sub>E</sub>	T4 N0 M0	Invasion of adjacent structures
Stage IV <sup>b</sup>	Disseminated extranodal involvement or concomitant supradiaphragmatic nodal involvement	III <sub>E</sub>	T1-4 N3 M0	Lymph nodes on both sides of the diaphragm/distant metastases (eg, bone marrow or additional extranodal sites)
		IV	T1-4 N0-3 M1	

Yahalom J et al. Extranodal Marginal Zone B-cell Lymphoma of Mucosa-Associated Lymphoid Tissue (MALT lymphoma) in Mauch et al eds. Non-Hodgkin's Lymphomas. Philadelphia: Lippincott, 2004:352. (<http://www.com>)

<sup>a</sup>Single primary or multiple, noncontiguous.

<sup>b</sup>Involvement of multiple extranodal sites in MALT lymphoma appears to be biologically distinct from multiple extranodal involvement in other lymphomas, and these patients may be managed by treating each site separately with excision or RT. In contrast, cases with disseminated nodal involvement appear to behave more like nodal marginal zone lymphoma or like disseminated follicular lymphoma.

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#### DIAGNOSIS

##### ESSENTIAL:

- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- Adequate immunophenotyping to establish diagnosis<sup>c,d</sup>
  - ▶ IHC panel: CD20, CD3, CD5, CD10, BCL2, kappa lambda, CD21 or CD23, cyclin D1  
or
  - ▶ Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10

##### USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Molecular analysis to detect: antigen receptor gene rearrangements; MYD88 mutation status to differentiate WM versus MZL if plasmacytic differentiation present; PCR for t(11;18)
- Cytogenetics or FISH: t(11;18), t(11;14), t(3;14)
- FISH or PCR: t(14;18)

#### WORKUP

##### ESSENTIAL:

- Physical exam with performance status
- CBC, differential, platelets
- Comprehensive metabolic panel
- LDH
- Hepatitis B testing<sup>e</sup> if rituximab contemplated
- Hepatitis C testing
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

##### USEFUL IN SELECTED CASES:

- MUGA scan/echocardiogram if anthracycline or anthracenedione-based regimen is indicated
- Bone marrow biopsy ± aspirate
- Endoscopy with multiple biopsies of anatomical sites<sup>f</sup>
- PET-CT scan
- MRI
- Discussion of fertility issues and sperm banking
- SPEP

→ [See Initial Therapy \(NGMLT-2\)](#)

<sup>a</sup>Typical sites of extranodal marginal zone lymphoma other than the stomach include the following: bowel (small and large), breast, head and neck, lung, ocular adnexa, ovary, parotid, prostate, and salivary gland. Infectious agents have been reported to be associated with many nongastric sites, but testing for these agents is not required for management.

<sup>b</sup>This guideline pertains to noncutaneous; for primary cutaneous marginal zone lymphoma, [see CUTB](#).

<sup>c</sup>Typical immunophenotype: CD10-, CD5-, CD20+, CD23-/+, CD43-/+, cyclin D1-, BCL2 follicles.

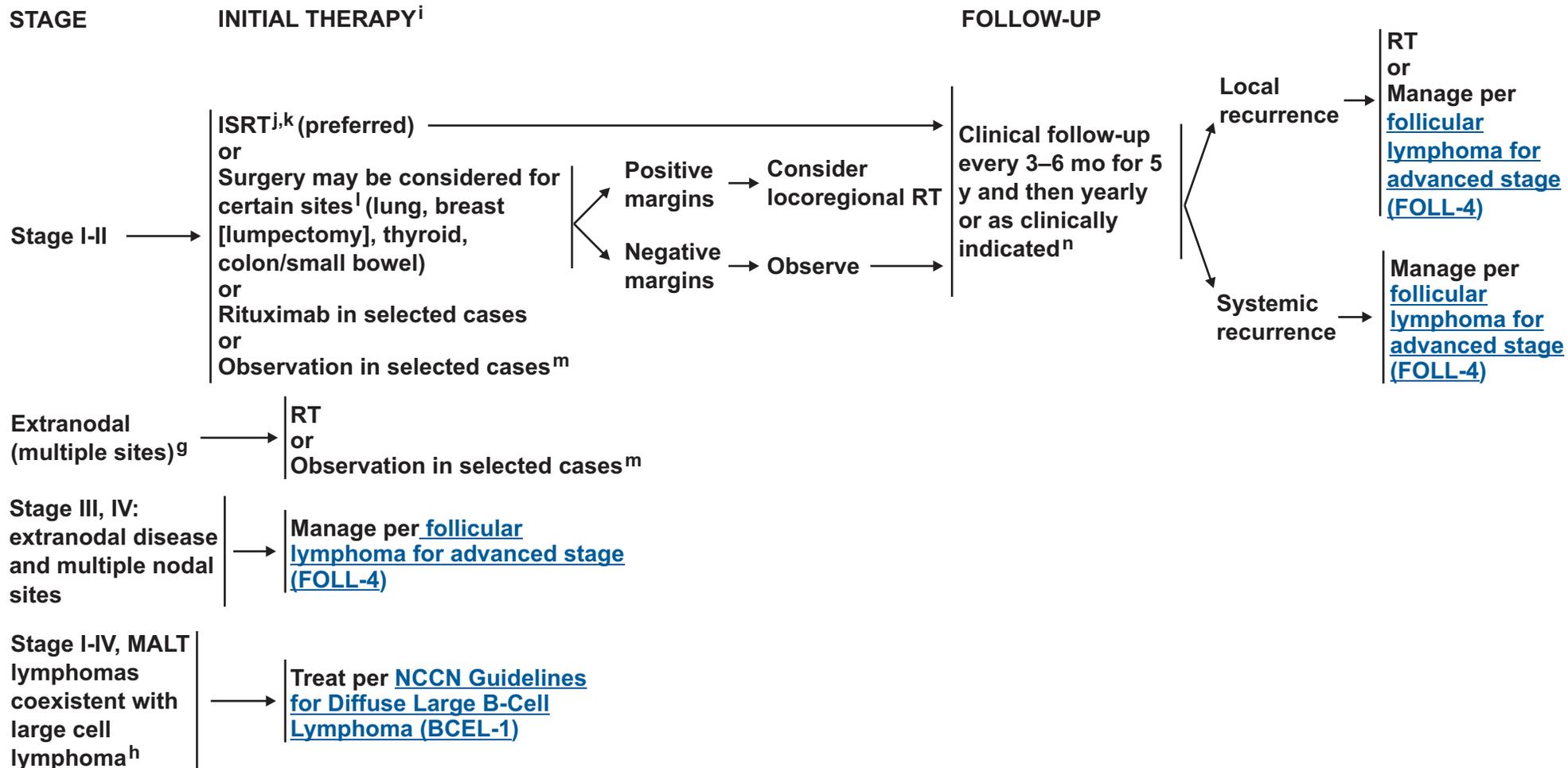
<sup>d</sup>[See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-cell and NK/T-cell Neoplasms \(NHODG-A\)](#).

<sup>e</sup>Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

<sup>f</sup>In cases where primary site is thought to be in head/neck or lungs, upper GI endoscopy should be considered.

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<sup>g</sup>Treatment of each site may be indicated (eg, bilateral conjunctiva) both at diagnosis and at relapse.

<sup>h</sup>DLBCL coexistent with MALT cell lymphoma is managed as DLBCL. [See NCCN Guidelines for Diffuse Large B-Cell Lymphoma \(BCEL-1\)](#).

<sup>i</sup>Based on anecdotal responses to antibiotics in ocular and cutaneous marginal zone lymphomas, some physicians will give an empiric course of doxycycline prior to initiating other therapy.

<sup>j</sup>Dose is site dependent with lower dose reserved for eye involvement.

<sup>k</sup>[See Principles of Radiation Therapy \(NHODG-D\)](#).

<sup>l</sup>Surgical excision for adequate diagnosis may be appropriate treatment for disease.

<sup>m</sup>Observation may be considered for patients whose diagnostic biopsy was excisional, or involved-field RT or systemic treatment could result in significant comorbidity.

<sup>n</sup>Follow-up includes diagnostic tests and imaging as clinically indicated.

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### DIAGNOSIS<sup>a</sup>

#### ESSENTIAL:

- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis. Histologic grading cannot be performed on an FNA.
- Adequate immunophenotyping to establish diagnosis<sup>b,c</sup>
  - IHC panel: CD20, CD3, CD5, CD10, BCL2, kappa/lambda, CD21 or CD23, cyclin D1 or
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10
- Pediatric nodal marginal zone lymphoma should be considered with localized disease in a young patient.

#### USEFUL UNDER CERTAIN CIRCUMSTANCES FOR CLARIFICATION OF DIAGNOSIS:

- Molecular analysis to detect: antigen receptor gene rearrangements; MYD88 mutation status to differentiate WM versus MZL if plasmacytic differentiation present; PCR for t(11;18)
- Cytogenetics or FISH: t(11;18), t(1;14), del(13q), del(7q)
- FISH or PCR: t(14;18)

<sup>a</sup>Nodal MZL is rare and occurs most commonly as spread from extranodal MALT; must also be distinguished from nodal FL, MCL, lymphoplasmacytic lymphoma, and CLL, all of which are more common.

<sup>b</sup>Typical immunophenotype: CD10-, CD5-, CD20+, CD23-/+, CD43-/+, and cyclin D1-, BCL2 follicles.

<sup>c</sup>See [Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms \(NHODG-A\)](#).

<sup>d</sup>Hepatitis B testing is indicated because of the risk of reactivation with

### WORKUP

#### ESSENTIAL:

- Physical exam with performance status
- CBC, differential, platelets
- Comprehensive metabolic panel
- LDH
- Hepatitis B testing<sup>d</sup> if rituximab contemplated
- Hepatitis C testing
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Bone marrow biopsy + aspirate to document clinical stage I-II disease<sup>e</sup>
- Evaluation to rule out extranodal primary sites
  - Neck nodes: ocular, parotid, thyroid, and salivary gland
  - Axillary nodes: lung, breast, and skin
  - Mediastinal/hilar nodes: lung
  - Abdominal nodes: splenic and GI
  - Inguinal/iliac nodes: GI and skin
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

#### USEFUL IN SELECTED CASES:

- MUGA scan/echocardiogram if anthracycline or anthracenedione-based regimen is indicated
- Additional imaging as appropriate
- PET-CT scan
- Discussion of fertility issues and sperm banking
- SPEP

immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

<sup>e</sup>Bilateral or unilateral provided core biopsy is >2 cm. If radioimmunotherapy is considered, bilateral cores are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. If observation is initial therapy, bone marrow biopsy may be deferred.

Manage per [NCCN Guidelines for Follicular Lymphoma \(FOLL-2\)](#)

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### DIAGNOSIS

#### ESSENTIAL:

- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.<sup>a</sup>
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.
- Adequate immunophenotyping to establish diagnosis<sup>b,c</sup>
  - IHC panel: CD20, CD3, CD5, CD10, BCL2, kappa/lambda, CD21 or CD23, cyclin D1, IgD, CD43, annexin A1; or
  - Cell surface marker analysis by flow cytometry (peripheral blood, bone marrow, or tissue): kappa/lambda, CD19, CD20, CD5, CD23, CD10, CD43, CD103

#### USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Molecular analysis to detect: antigen receptor gene rearrangements; MYD88 mutation status to differentiate WM versus MZL if plasmacytic differentiation present; *BRAF* mutation status to differentiate MZL from HCL by IHC or sequencing; PCR for t(11;18)
- Cytogenetics or FISH: CLL panel; t(11;18), t(11;14), del(7q)
- FISH or PCR: t(14;18)

<sup>a</sup>SMZL is most definitively diagnosed at splenectomy, since the immunophenotype is nonspecific and morphologic features on the bone marrow may not be diagnostic. However, the diagnosis of SMZL may be made on the basis of bone marrow ± peripheral blood involvement by small lymphoid cells with immunoglobulin (Ig) light chain restriction that lack characteristic features of other small B-cell neoplasms (CD5, CD10, cyclin D1). Plasmacytoid differentiation with cytoplasmic Ig detectable on paraffin sections may occur. In such cases, the differential diagnosis may include lymphoplasmacytic lymphoma. With a characteristic intrasinusoidal lymphocytic infiltration of the bone marrow, the diagnosis can strongly be suggested on bone marrow biopsy alone, if the immunophenotype is consistent.

### WORKUP

#### ESSENTIAL:

- Physical exam with performance status
- CBC, differential, platelets
- Comprehensive metabolic panel
- LDH
- Hepatitis B testing<sup>d</sup> if rituximab contemplated
- Hepatitis C testing
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Bone marrow biopsy ± aspirate
- SPEP and/or quantitative immunoglobulin levels
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

#### USEFUL IN SELECTED CASES:

- Additional imaging as appropriate
- PET-CT scan
- Discussion of fertility issues and sperm banking
- Immunofixation of blood (for elevated immunoglobulins or positive SPEP)
- Cryoglobulins
- Direct Coombs testing

→ [See Management \(SPLN-2\)](#)

<sup>b</sup>Typical immunophenotype: CD10-, CD5-, CD20+, CD23-/+, CD43-/+, and cyclin D1-, BCL2 follicles, annexin A1, CD103- (distinction from hairy cell leukemia) with expression of both IgM and IgD.

<sup>c</sup>[See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms \(NHODG-A\).](#)

<sup>d</sup>Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

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CLINICAL PRESENTATION

MANAGEMENT

Consider prophylaxis for tumor lysis syndrome (See [NHODG-B](#))

See monoclonal antibody and viral reactivation ([NHODG-B](#))

FOLLOW-UP

Asymptomatic, without progressive cytopenia, no splenomegaly

Observe

Hepatitis C positive

Hepatology consult

No contraindications for treatment of hepatitis

Appropriate treatment

CR/PR

No response

Contraindications for treatment of hepatitis

Clinical follow-up every 3-6 mo for 5 y and then yearly or as clinically indicated<sup>9</sup>

If progression of disease, manage per [NCCN Guidelines for Follicular Lymphoma for advanced stage \(FOLL-4\)](#)

Splenomegaly

Hepatitis C negative

Assess

- Cytopenias
- Symptoms

Splenectomy<sup>e</sup> or Rituximab<sup>f</sup>

No symptoms → Observe

<sup>e</sup>Pneumococcal and meningococcal vaccination should be given at least 2 weeks before splenectomy.

<sup>f</sup>Tsimberidou AM, Catovsky D, Schlette E, et al. Outcomes in patients with splenic marginal zone lymphoma and marginal zone lymphoma treated with rituximab with or without chemotherapy or chemotherapy alone. *Cancer* 2006;107:125-135.

<sup>9</sup>Follow-up includes diagnostic tests and imaging as clinically indicated.

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## Marginal Zone Lymphomas

Marginal zone lymphomas (MZLs) are a group of B-cell malignancies thought to originate from B lymphocytes that are normally present in the marginal zone of lymphoid follicles that can be found in the spleen, lymph nodes, and mucosal lymphoid tissues.<sup>1,2</sup> Three distinct subtypes of MZLs exist, which include extranodal MZL of mucosa-associated lymphoid tissue (MALT lymphoma), nodal MZL, and splenic MZL.<sup>3-5</sup> MZLs comprise about 10% of all non-Hodgkin's lymphomas (NHLs), with MALT lymphomas being the most common subtype (occurring in 7-8% of NHLs); nodal MZLs occur in <2% and splenic MZLs in <1% of NHLs.<sup>6</sup> Recent analysis from the SEER database suggested that survival outcomes were more favorable for patients with MALT lymphoma (5-year relative survival 89%) compared with those with splenic MZL (80%) or nodal MZL (76.5%).<sup>7</sup>

The etiology of MZLs has been associated with chronic immune stimulation due to infectious pathogens or inflammation; infection with *Helicobacter pylori* (*H. Pylori*) has been implicated in cases of gastric MALT lymphoma, and other pathogens such as *Chlamydia psittaci*, *Campylobacter jejuni*, *Borrelia burgdorferi*, and hepatitis C virus (HCV) have also been implicated in the putative pathogenesis of MZLs.<sup>1,4</sup> Positive HCV serology has been associated with MZLs (primarily splenic MZL) in about 30% of cases.<sup>8,9</sup> In addition, HCV positivity has also been reported in about 35% of patients with non-gastric MALT lymphomas.<sup>10</sup>

Since MZL are also characterized by clinical and pathological features that overlap with Waldenström's Macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL), it can be difficult to distinguish WM/LPL from MZLs in selected circumstances.<sup>11</sup> Recent studies have confirmed that the MYD88 L265P somatic mutation which is widely prevalent in

patients with WM/LPL could be useful in differentiating WM/LPL from other B-cell malignancies with overlapping clinical and pathological features.<sup>12-14</sup> In a retrospective study that analyzed the immunoglobulin heavy chain variable (*IGHV*) gene sequences and MYD88 mutation status in a series of 123 patients with a diagnosis of MZLs and WM/LPL, MYD88 mutation was found in 67% of patients with WM/LPL (18 of 27) compared to 4% of patients with splenic MZLs (2 out of 53), 7% of patients with MALT lymphomas (2 out of 28) and 0% of patients with nodal MZLs.<sup>13</sup> *IGHV* analysis clearly distinguished splenic MZLs and WM/LPL. Splenic MZLs were characterized by overrepresentation of *IGHV1-2* gene rearrangements with low or intermediate mutation rates whereas WM/LPL was associated with overrepresentation of *IGHV3-23* rearrangements and high mutation rates.<sup>13</sup> In selected circumstances when plasmacytic differentiation is present, MYD88 mutational analysis should be considered to differentiate MZLs from WM/LPL.

The following sections provide a brief summary of the diagnosis, workup, and treatment recommendations for the three subtypes of MZL: MALT lymphomas (gastric and non-gastric), nodal MZL, and splenic MZL.

### MALT Lymphomas

In MALT lymphomas, the gastrointestinal (GI) tract is the most common site of involvement (about 50% of MALT lymphomas) and within the GI tract, the stomach is the most common primary site (80-80% of gastric MALT lymphomas).<sup>4,15,16</sup> Common non-gastric sites of involvement in MALT lymphomas include the orbit (7-12%), lung (8-14%), and skin (9-12%).<sup>15-17</sup> MALT lymphomas tend to be indolent, with similar long-term outcomes reported between gastric and non-gastric subtypes. In a retrospective analysis of data from patients with MALT lymphomas

(N=108), the 10-year overall survival (OS) was not different between patients with gastric MALT lymphoma and non-gastric lymphoma (75% vs. 77%).<sup>16</sup> However, in this analysis, gastric MALT lymphoma was associated with longer time to progression (TTP) from start of treatment than non-gastric presentations (median TTP 8.9 years vs. 4.9 years;  $P=0.01$ ).<sup>16</sup> In a more recent retrospective study in patients with MALT lymphomas (N=98), gastric MALT lymphoma was associated with higher 3-year progression-free survival (PFS) compared with non-gastric cases (95% vs. 82%).<sup>18</sup> In another retrospective study of patients with non-gastric MALT lymphomas (N=180), the 5-year progression-free survival (PFS) and OS was 60% and 90%, respectively.<sup>17</sup> Although disease is localized in most patients with MALT lymphomas, about a third of patients present with disseminated disease; localized disease is more frequently observed with gastric MALT lymphomas than with non-gastric cases.<sup>17,19</sup> Bone marrow involvement has been reported in about 15 to 20% of MALT lymphomas.<sup>15,17,19</sup> In a retrospective analysis of patients with MALT lymphomas (N=158), similar long-term survival was observed between patients with disseminated and localized disease (10-year OS rate 80% in both cases).<sup>19</sup> Recent retrospective data, however, reported decreased PFS outcomes in patients with advanced MALT lymphomas compared with localized disease (3-year PFS rate 73% vs. 94%).<sup>18</sup>

A variety of chromosomal translocations have been implicated in the pathogenesis of MALT lymphomas.<sup>20</sup>  $t(11;18)$  is the most common translocation resulting in the formation of the chimeric fusion gene, *API2-MALT1* and is frequently detected in gastric and pulmonary MALT lymphomas.<sup>21,22</sup>  $t(1;14)$  results in the overexpression of BCL10 protein and it occurs in 1% to 2% of MALT lymphomas.<sup>23</sup> This translocation has been detected in MALT lymphomas of the stomach, lung and skin. Both  $t(11;18)$  and BCL10 overexpression are associated with locally

advanced disease, which is less likely to respond to *H. Pylori* eradication with antibiotic therapy.<sup>24</sup>  $t(14;18)$  results in the deregulated expression of *MALT1* gene and has been reported to occur in 15% to 20% of MALT lymphomas.<sup>22,25</sup> It is most frequently detected in MALT lymphomas of the liver, skin, ocular adnexa and the salivary gland.  $t(3;14)$  results in the upregulation of *FOXP1* gene and is associated with the MALT lymphomas of thyroid, ocular adnexa and skin.<sup>26</sup> The clinical significance of  $t(14;18)$  and  $t(3;14)$  is unknown.

### **Gastric MALT Lymphoma**

#### *Diagnosis*

Common clinical features of gastric MALT lymphoma include symptoms of dyspepsia, reflux, abdominal pain, nausea, or weight loss.<sup>1</sup> An endoscopic biopsy is required to establish the diagnosis of gastric MALT lymphoma, as a fine-needle aspiration is not adequate for diagnosis. Endoscopy may reveal erythema, erosions or ulcerations.<sup>1</sup> Adequate hematopathology review of biopsy material and immunophenotyping are needed to establish a diagnosis. The recommended markers for an immunohistochemistry (IHC) panel includes CD20, CD3, CD5, CD10, CD21 or CD23, kappa/lambda, CCND1, BCL2, and BCL6; the recommended markers for flow cytometry analysis include CD19, CD20, CD5, CD23, and CD10. The typical immunophenotype for MALT lymphoma is CD5-, CD10-, CD20+, CD23-/+ , CD43 -/+ , cyclin D1-, and BCL2 follicles-.

*H. pylori* infection has a critical role in the pathogenesis of gastric MALT lymphomas and its eradication can lead to tumor remission.<sup>1,27,28</sup> Therefore, staining for detection of *H. pylori* should be performed. However, *H. Pylori* infection is not evident in approximately 5-10% of patients with gastric MALT lymphomas and the translocation  $t(11;18)$  was reported to occur at a high frequency in *H. pylori*-negative patients

with gastric MALT lymphomas.<sup>29</sup> This chromosomal abnormality has been associated with disseminated disease and resistance to antibiotic treatment in patients with gastric MALT lymphoma.<sup>30,31</sup> Molecular analysis by PCR or FISH for the evaluation of t(11;18) is recommended. In some cases, molecular analysis for the detection of antigen receptor gene rearrangements and cytogenetic or FISH evaluation for t(3;14), t(1;14) and t(14;18), may also be useful.

#### Workup

The initial workup for patients with gastric MALT lymphoma is similar to the workup for other NHLs. A comprehensive physical examination should be performed with attention to non-gastric sites such as the eyes and skin, and performance status should be assessed. Laboratory evaluations should include a complete blood count with differentials and platelets, comprehensive metabolic panel, and measurement of serum LDH levels. Evaluation of bone marrow biopsy, with or without aspirates, may be useful under certain circumstances. Special aspects of the workup for gastric MALT lymphoma include direct endoscopic assessment of the GI tract and additional evaluation of the tumor specimen for the presence of *H.pylori*. If the *H.pylori* infection status is negative based on histopathology evaluation, other non-invasive testing methods may be employed to confirm negative status (i.e., stool antigen test, urea breath test, or blood antibody test) or to establish non-invasive surrogates for upper GI endoscopy. Non-diagnostic atypical lymphoid infiltrates that are *H.pylori* positive should be re-biopsied to confirm or exclude lymphoma prior to treatment of *H.pylori*. Testing for HBV is indicated for patients being considered for treatment with rituximab-containing regimens due to the risk of viral reactivation. Testing for HCV may be useful in selected cases, and given its association with other MZLs and demonstrated importance as a therapeutic target, HCV testing should be performed.

Appropriate imaging studies include CT scan with contrast of diagnostic quality for the chest, abdomen and pelvis. At some NCCN institutions, endoscopic ultrasound (EUS) is used to complement conventional endoscopy at the time of the initial workup and at follow-up. EUS also provides information regarding the depth of involvement in the gastric wall which provides essential information for some of the currently used staging systems; it also helps to distinguish benign lymphoid aggregates from lymphoma associated with *H. pylori* infection.<sup>32</sup> In addition, EUS staging is also useful in predicting the efficacy of *H. Pylori* eradication therapy.<sup>33,34</sup> EUS with multiple biopsies of anatomic sites is particularly useful for *H. pylori*-positive patients because the likelihood of tumor response to antibiotic therapy is related to depth of tumor invasion. A MUGA scan/echocardiogram should be performed if the patient is being considered for treatment with regimens containing anthracycline or anthracenedione.

Staging can remain a challenge, as it is not standardized for MALT lymphomas; because CT scans may not be optimal for the detection of occult extranodal disease, it is unknown whether staging for MALT lymphomas should follow standard staging systems (e.g., Ann Arbor system) used for nodal-type lymphomas.<sup>1,2</sup> Several different staging systems have been used for gastric MALT lymphomas. The widely used Lugano Staging System for GI lymphomas is a modification of the original Ann Arbor staging system.<sup>35</sup> In the Lugano Staging, stage I refers to disease confined to the GI tract (single primary or multiple non-contiguous lesions; in Stage I<sub>1</sub>, the infiltration is limited to mucosa with or without submucosa involvement, and in Stage I<sub>2</sub>, infiltration is present in the muscularis propria, serosa or both. Stage II refers to disease extending into the abdomen from the primary GI site; in Stage II<sub>1</sub>, local (perigastric) lymph nodes are involved, and in Stage II<sub>2</sub>, distant lymph nodes are involved. Stage IIE refers to lymphoma penetration of

serosa to involve adjacent organs or tissues; if both the lymph nodes and adjacent organs are involved, the above subscripts (1 or 2) for lymph node involvement may be added to the designation. Ann Arbor stage III has been removed, and stage IV in the Lugano Staging refers to disseminated extranodal involvement or concomitant supradiaphragmatic nodal involvement. The TNM staging system corresponds to the staging in gastric cancer and the depth of the lymphoma infiltration is measured by EUS. Involvement of multiple extranodal sites in MALT lymphoma appears to be biologically distinct from multiple extranodal involvements in other lymphomas, and these patients may be managed by treating each site separately with excision or RT or with rituximab. By contrast, cases with disseminated nodal involvement appear to behave more like nodal MZL or like disseminated follicular lymphoma (FL).

#### *Treatment Options Based on Clinical Stage*

The treatment approach for gastric MALT lymphomas depends on the *H. pylori* infection status and disease stage. *H. pylori* infection plays a central role in the pathogenesis of some cases of gastric MALT lymphoma. The efficacy of antibiotic therapy for the treatment for gastric MALT lymphoma has been evaluated in a number of retrospective and prospective studies.<sup>36-43</sup> In these studies, *H. pylori* eradication with antibiotic therapy resulted in lymphoma regression in 70-95% of patients with localized disease. In studies with long-term follow up, the 5-year OS rate with *H. pylori* eradication therapy was 90-95%, with a 5-year disease-free survival (DFS) or event-free survival (EFS) rate of 75-80%.<sup>38,40,42</sup> However, there is increasing evidence that late relapses can occur after antibiotic treatment and a long duration of follow-up is appropriate. If there is evidence of t(11;18), t(1;14) or t(14;18), treatment of the *H. pylori* infection with antibiotics may be ineffective; these patients should be considered for alternative therapy, though a

trial of antibiotics is still warranted in some patients.<sup>30</sup> *H. pylori* eradication therapy generally comprises a proton pump inhibitor (e.g., omeprazole or other agents such as lansoprazole or rabeprazole) along with a combination of antibiotics including clarithromycin and amoxicillin (or metronidazole for patients allergic to penicillin).<sup>1</sup>

Radiation therapy (RT) has been evaluated in patients with both gastric and non-gastric MALT lymphomas. In a retrospective study of patients who received treatment for localized MALT lymphomas (N=103; lymphoma of the stomach, n=17), the CR rate was 99% in the group of patients treated with involved field RT (IFRT; dose range 30-35 Gy) only (n=85).<sup>44</sup> The 5-year DFS and OS rates were 77% and 98%, respectively. The median follow up for patients treated with RT alone was 4.9 years. Among the patients with gastric MALT lymphoma or primary involvement of the thyroid, none had relapsed at the time of last follow up (failure-free survival rate 100%).<sup>44</sup> Long-term outcomes from this study with a median follow up of 7 years showed that patients with localized MALT lymphoma who received IFRT alone (n=144; dose range 25-35 Gy) had an estimated 10-year relapse-free rate and OS rate of 74% and 89%, respectively.<sup>45</sup> The estimated 10-year cancer-specific OS rate was 98%. Similar to the previous report,<sup>44</sup> outcomes were more favorable for patients with gastric or thyroid MALT lymphoma (n=46); the 10-year relapse-free rate for these patients was 89% compared with 68% for patients with lymphomas in other sites ( $P=0.004$ ).<sup>45</sup>

In another retrospective study in patients with localized gastric MALT lymphoma (N=115), initial therapy with RT alone (n=56) resulted in a CR rate of 96% and a 10-year cancer-specific OS rate of 94%.<sup>46</sup> Several studies suggested that RT may preclude the need for surgical resection and that surgery does not offer an advantage over other treatment modalities. In the randomized controlled study in patients with

localized gastric MALT lymphomas (N=241), the 10-year EFS rates for the groups randomized to treatment with surgery (n=80), RT (n=78), and chemotherapy (n=83) were 52%, 52%, and 87%, respectively ( $P<0.01$ ).<sup>47</sup> The median follow up in this study was 7.5 years. The 10-year OS rate was not significantly different between the groups treated with surgery, RT or chemotherapy (80% vs. 75% vs. 87%, respectively).<sup>47</sup> In an analysis of registry data from a German multicenter study in patients with localized gastric lymphomas, outcomes were compared between patients treated with RT alone and those treated with combined surgery and RT.<sup>48</sup> In the subgroup of patients with indolent gastric lymphomas (gastric MALT lymphomas, n=151), extended field RT (total dose 30 Gy followed by 10 Gy boost) alone resulted in an EFS and OS rate of 88% and 93%, respectively, after a median of 42 months of observation. These outcomes were not significantly different from those of patients with gastric MALT lymphomas who received combined modality therapy with surgery and RT (EFS and OS rates 72% and 82.5%, respectively).<sup>48</sup> This study had also included patients with gastric MALT lymphomas who experienced treatment failure with *H. pylori* eradication therapy. In a small study that evaluated RT alone (median total dose 30 Gy; range, 28.5-43.5 Gy) in patients with gastric MALT lymphoma without evidence of *H. pylori* or with persistent disease after *H. pylori* eradication therapy (N=17), the CR rate was 100% and the EFS rate was 100% after a median follow up of 27 months.<sup>49</sup> Long-term follow up data from other studies suggest that RT is an effective treatment modality in gastric MALT lymphoma after failure with *H. pylori* eradication therapy.<sup>42,46</sup> In the subgroup of patients with gastric MALT lymphomas who were unresponsive to *H. pylori* eradication therapy and underwent second-line therapy with RT (n=10) or single-agent chemotherapy with cyclophosphamide (n=12), the CR rate was 80% and 83%, respectively; the estimated 3-year OS (from start of second-line therapy) was 90% and 88%, respectively.<sup>42</sup> In

a retrospective analysis of data from patients who received RT following treatment failure with *H. pylori* eradication therapy (n=35), the CR rate was 89% and the 5-year cause-specific OS rate was 93%.<sup>46</sup>

Immunotherapy with the anti-CD20 monoclonal antibody rituximab has also been evaluated in the clinical setting of failure with *H. pylori* eradication therapy. A prospective study evaluated the activity of standard-dose rituximab in patients with gastric MALT lymphoma (N=27) relapsed/refractory to *H. pylori* eradication therapy or not eligible for eradication therapy (i.e., *H. pylori* negative disease).<sup>50</sup> The majority of patients (81%) had stage I or II<sub>1</sub> disease (Lugano Staging System). The ORR with rituximab was 77% with a CR rate of 46%; at a median follow up of 28 months from start of treatment, all patients were alive and 54% of patients were disease free.<sup>50</sup>

Chemotherapy (single agent or combination regimens) has been evaluated in patients with MALT lymphomas. In an early study of single-agent therapy with the alkylating agents chlorambucil or cyclophosphamide (given orally for 12-24 months) in patients with primarily gastric MALT lymphoma (N=24; advanced stage, n=7), CR was achieved in 75% of patients.<sup>51</sup> In a prospective study that evaluated the purine analog cladribine in patients with MALT lymphoma (N=27; gastric lymphoma, n=19), CR was achieved in 84% of patients.<sup>52</sup> Patients with *H. pylori* positive localized gastric disease underwent eradication therapy and were only enrolled if unresponsive to *H. pylori* eradication treatment. All patients with gastric MALT lymphoma treated with cladribine (n=18) achieved a CR whereas only 43% with non-gastric lymphoma achieved a CR. At a median follow up of 80 months, 84% of patients remained alive.<sup>53</sup> DFS at 6.7 years was 68.5% for all patients, and was higher for patients with gastric MALT lymphoma compared with those with extra-gastric lymphoma (78.5% vs. 33%).<sup>53</sup> Combination chemotherapy with mitoxantrone, chlorambucil and

prednisone (MCP) was retrospectively evaluated in patients with primarily advanced MALT lymphoma (N=15; gastric lymphoma, n=5 only).<sup>54</sup> Among the 5 patients with gastric MALT lymphoma (all were stage I or II), the MCP regimen induced a response in all patients, including a CR in 3 patients who had failed prior *H. pylori* eradication therapy, and a CR in 1 patient who received concurrent *H. pylori* eradication therapy. None of the patients have relapsed after a median follow up of 16 months.<sup>54</sup>

Several studies have evaluated chemoimmunotherapy combination regimens that incorporate rituximab in the treatment of MALT lymphomas.

A retrospective study evaluated rituximab combined with cyclophosphamide, doxorubicin (or mitoxantrone), vincristine, and prednisone (R-CHOP/R-CNOP) in patients with relapsed MALT lymphoma (N=26).<sup>55</sup> CR was achieved in 77% of patients. All patients were alive after a median follow up of 19 months, with 22 patients having ongoing remission.<sup>55</sup> A phase II study evaluated the chemoimmunotherapy combination of fludarabine and rituximab in patients with previously untreated MALT lymphoma (N=22; gastric lymphoma, n=12).<sup>56</sup> Among evaluable patients with gastric MALT lymphoma (n=11), the CR rate was 100% and the 2-year PFS rate was 100%. Another phase II study evaluated a different purine analog cladribine in combination with rituximab in patients with MALT lymphoma (N=40; gastric lymphoma, n=21).<sup>57</sup> The ORR was 81% with CR in 58% of patients. After a median follow up of 17 months, 88% of patients were alive. In the subgroup with gastric MALT, the ORR was 86% with a CR in 76% of patients.<sup>57</sup>

In a non-randomized observational study in patients with gastric MALT lymphoma (N=49), chlorambucil combined with rituximab resulted in

improved remission rates at week 25 compared with rituximab alone (93% vs. 81%); interestingly, this apparent benefit with the combined regimen over rituximab alone was observed in the subgroup with t(11;18) (remission rate at week 25: 100% vs. 66%) but not among t(11;18)-negative patients (66% vs. 92%).<sup>58</sup>

The international randomized IELSG-19 trial evaluated the combination of chlorambucil with rituximab in comparison to chlorambucil alone in patients with MALT lymphoma not previously treated with systemic anticancer therapy.<sup>59</sup> Eligible patients included those who were not responding to or not suitable for local therapy. Final data analysis was conducted in patients treated with chlorambucil alone (n=113) and chlorambucil combined with rituximab (n=114). The combination regimen resulted in higher CR rates (78% vs. 65%) and improved 5-year EFS (68% vs. 50%;  $P=0.002$ ), while the ORR (90% vs. 87%), 5-year PFS (71% vs. 62%) and OS rate (89% in both arms) were not significantly different.<sup>59</sup>

A multicenter phase II trial is investigating the combination of bendamustine and rituximab in patients with previously untreated MALT lymphoma (N=60; gastric lymphoma, n=20).<sup>60</sup> After 3 cycles of combination therapy, the ORR was 100% and CR rate was 76%; gastric lymphoma was associated with a higher CR rate compared with non-gastric disease (90% vs. 64%). The CR rate after completion of treatment was 98%, with most patients (85%) requiring only 4 or fewer cycles of therapy to achieve a CR. After a median follow up of 16 months, all patients remain relapse free and 1 patient died due to neurologic causes.<sup>60</sup>

The proteasome inhibitor bortezomib was evaluated in a phase II study in patients with relapsed/refractory MALT lymphoma (N=32; gastric lymphoma, n=14; median 2 prior therapies).<sup>61</sup> Among evaluable patients

(n=29), the ORR was 48% with a CR rate of 31%. After a median follow up of 24 months, 5 patients died, including 2 deaths due to disease progression.<sup>61</sup>

Although chemotherapy regimens may be active in patients with MALT lymphomas, long-term data from a larger group of patients are needed to evaluate their role in the management of localized disease. The international randomized LY03 trial of chlorambucil versus observation following *H. pylori* eradication in patients with localized gastric MALT lymphoma (N=110) showed no difference between study arms with regards to recurrence/progression rate, PFS, or OS outcomes.<sup>62</sup> Therefore, in the absence of data showing benefits with chemotherapy, localized gastric MALT lymphoma should be treated with *H. pylori* eradication therapy or RT, as appropriate. Chemotherapy regimens may be considered for patients with relapsed/refractory disease following RT or for those with advanced, systemic disease.<sup>63</sup>

#### NCCN Recommendations for Stage I-II

Antibiotic therapy in combination with a proton pump inhibitor to block gastric acid secretion is recommended for *H. Pylori*-positive. Patients who are *H. Pylori*-positive with t(11;18) could also be treated with antibiotic therapy to eradicate *H. Pylori* infection. However, since t(11;18) is a predictor for lack of response to antibiotic therapy, these patients should be considered for alternative therapy for lymphoma as described for patients who are *H. pylori*-negative. ISRT is the preferred treatment option for patients with *H. pylori* negative disease (negative status confirmed by both histology and blood antibody test). Rituximab is an option for patients with contraindications to RT.<sup>50</sup>

Patients treated with antibiotic therapy for *H. pylori* eradication should be restaged with endoscopy and biopsy after 3 months following therapy. Patients with stage IE2 or stage IIE disease with involvement

of submucosa or regional lymph nodes are much less likely to respond to antibiotic therapy. In symptomatic patients after antibiotic therapy, restaging can be done earlier than 3 months and RT may be considered earlier. Patients with responsive disease (*H. pylori* negative and lymphoma negative) can be observed. Patients who are *H. pylori* negative with persistent or recurrent lymphoma are treated with RT, if they are symptomatic. Asymptomatic patients can be observed for another 3 months; alternatively, locoregional RT can be considered as early as 3 months after observation but observation can be prolonged for up to 18 months (category 2B). If the patient initially had clinical stage I<sub>2</sub> or stage IIE disease, early RT should be considered if the lymphoma does not regress with antibiotic therapy. Patients with persistent *H. pylori* and regressing or stable lymphoma are treated with second-line antibiotics. Lastly, patients who are *H. pylori* positive with progressive or symptomatic lymphoma should be treated with RT and second-line antibiotics.

Patients treated with initial RT should be restaged with endoscopy and biopsy after 3-6 months following RT. Patients with responsive disease (*H. pylori* negative and lymphoma negative) can be observed. Antibiotic treatment can be considered for patients with persistent *H. pylori* and regressing lymphoma. However, patients with persistent lymphoma (regardless of presence of *H. pylori*) following RT should be managed according to recommendations for FL contained in these NCCN Guidelines for NHL.

Following observation or additional therapy with antibiotic therapy or RT (as discussed above), patients are again evaluated with endoscopy and biopsy after 3 months. The biopsy should rule out evidence of large-cell transformation. Any area of DLBCL should be treated according to recommendations for DLBCL in the NCCN Guidelines for NHL. For patients with a CR, clinical follow-up with

physical examination and laboratory assessment should be performed every 3-6 months for 5 years and then yearly thereafter (or as clinically indicated). The optimal interval for follow-up endoscopy and imaging is not known. At the present time, follow-up endoscopy and imaging at NCCN institutions are performed as clinically indicated based on symptoms. Patients with no response to second-line RT or recurrence following an initial CR should be treated with systemic therapy according to the guidelines for FL. Locoregional RT is indicated for patients with no response to second-line antibiotic therapy.

#### *NCCN Recommendations for Stage III or IV*

In patients with advanced stage disease (which is uncommon), treatment is similar to that described for patients with advanced stage FL. As with FL, asymptomatic patients without indications for treatment are monitored without therapy. The decision to treat is guided by end-organ dysfunction or the presence of symptoms (such as GI bleeding, early satiety), bulky disease at presentation, steady progression of disease, or patient preference. For patients with indications for treatment, enrollment in clinical trial is recommended given the incurability of advanced disease with conventional regimens. In the absence of suitable clinical trials, treatment may include chemoimmunotherapy or locoregional RT (30 Gy). Surgical resection is generally limited to specific clinical situations such as life-threatening hemorrhage. Although disease control is excellent with total gastrectomy, the long-term morbidity has precluded routine surgical resection. If there is evidence of recurrence (by endoscopy) following initial induction therapy, patients should be managed according to the FL guidelines.

#### **Non-gastric MALT Lymphomas**

MALT lymphomas can arise from a large number of non-gastric sites such as the bowel (small and large), breast, lung, ocular adnexa, ovary,

prostate, parotid, salivary glands and other head and neck regions.<sup>17</sup> The most common sites of presentation include the parotid and salivary glands (18-26%), skin (12-26%), conjunctiva/orbit (7-14%), head and neck (11%), lung (8-9%), thyroid (6%) and breast (2-3%).<sup>17,64</sup> Infectious pathogens (e.g., *Chlamydia psittaci*, *Campylobacter jejuni*) have been associated with MALT lymphomas of non-gastric sites<sup>4</sup> but testing for these pathogens is not required for disease workup or management.

#### *Diagnosis*

Adequate hematopathology review of biopsy materials and immunophenotyping are needed to establish a diagnosis. The recommended markers for an IHC panel include CD20, CD3, CD5, CD10, CD21 or CD23, kappa/lambda, CCND1, and BCL2; the recommended markers for flow cytometry analysis include CD19, CD20, CD5, CD23, and CD10. The typical immunophenotype for MALT lymphoma is CD5-, CD10-, CD20+, CD23-/+ , CD43 -/+, cyclin D1-, BCL2-. Molecular analysis to detect antigen receptor gene rearrangement or t(11;18) may be useful in certain cases. In addition, cytogenetics or FISH for t(11;18) t(3;14), t(11;14) and t(14;18) may also be considered under certain circumstances.

#### *Workup*

The workup for non-gastric MALT lymphoma is similar to the workup for other NHLs. A comprehensive physical examination should be performed and performance status should be assessed. Laboratory evaluations should include a complete blood count with differentials and platelets, comprehensive metabolic panel, and measurement of serum LDH levels. Evaluation of bone marrow biopsy, with or without aspirates, may be useful for patients with multifocal disease. In addition, endoscopy with multiple biopsies of anatomical sites may be useful in selected cases. Appropriate imaging studies include CT scan (with contrast of diagnostic quality) of the chest, abdomen and pelvis. A

MUGA scan/echocardiogram should be performed if the patient is being considered for treatment with regimens containing anthracycline or anthracenedione. Testing for hepatitis B virus is indicated for patients being considered for treatment with rituximab-containing regimens due to the risk of viral reactivation with chemoimmunotherapy. Testing for HCV may be useful in selected cases.

### *Treatment Options*

As discussed above in the section for 'Gastric MALT Lymphomas', RT alone has been shown to be an effective treatment strategy for both localized gastric and non-gastric MALT lymphomas. In the long-term follow up from a retrospective study in patients with localized MALT lymphomas treated with RT with or without chemotherapy (N=167; non-gastric lymphomas, n=142), the group who received IFRT alone (n=144; dose range 25-35 Gy; 25 Gy for orbit) had an estimated 10-year relapse-free rate and OS rate of 74% and 89%, respectively.<sup>45</sup> The 10-year relapse-free rates for patients with primary involvement of the thyroid (n=21), salivary gland (n=28), and orbital adnexa (n=71) were 95%, 68%, and 67%, respectively.<sup>45</sup>

Other treatment modalities such as chemotherapy (alone or with RT) or surgery (alone or with RT and/or chemotherapy) have been evaluated. In a retrospective study in patients with non-gastric MALT lymphomas (N=180; Ann Arbor stage IV in 27%), patients were treated with chemotherapy (n=78; with or without RT), RT alone (n=41), or surgery (n=68; with or without RT and/or chemotherapy).<sup>17</sup> More than half of patients with early-stage disease were treated with RT (55%; with or without other therapies), including RT alone in 30%; surgery or systemic chemotherapy (with or without other therapies, in both cases) was employed in 42% (surgery alone in 17%) and 31%, respectively. Among patients with advanced disease (stage IV), the large majority were treated with systemic chemotherapy (75.5%; with or without other

therapies); RT alone was used in only 4% of these patients. Surgery (with or without other therapies) was employed in 26.5% of patients with advanced disease, including 10% who received surgery alone.<sup>17</sup> Among evaluable patients (n=174), the ORR to treatment was 93% with a CR rate of 77%. Among patients who received chemotherapy, the ORR and CR rates were 92% and 72%, respectively. After a median follow up of 3.4 years, the estimated 5-year PFS and OS rates were 60% and 90%, respectively. The 5-year PFS and OS rates were both 100% for the subgroup of patients with primary involvement in the conjunctiva (n=18) and thyroid (n=10). In patients with primary disease in the orbit (n=13), however, the corresponding outcomes were 23% and 80%, respectively. For patients with primary disease in the salivary gland (n=46), the 5-year PFS and OS rates were 67% and 97%; for the patients with primary disease in the skin (n=22), the corresponding rates were 53% and 100%, respectively.<sup>17</sup>

In another retrospective study in patients with non-gastric MALT lymphomas (N=208; Ann Arbor stage III-IV in 44%), patients were treated with chemotherapy alone (45%; about half received single-agent alkylating agent while other received combination therapy), surgery (21%), or RT (19%).<sup>64</sup> The ORR to treatment was 90% with a CR rate of 73%. The ORR among patients treated with chemotherapy, RT, or surgery were 65%, 76%, and 90%, respectively. After a median follow up of 2.7 years, the median EFS rate was 2.4 years; the estimated 5-year EFS and OS rates were 37% and 83%, respectively.<sup>64</sup> Among patients with primary disease in the skin (n=55), the 5-year EFS and OS rates were 44% and 100%, respectively. Among patients with primary disease in the salivary glands (n=38), the 5-year EFS and OS rates were 30% and 86%, respectively; for patients with disease in the orbit/conjunctiva (n=30), the corresponding rates were 49% and 100%, respectively. As would be expected, 5-year OS rates were significantly

higher among patients with Ann Arbor stage I-II disease compared with those with stage III-IV disease (94% vs. 69%;  $P=0.001$ ). On multivariate analysis, bone marrow involvement was the only significant independent predictor of inferior outcomes for both EFS and OS.<sup>64</sup>

Rituximab either alone or in combination with chemotherapy has also been evaluated in patients with previously untreated or relapsed non-gastric MALT lymphoma. The IELSG evaluated the clinical activity of single agent rituximab in a phase II study in patients with untreated as well as relapsed MALT lymphomas (35 patients; 15 patients with gastric MALT lymphoma and 20 patients with non-gastric MALT lymphoma).<sup>65</sup> Among patients with non-gastric MALT lymphoma, treatment with rituximab resulted in an ORR of 80% (55% CR and 25% PR). For the entire study population, the ORR was significantly higher in the chemotherapy-naïve patients than in previously treated patients (87% and 45% respectively;  $P = .03$ ).

A phase II study evaluated the chemoimmunotherapy combination of fludarabine and rituximab in patients with previously untreated MALT lymphoma ( $N=22$ ).<sup>56</sup> In the primary non-gastric MALT subgroup ( $n=10$ ), the ORR was 100% with a CR rate of 80%; PFS at 2 years was 89% in this subgroup. Another phase II study evaluated a different purine analog cladribine in combination with rituximab in patients with MALT lymphoma ( $N=40$ ).<sup>57</sup> In the subgroup with primary non-gastric MALT ( $n=19$ ), the ORR was 74% with a CR in 37% of patients. The CR rate was lower than that reported for the subgroup with primary gastric MALT (76%).<sup>57</sup>

In the international randomized IELSG-19 trial that compared chlorambucil alone with the combination of chlorambucil and rituximab in patients with MALT lymphoma not previously treated with systemic anticancer therapy, CR rates, EFS, PFS, and OS rates were not

significantly different between patients with primary gastric and non-gastric lymphoma in either treatment arm.<sup>59</sup> In the multicenter phase II trial that investigated the combination of bendamustine with rituximab in patients with previously untreated patients with MALT lymphoma ( $N=60$ ), the CR rate was 64% in the subgroup of patients with primary non-gastric lymphoma ( $n=35$ ).<sup>60</sup>

#### *NCCN Recommendations*

ISRT (24-30 Gy) is the preferred treatment for patients with stage I-II disease. RT dose is site dependent, with lower doses usually reserved for orbital involvement. Rituximab is included as an option for selected patients. RT or observation is appropriate for patients with extranodal involvement. Based on anecdotal responses to antibiotics in ocular and cutaneous MZLs, some physicians may give an empiric course of doxycycline prior to initiating other therapy. Observation may be considered for patients whose diagnostic biopsy was excisional or in whom RT or systemic treatment could result in significant morbidity. For patients with stage I-II disease, surgical excision for adequate diagnosis may be appropriate treatment for certain sites of disease (e.g., lung, thyroid, colon, small intestine, and breast). If there is no residual disease following surgery, patients can be observed; for patients with positive margins post-surgery, locoregional RT should be considered.

Clinical follow-up (including repeat diagnostic tests and imaging based on the site of disease and as clinically indicated) should be conducted every 3-6 months for 5 years and then annually thereafter (or as clinically indicated). Local recurrence following primary treatment may be treated with RT or managed according to recommendations for advanced-stage FL. Systemic recurrence should be managed according to the recommendations for advanced FL, as should patients presenting with stage III-IV disease (extranodal disease and multiple nodal sites) at

diagnosis. MALT lymphomas coexistent with large-cell lymphoma should be managed according to the recommendations for DLBCL.

### Nodal Marginal Zone Lymphoma

In patients with nodal MZL, peripheral lymphadenopathy is present in nearly all cases (>95%); thoracic or abdominal lymph nodes may also be involved in about 50% of cases.<sup>15,66</sup> In addition, involvement of MZL in the bone marrow and peripheral blood may be seen in about 30-40% and 10% of cases, respectively.<sup>15,66</sup> Although advanced-stage disease is observed in about two-thirds of newly diagnosed nodal MZL, most tumors are non-bulky and B symptoms are present in only about 15% of cases.<sup>15,66</sup> The disease course of nodal MZL tends to be indolent, but long-term outcomes appear less favorable compared with MALT lymphomas. In a retrospective analysis of data from patients with MZL, the OS rate was lower in the subgroup of patients with nodal MZL (n=14) compared with those with MALT lymphoma (n=62)(56% vs. 81%); the 5-year failure-free survival rate was also lower among patients with nodal MZL (28% vs. 65%).<sup>15</sup> In a separate retrospective study in patients with non-MALT-type MZL (N=124), the median TTP (from start of treatment) and median OS was 1.3 years and 5.5 years, respectively, among the subgroup of patients with nodal MZL (n=37).<sup>66</sup>

#### Diagnosis

Adequate hematopathology review of biopsy materials and immunophenotyping are needed to establish a diagnosis. Nodal MZL is rare and occurs most commonly as disseminated disease from extranodal MALT lymphoma. The recommended markers for an IHC panel include CD20, CD3, CD5, CD10, CD21 or CD23, kappa/lambda, CCND1, and BCL2; the recommended markers for flow cytometry include CD19, CD20, CD5, CD23, and CD10. The typical immunophenotype for nodal MZLs is CD5-, CD10-, CD20+, CD23-/+ , CD43 -/+ , cyclin D1-, BCL2-. Pediatric nodal MZL should be considered

with located disease in young patients. Molecular analysis to detect antigen receptor gene rearrangement or t(11; 18) (by PCR) may be useful in certain cases. In addition, cytogenetics or FISH for t(11;18) t(3;14), t(11;14) , t(14;18), del(13q) and del(7q) may also be considered under certain circumstances.

#### Workup

The workup for nodal MZLs is similar to the workup for other NHL subtypes. A comprehensive physical examination should be performed and performance status should be assessed. Laboratory evaluations should include a complete blood count with differentials and platelets, comprehensive metabolic panel, and measurement of serum LDH levels. Evaluation of bone marrow biopsy with aspirates should be performed to document clinical stage I-II disease. Bone marrow biopsy may be deferred until treatment is indicated, however. Appropriate imaging studies include CT scan (with contrast of diagnostic quality) of the chest, abdomen and pelvis. Nodal MZL occurs primarily in the lymph nodes, although involvements of additional extranodal sites are common. The diagnosis of nodal MZL requires careful evaluation to rule out extranodal sites of primary disease and must be distinguished from nodal FL, MCL, lymphoplasmacytic lymphoma and CLL, all of which are more common. A MUGA scan/echocardiogram should be performed if the patient is being considered for treatment with regimens containing anthracycline or anthracenedione. Testing for hepatitis B virus is indicated for patients being considered for treatment with rituximab-containing regimens due to the risk of viral reactivation with chemoimmunotherapy. Testing for hepatitis C virus may be useful in select cases.

### **NCCN Recommendations**

The panel recommends that patients with nodal MZL be managed according to the recommendations for FL in the NCCN Guidelines for NHL.

### **Splenic Marginal Zone Lymphoma**

Splenic MZL is characterized by the presence of splenomegaly in all cases, which may become symptomatic when massive or when associated with cytopenias.<sup>2,5,66</sup> Peripheral lymph nodes are generally not involved while splenic hilar lymph nodes are often involved<sup>2,5</sup>; involvement of thoracic or abdominal lymph nodes may also be seen in about a third of patients with splenic MZL.<sup>8,66</sup> In addition, bone marrow involvement is present in the majority of patients (about 85%) and involvement of peripheral blood occurs in 30-50% of patients.<sup>2,8,66</sup> Although most patients with splenic MZL present with advanced-stage disease, the disease course is generally indolent. Among the subgroup of patients with splenic MZL (n=59) in a retrospective study in patients with non-MALT-type MZL, the median TTP (from start of treatment) and median OS was 6.9 years and 9.1 years, respectively.<sup>66</sup> Similarly, in a retrospective review of data from patients with splenic MZL (N=81), the median OS was 10.5 years.<sup>67</sup>

### **Diagnosis**

Adequate hematopathology review of biopsy materials and immunophenotyping are needed to establish a diagnosis. The diagnosis of splenic MZL requires bone marrow involvement with or without peripheral blood involvement by small lymphoid cells with immunoglobulin (Ig) light chain restriction that lack characteristic features of other small B-cell neoplasms (CD5, CD10, cyclin D1).<sup>68</sup> The recommended markers for an IHC panel include CD20, CD3, CD5, CD10, CD21 or CD23, CD43, kappa/lambda, IgD, CCND1, BCL2, and annexin A1; the recommended markers for flow cytometry analysis

include CD19, CD20, CD5, CD23, CD10, CD43, and CD103. The typical immunophenotype for splenic MZL is CD5-, CD10-, CD20+, CD23-/+, CD43-, cyclin D1-, BCL2 follicles-, annexinA1-, CD103-, and with expression of both IgM and IgD. This lymphoma is distinguished from CLL by the absence of CD5 expression, strong CD20 expression and variable CD23 expression, and from hairy cell leukemia (HCL) by the absence of CD103 expression.

Splenic MZL is most definitively diagnosed at splenectomy, since the immunophenotype is nonspecific and morphologic features on the bone marrow may not be diagnostic. However in a patient with splenomegaly (small or no M component) and a characteristic intra sinusoidal lymphocytic infiltration of the bone marrow, the diagnosis can strongly be suggested on bone marrow biopsy, if the immunophenotype is consistent. Plasmacytoid differentiation with cytoplasmic Ig detectable on paraffin sections may occur. In such cases, the differential diagnosis may include LPL. *MYD88* and *BRAF* mutation status can be useful in selected cases for differentiating splenic MZLs from WM/LPL and HCL respectively.<sup>13,69,70</sup> Conventional and real-time allele-specific polymerase chain reaction (AS-PCR) for *MYD88* (*L265P*) has been reported to be an useful test to differentiate WM from non-IgM LPL and other B-cell lymphomas with overlapping clinical and pathological features.<sup>71</sup>

### **Workup**

The initial workup for splenic MZL is similar to the other indolent lymphomas. A comprehensive physical examination should be performed and performance status should be assessed. Laboratory evaluations should include a complete blood count with differentials and platelets, comprehensive metabolic panel, and measurement of serum LDH levels. Serum protein electrophoresis (SPEP) and/or measurement of quantitative immunoglobulin levels should be performed. If elevated immunoglobulins or monoclonal immunoglobulin is detected, further

characterization by immunofixation of blood may be useful. Evaluation of bone marrow biopsy with or without aspirates should be performed.

Appropriate imaging studies include CT scan (with contrast of diagnostic quality) of the chest, abdomen and pelvis. A MUGA scan/echocardiogram should be performed if the patient is being considered for treatment with regimens containing anthracycline or anthracenedione. Testing for HCV is an essential part of initial workup. Hepatitis C has been associated with and implicated in the pathogenesis of splenic MZL and should be evaluated for all patients suspected of having this diagnosis.<sup>72</sup> Testing for HBV is indicated for patients being considered for treatment with rituximab-containing regimens due to the risk of viral reactivation. Other useful evaluations may include cryoglobulin testing for detection of abnormal proteins frequently associated with hepatitis C, and direct Coombs test for evaluation of autoimmune hemolytic anemia.

#### **Treatment Options**

As previously mentioned, HCV infection may be associated with some cases of MZLs. In a retrospective study in patients with MZLs, positive HCV serology was detected in 35% of the group of patients with splenic MZL.<sup>8</sup> Antiviral therapy with interferon (IFN)-alpha, with or without ribavirin, has been shown to induce virologic and hematologic responses in patients with HCV-positive MZLs, including in those with splenic disease.<sup>8,73-75</sup> A recent retrospective study evaluated the activity of antiviral therapy with IFN or pegylated-IFN, with or without ribavirin (84% received ribavirin), in a large series of patients with HCV-positive indolent B-cell NHLs (N=94; splenic MZL histology, n=30 [32%]).<sup>76</sup> Among the patients who received antiviral treatment as first-line therapy (n=76; splenic MZL, n=24), the ORR and CR rate was 77% and 47%, respectively, and a sustained virologic response was observed in 78% of patients. The median duration of response was 23 months after a

median follow up of 3.3 years. The 5-year PFS and OS rate was 78% and 94%, respectively.<sup>76</sup>

For patients with splenic MZL with negative HCV serology, various treatment modalities including splenectomy, single-agent chemotherapy, combination chemotherapy, immunotherapy with rituximab, and/or chemoimmunotherapy (rituximab combined with chemotherapy) have been evaluated. About 20% to 25% of patients may be observed without initiating treatment at diagnosis, in the absence of disease symptoms or cytopenias.<sup>67,77</sup> Splenectomy alone can result in an ORR of 80% to 90%, with a median OS of 93 months reported in retrospective series.<sup>77,78</sup> Splenectomy with adjuvant chemotherapy (e.g., CHOP-like regimens, alkylating agents, purine analogs) resulted in CR rates of about 50%, with median OS of 107.5 months (about 9 years).<sup>78,79</sup> In retrospective studies, splenectomy with or without chemotherapy have demonstrated favorable outcomes with a median OS exceeding 10 years and a 10-year OS rate of about 75%.<sup>67,78</sup> In a retrospective series of patients with splenic MZL (N=30) treated with splenectomy (followed by alkylating agent-based or anthracycline-based chemotherapy in the majority of patients) or chemotherapy alone with CHOP-like regimens and/or antiviral therapy for HCV positivity, the ORR and CR rates were 93% and 48%, respectively.<sup>8</sup> The median EFS was 3.3 years and the estimated 3-year OS rate was 75%.

Treatment of splenic MZL with purine analog agents (e.g., pentostatin, cladribine) alone resulted in CR rates of about 20%.<sup>80-82</sup> In a small phase II prospective study in patients with splenic MZL (N=16; previously treated, n=13), single-agent therapy with pentostatin induced an ORR of 68% with a CR in 23% of patients; after a median follow up of 35 months, the median PFS and OS was 18 months and 40 months, respectively.<sup>81</sup> In a retrospective analysis of patients with splenic MZL

(N=50), the subgroup of patients treated with cladribine alone (n=12) had a CR rate of 21%, with a 4-year PFS rate of 52%.<sup>80</sup> In another retrospective study in patients with splenic MZL (N=70), the patients treated with chemotherapy alone (n=11; purine analog regimens, n=10) had a CR rate of 18%, and a 3-year FFS rate of 45%; the 3-year OS rate was 55%.<sup>82</sup>

The anti-CD20 monoclonal antibody rituximab has also been evaluated as both monotherapy and in combination with chemotherapy in patients with splenic MZL. In retrospective series, rituximab alone (with or without maintenance rituximab) has shown high response rates (ORR 90% to 100%; CR/CRu rates 40% to 85%) with durable remissions.<sup>82-84</sup> In a retrospective series of patients with splenic MZL who received rituximab alone (n=26), the ORR and CR/CRu rates were 88% and 42%, respectively.<sup>82</sup> The 3-year FFS and OS rates were 86% and 95%, respectively. Combination therapy with rituximab and chemotherapy appears to provide benefits over purine analog therapy alone. In a small subgroup of patients who received rituximab combined with chemotherapy (n=6), the CR/CRu rate was 33% and both the 3-year FFS and OS rates were 100%.<sup>82</sup> A retrospective study compared outcomes of patients with splenic MZL treated with cladribine alone (n=12) versus cladribine with rituximab (n=38).<sup>80</sup> The combination regimen of cladribine and rituximab resulted in significantly higher CR rate (62.5% vs. 21%;  $P=0.004$ ) and 4-year PFS rate (83% vs. 52%;  $P=0.04$ ) compared with cladribine alone. After a median follow up of 45 months, the 4-year PFS rate for all patients was 67% and the estimated 6-year OS rate was 89%.<sup>80</sup> In a recent retrospective study that assessed treatment with rituximab in patients with splenic MZL (N=43), rituximab alone or in combination resulted in an ORR of 100% with a CR in 79% of patients.<sup>85</sup> This CR rate compared favorably to the 30% CR observed in patients treated with chemotherapy alone (n=10).

Moreover, single-agent rituximab resulted in similar CR rates compared with rituximab-based combination (90% vs. 79%), and was associated with less toxicity. The 3-year DFS was more favorable with rituximab-containing therapy (79%) compared with splenectomy alone (29%) or chemotherapy alone (25%). The 3-year OS with rituximab was 98%.<sup>85</sup>

### ***NCCN Recommendations***

Asymptomatic patients with no splenomegaly or progressive cytopenia can be observed until indications for treatment develop. Patients presenting with splenomegaly should be treated depending on their HCV serology status. Hepatology evaluation is recommended for patients with HCV positivity. For patients without contradictions for treatment of hepatitis, appropriate treatment with antiviral therapy should be initiated. In addition, patients requiring treatment for symptomatic splenomegaly can be further managed with splenectomy or rituximab therapy. Patients with contraindications should be managed as described below for patients with HCV-negative disease.

Patients who are HCV-negative can be observed if they are asymptomatic. Patients who are symptomatic (cytopenias or symptoms of splenomegaly, weight loss, early satiety or abdominal pain) should be treated with splenectomy or rituximab. Pneumococcal and meningococcal vaccination should be given at least 2 weeks before splenectomy. Patients should be monitored on a regular basis following treatment. Clinical follow up (including repeat diagnostic tests and imaging studies, as clinically indicated) should be performed every 3-6 months for 5 years and then annually or as clinically indicated thereafter. Patients with evidence of disease progression should be managed according to the recommendations for advanced-stage FL in the NCCN Guidelines.

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